A Switchable Dual Organocatalytic System & Enantioselective Total Synthesis of the Quadrane Sesquiterpene Suberosanone

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SUPPORTING INFORMATION

Content:

1. Experimental procedures and characterization data

1.1. General information

Reactions were carried out under an argon atmosphere in oven-dried reaction vessels sealed with Teflon screw caps in anhydrous solvents. All reagents were weighed and handled in air at room temperature. Unless otherwise stated, all commercially available reagents and solvents were used as received. Anhydrous methanol was obtained by refluxing over magnesium turning and then distilled under an argon atmosphere. Anhydrous dichloromethane and toluene were obtained from a solvent purification system. Crotonaldehyde, (*E*)-hex-2-enal and cinnamaldehyde were freshly distilled before use. The reactions were monitored by TLC visualized by UV (254 nm) and/or with *p*-anisaldehyde and H_2SO_4 in EtOH. Flash chromatography was performed on 40-63 μm silica gel generally eluted with EtOAc/petroleum ether (bp 40–60°C, herein abbreviated PE). NMR data were generally recorded at 300 or 400 MHz in chloroform-d_1 using as internal standards the residual chloroform signal for ^{1}H NMR (δ = 7.26 ppm) and the deuterated solvent signal for $^{13}C\{^1H\}$ NMR (δ = 77.16 ppm). In one case acetone-d_6 was used to record ^{13}C NMR, also using the solvent signals as internal standards (δ = 29.8, 206.3 ppm). Coupling constants (*J*) are in Hertz (Hz) and the classical abbreviations are used to describe the signal multiplicities. Melting points were measured with a Büchi B-540 apparatus. Specific rotations were recorded at 15 ºC, 20 ºC or 25 ºC on an Anton-Paar MCP 200 or a 241 Perkin-Elmer polarimeter at 589 nm and other wavelength (578, 546, 436 and 365 nm). Melting points and specific rotations were only measured on diastereomerically pure products (dr > 19:1). HPLC analyses for the determination of enantiomeric ratio were performed on a Merck-Hitachi system equipped with Chiralpak AD-H, Chiralcel OD-3, Chiralcel IF, Lux-Cellulose-4, Chiralpak IA, Chiralpak AZ-H, Chiralpak AS-H, (*S*,*S*)-Whelk-O1 and Lux-Cellulose-2 columns (see http://chirbase.u-3mrs.fr for details). High-resolution mass spectra were recorded at the Spectropole (http://fr-chimie.univ-amu.fr/spectropole//).

Non-commercially available substrates **4** were prepared by known methods involving microwave-assisted Wolff rearrangements of the corresponding diazo compounds in the presence of the appropriate nucleophiles.[1]

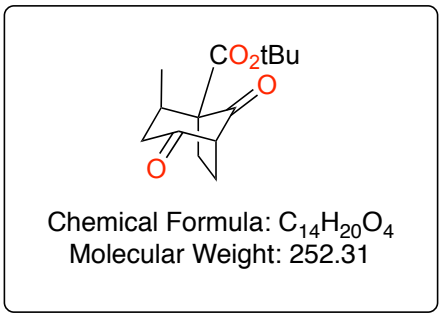
*1.2. General procedures for the synthesis of the bridge compounds **6a-m**:*

To a solution of α-activated cycloalkanone **4a-i** (0.50 mmol) and α,β-unsaturated aldehyde **5a-c** (1.0 mmol) in anhydrous solvent (0.4 mL) under an argon atmosphere, at 0, 15 or 25 ºC depending on cases (see procedures below), was added (*S*)-2-(bis(3,5-bis(trifluoromethyl)phenyl) ((trimethylsilyl)oxy)methyl) pyrrolidine (**I**, 15 mol%) or (2*S*,5*S*)-5-benzyl-2-(*tert*-butyl)-3-methyl imidazolidin-4-one (15 mol%). The resulting mixture was stirred at the same temperature until the starting material **4a-i** is no longer detectable by TLC analysis. Then, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (**II**, 3 or 20 mol% depending on cases, see Table 1 and procedures below) was added, eventually together with glacial acetic acid (20 mol%, see Table 1 and procedures below), and the reaction mixture was further stirred at constant temperature until no change is observable by TLC analysis. Removal of all volatiles in vacuum afforded the crude product **2a-m**. To a solution of this material in dichloromethane (5 mL) was added pyridinium chlorochromate (PCC, 1.0 mmol) and anhydrous magnesium sulfate (1 mmol), and the reaction mixture was stirred at 25 ºC for 14 hours and filtered over celite. The resulting filtrate was concentrated in vacuum, analyzed by ^{1}H NMR (dr determination), and purified by flash chromatography eluted with EtOAc/PE to afford the pure product **6a-m**.

The racemic materials **6a-m** required for the determination of the enantioselectivity were prepared by known methods[2] from **4a-i** and **5a-c** (1.5 equiv) using potassium carbonate (1.5 equiv) in acetone or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.5 equiv) in toluene, and oxidation with PCC as above.

1.3. Characterization data

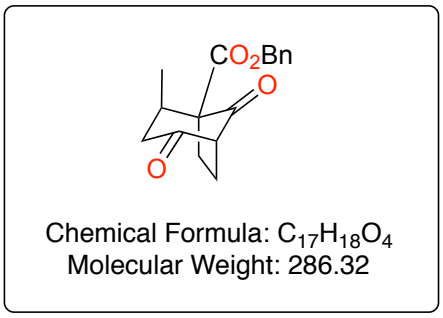
Product **6a**:



Chemical Formula: $C_{14}H_{20}O_4$
Molecular Weight: 252.31

Following the general procedure, the reaction between *tert*-butyl 2-oxocyclopentanecarboxylate (**4a**, 92 mg, 0.50 mmol) and crotonaldehyde (**5a**, 83 μL, 1.0 mmol) in toluene at 0 ºC using catalyst **I** (45 mg, 0.075 mmol) for 25 h and then catalyst **II** (39 mg, 0.10 mmol) for 47 h afforded, after oxidation with PCC (215 mg, 1.0 mmol) in the presence of anhydrous $MgSO_4$ (120 mg, 1.0 mmol), the product **6a** (white solid, 90 mg, 71% yield from **4a**) as a mixture of two diastereomers (dr = 4:1, er = 26:1 for the major diastereomer having an axial methyl group). $\mathbf{R_f}$ (PE/EtOAc: 4/1) = 0.26. **HRMS** (ESI+) for $C_{14}H_{21}O_4^+$: calcd. $[M+H]^+$: 253.1434, found: 253.1428. **^{13}C NMR** (100 MHz, $CDCl_3$): *major diastereomer (axial Me):* δ 205.1 (C), 200.4 (C), 169.6 (C), 82.1 (C), 65.7 (CH), 60.7 (C), 42.1 (CH_2), 32.5 (CH), 29.8 (CH_2), 28.1 (3 × CH_3, *t*-Bu), 21.6 (CH_2), 16.8 (CH_3); *minor diastereomer (equatorial Me):* δ 203.8 (C), 202.9 (C), 168.1 (C), 82.3 (C), 63.83 (CH), 62.6 (C), 42.9 (CH_2), 32.5 (CH), 28.1 (3 × CH_3, *t*-Bu), 22.1 (CH_2), 19.7 (CH_2), 15.8 (CH_3). **^{1}H NMR** (400 MHz, $CDCl_3$): *major diastereomer (axial Me):* δ 3.18 (t, J = 5.1 Hz, 1H), 2.95 (dd, J = 16.1, 7.9 Hz, 1H), 2.69 – 2.50 (m, 1H), 2.50 – 2.33 (m, 1H), 2.25 (ddd, J = 13.1, 10.2, 4.3 Hz, 1H), 2.21 – 2.16 (m, 1H), 2.16 – 2.05 (m, 1H), 2.03 – 1.80 (m, 1H), 1.45 (s, 9H), 0.89 (d, J = 7.0 Hz, 3H); *minor diastereomer (equatorial Me):* δ 3.18 (t, J = 5.1 Hz, 1H), 2.95 (dd, J = 16.1, 7.9 Hz, 1H), 2.69 – 2.50 (m, 1H), 2.50 – 2.33 (m, 1H), 2.25 (ddd, J = 13.1, 10.2, 4.3 Hz, 1H), 2.21 – 2.16 (m, 1H), 2.16 – 2.05 (m, 1H), 2.03 – 1.80 (m, 1H), 1.46 (s, 9H), 1.04 (d, J = 5.8 Hz, 3H). **HPLC** (Lux-Amylose-2, heptane/ethanol 80/20, 1.0 mL/min): $\tau_{\text{major dia}}$ = 6.50 min (major enantiomer) and 6.91 min (minor enantiomer).

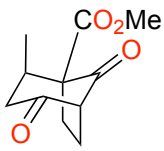
Product **6b**:



Chemical Formula: $C_{17}H_{18}O_4$
Molecular Weight: 286.32

Following the general procedure, the reaction between benzyl 2-oxocyclopentanecarboxylate (**4b**, 109 mg, 0.50 mmol) and crotonaldehyde (**5a**, 83 μL, 1.0 mmol) in methanol at 0 ºC using catalyst **I** (45 mg, 0.075 mmol) for 24 h and then catalyst **II** (39 mg, 0.10 mmol) for 22 h afforded, after oxidation with PCC (215 mg, 1.0 mmol) in the presence of anhydrous $MgSO_4$ (120 mg, 1.0 mmol), the product **6b** (pale yellow oil, 92 mg, 64% yield from **4b**) as a single diastereomer (dr > 20:1, er = 25:1). $\mathbf{R_f}$ (PE/EtOAc: 4/1) = 0.24. $\mathbf{[\alpha]_D^{25}}$ = –45.3 (*c* 1.0, $CHCl_3$). **HRMS** (ESI+) for $C_{17}H_{19}O_4^+$: calcd. $[M+H]^+$: 287.1278, found: 287.1278. **^{13}C NMR** (75 MHz, $CDCl_3$): δ 204.6 (C), 200.0 (C), 170.4 (C), 135.5 (C), 128.7 (2 × CH), 128.5 (CH), 128.2 (2 × CH), 67.2 (CH_2), 65.6 (CH), 60.5 (C), 42.1 (CH_2), 32.5 (CH), 29.7 (CH_2), 21.7 (CH_2), 16.9 (CH_3). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36 – 7.26 (m, 5H), 5.29 – 5.18 (m, 2H), 3.26 (d, J = 6.4 Hz, 1H), 2.99 (dd, J = 16.1, 7.8 Hz, 1H), 2.66 (m, 1H), 2.60 – 2.48 (m, 1H), 2.35 – 2.27 (m, 1H), 2.21 (dd, J = 17.2, 9.0 Hz, 2H), 2.05 – 1.90 (m, 1H), 0.94 (d, J = 6.9 Hz, 3H). **HPLC** (Chiralpak IC, heptane/ethanol 80/20, 1.0 mL/min): τ = 7.20 min (minor enantiomer) and 7.95 min (major enantiomer).

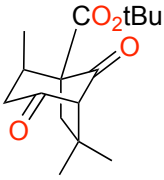
Product **6c**:



Chemical Formula: $C_{11}H_{14}O_4$
Molecular Weight: 210.23

Following the general procedure, the reaction between methyl 2-oxocyclopentanecarboxylate (**4c**, 95% purity, 66 μL, 0.50 mmol) and crotonaldehyde (**5a**, 83 μL, 1.0 mmol) in methanol at 0 ºC using catalyst **I** (45 mg, 0.075 mmol) for 24 h and then catalyst **II** (39 mg, 0.10 mmol) for 20 h afforded, after oxidation with PCC (215 mg, 1.0 mmol) in the presence of anhydrous $MgSO_4$ (120 mg, 1.0 mmol), the product **6c** (pale yellow solid, 74 mg, 70% yield from **4c**) as a mixture of two diastereomers (dr = 17:1, er = 13:1 for the major diastereomer having an axial methyl group). $\mathbf{R_f}$ (PE/EtOAc: 4/1) = 0.21. **HRMS** (ESI+) for $C_{11}H_{15}O_4^+$: calcd. $[M+H]^+$: 211.0965, found: 211.0965. ^{13}**C NMR** (100 MHz, $CDCl_3$): *major diastereomer (axial Me):* δ 204.6 (C), 200.2 (C), 170.9 (C), 65.4 (CH), 60.4 (C), 52.5 (CH_3), 42.0 (CH_2), 32.4 (CH), 29.8 (CH_2), 21.7 (CH_2), 16.9 (CH_3). ^{1}**H NMR** (400 MHz, $CDCl_3$): *major diastereomer (axial Me):* δ 3.78 (s, 3H), 3.24 (d, J = 6.4 Hz, 1H), 2.98 (dd, J = 16.1, 7.9 Hz, 1H), 2.70 – 2.59 (m, 1H), 2.58 – 2.49 (m, 1H), 2.29 (ddd, J = 12.1, 9.8, 4.2 Hz, 1H), 2.25 – 2.18 (m, 1H), 2.23 – 2.19 (m, 1H), 1.99 (ddd, J = 14.0, 7.9, 3.0 Hz, 1H), 0.91 (d, J = 7.0 Hz, 3H). **HPLC** (Chiralpak AD-H, heptane/ethanol 80/20, 1.0 mL/min, UV 220 nm): $\tau_{\text{major dia}}$ = 9.74 min (major enantiomer) and 11.25 min (minor enantiomer).

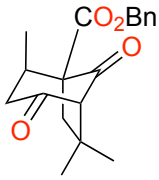
Product **6d**:



Chemical Formula: $C_{16}H_{24}O_4$
Molecular Weight: 280.36

Following the general procedure, the reaction between *tert*-butyl 4,4-dimethyl-2-oxocyclopentanecarboxylate (**4d**, 106 mg, 0.50 mmol) and crotonaldehyde (**5a**, 83 μL, 1.0 mmol) in methanol at 0 ºC using catalyst **I** (45 mg, 0.075 mmol) for 23 h and then catalyst **II** (39 mg, 0.10 mmol) and glacial acetic acid (6 μL, 0.10 mmol) for 3.5 days afforded, after oxidation with PCC (215 mg, 1.0 mmol) in the presence of anhydrous $MgSO_4$ (120 mg, 1.0 mmol), the product **6d** (white solid, 126 mg, 90% yield from **4d**) as a mixture of two diastereomers (dr = 2:1, er = 16:1 for the major diastereomer having an axial methyl group). $\mathbf{R_f}$ (PE/EtOAc: 4/1) = 0.67. **HRMS** (ESI+) for $C_{16}H_{28}NO_4^+$: calcd. $[M+NH_4]^+$: 298.2013, found: 298.2013. ^{13}**C NMR** (75 MHz, $CDCl_3$): *major diastereomer (axial Me):* δ 205.5 (C), 201.1 (C), 169.5 (C), 81.8 (C), 78.4 (CH), 62.3 (C), 45.7 (CH_2), 44.1 (CH_2), 35.5 (C), 31.9 (CH), 30.3 (CH_3), 27.9 (3 × CH_3), 24.2 (CH_3), 17.4 (CH_3); *minor diastereomer (equatorial Me):* δ 204.0 (C), 203.5 (C), 168.1 (C), 82.1 (C), 76.9 (CH), 63.9 (C), 44.6 (CH_2), 36.5 (CH_2), 36.0 (C), 32.3 (CH), 30.3 (CH_3), 28.0 (3 × CH_3), 24.6 (CH_3), 16.10 (CH_3). ^{1}**H NMR** (300 MHz, $CDCl_3$): *selected resonances for the major diastereomer (axial Me):* δ 1.42 (s, 9H), 1.00 (d, J = 6.9 Hz, 3H); *selected resonances for the minor diastereomer (equatorial Me):* δ 1.44 (s, 9H), 0.91 (d, J = 7.0 Hz, 3H). **HPLC** (Chiralpak AZ-H, heptane/ethanol 80/20, 1.0 mL/min): $\tau_{\text{major dia}}$ = 9.96 min (minor enantiomer) and 13.47 min (major enantiomer).

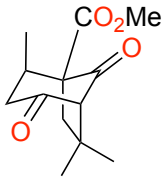
Product **6e**:



Chemical Formula: $C_{19}H_{22}O_4$
Molecular Weight: 314.38

Following the general procedure, the reaction between benzyl 4,4-dimethyl-2-oxocyclopentanecarboxylate (**4e**, 123 mg, 0.50 mmol) and crotonaldehyde (**5a**, 83 μL, 1.0 mmol) in methanol at 0 ºC using catalyst **I** (45 mg, 0.075 mmol) for 38 h and then catalyst **II** (39 mg, 0.10 mmol) and glacial acetic acid (6 μL, 0.10 mmol) for 4 days afforded, after oxidation with PCC (215 mg, 1.0 mmol) in the presence of anhydrous $MgSO_4$ (120 mg, 1.0 mmol), the product **6e** (pale yellow solid, 94 mg, 60% yield from **4e**) as a mixture of two diastereomers (dr = 2:1, er = 9:1 for the major diastereomer having an axial methyl group). $\mathbf{R_f}$ (PE/EtOAc: 4/1) = 0.47. **HRMS** (ESI+) for $C_{19}H_{23}O_4^+$: calcd. $[M+H]^+$: 315.1591, found: 315.1591. **^{13}C NMR** (75 MHz, $CDCl_3$): *major diastereomer (axial Me):* δ 205.0 (C), 200.8 (C), 170.2 (C), 135.6 (C), 128.7 (2 × CH), 128.3 (2 × CH), 127.9 (CH), 78.3 (CH), 67.0 (CH_2), 61.8 (C), 45.5 (CH_2), 44.0 (CH_2), 35.6 (C), 32.2 (CH_3), 30.5 (CH_3), 24.2 (CH_3), 17.6 (CH_3); *minor diastereomer (equatorial Me):* δ 203.6 (C), 202.9 (C), 169.1 (C), 135.5 (C), 128.7 (2 × CH), 128.4 (CH), 128.2 (2 × CH), 76.7 (CH), 67.5 (CH_2), 63.7 (C), 44.5 (CH_2), 36.5 (C), 36.2 (CH_2), 32.6 (CH_3), 30.5 (CH_3), 24.6 (CH_3), 16.2 (CH_3). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36 – 7.29 (m, 5H), 5.27 – 5.17 (m, 2H), 2.90 – 1.93 (m, 6H), 1.12 – 1.09 (m, 6H), 0.99 – 0.97 (m, 3H). **HPLC** (Chiralpak AD-H, heptane/ethanol 90/10, 1.0 mL/min): $\tau_{major\ dia}$ = 12.11 min (major enantiomer) and 21.04 min (minor enantiomer).

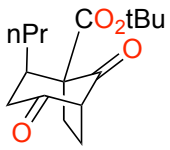
Product **6f**:



Chemical Formula: $C_{13}H_{18}O_4$
Molecular Weight: 238.28

Following the general procedure, the reaction between methyl 4,4-dimethyl-2-oxocyclopentanecarboxylate (**4f**, 85 mg, 0.50 mmol) and crotonaldehyde (**5a**, 83 μL, 1.0 mmol) in methanol at 0 ºC using catalyst **I** (45 mg, 0.075 mmol) for 38 h and then catalyst **II** (39 mg, 0.10 mmol) and glacial acetic acid (6 μL, 0.10 mmol) for 4 days afforded, after oxidation with PCC (215 mg, 1.0 mmol) in the presence of anhydrous $MgSO_4$ (120 mg, 1.0 mmol), the product **6f** (colorless oil, 71 mg, 60% yield from **4f**) as a mixture of two diastereomers (dr = 2:1, er = 13:1 for the major diastereomer having an axial methyl group). $\mathbf{R_f}$ (PE/EtOAc: 4/1) = 0.53. **HRMS** (ESI+) for $C_{13}H_{19}O_4^+$: calcd. $[M+H]^+$: 239.1278, found: 239.1278. **^{13}C NMR** (75 MHz, $CDCl_3$): *major diastereomer (axial Me):* δ 205.0 (C), 200.8 (C), 170.9 (C), 78.1 (CH), 61.7 (C), 52.5 (CH_3), 45.5 (CH_2), 43.9 (CH_2), 35.5 (C), 32.1 (CH), 30.5 (CH_3), 24.1 (CH_3), 17.5 (CH_3); *minor diastereomer (equatorial Me):* δ 203.5 (C), 202.9 (C), 169.6 (C), 76.6 (CH), 63.7 (C), 52.7 (CH_3), 44.4 (CH_2), 36.4 (CH_2), 36.1 (C), 32.6 (CH), 30.5 (CH_3), 24.5 (CH_3), 16.2 (CH_3). **^{1}H NMR** (300 MHz, $CDCl_3$): *selected resonances for the major diastereomer (axial Me):* δ 3.73 (s, 3H), 0.90 (d, J = 6.9 Hz, 3H); *selected resonances for the minor diastereomer (equatorial Me):* δ 3.75 (s, 3H), 0.97 (d, J = 6.3 Hz, 3H). **HPLC** (Chiralpak IE, heptane/ethanol 80/20, 1.0 mL/min): $\tau_{major\ dia}$ = 9.69 min (major enantiomer) and 10.89 min (minor enantiomer).

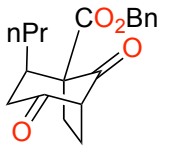
Product **6g**:



Chemical Formula: $C_{16}H_{24}O_4$
Molecular Weight: 280.36

Following the general procedure, the reaction between *tert*-butyl 2-oxocyclopentanecarboxylate (**4a**, 92 mg, 0.50 mmol) and (*E*)-hex-2-enal (**5b**, 116 μL, 0.97 mmol) in methanol at 0 ºC using catalyst **I** (45 mg, 0.075 mmol) for 25 h and then catalyst **II** (39 mg, 0.10 mmol) and glacial acetic acid (6 μL, 0.10 mmol) for 46 h afforded, after oxidation with PCC (215 mg, 1.0 mmol) in the presence of anhydrous $MgSO_4$ (120 mg, 1.0 mmol), the product **6g** (pale yellow solid, 86 mg, 61% yield from **4a**) as a mixture of two diastereomers (dr = 4:1, er = 16:1 for the major diastereomer having an axial n-propyl group). $\mathbf{R_f}$ (PE/EtOAc: 5/1) = 0.28. **HRMS** (ESI+) for $C_{16}H_{28}NO_4^+$: calcd. $[M+NH_4]^+$: 298.2013, found: 298.2013. ^{13}**C NMR** (100 MHz, $CDCl_3$): *major diastereomer (axial nPr):* δ 205.3 (C), 200.3 (C), 169.7 (C), 82.0 (C), 65.7 (CH), 60.8 (C), 38.3 (CH_2). 37.4 (CH), 32.5 (CH_2), 29.8 (CH_2), 28.1 (3 × CH_3), 21.6 (CH_2), 20.3 (CH_2), 13.8(CH_3); *minor diastereomer (equatorial n-Pr):* δ 204.0 (C), 202.8 (C), 168.2 (C), 82.2 (C), 64.3 (CH), 62.9 (C), 40.5 (CH_2), 36.7 (CH), 33.6 (CH_2), 22.1 (CH_2), 28.1 (3 × CH_3), 21.3 (CH_2), 20.3 (CH_2), 13.9 (CH_3). ^{1}**H NMR** (400 MHz, $CDCl_3$): *selected resonance for the major diastereomer (axial n-Pr):* δ 1.44 (s, 9H); *selected resonance for the minor diastereomer (equatorial n-Pr):* δ 1.46 (s, 9H). **HPLC** ((*S*,*S*)-Whelk-O1, heptane/ethanol 90/10, 1.0 mL/min): $\tau_{\text{major dia}}$ = 9.73 min (major enantiomer) and 10.56 min (minor enantiomer).

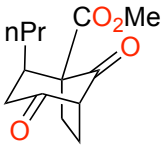
Product **6h**:



Chemical Formula: $C_{19}H_{22}O_4$
Molecular Weight: 314.38

Following the general procedure, the reaction between benzyl 2-oxocyclopentanecarboxylate (**6b**, 109 mg, 0.50 mmol) and (*E*)-hex-2-enal (**5b**, 120 μL, 1.0 mmol) in methanol at 25 ºC using the second generation MacMillan catalyst [(2*S*,5*S*)-5-benzyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one, 18 mg, 0.075 mmol] for 24 h and then catalyst **II** (39 mg, 0.10 mmol) for 2 days afforded, after oxidation with PCC (215 mg, 1.0 mmol) in the presence of anhydrous $MgSO_4$ (120 mg, 1.0 mmol), the product **6h** (yellow oil, 76 mg, 48% yield from **4b**) as a mixture of two diastereomers (dr = 15:1, er = 9:1). $\mathbf{R_f}$ (PE/EtOAc: 4/1) = 0.58. **HRMS** (ESI+) for $C_{19}H_{23}O_4^+$: calcd. $[M+H]^+$: 315.1591, found: 315.1591. ^{13}**C NMR** (75 MHz, $CDCl_3$): *major diastereomer (axial nPr):* δ 204.9 (C), 199.9 (C), 170.5 (C), 135.5 (C), 128.7 (CH), 128.5 (2 × CH), 128.3 (2 × CH), 67.17 (CH_2), 65.6 (CH), 60.56 (C), 38.3 (CH_2), 37.5 (CH), 32.5 (CH_2), 29.7 (CH_2), 21.8 (CH_2), 21.3 (CH_2), 13.8 (CH_3). ^{1}**H NMR** (300 MHz, $CDCl_3$): *major diastereomer (axial nPr):* δ 7.46 – 7.28 (m, 5H), 5.29 (d, *J* = 12.2 Hz, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 3.25 (d, *J* = 6.1 Hz, 1H), 2.95 – 2.73 (m, 1H), 2.57 – 2.33 (m, 3H), 2.35 – 2.14 (m, 2H), 2.05 – 1.92 (m, 1H), 1.47 – 1.10 (m, 4H), 0.81 (t, *J* = 7.0 Hz, 3H). **HPLC** (Chiralpak IC, hexane/ethanol 80/20, 1.0 mL/min): $\tau_{\text{major dia}}$ = 6.36 min (minor enantiomer) and 7.20 min (major enantiomer).

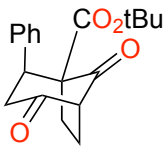
Product **6i**:



Chemical Formula: $C_{13}H_{18}O_4$
Molecular Weight: 238.28

Following the general procedure, the reaction between methyl 2-oxocyclopentanecarboxylate (**14c**, 95% purity, 66 μL, 0.50 mmol) and (*E*)-hex-2-enal (**5b**, 120 μL, 1.0 mmol) in methanol at 0 ºC using the second generation MacMillan catalyst [(2*S*,5*S*)-5-benzyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one, 18 mg, 0.075 mmol] for 25 h and then catalyst **II** (39 mg, 0.10 mmol) and glacial acetic acid (6 μL, 0.10 mmol) for 4 days afforded, after oxidation with PCC (215 mg, 1.0 mmol) in the presence of anhydrous $MgSO_4$ (120 mg, 1.0 mmol), the product **6i** (pale yellow solid, 60 mg, 50% yield from **4c**) as a single diastereomer (dr > 20:1, er = 42:1). $\mathbf{R_f}$ (PE/EtOAc: 5/1) = 0.35. **Mp** = 63–65 ºC (amorphous). $[\alpha]_D^{25}$ = –55.1 (*c* 0.5, $CHCl_3$). **HRMS** (ESI+) for $C_{13}H_{19}O_4^+$: calcd. $[M+H]^+$: 239.1278, found: 239.1278. **^{13}C NMR** (75 MHz, $CDCl_3$): δ 204.9 (C), 200.1 (C), 171.3 (C), 65.5 (CH), 60.6 (C), 52.6 (CH_3), 38.3 (CH_2), 37.4 (CH), 32.5 (CH_2), 29.8 (CH_2), 21.8 (CH_2), 21.2 (CH_2), 13.8 (CH_2). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.78 (s, 3H), 3.24 (d, J = 6.3 Hz, 1H), 2.82 (dd, J = 16.2, 7.5 Hz, 1H), 2.57 – 2.16 (m, 5H), 2.09 – 1.92 (m, 1H), 1.45 – 1.17 (m, 4H), 0.85 (t, J = 6.9 Hz, 3H). **HPLC** (Chiralpak AD-H, hexane/ethanol 80/20, 1.0 mL/min): τ = 6.36 min (major enantiomer) and 8.23 min (minor enantiomer).

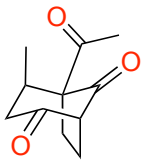
Product **6j**:



Chemical Formula: $C_{19}H_{22}O_4$
Molecular Weight: 314.38

Following the general procedure, the reaction between *tert*-butyl 2-oxocyclopentanecarboxylate (**4a**, 92 mg, 0.50 mmol) and cinnamaldehyde (**5c**, 125 μL, 0.99 mmol) in methanol at 15 ºC using the second generation MacMillan catalyst [(2*S*,5*S*)-5-benzyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one, 18 mg, 0.075 mmol] for 19 h and then catalyst **II** (39 mg, 0.10 mmol) for 11 days afforded, after oxidation with PCC (215 mg, 1.0 mmol) in the presence of anhydrous $MgSO_4$ (120 mg, 1.0 mmol), the product **6j** (white solid, 44 mg, 28% yield from **4a**) as a mixture of two diastereomers (dr = 2:1, er = 11:1 for the major diastereomer having an axial phenyl group). $\mathbf{R_f}$ (PE/EtOAc: 4/1) = 0.24. **HRMS** (ESI+) for $C_{19}H_{23}O_4^+$: calcd. $[M+H]^+$: 315.1591, found: 315.1591. **^{13}C NMR** (75 MHz, $CDCl_3$): *major diastereomer (axial Ph):* δ 206.2 (C), 200.2 (C), 168.6 (C), 140.2 (C), 128.4 (2 × CH), 128.3 (2 × CH), 127.6 (CH), 82.2 (C), 66.1 (CH), 59.9 (C), 44.9 (CH), 41.8 (CH_2), 30.6 (CH_2), 28.0 (3 × CH_3), 21.8 (CH_2); *minor diastereomer (equatorial Ph):* δ 203.3 (C), 202.1 (C), 167.5 (C), 138.4 (C), 128.6 (CH), 128.3 (2 × CH), 127.8 (2 × CH), 82.5 (C), 64.4 (CH), 62.7(C), 42.7 (CH), 42.7 (CH_2), 27.9 (3 × CH_3), 22.31 (CH_2), 21.38 (CH_2). **^{1}H NMR** (300 MHz, $CDCl_3$): *selected resonance for the major diastereomer (axial Ph):* δ 3.44 (d, J = 6.8 Hz, 1H), 1.33 (s, 9H); *selected resonance for the major diastereomer (equatorial Ph):* δ 1.30 (s, 9H). **HPLC** (Chiralcel OD-3, heptane/ethanol 80/20, 1.0 mL/min): $\tau_{\text{major dia}}$ = 5.85 min (major enantiomer) and 6.54 min (minor enantiomer).

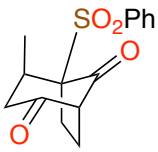
Product **6k**:



Chemical Formula: $C_{11}H_{14}O_3$
Molecular Weight: 194.23

Following the general procedure, the reaction between 2-acetyl cyclopentanone (**4g**, 62 μL, 0.51 mmol) and crotonaldehyde (**5a**, 83 μL, 1.0 mmol) in methanol at 0 ºC using catalyst **I** (45 mg, 0.075 mmol) for 25 h and then catalyst **II** (39 mg, 0.10 mmol) and glacial acetic acid (6 μL, 0.10 mmol) for 3 days afforded, after oxidation with PCC (215 mg, 1.0 mmol) in the presence of anhydrous $MgSO_4$ (120 mg, 1.0 mmol), the product **6k** (white solid, 54 mg, 54% yield from **4g**) as a mixture of diastereomers (dr = 8:1, er = 16:1 for the major diastereomer having an axial methyl group). $\mathbf{R_f}$ (PE/EtOAc: 4/1) = 0.20. **HRMS** (ESI+) for $C_{11}H_{15}O_3^+$: calcd. $[M+H]^+$: 195.1016, found: 195.1016. **^{13}C NMR** (75 MHz, $CDCl_3$): *major diastereomer (axial Me):* δ 205.2 (C), 205.1 (C), 203.1 (C), 65.8(C), 65.6 (CH), 41.9 (CH_2), 31.7 (CH), 28.2 (CH_3), 28.1 (CH_2), 21.8 (CH_2), 16.6 (CH_3). **^{1}H NMR** (300 MHz, $CDCl_3$): *major diastereomer (axial Me):* δ 3.25 (d, J = 6.1 Hz, 1H), 2.96 (dd, J = 16.1, 8.0 Hz, 1H), 2.79 – 2.67 (m, 1H), 2.40-2.31 (m, 1H), 2.29 (s, 3H), 2.25 –2.00 (m, 4H), 0.78 (d, J = 7.0 Hz, 3H). **HPLC** (Chiralpak AS-H, hexane/ethanol 80/20, 1.0 mL/min): $\tau_{\text{major dia}}$ = 6.48 min (major enantiomer) and 8.19 min (minor enantiomer).

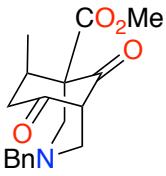
Product **6l**:



Chemical Formula: $C_{15}H_{16}O_4S$
Molecular Weight: 292.35

Following the general procedure, the reaction between 2-phenylsulfonyl cyclopentanone (**4h**, 112 mg, 0.38 mmol) and crotonaldehyde (**5a**, 64 μL, 77 mmol) in dichloromethane at 25 ºC using catalyst **I** (34 mg, 0.057 mmol) for 72 h and then catalyst **II** (29 mg, 0.075 mmol) for 72 h afforded, after oxidation with PCC (164 mg, 0.76 mmol) in the presence of anhydrous $MgSO_4$ (92 mg, 0.76 mmol), the product **6l** (pale yellow solid, 73 mg, 66% yield from **4h**) as a mixture of diastereomers (dr = 2:1, er = 9:1 for the major diastereomer having an axial methyl group). $\mathbf{R_f}$ (PE/EtOAc: 3/2) = 0.33. **HRMS** (ESI+) for $C_{15}H_{20}NO_4S^+$: calcd. $[M+NH_4]^+$: 310.1108, found: 310.1108. **^{13}C NMR** (75 MHz, $CDCl_3$): *major diastereomer (axial Me):* δ 202.9 (C), 196.8 (C), 137.3 (C), 134.5 (CH), 130.2 (2 × CH), 129.3 (2 × CH), 75.2 (C), 65.4 (CH), 44.1 (CH_2), 32.8 (CH), 27.4 (CH_2), 21.4 (CH_2), 17.3 (CH_3); *minor diastereomer (equatorial Me):* δ 201.8 (C), 200.0 (C), 136.8 (C), 134.5 (CH), 131.1 (2 × CH), 128.9 (2 × CH), 76.5 (C), 64.0 (CH), 44.1 (CH_2), 31.9 (CH), 21.8 (CH_2), 20.4 (CH_2), 16.4 (CH_3). **^{1}H NMR** (300 MHz, $CDCl_3$): *selected resonance for the major diastereomer (axial Me):* δ 8.00 (d, J = 8.6 Hz, 2H), 3.24 (d, J = 6.3 Hz, 1H), 3.03 (dd, J = 16.1, 7.5 Hz, 1H), 1.24 (d, J = 6.9 Hz, 3H); *selected resonance for the minor diastereomer (equatorial Me):* δ 8.12 (d, J = 8.7 Hz, 2H), 3.15 (d, J = 7.0 Hz, 1H), 1.42 (d, J = 6.9 Hz, 3H). **HPLC** (Chiralpak AS-H, hexane/ethanol 50/50, 1.0 mL/min): $\tau_{\text{major dia}}$ = 6.27 min (minor enantiomer) and 6.97 min (major enantiomer).

Product **6m**:

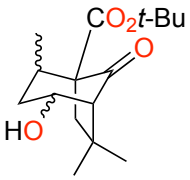


Chemical Formula: $C_{18}H_{21}NO_4$
Molecular Weight: 315.36

Following the general procedure, the reaction between methyl 1-benzyl-4-oxopiperidine-3-carboxylate (**4i**, 124 mg, 0.50 mmol, obtained from the corresponding commercially available hydrochloride salt) and crotonaldehyde (**5a**, 83 μL, 1.0 mmol) in chloroform at 25 ºC using catalyst **I** (45 mg, 0.075 mmol) for 69 h and then catalyst **II** (39 mg, 0.10 mmol) for 25 h afforded, after oxidation with PCC (215 mg, 1.0 mmol) in the presence of anhydrous $MgSO_4$ (120 mg, 1.0 mmol), the product **6m** (light yellow solid, 88 mg, 56% yield from **4i**) as a mixture of diastereomers (dr = 2:1, er = 6:1 for the major diastereomer having an axial methyl group). Alternatively, similar results were obtained with the second generation MacMillan catalyst [(2*S*,5*S*)-5-benzyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one, 15 mol%) then **II** (20 mol%) in chloroform at 25 ºC (45%, dr =2:1, er = 7:1). $\mathbf{R_f}$ (PE/EtOAc: 3/2) = 0.59. **HRMS** (ESI+) for $C_{18}H_{22}NO_4^+$: calcd. $[M+H]^+$: 316.1543, found: 316.1543. **^{13}C NMR** (75 MHz, $CDCl_3$): *major diastereomer (axial Me):* δ 207.2 (C), 202.4 (C), 169.6 (C), 136.8 (C), 128.8 (2 × CH), 128.8 (2 × CH), 127.9 (CH), 64.8 (CH), 62.8 (CH_2), 62.4 (C), 61.2 (CH_2), 59.3 (CH_2), 52.3 (CH_3), 48.9 (CH_2), 32.8 (CH), 19.6 (CH_3); *minor diastereomer (equatorial Me):* δ 206.2 (C), 203.4 (C), 170.1 (C), 137.1 (C), 129.2 (2 × CH), 128.8 (2 × CH), 128.0 (CH), 66.1 (CH), 62.6 (C), 61.5 (CH_2), 59.6 (CH_2), 56.4 (CH_2), 52.7 (CH_3), 47.9 (CH_2), 31.2 (CH), 16.4 (CH_3). **^{1}H NMR** (300 MHz, $CDCl_3$): *selected resonance for the major diastereomer (axial Me):* δ 3.71 (s, 3H), 2.28 (dd, J = 16.0, 6.2 Hz, 1H), 0.92 (d, J = 7.1 Hz, 3H); *selected resonance for the minor diastereomer (equatorial Me):* δ 3.70 (s, 3H), 0.87 (d, J = 6.2 Hz, 3H). **HPLC** (Chiralpak IC, heptane/ethanol 80/20, 1.0 mL/min): $\tau_{\text{major dia}}$ = 7.96 (minor enantiomer) min and 8.61 min (major enantiomer).

*1.4. Total synthesis of suberosanone (**1**) and formal synthesis of suberosenone*

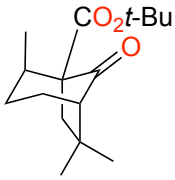
Product **2d**:



Chemical Formula: $C_{16}H_{26}O_4$
Molecular Weight: 282.38

To a solution of *t*-butyl 4,4-dimethyl-2-oxocyclopentanecarboxylate (**4d**, 10.0 g, 47.1 mmol) in methanol (95 mL) under an argon atmosphere was added (*S*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy) methyl) pyrrolidine (**I**, 97% purity, 4.35 g, 7.06 mmol). The resulting solution was cooled down to –30 ºC and crotonaldehyde (**5a**, 7.8 mL, 94.1 mmol) was added dropwise over 1 hour. The resulting reaction mixture was allowed to warm slowly to 0 ºC and stirred at that temperature for 24 h. The complete consumption of **4d** was verified by TLC analysis. Then, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (**II**, 97% purity, 3.77 g, 9.41 mmol) was added in a single portion and the reaction temperature was maintained at 0 ºC for an additional 72 hours. The complete consumption of the intermediate Michael adduct **3** was verified by TLC analysis. The reaction mixture was then concentrated in vacuum and directly purified by flash chromatography to afford the product **2d** as a yellow oil and a mixture of four diastereomers (12.0 g, 90%, dr = 5.3:4.6:4:1). The enantioselectivity of the reaction was confirmed by oxidation of an analytical sample of **2d** (141 mg, 0.50 mmol) as above to give **6d** (125 mg, 89%, dr = 2:1, er = 8:1). $\mathbf{R_f}$ (PE/EtOAc: 4:1) = 0.20 (average value for the 4 diastereomers of **5d**). **HRMS** (ESI+) for $C_{16}H_{26}NaO_4^+$: calcd. $[M+Na]^+$: 305.1723, found: 305.1723. **^{13}C & ^{1}H NMR** analyses of the diastereomeric mixture afforded clean but relatively complex spectra difficult to describe accurately (see copies of spectra below).

Product **7**:



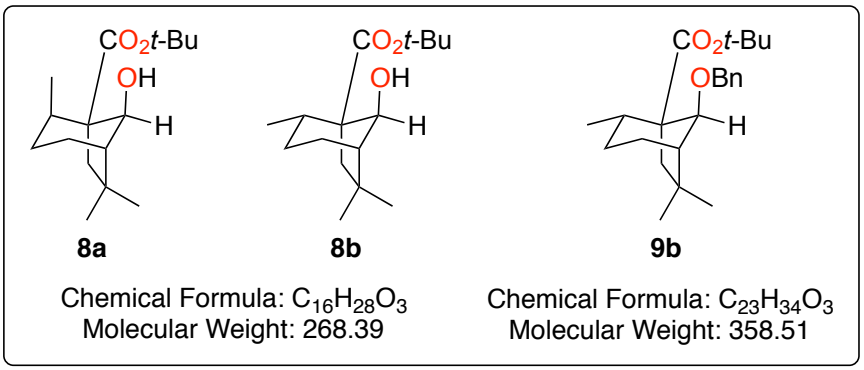
Chemical Formula: $C_{16}H_{26}O_3$
Molecular Weight: 266.38

Sodium hydride (60% dispersion in mineral oil, 2.12 g, 52.9 mmol) was suspended in hexane (30 mL) under an argon atmosphere at room temperature and decanted. Most of the liquid phase was removed with a syringe, and THF (200 mL) and CS_2 (25 mL, 416 mmol) were added. The mixture was cooled down to 0 ºC, and a solution of **2d** (11.5 g, 40.7 mmol) in THF (25 mL) was added over 25 minutes. The resulting mixture was stirred at 0 ºC for an additional 45 minutes, whereupon methyl iodide (5.1 mL, 81.9 mmol) was added. The reaction was allowed to warm slowly to room temperature (ca. 25 ºC) and stirred for 12 h. Then, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl and diethyl ether (200 mL) was added. The organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give the crude intermediate xanthate, which was used directly without purification.

To a solution of this material in toluene (200 mL) under an argon atmosphere were successively added tributyltin hydride (13.1 mL, 48.7 mmol) and azobisisobutyronitrile (AIBN, 669 mg, 4.07 mmol), and the reaction mixture was refluxed for 2 hours. The cooled reaction mixture was then concentrated in vacuum to afford the crude product. Flash chromatography of this material afforded the pure product **7** (9.22 g, 85% from **2d**, dr = 2:1) as a colorless oil. $\mathbf{R_f}$ (PE/EtOAc, 9:1) = 0.50 (average value for the two diastereomers). **HRMS** (ESI+) for $C_{16}H_{26}NaO_3^+$: calcd. $[M+Na]^+$: 289.1774, found: 289.1774. **^{13}C NMR** (75 MHz, ppm/$CDCl_3$): *major diastereomer (axial Me):* δ 213.8 (C), 171.1 (C), 80.7 (C), 62.5 (C), 58.3 (CH), 46.8 (CH_2), 42.2 (CH), 32.5 (C), 31.8 (CH_3), 28.5 (CH_2), 28.0 (3 × CH_3), 25.2 (CH_2), 22.8 (CH_3), 16.3 (CH_3); *minor diastereomer (equatorial Me):* δ 215.6 (C), 169.2 (C), 81.0 (C), 64.5 (C), 56.9 (CH),

42.4 (CH), 37.0 (CH_2), 32.7 (C), 32.0 (CH_3), 29.9 (CH_2), 28.2 (3 × CH_3), 27.1 (CH_2), 23.0 (CH_3), 17.0 (CH_3); **^{1}H NMR** (300 MHz, ppm/$CDCl_3$): *selected resonance for the major diastereomer (axial Me):* δ 1.32 (s, 9H), 1.08 (s, 3H), 1.02 (d, J = 7.1 Hz, 3H), 0.91 (s, 3H); *selected resonance for the minor diastereomer (equatorial Me):* δ 1.35 (s, 9H), 1.07 (s, 3H), 0.88 (s, 3H), 0.77 (d, J = 6.9 Hz, 3H).

Products **8a**, **8b** and **9b**:



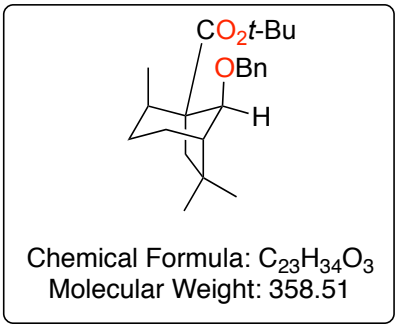
To a solution of **7** (480 mg, 1.80 mmol, dr = 2:1) in ethanol (20 mL) at room temperature was added $NaBH_4$ (170 mg, 4.49 mmol), and the resulting reaction mixture was refluxed for 10 h. The reaction mixture was then poured into saturated aqueous NH_4Cl and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give the crude product. Purification of this material by flash chromatography afforded a 2:1 mixture of the diastereomers **8a** and **8b** (372 mg, 77%).
To a solution of this material (372 mg, 1.39 mmol) in THF (30 mL) at 23 ºC was added benzyl bromide (198 µL, 1.66 mmol) and sodium hydride (60% dispersion in mineral oil, 62 mg, 1.55 mmol), and the resulting reaction mixture was stirred at 23 ºC for 12 h. The reaction mixture was then poured into saturated aqueous NH_4Cl and diethyl ether was added (50 mL). The organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give the crude product. Purification of this material by flash chromatography afforded, in that order, the benzyl ether **9b** (163 mg, 33%) and the unreacted alcohol **8a** (250 mg, 67%, dr > 50:1, er = 8:1) as a white solid. Recrystallization of this material from acetonitrile (0.16 M) at 0 ºC afforded after 10 days large colorless crystalline needles (193 mg, 77%) suitable for X-ray analysis (see below). Notably, the recrystallization allowed for a very efficient enantioenrichment of **8a** (er > 199:1), which allowed to confirm both its relative and absolute configurations to be as depicted.

Charaterization data for **8a**: **R_f** (PE/Et_2O, 5:1) **=** 0.38. **Mp** = 108–109 ºC (acetonitrile). **$[\alpha]_D^{25}$** = –32.0 (*c* 0.8, EtOH). **^{13}C NMR** (75 MHz, ppm/$CDCl_3$): δ 177.2 (C), 80.3 (C), 74.4 (CH), 54.8 (C), 47.9 (CH), 47.9 (CH_2), 37.1 (CH), 34.0 (CH_3), 33.6 (C), 28.2 (3 × CH_3), 25.1 (CH_2), 24.9 (CH_3), 19.5 (CH_3), 17.5 (CH_2). **^{1}H NMR** (300 MHz, ppm/$CDCl_3$): δ 4.49 (d, J = 4.3 Hz, 1H), 2.44 (br s, 1H), 2.05-1.98 (m, 3H), 1.64-1.49 (m, 3H), 1.43 (s, 9H), 1.38 – 1.22 (m, 2H), 1.15 (d, J = 6.9 Hz, 3H), 1.09 (s, 3H), 1.04 (s, 3H). **HPLC** (chiralpak AZ-H, heptane/ethanol 80/20, 1.0 mL/min): τ = 4.28 min (not detected) and 6.30 min (major).

Charaterization data for **8b**: **R_f** (PE/EtOAc, 9:1) = 0.53. **^{13}C NMR** (75 MHz, ppm/$CDCl_3$): δ 176.1 (C), 80.8 (C), 74.3 (CH), 56.5 (C), 47.4 (CH), 38.4 (CH_2), 34.3 (C), 33.5 (CH), 29.5 (CH_3), 28.1 (3 × CH_3), 27.2 (CH_2), 24.8 (CH_3), 20.3 (CH_2), 16.6 (CH_3). **^{1}H NMR** (300 MHz, ppm/$CDCl_3$): *selected resonances* δ 4.20 (d, J = 4.7 Hz, 1H), 2.82 (br s, 1H), 1.38 (s, 9H), 0.99 (s, 3H), 0.96 (s, 3H), 0.62 (d, J = 6.7 Hz, 3H).

Charaterization data for **9b** (contaminated by ca. 12% of benzyl bromide): $\mathbf{R_f}$ (PE/EtOAc, 20:1) = 0.65. **HRMS** (ESI+) for $C_{23}H_{34}NaO_3^+$: calcd. $[M+Na]^+$ 381.2400, found: 381.2400. **^{13}C NMR** (75 MHz, ppm/$CDCl_3$): δ 175.4 (C), 139.1 (C), 128.2 (2 × CH), 127.4 (2 × CH), 127.4 (CH), 83.9 (CH), 79.8 (C), 71.9 (CH_2), 57.3 (C), 46.5 (CH), 39.0 (CH_2), 34.6 (C), 33.3 (CH), 28.9 (CH_3), 28.2 (3 × CH_3), 27.8 (CH_2), 25.1 (CH_3), 21.0 (CH_2), 17.0 (CH_3). **^{1}H NMR** (300 MHz, ppm/$CDCl_3$): δ 7.30 – 7.15 (m, 5H), 4.45 (s, 2H), 3.96 (d, J = 4.6 Hz, 1H), 2.46 – 2.61 (m, 1H), 1.89 (d, J = 14.1 Hz, 1H), 1.77 (dddd, J = 13.9, 9.7, 6.5, 3.2 Hz, 1H), 1.62 – 1.58 (m, 1H), 1.48-1.41 (m, 1H), 1.35 (s, 9H), 1.26 – 1.11 (m, 2H), 0.98 (s, 3H), 0.96 (s, 3H), 0.84-0.75 (m, 1H), 0.68 (d, J = 6.5 Hz, 3H).

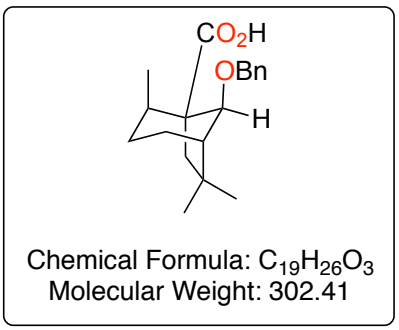
Product **9a** :



Chemical Formula: $C_{23}H_{34}O_3$
Molecular Weight: 358.51

To a solution of **8a** (193 mg, 0.72 mmol) in THF (7.2 mL) at room temperature (20–25 ºC) was added benzyl bromide (103 μL, 0.87 mmol) and potassium hydride (30% dispersion in mineral oil, 156 mg, 1.08 mmol), and the reaction mixture was stirred at room temperature for 7 h. The reaction mixture was then poured into saturated aqueous NH_4Cl (20 mL) and 20 mL of diethyl ether were added. The organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give the crude product. Purification of this material by flash chromatography afforded compound **9a** (232 mg, 90 %) as a colorless oil. $\mathbf{R_f}$ (PE/Et_2O, 15:1) = 0.63. $\mathbf{[\alpha]_D^{25}}$ = +15.1 (*c* 1.0, EtOH). **HRMS** (ESI+) for $C_{23}H_{34}NaO_3^+$: calcd. $[M+Na]^+$ 381.2400, found: 381.2400. **^{13}C NMR** (75 MHz, ppm/$CDCl_3$): δ 175.8 (C), 139.7 (C), 128.2 (2 × CH), 127.1 (2 × CH), 127.1 (CH), 82.3 (CH), 79.7 (C), 72.6 (CH_2), 55.1 (C), 49.5 (CH_2), 46.5 (CH), 36.4 (CH), 33.9 (C), 33.7 (CH_3), 28.2 (3 × CH_3), 25.3 (CH_2), 25.0 (CH_3), 19.8 (CH_3), 18.3 (CH_2). **^{1}H NMR** (300 MHz, ppm/$CDCl_3$): δ 7.30 – 7.12 (m, 5H), 4.53 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.33 (d, J = 4.6 Hz, 1H), 2.09 (ddd, J = 7.3, 7.0, 1.0 Hz, 1H), 2.01 – 1.79 (m, 2H), 1.63 (br s, 1H), 1.53 (*d*, J = 13.7 Hz, 1H), 1.47 (d, J = 13.7 Hz, 1H), 1.37 (s, 9H), 1.32 – 1.16 (m, 2H), 1.12 (d, J = 7.3 Hz, 3H), 1.02 (s, 3H), 0.98 (s, 3H).

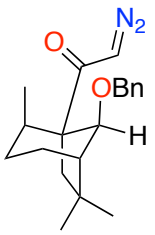
Product **10** :



Chemical Formula: $C_{19}H_{26}O_3$
Molecular Weight: 302.41

To a solution of the *tert*-butyl ester **9a** (232 mg, 0.65 mmol) in dichloromethane (13 mL) was added trifluoroacetic acid (1.0 mL, 13.0 mmol) at 0 ºC and the reaction mixture was warmed to room temperature (20–25 ºC), stirred for 2 hours, and concentrated under vacuum to afford the crude product. Purification of this material by flash chromatography afforded the corresponding carboxylic acid (194 mg, 99%) as a white solid. $\mathbf{R_f}$ (PE/EtOAc, 4:1) = 0.27. **Mp** = 134–135 ºC (amorphous). $\mathbf{[\alpha]_D^{25}}$ = +10.3 (*c* 1.0, EtOH). **HRMS** (ESI+) for $C_{19}H_{27}O_3^+$: calcd. $[M+H]^+$ 303.1955, found: 303.1960; $C_{19}H_{30}NO_3^+$: calcd. $[M+NH_4]^+$ 320.2226, found: 320.2220. **^{13}C NMR** (75 MHz, ppm/$(CD_3)_2CO$): δ 177.6 (C), 140.4 (C), 128.9 (2 × CH), 128.0 (2 × CH), 127.9 (CH), 83.0 (CH), 73.0 (CH_2), 54.9 (C), 50.0 (CH_2), 46.9 (CH), 36.9 (CH), 34.5 (C), 33.8 (CH_3), 25.8 (CH_2), 25.1 (CH_3), 20.4 (CH_3), 18.8 (CH_2). **^{1}H NMR** (300 MHz, ppm/$CDCl_3$): δ 10.91 (br. s, 1H), 7.41–7.26 (m, 5H), 4.63 (d, J = 11.8 Hz, 1H), 4.58 (d, J = 11.8 Hz, 1H), 4.44 (d, J = 4.6 Hz, 1H), 2.31 (ddd, J = 7.2, 6.9, 1.0 Hz, 1H),

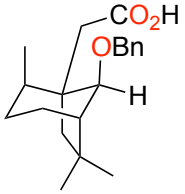
2.09–2.00 (m, 2H), 1.83 (d, *J* = 13.8 Hz, 1H), 1.82-1.79 (m, 1H), 1.67 (d, *J* = 13.7 Hz, 1H), 1.46–1.35 (m, 2H), 1.28 (d, *J* = 7.2 Hz, 3H), 1.16 (s, 3H), 1.10 (s, 3H).



Chemical Formula: $C_{20}H_{26}N_2O_2$
Molecular Weight: 326.43

To a solution of the above material (194 mg, 0.64 mmol) in benzene (13 mL) at room temperature was added oxalyl chloride (560 µL, 6.62 mmol). The resulting mixture was refluxed for 13 hours, cooled down to room temperature and concentrated under vacuum to afford the crude acyl chloride product which was used directly for the next step. To a solution of the above acyl chloride product in THF/acetonitrile (1:1, 13 mL) was added trimethylsilyldiazomethane (2.0 M in hexane, 650 µL, 1.30 mmol) at 0 ºC. The reaction solution was allowed to warm to room temperature (20–25 ºC), stirred for 10 h at that temperature, and 100 µL (1.75 mmol) of acetic acid were added. Removal of volatiles under vacuum afforded the crude methyldiazoketone product **10** (149 mg, 70% from **9a**) as yellow oil, which was used directly in the next step. $\mathbf{R_f}$ (PE/EtOAc, 9:1) = 0.42. **HRMS** (ESI+) for $C_{20}H_{27}N_2O_2^+$: calcd. $[M+H]^+$: 327.2067, found: 327.2067; $\mathbf{[\alpha]_D^{25}}$ = +64.3 (*c* 1.0, EtOH). **^{13}C NMR** (75 MHz, ppm/ $CDCl_3$): δ 200.3 (C), 138.8 (C), 128.5 (2 × CH), 127.5 (CH), 127.4 (2 × CH), 81.1 (CH), 72.0 (CH_2), 58.8 (C), 53.2 (CH), 48.6 (CH_2), 45.3 (CH), 37.9 (CH), 33.8 (CH_3), 33.6 (C), 25.6 (CH_2), 25.1 (CH_3), 19.7 (CH_3), 18.2 (CH_2). **^{1}H NMR** (300 MHz, ppm/$CDCl_3$): δ 7.29 – 7.12 (m, 5H), 5.40 (s, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.34 (d, *J* = 11.9 Hz, 1H), 4.09 (d, *J* = 4.4 Hz, 1H), 2.00 – 1.80 (m, 3H), 1.76 – 1.73 (m, 1H), 1.54 (d, *J* = 13.9 Hz, 1H), 1.48 (d, *J* = 13.9 Hz, 1H), 1.31 – 1.20 (m, 2H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.01 (s, 3H), 0.92 (s, 3H).

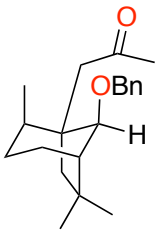
Product **11** :



Chemical Formula: $C_{20}H_{28}O_3$
Molecular Weight: 316.43

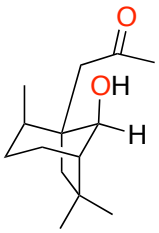
To a solution of crude methyldiazoketone **10** (149 mg, 0.45 mmol) in dioxane (4.5 mL) at room temperature was added H_2O (162 µL, 9.0 mmol) and silver benzoate (21 mg, 0.09 mmol), and the resulting reaction mixture was stirred at 80 ºC for 10 h. After cooling down to room temperature, water (10 mL), 1N aqueous HCl (1 mL) and diethyl ether (10 mL) were added. The organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give the clean crude product **11** (103 mg, 72 %) as a white solid. $\mathbf{R_f}$ (PE/EtOAc, 4:1) = 0.47. **Mp** = 108–109 ºC (amorphous). $\mathbf{[\alpha]_D^{25}}$ = +24.5 (*c* 1.0, EtOH). **HRMS** (ESI+) for $C_{20}H_{28}NaO_3^+$: calcd. $[M+Na]^+$ 339.1931, found: 339.1931. **^{13}C NMR** (75 MHz, ppm/$CDCl_3$): δ 178.9 (C), 139.3 (C), 128.4 (2 × CH), 127.4 (CH), 127.2 (2 × CH), 85.6 (CH), 72.2 (CH_2), 49.3 (CH_2), 46.0 (C), 44.9 (CH), 42.5 (CH_2), 37.3 (CH), 34.2 (C), 34.0 (CH_3), 26.5 (CH_2), 25.2 (CH_3), 19.0 (CH_3), 18.2 (CH_2). **^{1}H NMR** (300 MHz, ppm/$CDCl_3$): δ 11.43 (br s, 1H), 7.28 – 7.16 (m, 5H), 4.51 (d, *J* = 11.9 Hz, 1H), 4.27 (d, *J* = 11.9 Hz, 1H), 3.71 (d, *J* = 4.4 Hz, 1H), 2.73 (d, *J* = 14.4 Hz, 1H), 2.18 (d, *J* = 14.4 Hz, 1H), 1.94 – 1.76 (m, 2H), 1.74 – 1.65 (m, 2H), 1.54 (d, *J* = 14.0 Hz, 1H), 1.48 (d, *J* = 14.0 Hz, 1H), 1.38 – 1.10 (m, 2H), 1.13 (d, *J* = 7.4 Hz, 3H), 1.05 (s, 3H), 0.95 (s, 3H).

Product **12** :



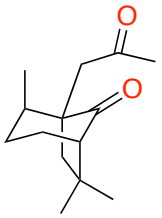
Chemical Formula: $C_{21}H_{30}O_2$
Molecular Weight: 314.46

To a solution of the carboxylic acid **11** (102 mg, 0.32 mmol) in Et_2O (3.2 mL) at 0 ºC was added methyllithium (1.6 M in diethyl ether, 410 µL, 0.66 mmol). The reaction mixture was allowed to warm slowly to room temperature (20–25 ºC), stirred at that temperature for 8 hours, and poured into saturated aqueous NH_4Cl. Diethyl ether (10 mL) was added, the organic layer was separated, and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give the crude product. Purification of this material by flash chromatography afforded the corresponding methyl ketone (90 mg, 89 %) as light yellow oil. $\mathbf{R_f}$ (PE/EtOAc, 9:1) = 0.67. $\mathbf{[\alpha]_D^{25}}$ = +84.8 (*c* 0.43, EtOH). **HRMS** (ESI+) for $C_{21}H_{31}O_2^+$: calcd. $[M+H]^+$ 315.2319, found: 315.2319. **^{13}C NMR** (75 MHz, ppm/ $CDCl_3$): δ 208.9 (C), 139.3 (C), 128.3 (2 × CH), 127.3 (CH), 127.1 (2 × CH), 86.0 (CH), 72.0 (CH_2), 50.8 (CH_2), 49.4 (CH_2), 46.1 (C), 44.5 (CH), 36.6 (CH), 34.3 (C), 34.0 (CH_3), 31.9 (CH_3), 26.3 (CH_2), 25.2 (CH_3), 19.1 (CH_3), 18.2 (CH_2). **^{1}H NMR** (300 MHz, ppm/$CDCl_3$): δ 7.38–7.24 (m, 5H), 4.60 (d, *J* = 11.9 Hz, 1H), 4.32 (d, *J* = 11.9 Hz, 1H), 3.72 (d, *J* = 4.5 Hz, 1H), 3.02 (d, *J* = 16.1 Hz, 1H), 2.25 (d, *J* = 16.1 Hz, 1H), 2.11 (s, 3H), 2.06 – 1.85 (m, 2H), 1.80 (ddd, *J* = 7.4, 7.0, 1.0 Hz, 1H), 1.75 – 1.70 (m, 1H), 1.65 (d, *J* = 13.8 Hz, 1H), 1.54 (d, *J* = 13.9 Hz, 1H), 1.38 – 1.32 (m, 1H), 1.25 (dd, *J* = 13.6, 5.2 Hz, 1H), 1.15 (d, *J* = 7.4 Hz, 3H), 1.13 (s, 3H), 1.03 (s, 3H).



Chemical Formula: $C_{14}H_{24}O_2$
Molecular Weight: 224.34

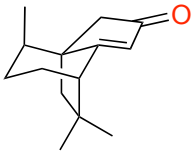
To a solution of the above methyl ketone (90 mg, 0.29 mmol) in MeOH (6 mL) was added 10% Pd/C (31 mg, 0.029 mmol) and the solution was saturated with hydrogen (bubbling through the solution for 5 minutes). The reaction mixture was then stirred vigorously under a hydrogen atmosphere at room temperature (20–25 ºC) for 5 hours, and filtered through a pad of celite. The filtrate was concentrated in vacuum to afford the crude product, and the purification of this material by flash chromatography afforded the corresponding secondary alcohol (58 mg, 90%) as yellow oil. $\mathbf{R_f}$ (PE/EtOAc, 4:1) = 0.25. $\mathbf{[\alpha]_D^{25}}$ = +10.8 (*c* 0.65, EtOH). **HRMS** (ESI+) for $C_{14}H_{25}O_2^+$: calcd. $[M+H]^+$ 225.1849, found: 225.1849; for $C_{14}H_{24}NaO_2^+$: calcd. $[M+Na]^+$ 247.1669, found: 247.1669. **^{13}C NMR** (75 MHz, ppm/$CDCl_3$): δ 209.9 (C), 78.3 (CH), 52.0 (CH_2), 51.2 (CH_2), 49.2 (CH), 46.3 (C), 37.7 (CH), 34.3 (C), 34.0 (CH_3), 32.0 (CH_3), 26.5 (CH_2), 25.0 (CH_3), 19.5 (CH_3), 17.7 (CH_2). **^{1}H NMR** (300 MHz, ppm/$CDCl_3$): δ 4.13 (d, *J* = 4.8 Hz, 1H), 2.82 (d, *J* = 16.3 Hz, 1H), 2.55 (br s, 1H), 2.43 (d, *J* = 16.3 Hz, 1H), 2.15 (s, 3H), 2.10 – 1.90 (m, 2H), 1.71 (ddd, *J* = 7.3, 7.0, 0.9 Hz, 1H), 1.60 (d, *J* = 13.8 Hz, 1H), 1.59 – 1.52 (m, 1H), 1.43 (d, *J* = 13.8 Hz, 1H), 1.41 – 1.35 (m, 1H), 1.29 – 1.21 (m, 1H), 1.11 (d, *J* = 7.5 Hz, 3H), 1.09 (s, 3H), 1.03 (s, 3H).



Chemical Formula: $C_{14}H_{22}O_2$
Molecular Weight: 222.32

To a solution of the above secondary alcohol (58 mg, 0.26 mmol) in ethyl acetate (5.2 mL) at room temperature was added 2-iodoxybenzoic acid (IBX, 728 mg, 2.60 mmol),[3] and the resulting mixture was refluxed for 4 h (TLC monitoring) and filtered over a pad of celite. The filtrate was concentrated in vacuum to afford the crude product, which was purified by flash chromatography to afford the diketone **12** (56 mg, 98 %) as light yellow oil. $\mathbf{R_f}$ (PE/EtOAc, 4:1) = 0.59. $\mathbf{[\alpha]_D^{25}}$ = –67.1 (*c* 0.5, EtOH). **MS** (ESI+): 245 $[M+Na]^+$. **^{13}C NMR** (75 MHz, ppm/ $CDCl_3$): δ 219.8 (C), 207.0 (C), 57.2 (CH), 53.1 (C), 46.3 (CH_2), 44.8 (CH_2), 43.6 (CH), 32.7 (CH_3), 32.4 (C), 31.4 (CH_3), 28.5 (CH_2), 25.8 (CH_2), 23.2 (CH_3), 15.5 (CH_3). **^{1}H NMR** (300 MHz, ppm/$CDCl_3$): δ 2.73 (d, *J* = 17.7 Hz, 1H), 2.47 (d, *J* = 17.7 Hz, 1H), 2.35 (ddd, *J* = 7.2, 7.0, 0.9 Hz, 1H), 2.19 – 1.82 (m, 4H), 2.09 (s, 3H), 1.79 – 1.74 (m, 1H), 1.65 (d, *J* = 13.6 Hz, 1H), 1.21 – 1.15 (m, 1H), 1.15 (s, 3H), 0.92 (s, 3H), 0.83 (d, *J* = 7.2 Hz, 3H). These data are in full agreement with previously reported data for the same compound.[4]

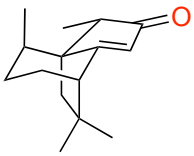
Product **13** :



Chemical Formula: $C_{14}H_{20}O$
Molecular Weight: 204.31

To a solution of diketone **12** (56 mg, 0.25 mmol) in THF (2.6 mL) at room temperature was added rapidly potassium *tert*-butoxide (100 mg, 0.89 mmol), and the reaction mixture was refluxed for 48 h. After cooling down to room temperature, the reaction mixture was poured into saturated aqueous NH_4Cl (10 mL) and diethyl ether (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give the crude product. Purification of this material by flash chromatography afforded **13** (46 mg, 89%) as light yellow oil. $\mathbf{R_f}$ (PE/EtOAc, 9:1) = 0.29. $\mathbf{[\alpha]_D^{25}}$ = –21.0 (*c* 0.15, EtOH). **MS** (ESI+): 227 $[M+Na]^+$. **^{13}C NMR** (75 MHz, ppm/ $CDCl_3$): δ 211.2 (C), 191.9 (C), 121.8 (CH), 54.1 (C), 50.1 (CH_2), 48.9 (CH), 48.8 (CH_2), 40.7 (CH), 40.2 (C), 33.3 (CH_3), 25.7 (CH_2), 24.4 (CH_2), 23.2 (CH_3), 14.7 (CH_3). **^{1}H NMR** (400 MHz, ppm/$CDCl_3$): δ 5.82 (s, 1H), 2.36 (d, *J* = 18.0 Hz, 1H), 2.37 – 2.33 (m, 1H), 2.11 – 1.90 (m, 2H), 2.06 (d, *J* = 17.9 Hz, 1H), 1.89 (d, *J* = 13.2 Hz, 1H), 1.82 – 1.73 (m, 2H), 1.35 (d, *J* = 13.2 Hz, 1H), 1.25 (ddd, *J* = 14.0, 5.0, 2.0 Hz, 1H), 1.20 (s, 3H), 0.89 (s, 3H), 0.74 (d, *J* = 7.0 Hz, 3H). These data are in full agreement with previously reported data for the same compound.[4]

Product **14**:

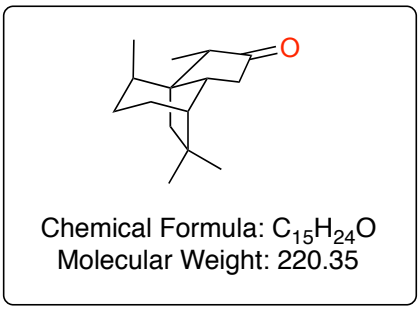


Chemical Formula: $C_{15}H_{22}O$
Molecular Weight: 218.33

A solution of lithium diisopropyl amide (LDA) was prepared by adding *n*-BuLi (1.6 M in hexanes, 172 µL, 0.28 mmol) to a solution of diisopropylamine (43 µL, 0.31 mmol) in THF (5 mL) at –78 °C and allow the solution to warm to –30 °C. To a solution of **13** (46 mg, 0.23 mmol) and hexamethylphosphoramide (HMPA, 52 µL, 0.30 mmol) in THF (5.8 mL) at –78 °C was added the prepared LDA solution via a cannula, and the resulting reaction mixture was stirred at –78 °C for 40 minutes. Iodomethane (29 µL, 0.46 mmol) was then added, and the reaction mixture was allowed to warm slowly to room temperature over 14 h, whereupon it was poured into saturated aqueous NH_4Cl (15 mL) and diethyl ether

(10 mL) was added. The organic layer was separated, and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give the crude product. Purification of this material by flash chromatography afforded the product **14** (43 mg, 85%) as a colorless oil. $\mathbf{R_f}$ (PE/EtOAc, 9:1) = 0.49. $\mathbf{[\alpha]_D^{25}}$ = –50.8 (*c* 0.2, EtOH). **MS** (ESI+): 241 $[M+Na]^+$. **^{13}C NMR** (75 MHz, ppm/ $CDCl_3$): δ 214.8 (C), 191.1 (C), 119.7 (CH), 57.8 (C), 49.2 (CH), 47.8 (CH), 42.2 (CH_2), 42.0 (CH), 39.6 (C), 32.4 (CH_3), 26.1 (CH_2), 24.9 (CH_2), 23.1 (CH_3), 15.7 (CH_3), 14.6 (CH_3). **^{1}H NMR** (400 MHz, ppm/$CDCl_3$): δ 5.78 (s, 1H), 2.35 (dd, *J* = 3.2, 3.1 Hz, 1H), 2.24 (q, *J* = 7.7 Hz, 1H), 2.11 – 1.98 (m, 2H), 1.87 – 1.75 (m, 2H), 1.60 (d, *J* = 13.5 Hz, 1H), 1.52 (d, *J* = 13.5 Hz, 1H), 1.26 (ddd, *J* = 13.2, 5.3, 2.1 Hz, 1H), 1.22 (s, 3H), 0.99 (d, *J* = 7.7 Hz, 3H), 0.87 (s, 3H), 0.75 (d, *J* = 7.0 Hz, 3H). These data are in full agreement with previously reported data for the same compound.[4]

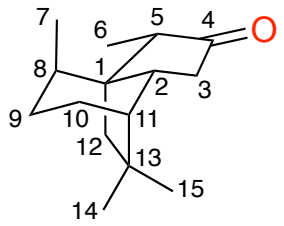
Suberosanone (**1**):



Chemical Formula: $C_{15}H_{24}O$
Molecular Weight: 220.35

To a solution of enone **14** (43 mg, 0.20 mmol) in ethyl acetate (6 mL) was added 10% Pd/C (21 mg, 0.02 mmol), and the solution was saturated with hydrogen (bubbling through the solution for 5 minutes). The reaction mixture was then stirred vigorously under a hydrogen atmosphere at room temperature (20–25 ºC) for 1 h, and filtered through a pad of celite. The filtrate was concentrated in vacuum to afford the clean crude product **1** (43 mg, >99%) as colorless oil that could not be clearly visualized on TLC (using UV or stain detection). $\mathbf{[\alpha]_D^{25}}$ = +20.0 (*c* 0.1, $CHCl_3$) or +11.0 (*c* 0.1, EtOH). **HRMS** (ESI+) for $C_{15}H_{24}NaO^+$: calcd. $[M+Na]^+$ 243.1719, found: 243.1719. **HPLC** (Lux-Cellulose-2, heptane/isopropanol (95/5), 1.0 mL/min) using a circular dichroism detector at 290 nm: the chromatogram showed a single peak at τ = 5.38 min (the racemic product was not available). **^{13}C NMR** (100 MHz, ppm/ $CDCl_3$): δ 220.4 (C), 57.0 (C), 50.1 (CH), 49.8 (CH), 47.9 (CH_2), 44.0 (CH), 40.8 (CH_2), 39.3 (C), 35.8 (CH), 34.4 (CH_3), 28.4 (CH_2), 27.1 (CH_2), 27.1 (CH_3), 17.1 (CH_3), 8.2 (CH_3). **^{1}H NMR** (400 MHz, ppm/$CDCl_3$): δ 2.52 – 2.32 (m, 4H), 2.05 (dddd, *J* = 14.1, 14.0, 7.2, 7.1 Hz, 1H), 1.88 (dq, *J* = 7.2, 7.0 Hz, 1H), 1.78 – 1.73 (m, 1H), 1.70 – 1.54 (m, 2H), 1.40 (d, *J* = 14.5 Hz, 1H), 1.33 (d, *J* = 14.5 Hz, 1H), 1.32 (dd, *J* = 14.1, 6.0 Hz, 1H), 1.13 (s, 3H), 1.08 (s, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H). These data are in full agreement with previously reported data for the same compound.[4,6]

Tabulated NMR data of known samples of suberosanone (**1**):

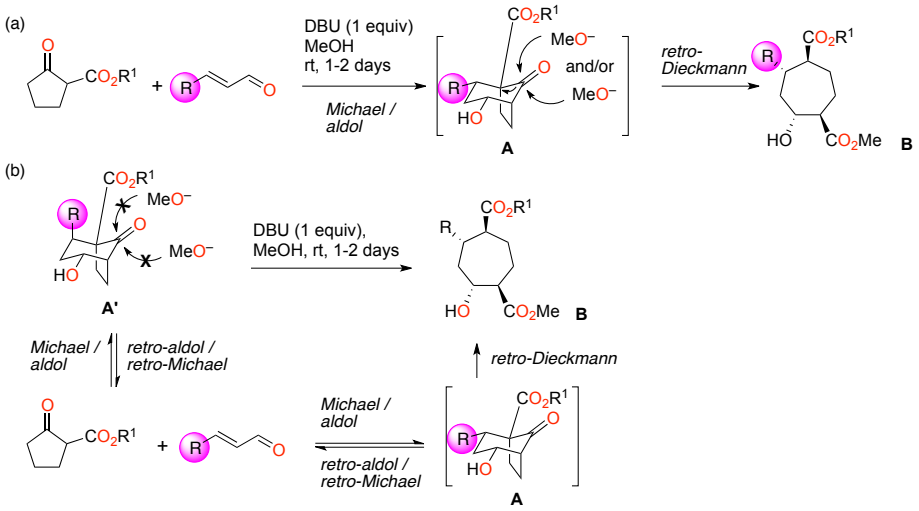


H atom	Litterature[6] (multiplicity, *J* in Hz)	Litterature[4] (multiplicity, *J* in Hz)	The present work (multiplicity, *J* in Hz)
2	2.38 (m)	2.36–2.41 (m)	2.32–2.52 (m)
3α	2.48 (dd, 7.0, 1.5)	2.35–2.52 (m)	2.32–2.52 (m)
3β	2.35 (dd, 7.0, 3.0)	2.35–2.52 (m)	2.32–2.52 (m)
5	2.39 (q, 7.0)	2.32–2.37 (m)	2.32–2.52 (m)
6	0.90 (d, 7.0)	0.89 (d, 6.8)	0.88 (d, 6.8)
7	1.04 (d, 7.0)	1.03 (d, 7.1)	1.03 (d, 7.0)
8	1.89 (q, 7.0)	1.88 (q, 7.2)	1.88 (dq, 7.2, 7.0)
9α	1.33 (dd, 7.0, 7.0)	1.33 (br d, 13.9)	1.32 (dd, 14.1, 6.0)
9β	2.06 (m)	2.05 (tt, 13.9, 7.0)	2.05 (dddd, 14.1, 14.0, 7.2, 7.1)
10α	1.62 (ddd, 13.5, 6.5, 2.5)	1.62 (dtd, 13.6, 6.0, 2.7)	1.54–1.70 (m)
10β	1.68 (m)	1.71–1.64 (m)	1.54–1.70 (m)
11	1.79 (br t, 3.0)	1.76 (br t, 3.0)	1.73–1.78 (m)
12α	1.34 (d, 14.5)	1.33 (d, 14.5)	1.33 (d, 14.5)
12β	1.40 (d, 14.5)	1.40 (d, 14.5)	1.40 (d, 14.5)
14	1.04 (s)[a]	1.13 (s)	1.13 (s)
15	1.09 (s)	1.09 (s)	1.08 (s)
C atom			
1	56.9 (s)	56.9 (s)	57.0 (s)
2	43.8 (d)	43.9 (d)	44.0 (d)
3	40.7 (t)	40.7 (t)	40.8 (t)
4	220.5 (s)	220.3 (s)	220.4 (s)
5	50.0 (s)[b]	50.0 (d)	50.1 (d)
6	8.1 (q)	8.1 (q)	8.2 (q)
7	17.0 (q)	17.0 (q)	17.1 (q)
8	35.6 (d)	35.7 (d)	35.8 (d)
9	26.9 (t)	26.9 (t)	27.1 (t)
10	28.3 (t)	28.3 (t)	28.4 (t)
11	49.6 (d)	49.7 (d)	49.8 (d)
12	47.7 (t)	47.7 (t)	47.9 (t)
13	39.2 (s)	39.1 (s)	39.3 (s)
14	27.0 (q)	27.0 (q)	27.1 (q)
15	34.3 (q)	34.3 (q)	34.4 (q)

[a]The actual value is 1.14 due to a typo error. We are grateful to Prof. J.-H. Sheu for making that information available to us (see the original ^{1}H NMR spectrum below). [b]We have attributed the reported singlet multiplicity for this resonance to a typo error in the original manuscript.

2. Origin of the variation in diastereoselectivity for products 6a-m

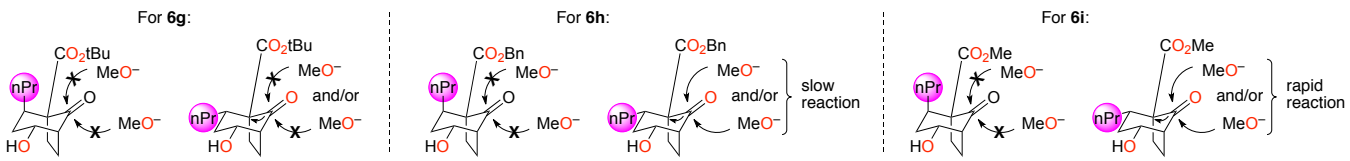
Back to 2008, our laboratory reported on the synthesis of seven-membered rings by the fragmentation of bridge bicyclo[3.2.1]octane derivatives.[5] More precisely, it was demonstrated that, in the presence of a Brønsted base and methanol, substituted bicyclo[3.2.1]octanol compounds of type **A** having equatorial substituents could undergo a retro-Dieckmann-type fragmentation to give the seven-membered ring product **B** (Scheme S1 (a)). It was also demonstrated that bicyclo[3.2.1]octanol compounds of type **A'** having an axial substituent could not undergo this retro-Dieckmann fragmentation due to steric effects (the most notable difference being the 1,3-diaxial interaction), but preferably underwent a base-catalyzed retro-aldol / retro-Michael / Michael / aldol / retro-Dieckmann sequence to afford the same product **B** (Scheme S1 (b)). Notably, and key to the success of the present work, the basic NHC **II** does not promote the retro-aldol / retro-Michael sequence at a significant rate in the presence of catalyst **I**.



Scheme S1. The Michael / Aldol / retro-Dieckman (MARDi) cascade

Thus, the observed differences in diastereoselectivity, for example in products **6g-i**, can be rationalized as follow (Scheme S2):

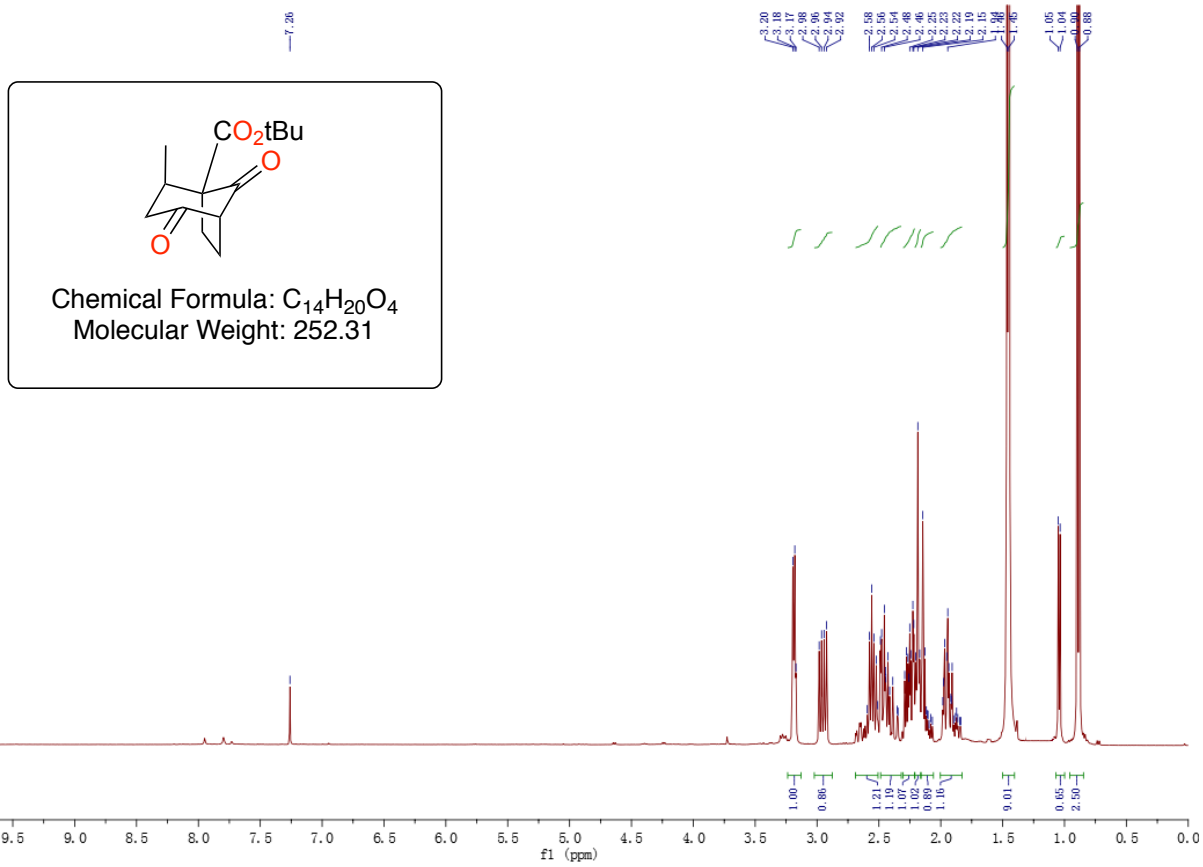
- for **6g**, dr = 4:1: in this case, the *tert*-butyl ester is bulky enough to avoid the approach of methanol in both diastereomers of **2g**, leaving the dr unchanged after the aldolization.
- for **6h**, dr =15:1: this case is an intermediate case, the benzyl ester is less bulky than its *tert*-butyl counter-part, allowing some retro-Dieckmann fragmentation of the minor diastereomer of **2h** with the equatorial substituent (slow reaction, not complete after 2 days).
- for **6i**, dr >20:1: in this case, the small methyl ester allows for a complete fragmentation of the minor diastereomer **2i** having the equatorial substituent, resulting in an excellent dr of the final isolated product with the desired axial substituant.

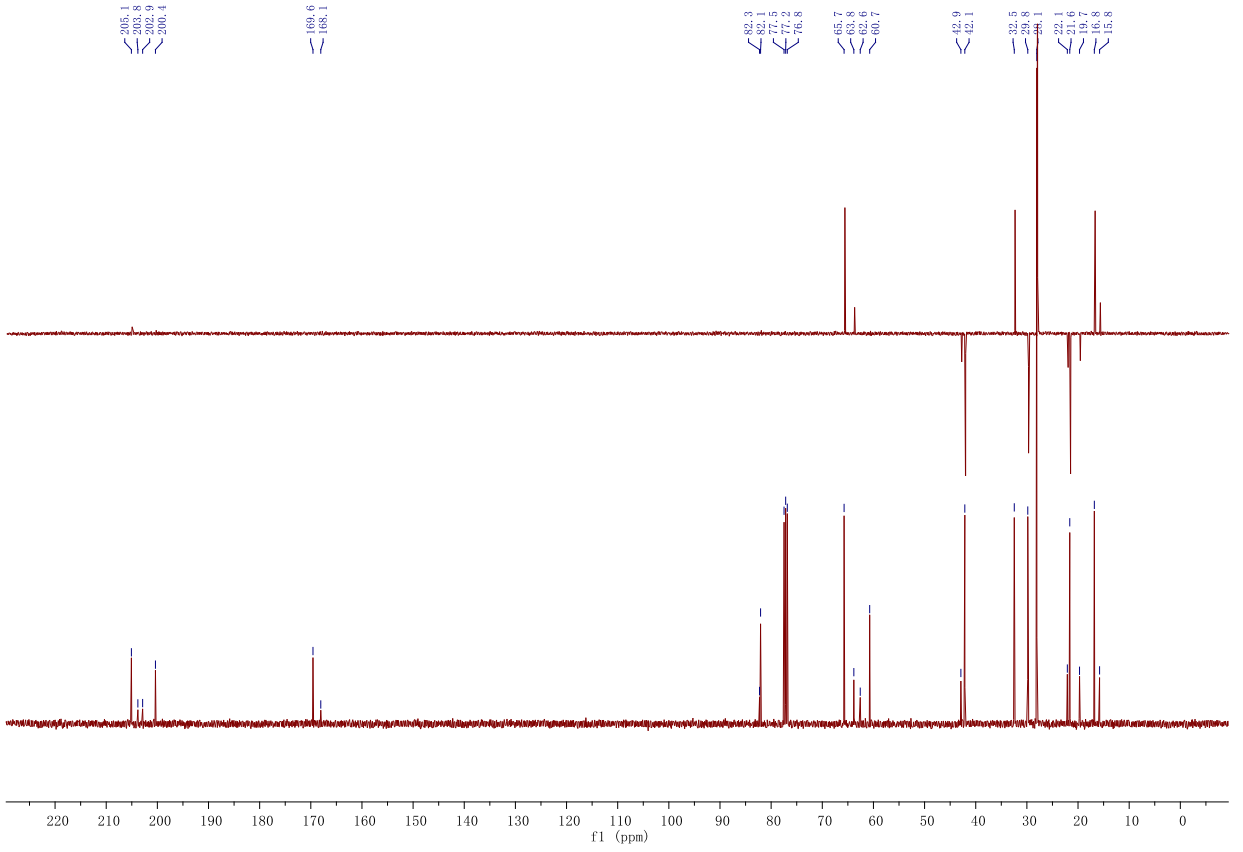


Scheme S2. A case study with products **6g-i**

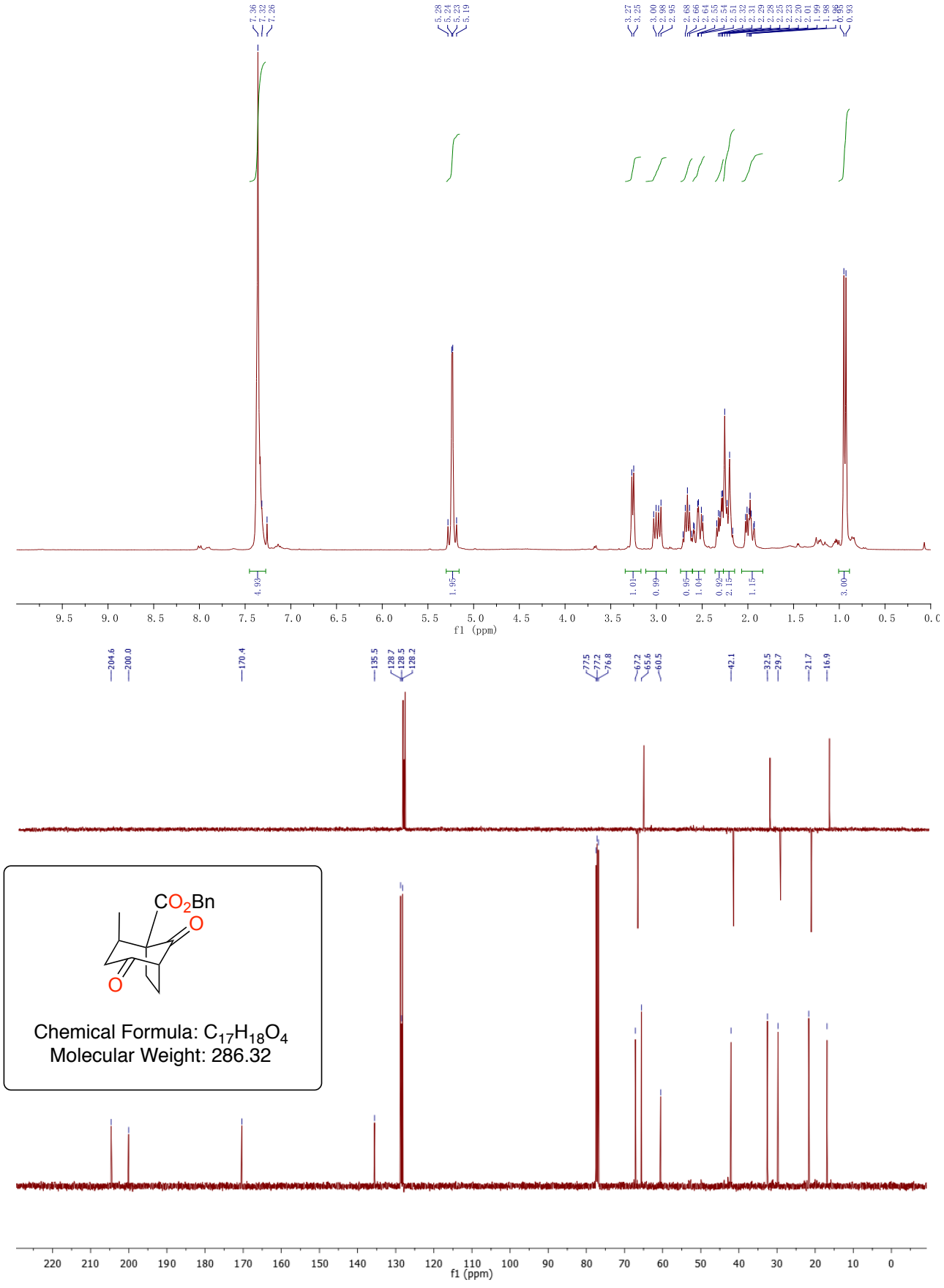
3. Copies of NMR spectra (^{1}H, ^{13}C{^{1}H}, and ^{13}C DEPT-135)

Product **6a** (4:1 dr, ^{1}H NMR @ 400 MHz, ^{13}C NMR @ 100 MHz, in $CDCl_3$):

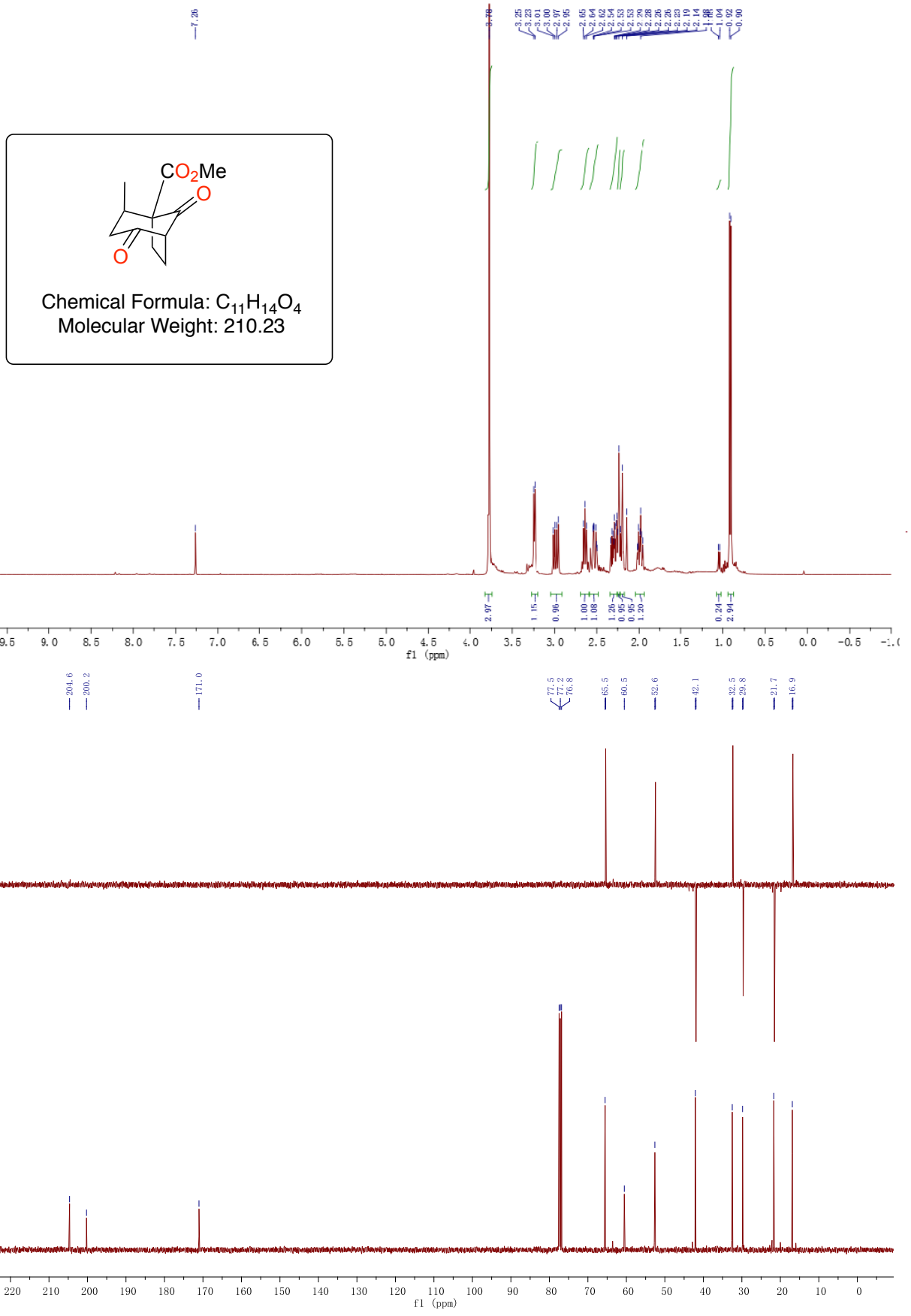




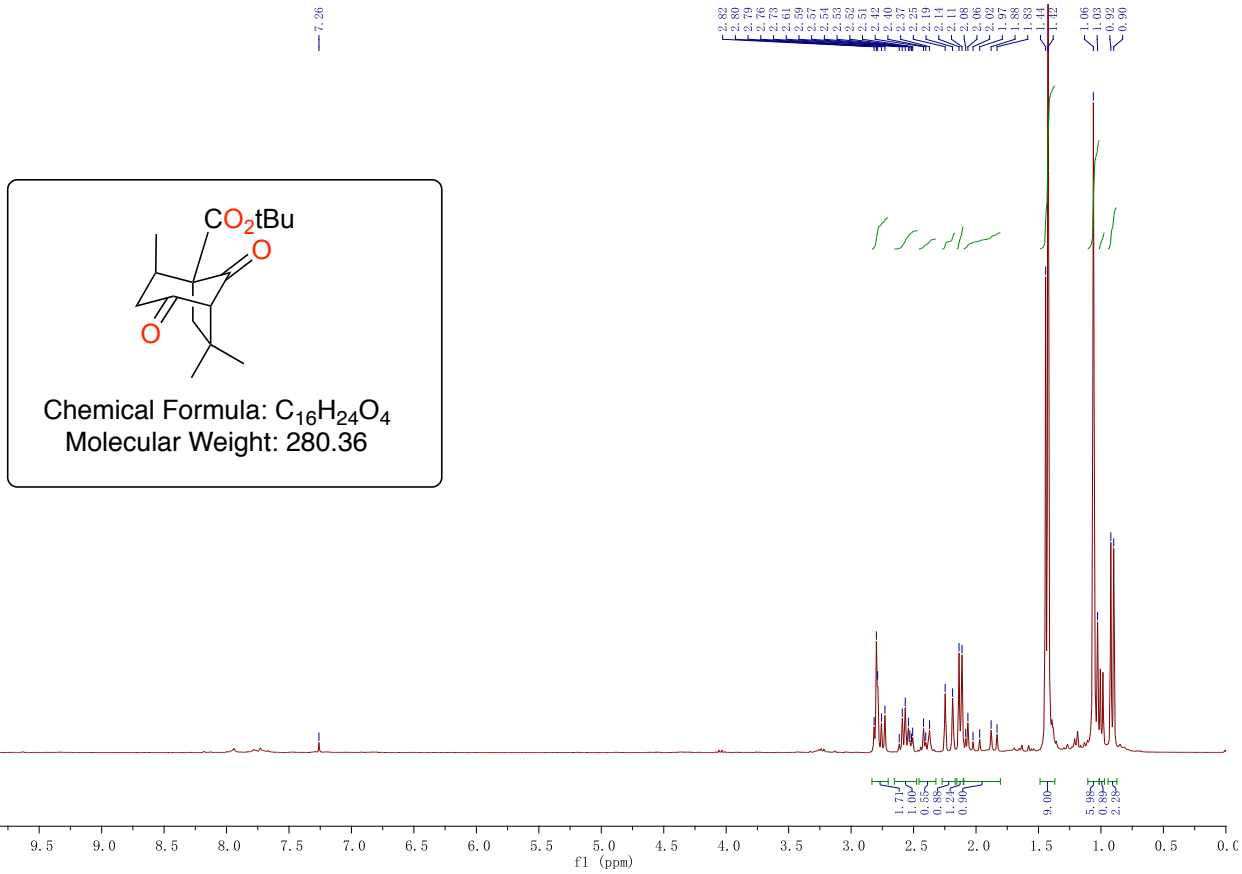
Product **6b** (>20:1 dr, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):

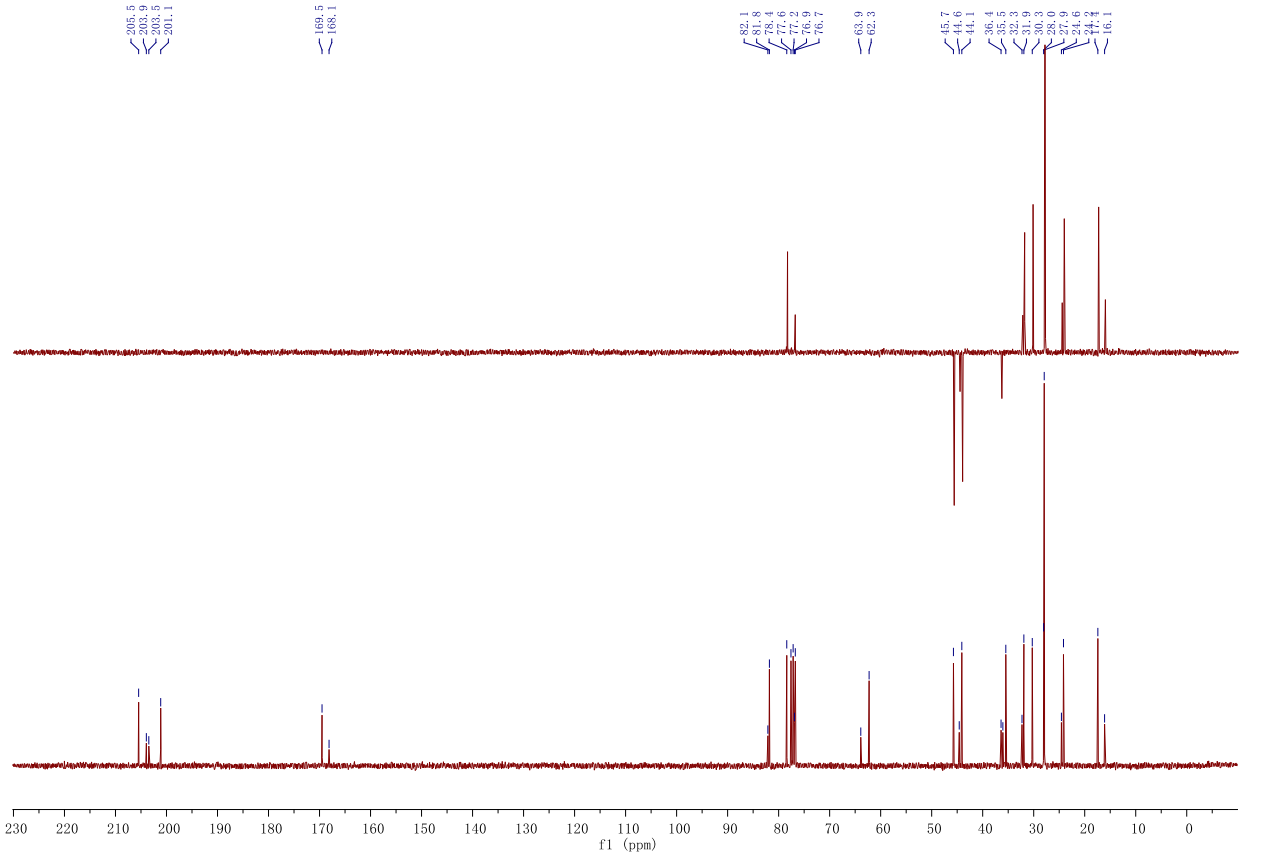


Product **6c** (17:1 dr, ^{1}H NMR @ 400 MHz, ^{13}C NMR @ 100 MHz, in $CDCl_3$):

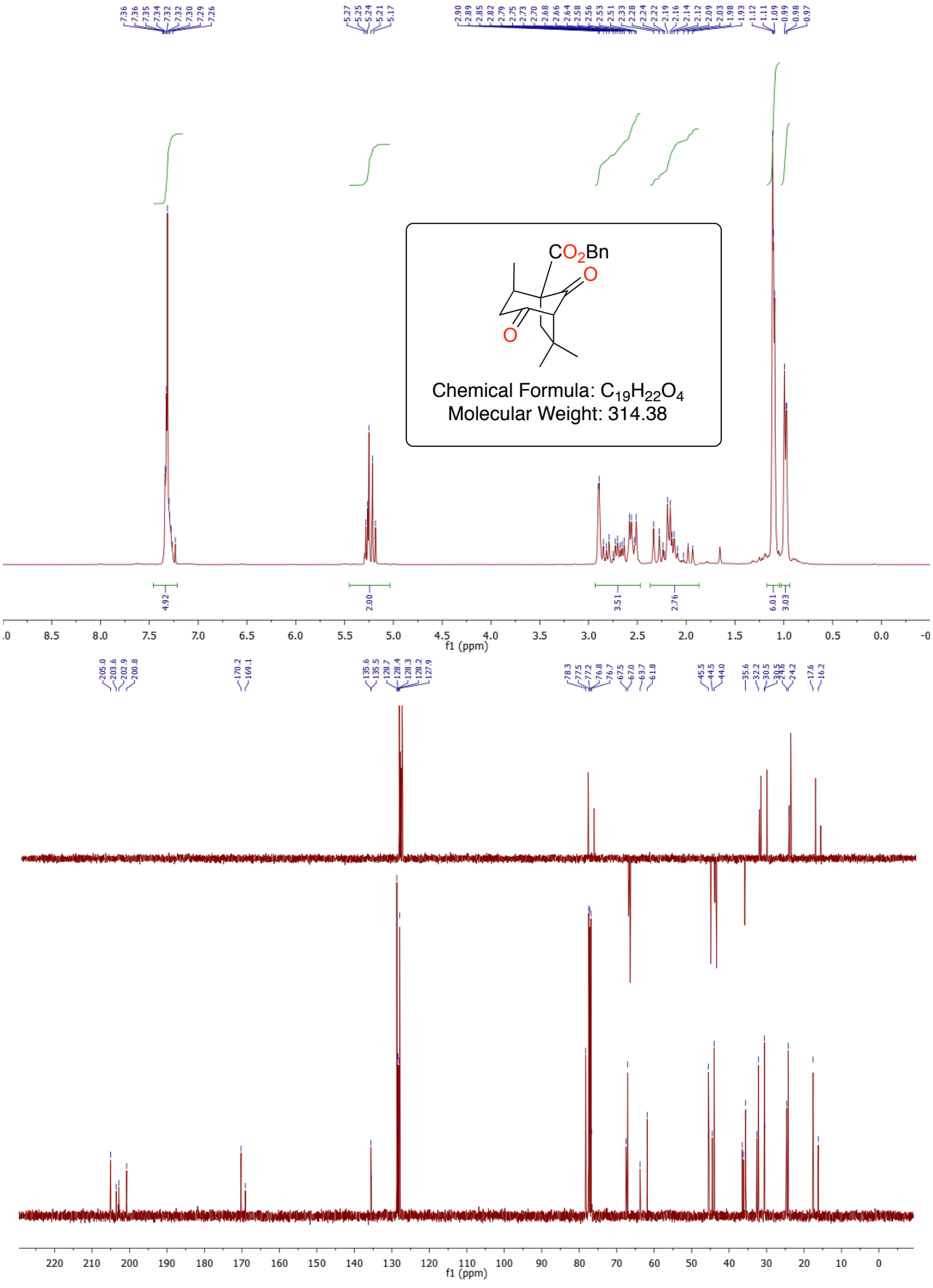


Product **6d** (2:1 dr, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):

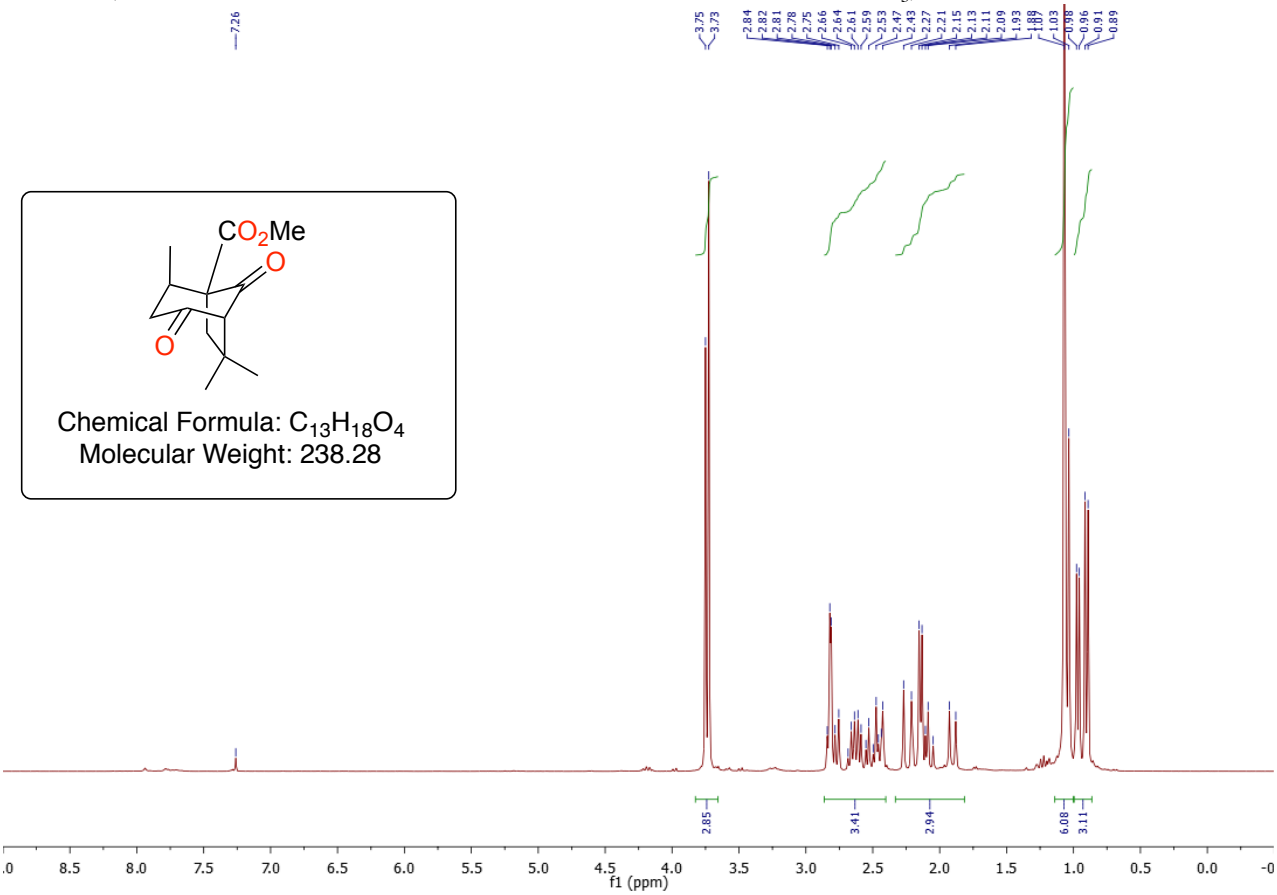


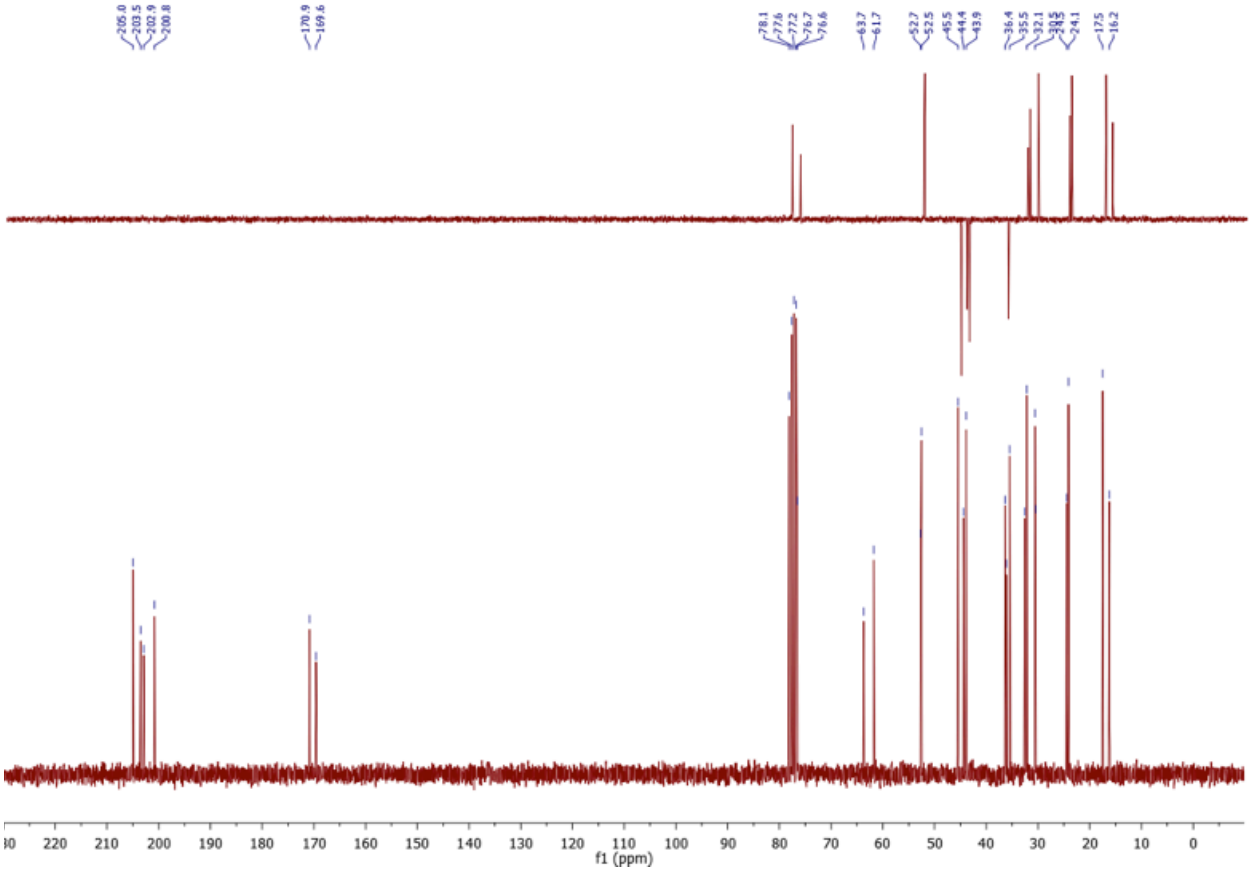


Product **6e** (2:1 dr, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):

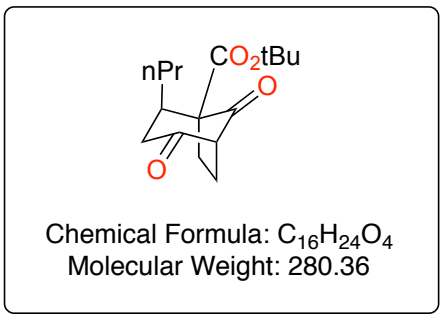


Product **6f** (2:1 dr, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):

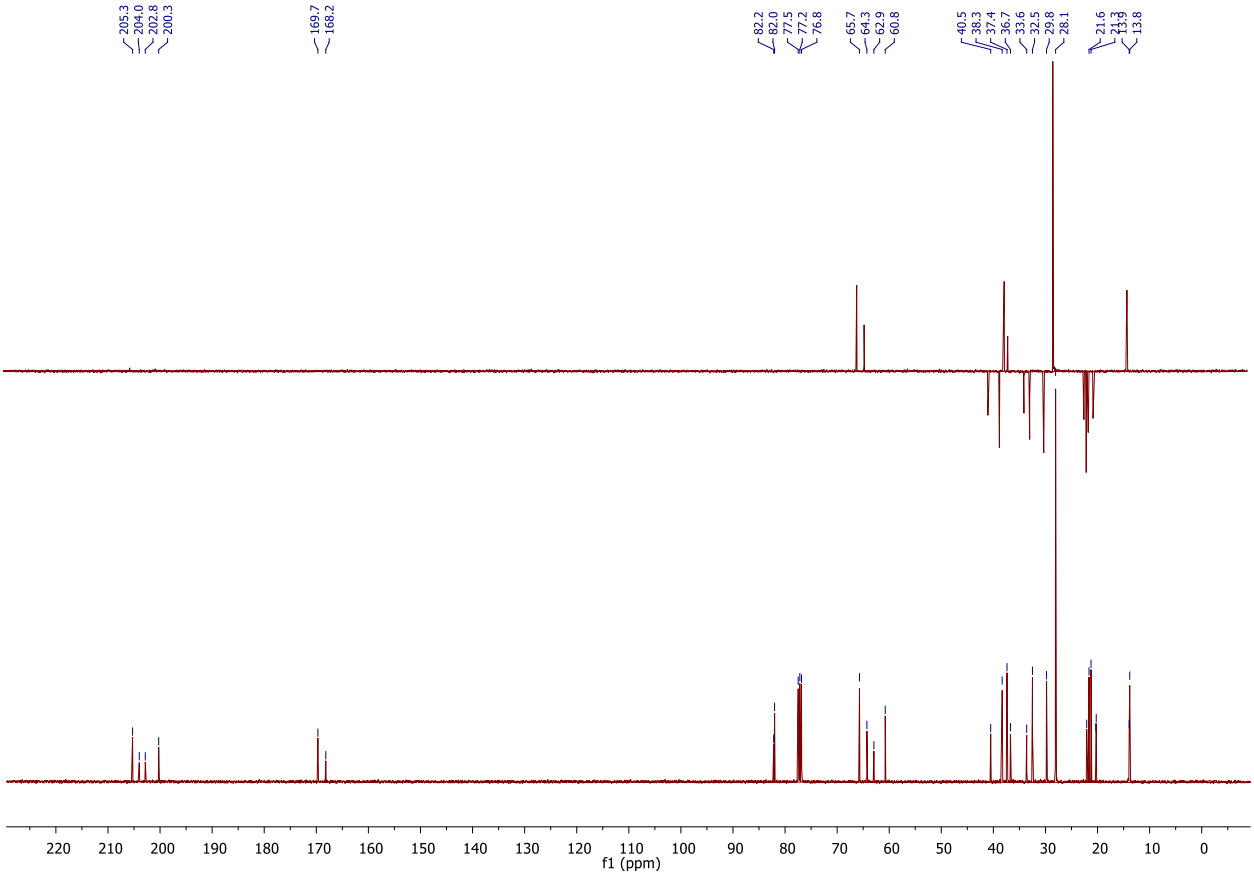




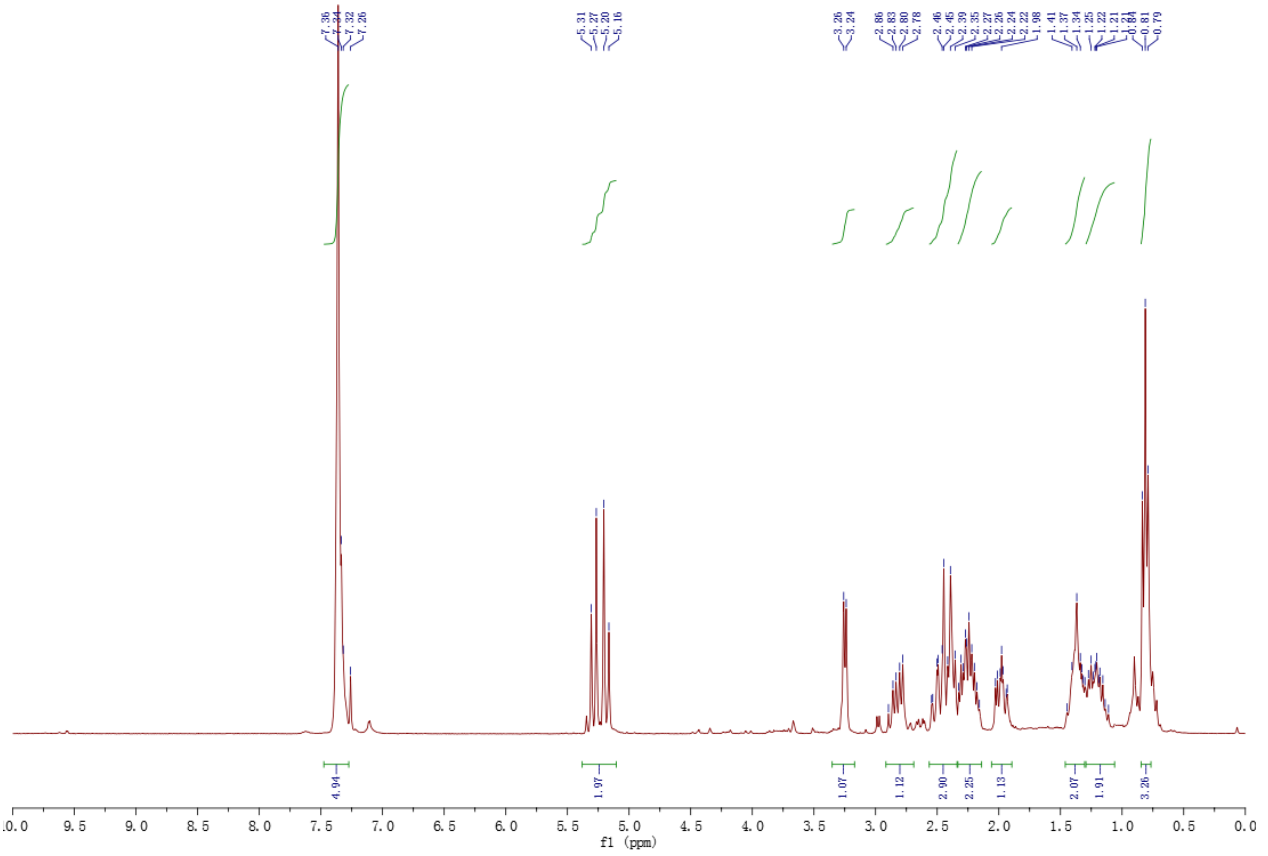
Product **6g** (2:1 dr sample, ^{1}H NMR @ 400 MHz, ^{13}C NMR @ 100 MHz, in $CDCl_3$):

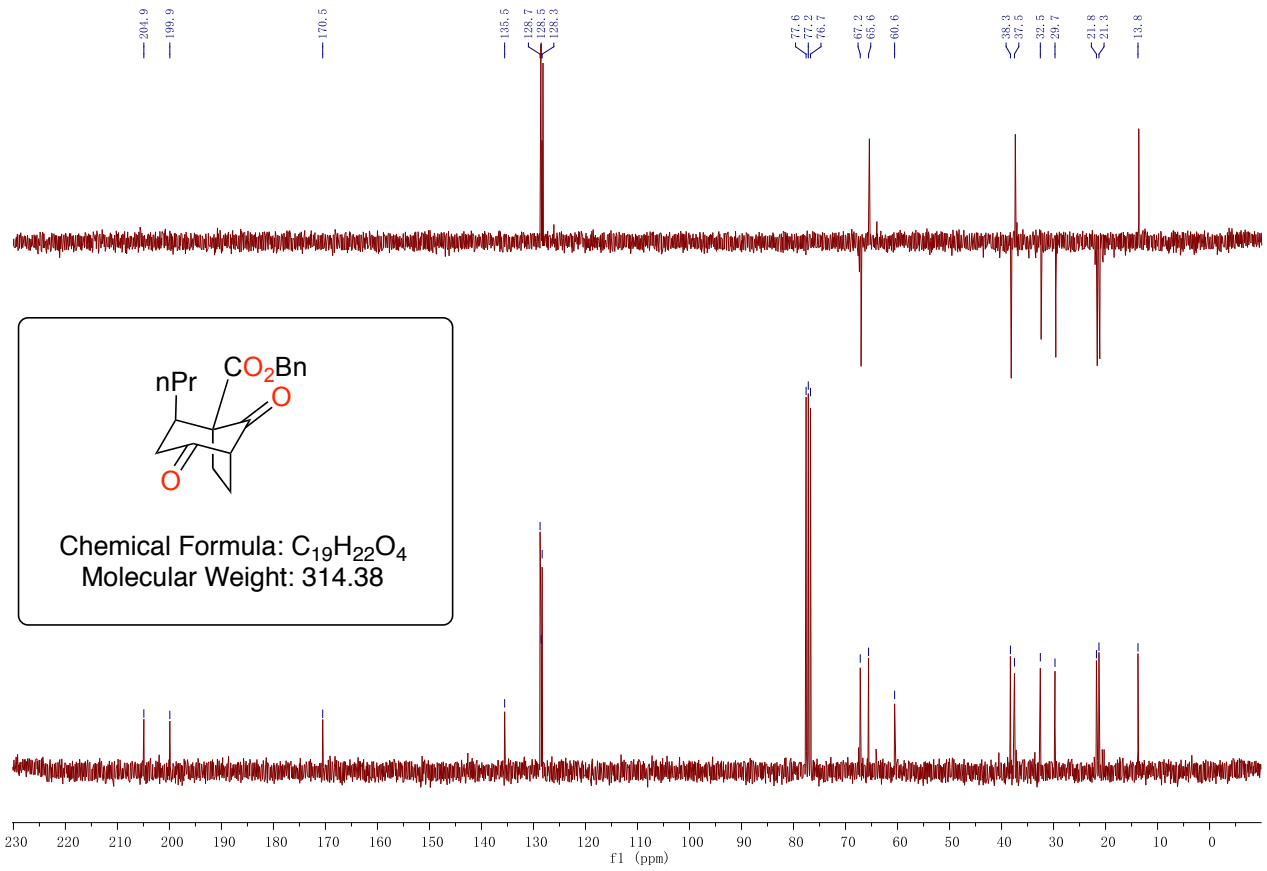


Chemical Formula: $C_{16}H_{24}O_4$
Molecular Weight: 280.36

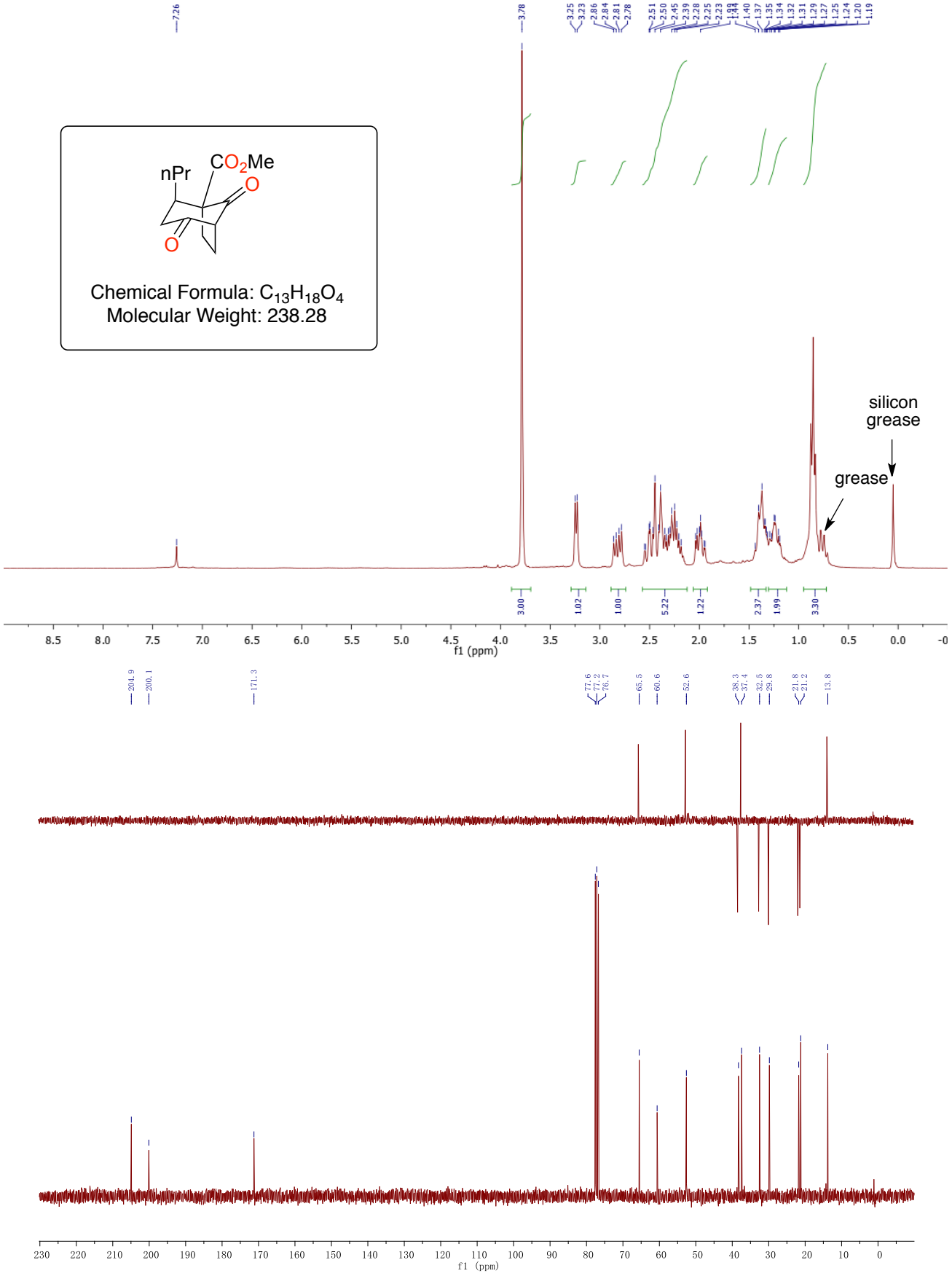


Product **6h** (15:1 dr, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):

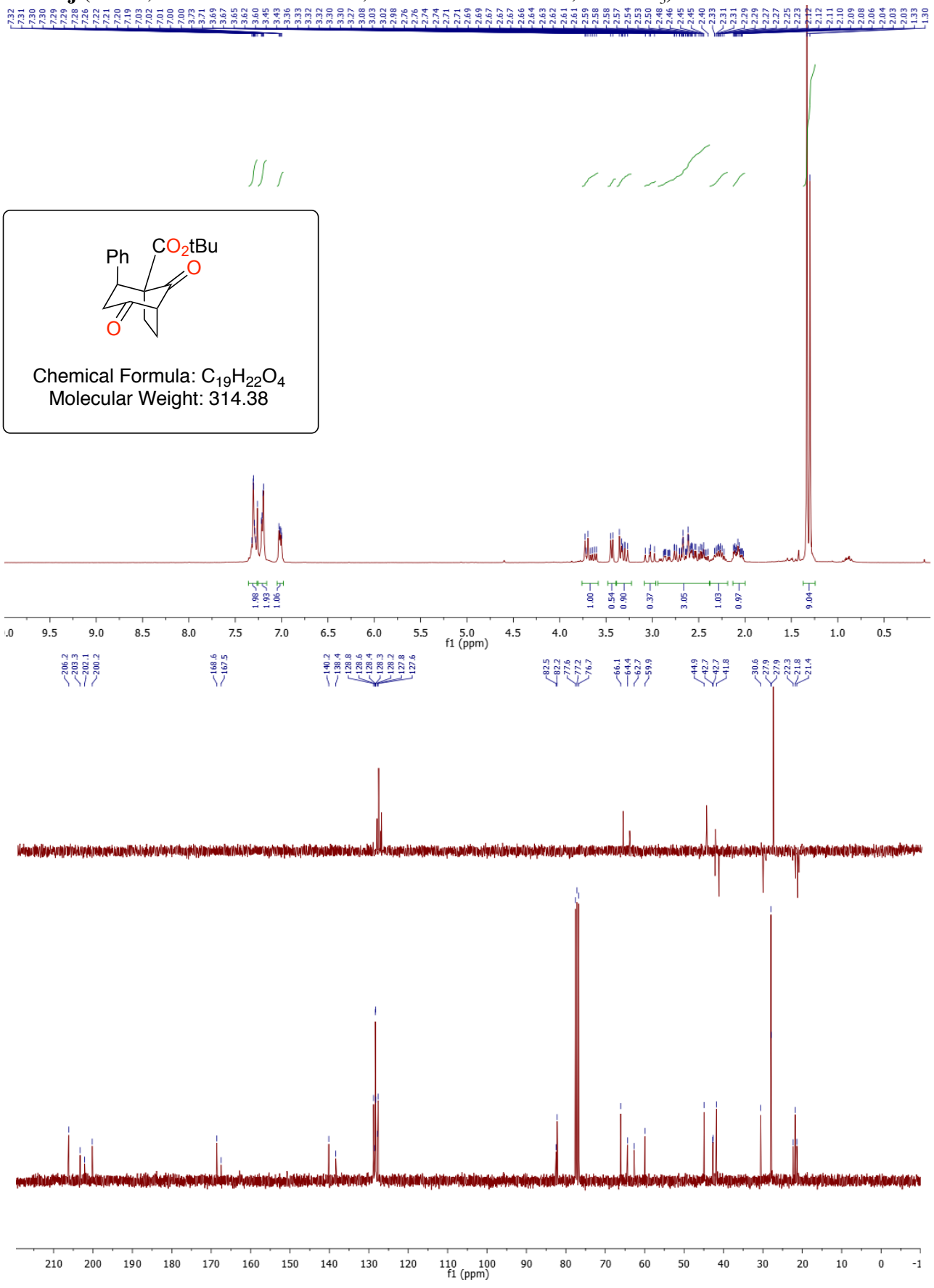




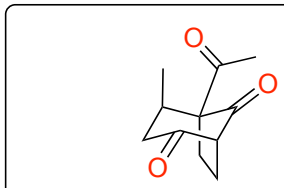
Product **6i** (> 20:1 dr, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):



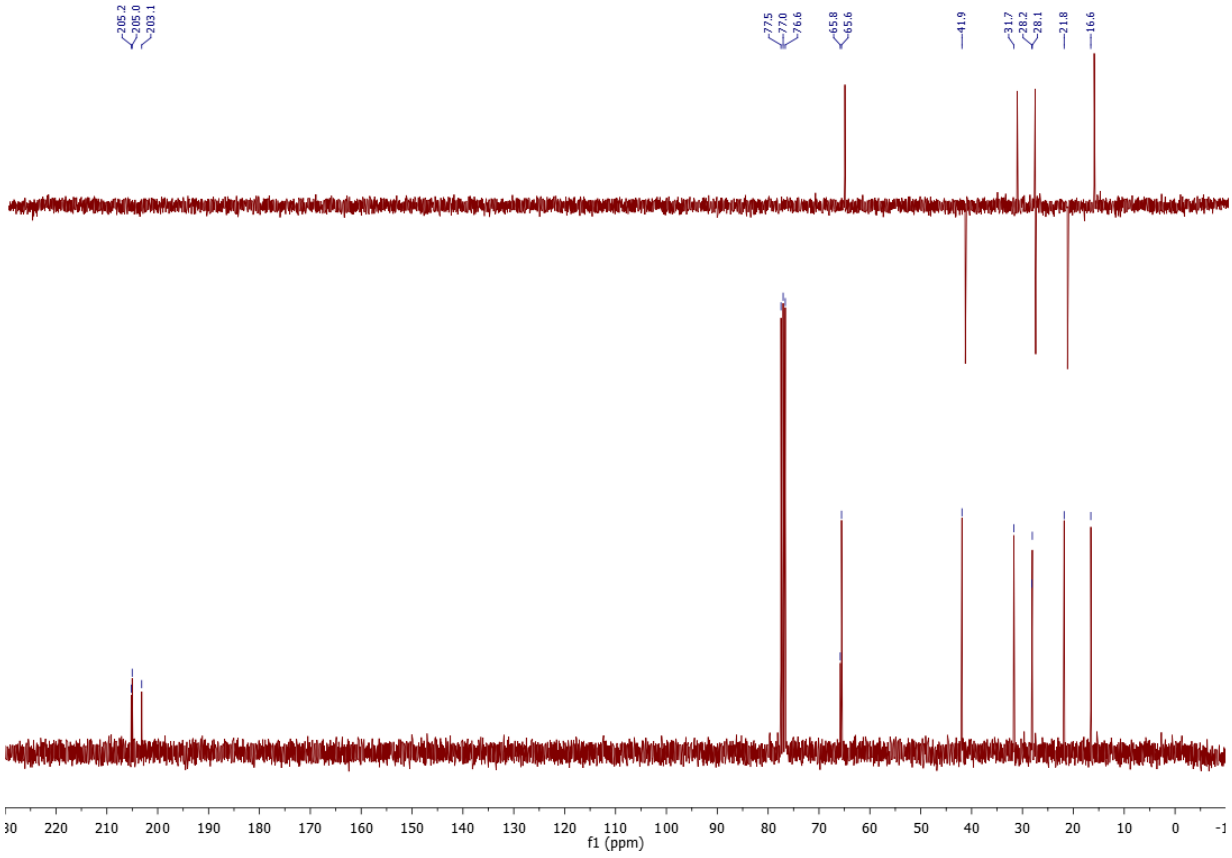
Product **6j** (2:1 dr, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):



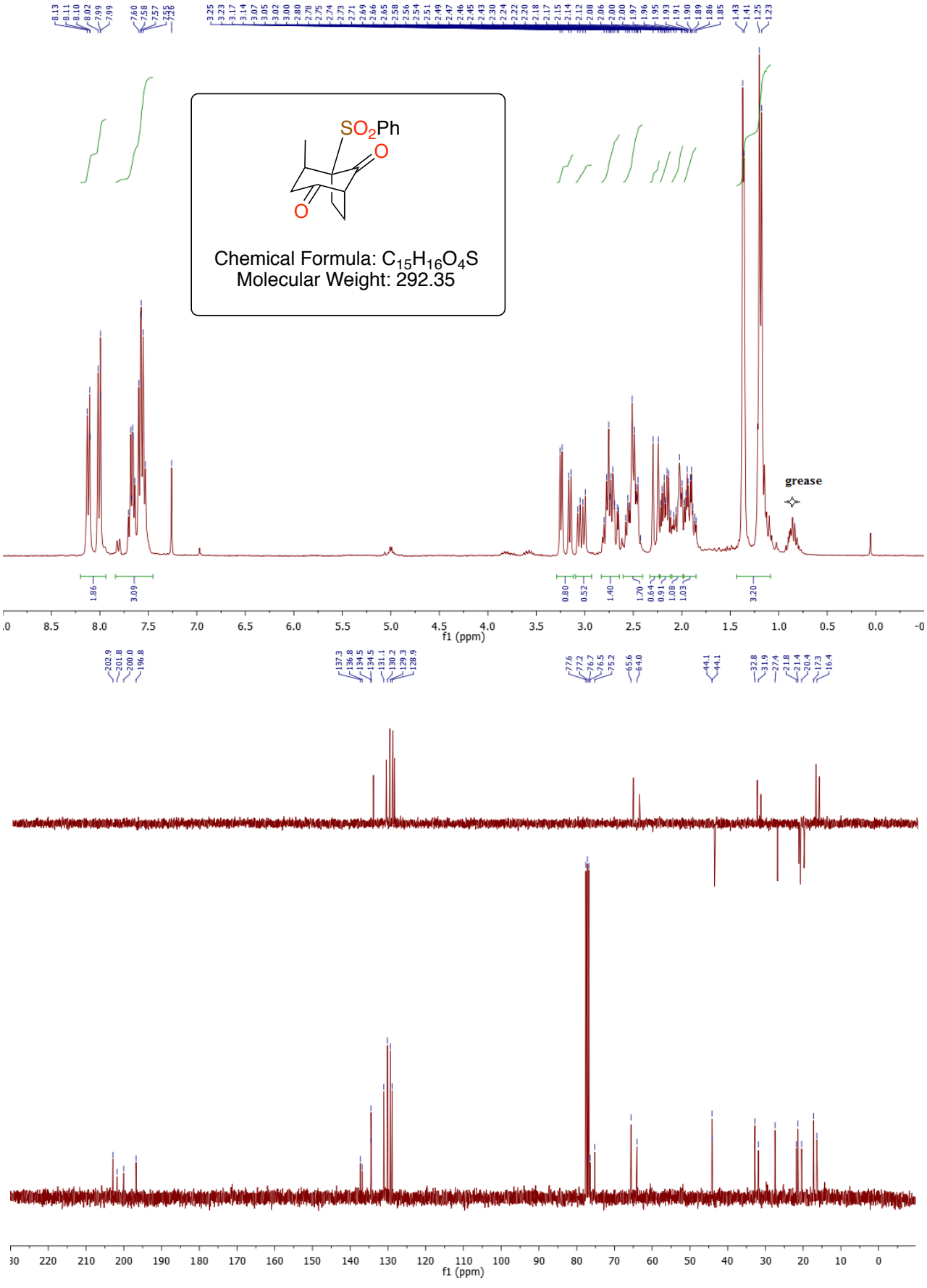
Product **6k** (dr > 20:1, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):



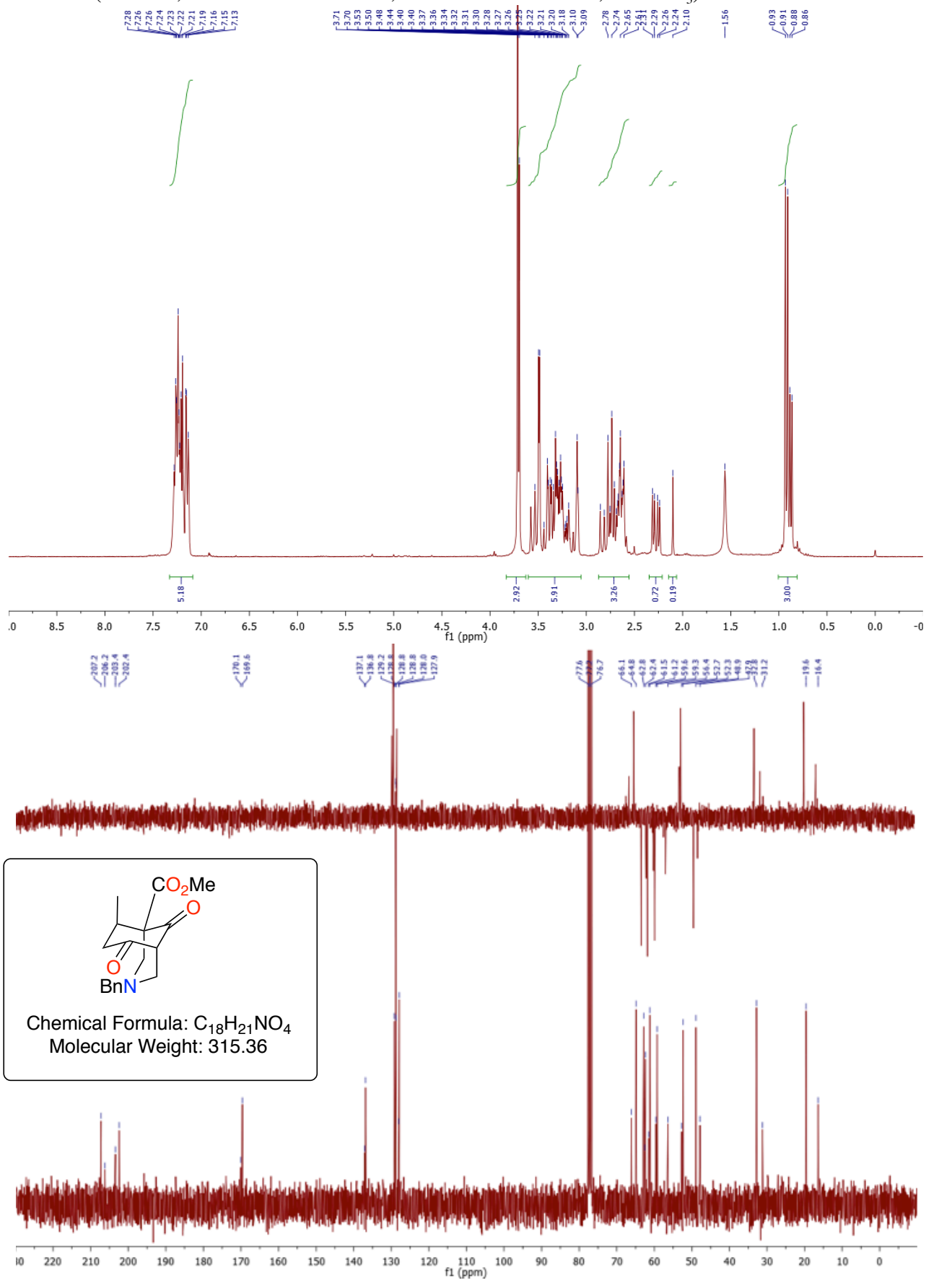
Chemical Formula: $C_{11}H_{14}O_3$
Molecular Weight: 194.23



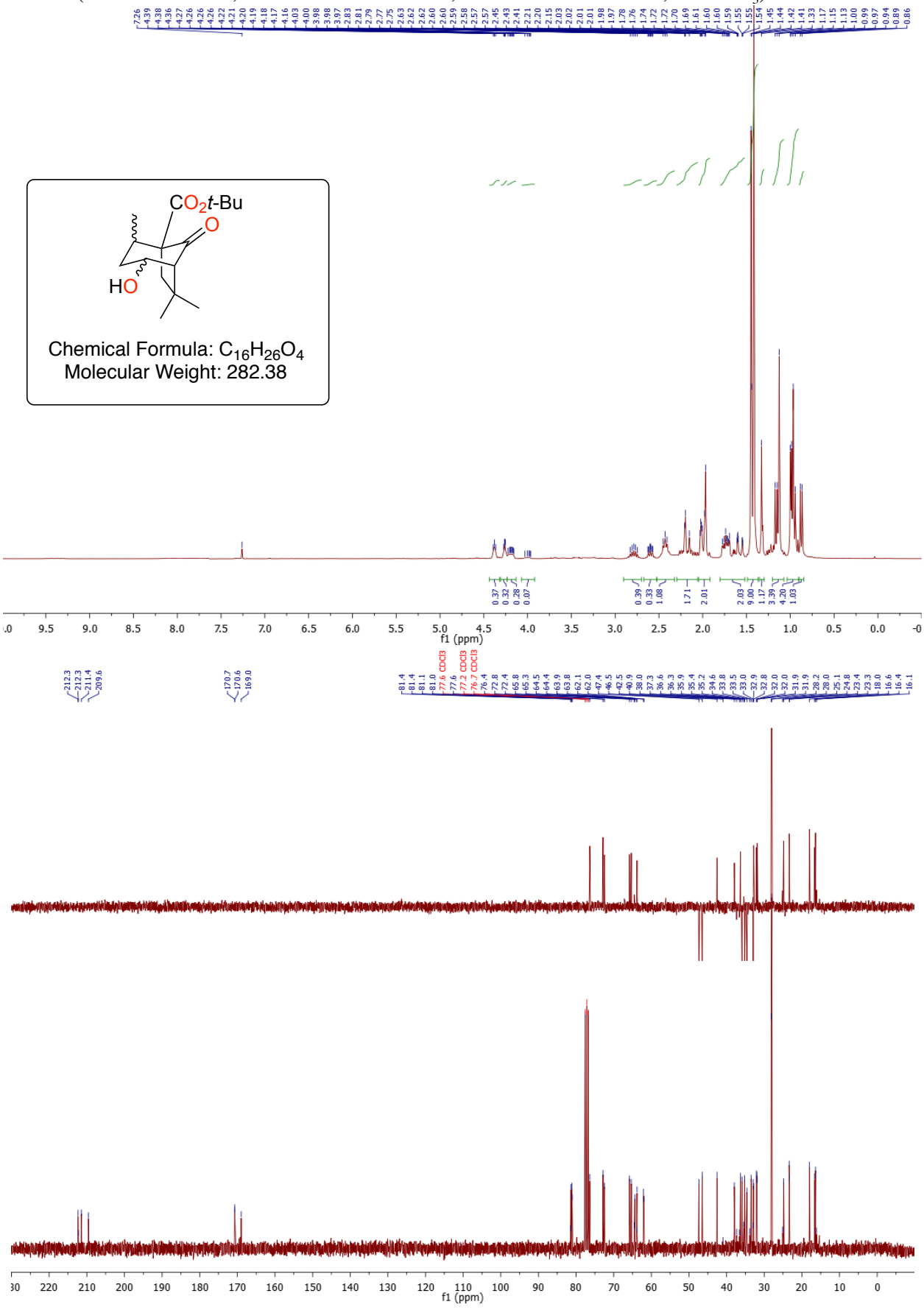
Product **6l** (dr = 1.5:1, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):



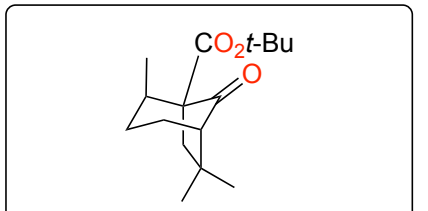
Product **6m** (dr = 2:1, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):



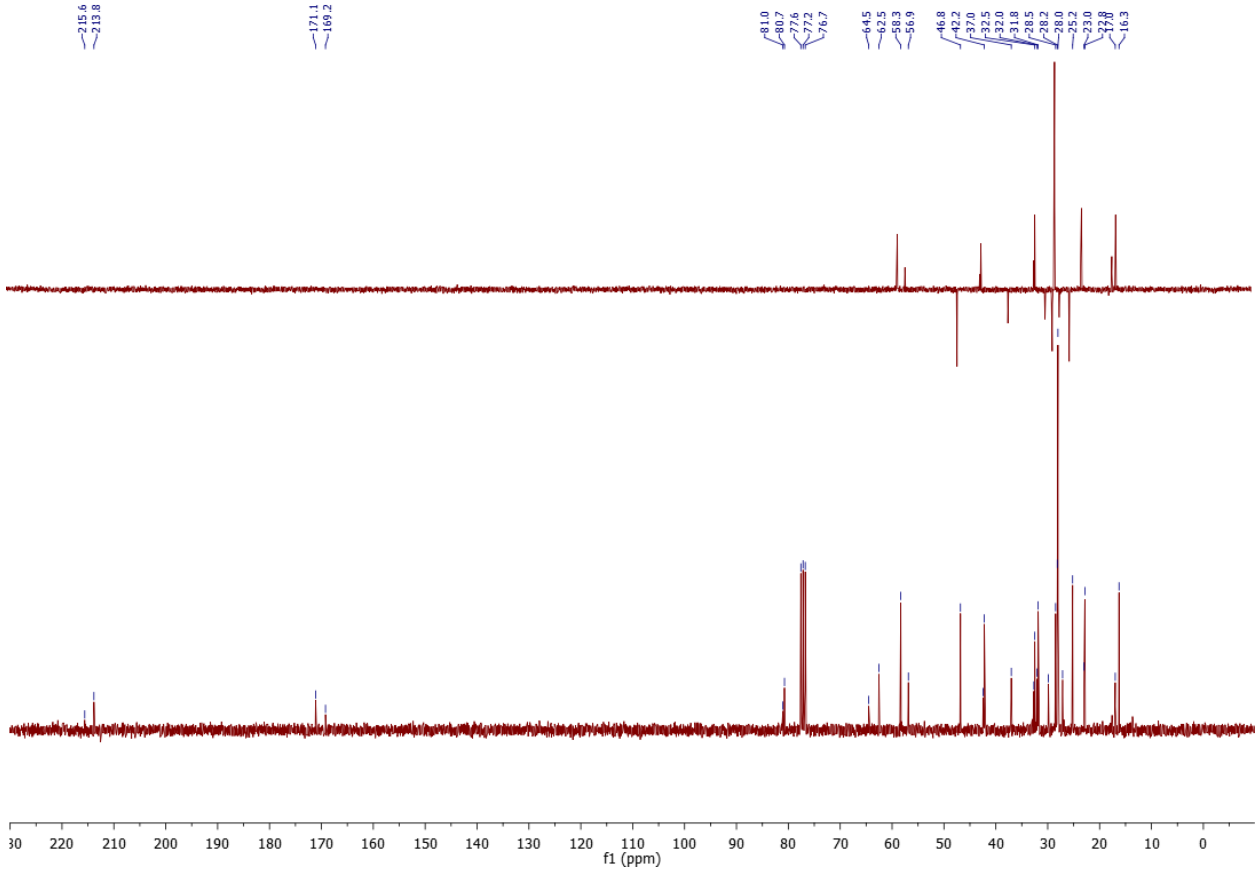
Product **2d** (dr = 5.3:4.6:4:1, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):



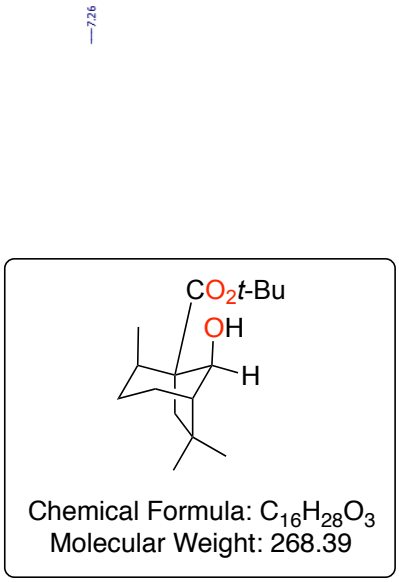
Product **7** (dr = 2:1, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):



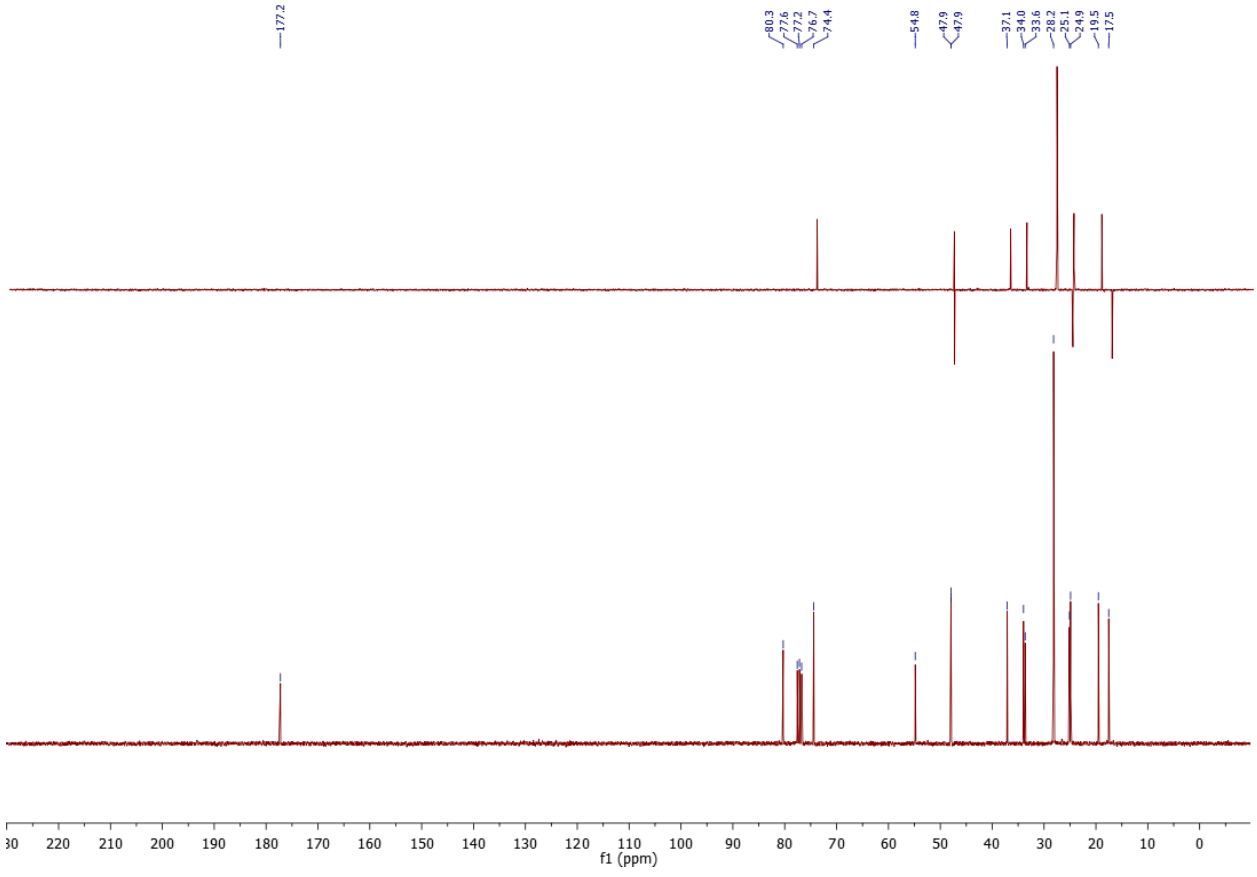
Chemical Formula: $C_{16}H_{26}O_3$
Molecular Weight: 266.38



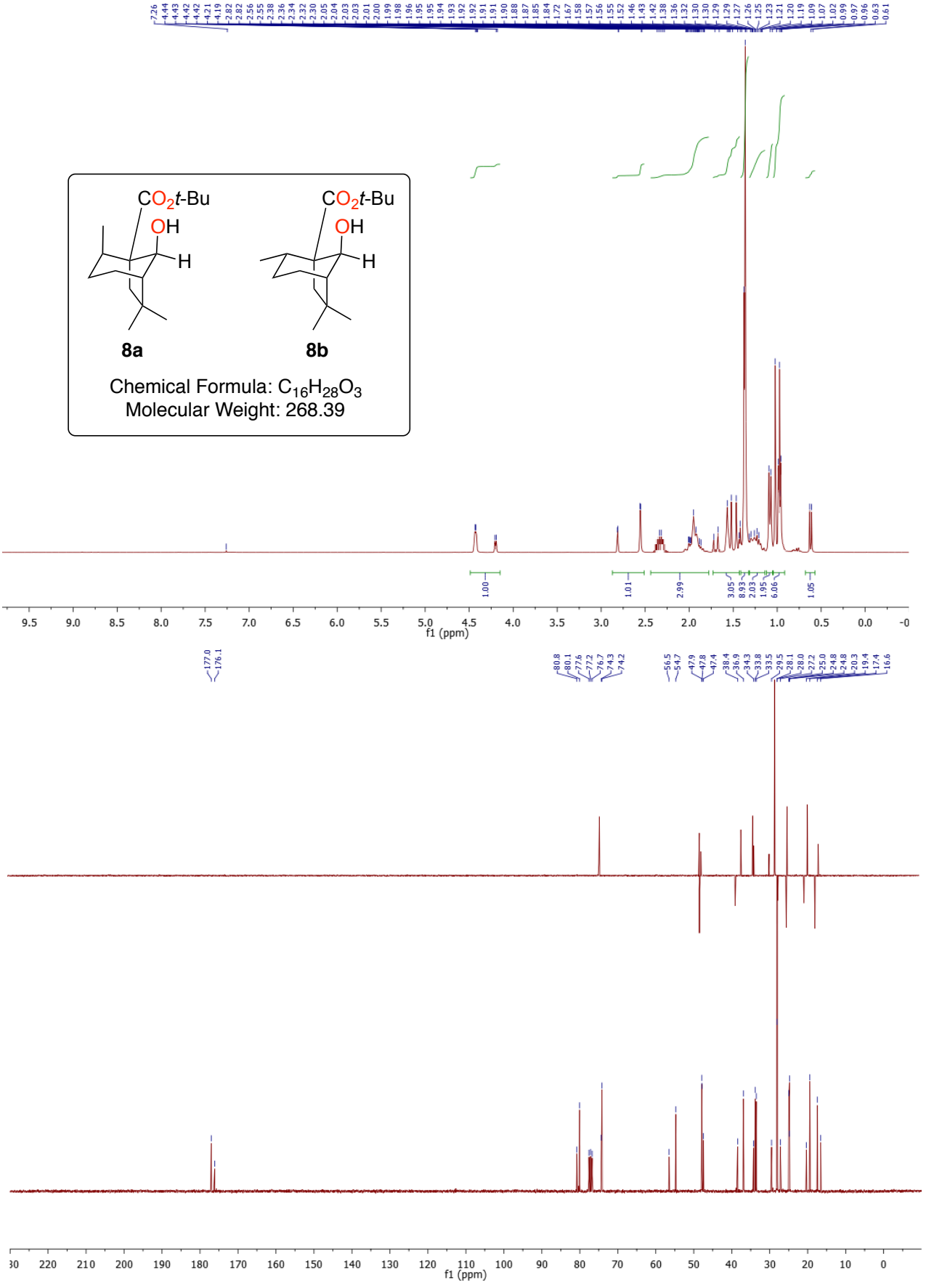
Product **8a** (dr > 50:1, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):



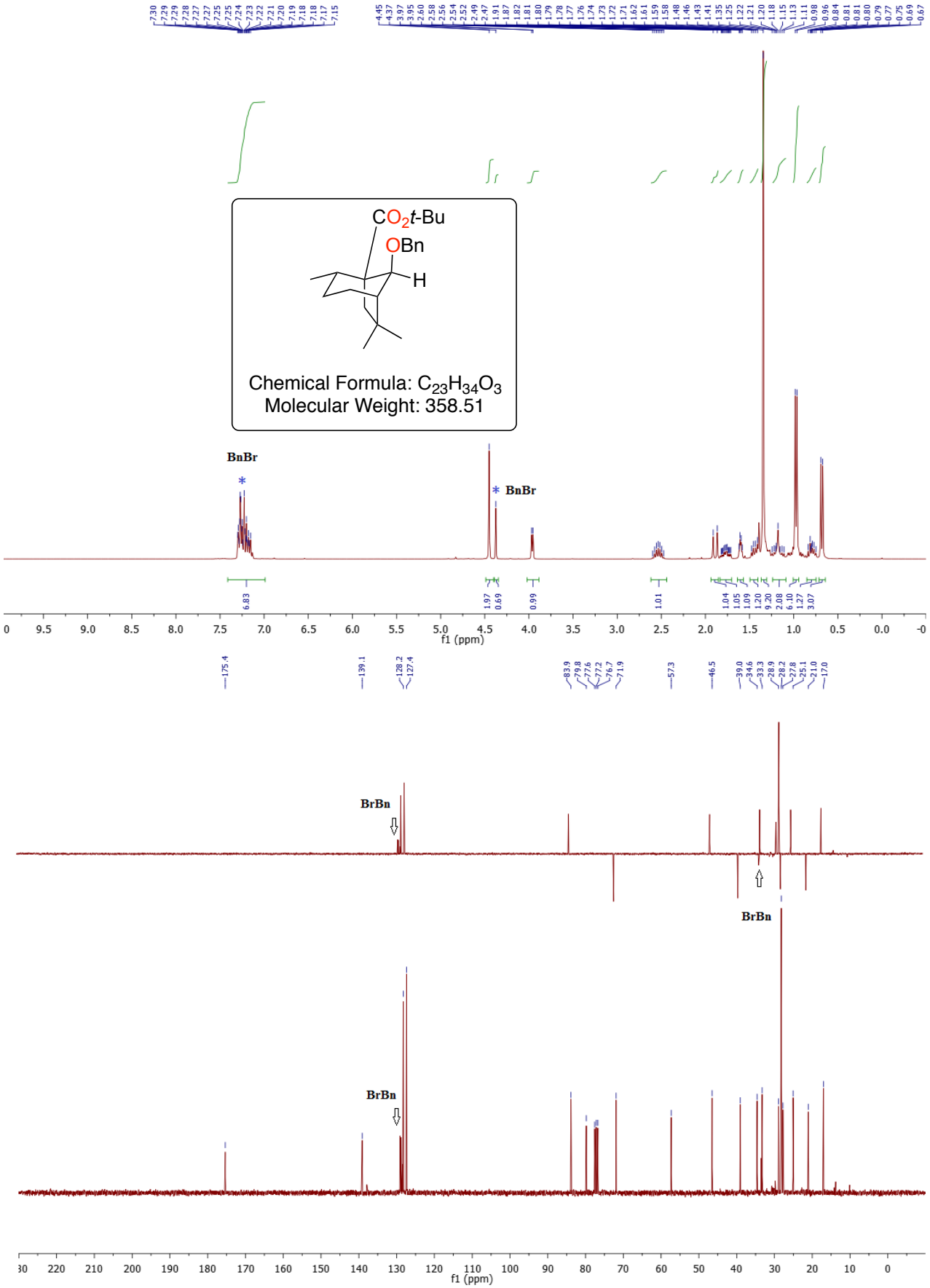
Chemical Formula: $C_{16}H_{28}O_3$
Molecular Weight: 268.39



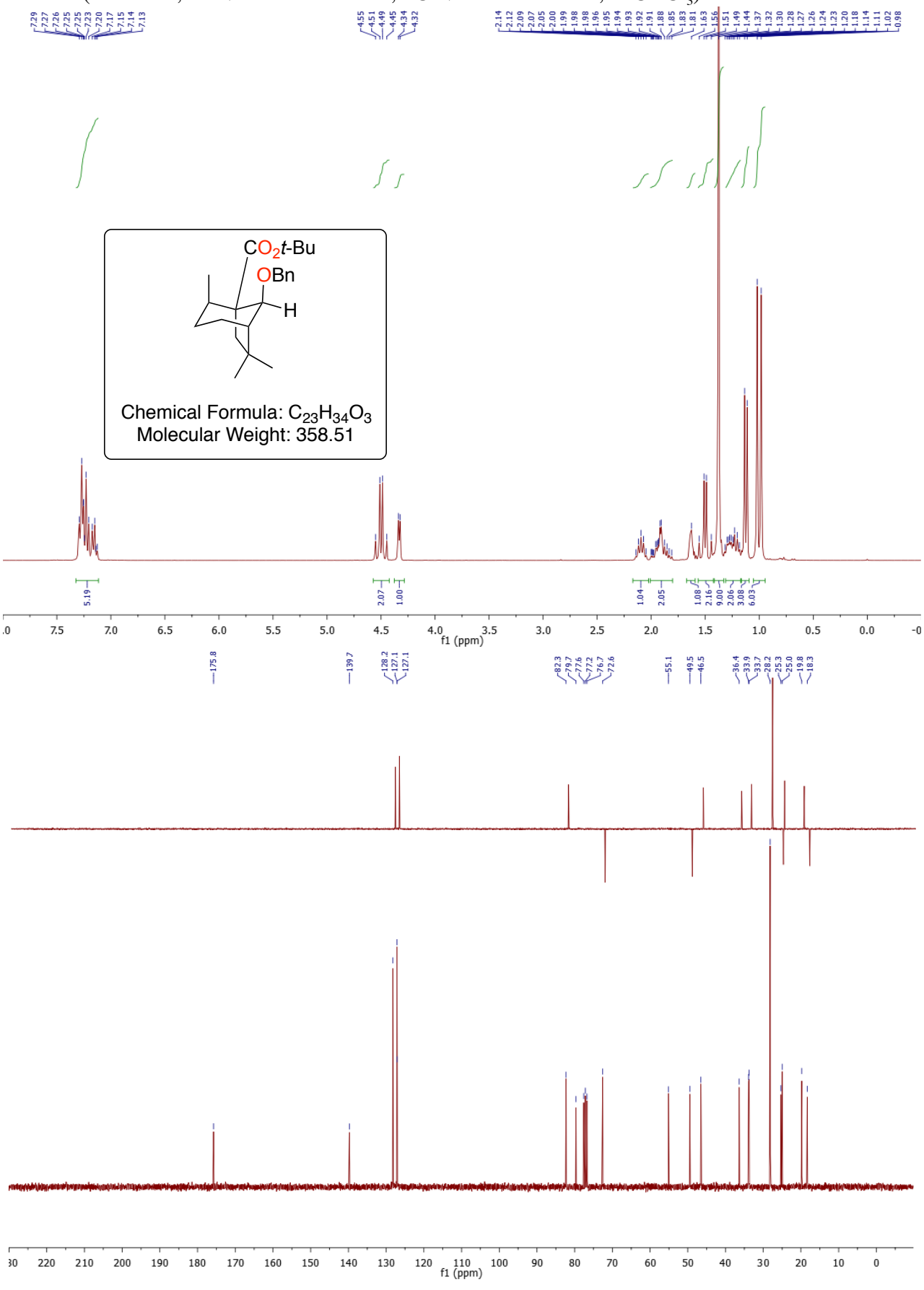
Products **8a** and **8b** (dr **8a**:**8b** = 2:1, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):



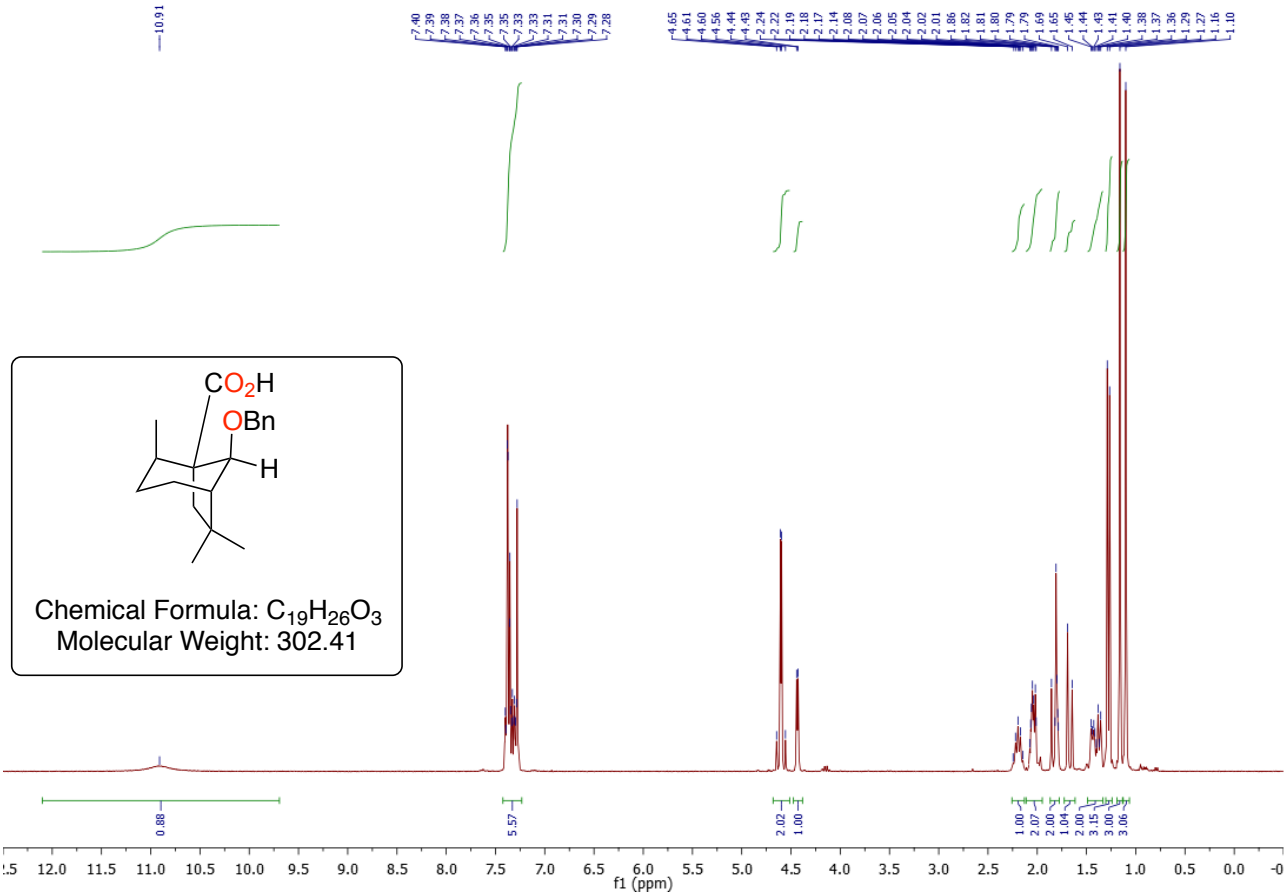
Product **9b** (with ca. 12% of BrBn, dr > 50:1, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):

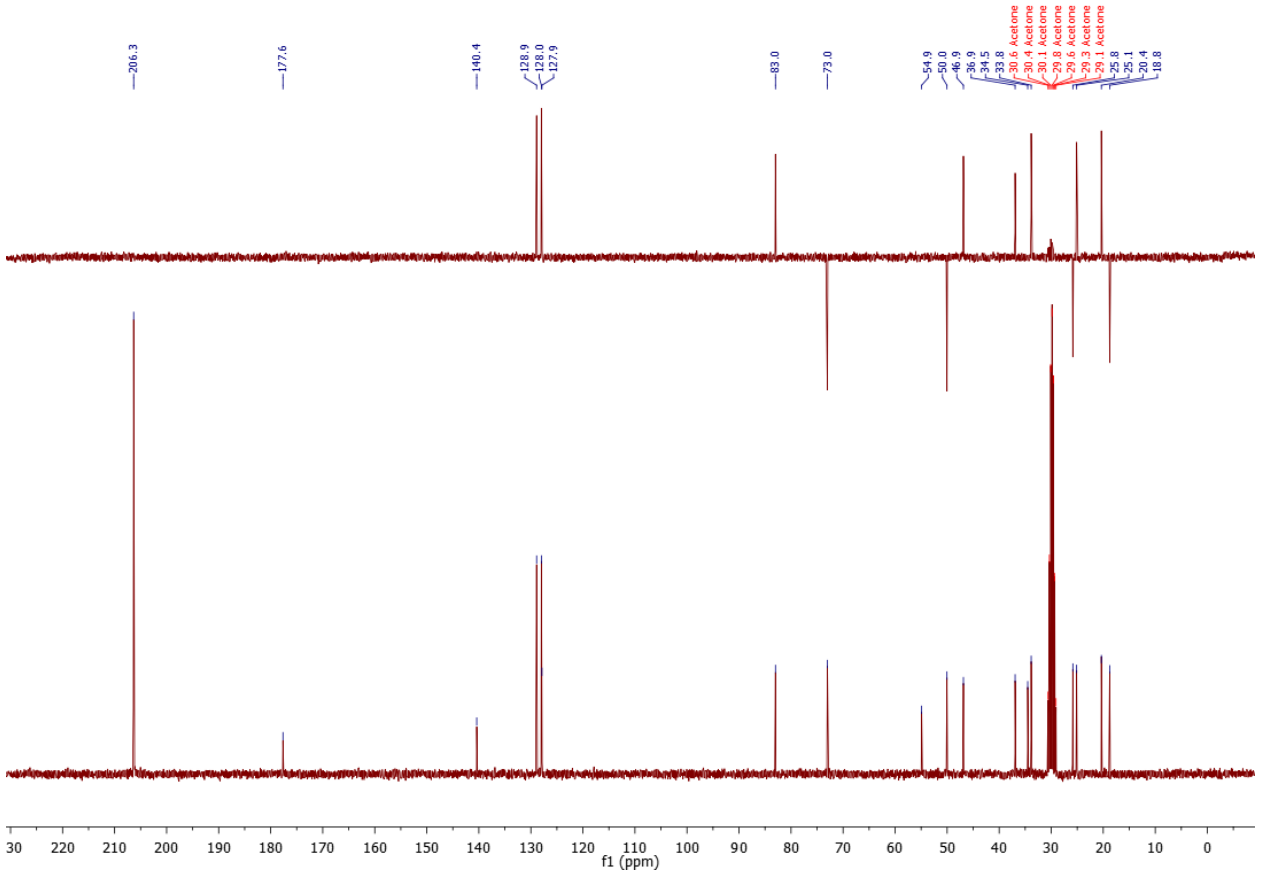


Product **9a** (dr > 50:1, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):

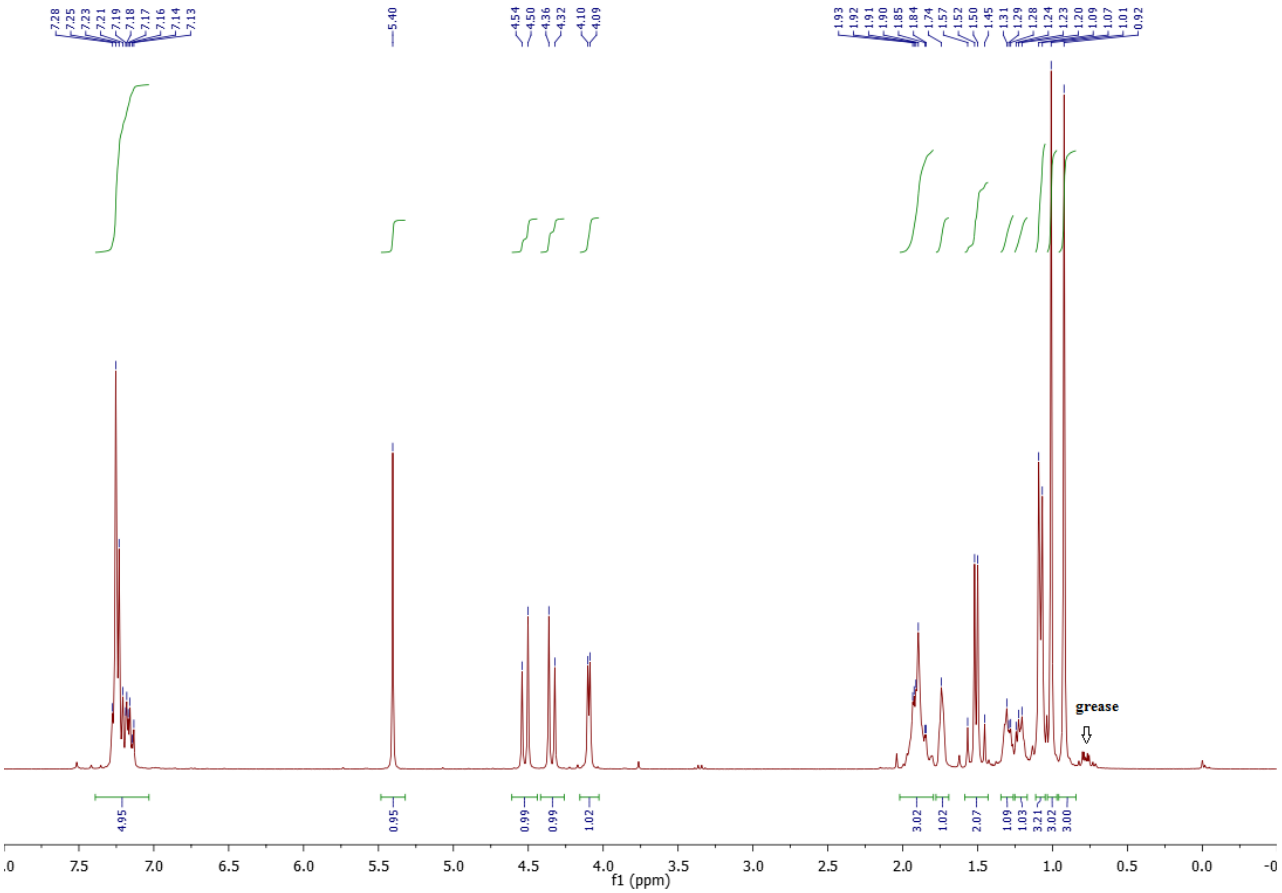


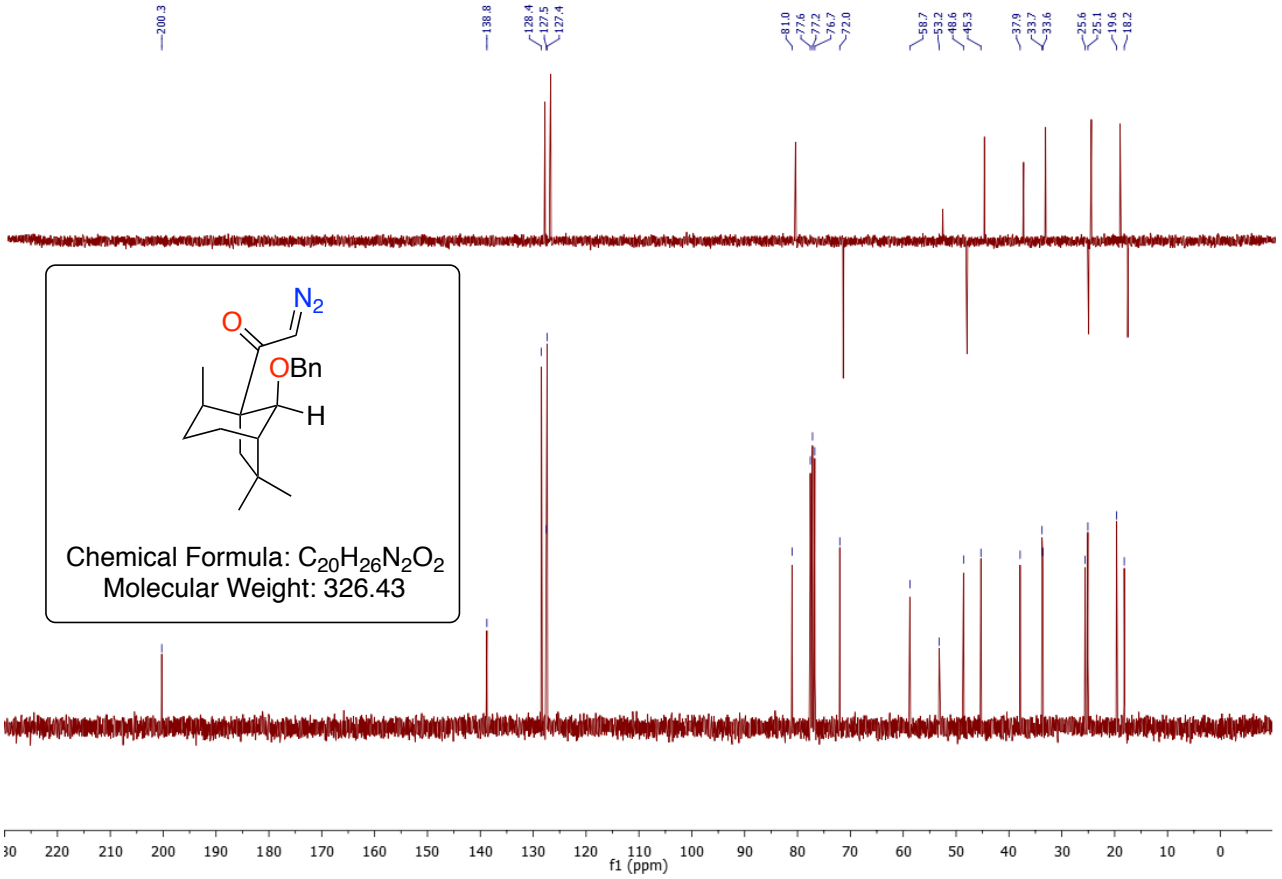
Acid derived from **9a**: (dr > 50:1, ^{1}H NMR @ 300 MHz in $CDCl_3$, ^{13}C NMR @ 75 MHz in $(CD_3)_2CO$):



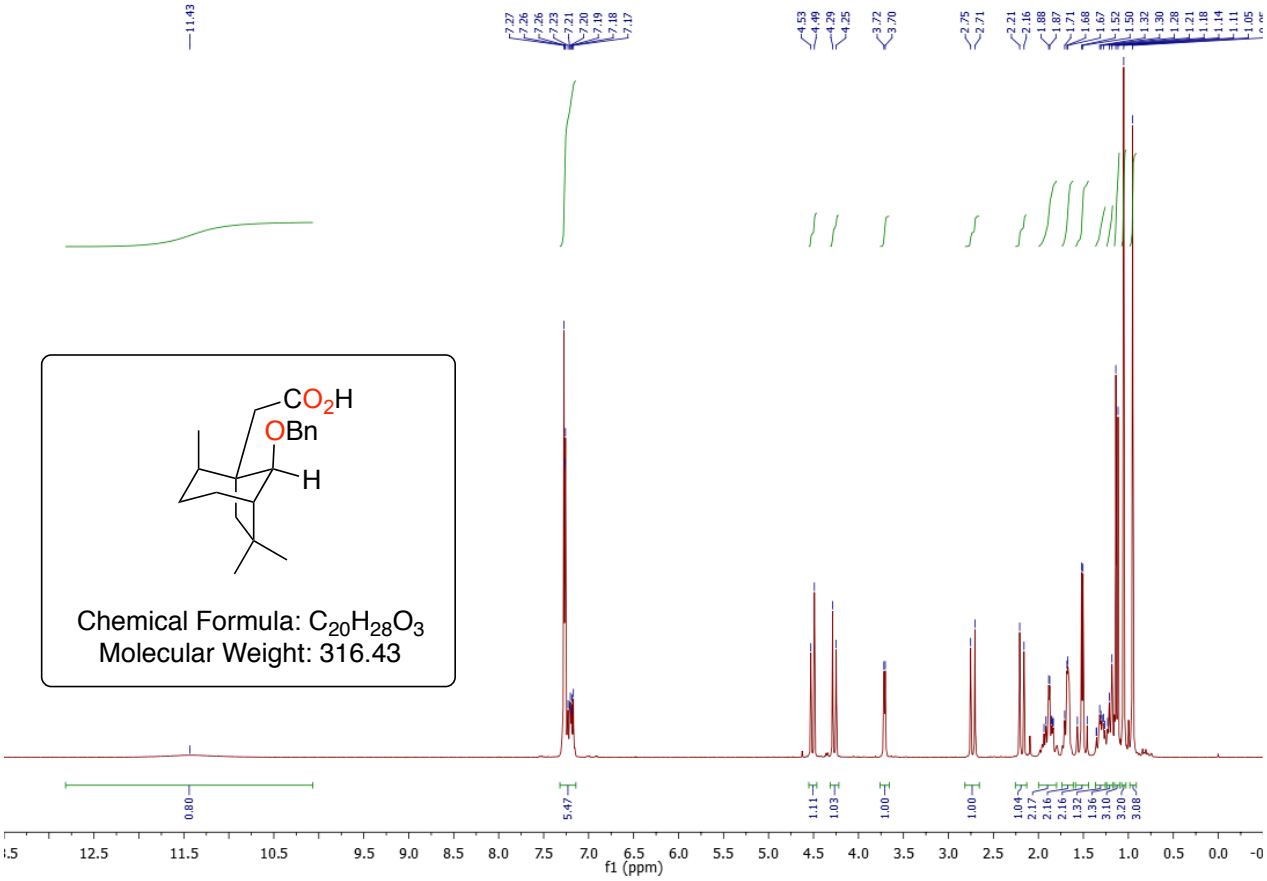


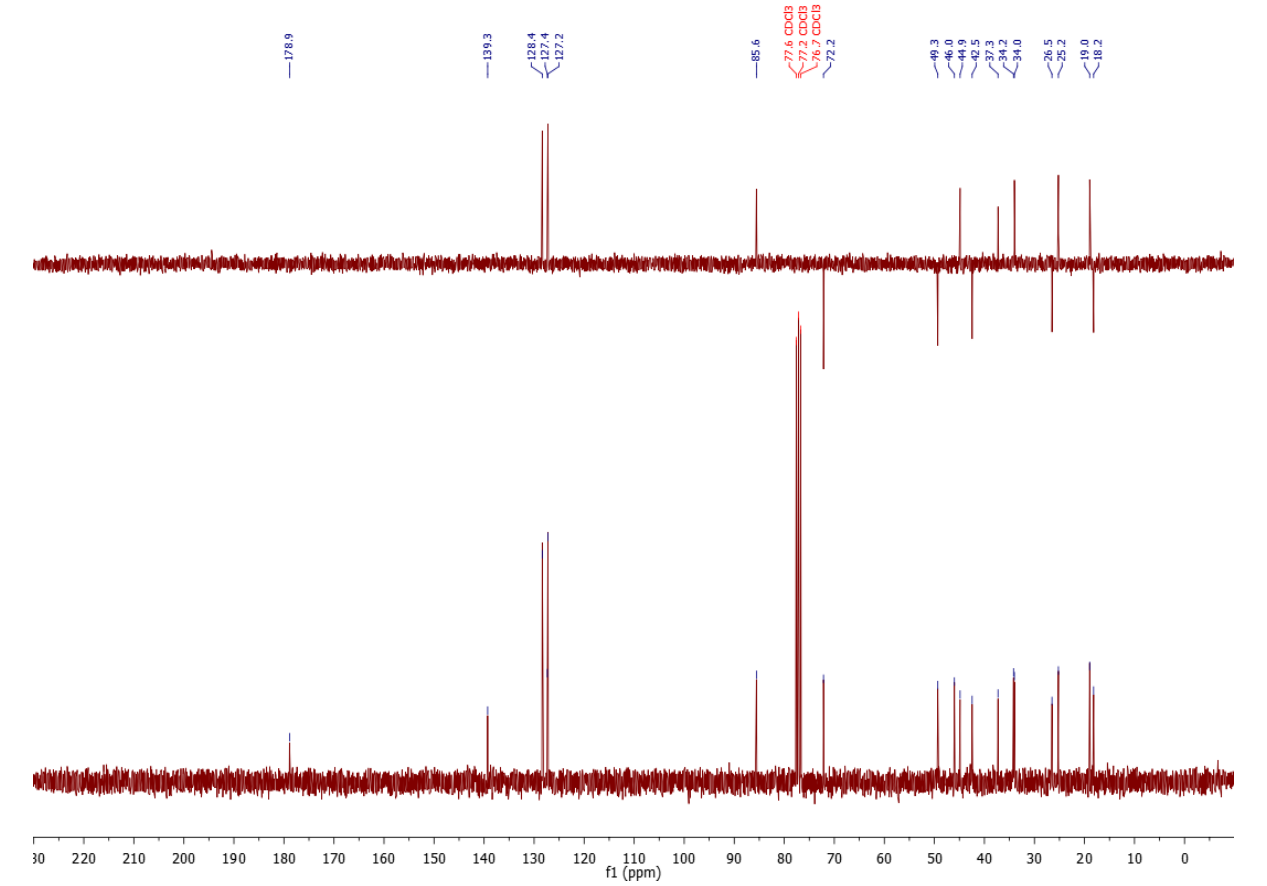
Product **10** (crude, dr > 50:1, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):



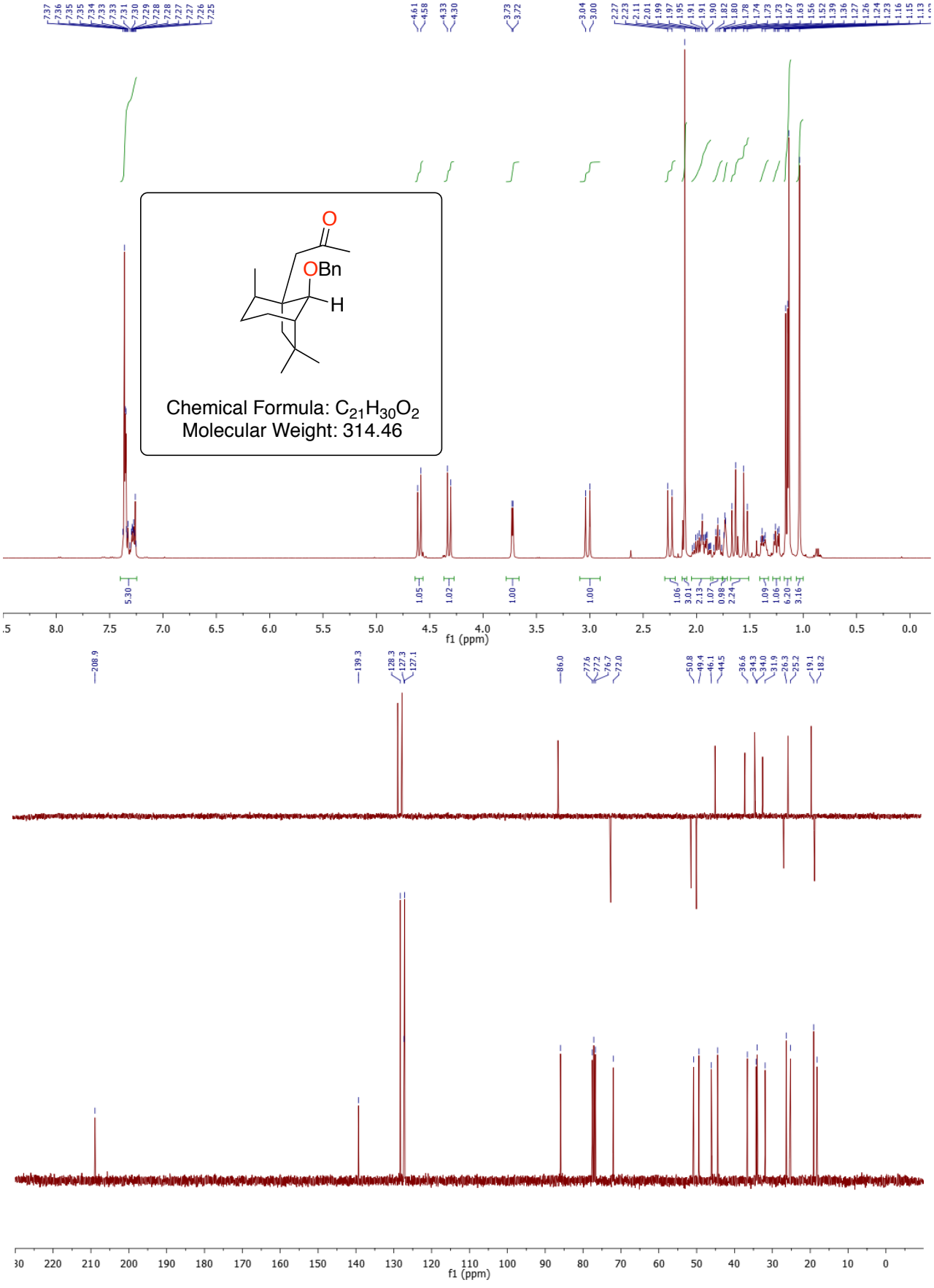


Product **11** (crude, dr > 50:1, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):

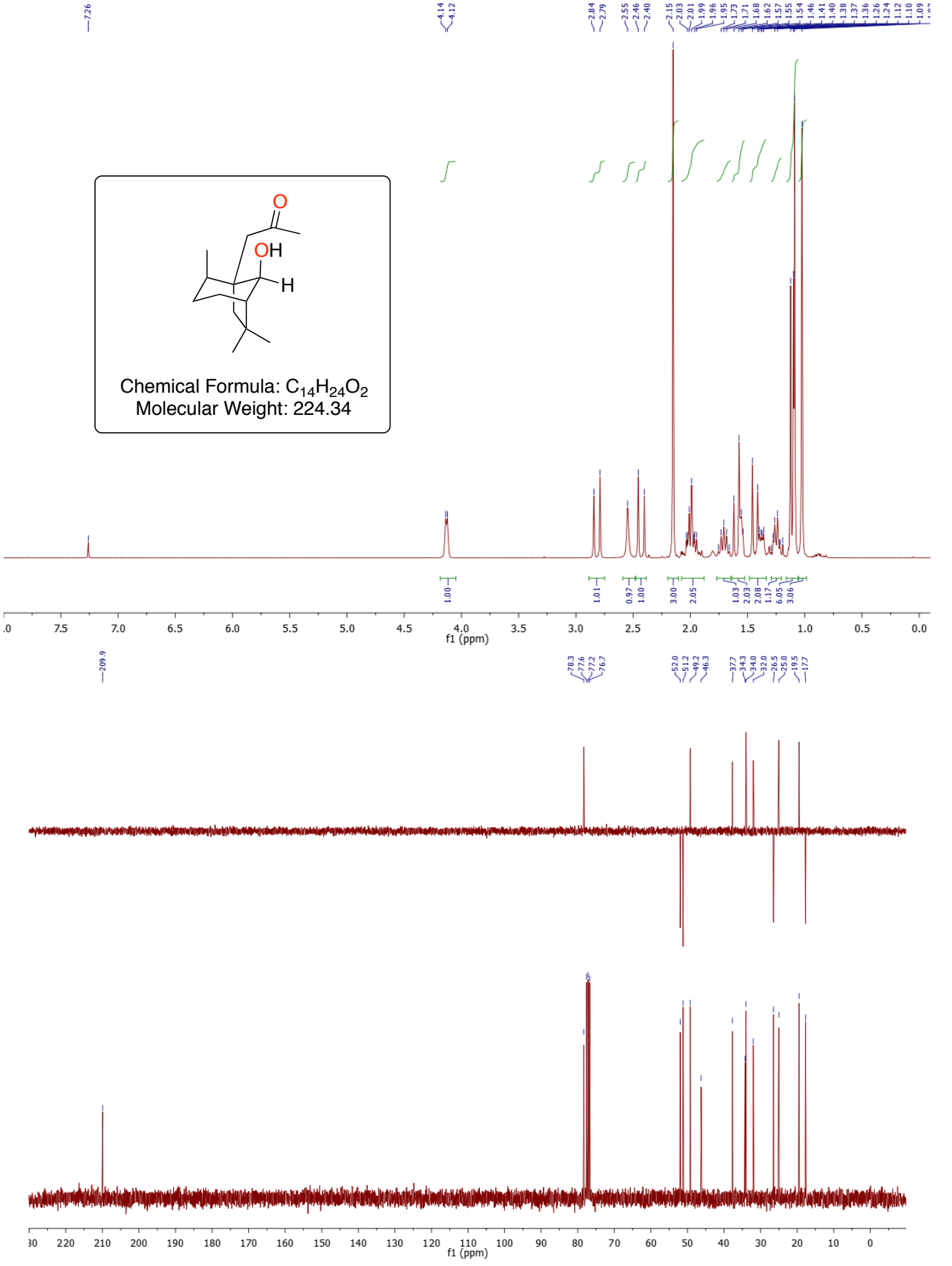




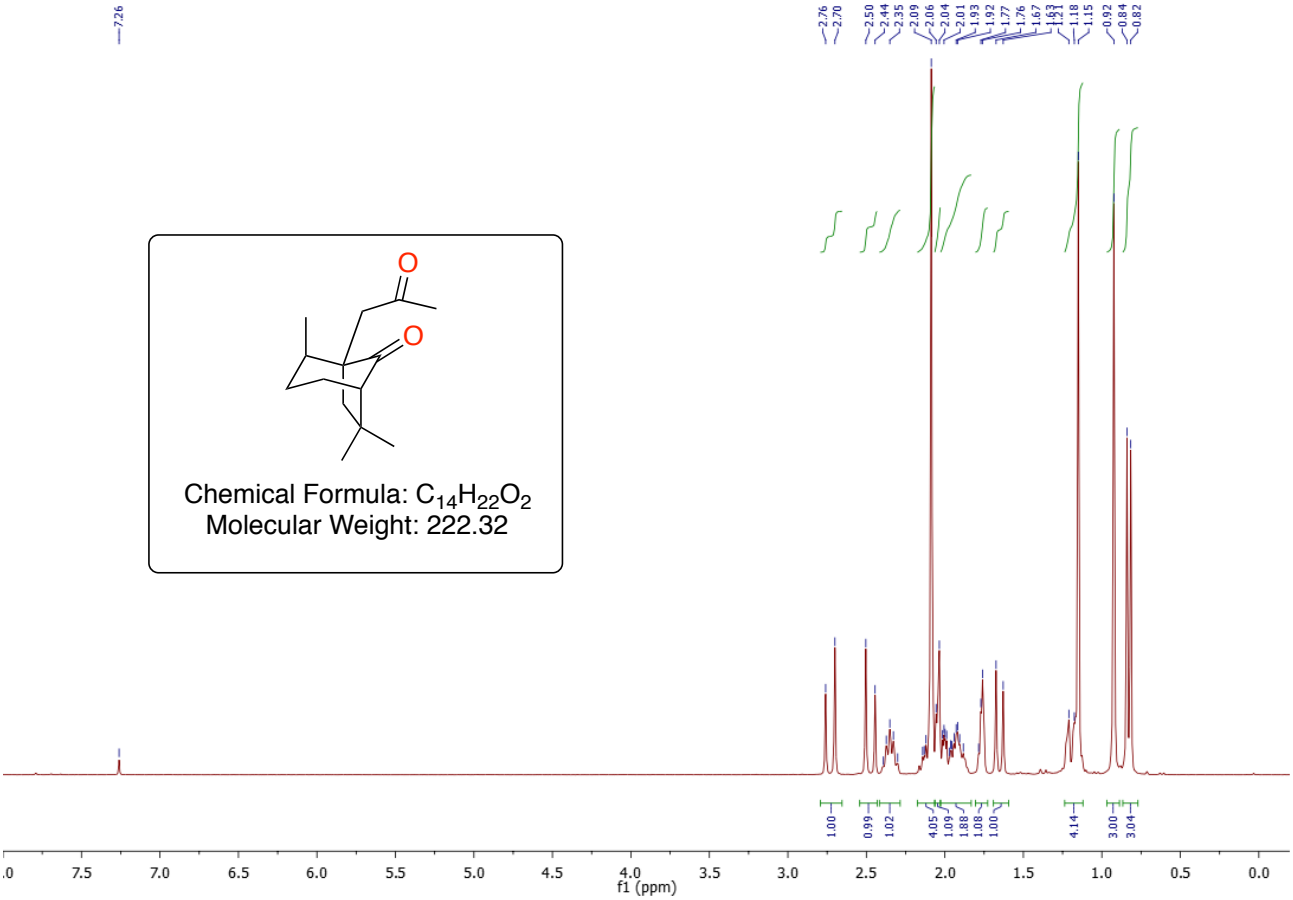
Methyl ketone derived from **11** (dr > 50:1, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):

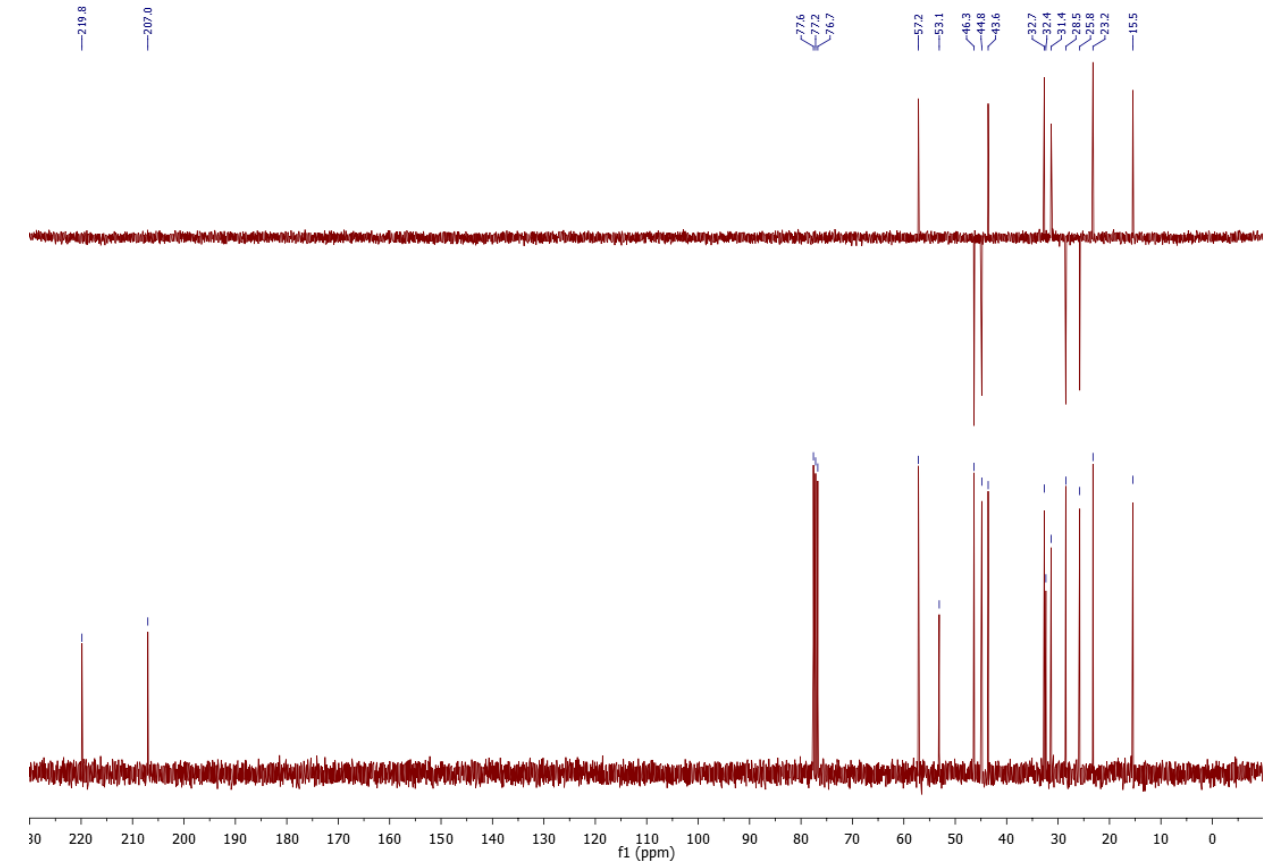


Deprotected alcohol derived from **11** (dr > 50:1, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):

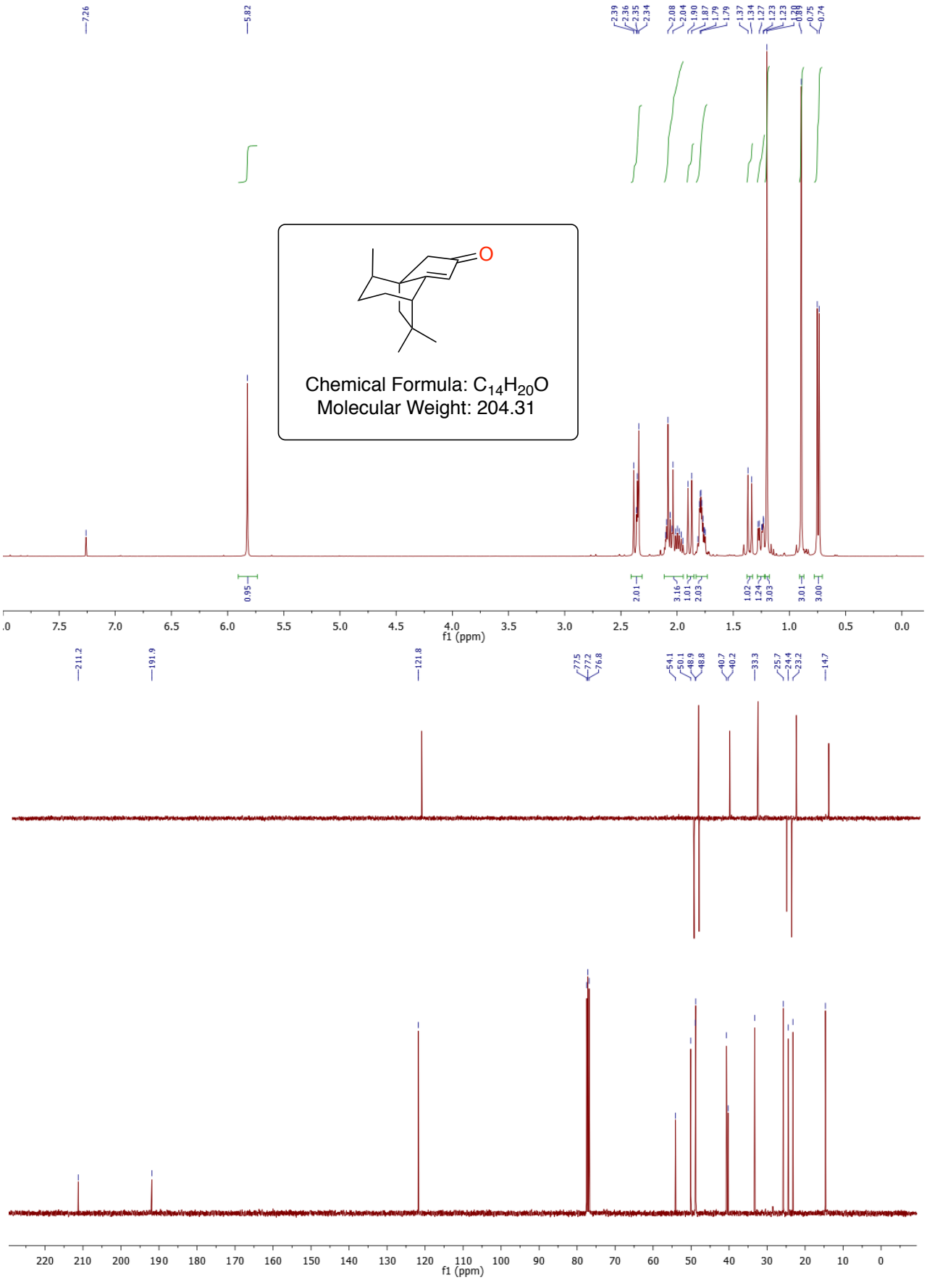


Product **12** (dr > 50:1, ^{1}H NMR @ 300 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):

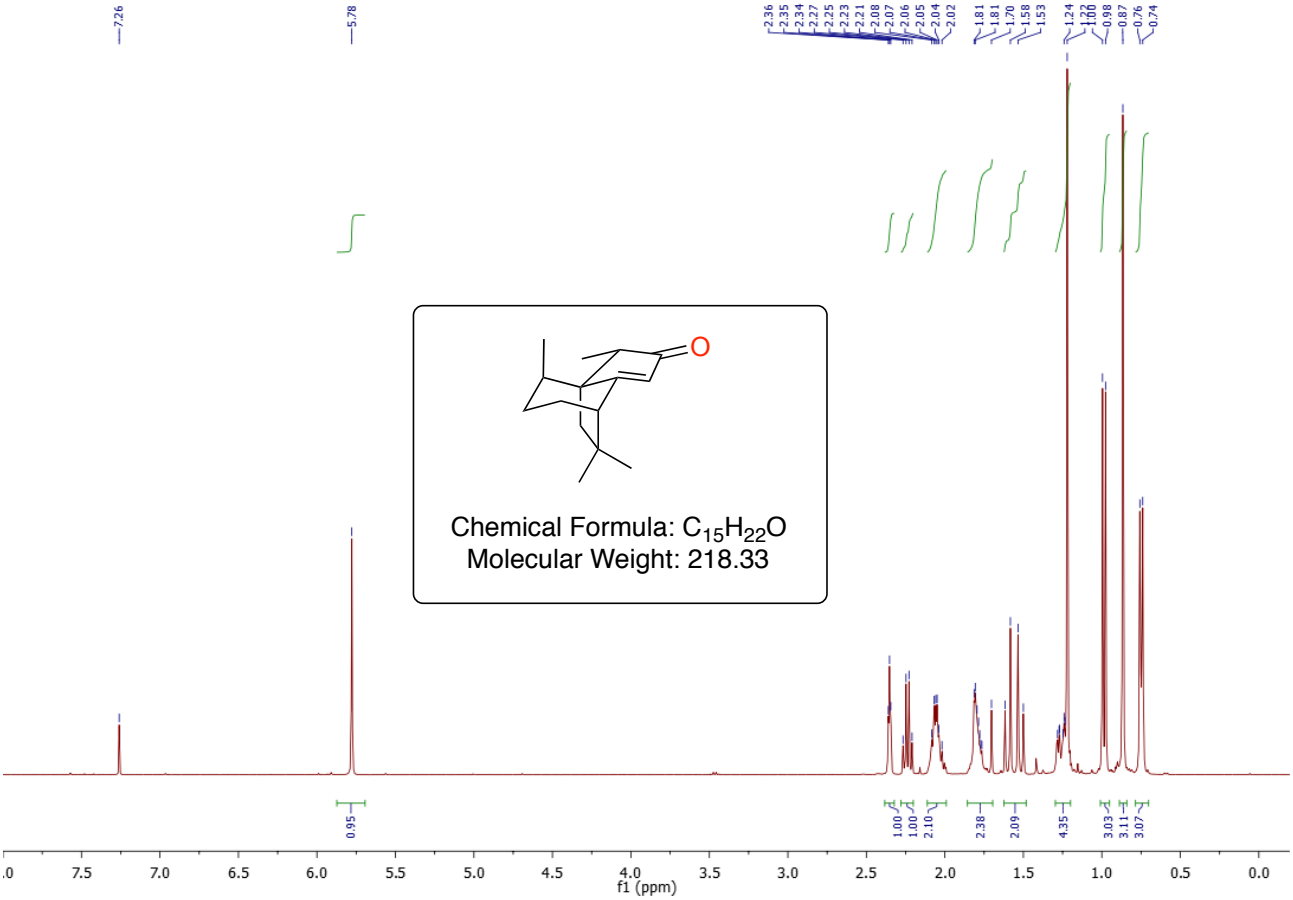


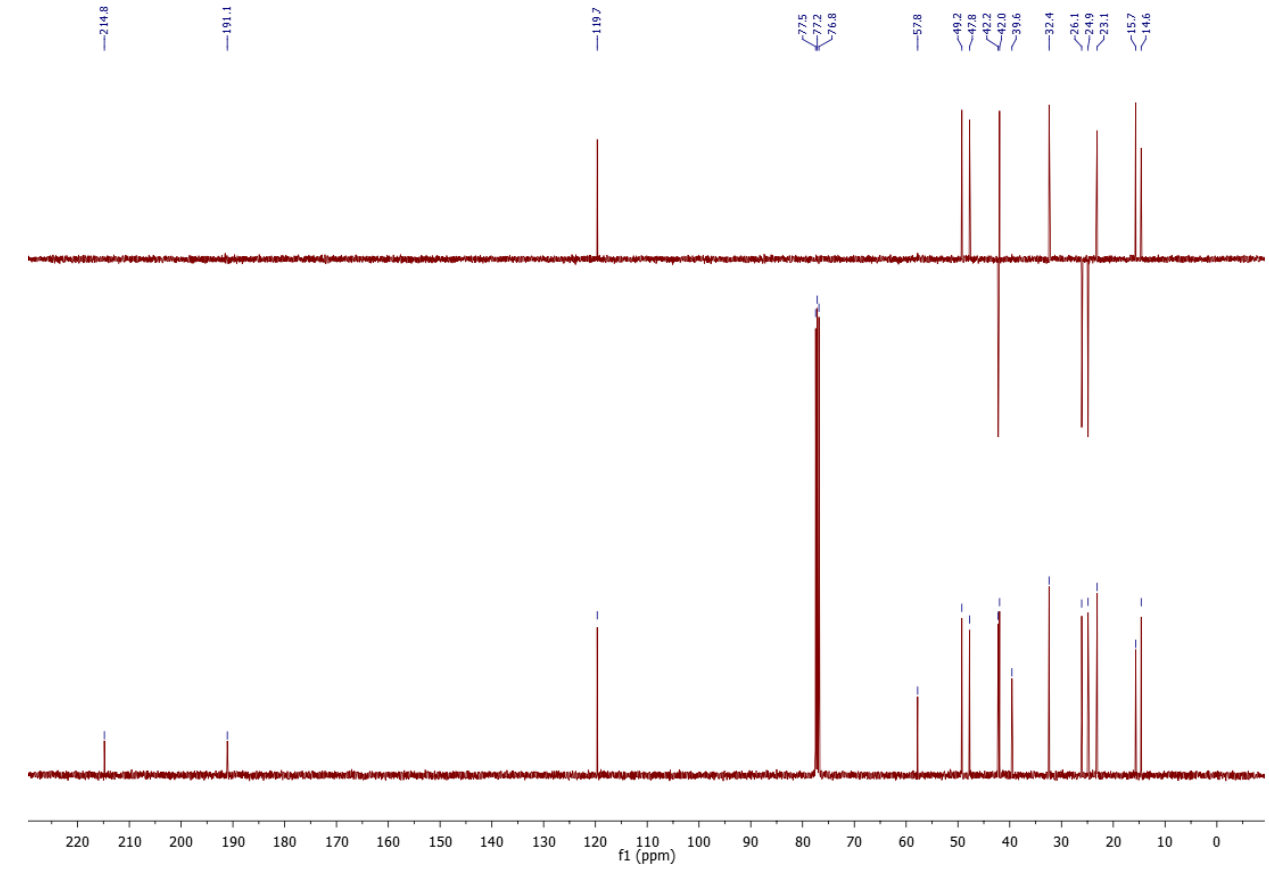


Product **13** (dr > 50:1, ^{1}H NMR @ 400 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):

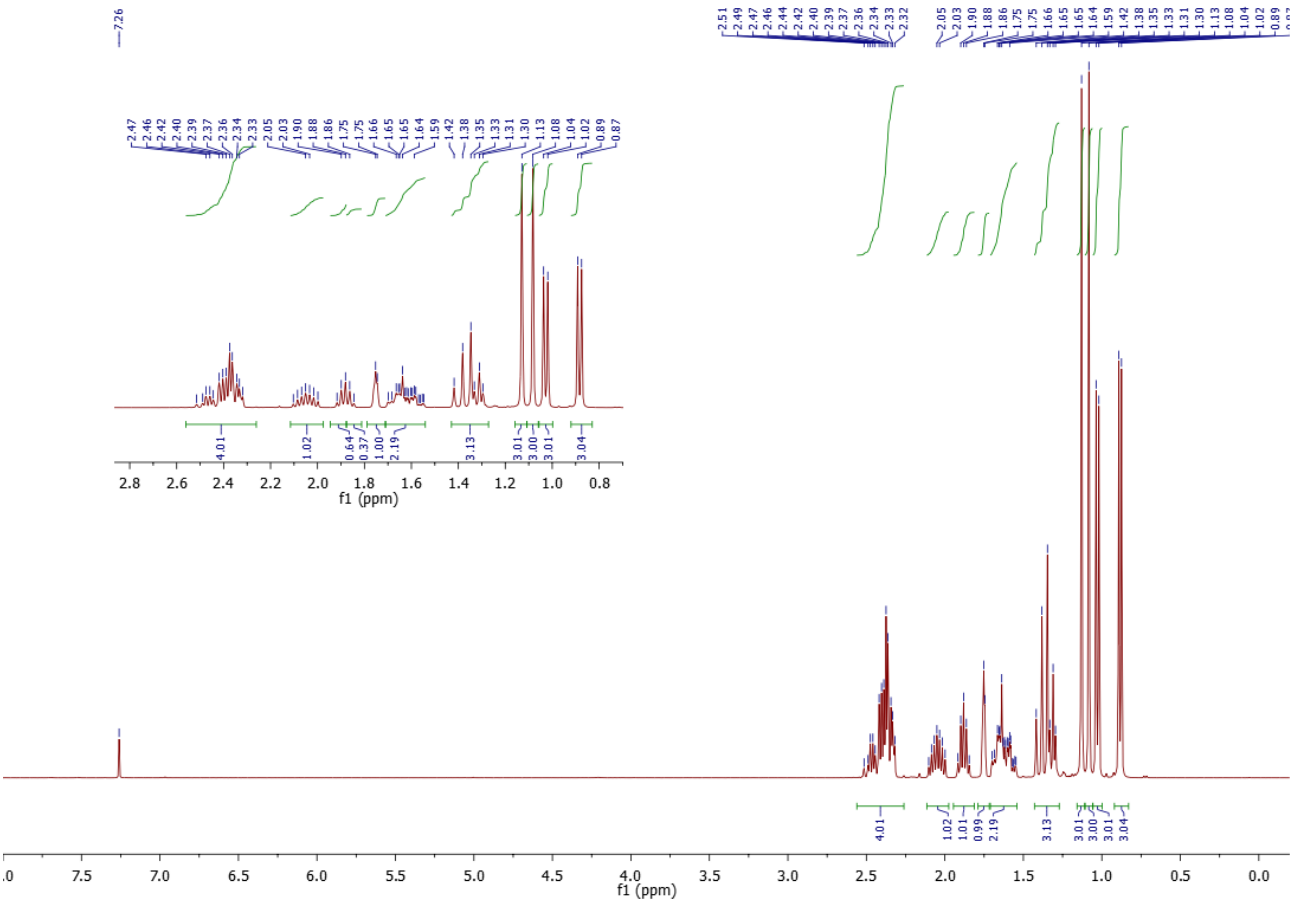


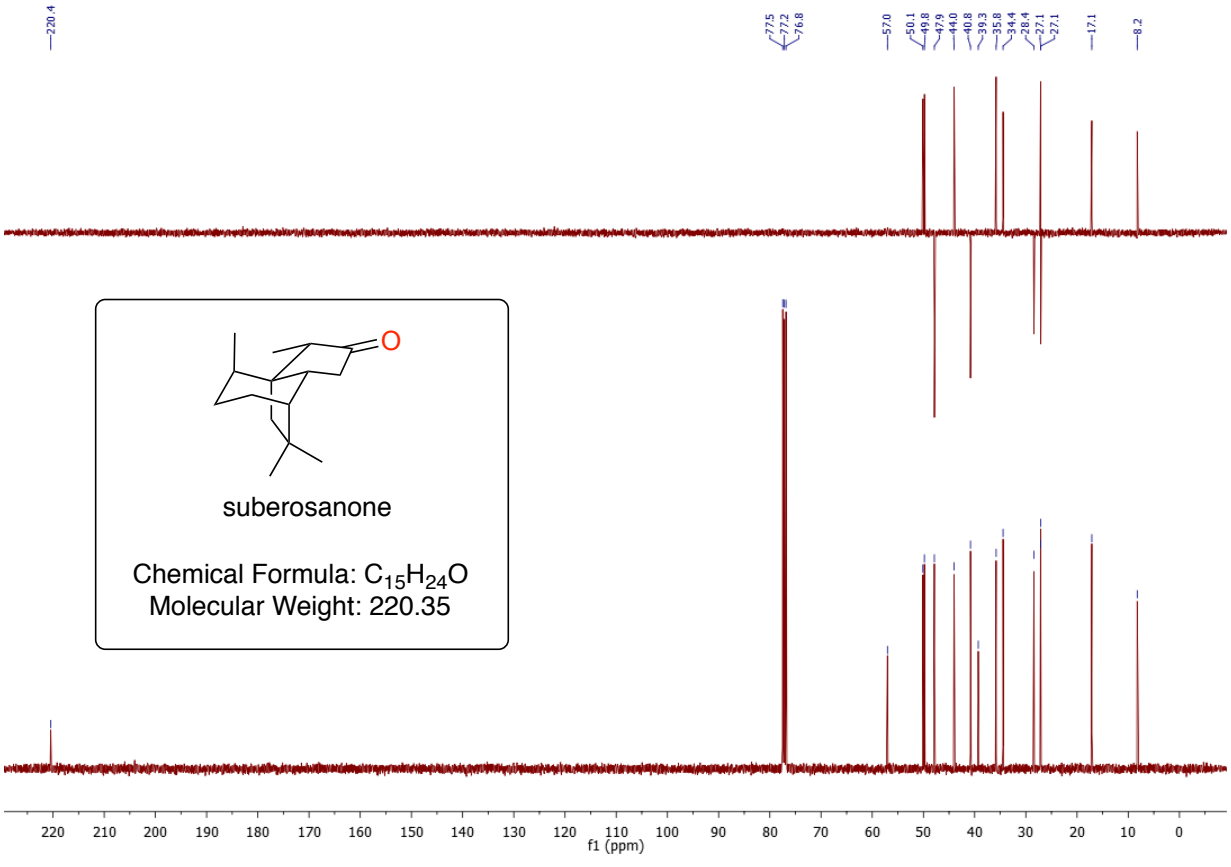
Product **14** (dr > 50:1, ^{1}H NMR @ 400 MHz, ^{13}C NMR @ 75 MHz, in $CDCl_3$):





Product **1** (dr > 50:1, ^{1}H NMR @ 400 MHz, ^{13}C NMR @ 100 MHz, in $CDCl_3$):





Naturally occurring suberosanone (^{1}H NMR @ 500 MHz, in $CDCl_3$), courtesy of Prof. J.-H. Sheu:

Original ^{1}H NMR spectrum obtained by Prof. Jyh-Horng Sheu (National Sun Yat-sen University) and co-workers at the time of isolation from natural sources (see reference 6 for details). We would like to express here our deepest gratitude to Prof. J.-H. Sheu for making that information available to us.

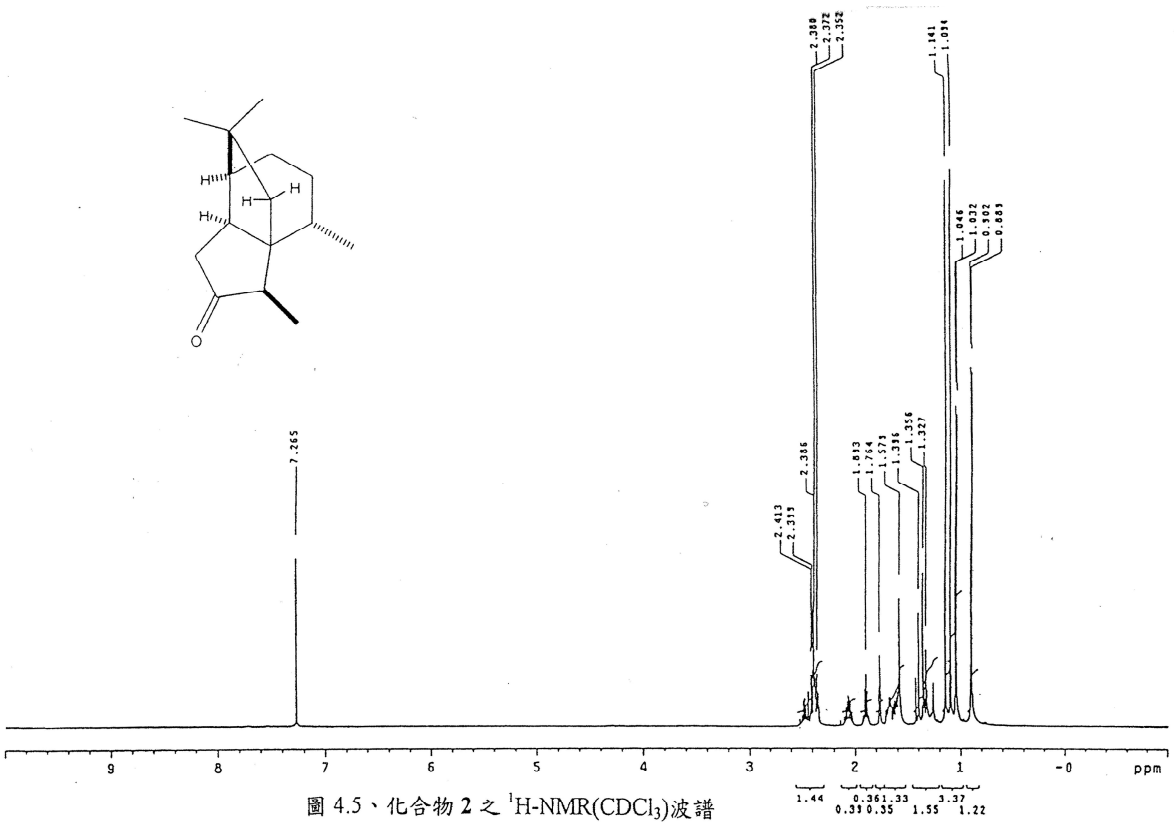
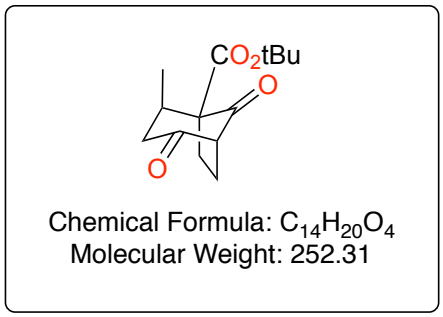


圖 4.5、化合物 **2** 之 ^{1}H-NMR($CDCl_3$)波譜

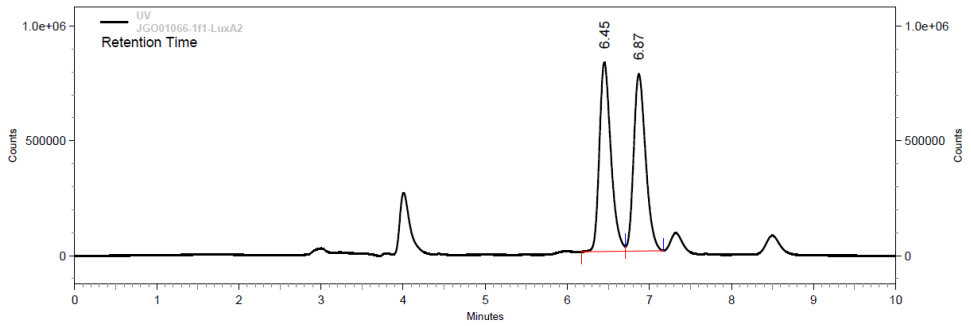
4. Copies of HPLC chromatograms

Product **6a**:



Chemical Formula: $C_{14}H_{20}O_4$
Molecular Weight: 252.31

Sample : JGO01066-1f1-LuxA2
Method description : Lux-Amylose-2, Hexane/ethanol 80/20, 1 ml/min, UV 220 nm et CD 220nm

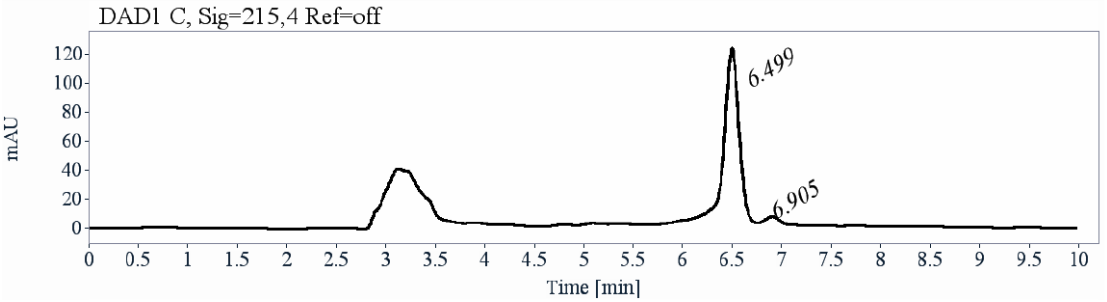


UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.45	8040193	50.73	1.15	1.00	0.00
6.87	7807540	49.27	1.29	1.12	1.60
Totals	15847733	100.00			

Sample name: RYJ04075
Column: Lux-Amylose-2

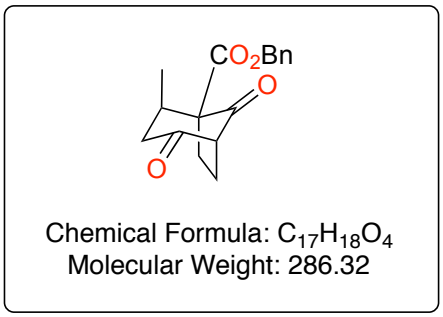
Temperature: 25 degres
Mobile phase: Heptane/Ethanol (80/20), 1 mL/min



Signal: DAD1 C, Sig=215,4 Ref=off

RT [min]	Area	Area%	Capacity Factor	Enantioselectivity	Resolution (USP)
6.50	1258	96.27	1.20		
6.91	49	3.73	1.34	1.11	1.58
Sum	1307	100.00			

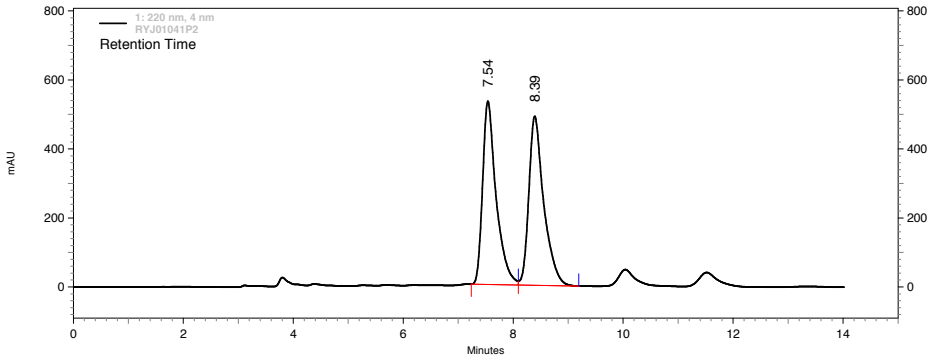
Product **6b**:



Chemical Formula: $C_{17}H_{18}O_4$
Molecular Weight: 286.32

Sample : RYJ01041P2

Method description : Chiralpak IC, Hexane/Ethanol 80/20, 1 ml/min, DAD and polarimeter

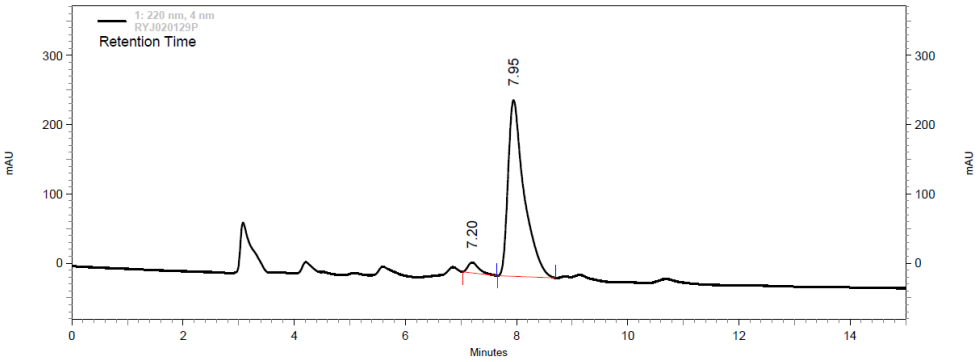


1: 220 nm, 4 nm
Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
7.54	36263922	49.57	1.51	1.00	0.00
8.39	36898627	50.43	1.80	1.19	1.88
Totals	73162549	100.00			

Sample : RYJ020129P

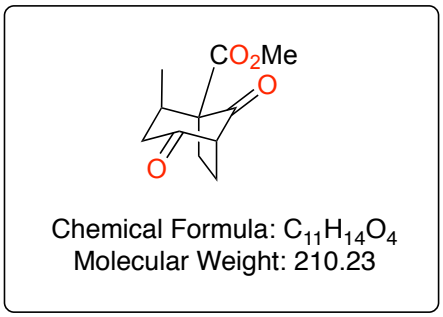
Method description : Chiralpak IC, Heptane/Ethanol 80/20, 1 ml/min, DAD and polarimeter



1: 220 nm, 4 nm
Results

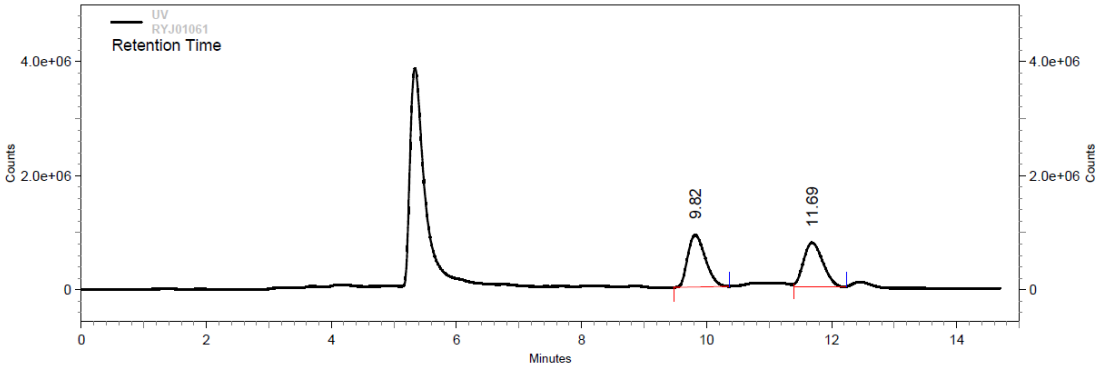
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
7.20	822733	3.89	1.40	0.00	0.00
7.95	20351805	96.11	1.65	0.00	1.74
Totals	21174538	100.00			

Product **6c**:



Chemical Formula: $C_{11}H_{14}O_4$
Molecular Weight: 210.23

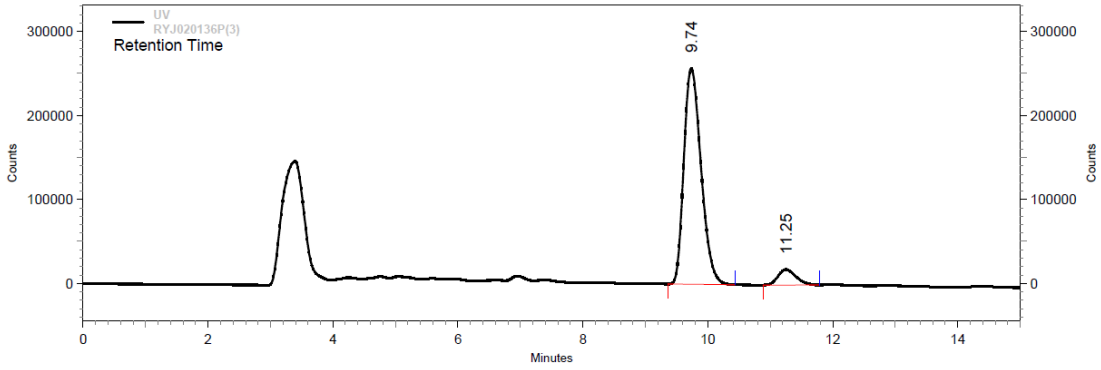
Sample : RYJ01061
Method description : Chiralpak AD-H, Hexane/ethanol 80/20, 1 ml/min, UV 220 nm et polarimètre



UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
9.82	17817402	52.20	2.27	0.00	0.00
11.69	16317480	47.80	2.90	0.00	3.36
Totals	34134882	100.00			

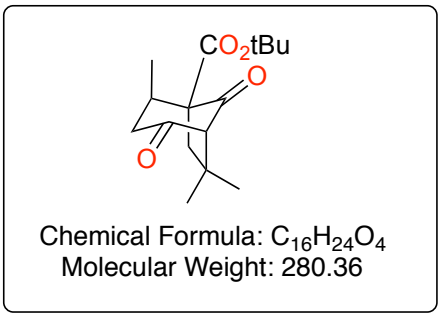
Sample : RYJ020136P(3)
Method description : Chiralpak AD-H, Heptane/ethanol 80/20, 1 ml/min, UV 220 nm et polarimètre



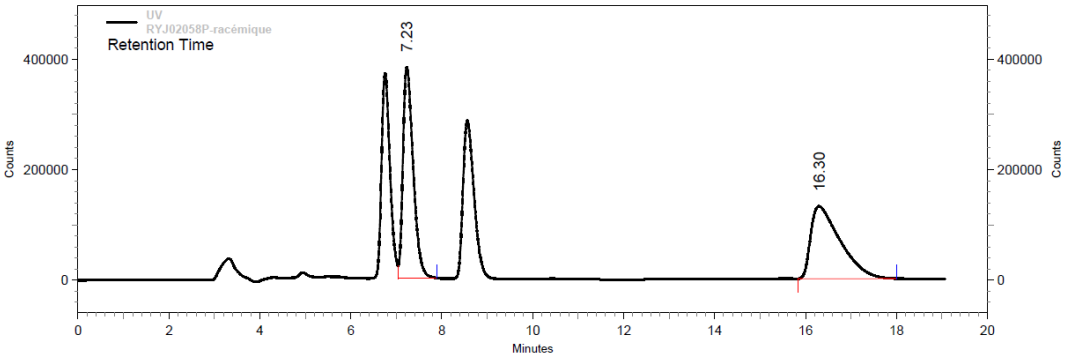
UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
9.74	4916132	92.91	2.25	0.00	0.00
11.25	375228	7.09	2.75	0.00	2.87
Totals	5291360	100.00			

Product **6d**:



Sample : RYJ02058P-racémique
Method description : Chiralpak AZ-H, Heptane/ethanol 80/20, 1 ml/min, UV 220 nm et CD220nm

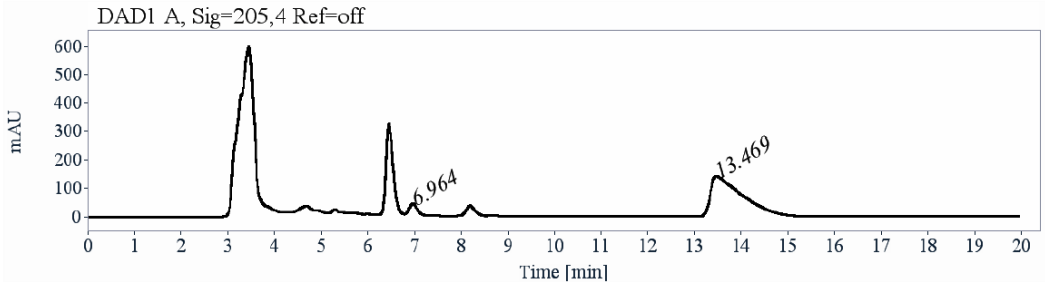


UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
7.23	5999885	50.36	1.41	0.00	0.00
16.30	5913235	49.64	4.43	0.00	11.07
Totals	11913120	100.00			

Sample name: RYJ04071(3)
Column: Chiralpak AZ-H

Temperature: 25 degres
Mobile phase: Heptane/Ethanol (80/20), 1 mL/min

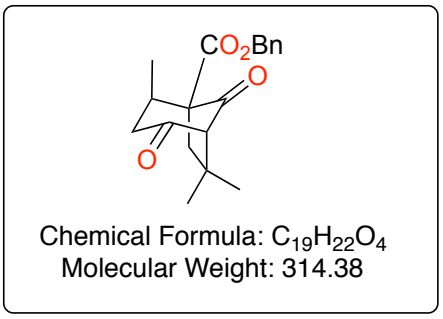


Signal: DAD1 A, Sig=205,4 Ref=off

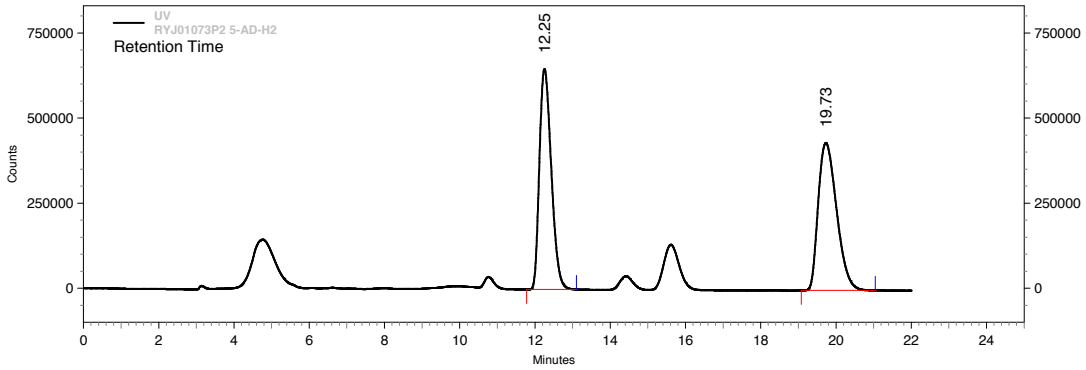
RT [min]	Area	Area%	Capacity Factor	Enantioselectivity	Resolution (USP)
6.96	443	6.05	1.36		
13.47	6872	93.95	3.57	2.62	7.91
Sum	7315	100.00			

The variations in retention times are essentially due to column wear, 18 months passed between the analysis of the racemic sample and the enantio-enriched one. HPLC retention times were not used to determine the identity of the sample, NMR was.

Product **6e**:



Sample : RYJ01073P2 5-AD-H2
Method description : Chiralpak AD-H, Hexane/ethanol 90/10, 1 ml/min, UV 220 nm et polarimetre

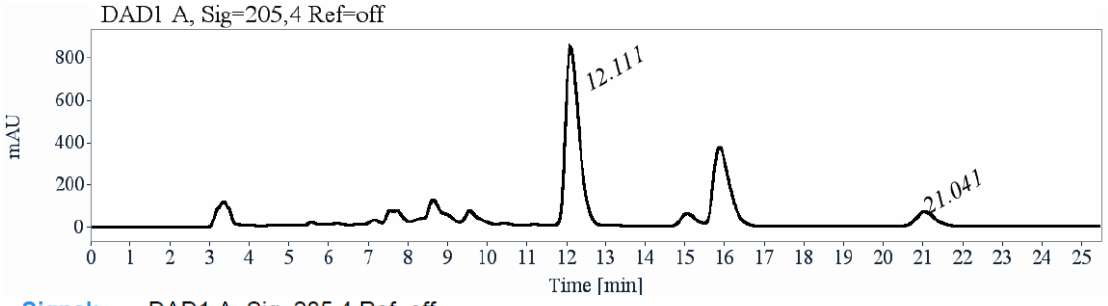


UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
12.25	14211551	49.11	3.08	1.00	0.00
19.73	14724435	50.89	5.58	1.81	9.99
Totals	28935986	100.00			

Sample name: RYJ04079
Column: Chiralpak AD-H

Temperature: 25 degres
Mobile phase: Heptane/Ethanol (90/10), 1 mL/min

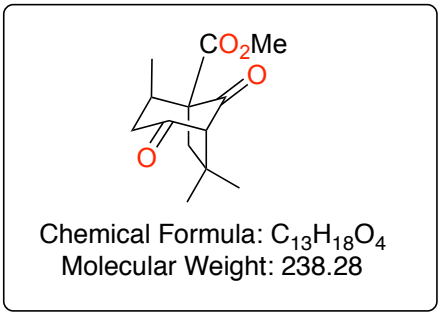


Signal: DAD1 A, Sig=205,4 Ref=off

RT [min]	Area	Area%	Capacity Factor	Enantioselectivity	Resolution (USP)
12.11	20037	89.60	3.11		
21.04	2326	10.40	6.13	1.97	12.03
Sum	22364	100.00			

The variations in retention times are essentially due to column wear, 30 months passed between the analysis of the racemic sample and the enantio-enriched one. HPLC retention times were not used to determine the identity of the sample, NMR was.

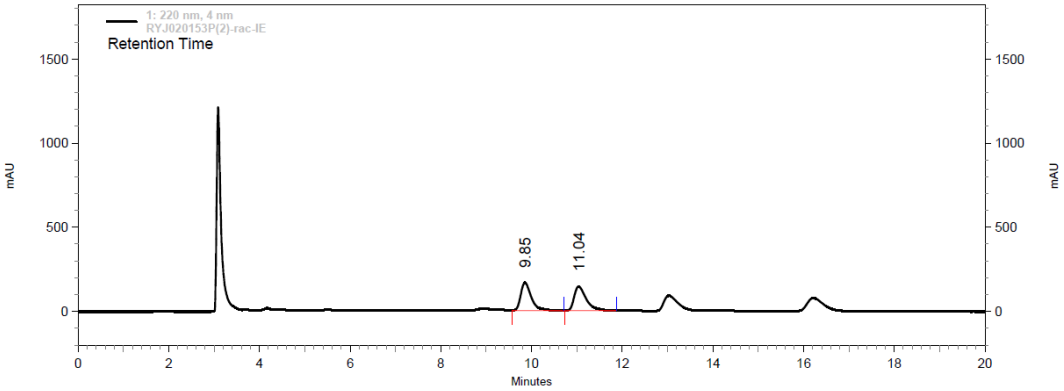
Product **6f**:



Chemical Formula: $C_{13}H_{18}O_4$
Molecular Weight: 238.28

Sample : RYJ020153P(2)-rac-IE

Method description : Chiralpak IE, Heptane/Ethanol 80/20, 1 ml/min, DAD and polarimeter

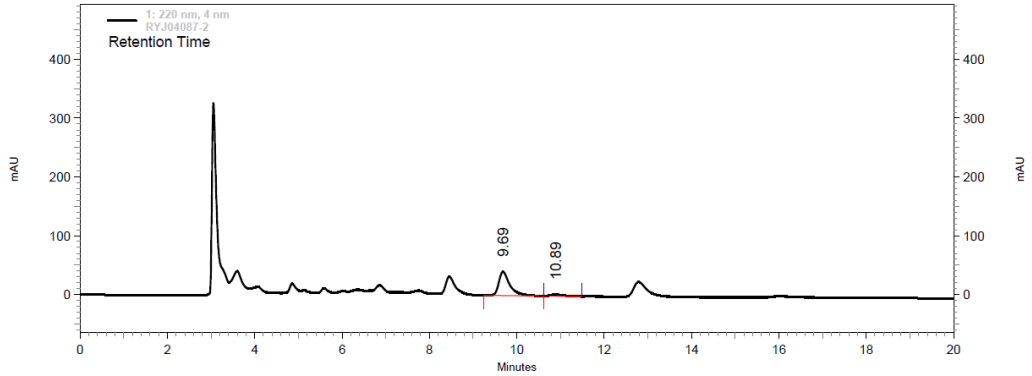


1: 220 nm, 4 nm
Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
9.85	10702008	50.36	2.28	1.00	0.00
11.04	10546992	49.64	2.68	1.17	2.68
Totals	21249000	100.00			

Sample : RYJ04087-2

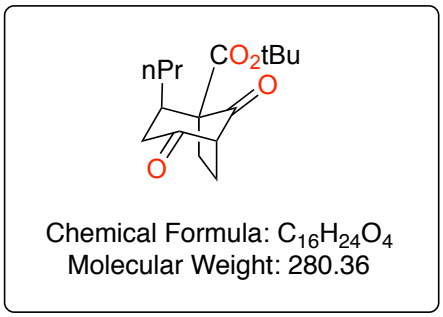
Method description : Chiralpak IE, Heptane/Ethanol 80/20, 1 ml/min, DAD and polarimeter



1: 220 nm, 4 nm
Results

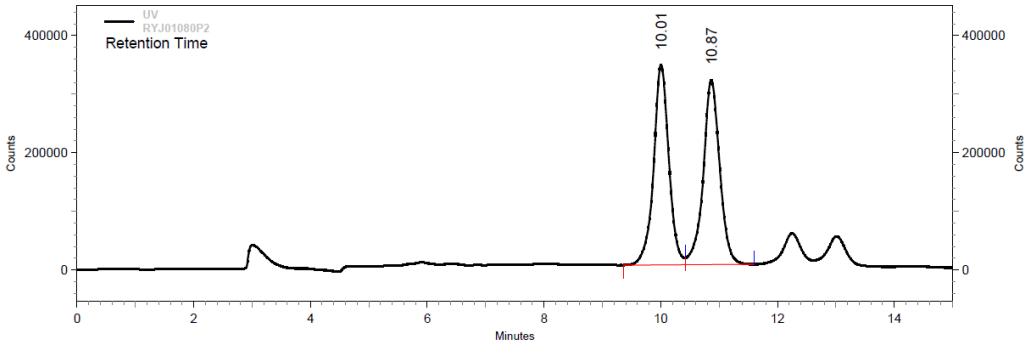
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
9.69	2876025	92.78	2.23	1.00	0.00
10.89	223676	7.22	2.63	1.18	2.64
Totals	3099701	100.00			

Product **6g**:



Chemical Formula: $C_{16}H_{24}O_4$
Molecular Weight: 280.36

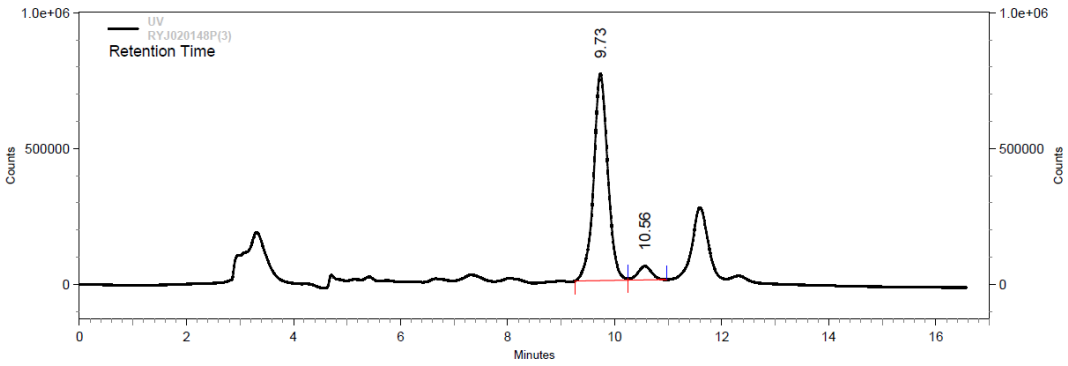
Sample : RYJ01080P2
Method description : (S,S)-Whelk-O1, Hexane/ethanol 90/10, 1 ml/min, UV 220 nm et polarimetre



UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
10.01	6201212	49.99	2.34	1.00	0.00
10.87	6204438	50.01	2.62	1.12	1.77
Totals	12405650	100.00			

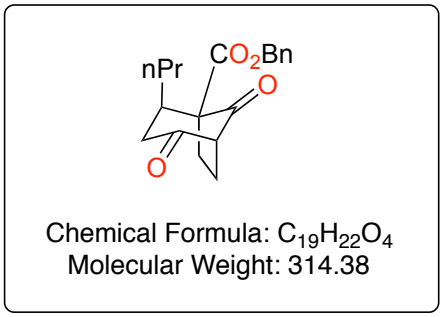
Sample : RYJ020148P(3)
Method description : (S,S)-Whelk-O1, Heptane/ethanol 90/10, 1 ml/min, UV 220 nm et polarimetre



UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
9.73	14004682	93.93	2.24	0.00	0.00
10.56	904684	6.07	2.52	0.00	1.74
Totals	14909366	100.00			

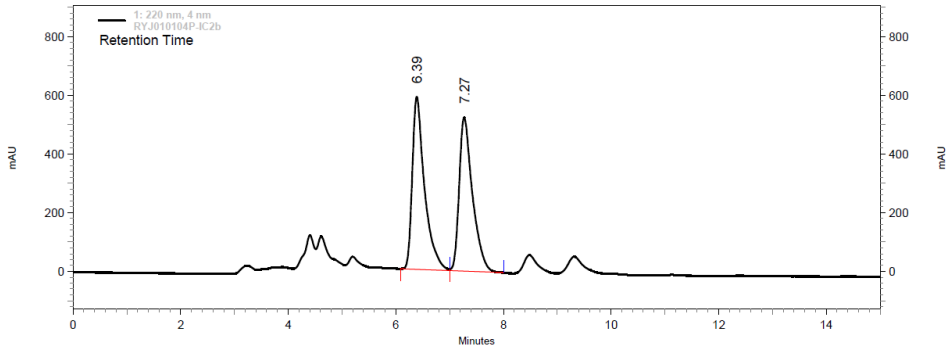
Product **6h**:



Chemical Formula: $C_{19}H_{22}O_4$
Molecular Weight: 314.38

Sample : RYJ010104P-IC2b

Method description : Chiralpak IC, Hexane/Ethanol 80/20, 1 ml/min, DAD and CD 220nm



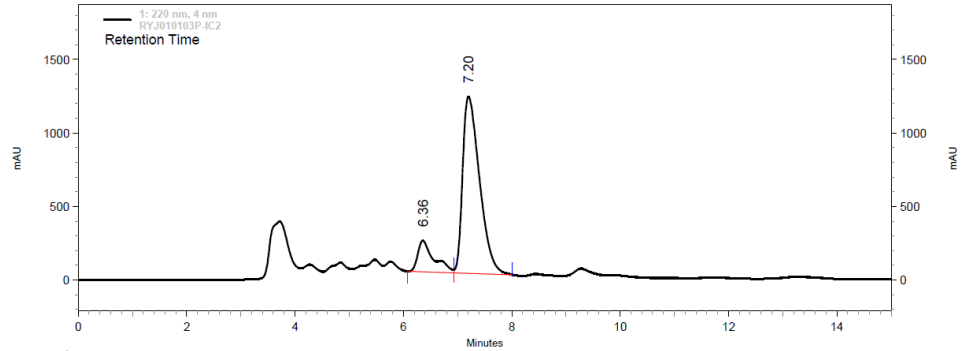
1: 220 nm, 4 nm

Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.39	37412975	50.94	1.13	0.00	0.00
7.27	36035946	49.06	1.42	0.00	2.12
Totals	73448921	100.00			

Sample : RYJ010103P-IC2

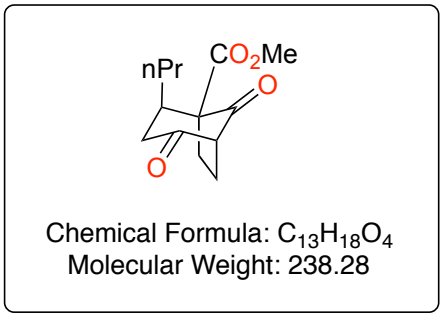
Method description : Chiralpak IC, Hexane/Ethanol 80/20, 1 ml/min, DAD and CD 220nm



Results

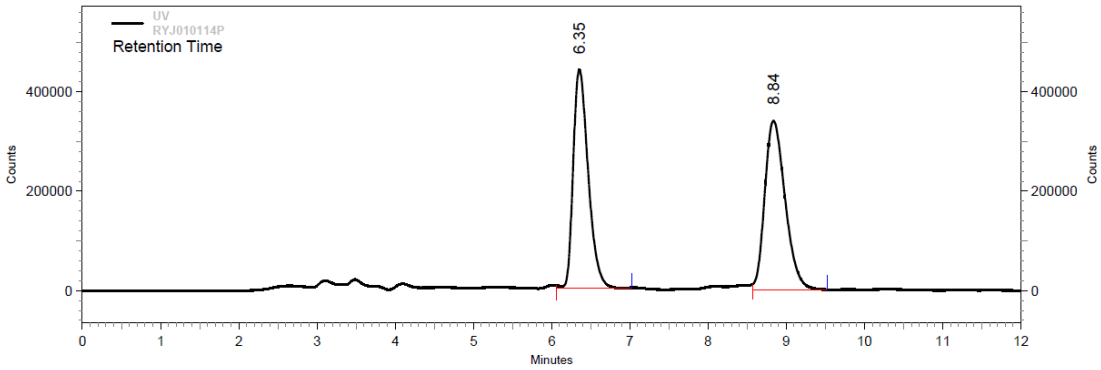
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.36	1447892	10.60	1.12	0.00	0.00
7.20	12217892	89.40	1.40	0.00	1.79
Totals	13665784	100.00			

Product **6i**:



Chemical Formula: $C_{13}H_{18}O_4$
Molecular Weight: 238.28

Sample : RYJ010114P
Method description : Chiralpak AD-H, Hexane/ethanol 80/20, 1 ml/min, UV 220 nm et polarimètre

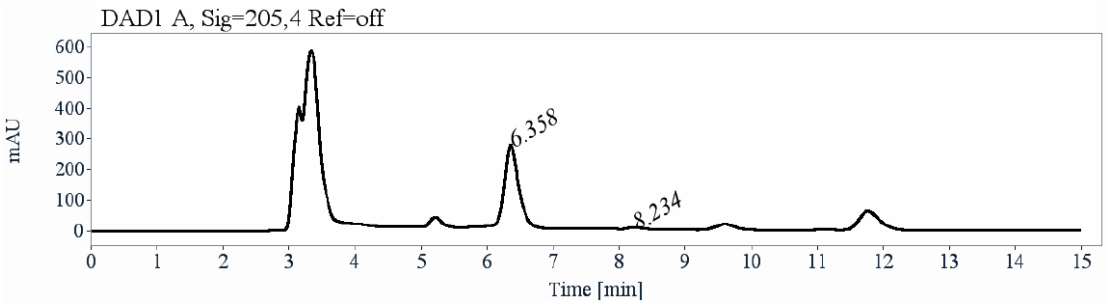


UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.35	5825341	48.64	1.12	0.00	0.00
8.84	6150279	51.36	1.95	0.00	5.97
Totals	11975620	100.00			

Sample name: RYJ04083
Column: Chiralpak AD-H

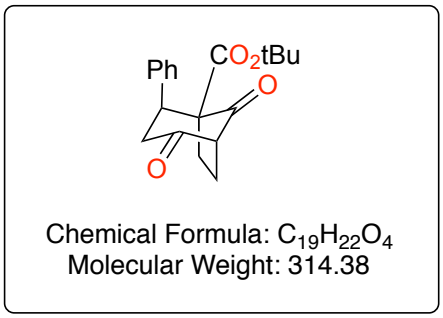
Temperature: 25 degres
Mobile phase: Heptane/Ethanol (80/20), 1 mL/min



Signal: DAD1 A, Sig=205,4 Ref=off

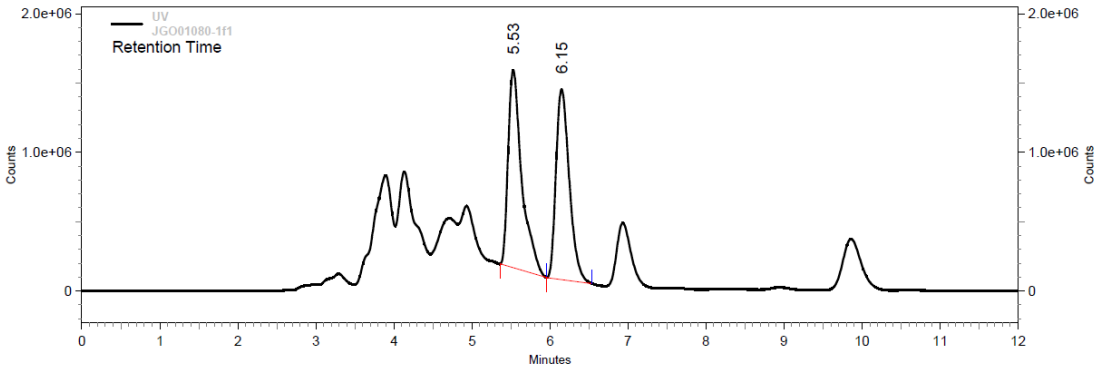
RT [min]	Area	Area%	Capacity Factor	Enantioselectivity	Resolution (USP)
6.36	3955	97.69	1.16		
8.23	94	2.31	1.79	1.55	4.86
Sum	4049	100.00			

Product **6j**:



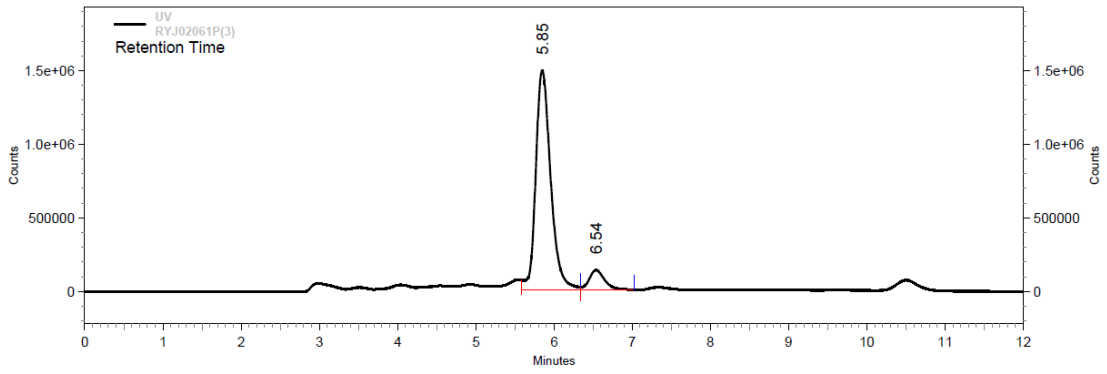
Chemical Formula: $C_{19}H_{22}O_4$
Molecular Weight: 314.38

Sample : JGO01080-1f1
Method description : Chiralcel OD-3 Hexane/ethanol 80/20, 1 ml/min, UV 220 nm et CD 220nm



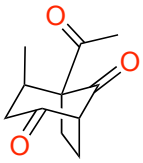
UV Results Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
5.53	17394457	51.63	0.84	1.00	0.00
6.15	16297051	48.37	1.05	1.25	2.01
Totals	33691508	100.00			

Sample : RYJ02061P(3)
Method description : Chiralcel OD-3, Heptane/ethanol 80/20, 1 ml/min, UV 220 nm et CD 220nm



UV Results Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
5.85	19749501	91.74	0.95	0.00	0.00
6.54	1777176	8.26	1.18	0.00	1.99
Totals	21526677	100.00			

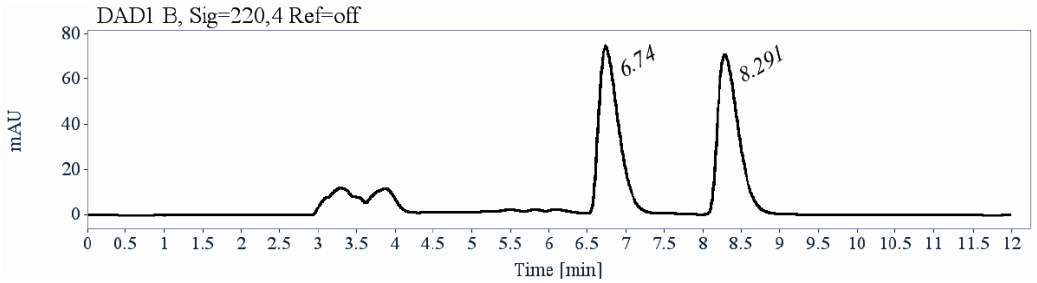
Product **6k**:



Chemical Formula: $C_{11}H_{14}O_3$
Molecular Weight: 194.23

Sample name: RAC03028
Column: Chiralpak AS-H

Temperature: 25 degres
Mobile phase: Heptane/Ethanol (80/20), 1 mL/min

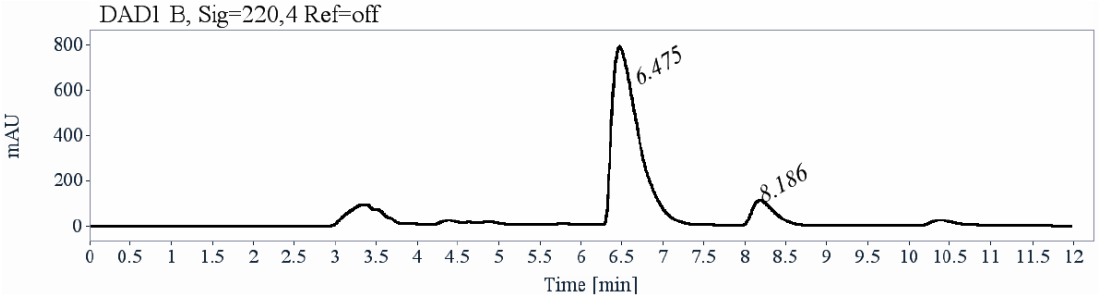


Signal: DAD1 B, Sig=220,4 Ref=off

RT [min]	Area	Area%	Capacity Factor	Enantioselectivity	Resolution (USP)
6.74	1330	50.21	1.28		
8.29	1319	49.79	1.81	1.41	3.23
Sum	2649	100.00			

Sample name: RYJ03028P(3)
Column: Chiralpak AS-H

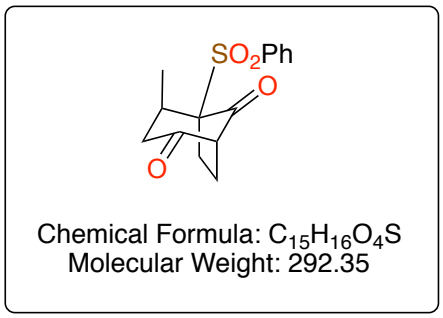
Temperature: 25 degres
Mobile phase: Heptane/Ethanol (80/20), 1 mL/min



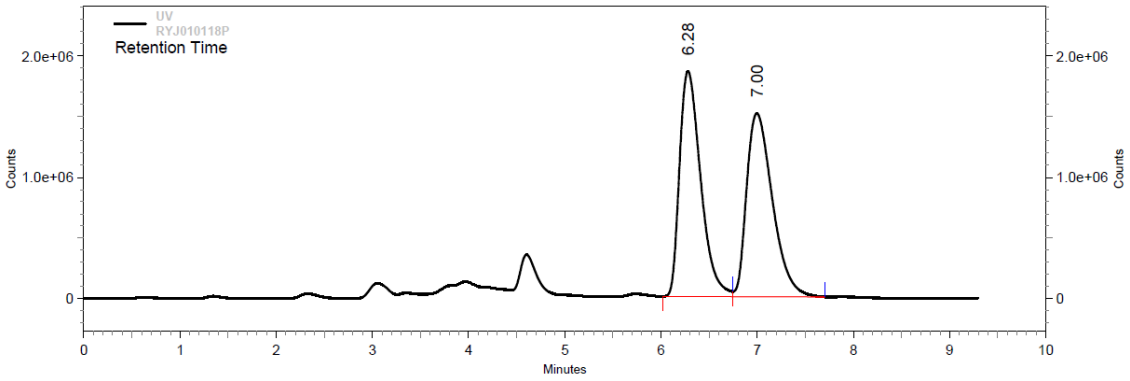
Signal: DAD1 B, Sig=220,4 Ref=off

RT [min]	Area	Area%	Capacity Factor	Enantioselectivity	Resolution (USP)
6.48	17645	89.11	1.20		
8.19	2156	10.89	1.77	1.49	3.15
Sum	19801	100.00			

Product **6l**:



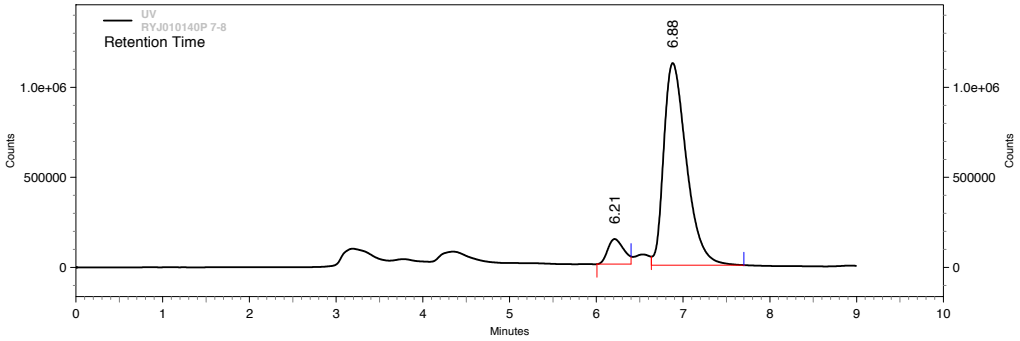
Sample : RYJ010118P
Method description : Chiralpak AS-H, Hexane/ethanol 50/50, 1 ml/min, UV 220 nm et CD254nm



UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.28	28311627	50.09	1.09	1.00	0.00
7.00	28210201	49.91	1.33	1.22	1.61
Totals	56521828	100.00			

Sample : RYJ010140P 7-8
Method description : Chiralpak AS-H, Heptane/ethanol 50/50, 1 ml/min, UV 220 nm et CD254nm

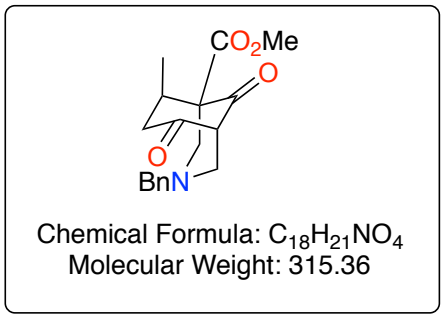


UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.21	1794272	8.09	1.07	1.00	0.00
6.88	20387721	91.91	1.29	1.21	0.00
Totals	22181993	100.00			

The er measurement was complicated by the presence of a UV-visible minor impurity (not visible on the corresponding NMR spectra) eluted between the two enantiomers. We apologize to the readers for the bigger experimental error in this case.

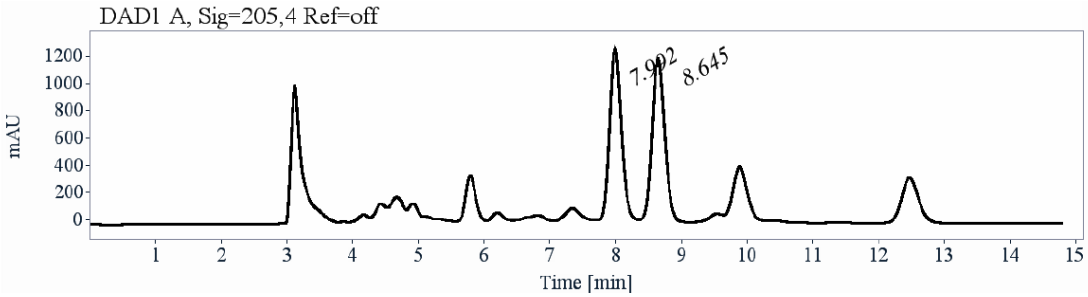
Product **6m**:



Chemical Formula: $C_{18}H_{21}NO_4$
Molecular Weight: 315.36

Sample name: RYJ020166
Column: Chiralpak IC

Temperature: 25 degres
Mobile phase: Heptane/Ethanol (80/20), 1 mL/min

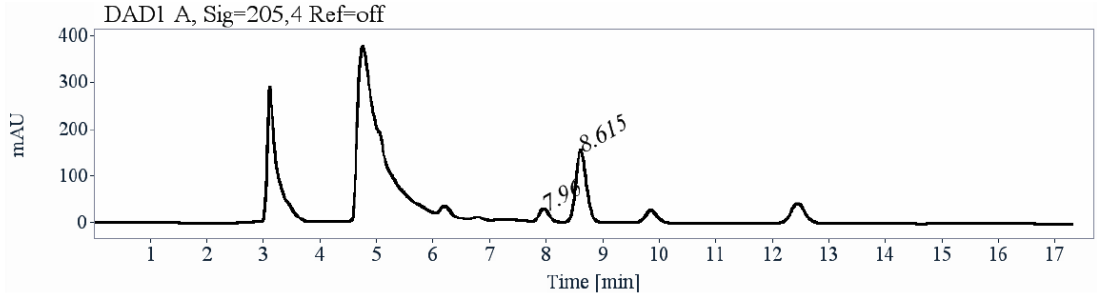


Signal: DAD1 A, Sig=205,4 Ref=off

RT [min]	Area	Area%	Capacity Factor	Enantioselectivity	Resolution (USP)
7.99	15650	49.64	1.71		
8.64	15874	50.36	1.93	1.13	1.94
Sum	31524	100.00			

Sample name: RYJ03018P(3)
Column: Chiralpak IC

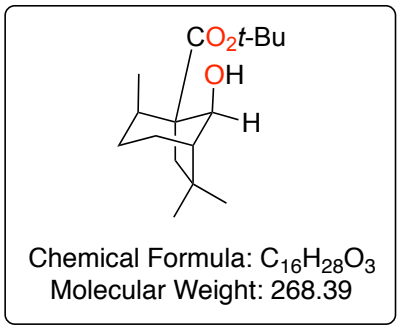
Temperature: 25 degres
Mobile phase: Heptane/Ethanol (80/20), 1 mL/min



Signal: DAD1 A, Sig=205,4 Ref=off

RT [min]	Area	Area%	Capacity Factor	Enantioselectivity	Resolution (USP)
7.96	335	14.15	1.70		
8.61	2031	85.85	1.92	1.13	1.98
Sum	2366	100.00			

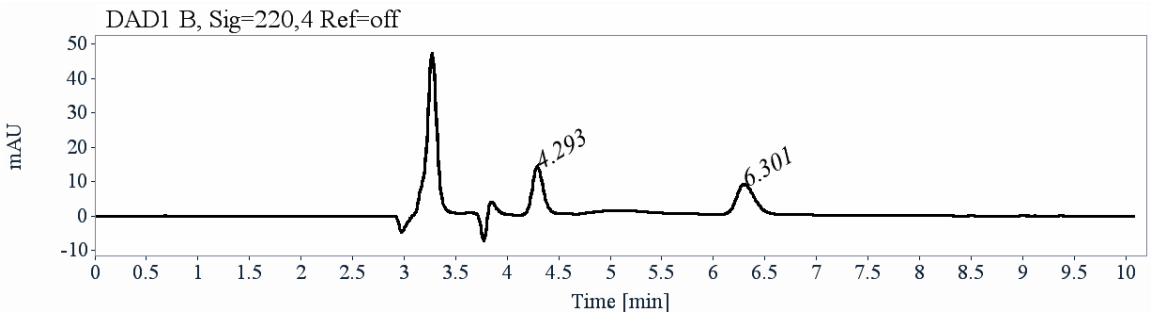
Product **8a**: (under two distinct sets of conditions with opposite elution orders of the enantiomers)



Chemical Formula: $C_{16}H_{28}O_3$
Molecular Weight: 268.39

Sample name: RYJ030193 crystal batch4
Column: Chiralpak AZ-H

Temperature: 25 degres
Mobile phase: Heptane/Ethanol (80/20), 1 mL/min

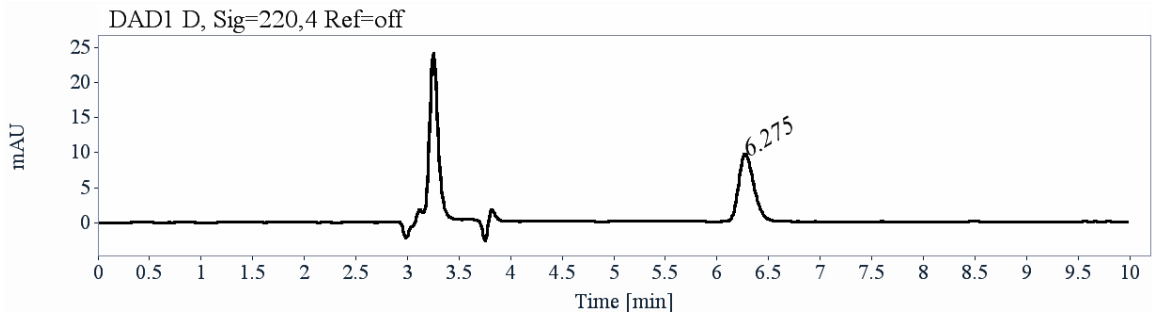


Signal: DAD1 B, Sig=220,4 Ref=off

RT [min]	Area	Area%	Capacity Factor	Enantioselectivity	Resolution (USP)
4.29	105	48.77	0.46		
6.30	110	51.23	1.14	2.50	7.73
Sum	215	100.00			

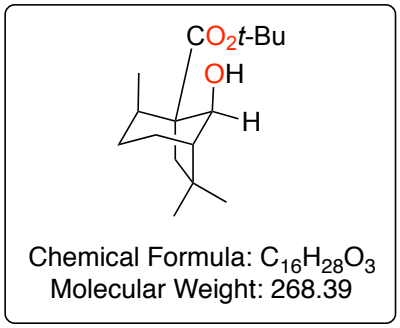
Sample name: RYJ030193-crystal
Column: Chiralpak AZ-H

Temperature: 25 degres
Mobile phase: Heptane/Ethanol (80/20), 1 mL/min



Signal: DAD1 D, Sig=220,4 Ref=off

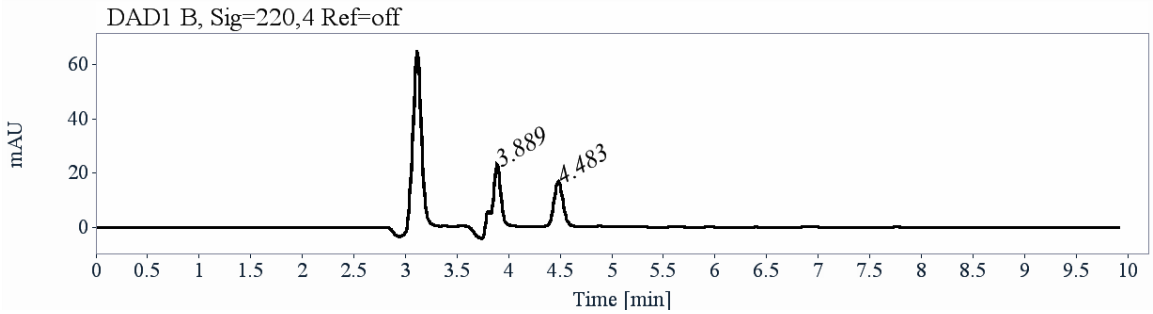
RT [min]	Area	Area%	Capacity Factor	Enantioselectivity	Resolution (USP)
6.27	99	100.00	1.13		
Sum	99	100.00			



Chemical Formula: $C_{16}H_{28}O_3$
Molecular Weight: 268.39

Sample name: RYJ030193 crystal batch4
Column: Lux-Amylose-2

Temperature: 25 degres
Mobile phase: Heptane/Ethanol (80/20), 1 mL/min

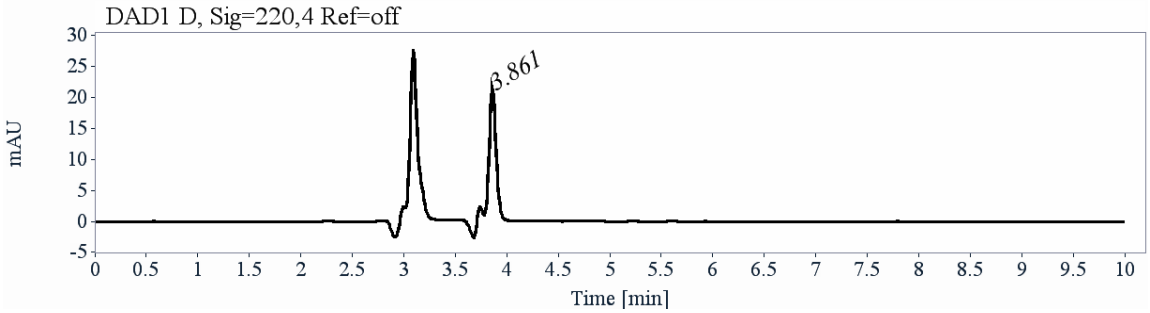


Signal: DAD1 B, Sig=220,4 Ref=off

RT [min]	Area	Area%	Capacity Factor	Enantioselectivity	Resolution (USP)
3.89	78	42.51	0.32		
4.48	105	57.49	0.52	1.63	4.43
Sum	183	100.00			

Sample name: RYJ030193-crystal
Column: Lux-Amylose-2

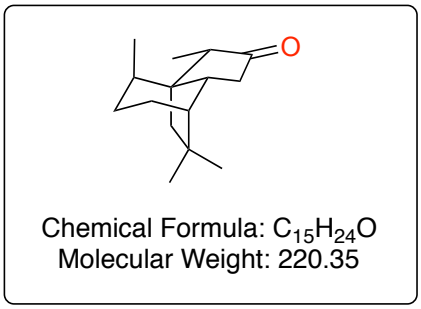
Temperature: 25 degres
Mobile phase: Heptane/Ethanol (80/20), 1 mL/min



Signal: DAD1 D, Sig=220,4 Ref=off

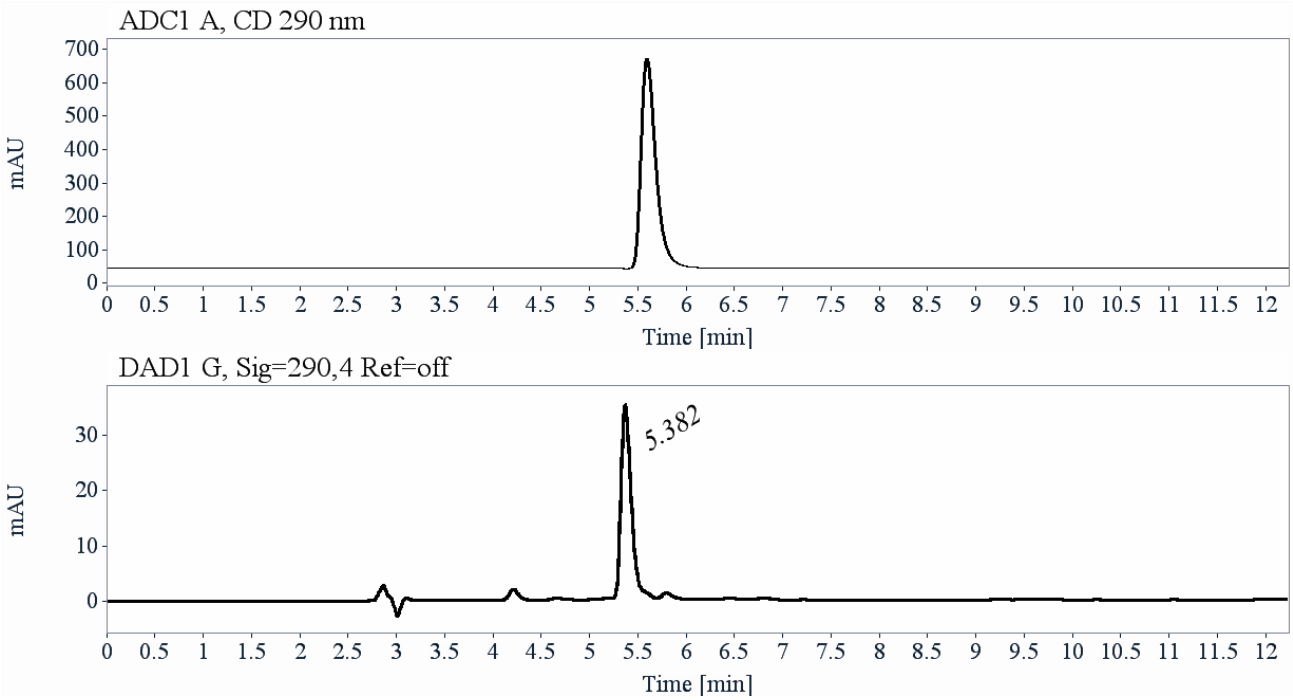
RT [min]	Area	Area%	Capacity Factor	Enantioselectivity	Resolution (USP)
3.86	93	100.00	0.31		
Sum	93	100.00			

Product **1**:



Sample name: RYJ04068-Fr2
Column: Lux-Cellulose-2

Temperature: 25 degres
Mobile phase: Heptane/isopropanol (95/5), 1 mL/min



Signal: DAD1 G, Sig=290,4 Ref=off

RT [min]	Area	Area%	Capacity Factor	Enantioselectivity	Resolution (USP)
5.38	263	100.00	0.82		
Sum	263	100.00			

Data file: C:\CHEM32\1\DATA\COQUEREL\RYJ030178\11-09-2015\RYJ04068-FR2_LC2_1.D
Injection date: 9/16/2015 9:25:39 AM
Injection volume: 20.000
Acq. method: I-5-CD290NM.M
Analysis method: I-5-CD290NM.M
Last changed: 10/19/2015 10:10:28 AM
Location: Vial 51
Column void time (min) 2.950

5. X-ray diffraction analysis of 8a

A suitable crystal of compound **8a** was measured on a Rigaku Oxford Diffraction SuperNova diffractometer at 223 K at the CuKα radiation (λ = 1.54184 Å, Table S1). Data collection reduction and multiscan ABSPACK correction were performed with CrysAlisPro (Rigaku Oxford Diffraction). The structure was solved by direct methods with SHELXS and SHELXL was used for full matrix least squares refinement.[7] All H-atoms were found experimentally and their coordinates and Uiso parameters were constraint to 1.5Ueq(parent atoms) for the methyls and the hydroxyle and to 1.2Ueq(parent atom) for the other carbons (Figure S1).
The absolute configuration was unambiguously determined and confirmed by the Flack parameter value equal to 0.05(6) calculated on 1146 quotients. The choice for the enantiomer was also confirmed by the Hooft analysis (y = 0.05(7), P2/3(true) = 1., P3(false) = 0.2*10-43)[8] as well as by the Bijvoet average and difference plots (Figure S2).[9]

Table S1. Crystallographic data for compound **8a**

Compound	**8a**
Formula	$C_{16}H_{28}O_3$
Mw	268.38
Crystal system	orthorhombic
Measurement temperature/ K	223
Space group	P $2_12_12_1$
a/ Å	6.67202(7)
b/ Å	12.80551(14)
c/ Å	18.3291(2)
V/ $Å^3$	1566.02(3)
Z	4
Dc/g.cm^{-3}	1.138
Crystal colour	colorless
Crystal size/mm^3	0.22*0.2*0.08
μ(Mo-Kα)/mm^{-1}	0.605
N° of refl. measured	5568
N° of unique refl.	2867
N° of observed refl.[$F^2 > 4\sigma F^2$]	2805
N° parameters refined	179
R_1 [$F^2>4\sigma F^2$]	0.0338
wR_1 [$F^2>4\sigma F^2$]	0.0889[a]
R_2 [all refl.]	0.0345
wR_2 [all refl.]	0.0899
Goodness of fit [all refl.]	1.031
Residual Fourier/e. $Å^{-3}$	-0.155; 0.191
Flack; n° quotients	0.05(6); 1146

[a] w=1/[s2(Fo2)+(0.0632P)2+0.1045P] where P=(Fo2+2Fc2)/3

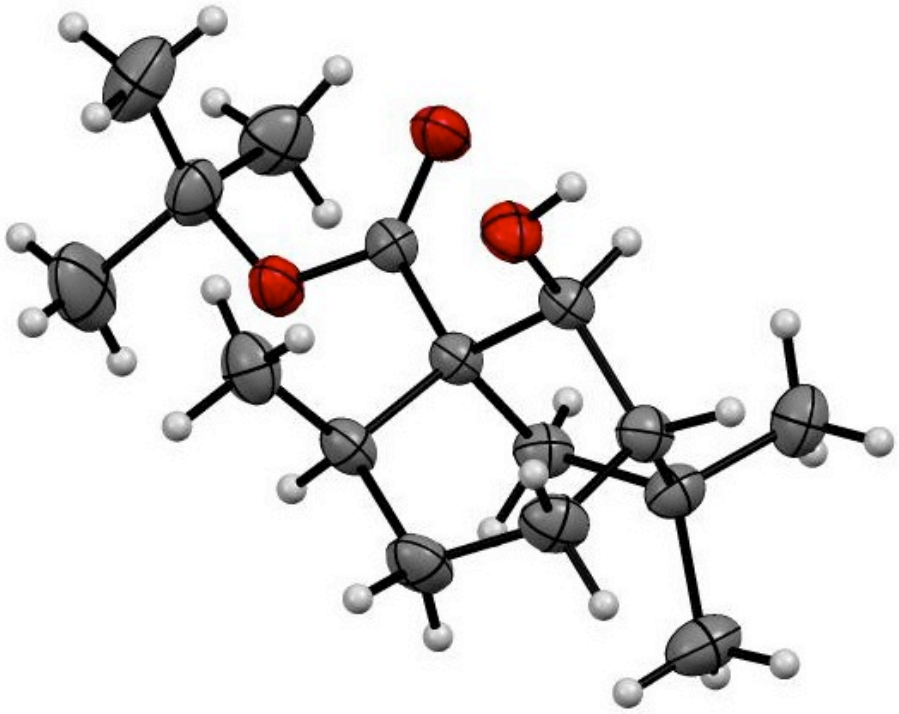
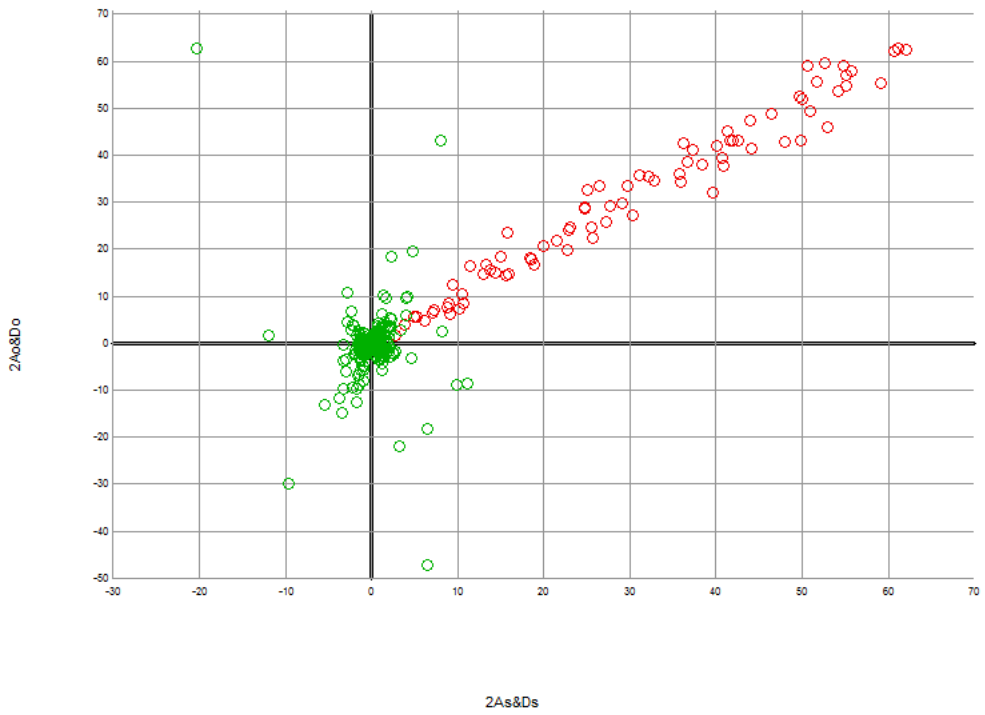


Figure S1. Representation of **8a** obtained by X-ray diffraction analysis. Ellipsoids are drawn at 50% probability level and hydrogen atoms are represented as fixed-size spheres of radius 0.15 Å. CCDC 1449766 contains the supplementary crystallographic data (CIF) for compound **8a**, available free of charge from the Cambridge Crystallographic Data Center.

a)



b)

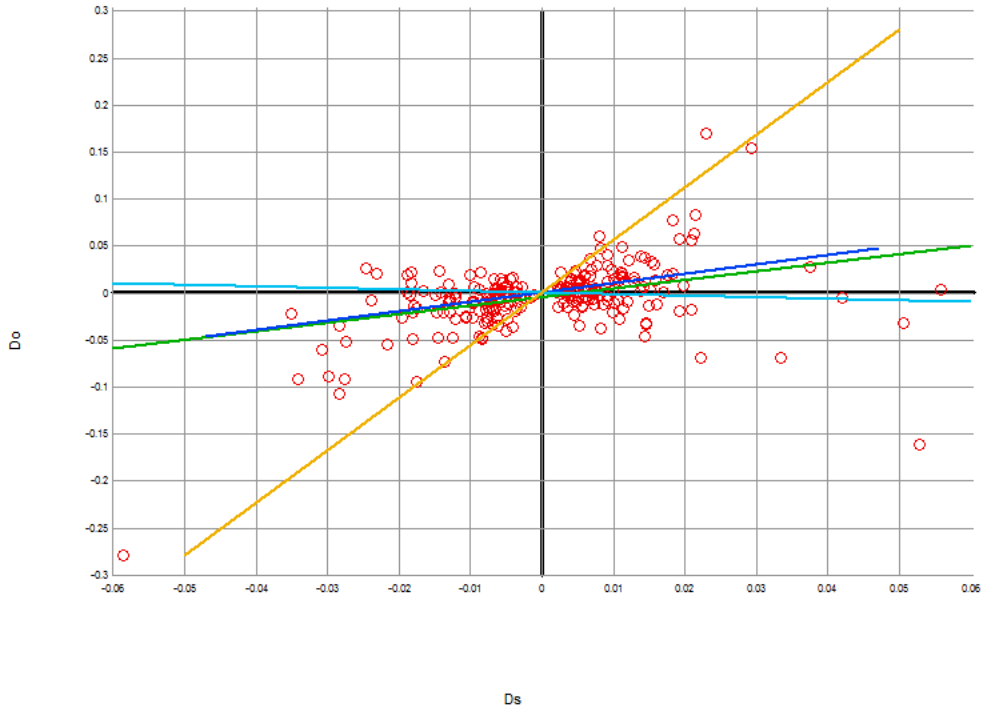


Figure S2. Bijvoet average and difference plots for the 231 most significant reflections. **a)** 2AD plot. The 2Ao/As (red) and Do/Ds (green) points lie on the same unit slope line. **b)** Anomalous difference plot. The best fitting line (green) for experimental difference Do points (red circles) fits the unit slope line (blue).

6. Chiroptical studies of synthetic (1*R*)-suberosanone (1)

Optical rotation dispersion (ORD)

Table S2. Optical rotation dispersion of synthetic (1*R*)-suberosanone **1** and calculated values. Measurements were performed in double-jacketed 10 cm cell at 25°C.

λ (nm)	$[\alpha]_{\lambda}^{25}$ ($CHCl_3$, c = 0.1)	$[\alpha]_{\lambda}^{25}$ (ethanol, c = 0.1)	Calculated $[\alpha]_{\lambda}$ by Stephens et al.[10]
589	+ 20	+ 11	- 20.6
578	+ 21	+ 12	- 20.1
546	+ 32	+ 16	- 17.6
436	+ 126	+ 95	+ 35.0
365	+ 457	+ 379	+ 300.9

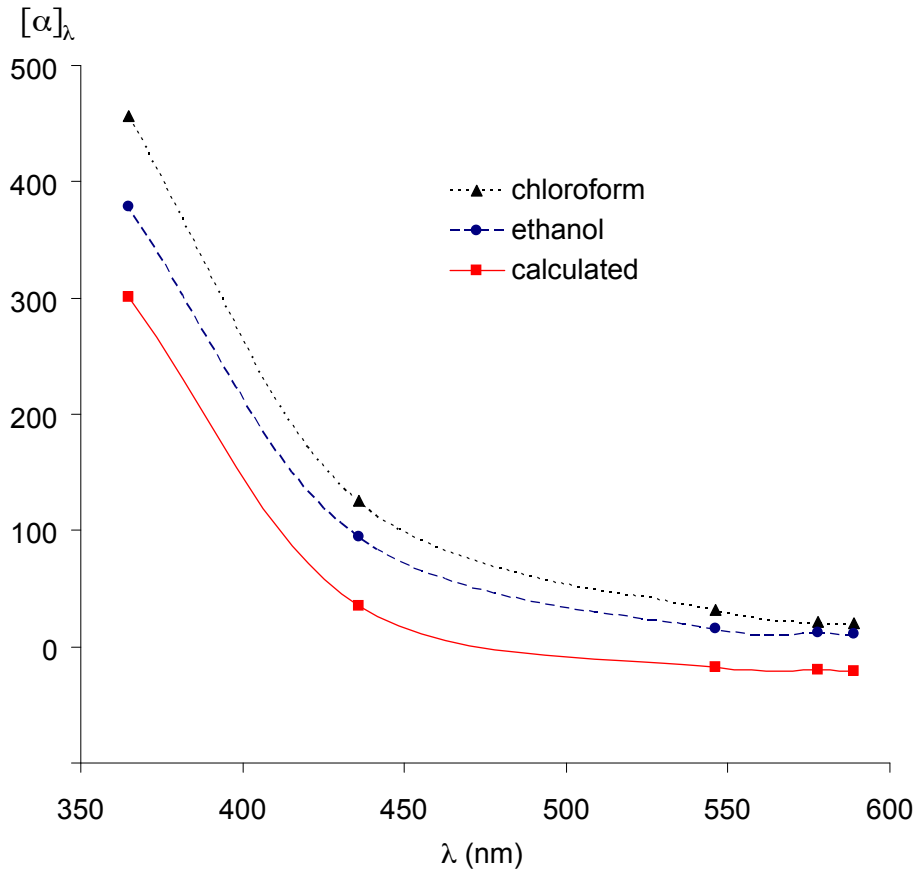


Figure S3. Optical rotation dispersion of synthetic (1*R*)-suberosanone **1** and predicted values.

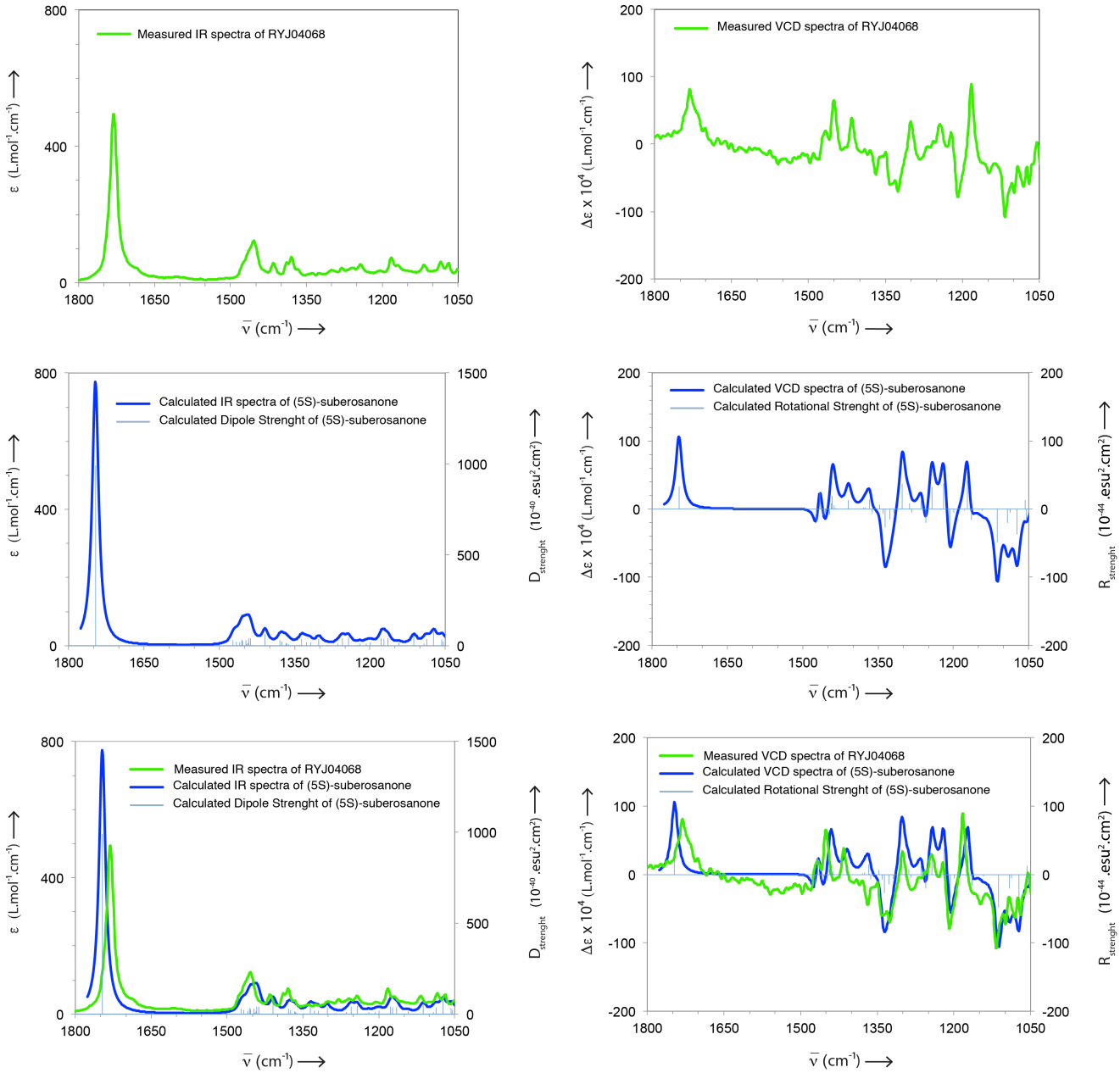
Vibrational circular dichroism (VCD) and electronic circular dichroism (ECD) measurements

Infrared (IR) and vibrational circular dichroism (VCD) spectra were recorded on a Bruker PMA 50 accessory coupled to a Vertex70 Fourier transform infrared spectrometer. A photoelastic modulator (Hinds PEM 90) set at l/4 retardation was used to modulate the handedness of the circular polarized light at 50 kHz. Demodulation was performed by a lock-in amplifier (SR830 DSP). An optical low-pass filter (< 1800 cm^{-1}) before the photoelastic modulator was used to enhance the signal/noise ratio. A transmission cell equipped with BaF_2 windows and of 200 μm of optical pathlength was used. Solutions with a concentration of 0.1 mol L^{-1} were prepared by dissolving the solid samples in CD_2Cl_2. The VCD spectra of the pure enantiomer (1*R*)-suberosanone (**1**) was measured at room temperature and the baseline of the spectra was corrected by subtraction of the spectra of the solvent. For each individual spectrum, about 48000 scans were averaged at 4 cm^{-1} resolution (corresponding to twelves hours measurement time). For IR absorption spectra, the cell filled with CD_2Cl_2 served as a reference. The spectra are presented without smoothing and further data processing.

ECD spectra were measured on a JASCO J-815 spectrometer equipped with a JASCO Peltier cell holder PTC-423 to maintain the temperature at 20.0 ± 0.2 °C. A quartz cell of 2 mm of optical path length was used. Solutions with a concentration of 6 x 10^{-3} mol L^{-1} were prepared in n-hexane (HPLC grade). The CD spectrometer was purged with nitrogen during the recording of spectra. The UV absorption and ECD spectra were recorded using n-hexane as a reference and are presented without smoothing and further data processing.

Theoretical calculations

Calculations were performed on the *(*1*R)*-suberosanone enantiomer (**1**). The conformational study was done using a systematic exploration of the potential energy surface (PES) using density functional theory (DFT) level. Two conformations were found. The geometry optimizations, vibrational frequencies, IR absorption and VCD intensities were calculated with Density Functional Theory (DFT) using CAM-B3LYP functional combined with DGTZVP basis set. Average solvent effects were introduced using the SMD solvation model. Computed harmonic frequencies are generally larger than those experimentally observed. They have been calibrated using a scaling factor of 0.96. IR absorption and VCD spectra were constructed from calculated dipole and rotational strengths assuming Lorentzian band shape with a half-width at half maximum of 8 cm^{-1}. Based on CAM-B3LYP/DGTZVP optimized geometries, the ECD and UV spectra were calculated using time dependent density functional theory (TD-DFT) with CAM-B3LYP functional and AUG-cc-pVDZ basis set. Calculations were performed for vertical 1A singlet excitation using 50 states. For a comparison between theoretical results and the experimental values, the calculated UV and ECD spectra have been modeled with a Gaussian function, using a half-width of 0.3 eV. Several combination of funtionnal and basis set were used to calculate VCD and ECD spectra in order to check the reliability of the calculations. All are similar and converge to the same absolute configuration: (+)-(1*R*)-suberosanone. However, only SMD/CAM-B3LYP/DGTZVP for VCD and CAM-B3LYP/AUG-cc-pVDZ are given in Figures S4 and S5. All calculations were performed using Gaussian 09 package.[11]



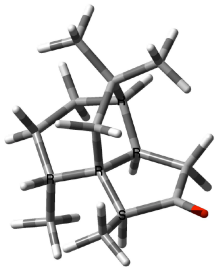


Figure S4. Experimental and theoretical VCD spectra of (1*R*)-suberosanone **1** (above denominated RYJ04068 or (5S)-suberosanone)

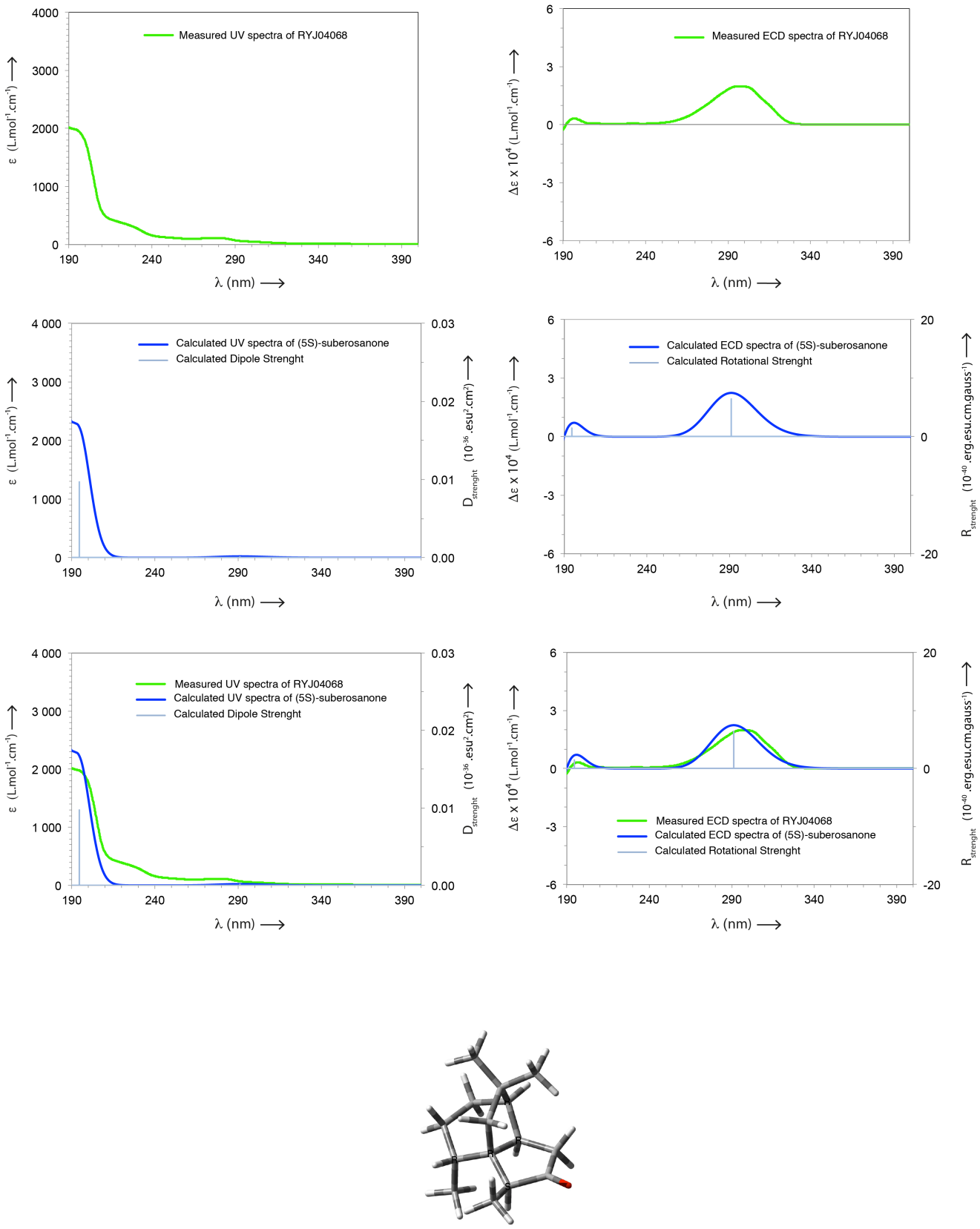


Figure S5. Experimental and theoretical ECD spectra of (1*R*)-suberosanone **1** (above denominated RYJ04068 or (5S)-suberosanone)

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