Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

Angew. Chem.

Enantioselective Total Synthesis of Sceptrin and Ageliferin by Programmed Oxaquadracyclane Fragmentation

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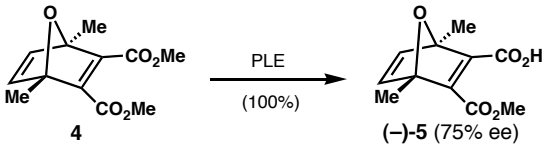
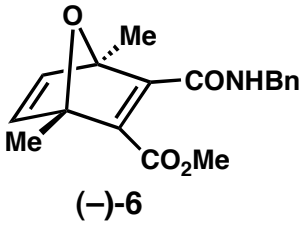
General Procedures. All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, acetonitrile (CH_3CN), dimethylformamide, methanol, diethyl ether (Et_2O) and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and either an ethanolic solution of phosphomolybdic acid and cerium sulfate or vanillin in ethanol/aqueous H_2SO_4, and heat as developing agents. NMR spectra were recorded on either Bruker AMX-400 or Varian Inova-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, quin = quintuplet, sext = sextet, sep = septet, b = broad, bs = broad singlet. IR spectra were recorded on a Perkin-Elmer 1600 series or a Perkin-Elmer Spectrum BX FT-IR spectrometer. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on an API 100 Perkin Elmer SCIEX single quadrupole mass spectrometer at 4000V emitter voltage. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer using ESI. Melting points (m.p.) are uncorrected and were recorded on a Fisher-Johns 12-144 melting point apparatus. Circular dichroism measurements were obtained on an AVIV model 62DS spectrophotometer.



4 **(–)-5** (75% ee)

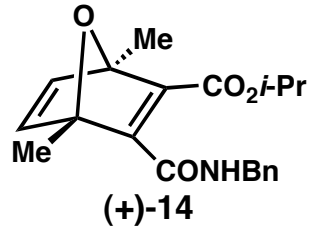
Monoacid 5: To a solution of the Diels-Alder adduct **4** (6.0 g, 25.2 mmol) in acetone (80 mL) and phosphate buffer (0.1 M, pH= 8.0, 400 mL) was added pig liver esterase (350 μL, 1250

units). The solution was stirred at 23 °C for 7 days, then the pH of the solution was adjusted to 2 by adding 2N HCl. The yellow solution was extracted with ethyl acetate (2 × 500 mL). The organic layers were combined and dried over $MgSO_4$. The solvent was removed *in vacuo* and the monoacid **5** was obtained as light yellow oil (5.65g, quantitative, 75% ee). The ee value was determined by converting **5** to the corresponding chiral amide with (S)-α-methylbenzylamine, (see spectra below). **5:** R_f = 0.12 (SiO_2, 3:1 CH_2Cl_2: MeOH); $[\alpha]_D$ = – 42° (c = 1.2, $CHCl_3$); IR (film) ν_{max} 2360, 1700, 1291, 1156 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J* = 5.2 Hz, 1H), 6.87 (d, *J* = 5.2 Hz, 1H), 3.93 (s, 3H), 1.86 (s, 3H), 1.82 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 163.2, 160.9, 154.9, 147.4, 146.5, 92.6, 91.5, 53.5, 16.1, 15.7; HRMS (ESI-TOF) calcd. for $C_{11}H_{12}O_5Na$ [M + Na^+] 247.0577, found 247.0586.



(–)-6

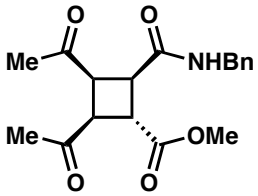
Methyl benzylamide 6: Monoacid **5** (5.65 g, 25.2 mmol) was dissolved in THF (90 mL). To the resulting solution was added benzylamine (2.84 g, 26.46 mmol) and DMT-MM (7.32 g, 26.46 mmol). The solution was stirred for 3 hours, then concentrated to dryness. The residue was dissolved in ethyl acetate and washed with 2N HCl (2 x 125 mL). The organic layer was dried (Na_2SO_4) and evaporated to give **6**. The crude product was routinely carried on to the next step but an analytically pure sample could be obtained by column chromatography (SiO_2, hexanes: EtOAc = 2:1) to afford **6** as light yellow oil (7.26 g, 92%), which solidified upon standing. **6:** R_f = 0.23 (SiO_2, 2:1 hexanes: EtOAc); $[\alpha]_D$ = – 80° (c = 1.8, $CHCl_3$); IR (film) ν_{max} 3312, 1712, 1624, 1533, 1299, 1266, 1156, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (bs, 1H), 7.35-7.27 (m, 5H), 7.02 (d, *J* = 5.2 Hz, 1H), 6.87 (d, *J* = 5.2 Hz, 1H), 4.52 (d, *J* = 5.6 Hz, 2H), 3.69 (s, 3H), 1.83 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 163.1, 161.3, 148.9, 147.0, 145.9, 137.7, 128.6, 127.7, 127.5, 92.8, 91.6, 52.2, 43.4, 15.9, 15.4; HRMS (ESI-TOF) calcd. for $C_{18}H_{19}NO_4Na$ [M + Na^+] 336.1206, found 336.1200.



(+)-14

***i*-Propyl benzylamide 14:** Monoacid **5** (7 g, 31.2 mmol) was dissolved in *i*-PrOH (70 mL). To the resulting solution was added DMAP (0.19 g, 0.16 mmol) and DMT-MM (9.07 g, 32.76 mmol). The solution was stirred for 3 hours at 50 °C, was then concentrated to dryness and redissolved in ethyl acetate. The solution was washed with 2N HCl (2 x 125 mL). The organic layer was dried (Na_2SO_4) and evaporated to give the crude

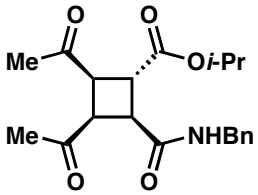
diester product. Without further purification, the yellow oil (7.9 g) was dissolved in THF/H_2O (1:1, 300 mL), LiOH (0.79 g, 34.3 mmol) was added to the above solution and the resulting solution was stirred at room temperature and monitored by TLC analysis. After two hours, additional LiOH (0.1 g) was added to the reaction mixture. When all the starting material was completely consumed, the reaction was immediately quenched with 2N HCl (200 mL) The mixture was extracted with EtOAc (2 × 250 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting oil was used for the next step without further purification. The yellow oil was dissolved in THF (100 mL) and benzylamine (3.33 g, 32.12 mmol) was added. The mixture was stirred for 5 min before DMT-MM (8.89 g, 32.12 mmol) was added. The resulting white suspension was stirred at room temperature for 3 h until TLC analysis indicated that the reaction was complete. The solvent was removed and the residue was dissolved in EtOAc and washed with 2N HCl (200 mL × 2). The organic layer was dried over $MgSO_4$ and concentrated to give a yellow solid. The crude product was routinely carried on to the next step but an analytically pure sample could be obtained by column chromatography (SiO_2, hexanes: EtOAc = 3:1) to give the product as a light yellow solid (8.52 g, 80% over three steps). **14**: m.p. = 75-77 °C (hexanes); R_f = 0.33 (SiO_2, 2:1 hexanes: EtOAc); $[\alpha]_D$ = + 90° (c = 2.0, $CHCl_3$); IR (film) ν_{max} 3297, 1706, 1618, 1540, 1382, 1273, 1107, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (bs, 1H), 7.33-7.28 (m, 5H), 7.02 (d, *J* = 5.2 Hz, 1H), 6.86 (d, *J* = 5.2 Hz, 1H), 5.08 (sep, 1H), 4.52 (ABX, *J* = 14.8 Hz, *J* = 6 Hz, υ_{AB} = 20.4 Hz, 2H), 1.84 (s, 3H), 1.80 (s, 3H), 1.26, (d, *J* = 6.4 Hz, 3H), 1.21 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 163.4, 160.7, 150.0, 147.2, 146.1, 138.0, 128.8, 127.9, 127.6, 92.9, 91.7, 69.8, 43.6, 21.8 (2 C), 16.2 , 15.7; HRMS (ESI-TOF) calcd. for $C_{20}H_{24}NO_4$ [M + H^+] 342.1700, found 342.1703.



(–)-10 (75% ee)

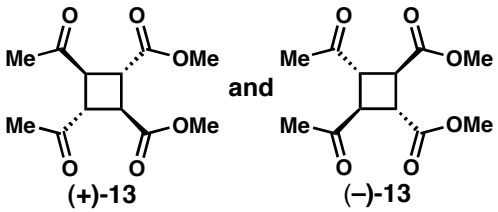
Cyclobutane 10: Compound **6** (6 × 1g, 19.2 mmol) was dissolved in dry THF (6 × 100 mL) and degassed with bubbling N_2 for 30 min. The solution was subject to UV light irradiation (450 W Havovia lamp, pyrex filter) in 6 sealed pyrex tubes (120 mL) until the photocycloaddition was complete, as determined by ^1H NMR (approx. 72 h). The solvent was removed and the yellow oil (6 g) was redissolved in THF/MeOH (1:1, 400 mL). Concentrated sulfuric acid (1 mL) was diluted with MeOH (15 mL) and cooled to room temperature before it was added dropwise to the reaction solution. After the addition of H_2SO_4, the solution was stirred at room temperature for 3 h before H_2O (50 mL) was added. The mixture was stirred for another hour and quenched with saturated

aqueous $NaHCO_3$ (200 mL). The mixture was extracted with DCM (2 × 500 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography. (SiO_2, hexanes: EtOAc = 4:1 to 1:1) to give **10** (3.2 g, ~50%) as white solid. **10:** 75% ee as determined by Mosher analysis (see spectra below); R_f = 0.23 (hexanes:EtOAc = 1:1); M.p. = 142-144 °C, EtOAc/hexanes; $[\alpha]_D$ = – 24° (c = 0.8, $CHCl_3$); After recrystalization in hexane/EtOAc (1:1), the ee was improved to > 95% (55% recovery). $[\alpha]_D$ = – 32.1° (c = 0.8, $CHCl_3$); IR (film) ν_{max} 3303, 1731, 1709, 1546, 1318, 1221, 1180, 755, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (m, 5H), 6.75 (br, 1H), 4.46 (d, *J* = 6 Hz, 2H), 3.89 (t, *J* = 10.4 Hz, 1H), 3.82 (t, *J* = 8.5 Hz, 1H), 3.55 (dd, *J* = 10.4 Hz, *J* = 8.5 Hz, 1H), 3.33 (dd, *J* = 10.4 Hz, *J* = 8.5 Hz, 1H), 2.31 (s, 3H), 2.05 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 206.5, 172.0, 170.8, 137.9, 128.7, 127.5, 127.4, 52.3, 47.9, 47.4, 44.2, 43.5, 40.0, 32.7, 27.0. HRMS (ESI-TOF) calcd. for $C_{18}H_{22}NO_5$ [M + H^+] 332.1498, found 332.1490.



(+)-17 (75% ee)

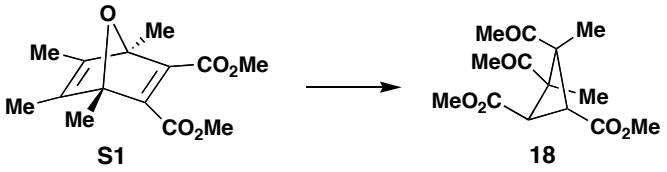
Cyclobutane 17: Following a procedure identical to that used for **10**, **17** was obtained as white solid in ~50% yield. **17:** 75% ee as determined by Mosher analysis (see spectra below); M.p. = 140-143°C, EtOAc/hexanes; R_f = 0.29 (hexanes:EtOAc = 1:1); $[\alpha]_D$ = + 33° (c = 0.9, $CHCl_3$) (after recrystalization (50% recovery) from (hexanes: EtOAc= 2:1): $[\alpha]_D$ = + 44° (c = 0.6, $CHCl_3$)); IR (film) ν_{max} 3305, 2360, 1710, 1645, 1542, 1314, 1222, 1181, 1108, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H), 6.84 (br, 1H), 4.95 (sep, 1H), 4.45 (d, *J* = 5.6 Hz, 2H), 3.90 (t, *J* = 10 Hz, 1H), 3.75 (dd, *J* = 10 Hz, *J* = 8.5 Hz, 1H), 3.57 (t, *J* = 8.5 Hz, 1H), 3.21 (dd, *J* = 10 Hz, *J* = 8.5 Hz, 1H), 2.31 (s, 3H), 2.06 (s, 3H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.12 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.5, 206.7, 171.2, 170.1, 137.9, 128.6, 127.4 (2 C), 69.3, 47.7, 47.0, 44.3, 43.4, 40.3, 33.1, 27.0, 21.6, 21.4. HRMS (ESI-TOF) calcd. for $C_{20}H_{26}NO_5$ [M + H^+] 360.1811, found 360.1800.



(+)-13 **(–)-13**

Cyclobutane 13. Compound **10** (1.4 g, 4.23 mmol) was dissolved in toluene (120 mL), then *p*-toluenesulfonic acid (2.91 g, 17 mmol) and methanol (3.4 mL, 84.6 mmol) were added. The solution was heated to 105°C in a sealed tube overnight (12 h) and then cooled to room temperature. If TLC analysis indicated that the reaction was not complete, additional TsOH (1.45 g, 8.5 mmol) and MeOH (1.8 mL, 44 mmol) were added. The solution was heated in the sealed tube at 105 °C until

the reaction was complete. The reaction mixture was diluted with EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$ and water. The organic layer was dried over $MgSO_4$ and the solvent was removed to give (-)-**13** as white solid (980 mg, 90%); $[\alpha]_D = -18°$, (c = 0.8, $CHCl_3$). The spectroscopic data were identical to those reported previously (ref **3a**). A similar procedure was followed for (+)-**17** to give (+)-**13** ($[\alpha]_D = +18°$, (c = 0.9, $CHCl_3$)) in 90% yield.



Compound 18: Oxaquadracyclane precursor **S1** [Prinzbach *et al.*, *Chimia*, *21*, **1967**, 469] (200 mg, 0.75 mmol) was dissolved in THF (35 mL) and irradiated under UV light for 24 h until ^1H NMR analysis indicated that the reaction was complete. A portion of the THF solution (10 mL) was diluted with MeOH (10 mL) and SiO_2 (150 mg) was added. The suspension was stirred for 20 min before the SiO_2 was filtered off through a pad of celite. The solvent was removed under reduced pressure and the residue was purified by column chromatography. (SiO_2, hexanes: ether = 3:1) to give **18** as colorless oil (30 mg, 49.5 %). $R_f = 0.28$ (hexanes: ether = 1:1); IR (film) ν_{max}: 1733, 1201, 1022, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.11 (d, *J* = 9.6 Hz, 1H), 3.79 (s, 3H), 3.63 (s, 3H), 3.15 (d, *J* = 9.6 Hz, 1H), 2.24 (s, 3H), 2.22 (s, 3H), 1.60 (s, 3H), 1.16 (s, 3H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2, 212.2, 171.7, 171.1, 57.5, 56.4, 52.2, 51.9, 45.2, 44.9, 29.7, 26.2, 19.6, 16.3; HRMS (ESI-TOF) calcd. for $C_{14}H_{21}O_6$ $[M + H^+]$ 285.1333, found 285.1332.

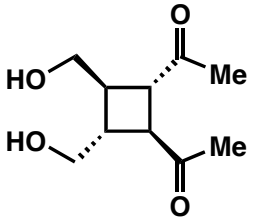
ee determination of mono acid 5

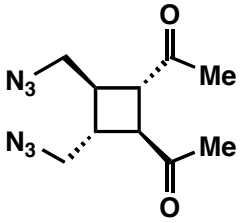
To a solution of crude monoacid **5** ((-)-**5** or racemic **5**) (25 mg, 0.11 mmol) and triethylamine (13.5 mg, 0.13 mmol) in methylene chloride (2 mL) at 0 °C was added methyl chloroformate (12 mg, 0.127 mmol). The mixture was stirred at 0 °C for 15 min, then (*S*)-α-methylbenzylamine (15 mg, 0.12 mmol) was added dropwise. The mixture was then allowed to warm to room temperature and stirred for another 20 min. The reaction was quenched with water and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and passed through a small silica plug to remove polar impurities. After the solvent was removed, a light yellow oil was obtained as the product. For the absolute configuration determination, see the X-ray analysis the salt of (-)-**5** with (*S*)-α-methylbenzylamine below.

Mosher ester analysis

The diol (2 ~ 5 mg, 0.1 ~ 0.25 mmol) was dissolved in $CDCl_3$ (0.4 mL) in a 5 mm NMR tube and anhydrous pyridine (50 μL) was added. The solution was shaken to homogeneity before Mosher acyl chloride (15 μL, 0.08 mmol) was added. The tube was shaken well before the ^1H NMR was taken.

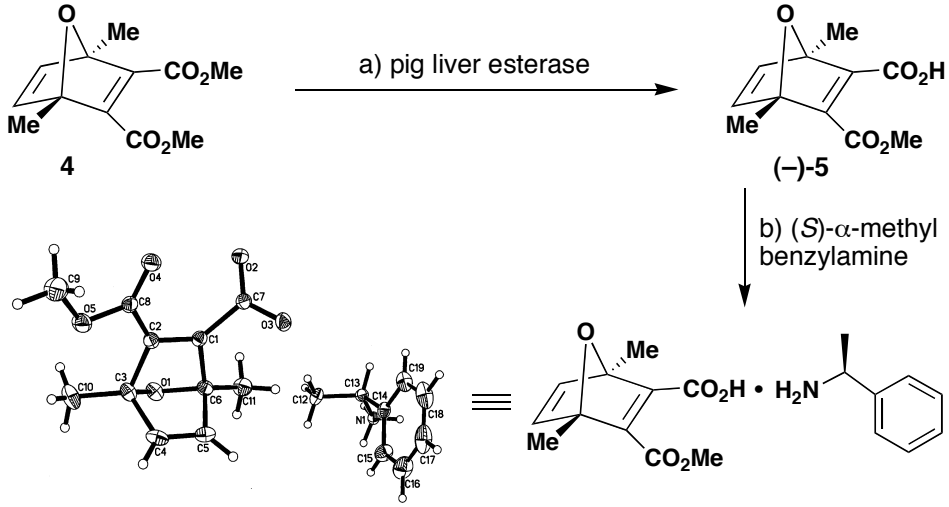
Optical rotation for advanced intermediates:

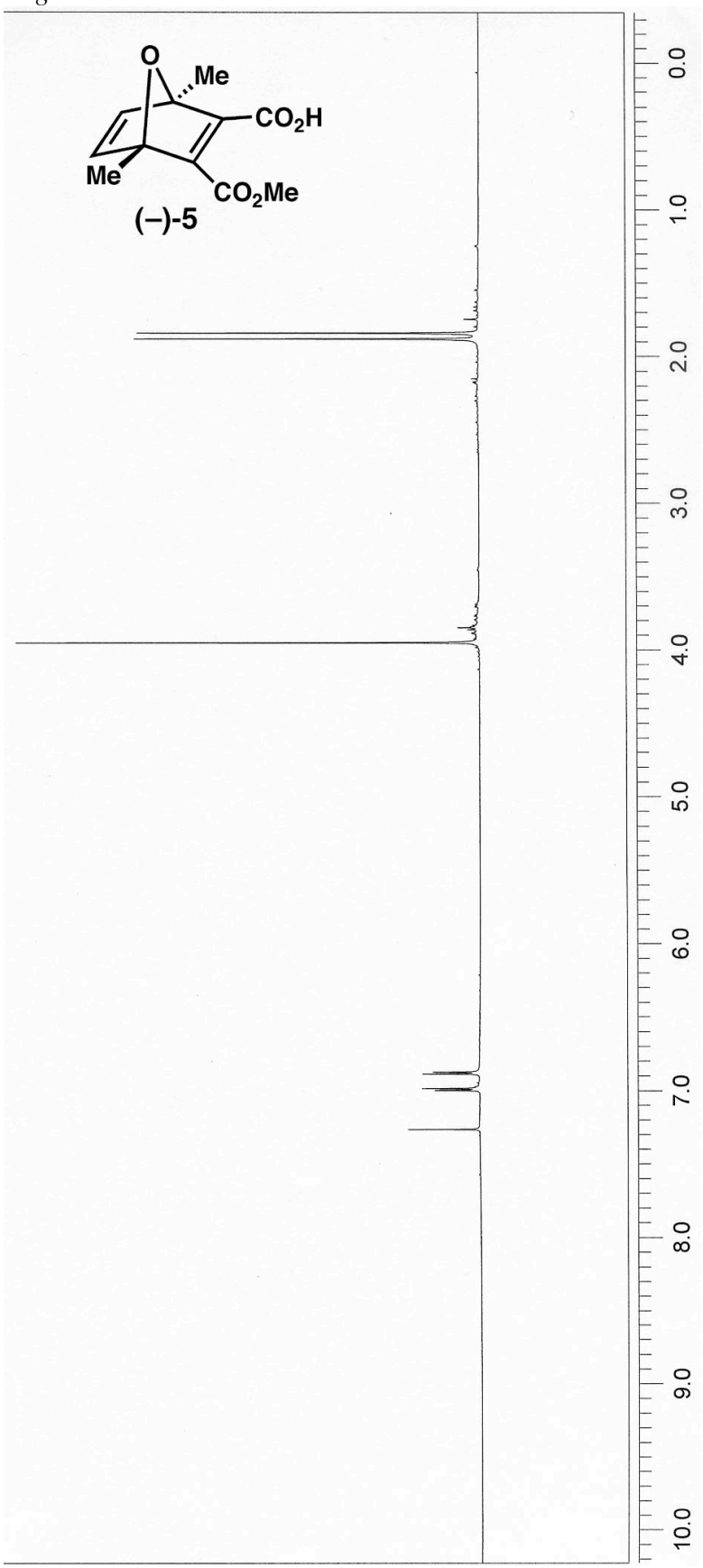




natural series: $[\alpha]_D$ = +13.2 (c 0.83, MeOH) $[\alpha]_D$ = –17.6 (c 0.63, MeOH)
unnatural series: $[\alpha]_D$ = –13.1 (c 1.0, MeOH) $[\alpha]_D$ = +16.5 (c 2.5, MeOH)

Absolute configuration determination of **5** by X-ray analysis:

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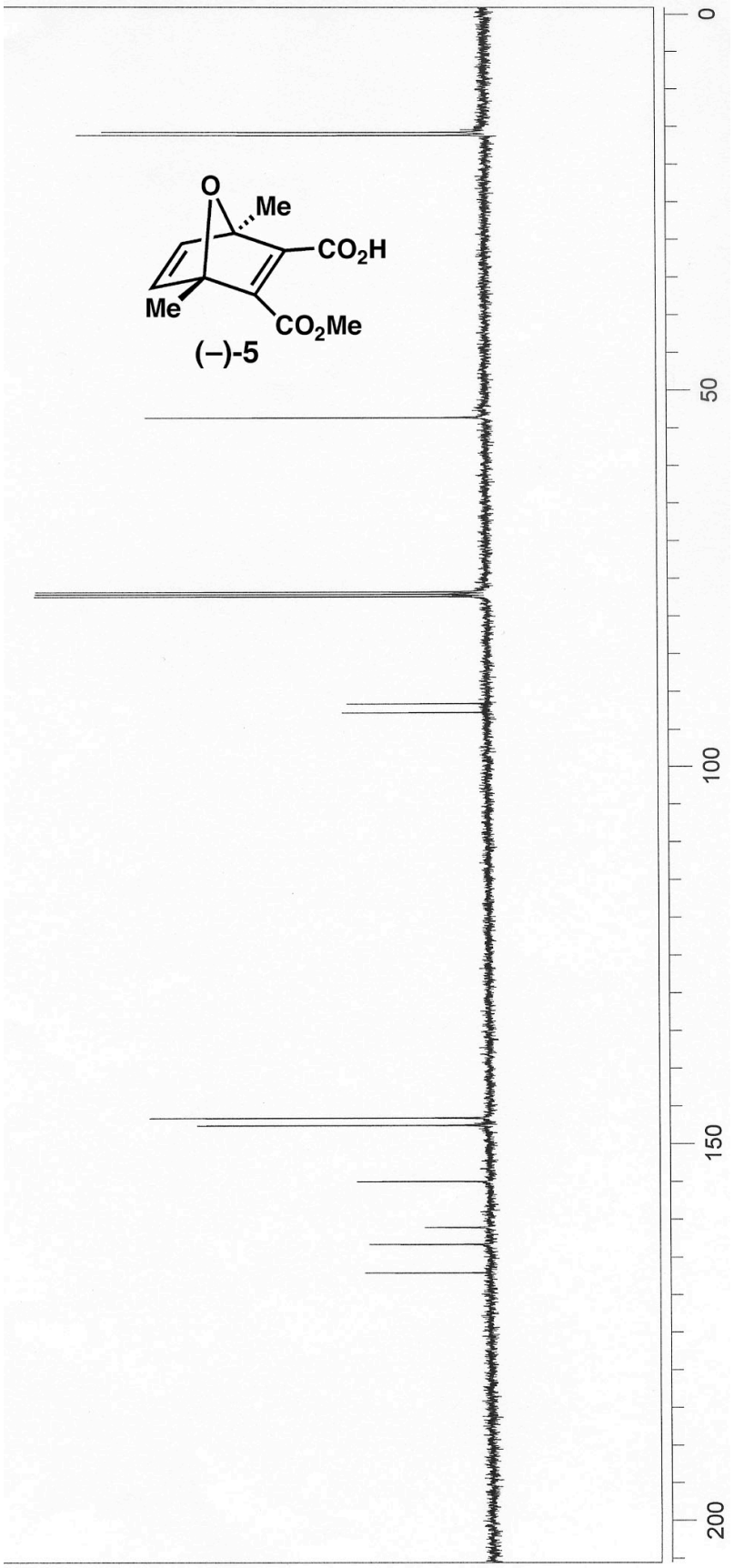
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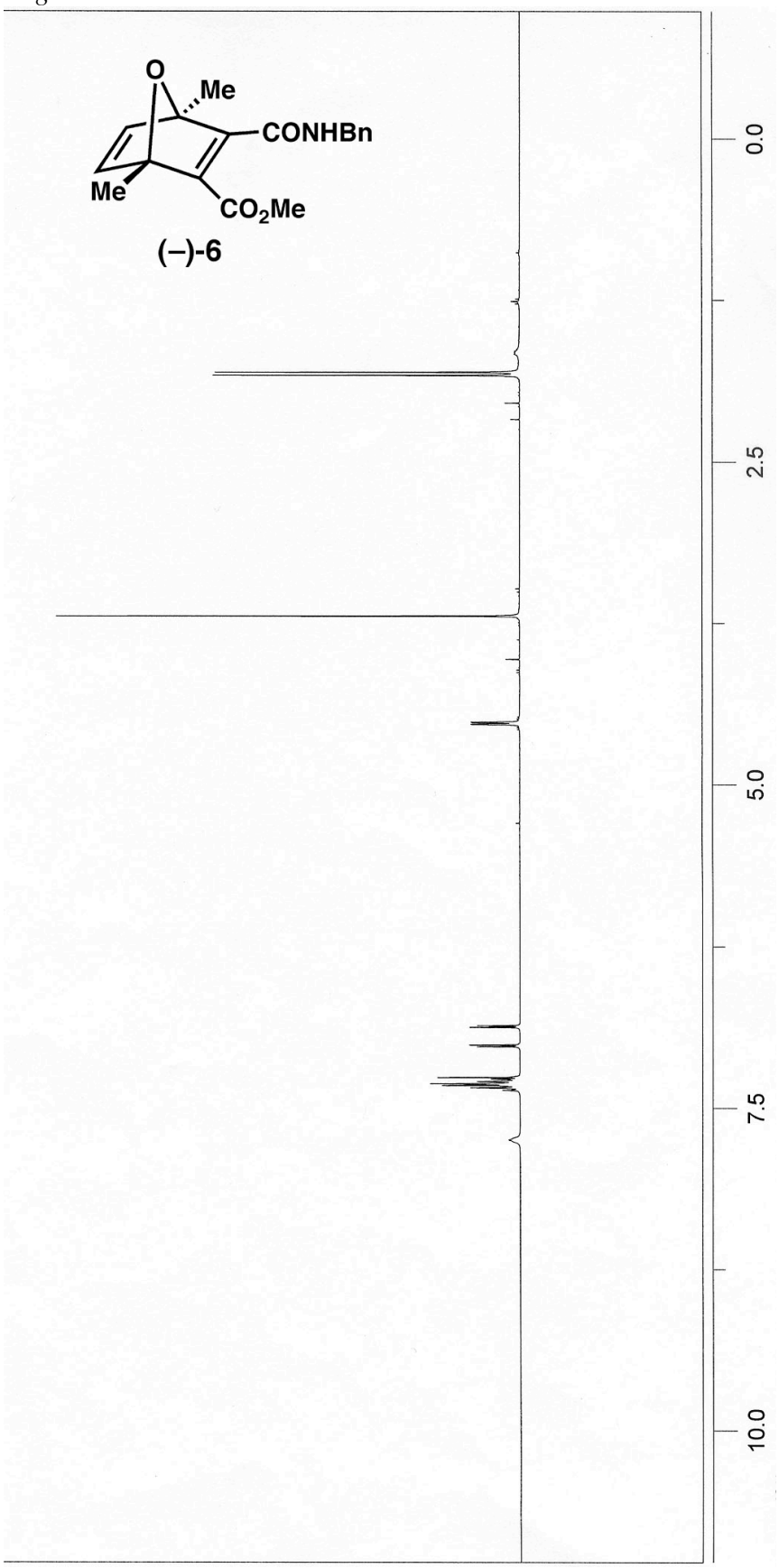
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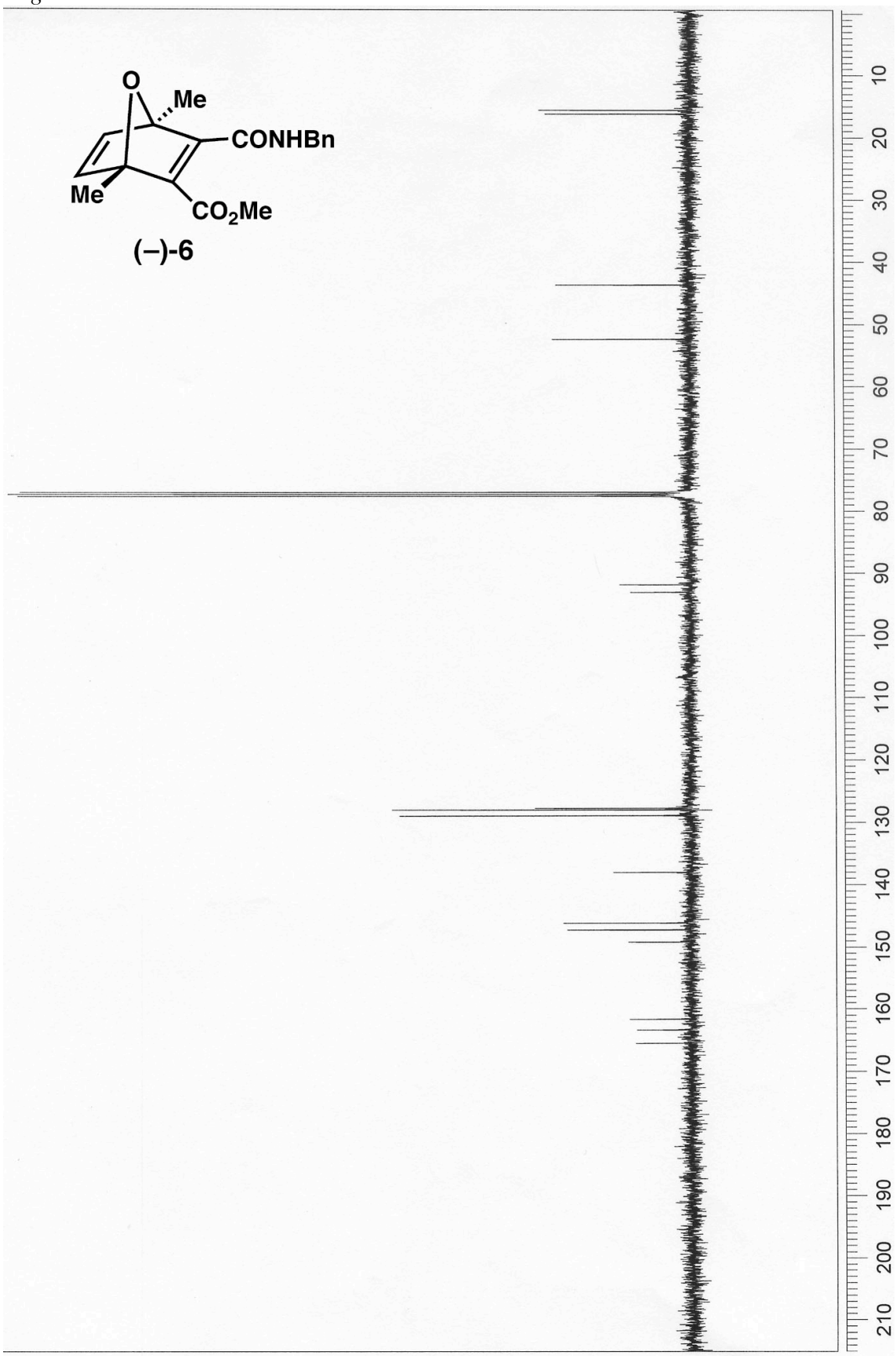
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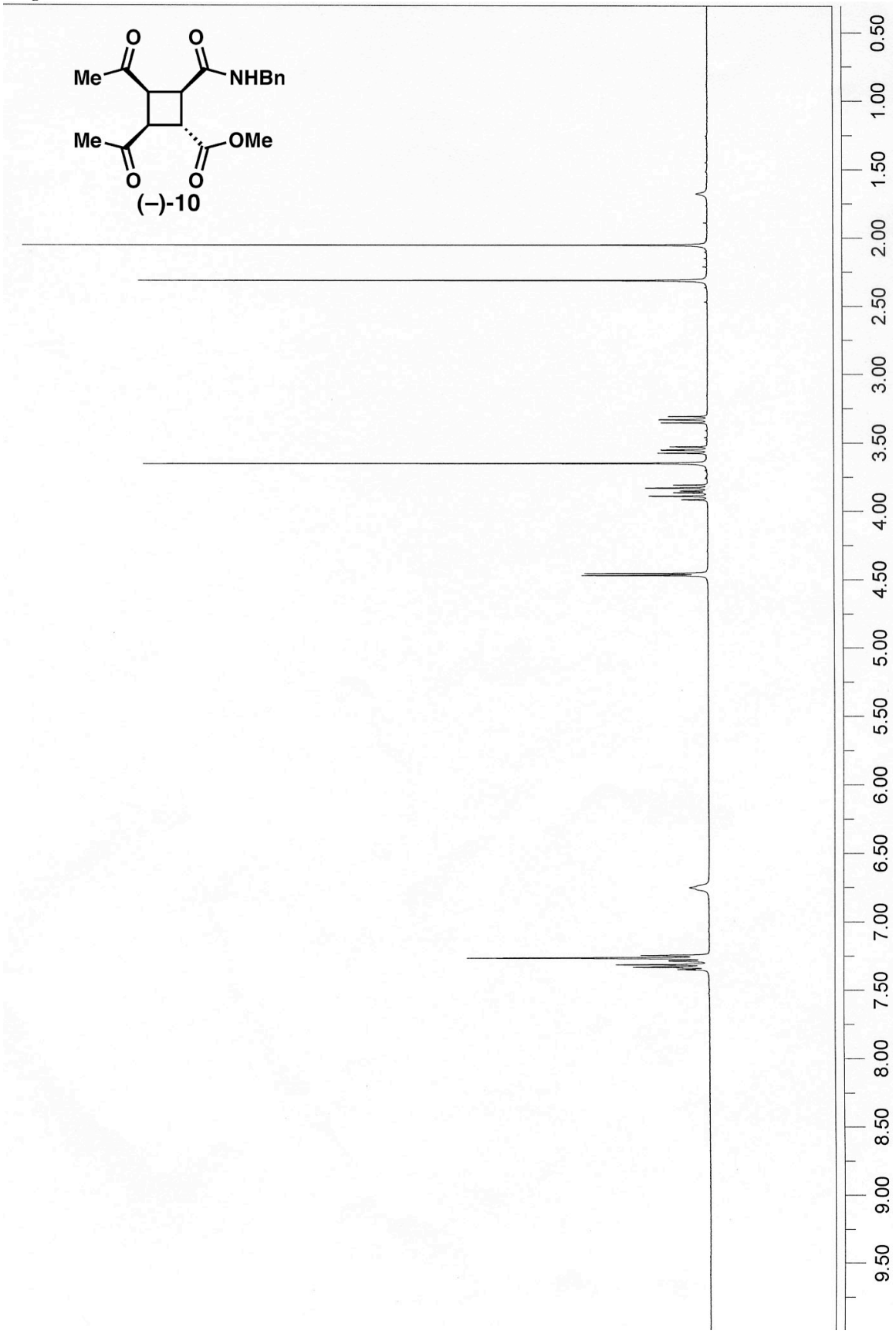
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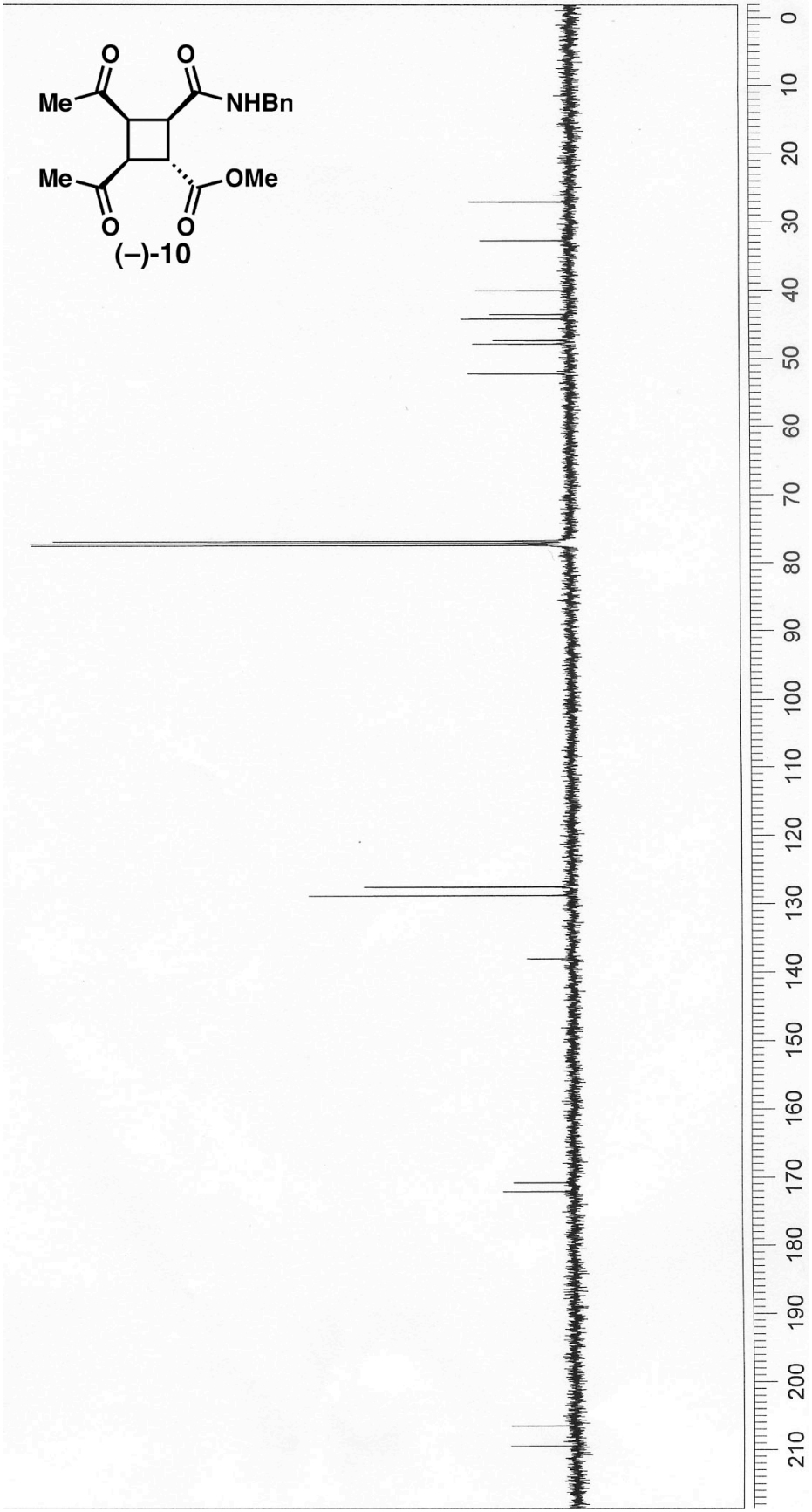
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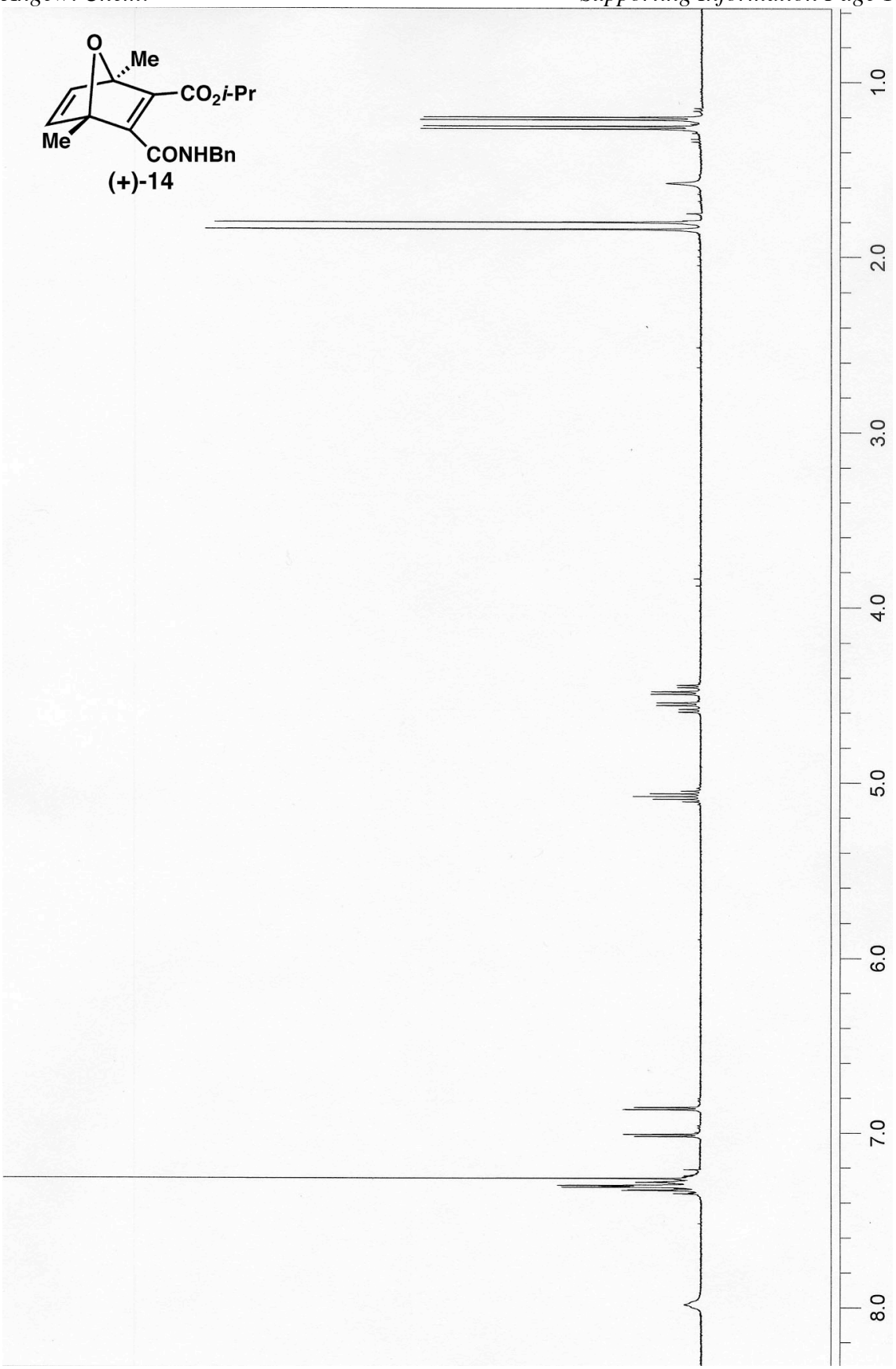
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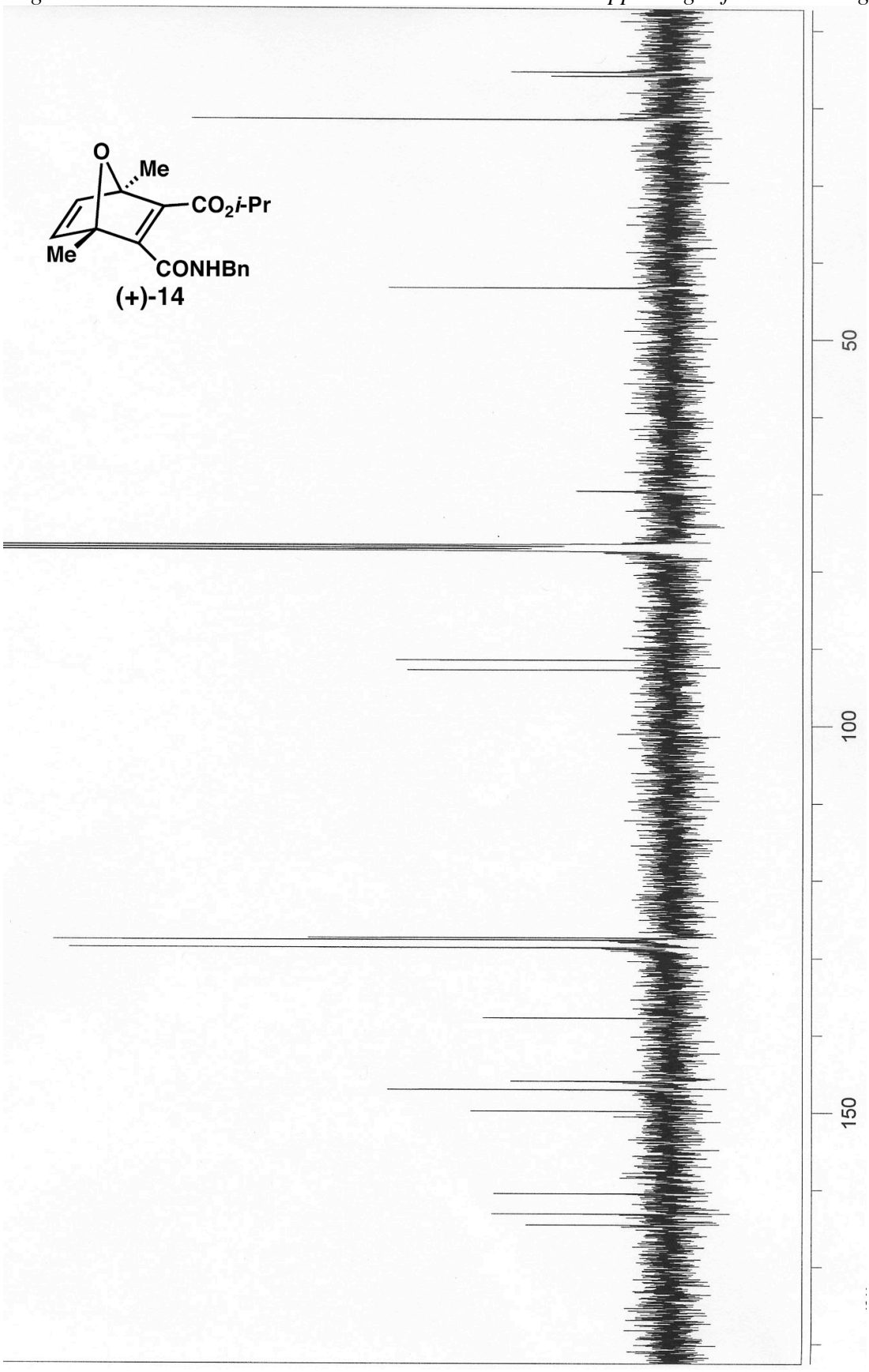
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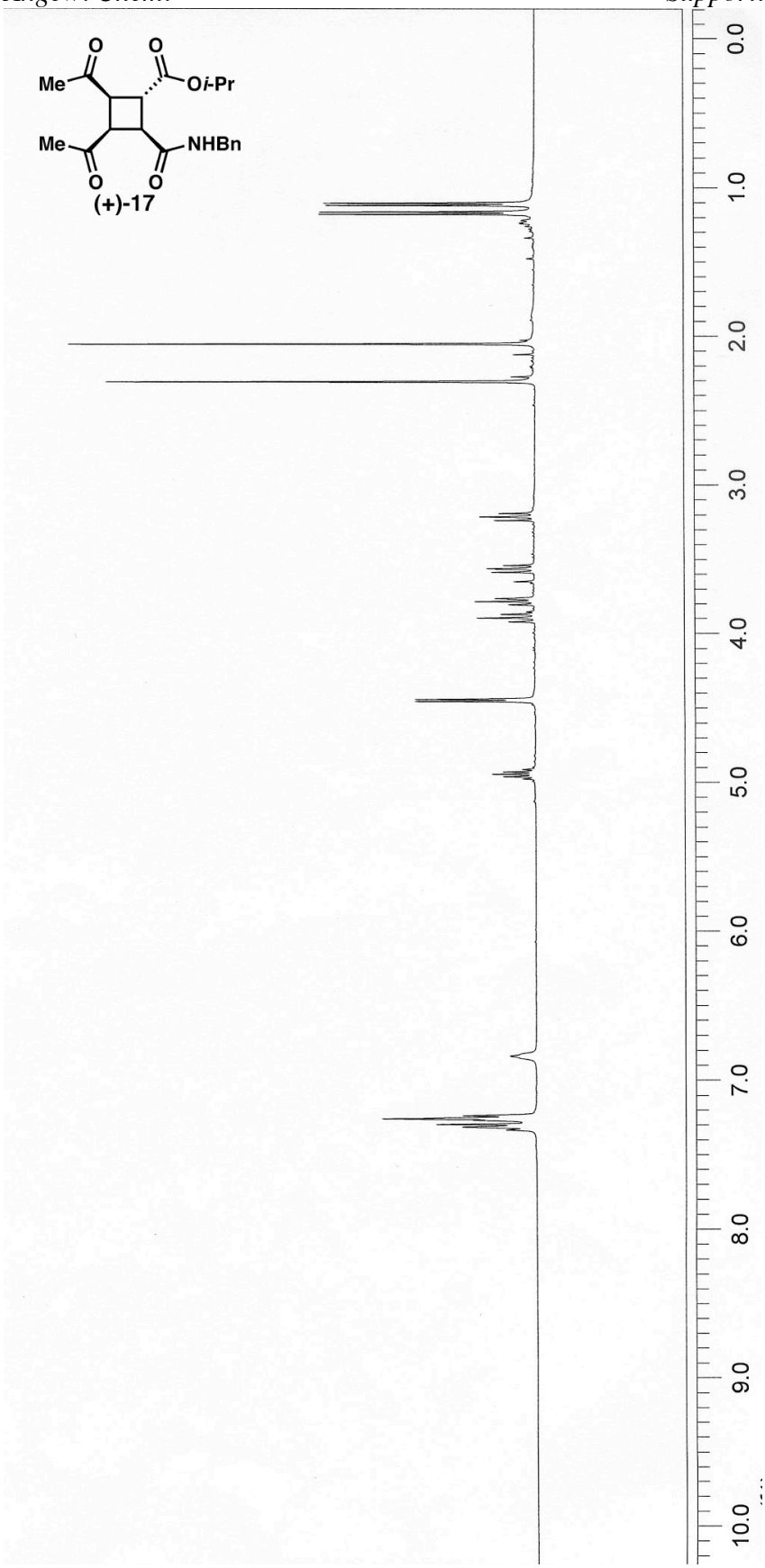
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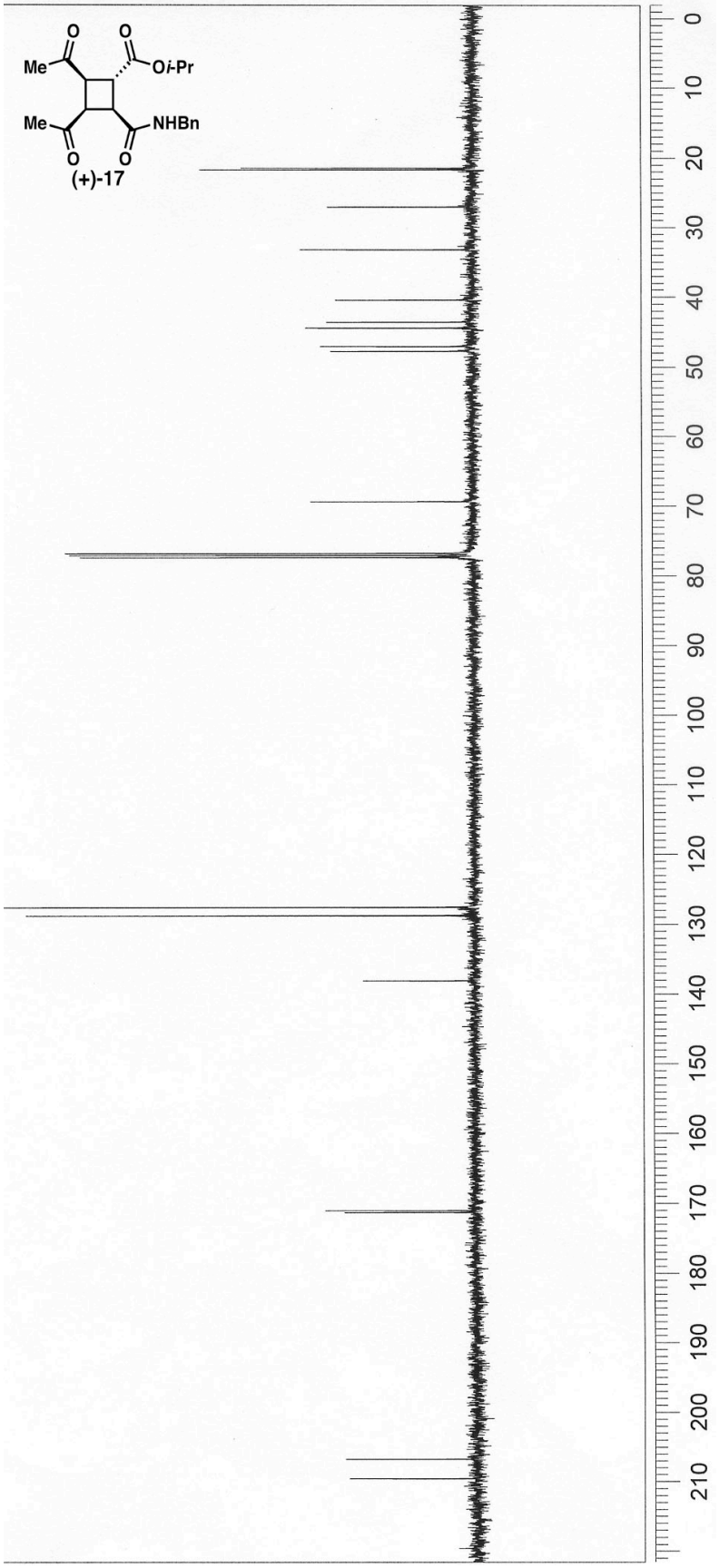
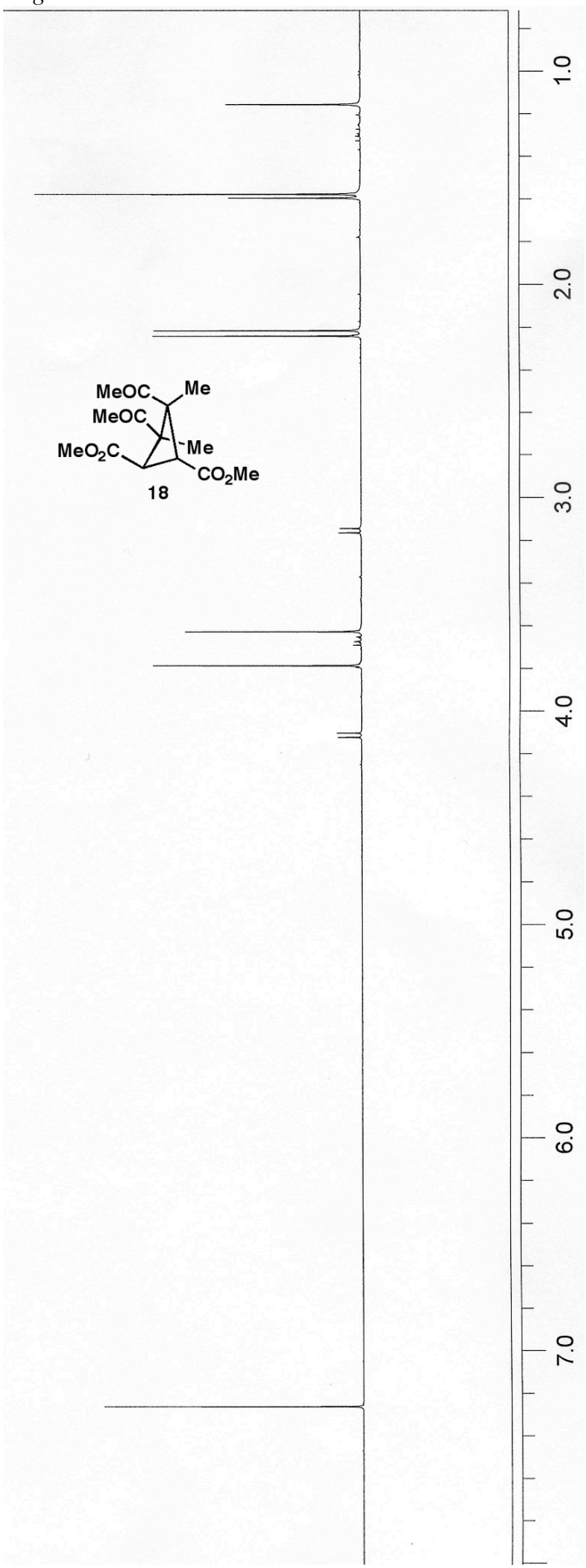
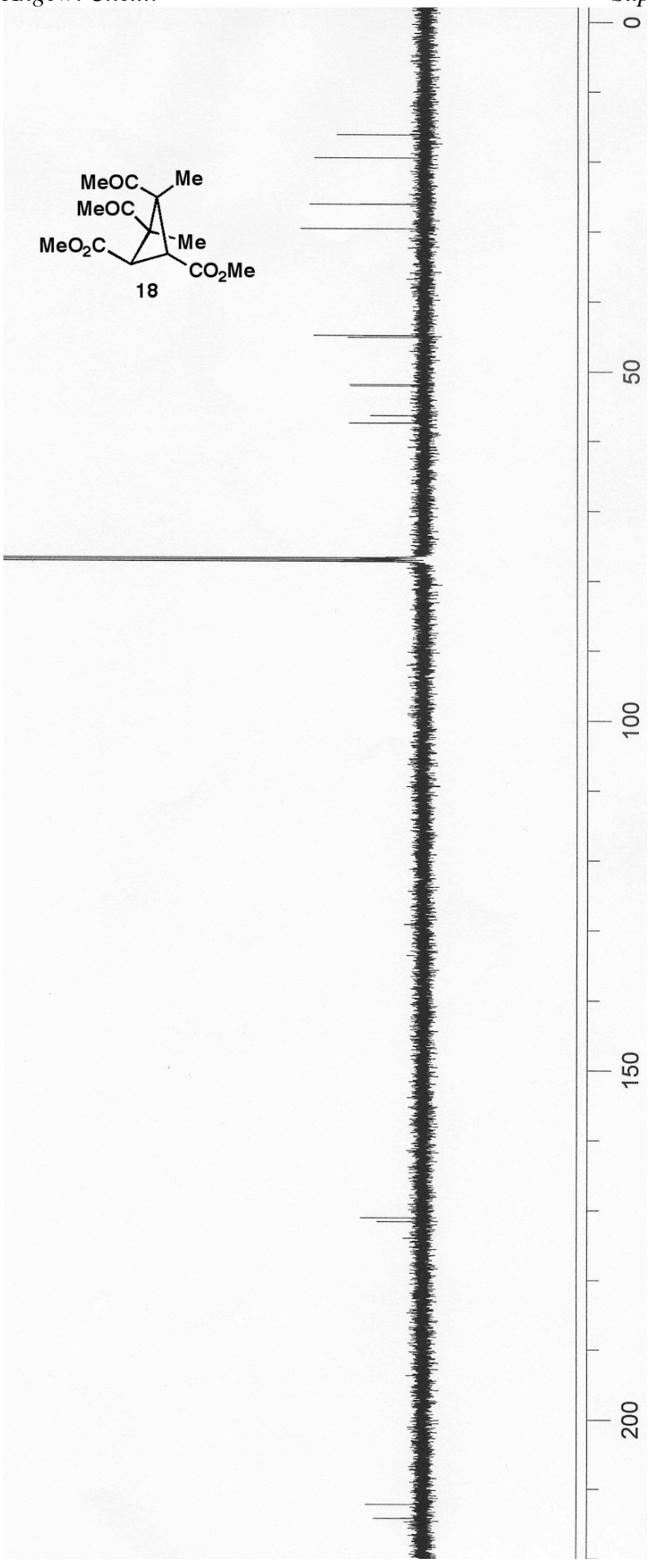
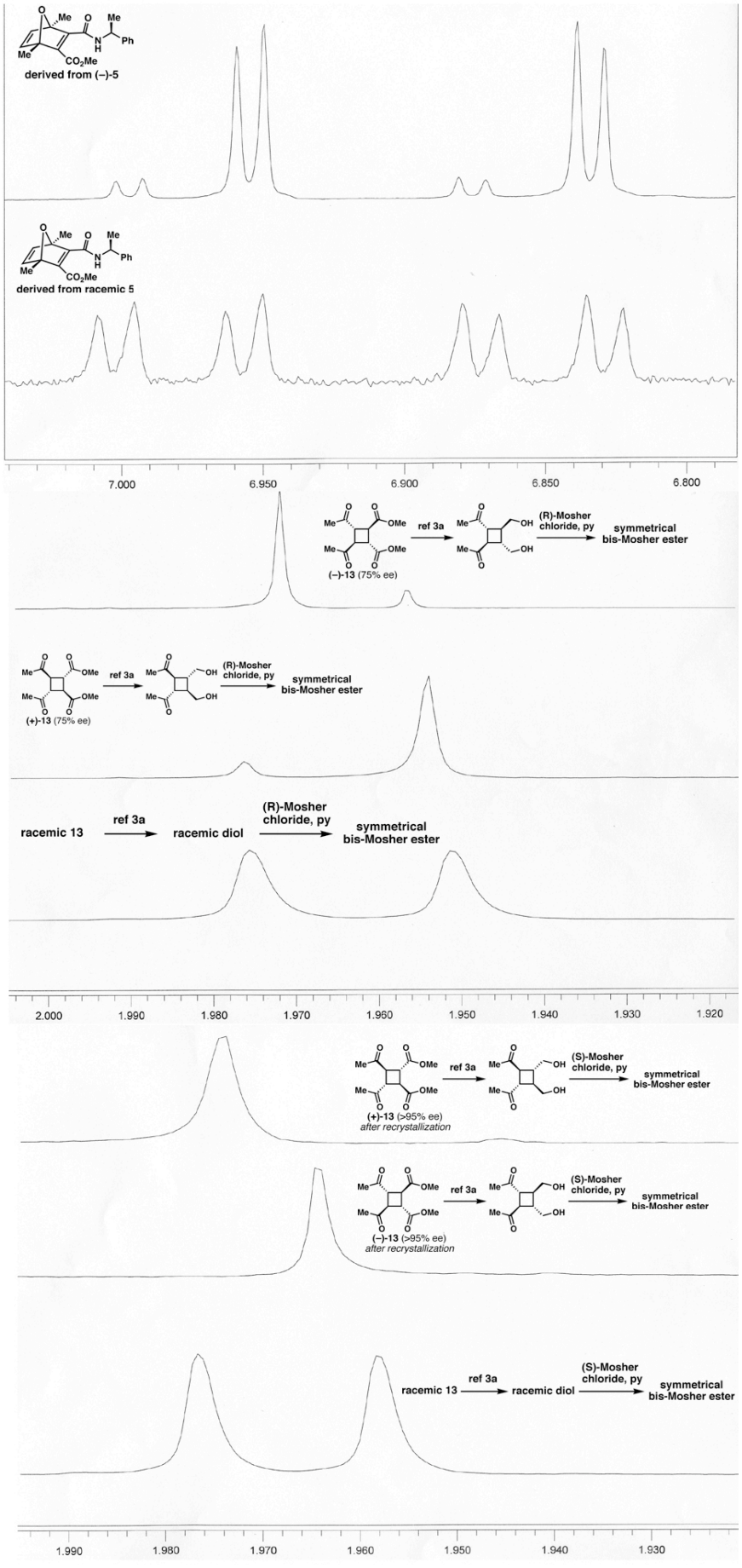
9.0
10.0


Me
O
O
Oi-Pr
Me
NHBn
O
O
(+)-17
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


MeOC
Me
MeOC
MeO2C
Me
CO2Me
18
1.0
2.0
3.0
4.0
5.0
6.0
7.0


MeOC
Me
MeOC
MeO2C
Me
CO2Me
18
0
50
100
150
200


derived from (–)-5
derived from racemic 5
7.000
6.950
6.900
6.850
6.800
ref 3a
(R)-Mosher chloride, py
symmetrical bis-Mosher ester
(–)-13 (75% ee)
(+)-13 (75% ee)
racemic 13
racemic diol
2.000
1.990
1.980
1.970
1.960
1.950
1.940
1.930
1.920
(S)-Mosher chloride, py
(+)-13 (>95% ee)
after recrystallization
(–)-13 (>95% ee)
after recrystallization