Concise Total Synthesis of (±)-Salinosporamide A, (±)-Cinnabaramide A, and Derivatives via Bis-Cyclization Process: Implications for a Biosynthetic Pathway?

Gil Ma, Henry Nguyen, and Daniel Romo*

Department of Chemistry, P.O. Box 30012, Texas A&M University,
College Station, TX 77842-3012

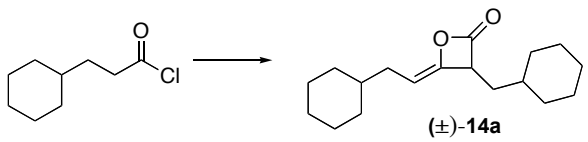
Supporting Information Available. General procedures for ketene-dimerizations, bis-cyclizations and subsequent transformations with characterization data (including ^{1}H and ^{13}C NMR spectra) for β-lactones **3, 4, 19a-d, 23a, 27, 29, 31, 34, 36, 37** and products **11a-b, 12a-b, 14b, 16a-c, 17a-c, 25, 26, 32, 33**. This material is available free of charge *via* the Internet at http://pubs.acs.org

General Procedure

All reactions were carried out under nitrogen atmosphere in flame-dried glassware. Dichloromethane, acetonitrile, methanol, tetrahydrofuran, and ethyl ether were purified by passage through activated molecular sieves. Hünig's base and triethylamine were distilled from potassium hydroxide prior to use. All other commercially obtained reagents were used as received. The preparation of modified Mukaiyama reagent **18** has been reported previously.[1] Ketene dimers were prepared by procedures similar to those previously described. ^{1}H NMR chemical shifts are reported as δ values in ppm relative to $CDCl_3$ (7.27 ppm) and coupling constants (*J*) are reported in Hertz (Hz). Unless indicated otherwise, deuterochloroform ($CDCl_3$) served as an internal standard (77.23 ppm) for all ^{13}C spectra. Flash column chromatography was performed using 60Å Silica Gel (Silicycle, 230-400 mesh) as a stationary phase. Mass spectra were obtained at the Center for Chemical Characterization and Analysis (Texas A&M University). Thin layer chromatography (TLC) was performed using glass-backed silica gel 60_{F254} (250 μm thickness).

[1] Oh, S. H.; Cortez, G. S.; Romo, D. *J. Org. Chem.* **2005**, *70*, 2835.

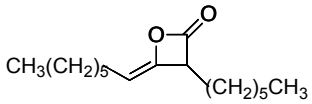
Representative Procedure for Ketene-Dimerization[2] as Described for (*Z*)-4-(2-cyclohexyl-ethylidene)-3-cyclohexylmethyl-oxetan-2-one, (±)-14a:[2]



(±)-**14a**

To a solution of 3-cyclohexyl propionyl chloride (17.5 g, 100 mmol) in Et_2O (75 mL) was added triethylamine (16.0 mL, 110 mmol) at a rate sufficient to maintain gentle refluxing. During addition of triethylamine, a white solid precipitated. After complete addition of triethylamine, the reaction mixture was refluxed for an additional 1 h, cooled to ambient temperature, and filtered through a pad of Celite and SiO_2. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (95:5 pentane:Et_2O) to afford ketene dimer (±)-**14a** (8.25 g, 60 %) as a colorless oil.

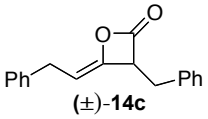
(*Z*)-4-Heptylidene-3-hexyl-oxetan-2-one, (±)-14b:



(±)-14b

Prepared according to the representative procedure using octanoyl chloride (5.4 g, 33 mmol) in Et_2O (25 mL) and triethylamine (5.2 mL, 37 mmol). Purification by flash chromatography on SiO_2 (95:5 pentane:Et_2O) gave ketene dimer (±)-**14b** (3.0 g, 65%) as a clear oil. R_f = 0.74 (20% EtOAc/hexanes); IR (neat) 1863, 1723 cm^{-1}; 1H NMR (500 MHz, C_6D_6) δ 4.36 (dt, *J* = 1.5, 7.5 Hz, 1H), 3.33 (dt, *J* = 1.0, 7.0 Hz, 1H), 2.01-2.15 (m, 2H), 1.02-1.36 (m, 18H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.84 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 169.0, 146.5, 101.0, 54.0, 31.9, 31.7, 29.8, 29.10, 29.08, 27.6, 26.5, 25.0, 23.0, 22.8, 14.3, 14.2; LRMS (CI) Calcd. for $C_{16}H_{28}O_2$ [M+H] 253, found 253; HRMS (ESI) Calcd. for $C_{16}H_{28}O_2$ [M+H] 253.2168, found 253.2169.

(*Z*)-3-Benzyl-4-phenethylidene-oxetan-2-one, (±)-14c:[2]



(±)-**14c**

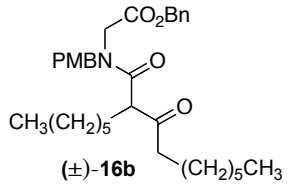
Prepared according to the representative procedure using hydrocinnamoyl chloride (5.0 g, 30 mmol) in diethyl ether (25 mL) and triethylamine (4.6 mL, 33 mmol). Purification by flash chromatography on SiO_2 (95:5 pentane:Et_2O) gave ketene dimer (±)-**14c** (1.75 g, 46%) as a clear oil.

[2] (a) Duffy, R. J.; Morris, K. A.; Romo, D. *J. Am. Chem. Soc.*, **2005**, 127, 16754-16755. (b) Purohit, V. C.; Richardson, R. D.; Smith, J. W.; Romo, D. *J. Org. Chem*. **2006**, *71*, 4549-4558.

Representative Procedure for Ring Opening of Ketene Dimers to give Ketoamides as Described for [(5-cyclohexyl-2-cyclohexylmethyl-3-oxo-pentanoyl)-(4-methoxy-benzyl)-amino]-acetic acid benzyl ester, (±)-16a:

To a solution of (4-methoxy-benzylamino)-acetic acid benzyl ester (178 mg, 0.624 mmol) and 2-hydroxypyridine (59 mg, 0.624 mmol) in THF (2 mL) was added ketene dimer (±)-**14a** (259 mg, 0.936 mmol). The reaction mixture was stirred at 50 °C for 1 day (or treated at 60 °C for 3 with microwave irradiation) and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (1:4 EtOAc/hexanes) to afford keto ester (±)-**16a** (303 mg, 86%) as a colorless oil and as a 2.2:1 ratio of rotamers: IR (neat) 1749, 1652 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7-40 (m, 5 H), 7.07-7.13 (m, 2 H), 6.81-6.89 (m, 2 H), 5.15 (s, 1.4 H), 5.14 (0.6 H), 4.73 (d, *J* = 16.5 Hz, 0.7H), 4.68 (d, *J* = 15.3 Hz, 0.3H), 4.49 (d, *J* = 15.6 Hz, 0.3H), 4.43 (d, *J* = 16.5 Hz, 0.7H), 4.27 (d, *J* = 17.1 Hz, 0.7H), 4.13 (d, *J* = 18.6 Hz, 0.3H), 3.94 (d, *J* = 17.4 Hz, 0.7H), 3.93 (d, *J* = 18.3 Hz, 0.3H), 3.78-3.83 (m, 3.7 H) 3.55 (t, *J* = 9.0 Hz, 0.3H), 2.40-2.58 (m, 2H), 0.76-1.94 (m, 26H); ^{13}C NMR were complex due to the presence of rotamers and attempted VT NMR did not lead to coalescence so these are not included; LRMS (ESI) Calcd. for $C_{35}H_{47}NO_5$ [M+H] 561, found 562.

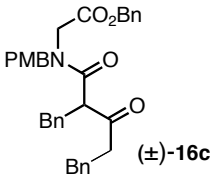
[(2-Hexyl-3-oxo-decanoyl)-(4-methoxy-benzyl)-amino]-acetic acid benzyl ester, (±)-16b:



Prepared according to the representative procedure using (4-methoxy-benzylamino)-acetic acid benzyl ester (910 mg, 3.02 mmol), 2-hydroxypyridine (304 mg, 3.02 mmol) in THF (13 mL), and ketene-dimer (±)-**14b** (800 mg, 3.02 mmol). Purification by flash chromatography on SiO_2 (1:4 EtOAc/hexanes) gave keto ester (±)-**16b** (1.36 g, 82%) as a colorless oil and as a 2.2:1 ratio of rotamers: IR (neat) 1750, 1646 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.38 (m, 5H), 7.11 (d, *J* = 8.0 Hz, 0.6H), 7.08 (d, *J* = 8.5 Hz, 1.4H), 6.87 (d, *J* = 8.5 Hz, 1.4H), 6.82 (d, *J* = 8.5 Hz, 0.6H), 5.09-5.17 (m, 2H), 4.72 (d, *J* = 16.5 Hz, 0.7H), 4.64 (d, *J* = 15.0 Hz, 0.3H), 4.53 (d, *J* = 15.0 Hz, 0.3H), 4.43 (d, *J* = 16.5 Hz, 0.7H), 4.25 (d, *J* = 17.5 Hz, 0.7H), 4.13 (d, *J* = 19.0 Hz, 0.3H), 3.93 (d, *J* = 18.5 Hz, 0.3H), 3.92 (d, *J* = 17.5 Hz, 0.7H), 3.80 (s, 2.1H), 3.78 (s, 0.9H), 3.65 (t, *J* = 7.0 Hz, 0.7H), 3.40 (t, *J* = 7.0 Hz, 0.3H), 2.42-2.57 (m, 2H), 1.94-2.01 (m, 1H), 1.79-1.86 (m, 1H), 1.47-1.55 (m, 2H), 1.17-1.31 (m, 16H), 0.86-0.90 (m, 6H); ^{13}C NMR

were complex due to the presence of rotamers and attempted VT NMR did not lead to coalescence so these are not included; LRMS (ESI) Calcd. for $C_{33}H_{47}NO_5$ [M+Li] 544, found 544.

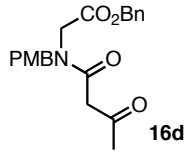
[(2-Benzyl-3-oxo-5-phenyl-pentanoyl)-(4-methoxy-benzyl)-amino]-acetic acid benzyl ester, (±)-16c:



(±)-16c

Prepared according to the representative procedure using (4-methoxy-benzylamino)-acetic acid benzyl ester (636 mg, 2.23 mmol), 2-hydroxypyridine (212 mg, 2.23 mmol) in THF (22 mL), and ketene-dimer (±)-**14c** (588 mg, 2.22 mmol). Purification by flash chromatography on SiO_2 (1:4 EtOAc/hexanes) gave keto ester (±)-**16c** (1.04 g, 85%) as a colorless oil. 2.2:1 ratio of rotamers: IR (neat) 1745 1642 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.08-7.38 (m, 15H), 6.98 (d, *J* = 8.5 Hz, 0.6H), 6.78 (d, *J* = 9.0 Hz, 0.6H), 6.72 (d, *J* = 8.5 Hz, 1.4H), 6.69 (d, *J* = 9.0 Hz, 1.4H), 5.14 (s, 1.4H), 5.05 (s, 0.6H), 4.77 (d, *J* = 14.5 Hz, 0.3H), 4.56 (d, *J* = 16.5 Hz, 0.7H), 4.31 (d, *J* = 17.5 Hz, 0.7H), 4.28 (d, *J* = 12.5 Hz, 0.3H), 4.18 (d, *J* = 16.5 Hz, 0.7H), 3.96 (d, *J* = 8.5 Hz, 0.3H), 3.95 (d, *J* = 9.0 Hz, 0.3H), 3.79 (s, 0.9H), 3.78 (s, 2.1H), 3.64-3.72 (m, 1.7H), 3.29 (dd, *J* = 9.0, 14.0 Hz, 0.7H), 3.16-3.24 (m, 0.6H), 3.12 (dd, *J* = 5.5, 13.5 Hz, 0.7H), 2.77-2.96 (m, 4H); ^{13}C NMR were complex due to the presence of rotamers and attempted VT NMR did not lead to coalescence so these are not included; LRMS (ESI) Calcd. for $C_{35}H_{35}NO_5$ [M+Li] 556, found 556.

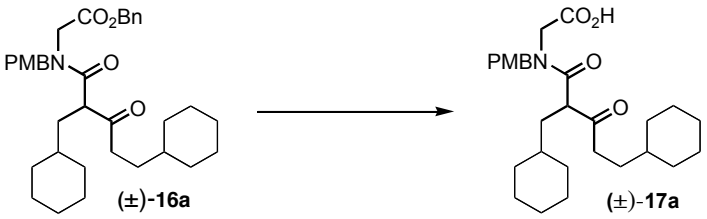
[(4-Methoxy-benzyl)-(3-oxo-butyryl)-amino]-acetic acid benzyl ester, (±)-16d:



16d

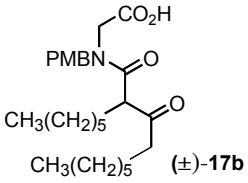
Prepared according to the representative procedure using (4-methoxy-benzylamino)-acetic acid benzyl ester (910 mg, 3.19 mmol), 2-hydroxypyridine (304 mg, 3.20 mmol) in THF (25 mL), and ketene dimer **14d** (1.0 mL, 16 mmol). Purification by flash chromatography on SiO_2 (1:4 EtOAc/hexanes) gave keto ester **16d** (930 mg, 78%) as a colorless oil. Due to the presence of enol tautomers and amide rotamers, the NMR spectra of this compound is extremely complex and so line listing is not provided. R_f = 0.28 (33% EtOAc/hexanes); IR (neat) 1747, 1720, 1646 cm^{-1}; LRMS (ESI) Calcd. for $C_{21}H_{23}NO_5$ [M+H] 370, found 370; HRMS (ESI) Calcd. for $C_{21}H_{23}NO_5$ [M+H] 370.1654, found 370.1655.

Representative Procedure for Preparation of Keto-Acid intermediate from Benzyl Ester as Described for [(5-cyclohexyl-2-cyclohexylmethyl-3-oxo-pentanoyl)-(4-methoxy-benzyl)-amino]-acetic acid, (±)-17a:



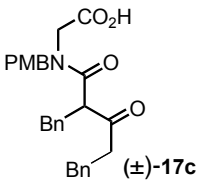
A racemic mixture of keto ester benzyl ester **(±)-16a** (270 mg, 0.481 mmol), and 10wt% palladium on carbon (27 mg) in a mixture of solvent THF (10 mL) was stirred at ambient temperature for 3 h under H_2 atmosphere. The reaction mixture was filtered through a pad of Celite, and concentrated to afford keto acid (±)-**17a** (222 mg, 98%) as a white solid and as a 2.2:1 ratio of two rotamers: IR (neat) 1729, 1652 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.5 Hz, 0.6H), 7.09 (d, *J* = 8.5 Hz, 1.4H), 6.89 (d, *J* = 9.0 Hz, 1.4H), 6.84 (d, *J* = 9.0 Hz, 0.6H), 4.71 (d, *J* = 16.5 Hz, 0.7H), 4.68 (d, *J* = 13.5 Hz, 0.3H), 4.47 (d, *J* = 15.0 Hz, 0.3H), 4.42 (d, *J* = 16.5 Hz, 0.7H), 4.25 (d, *J* = 17.5 Hz, 0.7H), 4.13 (d, *J* = 19.0 Hz, 0.3H), 3.94 (d, *J* = 18.0 Hz, 0.3H), 3.90 (d, *J* = 17.0 Hz, 0.7H), 3.81 (s, 3H), 3.79 (dd, *J* = 1.5, 4.5 Hz, 0.7H), 3.57 (t, *J* = 7.0 Hz, 0.3H), 2.44-2.56 (m, 2H), 1.88-1.94 (m, 1H), 1.54-1.74 (m, 11H), 1.35-1.43 (m, 2H), 1.07-1.20 (m, 8H), 0.78-0.92 (m, 4H); LRMS (APCI) Calcd. for $C_{28}H_{41}NO_5$ [M–H] 470, found 470.

[(2-Hexyl-3-oxo-decanoyl)-(4-methoxy-benzyl)-amino]-acetic acid, (±)-17b:



Prepared according to the representative procedure for preparation of keto-acid intermediate from benzyl ester (±)-**16b** (415 mg, 0.772 mmol), palladium on carbon (40 mg) in a mixture of solvent THF (10 mL) afford keto acid (±)-**17b** (340 mg, 98%) as a colorless oil and as a 3:1 ratio of rotamers: IR (neat) 1721, 1649, 1614 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.5 Hz, 0.5H), 7.09 (d, *J* = 8.5 Hz, 1.5H), 6.89 (d, *J* = 9.0 Hz, 1.5H), 6.84 (d, *J* = 8.5 Hz, 0.5H), 4.71 (d, *J* = 16.5 Hz, 0.75H), 4.65 (d, *J* = 14.5 Hz, 0.25H), 4.51 (d, *J* = 14.5 Hz, 0.25H), 4.42 (d, *J* = 16.5 Hz, 0.75H), 4.23 (d, *J* = 17.5 Hz, 0.75H), 4.12 (d, *J* = 19.0 Hz, 0.25H), 3.94 (d, *J* = 19.0 Hz, 0.25H), 3.89 (d, *J* = 17.5 Hz, 0.75H), 3.81 (s, 2.25H), 3.79 (s, 0.75H), 3.66 (dd, *J* = 6.0, 8.0 Hz, 0.75H), 3.43 (t, *J* = 7.0 Hz, 0.25H), 2.45-2.55 (m, 2H), 1.95-2.04 (m, 1H), 1.79-1.87 (m, 1H), 1.48-1.55 (m, 2H), 1.16-1.34 (m, 16H), 0.85-0.88 (m, 6H); LRMS (ESI) Calcd. for $C_{26}H_{41}NO_5$ [M-H] 446, found 446.

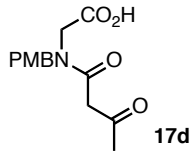
[(2-Benzyl-3-oxo-5-phenyl-pentanoyl)-(4-methoxy-benzyl)-amino]-acetic acid, (±)-17c:



(±)-**17c**

Prepared according to the representative procedure for preparation of keto-acid intermediate from benzyl ester (±)-**16c** (985 mg, 1.79mmol), palladium on carbon (99 mg) in a mixture of solvent THF (20 mL) and MeOH (4 mL) afford keto acid (±)-**17c** (0.70g, 85%) as a white solid and as a 2.2:1 ratio of rotamers: IR (neat) 1722, 1634, 1612 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.10-7.28 (m, 10H), 6.98 (d, *J* = 8.5 Hz, 0.6H), 6.79 (d, *J* = 9.0 Hz, 0.6H), 6.73 (d, *J* = 9.0 Hz, 1.4H), 6.69 (d, *J* = 9.0 Hz, 1.4H), 4.81(d, *J* = 15.0 Hz, 0.3H), 4.50 (d, *J* = 16.5 Hz, 0.7H), 4.22 (d, *J* = 14.5 Hz, 0.3H), 4.21 (d, *J* = 17.0 Hz, 0.7H), 4.14 (d, *J* = 16.5 Hz, 0.7H), 3.96 (d, *J* = 9.0 Hz, 0.3H), 3.95 (d, *J* = 9.0 Hz, 0.3H), 3.78 (s, 0.9H), 3.77 (s, 2.1H), 3.69 (d, *J* = 17.5 Hz, 0.7H), 3.30 (dd, *J* = 9.0, 13.0 Hz, 0.7H), 3.24 (dd, *J* = 9.0, 13.0 Hz, 0.3H), 3.18 (dd, *J* = 5.0, 13.5 Hz, 0.3H), 3.12 (dd, *J* = 5.0, 13.5 Hz, 0.7H), 2.76-2.97 (m, 5H); LRMS (ESI) Calcd. for $C_{28}H_{29}NO_5$ [M-H] 458, found 458.

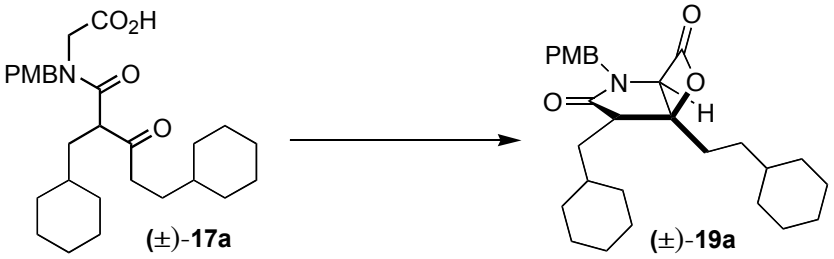
[(4-Methoxy-benzyl)-(3-oxo-butyryl)-amino]-acetic acid, 17d:



17d

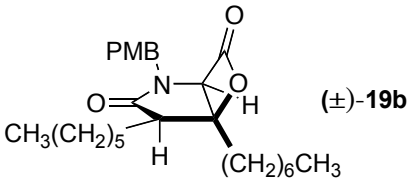
Prepared according to the representative procedure for preparation of keto-acid intermediate from benzyl ester **16d** (0.320 mg, 0.866 mmol), palladium on carbon (35 mg) in a mixture of solvent THF (10 mL) afford keto acid **17d** (250 mg, 99%) as a colorless oil. IR (neat) 1723, 1612 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 4.51 (s, 2H), 4.05 (s, 2H), 3.81 (s, 3H), 3.68 (s, 2H), 2.30 (s, 3H) (only major peaks were assigned); LRMS (ESI) Calcd. for $C_{14}H_{17}NO_5$ [M–H] 278, found 278; HRMS (ESI) Calcd. for $C_{14}H_{17}NO_5$ [M–H] 278.1028, found 278.1025.

Representative Procedure for Preparation of *β*-Lactone via Biscyclization as Described for 5-(2-cyclohexyl-ethyl)-4-cyclohexylmethyl-2-(4-methoxy-benzyl)-6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, (±)-19a:



To a suspension of *N*-propyl-2-bromo pyridinium triflate (95 mg, 0.27 mmol) and 4-pyrrolidinopyridine (40 mg, 0.27 mmol) in CH_2Cl_2 (4 mL) was added Hünig's base (63 μL, 0.36 mmol) at 0 °C. After stirring for 10 min, a solution of keto-acid **(±)-17a** (85 mg, 0.18 mmol) in CH_2Cl_2 (3 mL) was added via syringe pump over 1 h at 0 °C. The resulting suspension was stirred for 2 h at 0 °C. The crude reaction mixture was diluted with Et_2O (50 mL) and washed with aqueous NH_4Cl solution and brine (each 30 mL). The organic layer were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (1:10 EtOAc/hexanes) to give a mixture of two *β*-lactones (76 mg, 93%, dr 2.2:1) as a colorless oil. **(±)-19a** (major): R_f = 0.76 (40% EtOAc/hexanes); IR (neat) 1825, 1709 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.03 (d, *J* = 14.5 Hz, 1H), 4.34 (s, 1H), 4.04 (d, *J* = 14.5 Hz, 1H), 3.81 (s, 3H), 2.70 (dd, *J* = 6.0, 7.5 Hz, 1H), 1.86-1.97 (m, 2H), 1.60-1.81 (m, 11H), 1.08-1.32 (m, 10H), 0.80-1.00 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 166.2, 159.5, 130.0, 126.8, 114.3, 83.1, 68.2, 53.3, 45.2, 43.8, 37.3, 34.8, 33.6, 33.4, 33.2, 32.9, 32.6, 32.5, 31.2, 26.5, 26.4, 26.2, 26.1, 26.0 (2); LRMS (ESI) Calcd. for $C_{28}H_{39}NO_4$ [M+Li] 460, found 460.

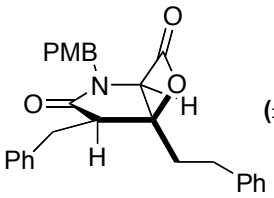
4,5-Dihexyl-2-(4-methoxy-benzyl)-6-oxa-2-aza-bicyclo[3.2.0]heptane-3,7-dione, (±)-19b:



Prepared according to the representative procedure for preparation of *β*-lactone via bis-cyclization using *N*-propyl-2-bromo pyridinium triflate (141 mg, 0.402 mmol), 4-pyrrolidinopyridine (60 mg, 0.40 mmol), Hünig's base (93 μL, 0.54 mmol), and keto-acid **(±)-17b** (120 mg, 0.268 mmol) in CH_2Cl_2 (11 mL). Purification by flash chromatography on SiO_2 (1:10 EtOAc/hexanes) gave a mixture of two *β*-lactones (104 mg, 90%, dr = 2.2:1). **(±)-19b** (major): IR (neat) 1836, 1705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.04 (d, *J* = 15.0 Hz, 1H), 4.36 (s, 1H), 4.05 (d, *J* = 15.0 Hz, 1H), 3.80 (s, 3H), 2.55 (dd, *J* = 5.5, 9.0 Hz, 1H), 1.85-2.00 (m, 3H), 1.69-1.77 (m, 1H), 1.47-1.58 (m, 2H), 1.18-1.39 (m, 16H), 0.89 (t, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 174.5, 166.3, 159.7, 130.2, 127.0, 114.5, 83.0, 68.5, 55.4, 47.4, 45.4, 35.6, 31.74, 31.68, 29.5, 29.4, 29.1, 28.0, 26.3, 24.0, 22.8, 22.7, 14.24, 14.19; LRMS (ESI) Calcd. for $C_{26}H_{39}NO_4$ [M+H] 430, found 430.

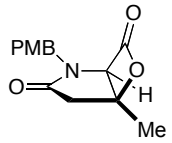
4-Benzyl-2-(4-methoxy-benzyl)-5-phenethyl-6-oxa-2-aza-bicyclo[3.2.0]heptane-3,7-dione, (±)-19c:



(±)-19c

Prepared according to the representative procedure for preparation of *β*-lactone via biscyclization using *N*-propyl-2-bromo pyridinium triflate (84.6 mg, 0.245 mmol), 4-pyrrolidinopyridine (36.2 mg, 0.245 mmol), Hünig's base (57 μL, 0.33 mmol), and keto-acid **(±)-17c** (75 mg, 0.16 mmol) in CH_2Cl_2 (6.5 mL). Purification by flash chromatography on SiO_2 (1:4 EtOAc/hexanes) gave *β*-lactone **(±)-19c** (61 mg, 85%, dr = 2.5:1). R_f = 0.29 (20% EtOAc/hexanes); IR (neat) 1830, 1702, 1612 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.83-7.34 (m, 14H), 4.99 (d, *J* = 15.0 Hz, 1H), 4.12 (s, 1H), 4.07 (d, *J* = 14.0 Hz, 1H), 3.83 (s, 3H), 3.38 (dd, *J* = 3.0, 13.0 Hz, 1H), 2.98 (dd, *J* = 11.5, 13.0 Hz, 1H), 2.92 (dd, *J* = 3.5, 11.5 Hz, 1H), 2.34-2.43 (m, 2H), 1.63-1.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 166.1, 159.7, 139.3, 138.6, 130.4, 129.4, 128.9, 128.8, 128.1, 127.0, 126.7, 126.6, 114.5, 82.5, 68.8, 55.5, 49.7, 45.6, 36.2, 31.6, 30.1; LRMS (ESI) Calcd. for $C_{28}H_{27}NO_4$ [M+H] 442, found 442.

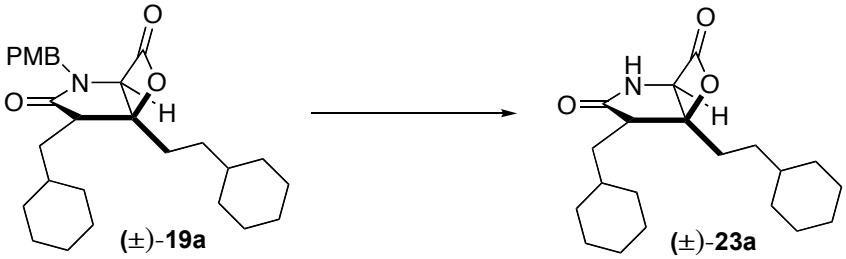
2-(4-Methoxy-benzyl)-6-oxa-2-aza-bicyclo[3.2.0]heptane-3,7-dione, (±)-19d:



(±)-19d

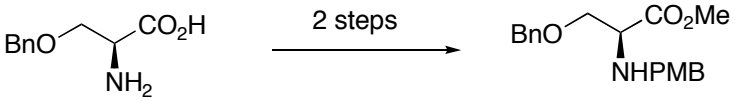
Prepared according to the representative procedure for preparation of *β*-lactone via biscyclization using *N*-propyl-2-bromo pyridinium triflate (188 mg, 0.537 mmol), 4-pyrrolidinopyridine (79.6 mg, 0.577 mmol), Hünig's base (125 μL, 0.716 mmol), and keto-acid **17d** (100 mg, 0.358 mmol) in CH_2Cl_2 (14 mL). Purification by flash chromatography on SiO_2 (2:3 EtOAc/hexanes) gave *β*-lactone **(±)-19d** (23 mg, 25%). R_f = 0.14 (33% EtOAc/hexanes); IR (neat) 1836, 1702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.06 (d, *J* = 14.7 Hz, 1H), 4.41 (s, 1H), 4.07 (d, *J* = 14.7 Hz, 1H), 3.82 (s, 3H), 3.05 (d, *J* = 18.9 Hz, 1H), 2.70 (d, *J* = 18.6 Hz, 1H), 1.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 165.8, 159.8, 130.4, 126.7, 114.5, 77.9, 71.7, 55.5, 45.5, 41.6, 22.2; LRMS (APCI) Calcd. for $C_{14}H_{15}NO_4$ [M+Li] 268, found 268.

Representative Procedure for PMB-deprotection as Described for 5-(2-cyclohexyl-ethyl)-4-cyclohexylmethyl-6-oxa-2-aza-bicyclo[3.2.0]heptane-3,7-dione, (±)-23a:



To a solution of **(±)-19a** (20 mg, 0.044 mmol) in CH_3CN (1 mL) was added an aqueous solution of CAN (123 mg, 0.225 mmol) in H_2O (0.4 mL) at 0 °C dropwise. After stirring at ambient temperature for 1 h, the reaction mixture was diluted with saturated $NaHCO_3$ (2 mL) and extracted EtOAc (5 mLx5). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (1:6 to 1:1 EtOAc/hexanes) to give the desired product **(±)-23a** (13 mg, 89%) as a white solid. A crystal suitable for X-ray analysis was obtained by slow evaporation from Et_2O with ~5% CH_2Cl_2. R_f = 0.55 (40% EtOAc/hexanes); IR (neat) 1832, 1709 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.48 (s, 1H), 4.61 (s, 1H), 2.62 (dd, *J* = 6.5, 8.5 Hz, 1H), 1.98-2.02 (m, 2H), 1.51-1.81 (m, 13H), 1.12-1.35 (m, 9H), 0.87-0.98 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 166.7, 85.6, 65.2, 42.8, 37.5, 34.7, 33.7, 33.2, 33.1, 32.9, 32.7, 32.5, 31.4, 26.44, 26.37, 26.12, 26.09, 26.08, 26.0; LRMS (ESI) Calcd. for $C_{20}H_{31}NO_3$ [M+H] 334, found 334.

(*S*)-3-Benzyloxy-2-(4-methoxy-benzylamino)-propionic acid methyl ester, 11a:

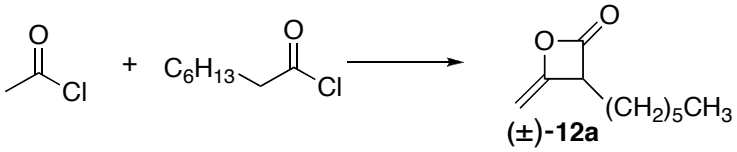


To the suspension of *O*-benzyl-*L*-serine **24** (3.85 g, 19.6 mmol) and *p*-anisaldehyde (3.21 g, 23.5 mmol) in MeOH (40 mL) was added triethylamine (3.28 mL, 23.5 mmol) at ambient temperature. The resulting suspension was stirred at ambient temperature for 1 h. The resulting solution was diluted with additional MeOH (40 mL) and $NaBH_4$ (1.11 g, 29.4 mmol) was added at 0 °C portionwise. After stirring at ambient temperature for 2 h, all volatiles were removed under reduced pressure. The remained solid was dissolved in water (50 mL) and acidified to pH 2 with 1 N HCl. The precipitate white solid was filtered, washed with water (2 X 30 mL) and Et_2O (2 X 30 mL), and dried under vacuum to give *O*-benzyl-*N*-PMB serine (5.21g, 84%) as a white solid.

The suspension of *O*-benzyl-*N*-PMB serine (2.00 g, 6.34 mmol) in MeOH/Et_2O (each 16 mL) was added $TMSCHN_2$ (2 M in Et_2O, 6.4 mL, 12.8 mmol) dropwise until a yellow tint persisted. The reaction mixture was stirred at ambient temperature for additional 30 min and the all volatiles were removed under reduced pressure. The residue was purified by flash chromatography (1:3 EtOAc/hexanes) to give the desired

methyl ester **11a** (1.43 g, 69%) as a yellow oil. R_f = 0.12 (20% EtOAc/hexanes); IR (neat) 1737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.35 (m, 5 H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.53 (d, *J* = 12.5 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 3.82 (d, *J* = 12.5 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.71 (dd, *J* = 5.5, 9.5 Hz, 1H), 3.66 (dd, *J* = 5.0, 9.5 Hz, 1H), 3.65 (d, *J* = 13.0 Hz, 1H), 3.50 (t, *J* = 5.0 Hz, 1H), 2.15 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 158.7, 137.8, 131.6, 129.5, 128.3, 127.6, 127.5, 113.7, 73.1, 70.9, 60.3, 55.2, 51.9, 51.4; LRMS (ESI) Calcd. for $C_{19}H_{23}NO_4$ [M+H] 330, found 330.

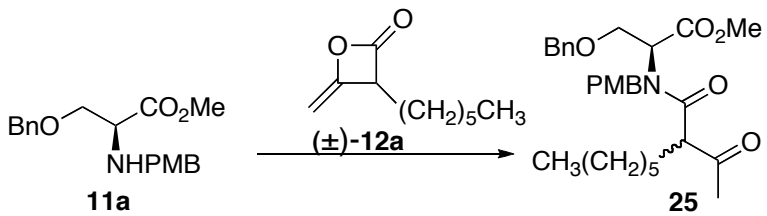
Representative Procedure for Ketene-Heterodimerization as Described for 3-hexyl-4-methylene-oxetan-2-one, (±)-12a:



(±)-12a

To a solution of acetyl chloride (9.0 mL, 120 mmol) and octanoyl chloride (10.2 mL, 60 mmol) in Et_2O (90mL) was added triethylamine (27 mL, 192 mmol) at a rate sufficient to maintaining reflux. During addition of triethylamine, the triethylamine hydrochloride precipitated as a white solid. The reaction mixture was stirred for an additional 1 h without further heating and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the crude residue was distilled under vacuum to give a mixture of two ketene-dimers, which was the further purified by flash chromatography (5:95 Et_2O/hexanes) to afford ketene-dimer (±)-**12a** (0.5 g, 5%) as a colorless oil. R_f = 0.54 (10% EtOAc/hexanes); IR (neat) ν_{max} 1888, 1860 1702 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 4.51 (dd, *J* = 2.0, 4.0 Hz, 1H), 3.91 (dd, *J* = 1.0, 4.0 Hz, 1H), 3.21 (t, *J* = 7.0 Hz, 1H), 0.94-1.30 (m, 10 H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, benzene-d_6) δ 168.4, 154.2, 84.8, 54.6, 31.6, 29.0, 27.2, 26.3, 22.8, 14.2; LRMS (ESI) Calcd. for $C_{10}H_{16}O_2$ [M+H] 169, found 169.

Representative Procedure for Ring Opening of Hetero-Ketene Dimers to give Ketoamides as Described for 2-[(2-acetyl-octanoyl)-(4-methoxy-benzyl)-amino]-3-benzyloxy-propionic acid methyl ester, 25:

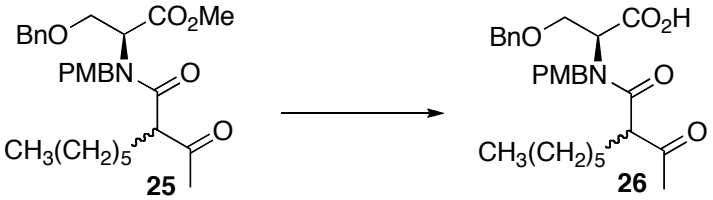


11a **(±)-12a** **25**

To a solution of (*S*)-3-benzyloxy-2-(4-methoxy-benzylamino)-propionic acid methyl ester **11a** (670 mg, 2.03 mmol) and 2-hydroxypyridine (251 mg, 2.64 mmol) in THF (5 mL) was added ketene-dimer (±)-**12a** (450 mg, 2.64 mmol). The reaction mixture was stirred at 50 °C for 2 days and the solvent was

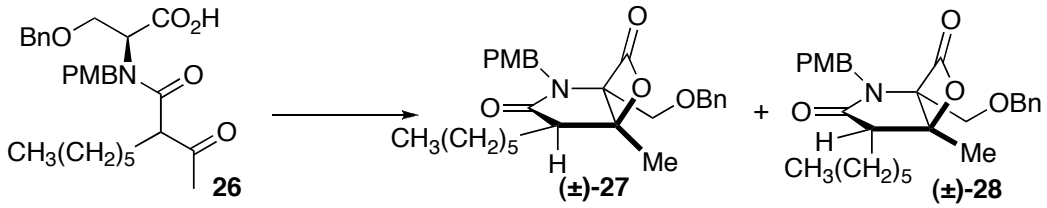
evaporated under reduced pressure. The residue was purified by flash chromatography (1:10 EtOAc/hexanes) to afford a 1:1 mixture of diastereomeric keto esters **25** (855 mg, 85%) as a colorless oil. **25a**: R_f = 0.24 (20% EtOAc/hexanes); IR (neat) 1743, 1648 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20-7.38 (m, 7H), 6.86 (d, *J* = 8.7 Hz, 2 H), 4.83 (d, *J* = 17.1 Hz, 1H), 4.52-4.65 (m, 2H), 4.41 (d, *J* = 7.8 Hz, 1H), 4.39 (d, *J* = 7.8 Hz, 1H), 4.00 (dd, *J* = 7.2, 10.2 Hz, 1 H), 3.94 (dd, *J* = 4.5, 10.2 Hz, 1 H), 3.81 (s, 3H), 3.72 (s, 3H), 3.53 (t, *J* = 3.6 Hz, 1 H), 2.15 (s, 3 H), 1.93-2.02 (m, 1H), 1.68-1.80 (m, 1H), 1.08-1.35 (m, 8H), 0.88 (t, *J* = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 170.6, 169.3, 159.2, 137.8, 128.9, 128.6, 128.3, 128.0, 127.8, 114.1, 73.4, 68.4, 59.7, 58.8, 55.3, 52.2, 51.7, 31.6, 29.7, 29.1, 27.5, 27.0, 22.6, 14.1; LRMS (ESI) Calcd. for $C_{29}H_{39}NO_6$ [M+H] 498, found 498. **25b**: R_f = 0.16 (20% EtOAc/hexanes); IR (neat) 1742, 1645 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21-7.36 (m, 7H), 6.87 (d, *J* = 9.0 Hz, 2 H), 4.68 (s, 2H), 4.42-4.48 (m, 3H), 4.03 (dd, *J* = 5.0, 10.5 Hz, 1 H), 4.00 (dd, *J* = 7.5, 10.5 Hz, 1 H), 3.81 (s, 3H), 3.69 (s, 3H), 3.57 (t, *J* = 6.5 Hz, 1 H), 2.08 (s, 3 H), 1.82-1.89 (m, 2H), 1.18-1.31 (m, 8H), 0.87 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 170.9, 169.3, 159.3, 137.9, 128.7, 128.48, 128.46, 127.8, 127.7, 114.2, 73.4, 68.8, 60.0, 58.0, 55.4, 52.6, 52.2, 31.7, 29.5, 29.3, 27.7, 27.6, 22.7, 14.2.

2-[(2-Acetyl-octanoyl)-(4-methoxy-benzyl)-amino]-3-benzyloxy-propionic acid, 26:



To a solution of diastereomeric methyl esters **25** (320 mg, 0.643 mmol) in 1,2-dichloroethane (4.5 mL) and in a sealed tube was added trimethyltin hydroxide (349 mg, 1.93 mmol) at ambient temperature. The reaction mixture was stirred at 80 °C for 8 h and diluted with EtOAc. The organic layer was washed with 0.5 N HCl (3 X 25 mL) and brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (1:10 EtOAc/hexanes to 1:1 CH_2Cl_2/EtOAc) to give the desired acid **26** (215 mg, 69%) and the recovered ester (68 mg, 21%) as colorless oils. Data for one diastereomer: IR (neat) 3153, 1726, 1650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.81 (br, 1H), 7.18-7.35 (m, 7H), 6.86 (d, *J* = 8.5 Hz, 2 H), 4.81 (d, *J* = 17.0 Hz, 1H), 4.62 (dd, *J* = 4.0, 7.5 Hz, 1H), 4.57 (d, *J* = 17.0 Hz, 1H), 4.41 (s, 2 H), 4.00 (dd, *J* = 8.0, 10.0 Hz, 1 H), 3.96 (dd, *J* = 4.0, 10.5 Hz, 1 H), 3.80 (s, 3H), 3.53 (dd, *J* = 6.0, 7,5 Hz, 1 H), 2.18 (s, 3 H), 1.92-2.01 (m, 1H), 1.70-1.76 (m, 1H), 1.06-1.28 (m, 8H), 0.85 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 173.9, 170.9, 159.3, 137.6, 128.6, 128.5, 128.3, 127.9, 127.8, 114.3, 73.5, 68.3, 59.7, 58.8, 55.4, 51.9, 31.7, 29.7, 29.1, 27.6, 27.1, 22.7, 14.2; LRMS (ESI) Calcd. for $C_{28}H_{37}NO_6$ [M–H] 482, found 482.

Representative Procedure for Bis-cyclization Process to give Bicyclic-*β*-lactone as Described for 1-benzyloxymethyl-4-hexyl-2-(4-methoxy-benzyl)-5-methyl-6-oxa-2-aza-bicyclo[3.2.0]heptane-3,7-dione, (±)-27:



To a suspension of *N*-propyl-2-bromo pyridinium triflate (343 mg, 0.993 mmol) and 4-pyrrolidinopyridine (294 mg, 1.98 mmol) in CH_2Cl_2 (6.5 mL) was added Hünig's base (86 μL, 0.50 mmol) at 0 °C. After stirring for 10 min, a solution of keto-acids **26** (240 mg, 0.496 mmol) in CH_2Cl_2 (6 mL) was added via syringe pump over 1 h at 0 °C. The resulting suspension was stirred for 7 h at 0 °C, at which point the volatiles were removed to reduce to two-thirds original volume under reduced pressure. The crude reaction mixture was diluted with Et_2O (100 mL) and washed with aqueous NH_4Cl solution and brine (each 30 mL). The organic layer were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (1:10 EtOAc/hexanes) to give a mixture of two *β*-lactones (±)-**27**:**28** (105 mg, 45%, dr 3.3:1, 500 MHz ^{1}H NMR) as a colorless oil. (±)-**27**: R_f = 0.36 (20% EtOAc/hexanes); IR (neat) 1835, 1704 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.06-7.18 (m, 5H), 6.99 (dd, *J* = 1.5, 8.0 Hz, 2H), 6.71 (dd, *J* = 2.5, 7.0 Hz, 2H), 4.83 (d, *J* = 15.5 Hz, 1H), 4.32 (d, *J* = 15.5 Hz, 1H), 3.78 (s, 2H), 3.42 (d, *J* = 11.5 Hz, 1H), 3.32 (d, *J* = 11.5 Hz, 1H), 3.24 (s, 3H), 2.19 (dd, *J* = 6.0, 9.0 Hz, 1H), 1.99-2.06 (m, 1H), 1.70-1.77 (m, 1H), 1.44-1.53 (m, 2H), 1.31 (s, 3H), 1.18-1.27 (m, 6H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 174.8, 166.8, 159.3, 136.7, 129.4, 129.0, 128.7, 128.3, 128.1, 114.0, 84.1, 79.2, 73.6, 61.9, 55.4, 48.7, 44.4, 31.7, 29.5, 28.1, 25.8, 22.8, 20.3, 14.2; LRMS (ESI) Calcd. for $C_{28}H_{35}NO_5$ [M+Li] 472, found 472.

The diastereomers were not readily separable and thus the minor diastereomer was characterized following subsequent benzyl group deprotection.

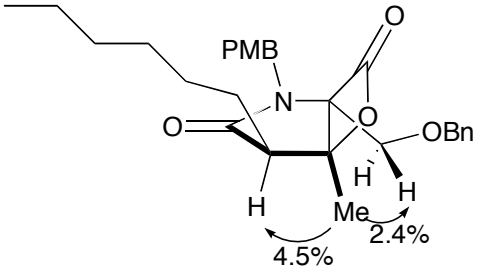
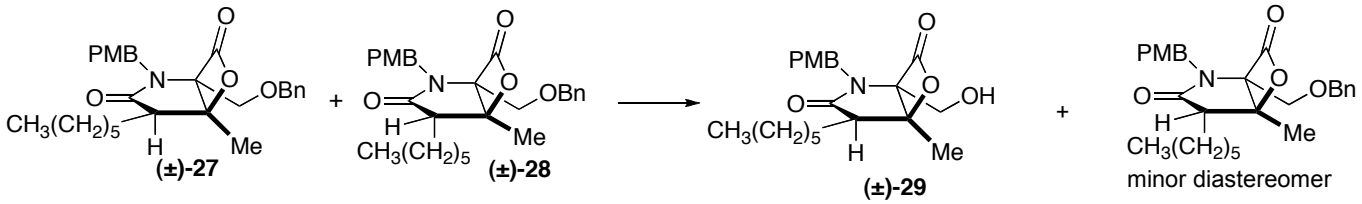


Figure 1. NOE analysis of (±)-**27** to determine relative stereochemistry.

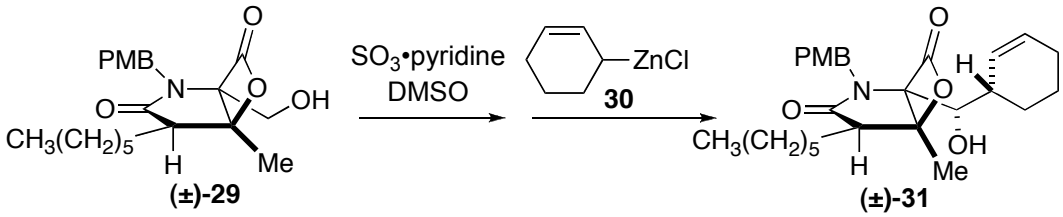
Representative Procedure for Debenzylation as Described for hexyl-1-hydroxymethyl-2-(4-methoxy-benzyl)-5-methyl-6-oxa-2-aza-bicyclo[3.2.0]heptane-3,7-dione, (±)-29:



A mixture of *β*-lactones (±)-**27** and (±)-**28** (61 mg, 0.13 mmol, dr ~3.3:1) and 10 wt% palladium on carbon (10 mg) in THF (1.5 ml) was stirred at ambient temperature for 3 h under H_2 atmosphere. The reaction mixture was filtered through a pad of Celite, concentrated, and purified by flash chromatography (1:5 to 1:1 EtOAc/hexanes) to give the desired major diastereomer (±)-**29** (39 mg, 79%) and minor diastereomer (7 mg, 14%) as waxy solids. (±)-**29**: R_f = 0.20 (33% EtOAc/hexanes); IR (neat) 1831, 1700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.07 (d, *J* = 15.0 Hz, 1H), 4.10 (d, *J* = 15.5 Hz, 1H), 3.92 (dd, *J* = 8.0, 13.0 Hz, 1H), 3.85 (dd, *J* = 3.5, 13.5 Hz, 1H), 3.80 (s, 3H), 2.52 (dd, *J* = 5.5, 8.5 Hz, 1H), 1.88-1.95 (m, 1H), 1.79 (s, 3H), 1.69-1.74 (m, 1H), 1.52-1.64 (m, 2H), 1.28-1.41 (m, 6H), 1.07 (dd, *J* = 4.5, 8.5 Hz, 1H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 167.3, 160.0, 129.3, 129.2, 114.9, 84.4, 80.2, 55.5, 55.3, 48.8, 44.3, 31.7, 29.5, 28.1, 25.7, 22.8, 20.1, 14.2; LRMS (ESI) Calcd. for $C_{21}H_{29}NO_5$ [M+Li] 382, found 382.

Minor diatstereomer: R_f = 0.33 (33% EtOAc/hexanes); IR (neat) 3424, 1830, 1679 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.11 (d, *J* = 8.1 Hz, 2H), 6.62 (d, *J* = 8.7 Hz, 2H), 5.07 (d, *J* = 15.0 Hz, 1H), 3.96 (d, *J* = 15.0 Hz, 1H), 3.51 (dd, *J* = 5.1, 13.8 Hz, 1H), 3.43 (dd, *J* = 8.1, 13.5 Hz, 1H), 3.16 (s, 3H), 2.67 (t, *J* = 6.3 Hz, 1H), 1.40-1.60 (m, 4H), 1.23 (s, 3H), 1.12-1.22 (m, 7H), 0.87 (t, *J* = 6.3 Hz, 3H), 0.54 (dd, *J* = 5.1, 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 167.5, 159.7, 129.4, 129.1, 114.9, 85.1, 81.0, 55.5, 55.3, 49.1, 44.2, 31.7, 29.5, 27.1, 22.8, 16.3, 14.3; LRMS (ESI) Calcd. for $C_{21}H_{29}NO_5$ [M+H] 376, found 376.

1-(Cyclohex-2-enyl-hydroxy-methyl)-4-hexyl-2-(4-methoxy-benzyl)-5-methyl-6-oxa-2-aza-bicyclo[3.2.0]heptane-3,7-dione, (±)-31:

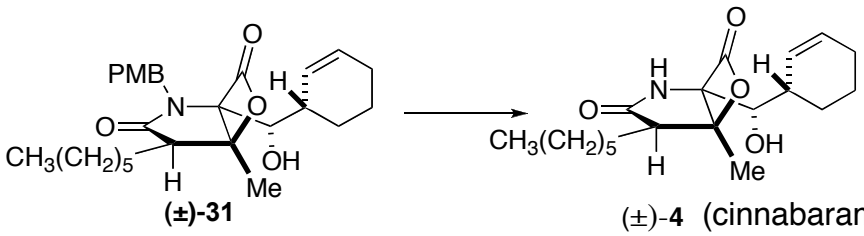


To a solution of alcohol (±)-**29** (78.0 mg, 0.208 mmol) and Et_3N (116 μL, 0.832 mmol) in DMSO/CH_2Cl_2 (1.6 mL/0.8 mL) was added SO_3•pyridine (132 mg, 0.832 mmol) at 0 °C. The reaction mixture was stirred at ambient temperature for 1 h and diluted with Et_2O (100 mL). The organic layer was washed with 0.2 N

HCl and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was used for the next step without further purification due to some instability of resulting aldehyde on purification by flash chromatography. Based on ^{1}H NMR, conversion to the aldehyde was ~86%.

A solution of tri-*n*-butyl-2-cyclohexenyltin (309 mg, 0.832 mmol) in THF (1.6 mL) was treated with *n*-BuLi (2.5 M in hexanes, 0.37 mL, 0.92 mmol) at –78 °C. After 30 min, the mixture was further treated with $ZnCl_2$ (0.5 M in THF, 1.66 mL, 0.832 mmol). After 30 min, a solution of the crude aldehyde in THF (2 mL) was slowly added to the freshly prepared zinc reagent **30**. The resulting mixture was stirred at –78 °C for 8 h, quenched with water and diluted with EtOAc (100 mL). The organic layer was washed with saturated NH_4Cl and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (1:4 EtOAc/hexanes) to give a mixture of two diastereomers (54 mg, 57% over 2 steps, dr 4.7:1, 500 MHz ^{1}H NMR) as colorless oils and the desired diastereomer (±)-**31** was the major as confirmed by subsequent conversion to the Bayer isolate (below). (±)-**31**: R_f = 0.65 (33% EtOAc/hexanes); IR (neat) 1828, 1700, 1683 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 5.78-5.82 (m, 1H), 5.51-5.56 (m, 1H), 4.67 (d, *J* = 15.5 Hz, 1H), 4.45 (d, *J* = 15.5 Hz, 1H), 4.09 (t, *J* = 7.0 Hz, 1H), 3.79 (s, 3H), 2.52 (dd, *J* = 6.0, 7.5 Hz, 1H), 2.27 (br, 1H), 2.05 (d, *J* = 6.5 Hz, 1H), 1.90 (s, 3H), 1.59-1.89 (m, 5H), 1.30-1.42 (m, 9H), 0.99-1.06 (m, 1H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 168.0, 159.5, 130.8, 130.0, 128.9, 126.1, 114.3, 85.9, 82.2, 70.7, 55.5, 49.0, 45.7, 37.4, 31.8, 29.6, 28.3, 25.9, 25.5, 24.9, 22.8, 21.4, 21.2, 14.3; LRMS (APCI) Calcd. for $C_{27}H_{37}NO_5$ [M+H] 456, found 456.

Representative Procedure for PMB-Deprotection as Described for 1-(cyclohex-2-enyl-hydroxy-methyl)-4-hexyl-5-methyl-6-oxa-2-aza-bicyclo[3.2.0]heptane-3,7-dione, (±)-4:



To a solution of alcohol (±)-**31** (6.2 mg, 0.018 mmol), along with trace amounts of a diastereomer from the previous step, in CH_3CN (0.6 mL) was added an aqueous solution of CAN (146 mg, 0.266 mmol) in H_2O (0.2 mL) at 0 °C dropwise. After stirring at 0 °C for 4 h, the reaction mixture was diluted with EtOAc (25 mL) and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (1:5 EtOAc/CH_2Cl_2) to give cinnabaramide A (±)-**4** (2.2 mg, 48%) as a white solid (dr >19:1, 500 MHz ^{1}H NMR). A crystal suitable for X-ray analysis was obtained by slow evaporation from Et_2O with ~5% CH_2Cl_2: R_f = 0.50 (33%

EtOAc/hexanes); IR (neat) 3346, 1820, 1698 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.96 (s, 1H), 5.84 (d, *J* = 11.5 Hz, 1H), 5.75-5.77 (m, 1H), 5.56 (d, *J* = 8.0 Hz, 1H), 3.70 (dd, *J* = 8.0, 9.0 Hz, 1H), 2.46 (dd, *J* = 6.0, 8.0 Hz, 1H), 2.29-2.36 (m, 1H), 1.92-1.98 (m, 1H), 1.81-1.88 (m, 1H), 1.77 (s, 3H), 1.24-1.75 (m, 13H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 177.0, 169.9, 129.5, 128.8, 87.2, 79.6, 70.1, 48.7, 38.7, 32, 29.8, 28.1, 26.3, 25.7, 25.6, 23.0, 22.0, 21.1, 15.0; LRMS (ESI) Calcd. for $C_{19}H_{29}NO_4$ [M+Li] 342, found 342.

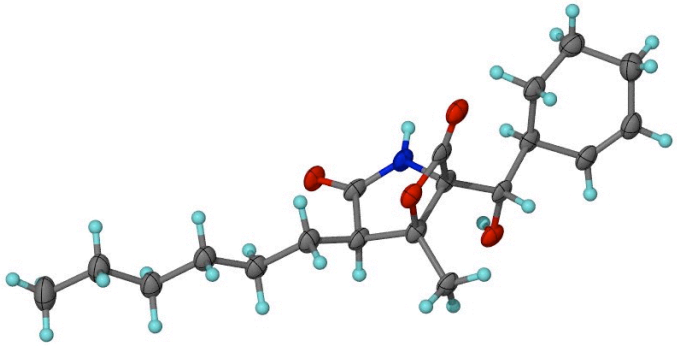
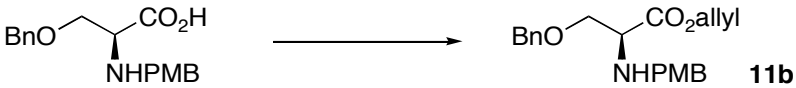


Figure 2. ORTEP plot of the X-ray structure of cinnabaramide A, **(±)-4**.

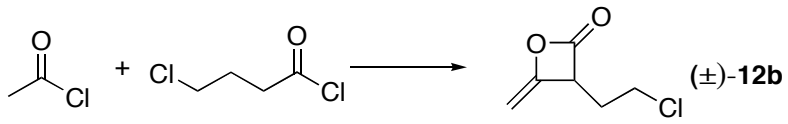
(*S*)-3-Benzyloxy-2-(4-methoxy-benzylamino)-propionic acid allyl ester, 11b.



11b

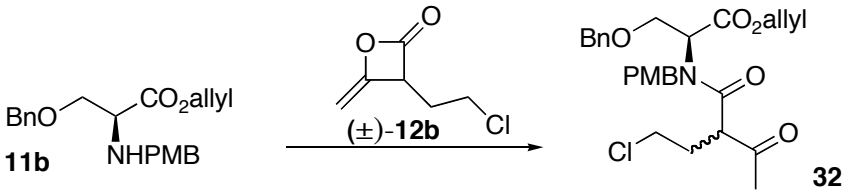
The suspension of *O*-benzyl-*N*-PMB serine (12.8 g, 40.6 mmol) and *p*-TsOH (9.65 g, 50.8 mmol) in allyl alcohol (30 mL) and benzene (100 mL) was stirred at reflux with a Dean-Stark apparatus until the calculated amount of water had been collected. The resulting solution was concentrated in *vacuo*, re-suspended in 5% aqueous $NaHCO_3$ (100 mL), the pH was adjusted to 9.0 with 1 M NaOH, and the product was extracted with Et_2O:EtOAc (1:1, 100 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (1:6 EtOAc/hexanes) to give the desired allyl ester **11b** (12.7 g, 88%) as a yellow oil. R_f = 0.61 (33% EtOAc/hexanes); IR (neat) 1738, 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.40 (m, 7 H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.88-6.01 (m, 1 H), 5.26-5.40 (m, 2 H), 4.69 (dt, *J* = 1.2, 5.7 Hz, 2H), 4.58 (d, *J* = 12.3 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 3.89 (d, *J* = 12.6 Hz, 1H), 3.82 (s, 3H), 3.70-3.82 (m, 2H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.57 (t, *J* = 4.8 Hz, 1H), 2.28 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 158.9, 138.0, 132.1, 131.8, 129.6, 128.4, 127.8, 127.7, 118.6, 113.9, 73.3, 71.2, 65.6, 60.5, 55.3, 51.5; LRMS (ESI) Calcd. for $C_{21}H_{26}NO_4$ [M+H] 356, found 356.

3-(2-Chloroethyl)-4-methyleneoxetan-2-one, (±)-12b:



Prepared according to the representative procedure for ketene-heterodimerization using acetyl chloride (10.0 g, 0.127mol), 4-chrorobutyrylchloride (15.0 g, 0.106 mol), and triethylamine (34.0 mL, 0.245 mol) in Et_2O (160 mL). Purification by flash chromatography on SiO_2 (95:5 pentane:Et_2O) gave ketene dimer (±)-**12b** (1.9 g, 12 %) as a clear oil. R_f = 0.67 (30% EtOAc/hexanes); IR (neat) 1860, 1694 cm^{-1}; ^1H NMR (300 MHz, benzene-d_6) δ 4.41 (dd, *J* = 2.1, 4.5 Hz, 1H), 3.80 (dd, *J* = 1.5, 4.5 1H), 3.35 (t, *J* = 7.8 Hz, 1H), 2.79-2.95 (m, 2H), 1.25-1.46 (m, 2H); ^{13}C NMR (125 MHz, benzene-d_6) δ 167.4, 152.6, 85.7, 51.7, 40.9, 29.9; LRMS (CI) Calcd. for $C_6H_7ClO_2$ [M+H] 147, found 147.

3-Benzyloxy-2-[[2-(2-chloro-ethyl)-3-oxo-butyryl]-(4-methoxy-benzyl)-amino]-propionic acid allyl ester, 32:



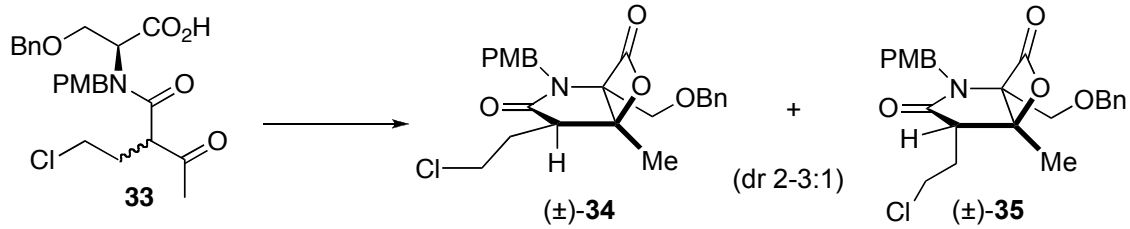
Prepared according to the representative procedure for ring opening of hetero-ketene dimers using allyl ester **11b** (1.92 g, 5.40 mmol), 2-hydroxypyridine (642 mg, 6.75 mmol) in THF (14 mL), and ketene-dimer (±)-**12b** (990 mg, 6.75 mmol). The reaction mixture was stirred at 60 °C for 36 h and purification by flash chromatography on SiO_2 (1:4 EtOAc:Hexanes) gave a mixture of two diastereomers **32** (2.17 g, 80%) as a colorless oil.

32a: R_f = 0.58 (40% EtOAc/Hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.18-7.36 (m, 7H), 6.87 (d, *J* = 8.0 Hz, 2H), 5.85-5.93 (m, 1H), 5.24-5.33 (m, 2H), 4.82 (d, *J* = 16.5 Hz, 1H), 4.66 (d, *J* = 17.0 Hz, 1H), 4.59-4.61 (m, 2H), 4.50 (dd, *J* = 4.0, 8.5 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.08 (dd, *J* = 8.5, 10.0 Hz, 1H), 4.01 (dd, *J* = 3.5, 10.0 Hz, 1H), 3.93 (dd, *J* = 5.5, 8.5 Hz, 1H), 3.81 (s, 3H), 3.46-3.58 (m, 2H), 2.34-2.43 (m,1H), 2.17-2.24 (m, 1H), 2.11 (s, 3H); LRMS (APCI) Calcd. for $C_{27}H_{32}ClNO_6$ [M+H] 502, found 502. **32b:** R_f = 0.50 (40% EtOAc/Hexanes); IR (neat) 1738, 1642, 1613 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25-7.36 (m, 7H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.86-5.94 (m, 1H), 5.24-5.33 (m, 2H), 4.88 (d, *J* = 16.5 Hz, 1H), 4.69 (d, *J* = 17.0 Hz, 1H), 4.57-4.66 (m, 3H), 4.50 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.03-4.06 (m, 2H), 3.92 (t, *J* = 7.0 Hz, 1H), 3.82 (s, 3H), 3.57 (t, *J* = 6.0 Hz, 2H), 2.34-2.41 (m, 1H), 2.15-2.21 (m, 1H), 1.97 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 202.5, 170.9, 168.5, 159.5, 137.8, 131.8, 128.8, 128.7, 128.6, 128.0, 127.9, 119.1, 114.4, 73.6, 68.5, 66.3, 60.3, 55.5, 53.7, 52.7, 43.3, 31.9, 28.7.

3-Benzyloxy-2-[[2-(2-chloro-ethyl)-3-oxo-butyryl]-(4-methoxy-benzyl)-amino]-propionic acid, 33:

To a solution of allyl ester **32** (1.24 g, 2.47 mmol) in THF (20 mL) was added morpholine (646 mg, 7.41 mmol) and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) at ambient temperature. The reaction mixture was stirred at ambient temperature for 7 h and diluted with Et_2O (200 mL). The organic layer was washed with 0.2 N HCl and brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on SiO_2 (15:85 acetone:CH_3Cl) to give acid **33** (620 mg, 75%). Data provided for only one diastereomer: IR (neat) 1721, 1639 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20-7.40 (m, 7H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.82 (d, *J* = 16.5 Hz, 1H), 4.70 (d, *J* = 16.5 Hz, 1H), 4.48 (s, 2H), 4.41-4.45 (m, 1H), 4.00-4.10 (m, 3H), 3.84 (s, 3H), 3.50-3.65 (m, 2H), 2.20-2.50 (m, 2H), 2.13 (s, 3H); LRMS (ESI) Calcd. for $C_{24}H_{28}ClNO_6$ [M–H] 460, found 460.

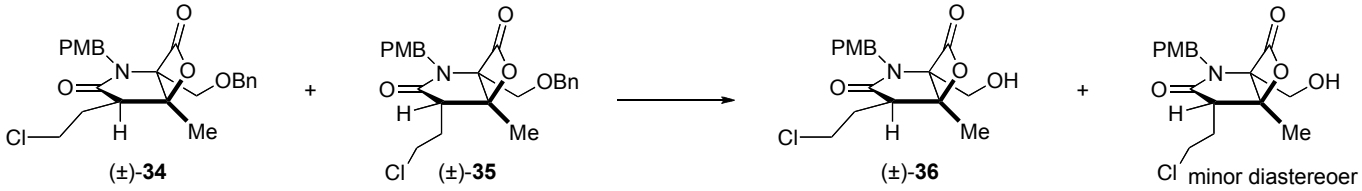
1-(Benzyloxymethyl)-4-(2-chloroethyl)-2-(4-methoxybenzyl)-5-methyl-6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, (±)-34:



Prepared according to the representative procedure for bis-cyclization process using *N*-propyl-2-bromo pyridinium triflate (273 mg, 0.789 mmol), 4-pyrrolidinopyridine (223 mg, 1.56 mmol), Hünig's base (70 μL, 0.39 mmol), and keto-acid **33** (180 mg, 0.390 mmol) in CH_2Cl_2 (15 mL). Purification by flash chromatography (SiO_2, 10% EtOAc/hexanes) gave a mixture of two *β*-lactones **34** and **35** (59 mg, 34 %, dr = 2:1, 500 MHz ^1H NMR).

(±)-**34:** R_f = 0.32 (20% EtOAc/hexanes); IR (neat) 1830, 1703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.36 (m, 3H), 7.13-7.15 (m, 4H), 6.80 (d, *J* = 8.5 Hz, 2H), 4.73 (d, *J* = 15.5 Hz, 1H), 4.31 (d, *J* = 15.5 Hz, 1H), 4.17 (d, *J* = 12.0 Hz, 1H), 4.13 (d, *J* = 11.5 Hz, 1H), 4.01 (ddd, *J* = 5.0, 7.5, 12.5 Hz, 1H), 3.77-3.81 (m, 1H), 3.77 (s, 3H), 3.73 (d, *J* = 11.5 Hz, 1H), 3.57 (d, *J* = 11.5 Hz, 1H), 2.91 (t, *J* = 7.5 Hz, 1H), 2.31-2.38 (m, 1H), 2.10-2.16 (m, 1H), 1.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 166.1, 159.2, 136.4, 129.2, 128.6, 128.5, 128.2, 128.0, 113.9, 83.4, 79.3, 73.5, 61.6, 55.2, 45.0, 44.3, 42.5, 28.4, 19.2; LRMS (ESI) Calcd. for $C_{24}H_{26}ClNO_5$ [M+H] 444, found 444.

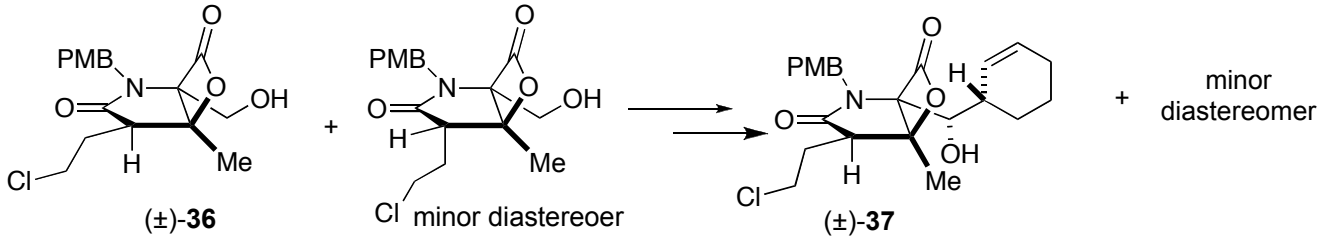
4-(2-Chloro-ethyl)-1-hydroxymethyl-2-(4-methoxy-benzyl)-5-methyl-6-oxa-2-aza-bicyclo[3.2.0]heptane-3,7-dione, (±)-36:



Prepared according to the representative procedure for debenzylation using the mixture of *β*-lactones (38 mg, 0.13 mmol, dr 6:1) and 10 wt% palladium on carbon (10 mg) in THF (5 mL) at ambient temperature for 5 h under H_2 atmosphere. Purification by flash chromatography (1:40 EtOAc/CH_2Cl_2) gave the desired alcohol (±)-**36** along with the minor diastereomer (29.9 mg, 98%, dr 6:1) as a waxy solid. Further purification allowed enrichment to ~10-19:1 dr (500 MHz ^{1}H NMR).

(±)-**36**: R_f = 0.29 (4.8% EtOAc/CH_2Cl_2); IR (neat) 3449, 1831, 1687 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.13 (d, *J* = 15.0 Hz, 1H), 4.06 (d, *J* = 15.5 Hz, 1H), 4.03 (ddd, *J* = 5.5, 7.5, 12.5 Hz, 1H), 3.92 (dd, *J* = 9.0, 13.5 Hz, 1H), 3.85 (dd, *J* = 4.5, 13.5 Hz, 1H), 3.80 (s, 3H), 3.78-3.82 (m, 1H), 2.94 (t, *J* = 7.0 Hz, 1H), 2.32-2.38 (m, 1H), 2.01-2.18 (m, 1H), 1.77 (s, 3H), 0.86 (dd, *J* = 5.0, 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 166.7, 159.6, 129.0, 128.7, 114.7, 83.6, 80.2, 55.3, 55.1, 44.9, 44.1, 42.4, 28.4, 19.1; LRMS (ESI) Calcd. for $C_{17}H_{20}ClNO_5$ [M+H] 354, found 354.

4-(2-Chloro-ethyl)-1-(cyclohex-2-enyl-hydroxy-methyl)-2-(4-methoxy-benzyl)-5-methyl-6-oxa-2-aza-bicyclo[3.2.0]heptane-3,7-dione, (±)-37:

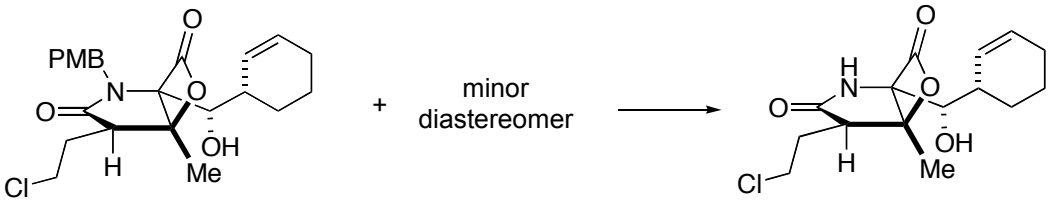


To a solution of diastereomeric alcohols, (±)-**36** plus minor diastereomer (29 mg, 0.082 mmol, dr >10:1), in DMSO/toluene (0.8 mL/0.8 mL) was added EDCI (79 mg, 0.41 mmol), followed by dichloroacetic acid (14 μL, 0.16 mmol) at ambient temperature. The reaction mixture was stirred at ambient temperature for 2 h and diluted with EtOAc (50 mL). The organic layer was washed with 0.1 N HCl, and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was used for the next step without further purification due to some instability of resulting aldehyde to column chromatography.

A solution of tri-*n*-butyl-2-cyclohexenyltin (140 mg, 0.377 mmol) in THF (0.7 mL) was treated with *n*-BuLi (2.5 M in hexanes, 133 μL, 0.333 mmol) at –78 °C. After 30 min, $ZnCl_2$ (0.5 M in THF, 0.77 mL, 0.39 mmol) was added and following an additional 30 min, a solution of the crude aldehyde in THF (1.3

mL) was slowly added to the freshly prepared zinc reagent **30**. The resulting mixture was stirred at –78 °C for 2.5 h, quenched with water and diluted with EtOAc (50 mL). The organic layer was washed with saturated NH_4Cl and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (1:6 EtOAc/hexanes) to give a mixture of predominantly two diastereomers (12 mg, 33%, dr 3.5:1 + trace minor diasts., 500 MHz ^{1}H NMR) as a colorless oil which was carried directly to the next step without further characterization. The major diastereomer **37** was confirmed to possess the correct relative stereochemistry following subsequent conversion to salinosporamide A (below): R_f = 0.64 (40% EtOAc/Hexanes); IR (neat) 3467, 1828, 1692 cm^{-1}; LRMS (ESI) Calcd. for $C_{23}H_{28}ClNO_5$ [M+Li] 440, found 440.

***Rac*-Salinosporamide A, 4-(2-Chloro-ethyl)-1-(cyclohex-2-enyl-hydroxy-methyl)-5-methyl-6-oxa-2-aza-bicyclo[3.2.0]heptane-3,7-dione, (±)-3:**



37 (±)-**3** (salinosporamide A)

To a mixture of diastereomer (±)-**37** (10 mg, 0.023 mmol, dr = 3.5:1) in CH_3CN (0.1 mL) was added an aqueous solution of CAN (63 mg, 0.12 mmol) in H_2O (25 μL) at 0 °C. After stirring at 0 °C for 2 h, the reaction mixture was diluted with EtOAc (25 mL) and washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (1:10 to 1:4 EtOAc/CH_2Cl_2) providing diastereomerically pure salinosporamide A (±)-**3** (3.5 mg, 49%) as a white solid (dr >19:1, 500 MHz ^{1}H NMR). A crystal suitable for X-ray analysis was obtained by slow evaporation from CH_2Cl_2 with ~5% CH_3CN: R_f = 0.09 (5% EtOAc/CH_2Cl_2); IR (neat) 3413, 1821, 1700 cm^{-1}; ^{1}H NMR (500 MHz, pyridine-d_5) δ 10.63 (s, 1H), 6.42 (d, *J* = 10.5 Hz, 1H), 5.86-5.90 (m, 1H), 4.26 (t, *J* = 9.0 Hz, 1H), 4.13 (dt, *J* = 7.5, 10.5 Hz, 1H), 4.02 (dt, *J* = 7.0, 10.5 Hz, 1H), 3.18 (t, *J* = 7.0 Hz, 1H), 2.82-2.89 (m, 1H), 2.45-2.52 (m, 1H), 2.27-2.36 (m, 2H), 2.07 (s, 3H), 1.89-1.95 (m, 2H), 1.66-1.72 (m, 1H), 1.35-1.40 (m, 1H) 1H was overlapped with H_2O.; ^{13}C NMR (125 MHz, pyridine-d_5) δ 176.9, 169.4, 129.1, 128.7, 86.3, 80.4, 71.0, 46.2, 43.3, 39.3, 29.0, 26.5, 25.4, 21.7, 20.0; LRMS (ESI) Calcd. for $C_{15}H_{20}ClNO_4$ [M+Li] 314, found 314.

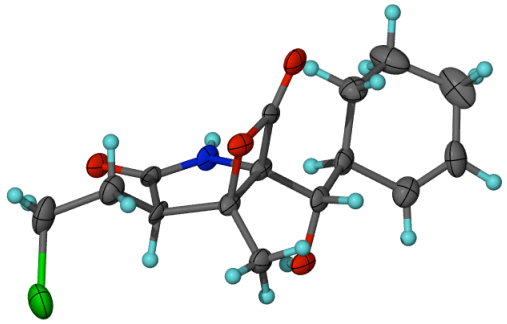
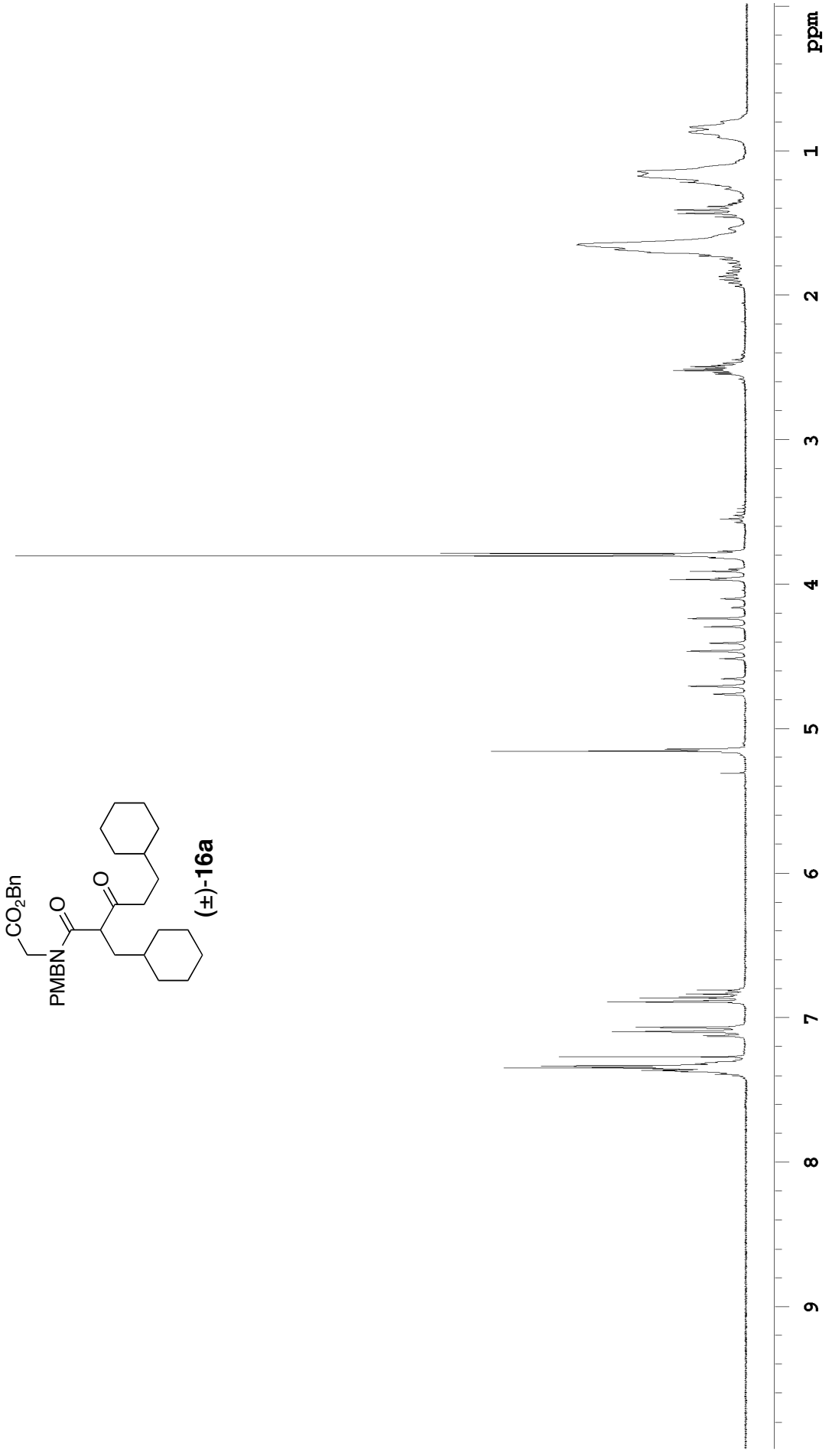
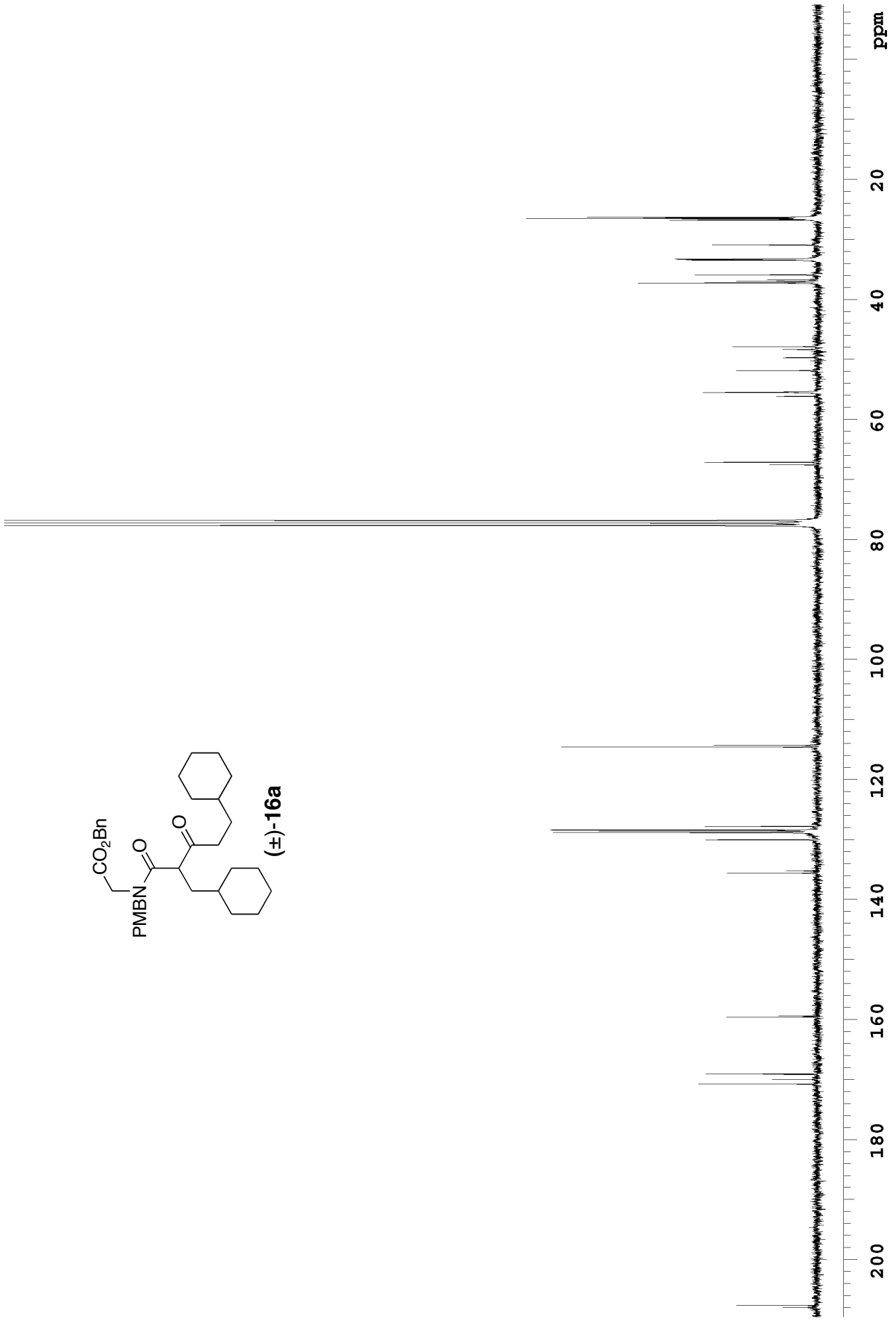
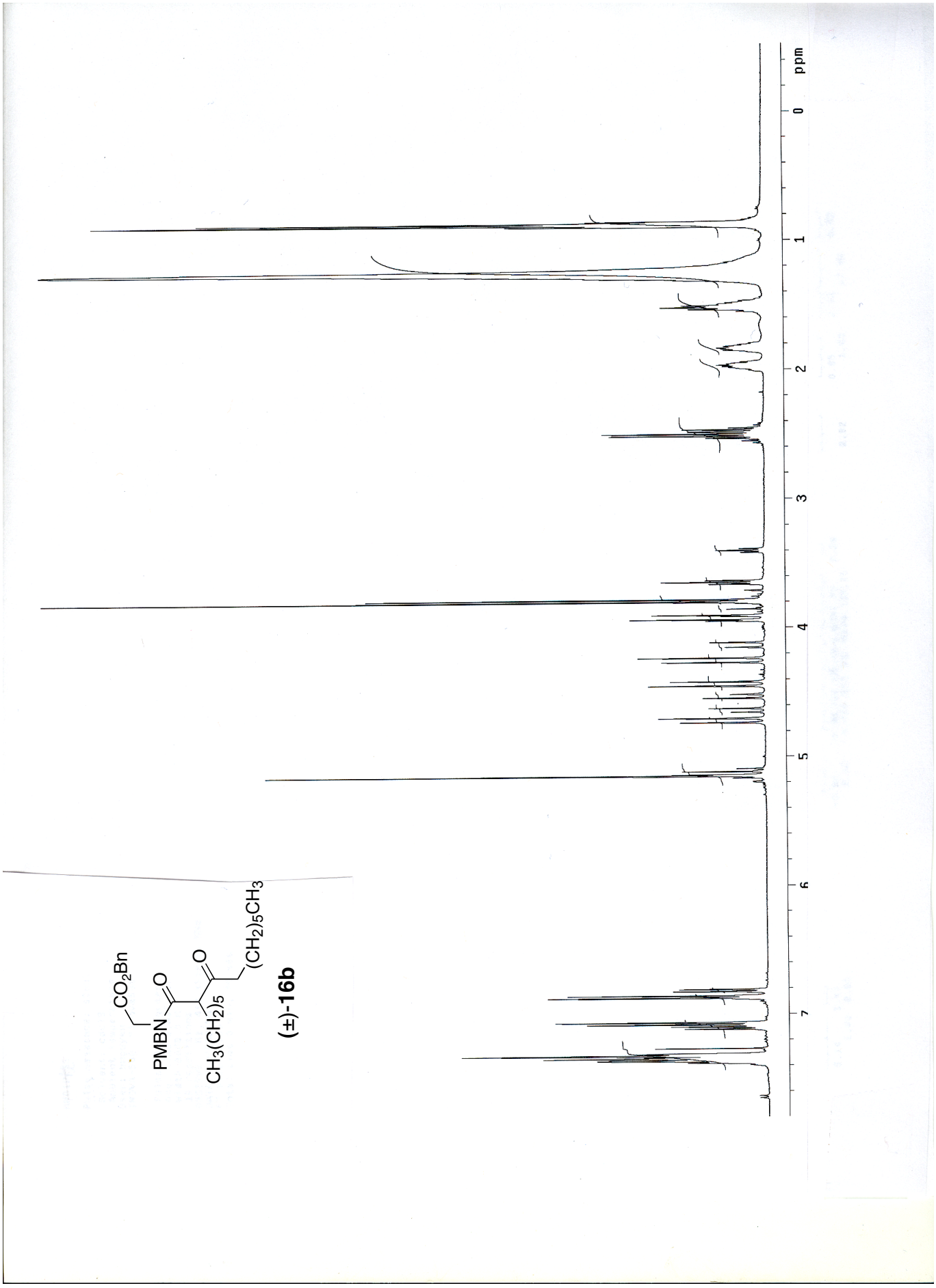
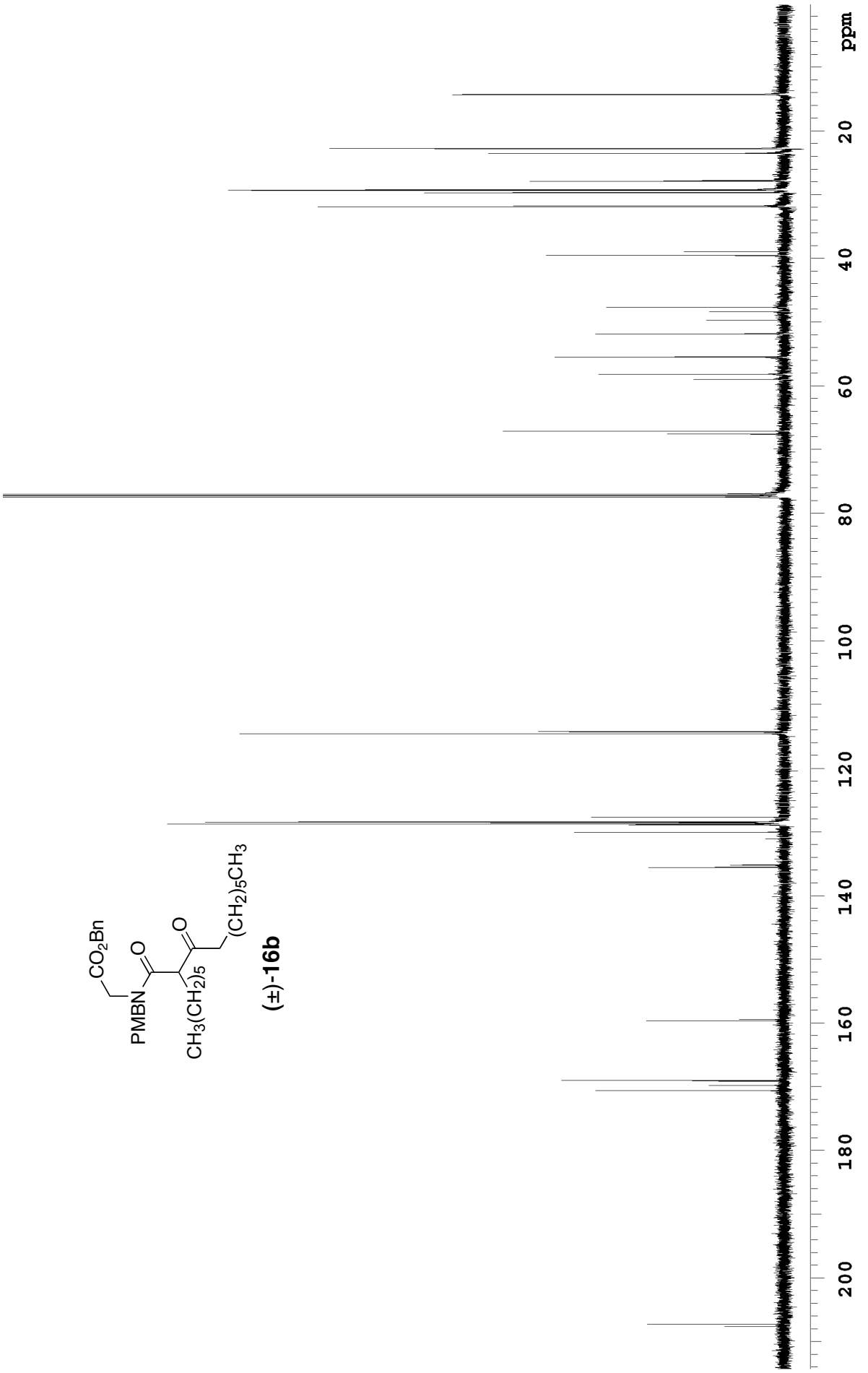


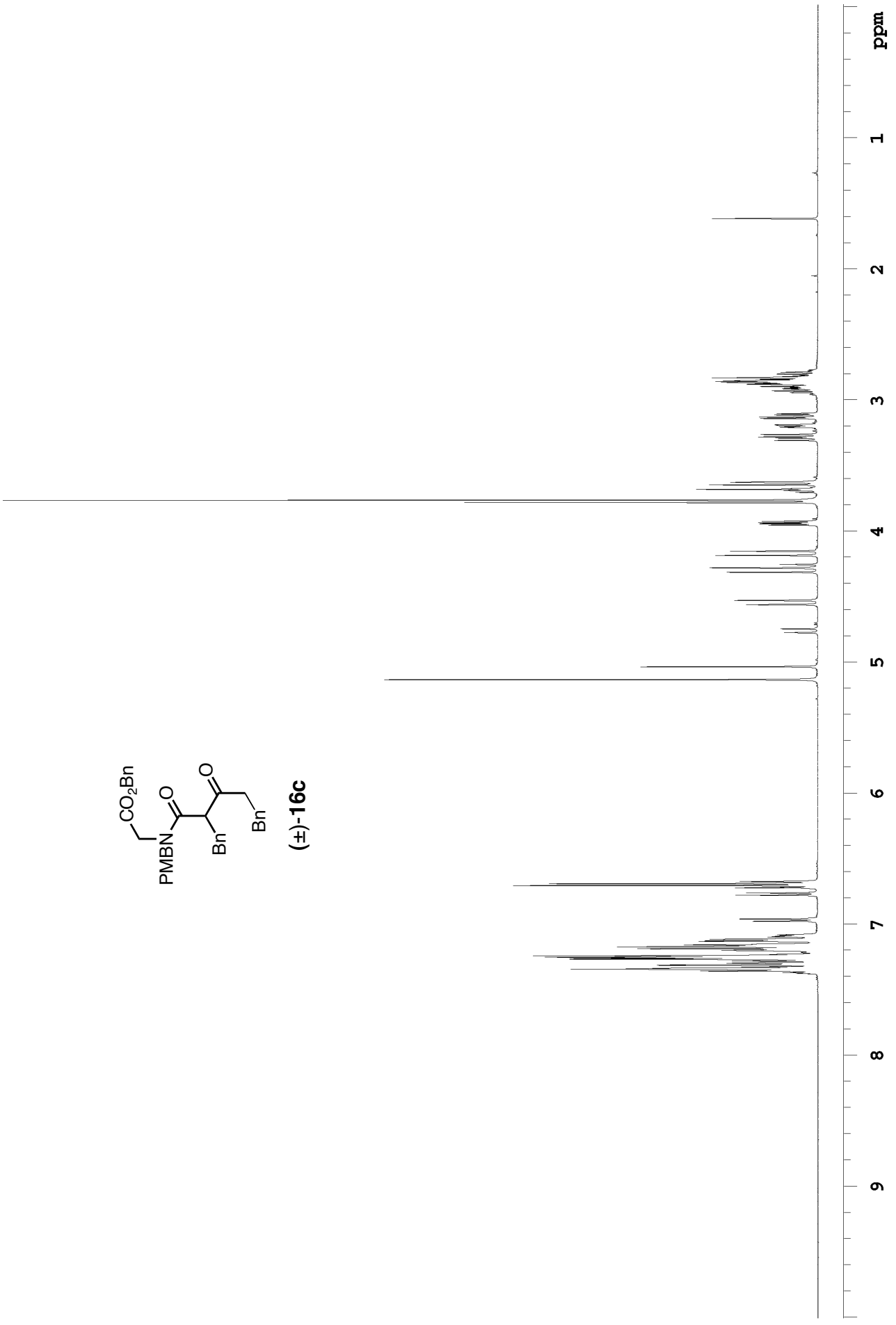
Figure 3. ORTEP plot of the X-ray structure of *rac*-salinosporamide A, **(±)-3**

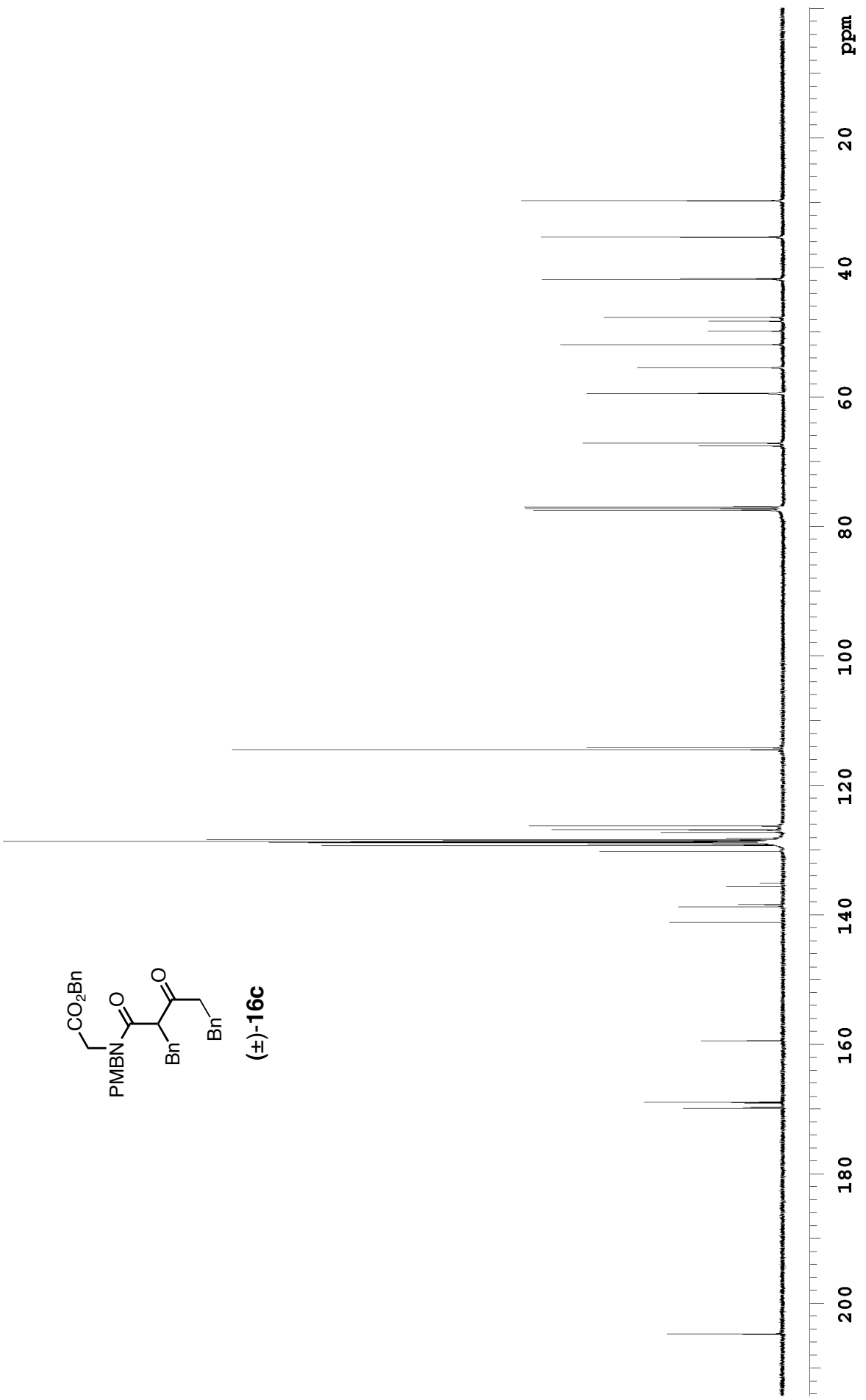

CO2Bn
PMBN
O
O
(±)-16a
ppm
1
2
3
4
5
6
7
8
9

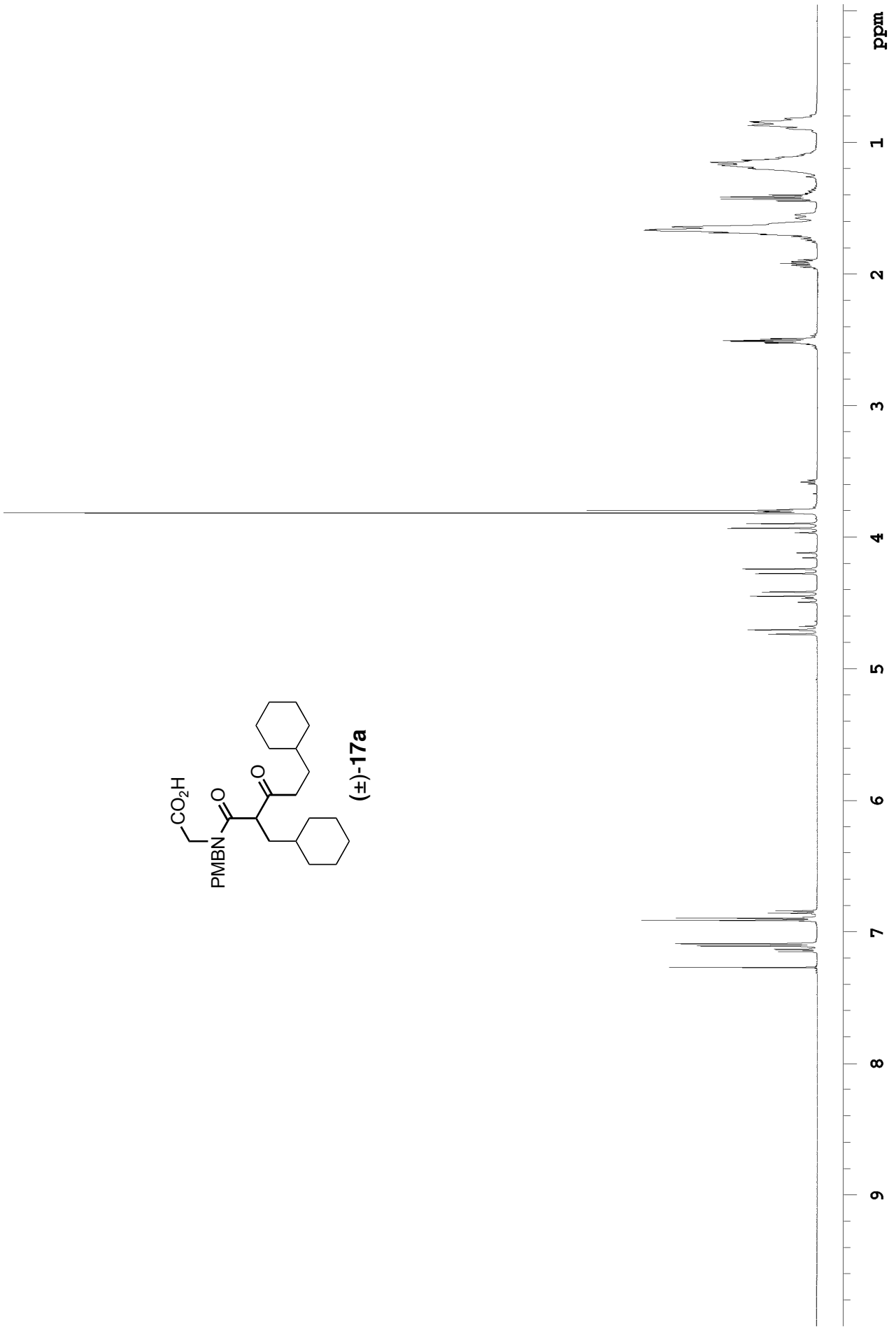

ppm
20
40
60
80
100
120
140
160
180
200
CO2Bn
PMBN
O
O
(±)-16a

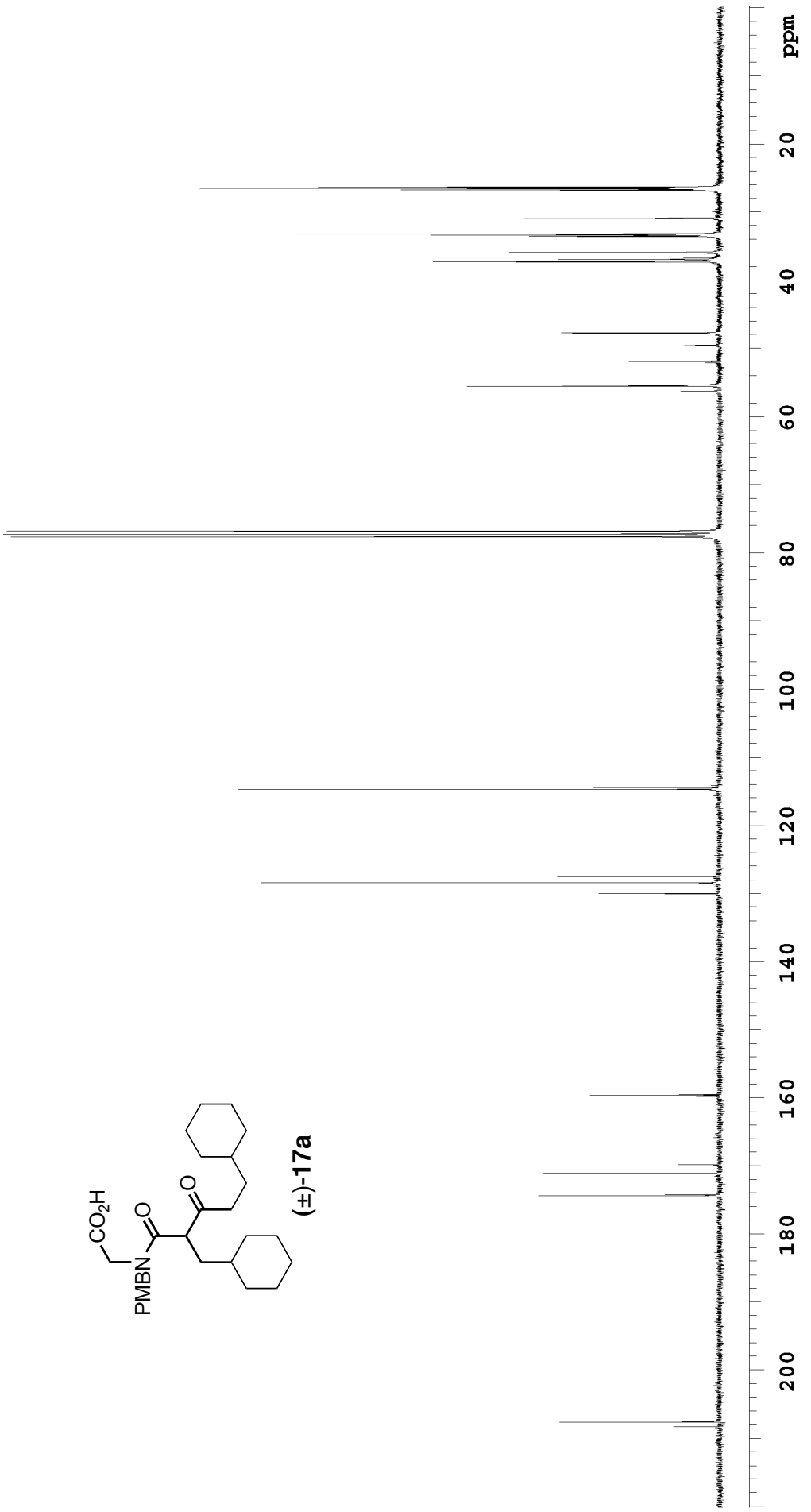

CO2Bn
PMBN
O
CH3(CH2)5
O
(CH2)5CH3
(±)-16b
ppm
0
1
2
3
4
5
6
7

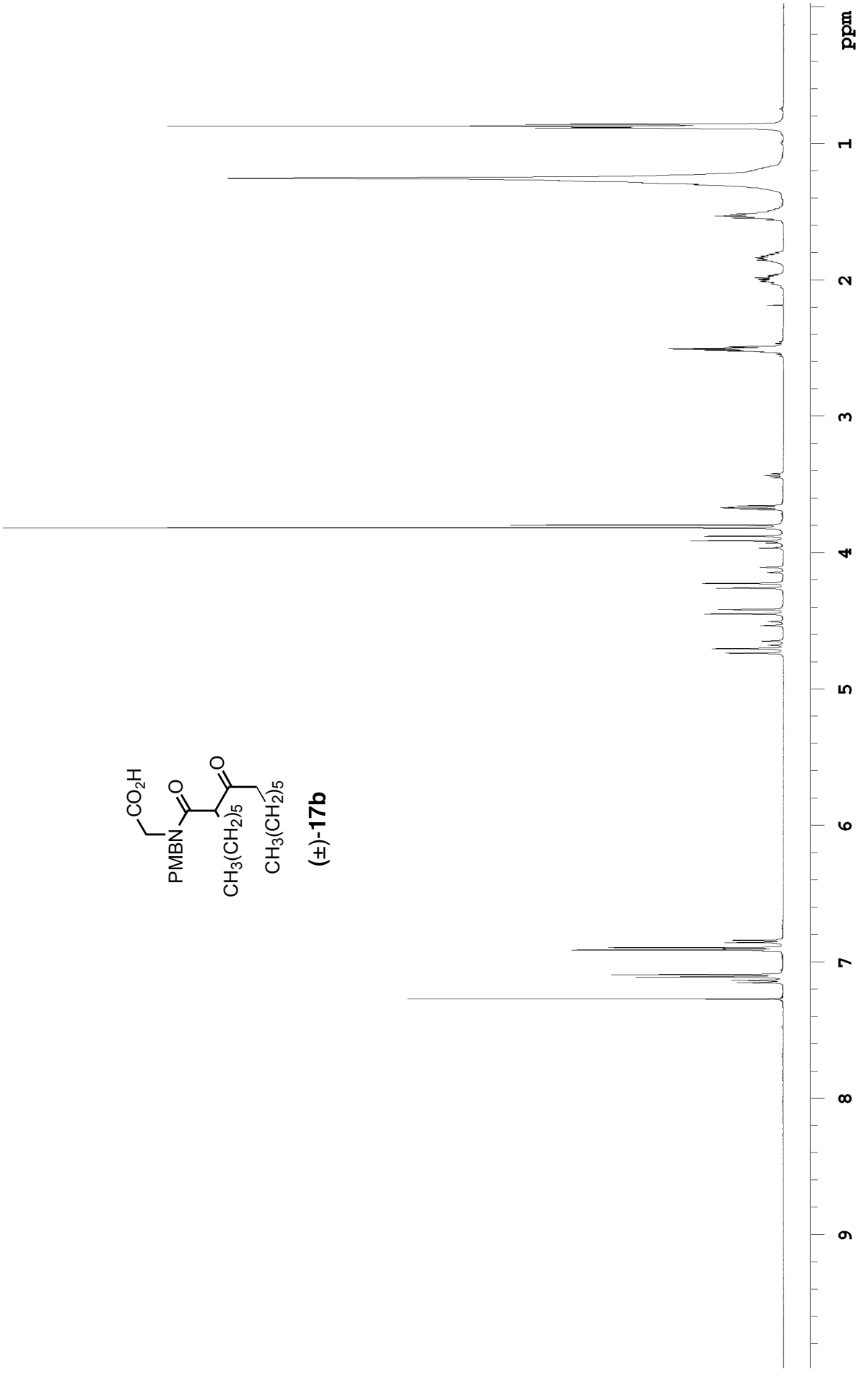

CO2Bn
PMBN
O
CH3(CH2)5
O
(CH2)5CH3
(±)-16b
ppm
20
40
60
80
100
120
140
160
180
200

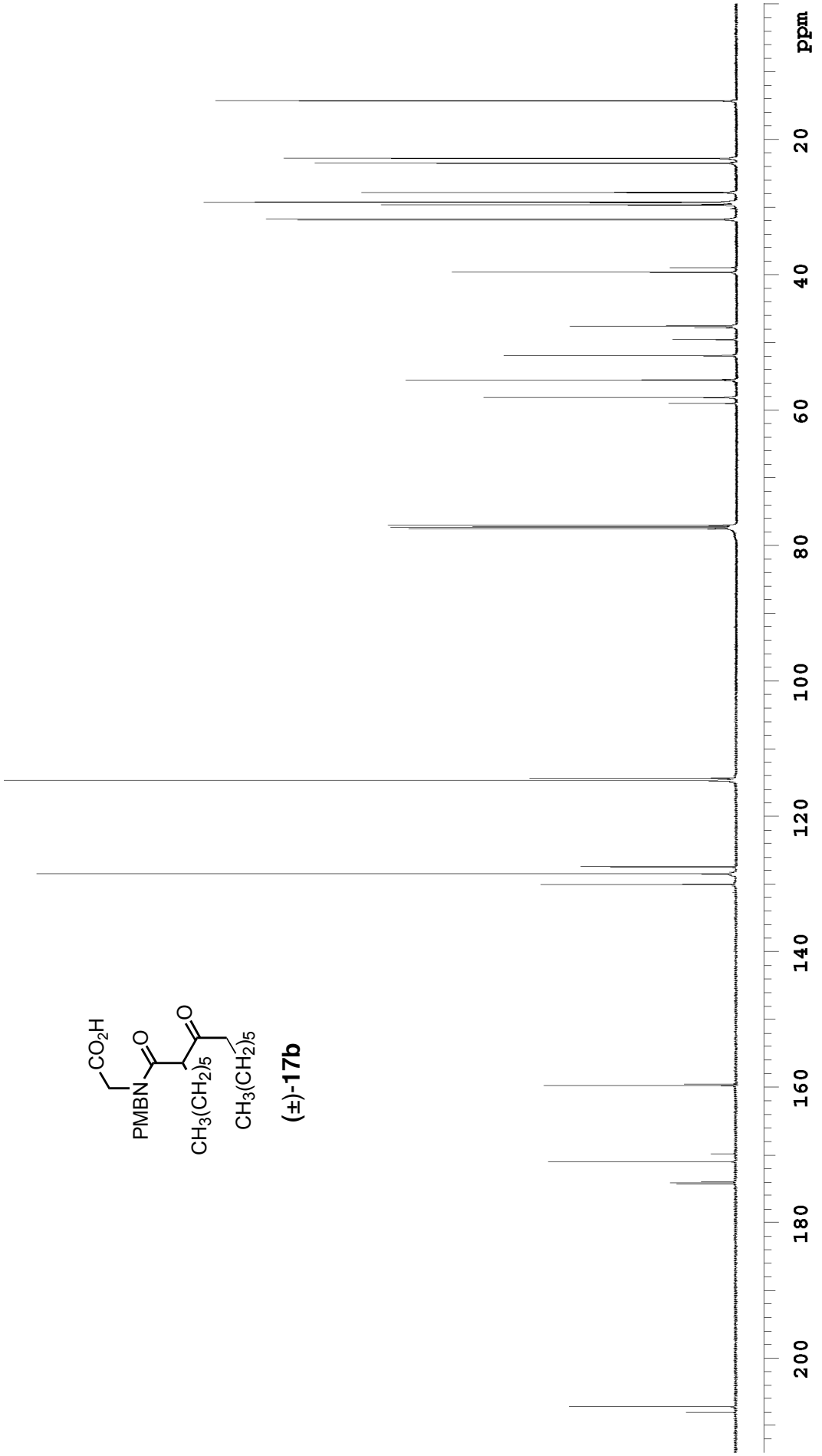

ppm
1
2
3
4
5
6
7
8
9
CO2Bn
PMBN
O
Bn
O
Bn
(±)-16c


CO2Bn
PMBN
O
Bn
O
Bn
(±)-16c
ppm
200
180
160
140
120
100
80
60
40
20

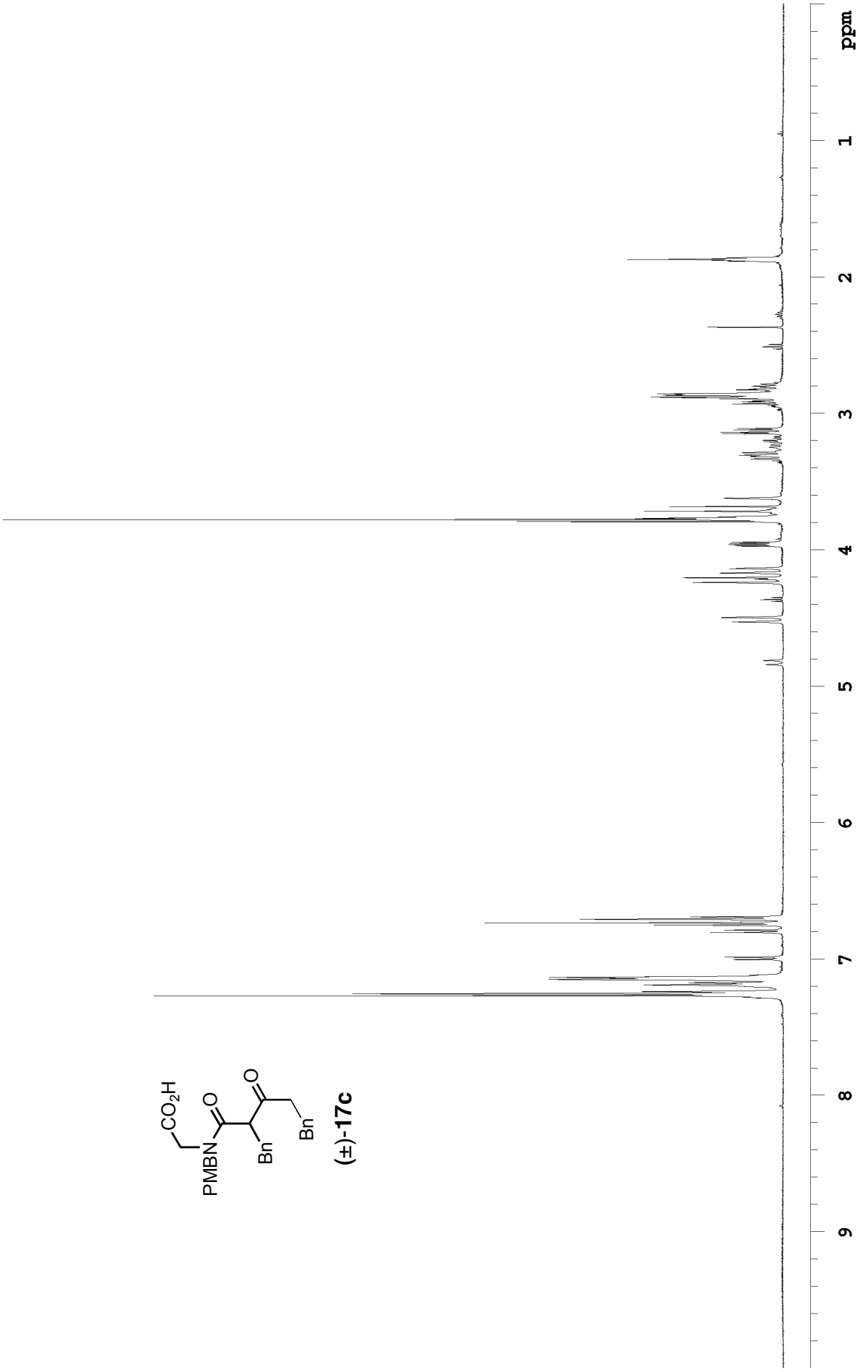

ppm
1
2
3
4
5
6
7
8
9
PMBN
CO2H
O
O
(±)-17a

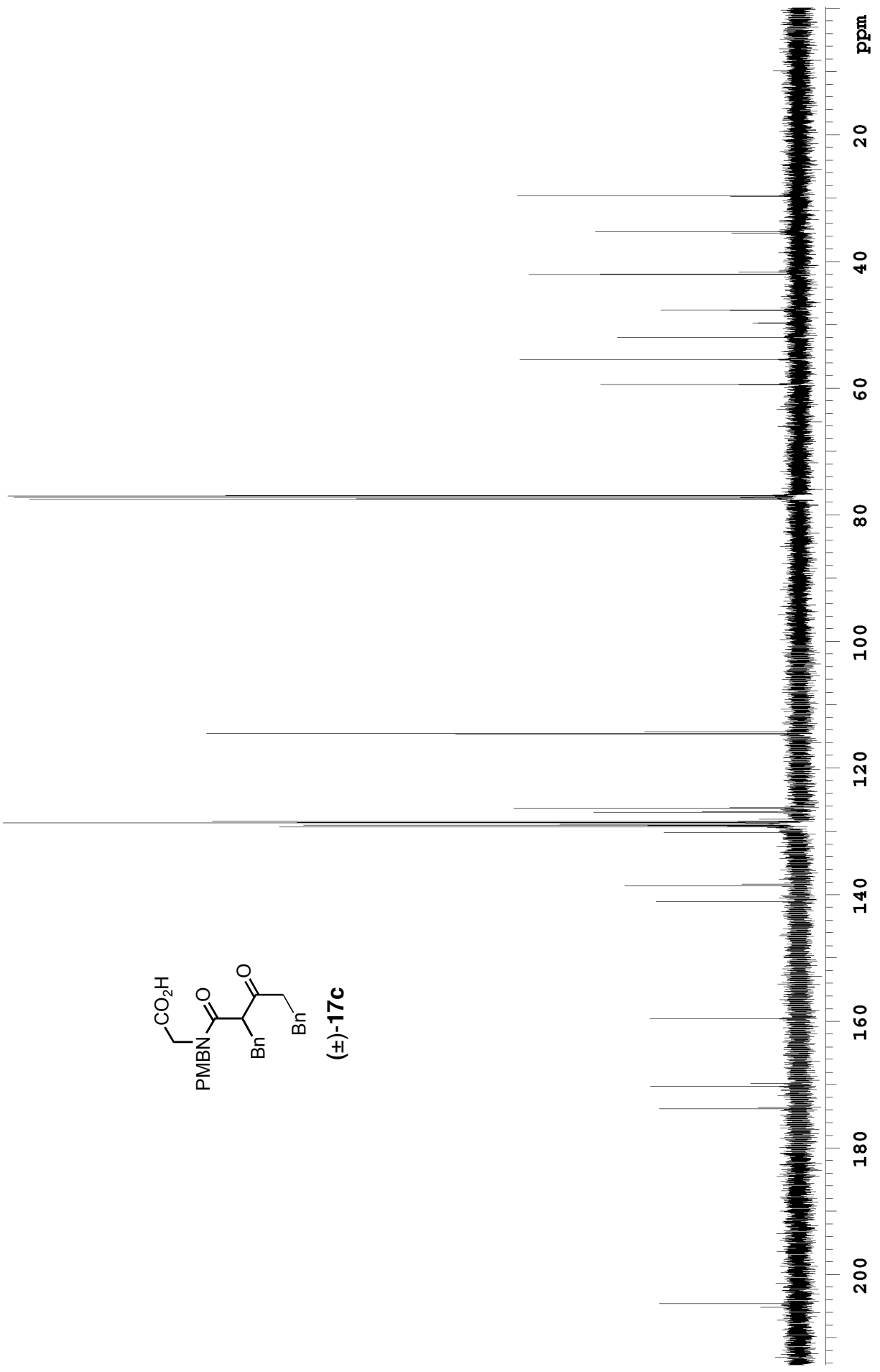

ppm
20
40
60
80
100
120
140
160
180
200
CO2H
PMBN
O
O
(±)-17a


CO2H
PMBN
O
CH3(CH2)5
O
CH3(CH2)5
(±)-17b
ppm
1
2
3
4
5
6
7
8
9

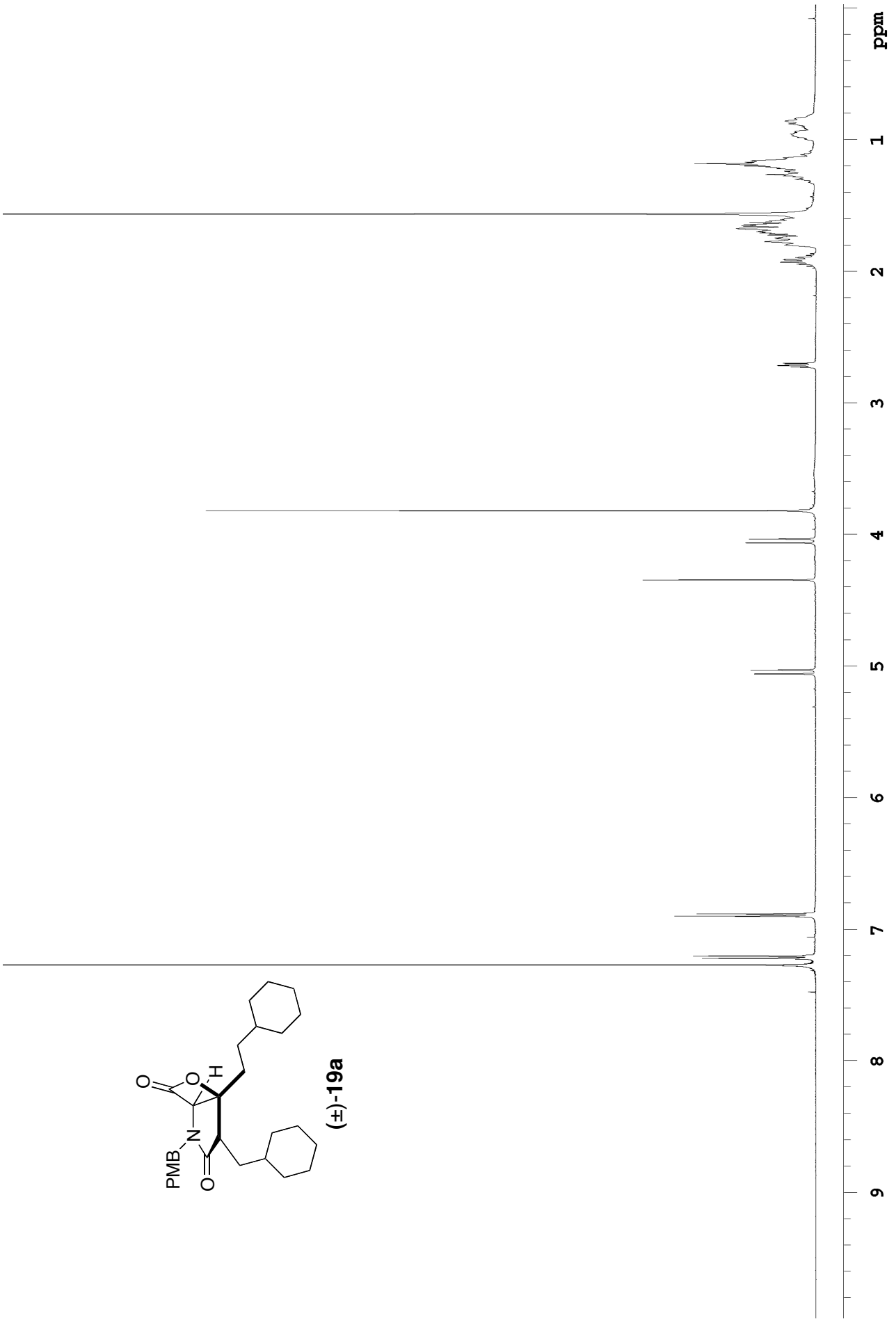

ppm
20
40
60
80
100
120
140
160
180
200
CO2H
PMBN
O
O
CH3(CH2)5
CH3(CH2)5

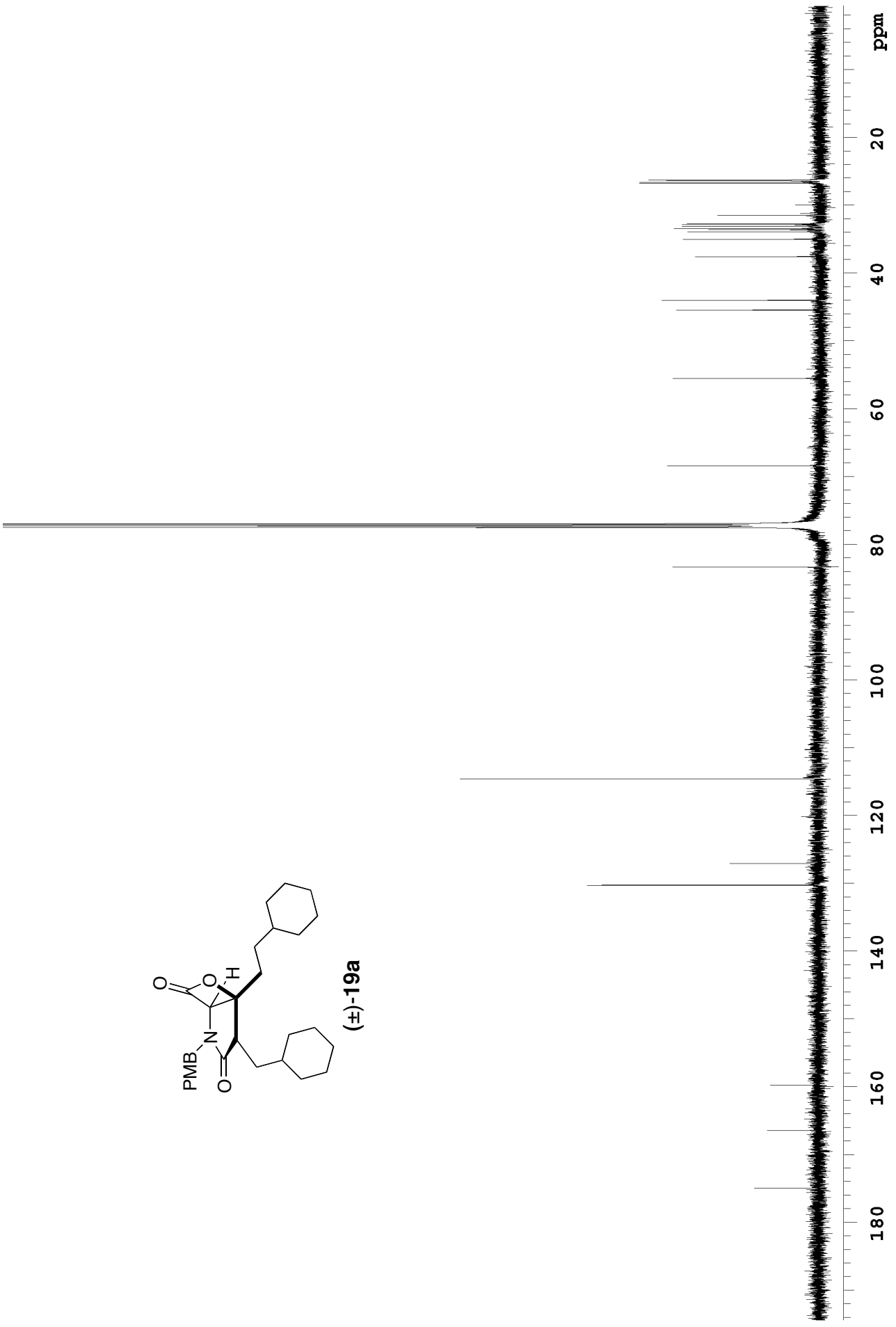
(±)-**17b**

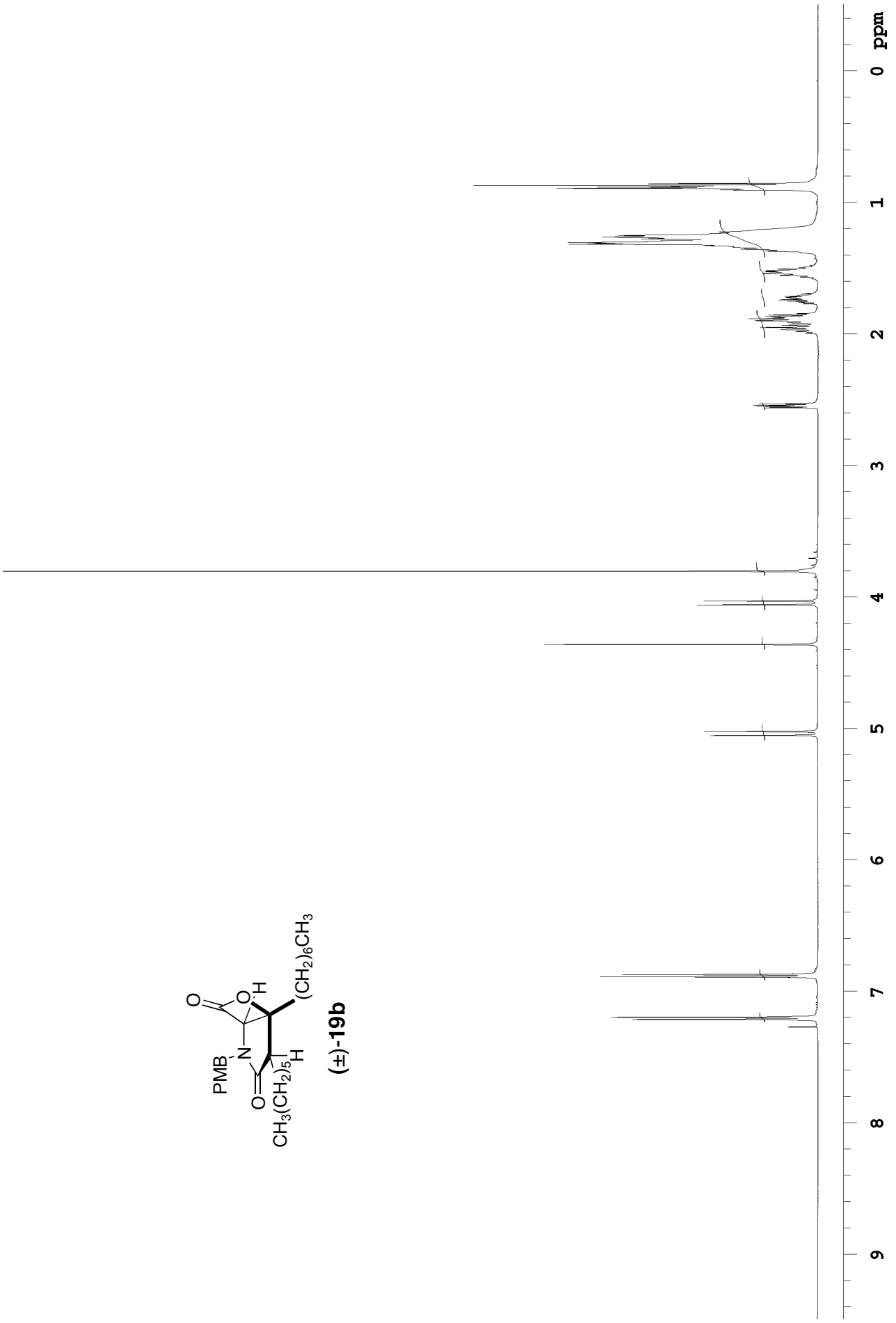

CO2H
PMBN
O
Bn
O
Bn
(±)-17c
ppm
1
2
3
4
5
6
7
8
9



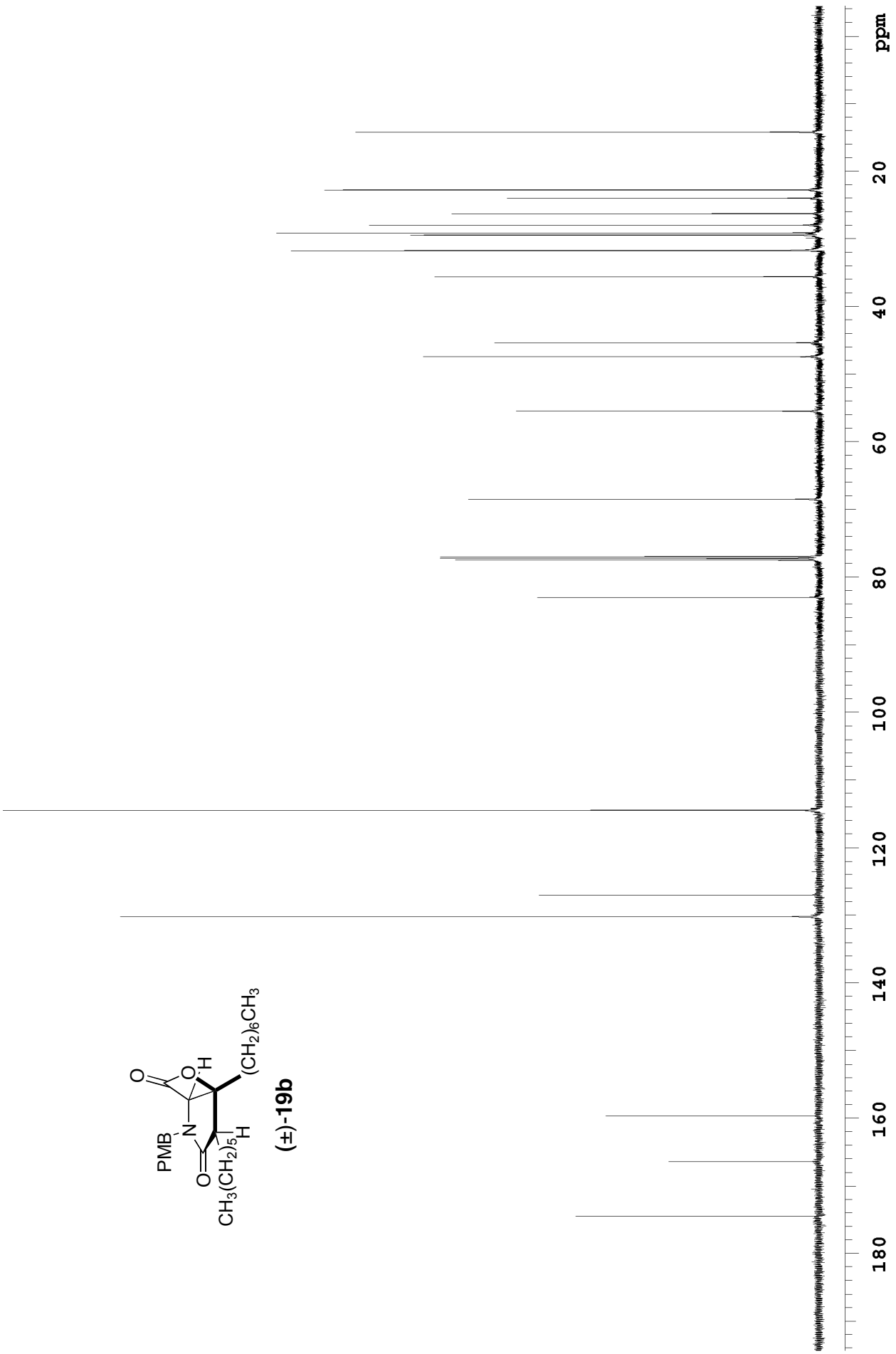
(±)-17c

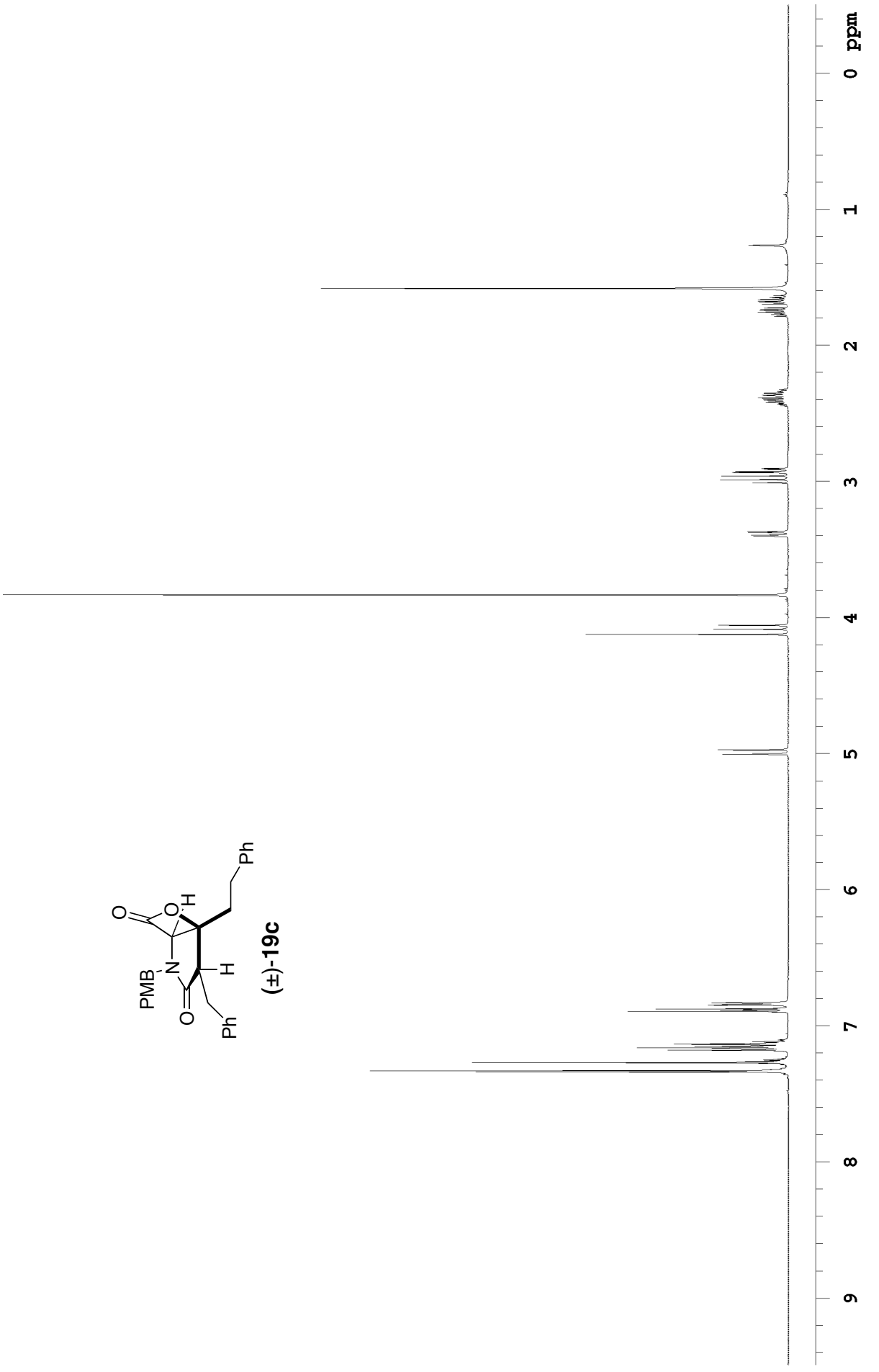

ppm
1
2
3
4
5
6
7
8
9
O
O
H
N
PMB
O
(±)-19a

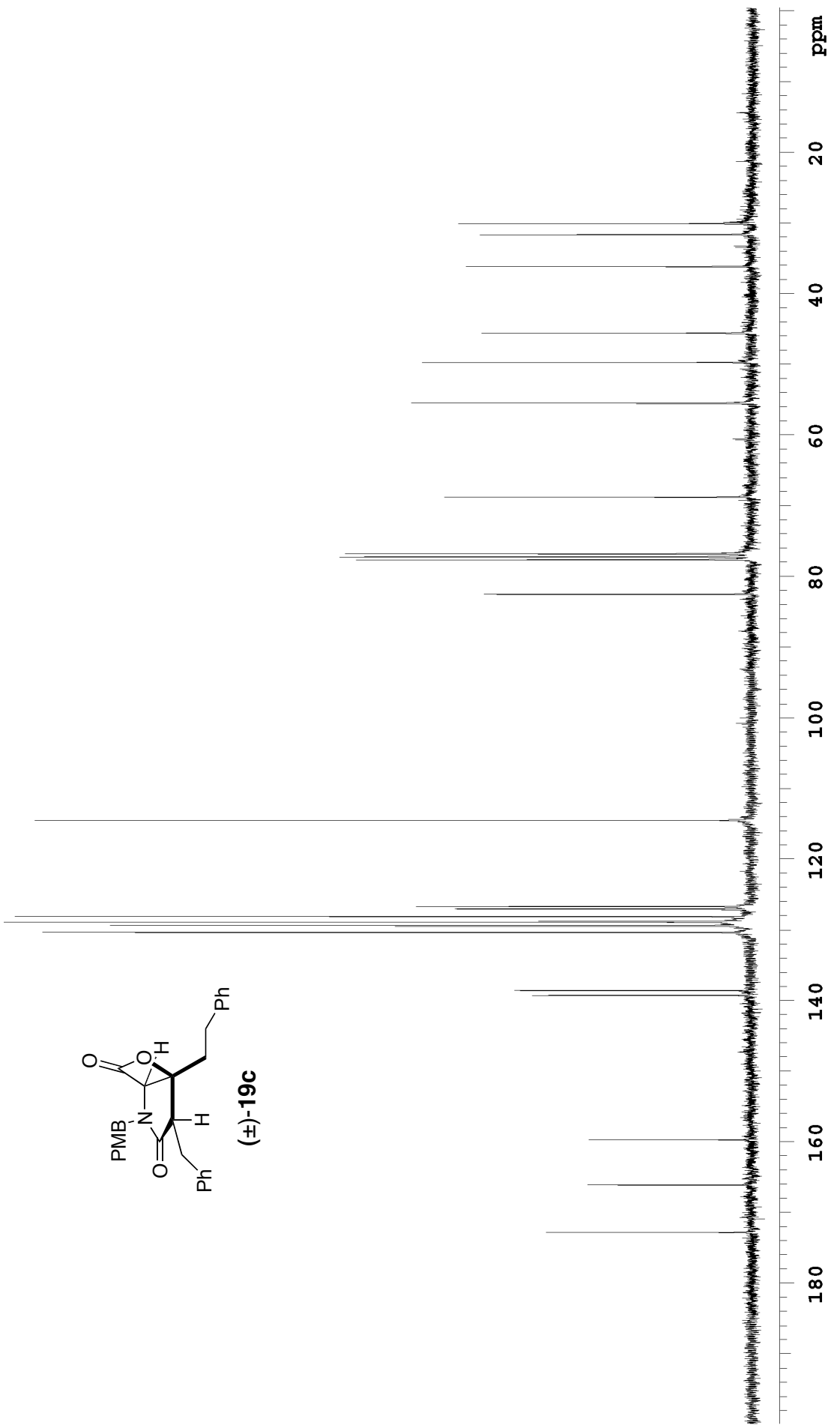

ppm
20
40
60
80
100
120
140
160
180
O
O
H
N
PMB
O
(±)-19a

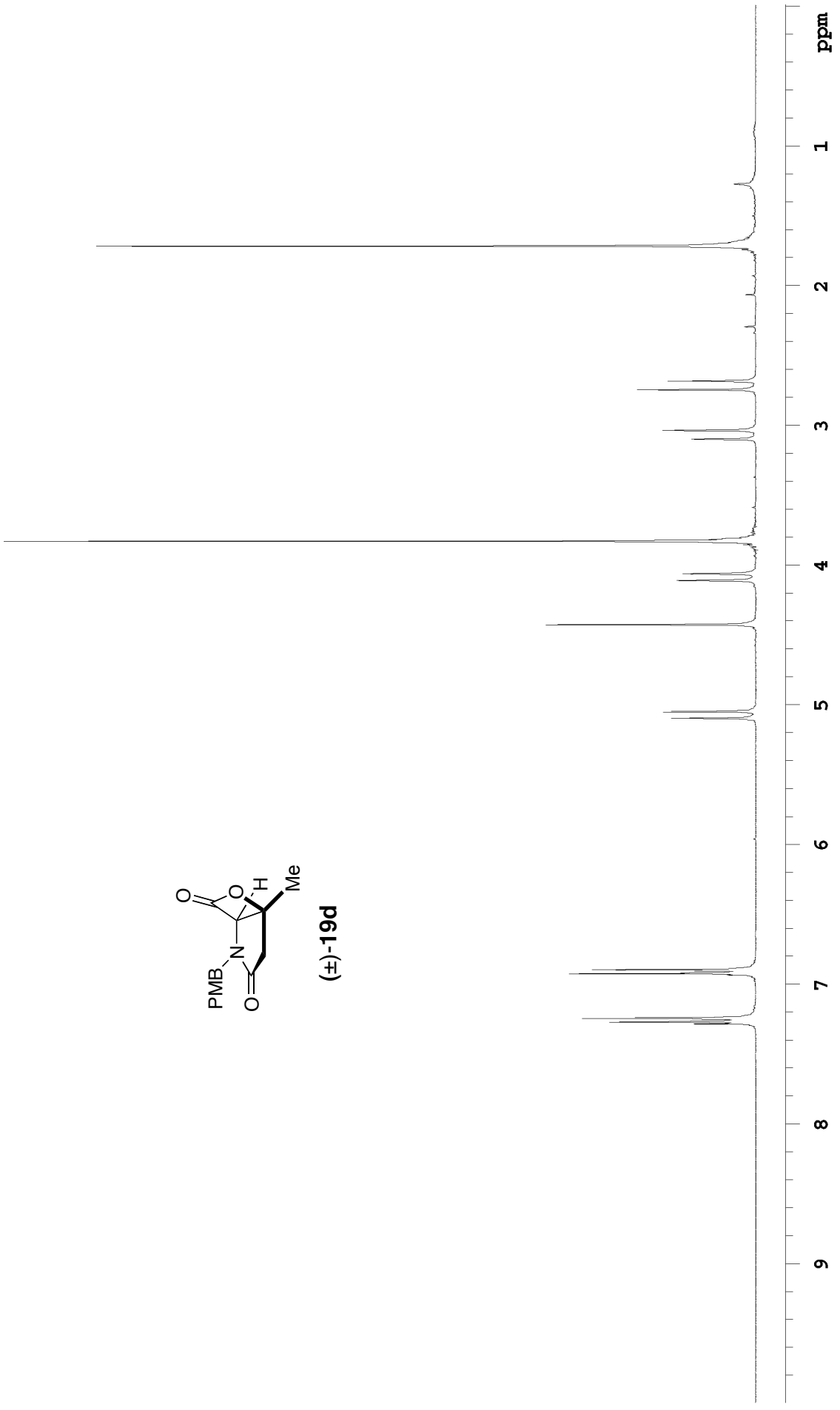


(±)-19b

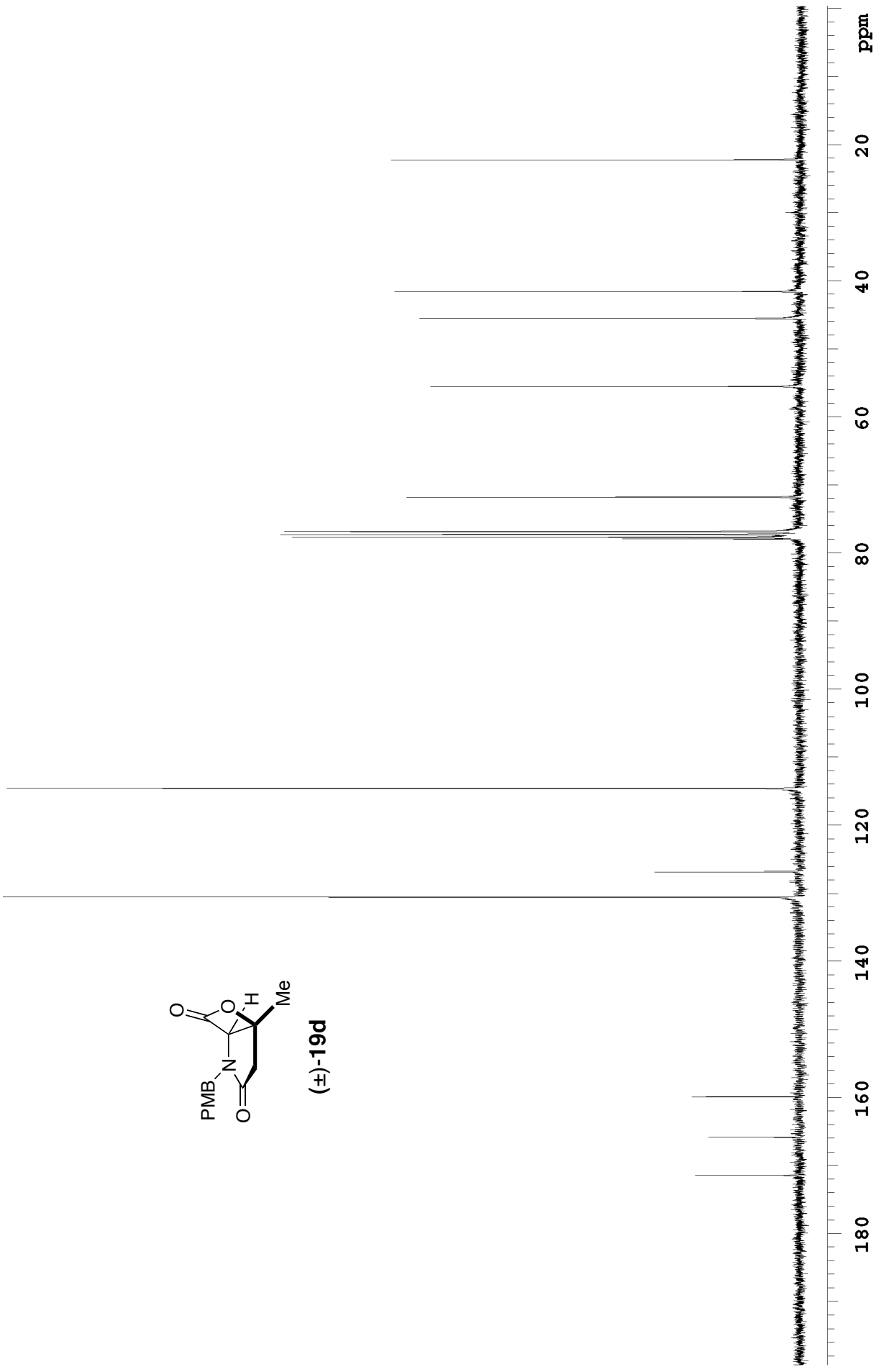

ppm
20
40
60
80
100
120
140
160
180
PMB
N
O
O
H
O
H
$CH_3(CH_2)_5$
$(CH_2)_6CH_3$
(±)-19b


PMB
N
O
O
H
H
O
Ph
Ph
(±)-19c
0 ppm
1
2
3
4
5
6
7
8
9

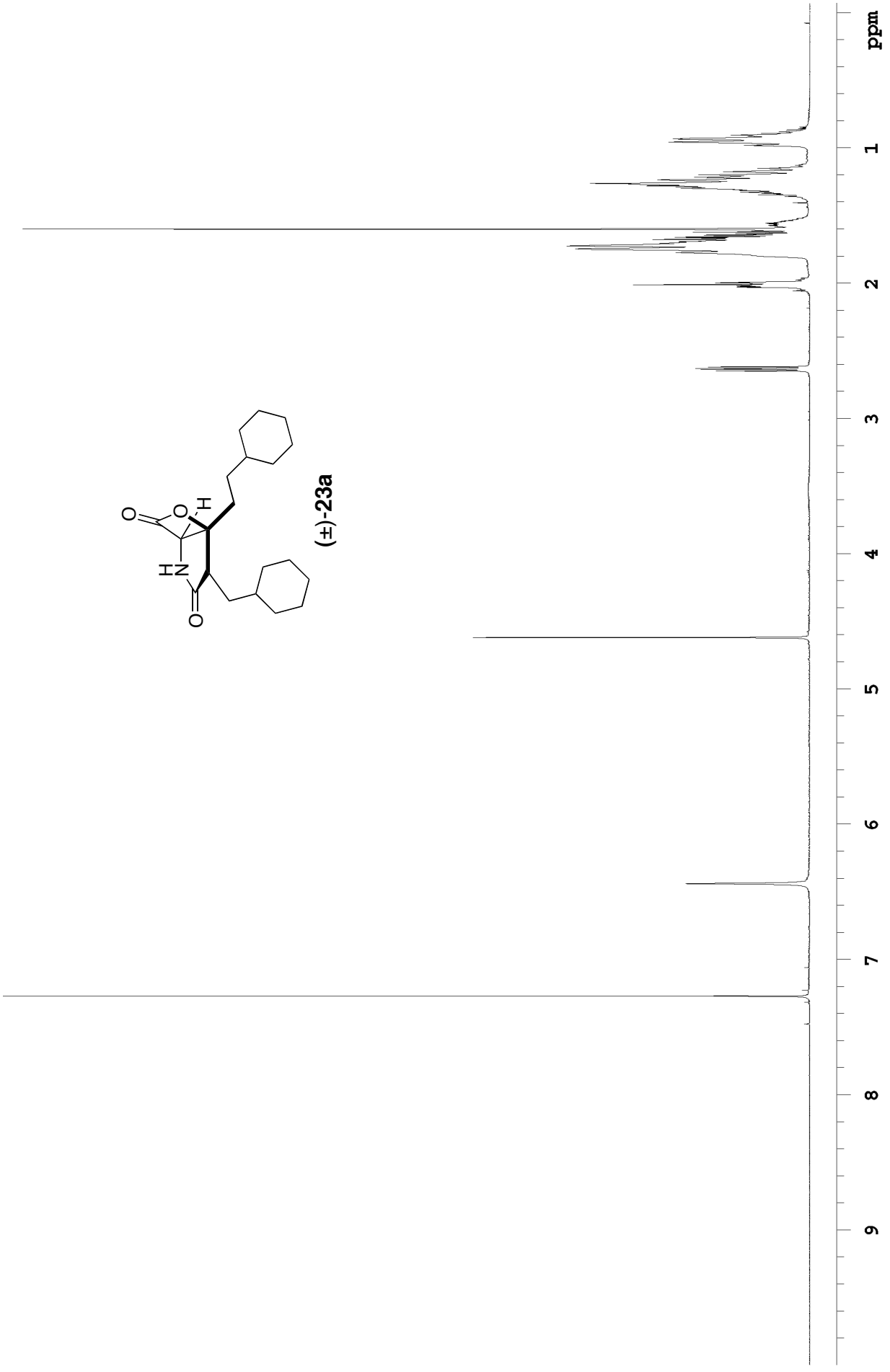

ppm
20
40
60
80
100
120
140
160
180
O
O
H
PMB
N
H
O
Ph
Ph
(±)-19c



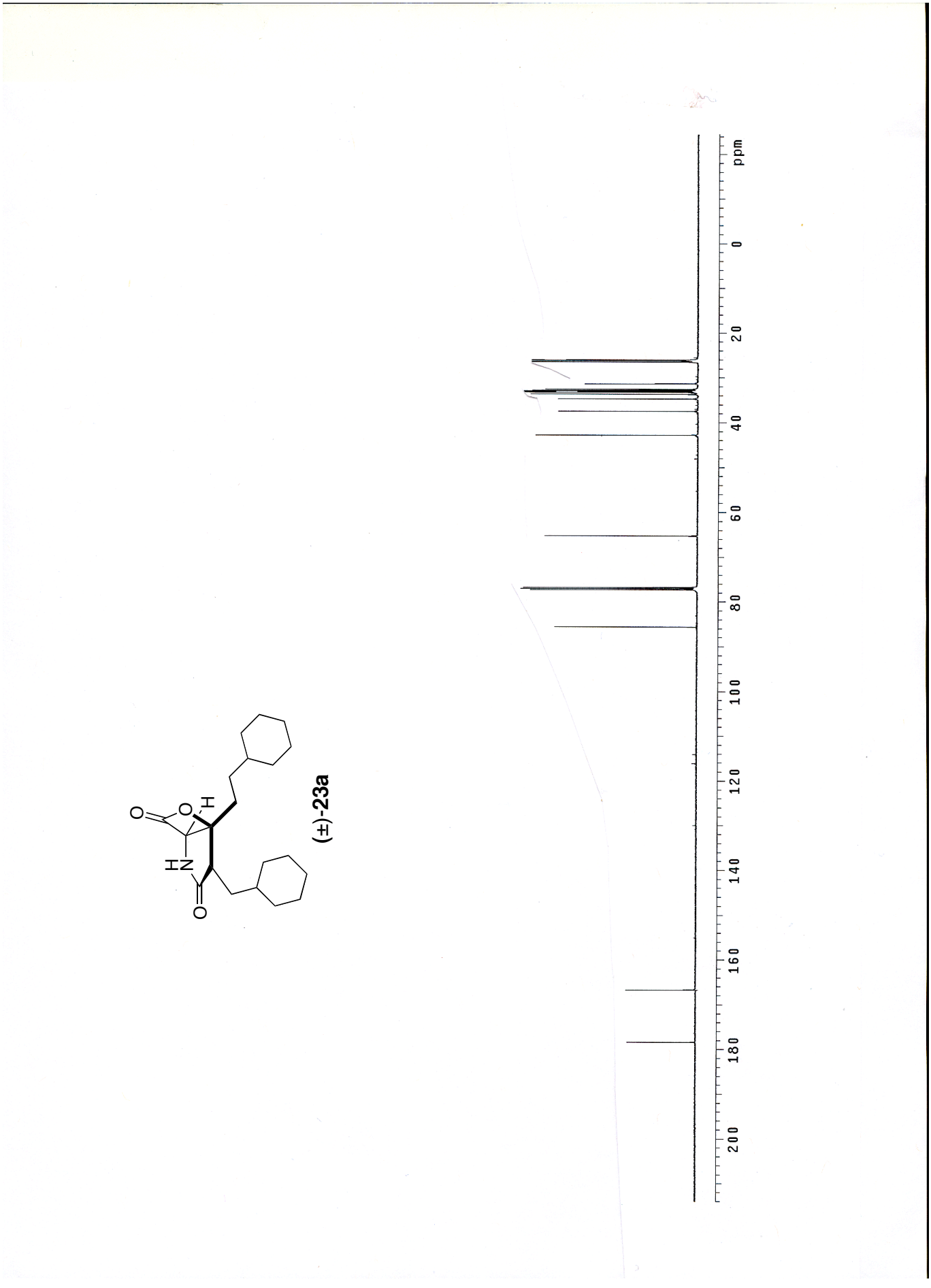
(±)-19d

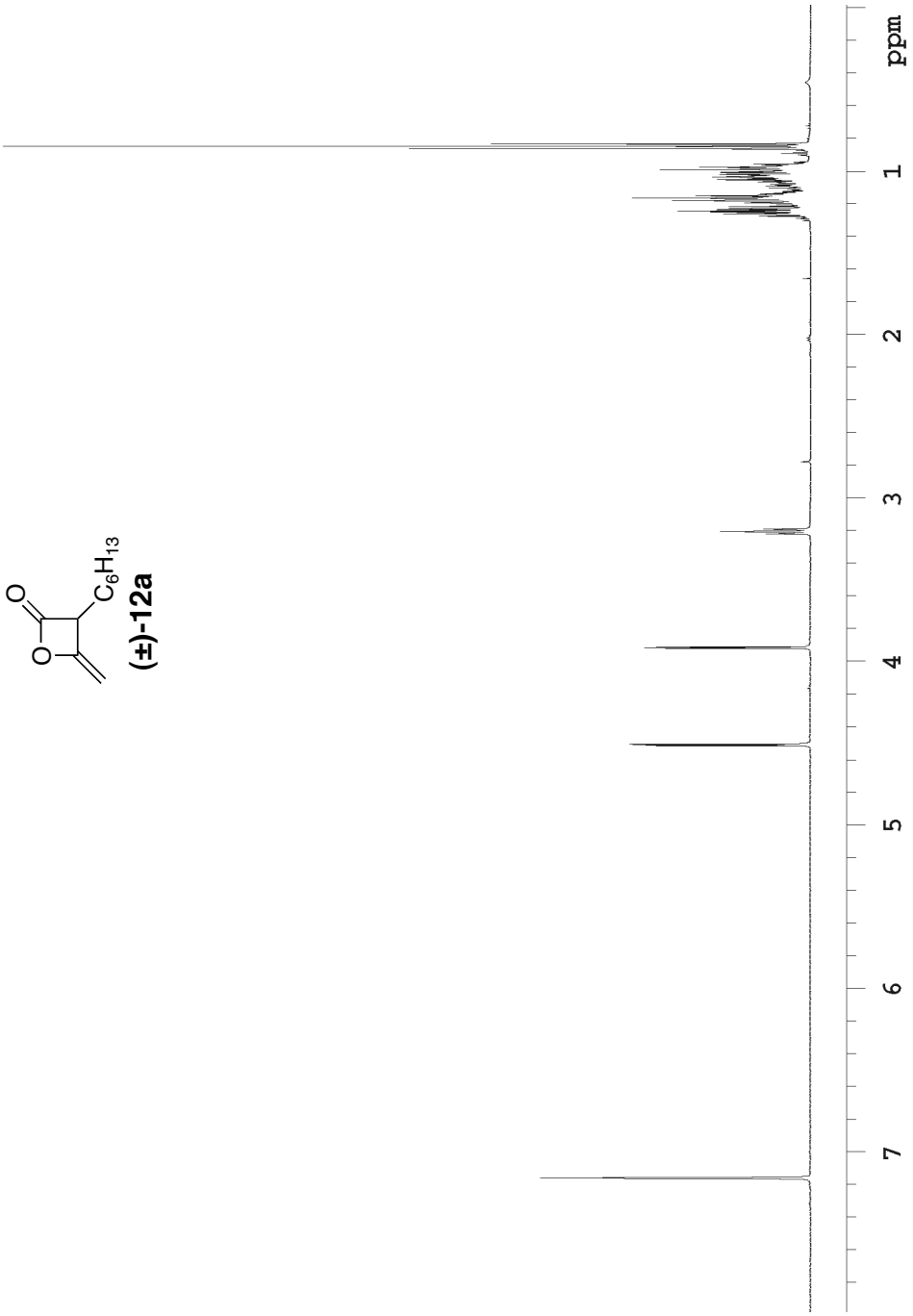


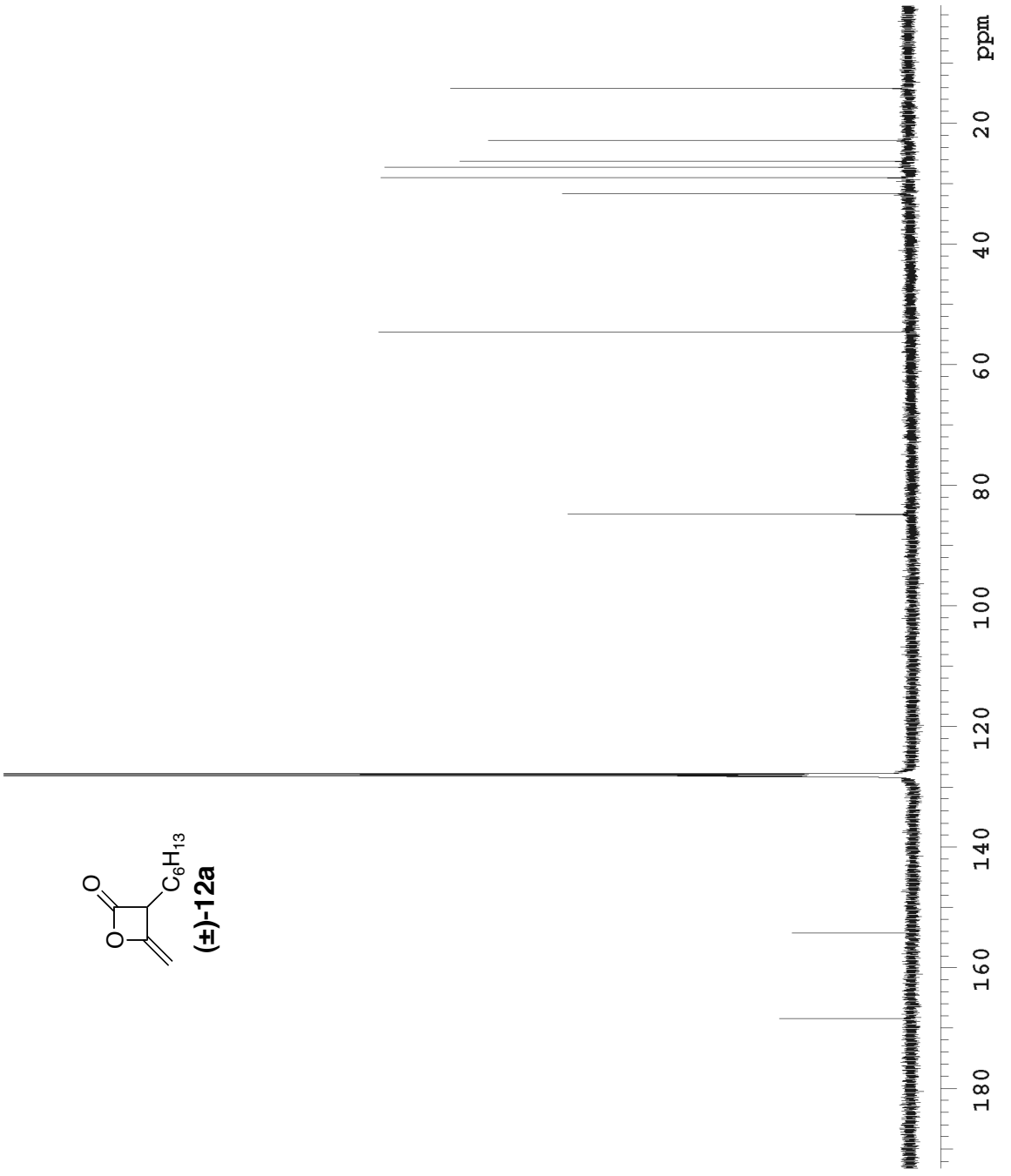
(±)-19d

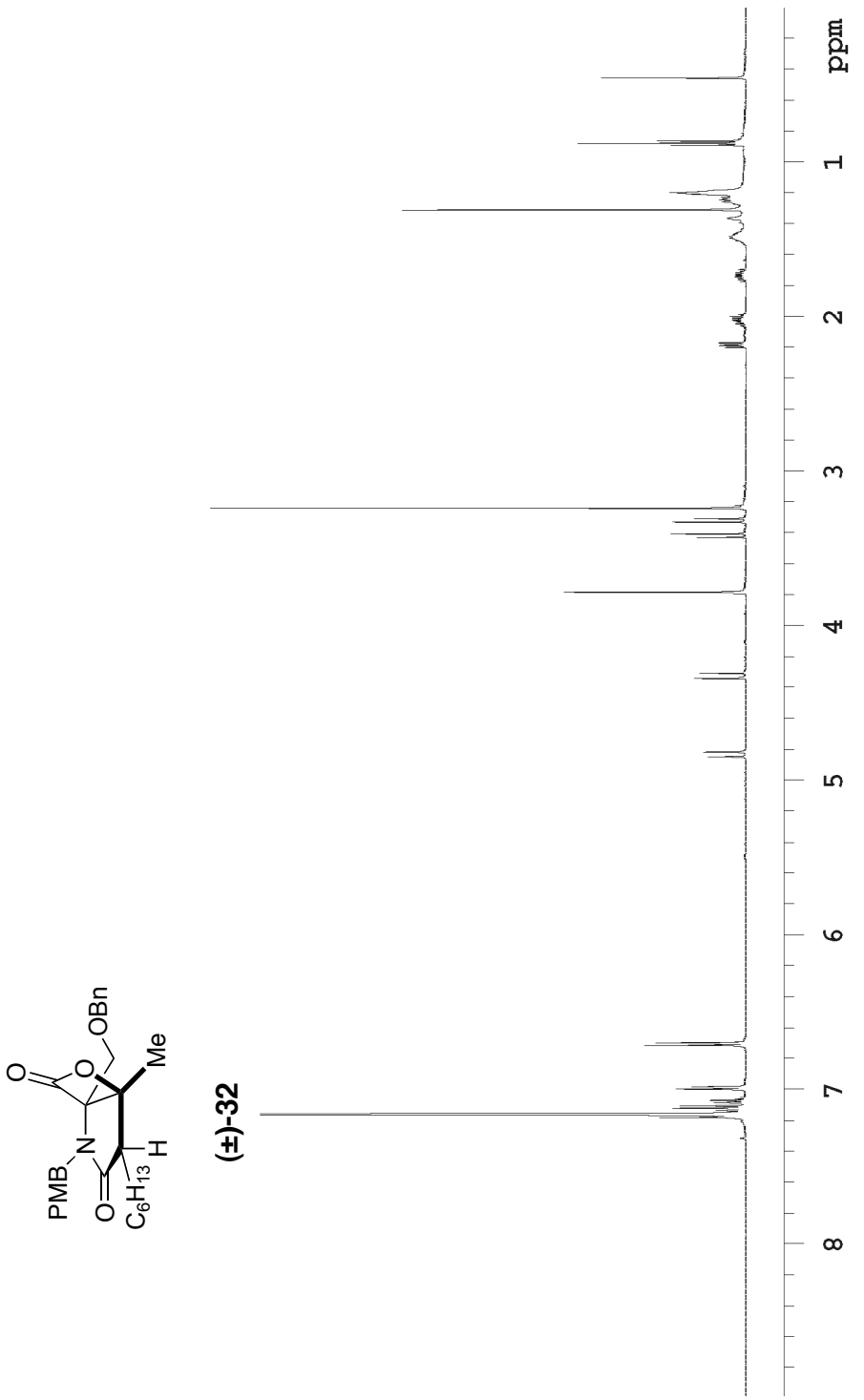


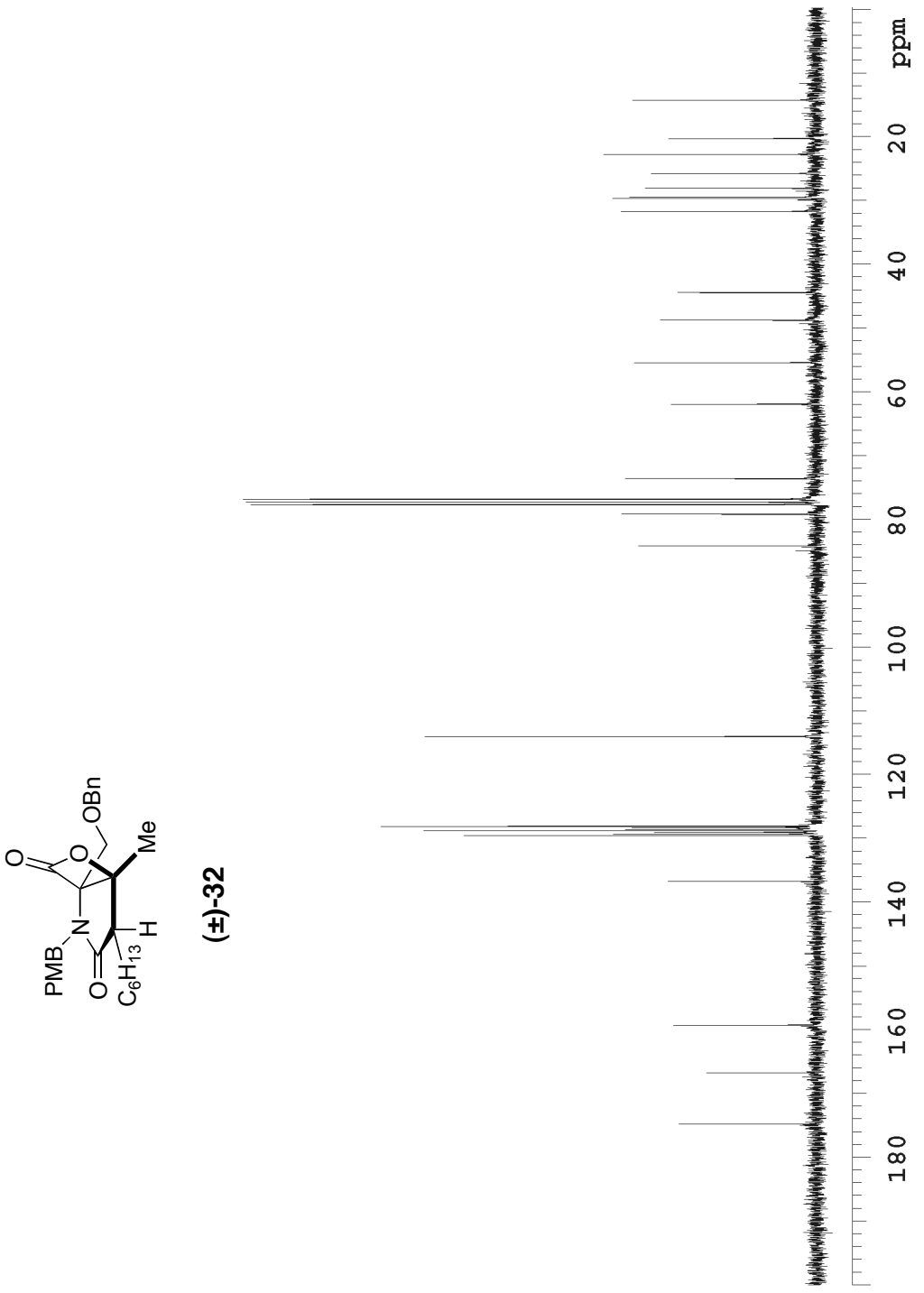
(±)-23a

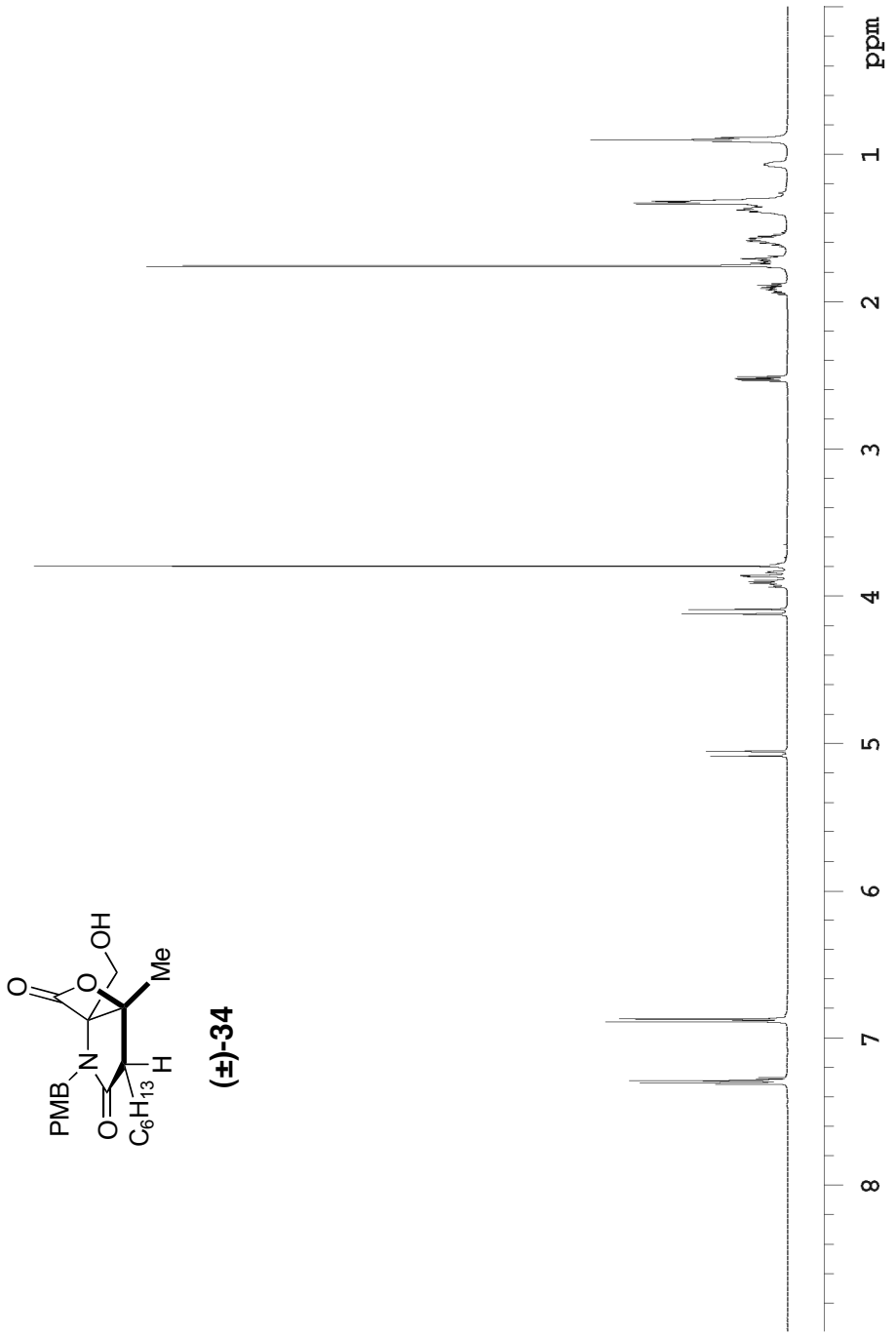

O
O
H
HN
O
(±)-23a
ppm
0
20
40
60
80
100
120
140
160
180
200


O
O
C_6H_{13}
(±)-12a
ppm
1
2
3
4
5
6
7

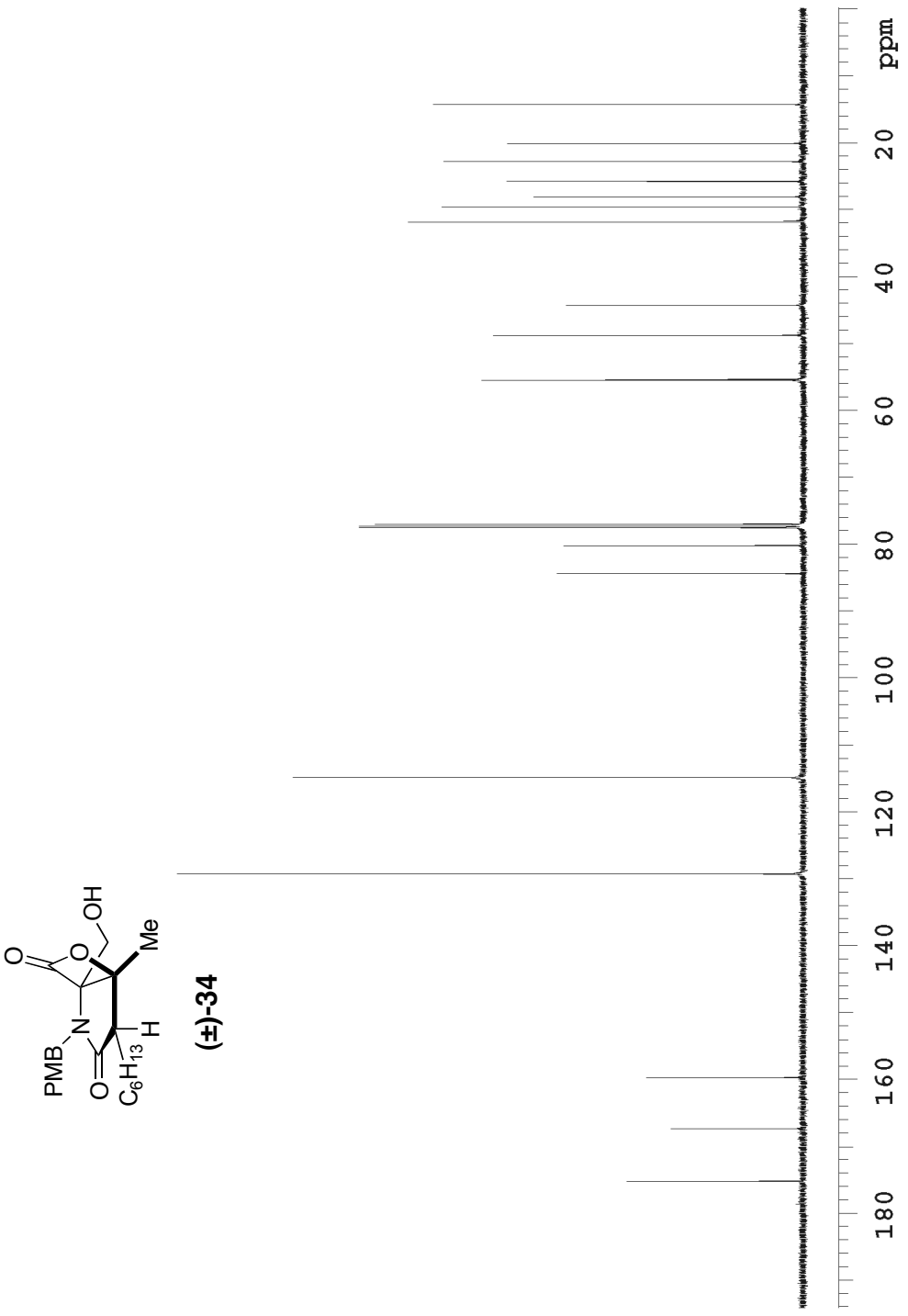

O
O
C_6H_{13}
(±)-12a
ppm
20
40
60
80
100
120
140
160
180

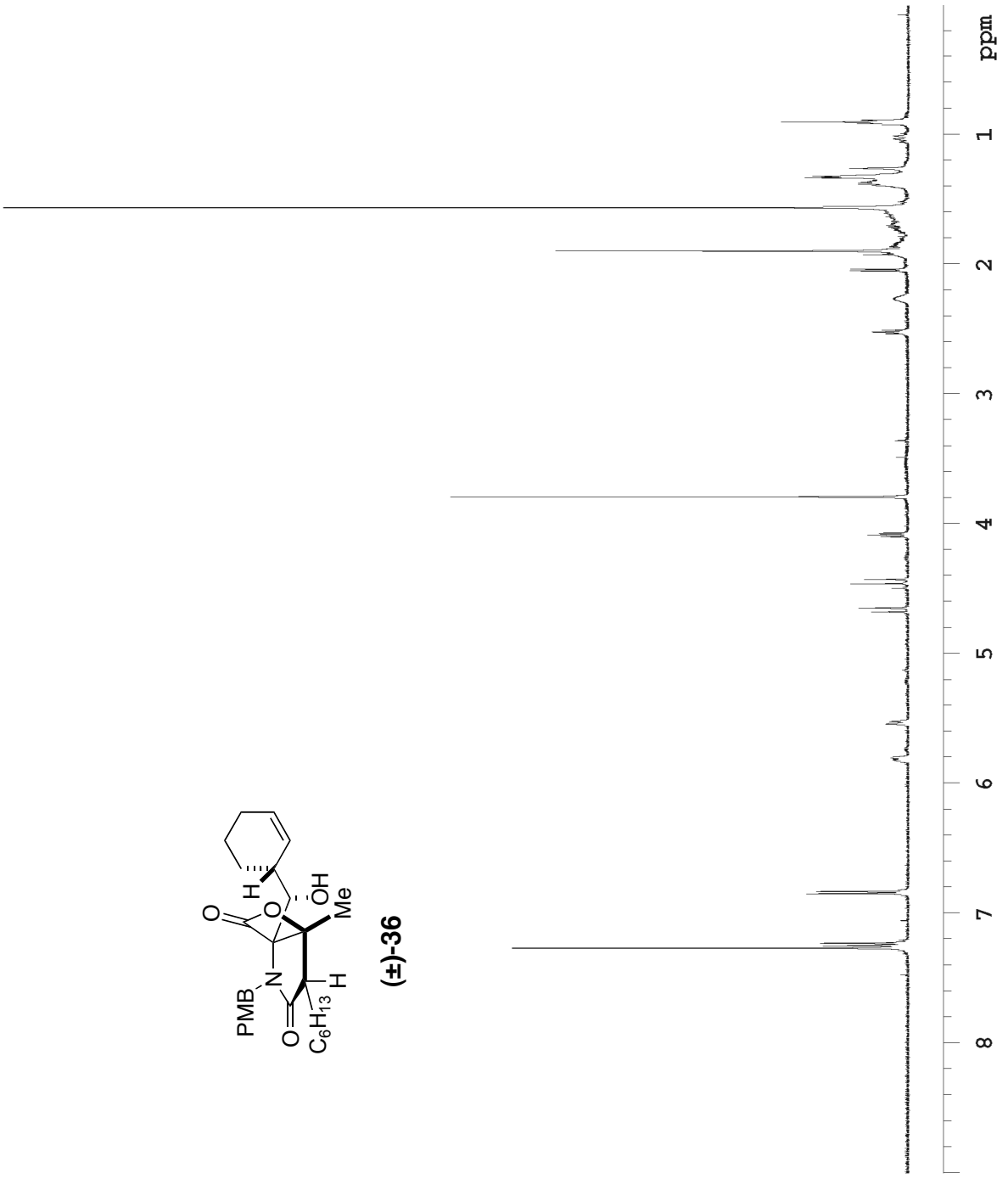

(±)-32
PMB
N
O
O
O
OBn
Me
H
C_6H_{13}
ppm
1
2
3
4
5
6
7
8


O
O
OBn
Me
N
PMB
O
C_6H_{13}
H
(±)-32
ppm
20
40
60
80
100
120
140
160
180

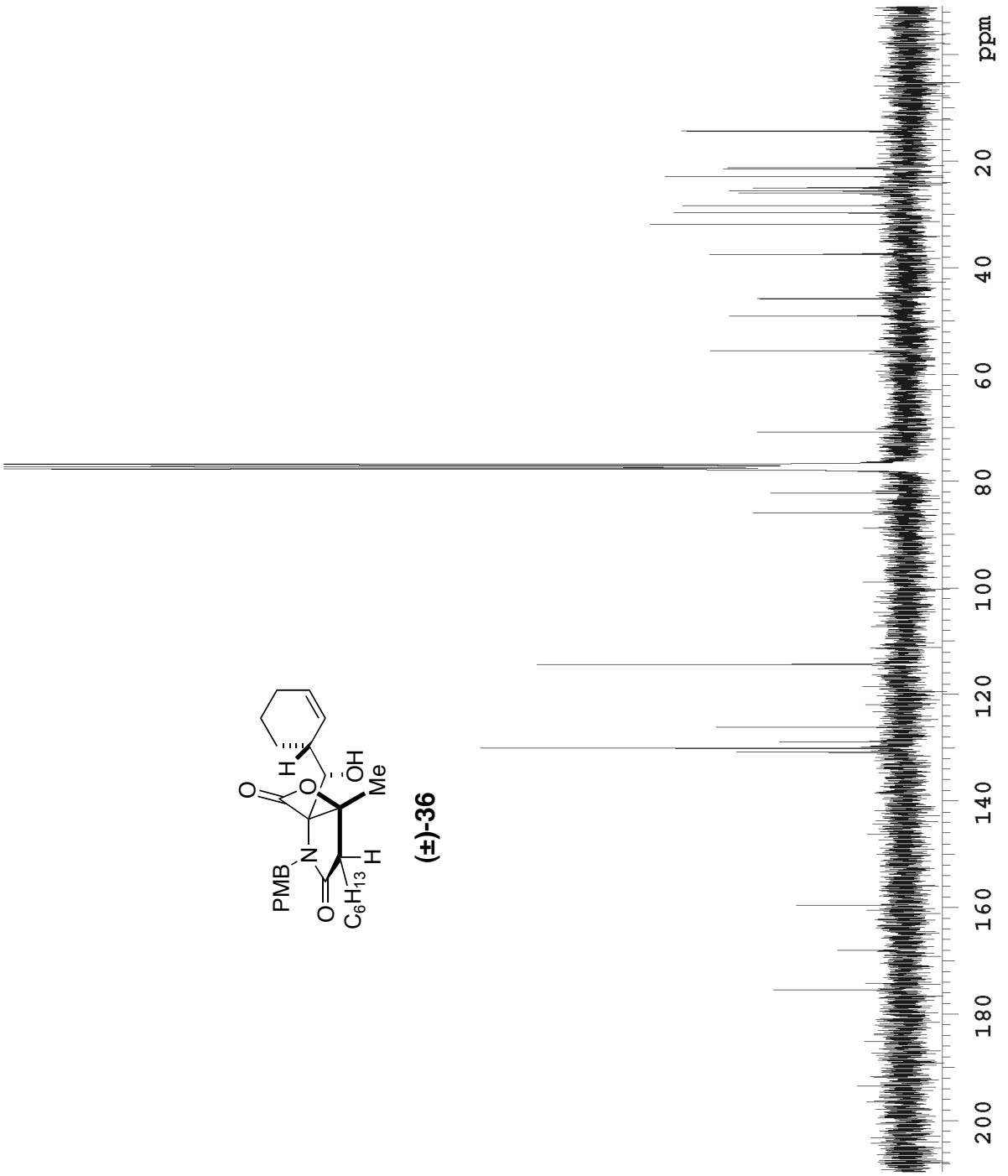


(±)-34

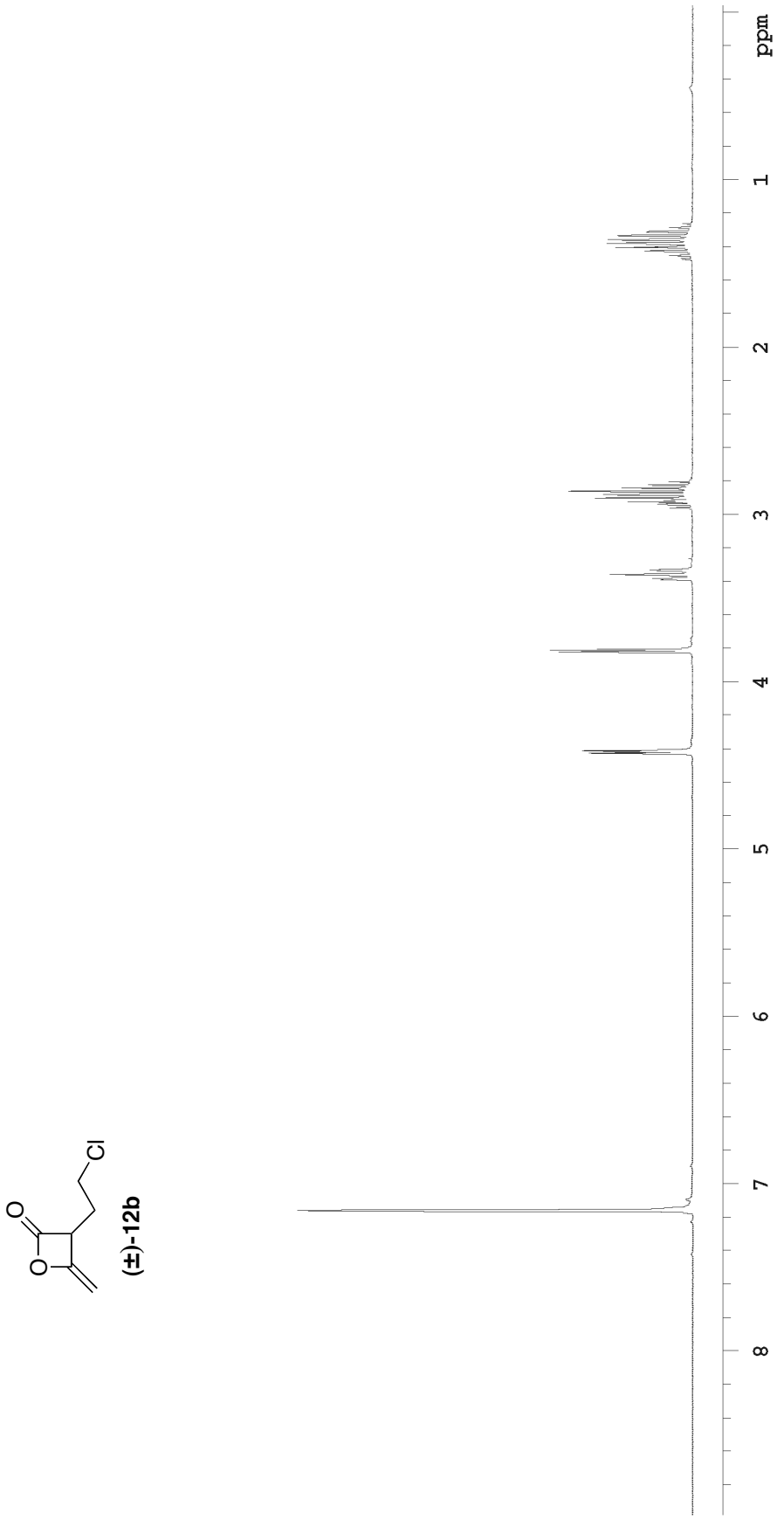

O
O
OH
Me
PMB
N
O
C_6H_{13}
H
(±)-34
ppm
180
160
140
120
100
80
60
40
20



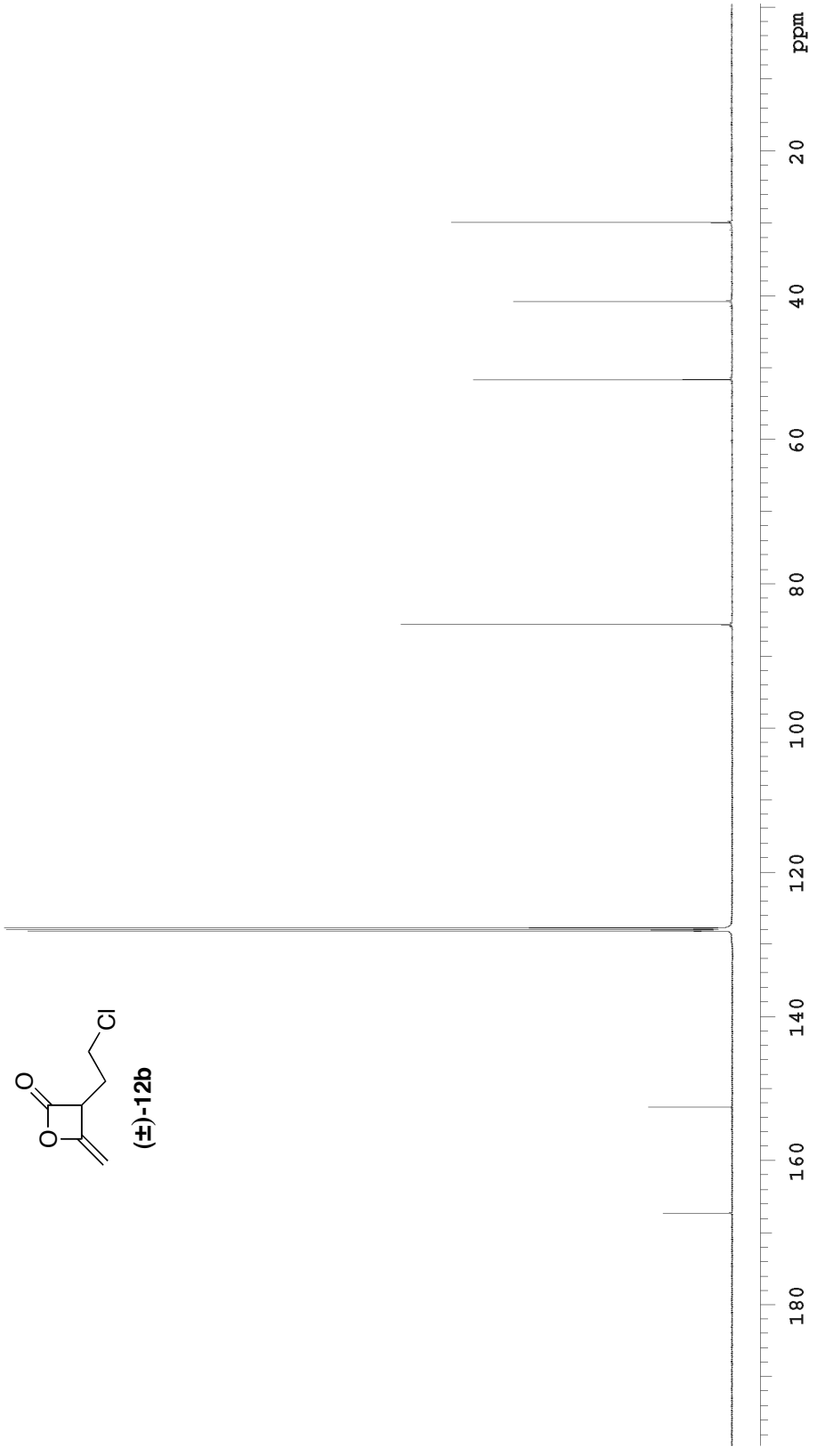
(±)-36



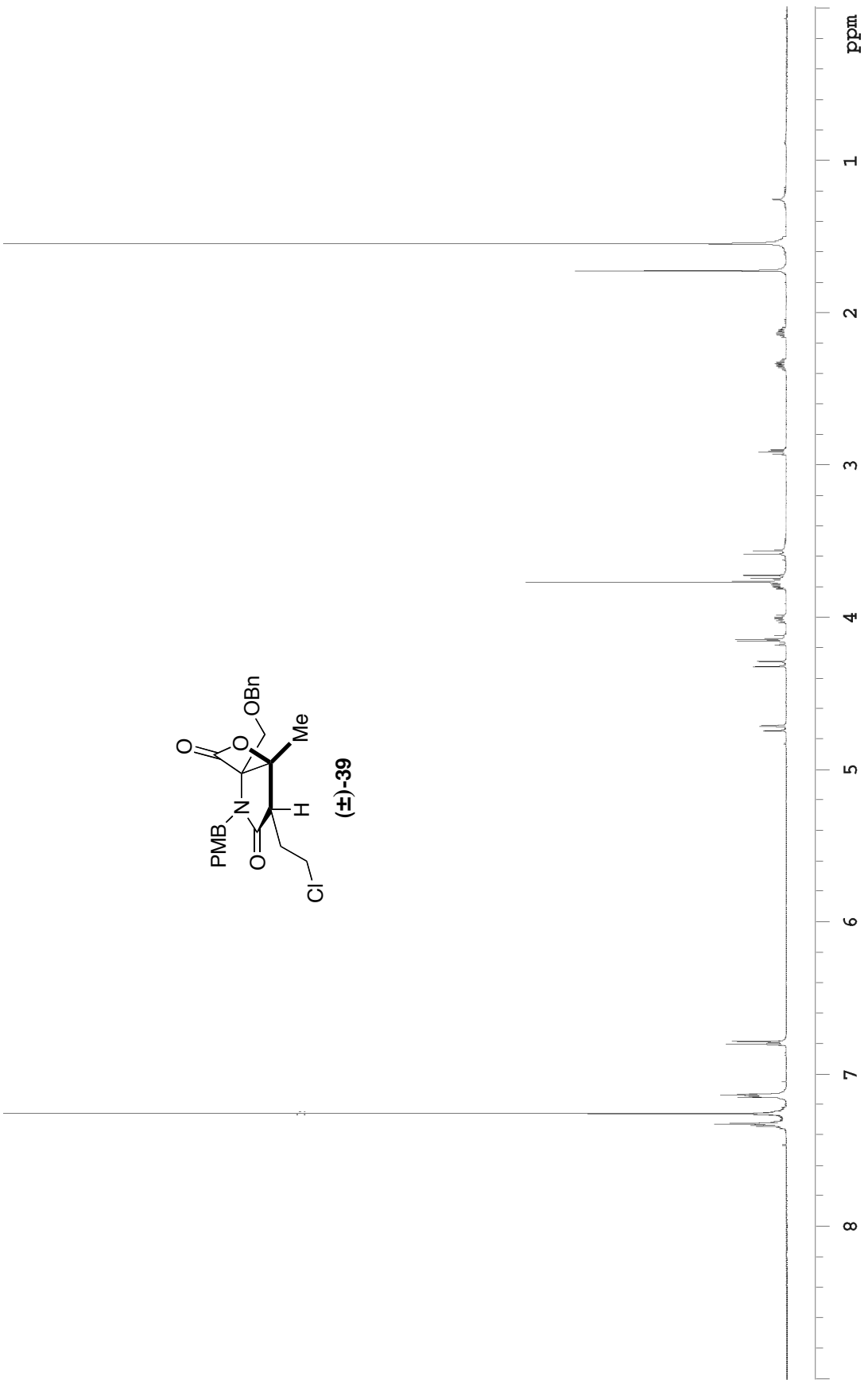
(±)-36



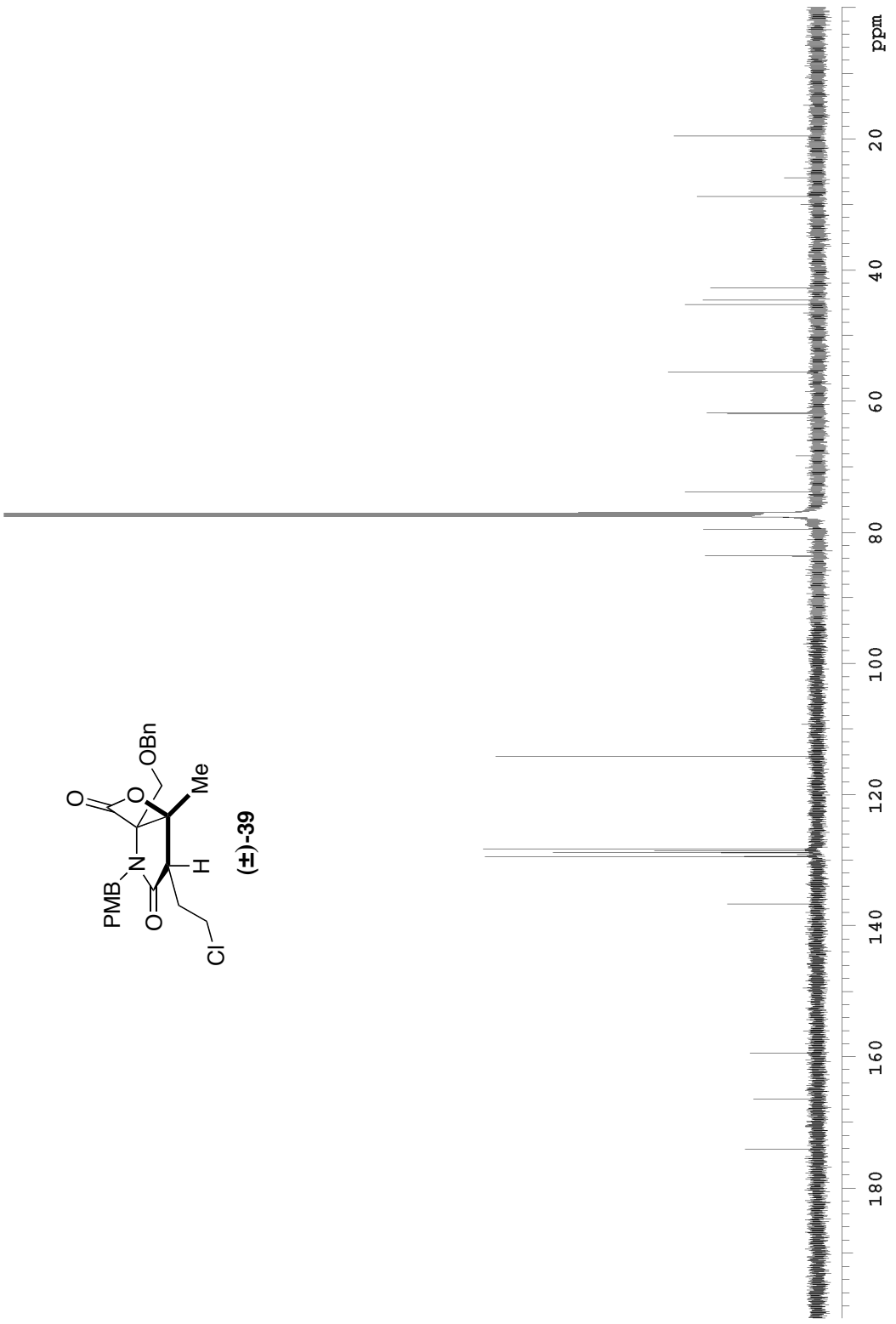
(±)-12b



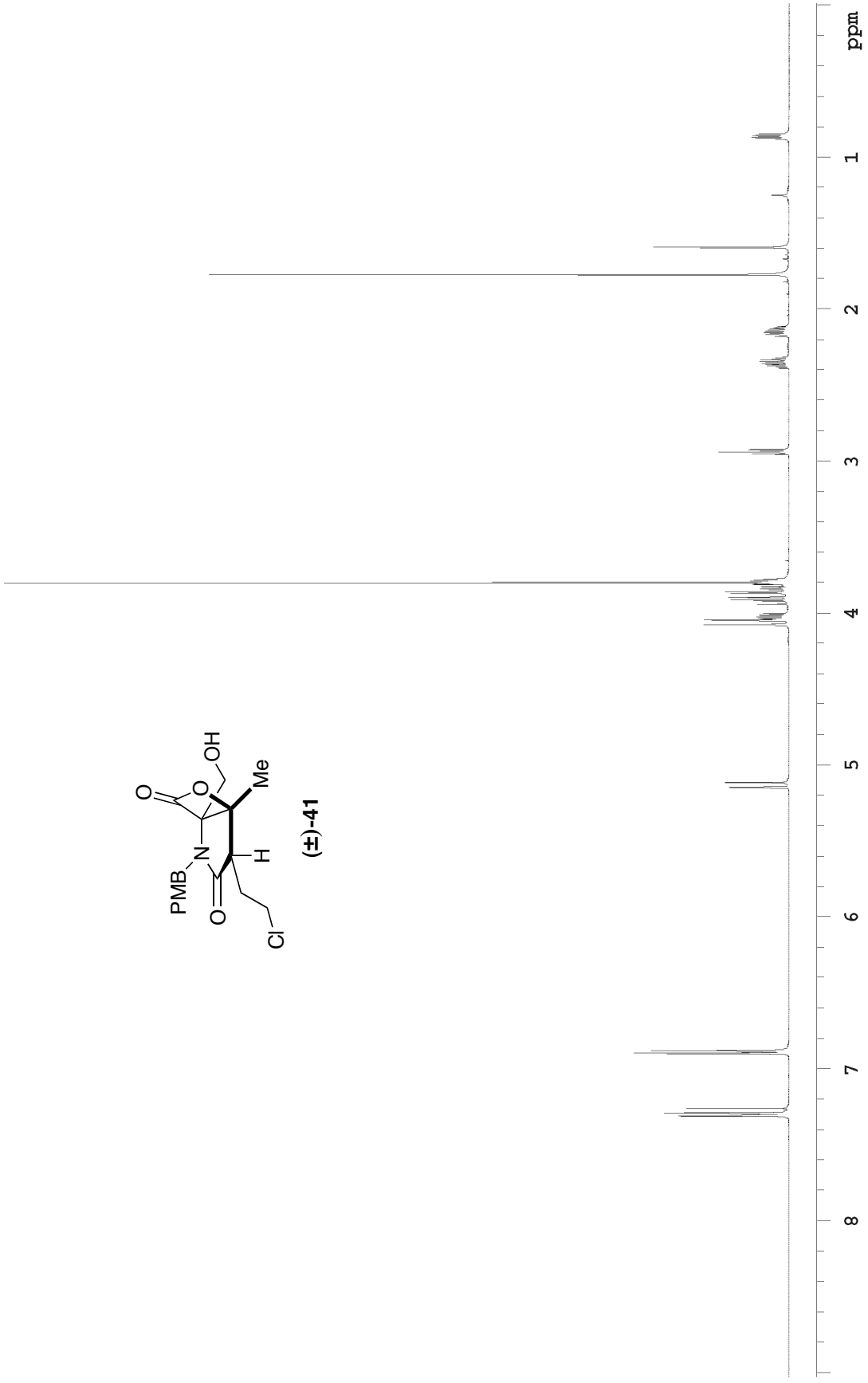
(±)-12b



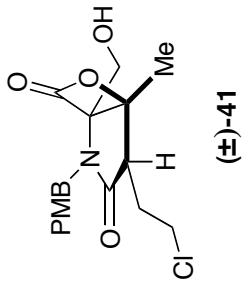
(±)-39



(±)-39



(±)-41



(±)-41