Design, Synthesis and Structural Analysis of D,L-Mixed Polypyrrolinones 2: Macrocyclic Hexapyrrolinones

SUPPORTING INFORMATION

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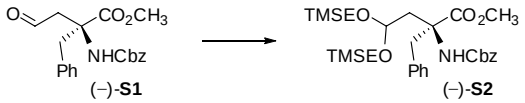
Materials and Methods.

Reactions were carried out in oven or flame-dried glassware under an argon atmosphere, unless otherwise noted. All solvents were reagent grade. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were freshly distilled from sodium / benzophenone under argon. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates. Progress of the imine forming reactions can be monitored by NMR (C_6D_6). Flash chromatography was performed with silica gel 60 (particle size 0.040 – 0.062 mm) supplied by Silicycle and Sorbent Technologies. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. All melting points were obtained on a Thomas-Hoover apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 283B spectrophotometer or a Jasco Model FT/IR-480 Plus spectrometer. Proton and carbon-13 NMR spectra were recorded on a Bruker AMX-500 spectrometer. Chemical shifts are reported relative to chloroform (δ 7.26), methylene chloride (δ 5.32), methanol (δ 3.31), or benzene (δ 7.15) for ^{1}H-NMR and chloroform (δ 77.0), methylene chloride (δ 53.8), methanol (δ 49.15), or benzene (δ 128.0) for ^{13}C NMR. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. High resolution mass spectra were measured at the University of Pennsylvania Mass Spectrometry Service Center on either a VG Micromass 70/70 H or VG ZAB-E spectrometer.

Molecular mechanics calculations were performed using the Batchmin accessory of MacroModel [Version 6.5].

Crystallographic data for hexapyrrolinone (+)-**3**: $C_{108}H_{108}N_{12}O_{12}.2x0.5C_2F_3H_3O$, M_w=3732.22 g/mol, monoclinic, space group $P2_1$ (no. 4), a=12.3950(1), b=25.9290(1), c=17.6040(1) Å, β=110.242(1)°, V=5308.3(6) Å^3, Z=4 (the asymmetric unit consists of 2 molecules of (+)-**3** plus two molecules of trifluoroethanol solvent that have occupancies of 0.5), ρ_{calcd}=1.168 g cm^{-3}, T=-173.2 °C. Data collection was performed using synchrotron radiation at beamline 5.0.2 of the Advanced Light Source (Berkeley, CA) with a monochromatic X-ray beam

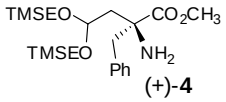
and ADSC Quantum-315 detector.[1] The crystals, dipped in paratone oil, were mounted in a loop and frozen at 100 K in nitrogen. The complete reflection sphere was collected (ϕ-oscillations of 1°), measuring 7371 reflections, (λ=1.000 Å), with dataset resolution of 1.10 Å. Data reduction was achieved with DENZO and SCALEPACK. 3861 unique reflections were recorded with R_{merge}=0.049. The structure was solved by using SIR2004[2] and refined against F^2 with SHELXL-97, 1373 parameters, 33 restraints (applied to the partially occupied trifluoroethanol molecules), hydrogen atoms riding, R1=0.0662 for 3728 reflections with $F_o > 4\sigma(F_o)$, wR2=0.1810. CCDC 293488 contains the supplementary crystallographic data for (+)-**3**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



Acetal (–)-**S2.** A solution of known aldehyde (–)-**S1**[3] (13.7 g, 38.6 mmol), 2-(trimethylsilyl)-ethanol (15.4 mL, 108 mmol), and camphorsulfonic acid (0.126 mg, 0.5 mmol) in benzene (100 mL) was stirred under reflux for 2 h, using a Dean-Stark trap. After cooling and addition of Et_3N (3 mL), the reaction mixture was diluted with EtOAc (70 mL), washed with H_2O (3 x 15 mL), dried over Na_2SO_4, and concentrated. Purification by flash chromatography (EtOAc/hexanes 1:9) yielded acetal (–)-**S2** (22.0 g, 99%) as a colorless oil: $[\alpha]_D^{23}$ –35.0 (*c* 0.90, $CHCl_3$); IR (film) 3416 (m), 2851 (m), 1723 (s), 1496 (s), 1457 (m), 1437 (m), 1303 (w), 1248 (s), 1058 (s), 858 (s), 835 (s), 699 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20-7.33 (m, 5 H), 7.12-7.18 (m, 3 H), 6.90-6.93 (m, 2 H), 5.89 (s, 1 H), 5.21 (d, *J* = 12.3 Hz, 1 H), 5.10 (d, *J* = 12.3 Hz, 1 H), 4.41 (dd, *J* = 8.0, 3.4 Hz, 1 H), 3.72 (s, 3 H), 3.45-3.63 (m, 4 H), 3.28-3.34 (m, 1 H), 3.09 (d, *J* = 13.5 Hz, 1 H), 2.77 (dd, *J* = 14.1, 3.4 Hz, 1 H), 2.28 (dd, *J* = 14.1, 8.0 Hz, 1 H), 0.88-0.93 (m, 2 H), 0.79-0.84 (m, 2 H), 0.02 (s, 9 H), -0.02 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 154.3, 136.8, 135.7, 129.8,

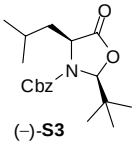
(1) Preliminary in-house diffraction experiments for (+)-**3** at 140 K using a conventional X-ray source permitted only the determination of the unit cell parameters (resolution ~2.0 A).
(2) Burla, M. C.; Caliandro, R.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; De Caro, L.; Giacovazzo, C.; Polidori, G.; Spagna, R. *J. Appl. Cryst.* **2005**, *38*, 381.
(3) Smith, III, A. B.; Wang, W.; Sprengeler, P.; Hirschmann, R. *J. Am. Chem. Soc.* **2000**, *122*, 11037.

128.5, 128.3, 128.1, 128.1, 126.8, 100.1, 66.2, 65.1, 64.0, 62.5, 52.3, 41.1, 39.8, 18.3, 18.0, -1.4, -1.5; high resolution mass spectrum (ES+) *m/z* 596.2844 [$(M+Na)^+$; calcd for $C_{30}H_{47}NO_6Si_2Na$: 596.2839].



(+)-**4**

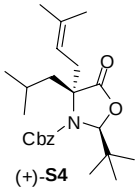
Amine (+)-**4.** Pd/C (10% wt, 2.0 g) was added to a solution of acetal (–)-**S2** (22.0 g, 38.0 mol) in EtOAc (200 mL). The resulting mixture was stirred under H_2 (1 atm) at room temperature for 10 h. The catalyst was removed by filtration through celite and the resulting clear solution was concentrated to yield amine (+)-**4** (16.4 g, 98%) as colorless oil, which was used without further purification: $[\alpha]_D^{23}$ +1.78 (*c* 1.07, $CHCl_3$); IR (film) 3390 (m), 2951 (s), 2895 (m), 1734 (s), 1604 (w), 1495 (m), 1454 (m), 1351 (m) 1249 (s), 1197 (s), 1116 (s), 939 (m), 859 (s), 835 (s), 767 (m), 701 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21-7.26 (m, 3 H), 7.10-7.13 (m, 2 H), 4.58 (app t, *J* = 5.7 Hz, 1 H), 3.66 (s, 3 H), 3.70-3.59 (m, 2 H), 3.43-3.48 (m, 2 H), 3.11 (d, *J* = 13.1 Hz, 1 H), 2.76 (d, *J* = 13.1 Hz, 1 H), 2.30 (dd, *J* = 14.0, 5.7 Hz, 1 H), 1.94 (dd, *J* = 14.0, 5.6 Hz, 1 H), 1.75 (s br, 2 H), 0.92-0.86 (m, 4 H), 0.00 (apparent s, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 135.9, 129.9, 128.2, 126.8, 100.2, 63.8, 63.4, 60.2, 51.7, 47.0, 43.4, 18.2, 18.1, -1.5, -1.5; high resolution mass spectrum (ES+) *m/z* 440.2643 [$(M+H)^+$; calcd for $C_{22}H_{42}NO_4Si_2$: 440.2652].



(–)-**S3**

Oxazolidinone (–)-**S3.** A solution of NaOH (12.4 g, 310 mmol) in H_2O (50 mL) was added to a solution of L-leucine (45.9 g, 350 mmol) in EtOH (800 mL). The resulting mixture was stirred at room temperature for 2 h and then concentrated. Pentane (1 L) and *t*-BuCHO (57 mL, 525 mmol) were added, and the resulting suspension was heated to reflux for 2 d using a Dean-Stark trap. The mixture was concentrated, toluene (500 mL) added, and concentrated again. The solid residue was dried under high vacuum and CH_2Cl_2 (800 mL) was added. The resulting suspension

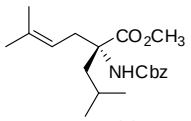
was cooled to 0 °C and CbzCl (79 mL, 525 mmol) was added. After keeping the suspension at 0 °C for 14 d, H_2O (450 mL) and a catalytic amount of DMAP were added. After stirring at room temperature overnight, the organic phase was separated, washed with 10% $NaHSO_4$ solution, saturated aqueous $NaHCO_3$ solution, and H_2O (300 mL each), dried over $MgSO_4$, and concentrated. The crude product (130 g, 83:17 dr) was purified by flash chromatography (EtOAc/hexanes 1:2) to yield oxazolidinone (–)-**S3** (71.2 g, 61 %, dr > 98:2) as a colorless oil: $[\alpha]_D^{23}$ –38.4 (*c* 0.89, $CHCl_3$); IR (film) 2959 (m), 1792 (s), 1718 (s), 1456 (m), 1394 (m), 1327 (m), 1232 (m), 1198 (m), 1111 (w), 1038 (m), 972 (w), 698 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.40 (m, 5 H), 5.53 (s, 1 H), 5.18 (d, *J* = 11.9 Hz, 1 H), 5.15 (d, *J* = 12.0 Hz, 1 H), 4.30-4.35 (m, 1 H), 1.90-2.05 (m, 1 H), 1.79 (ddd, *J* = 13.8, 7.8, 6.4 Hz, 1 H), 1.65 (ddd, *J* = 13.7, 7.7, 6.2 Hz, 1 H), 0.95 (s, 9 H), 0.93 (d, *J* = 6.3 Hz, 3 H), 0.92 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 155.9, 135.1, 128.6, 128.6, 128.6, 96.1, 68.3, 55.4, 42.3, 36.8, 24.8, 24.8, 22.6, 21.8; high resolution mass spectrum (CI) *m/z* 334.2012 [$(M+H)^+$; calcd for $C_{19}H_{28}NO_4$: 334.2018].



(+)-**S4**

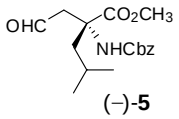
Oxazolidinone (+)-**S4.** A solution of oxazolidinone (–)-**S3** (24.9 g, 74.5 mmol) in THF (373 mL) was cooled to –78 °C and a 0.5 M KHMDS solution in toluene (180 ml, 90 mmol) was added at such a rate that the reaction temperature did not exceed –70 °C. Then 1-bromo-3-methyl-2-butene (17.2 mL, 149 mmol) was added over a period of 15 min. The resulting solution was stirred at –78 °C for 80 min. and quenched with 10% $NaHSO_4$ solution (200 mL). The mixture was extracted with EtOAc (2 x 200 mL) and the organic phases dried over $MgSO_4$. Flash chromatography (EtOAc/hexanes 1:10) yielded oxazolidinone (+)-**S4** (28.1 g, 90%, dr > 98:2) as a colorless oil: $[\alpha]_D^{23}$ +32.4 (*c* 1.12, $CHCl_3$); IR (film) 2959 (s), 1792 (s), 1717 (s), 1456 (m), 1384 (m), 1325 (s), 1299 (m), 1188 (m), 1049 (m), 1014 (m), 751 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.39 (m, 5 H), 5.42 (s, 1 H), 5.24 (d, *J* = 12.0 Hz, 1 H), 5.03 (d, *J* = 12.0 Hz, 1 H), 4.73-

4.76 (m, 1 H), 2.84-3.04 (m, 1 H), 2.44 (dd, *J* = 14.6, 6.9 Hz, 1 H), 1.98-2.18 (m, 1 H), 1.94 (dd, *J* = 14.6, 5.7 Hz, 1 H), 1.87 (dd, *J* = 14.6, 5.2 Hz, 1 H), 1.63 (s, 3 H), 1.53 (s, 3 H), 0.96 (s, 9 H), 0.88-0.96 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 137.8, 135.3, 128.6, 128.5, 128.5, 115.9, 95.1, 67.7, 67.4, 46.1, 37.9, 36.0 (br), 26.0, 25.6, 24.8, 24.6, 24.5, 23.7, 18.0; high resolution mass spectrum (CI) *m/z* 402.2636 [$(M+H)^+$; calcd for $C_{24}H_{36}NO$: 402.2644].



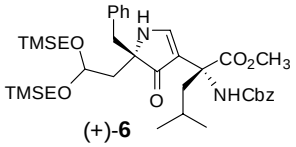
(–)-**S5**

Ester (–)-**S5.** An aqueous 3 M NaOH solution (250 mL) was added to a solution of oxazolidinone (+)-**S4** (27.6 g, 68.7 mmol) in MeOH (250 mL) and the resulting solution was stirred under reflux for 16 h. The MeOH was evaporated and the remaining solution was acidified with aqueous 10% $NaHSO_4$ solution to pH 3. The mixture was extracted with EtOAc (3 x 300 ml), the organic phases dried over $MgSO_4$ and concentrated. The obtained acid was then dissolved in DMF (100 mL) and treated with K_2CO_3 (23.5 g, 170 mmol). The reaction was cooled to 0 °C and then MeI (8.6 mL, 137 mmol) was added. After stirring for 30 min, the ice bath was removed and the reaction was allowed to warm to room temperature and stir for 1 h. The mixture was diluted with EtOAc (800 mL), washed with H_2O (2 $\times$ 70 ml) and brine (50 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (EtOAc/hexanes 1:10 $\rightarrow$ 1:5) yielded ester (–)-**S5** (21.9 g, 92%) as a colorless oil: $[\alpha]_D^{23}$ –38.4 (*c* 1.05, $CHCl_3$); IR (film) 3424 (m), 2956 (s), 1722 (s), 1504 (s), 1455 (s), 1319 (m), 1238 (s), 1075 (m), 1041 (m), 741 (w), 698 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.37 (m, 5 H), 5.90 (s, 1 H), 5.09 (d, *J* = 12.5 Hz, 1 H), 5.06 (d, *J* = 12.5 Hz, 1 H), 4.85-4.89 (m, 1 H), 3.72 (s, 3 H), 3.04 (dd, *J* = 14.3, 7.4 Hz, 1 H), 3.37-3.44 (m, 2 H), 1.69 (dd, *J* = 14.1, 7.7 Hz, 1 H), 1.64 (s, 3 H), 1.54-1.61 (m, 1 H), 1.52 (s, 3 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.76 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 153.9, 136.8, 135.6, 128.4, 127.9, 127.9, 117.6, 66.0, 63.6, 52.3, 43.7, 35.4, 25.9, 24.5, 23.7, 22.4, 17.7; high resolution mass spectrum (CI) *m/z* 348.2177 [$(M+H)^+$; calcd for $C_{20}H_{30}NO_4$: 348.2174].



(–)-**5**

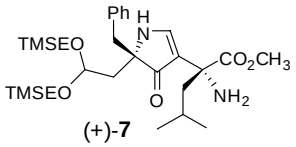
Aldehyde (–)-**5.** A solution of alkene (–)-**S5** (22.3 g, 64.2 mmol) in CH_2Cl_2 (640 mL) was cooled to –78 °C and treated with O_3 until the solution developed a persistent blue color. Excess O_3 was then removed by bubbling Ar through the solution before PPh_3 (18.5 g, 70.6 mmol) was added in portions. The solution was allowed to warm to room temperature and the solvent was evaporated in vacuo. Flash chromatography (EtOAc/hexanes 1:4 → 1:2) yielded aldehyde (–)-**5** (19.7 g, 96 %) as a colorless oil: $[\alpha]_D^{23}$ –4.2 (*c* 1.09, $CHCl_3$); IR (film) 3420 (m), 2957 (s), 1719 (s), 1499 (s), 1454 (m), 1313 (m), 1240 (s), 1089 (m), 1061 (s), 741 (w), 698 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.60 (s, 1 H), 7.30-7.40 (m, 5 H), 6.07 (s, 1 H), 5.09 (d, *J* = 12.3 Hz, 1 H), 5.02 (d, *J* = 12.3 Hz, 1 H), 3.77 (s, 3 H), 3.74 (d, *J* = 17.9 Hz, 1 H), 2.93 (d, *J* = 17.9 Hz, 1 H), 2.30-2.40 (m, 1 H), 1.54-1.61 (m, 2 H), 0.87 (d, *J* = 6.2 Hz, 3 H), 0.79 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 173.2, 154.1, 136.3, 128.4, 128.0, 127.8, 66.4, 59.5, 52.8, 49.7, 44.0, 23.8, 23.5, 23.0; high resolution mass spectrum (CI) *m/z* 322.1643 [$(M+H)^+$; calcd for $C_{17}H_{24}NO_5$: 322.1654].



(+)-**6**

Monopyrrolinone (+)-**6.** A mixture of amine (+)-**4** (10.4 g, 23.7 mmol) and aldehyde (–)-**5** (7.6 g, 23.7 mmol) was azeotropically dehydrated with benzene (6 x 100 mL) and then stored for 1 h under high vacuum. The resulting crude imine was dissolved in THF (400 mL), cooled to 0 °C, and treated with a 0.5 M solution of KHMDS in toluene (236 mL, 118.0 mmol). The reaction mixture was stirred for an additional 40 min, before being quenched with saturated aqueous NH_4Cl (75 mL) and diluted with EtOAc (200 mL). The aqueous layer was further extracted with EtOAc (3 x 100 mL), and the combined organic extracts were washed with water and brine (100 mL each), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 15% ethyl acetate in hexanes as eluent to afford monopyrrolinone (+)-**6**

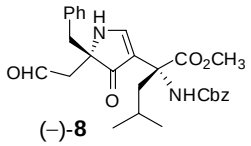
(13.3 g, 79% yield) as a colorless glassy solid: $[\alpha]_D^{23}$ +16.6 (*c* 0.93, $CHCl_3$); IR (film) 3291 (m), 2953 (s), 1734 (s), 1634 (m), 1496 (s), 1249 (s), 1073 (m), 836 (s), 699 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 3.7 Hz, 1 H), 7.30-7.34 (m, 6 H), 7.09-7.19 (m, 5 H), 6.25 (d, *J* = 3.7 Hz, 1 H), 5.03 (d, *J* = 12.5 Hz, 1 H), 4.93 (d, *J* = 12.5 Hz, 1 H), 4.60 (dd, *J* = 6.5, 4.9 Hz, 1 H), 3.44-3.77 (m, 7 H), 2.93 (d, *J* = 13.6 Hz, 1 H), 2.89 (d, *J* = 13.3 Hz, 1 H), 2.17 (dd, *J* = 14.1, 4.5 Hz, 1 H), 2.05 (dd, *J* = 14.5, 4.8 Hz, 1 H), 1.96 (dd, *J* = 14.0, 7.0 Hz, 1 H), 1.76 (dd, *J* = 14.4, 6.6 Hz, 1 H), 1.05-1.15 (m, 1 H), 0.95-1.00 (m, 2 H), 0.86-0.91 (m, 2 H), 0.71 (d, *J* = 6.6 Hz, 3 H), 0.65 (d, *J* = 6.7 Hz, 3 H), 0.05 (s, 9 H), 0.02 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 173.4, 162.2, 154.2, 136.8, 134.9, 130.1, 128.2, 127.8, 127.7, 127.6, 126.6, 110.7, 99.9, 69.5, 65.8, 64.5, 64.2, 59.9, 52.5, 41.9, 40.5, 39.9, 24.2, 23.7, 23.1, 18.5, 18.4, -1.4, -1.4; high resolution mass spectrum (ES+) *m/z* 733.3672 [$(M+Na)^+$; calcd for $C_{38}H_{58}N_2O_7Si_2Na$: 733.3680].



(+)-**7**

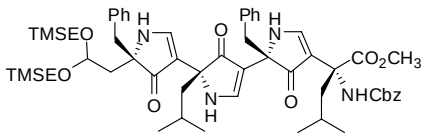
Amine (+)-**7.** Pd/C (10% wt, 1.0 g) was added to a solution of monopyrrolinone (+)-**6** (9.6 g, 13.5 mmol) in EtOAc (75 mL). The resulting mixture was stirred under H_2 (1 atm) at room temperature for 4 h. The catalyst was removed by filtration through celite and the resulting clear solution was concentrated *in vacuo*. The crude product was purified by flash chromatography using ethyl acetate-hexanes (1:1) as eluent to afford amine (+)-**7** (7.8 g, 93%) as a pale yellow oil: $[\alpha]_D^{23}$ +51.9 (*c* 1.13, $CHCl_3$); IR (film) 3256 (m), 2952 (s), 1734 (s), 1636 (s), 1553 (s), 1443 (w), 1248 (s), 1179 (m), 1125 (m), 1053 (m), 860 (s), 845 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 3.9 Hz, 1 H), 7.15-7.21 (m, 3 H), 7.10-7.14 (m, 2 H), 6.12 (d, *J* = 3.9 Hz, 1 H), 4.60 (apparent t, *J* = 5.6 Hz, 1 H), 3.70 (m, 1 H), 3.64 (s, 3 H), 3.59 (m, 1 H), 3.48 (m, 2 H), 2.94 (d, *J* = 13.2 Hz, 1 H), 2.88 (d, *J* = 13.2 Hz, 1 H), 2.05 (dd, *J* = 14.4, 5.4 Hz, 1 H), 2.01 (br s, 2 H), 1.81 (dd, *J* = 14.4, 6.8 Hz, 1 H), 1.50-1.65 (m, 3 H), 0.97 (apparent t, *J* = 8.6 Hz, 2 H), 0.88 (apparent t, *J* = 8.45 Hz, 2 H), 0.84 (d, *J* = 6.3 Hz, 3 H), 0.76 (d, *J* = 6.3 Hz, 3 H), 0.05 (s, 9 H), 0.01 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 175.9, 160.3, 135.2, 130.2, 127.7, 127.6, 115.9, 99.8, 68.8, 64.3,

63.7, 58.0, 52.0, 46.9, 40.8, 39.4, 24.5, 23.7, 22.9, 18.5, 18.4, -1.5, -1.5; high resolution mass spectrum (ES+) *m/z* 599.3290 [(M+Na)$^+$; calcd for $C_{30}H_{52}N_2O_5NaSi_2$: 599.3312].



(–)-**8**

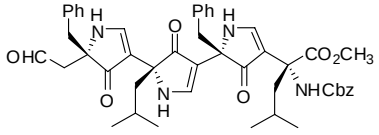
Aldehyde (–)-**8.** A solution of monopyrrolinone (+)-**6** (6.5 g, 9.2 mmol) in wet CH_3CN (150 mL, 1 % H_2O) was cooled to 0 °C and treated with a 1 M solution of $LiBF_4$ in CH_3CN (73 mL). After stirring for 3 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL), diluted with EtOAc (100 mL), and then the aqueous layer was further extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with water and brine (150 mL each), dried over Na_2SO_4, and then concentrated *in vacuo*. Flash chromatography (EtOAc/hexanes 3:7 $\rightarrow$ 1:1) yielded aldehyde (–)-**8** (2.6 g, 58%) as a white foam: $[\alpha]_D^{23}$ –12.3 (*c* 0.71, $CHCl_3$); IR (film) 3296 (s), 2954 (s), 1726 (s), 1644 (s), 1558 (s), 1497 (s), 1455 (s), 1277 (s), 1235 (s), 1175 (m), 1075 (m), 1023 (m), 753 (m), 700 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (d, *J* = 2.4 Hz, 1 H), 7.99 (s, 1 H), 7.08-7.33 (m, 10 H), 6.67 (s, 1 H), 5.92 (s, 1 H), 5.03 (d, *J* = 12.2 Hz, 1 H), 4.94 (d, *J* = 12.4 Hz, 1 H), 3.71 (s, 3 H), 2.95 (d, *J* = 13.4 Hz, 1 H), 2.89 (d, *J* = 13.6 Hz, 1 H), 2.76 (dd, *J* = 16.9, 2.5 Hz, 1 H), 2.67 (d, *J* = 17.1 Hz, 1 H), 2.32-2.37 (m, 1 H), 1.92 (dd, *J* = 13.9, 6.4 Hz, 1 H), 1.31-1.39 (m, 1 H), 0.77 (d, *J* = 6.6 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 199.0, 173.0, 162.1, 154.0, 136.7, 134.2, 128.3, 129.9, 128.2, 127.8, 127.6, 127.1, 111.8, 67.8, 66.0, 59.1, 52.6, 48.5, 41.8, 41.4, 23.9, 23.8, 23.2; high resolution mass spectrum (ES+) *m/z* 515.2179 [(M+Na)$^+$; calcd for $C_{28}H_{32}N_2O_6Na$: 515.2158].



(–)-**S6**

Trispyrrolinone (–)-**S6.** A mixture of amine (+)-**7** (7.2 g, 12.5 mmol) and aldehyde (–)-**8** (6.2 g, 12.5 mmol) was azeotropically dehydrated with benzene (6 x 100 mL) and then stored for 1 h

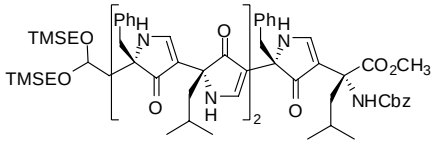
under high vacuum. The resulting crude imine was dissolved in THF (400 mL) and treated at 0 °C with a 0.5 M solution of KHMDS in toluene (201 mL, 100.3 mmol). The reaction mixture was allowed to warm to room temperature and stir for an additional 1 h before being quenched with saturated aqueous NH_4Cl (200 mL) and diluted with EtOAc (200 mL). The aqueous layer was further extracted with EtOAc (3 x 100 mL), and the combined organic extracts were washed with water and brine (100 mL each), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography using ethyl acetate-hexanes (1:4 $\rightarrow$ 1:1) as eluent to afford trispyrrolinone (–)-**S6** (10.4 g, 82% yield) as a colorless glassy solid: $[\alpha]_D^{23}$ –28.3 (*c* =0.69, $CHCl_3$); IR (film) 3323 (s), 2954 (s), 1734 (s), 1645 (s), 1576 (s), 1496 (m), 1456 (m), 1249 (m), 1168 (m), 836 (m), 735 (m), 699 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 3.9 Hz, 1 H), 7.91 (d, *J* = 4.0 Hz, 1 H), 7.82 (s, 1 H), 7.09-7.38 (m, 18 H), 6.54 (s, 1 H), 5.01 (d, *J* = 12.5 Hz, 1 H), 4.91 (d, *J* = 12.5 Hz, 1 H), 4.75 (dd, *J* = 8.2, 3.2 Hz, 1 H), 3.75-3.81 (m, 1 H), 3.65 (s, 3 H), 3.48-3.61 (m, 3 H), 3.13 (d, *J* = 13.4 Hz, 1 H), 2.93-3.02 (m, 3 H), 2.15-2.20 (m, 1 H), 2.03-2.07 (m, 1 H), 1.88-1.94 (m, 1 H), 1.54-1.59 (m, 1 H), 1.23 (dd, *J* = 13.9, 4.3 Hz, 1 H), 1.11-1.18 (m, 1 H), 0.83-1.05 (m, 6 H), 0.65-0.72 (m, 12 H), 0.06 (s, 9 H), 0.00 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6, 201.7, 198.4, 173.4, 162.1, 160.8, 160.2, 153.9, 136.4, 134.8, 130.3, 130.0, 128.3, 127.7, 127.6, 127.4, 127.2, 126.7, 126.2, 110.1, 108.5, 107.9, 99.3, 69.1, 68.4, 68.2, 65.8, 65.6, 63.9, 63.8, 59.2, 52.5, 48.4, 43.6, 41.6, 39.6, 24.3, 24.0, 23.9, 23.8, 23.8, 23.0, 18.4, 18.3, 15.1, -1.5, -1.6; high resolution mass spectrum (ES+) *m/z* 1041.5192 $[(M+Na)^+$; calcd for $C_{57}H_{78}N_4O_9Si_2Na$: 1041.5205].



(–)-**9**

Aldehyde (–)-**9.** A solution of trispyrrolinone (–)-**S6** (3.0 g, 3.0 mmol) in wet CH_3CN (160 mL, 1 % H_2O) was cooled to 0 °C and treated with a 1 M solution of $LiBF_4$ in CH_3CN (59 mL). The reaction mixture was then allowed to warm to room temperature and stir for an additional 45 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL), diluted with EtOAc

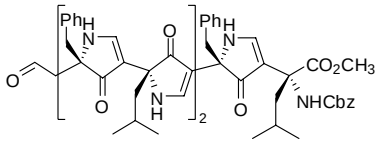
(50 mL), and then the aqueous layer was further extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with water and brine (50 mL each), dried over Na_2SO_4, and then concentrated *in vacuo*. Flash chromatography (EtOAc/hexanes 1:1 → 3:1) provided aldehyde (–)-**9** (1.65 g, 70%) as a colorless glassy solid: $[\alpha]_D^{23}$ –88.2 (*c* 0.21, $CHCl_3$); IR (film) 3307 (s), 3063 (w), 3031 (w), 2954 (m), 2870 (w), 1717 (s), 1644 (s), 1574 (s), 1497 (s), 1455 (m), 1279 (w), 1236 (w), 1169 (m), 1076 (w), 1025 (w), 912 (w), 733 (m), 699 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.57 (s, 1 H), 8.12 (d, *J* = 3.8 Hz, 1 H), 7.86 (d, *J* = 3.6 Hz, 1 H), 7.74 (apparent s, 1 H), 7.47 (apparent s, 1 H), 6.99-7.45 (m, 16 H), 6.90 (apparent s, 1 H), 6.66 (br s, 1 H), 5.04 (d, *J* = 12.4 Hz, 1 H), 4.92 (d, *J* = 12.4 Hz, 1 H), 3.67 (s, 3 H), 3.17 (d, *J* = 13.5 Hz, 1 H), 3.06 (d, *J* = 13.6 Hz, 1 H), 3.01 (d, *J* = 13.5 Hz, 1 H), 2.97 (d, *J* = 13.6 Hz, 1 H), 2.86 (d, *J* = 18.2 Hz, 1 H), 2.61 (d, *J* = 18.1 Hz, 1 H), 2.15-2.20 (m, 1 H), 1.81-1.90 (m, 1 H), 1.41-1.47 (m, 2 H), 1.02-1.21 (m, 2 H), 0.78 (d, *J* = 6.2 Hz, 3 H), 0.76 (d, *J* = 6.4 Hz, 3 H), 0.70 (d, *J* = 6.6 Hz, 3 H), 0.68 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.0, 199.5, 198.1, 197.8, 173.5, 162.1, 162.0, 162.0, 153.7, 136.2, 135.2, 134.0, 130.5, 130.2, 130.0, 128.5, 128.0, 127.9, 127.6, 127.5, 127.1, 126.1, 110.9, 108.7, 107.5, 69.1, 68.1, 68.0, 66.0, 58.4, 52.7, 49.3, 48.7, 43.1, 41.5, 40.8, 24.4, 24.2, 23.9, 23.7, 23.1; high resolution mass spectrum (ES+) *m/z* 823.3694 $[(M+Na)^+$; calcd for $C_{47}H_{52}N_4O_8Na$: 823.3682].



(–)-**10**

Pentapyrrolinone (–)-**10.** A mixture of amine (+)-**7** (1.8 g, 3.12 mmol) and aldehyde (–)-**9** (2.0 g, 2.55 mmol) was azeotropically dehydrated with benzene (6 x 50 mL) and then stored for 1 h under high vacuum. The resulting crude imine was dissolved in THF (200 mL), cooled to 0 °C, and treated with a 0.5 M solution of KHMDS in toluene (63 mL, 31.2 mmol). The reaction mixture was allowed to warm to room temperature and stir for an additional 3 h, and then quenched with saturated aqueous NH_4Cl (50 mL) and diluted with EtOAc (100 mL). The aqueous layer was

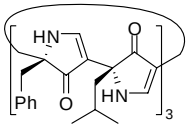
further extracted with EtOAc (3 x 50 mL), and the combined organic extracts were washed with water and brine (50 mL each), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography using ethyl acetate-hexanes (3:7 → 1:1) as eluent to afford pentapyrrolinone (–)-**10** (1.64 g, 61% yield) as a colorless glassy solid: $[\alpha]_D^{23}$ –56.5 (*c* 0.20, $CHCl_3$); IR (film) 3334 (s), 3063 (w), 3031 (w), 2953 (m), 2925 (m), 2869 (w), 1717 (m), 1637 (s), 1570 (s), 1496 (m), 1454 (m), 1249 (w), 1158 (m), 1027 (m), 858 (m), 836 (m), 698 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 4.1 Hz, 1 H), 8.00 (d, *J* = 4.0 Hz, 1 H), 7.87-7.90 (m, 2 H), 7.80 (apparent s, 1 H), 7.00-7.35 (m, 25 H), 6.62 (d, *J* = 4.0 Hz, 1 H), 5.00 (d, *J* = 12.6 Hz, 1 H), 4.89 (d, *J* = 12.6 Hz, 1 H), 4.73 (dd, *J* = 8.1, 3.0 Hz, 1 H), 3.73-3.78 (m, 1 H), 3.57-3.63 (m, 4 H), 3.48-3.54 (m, 2 H), 3.23 (d, *J* = 13.3 Hz, 1 H), 3.16 (d, *J* = 13.5 Hz, 1 H), 3.05 (d, *J* = 13.3 Hz, 1 H), 2.89-2.95 (m, 3 H), 2.00-2.20 (m, 1 H), 2.02 (dd, *J* = 14.6, 2.9 Hz, 1 H), 1.86 (dd, *J* = 13.9, 7.0 Hz, 1 H), 1.51 (dd, *J* = 14.5, 8.2 Hz, 1 H), 1.31 (dd, *J* = 14.4, 4.8 Hz, 1 H), 1.19 (dd, *J* = 14.3, 4.6 Hz, 1 H), 0.73-1.15 (m, 9 H), 0.66-0.73 (m, 15 H), 0.64 (d, *J* = 6.7 Hz, 3 H), 0.05 (s, 9 H), 0.01 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 201.9, 201.6, 200.5, 198.2, 173.4, 170.9, 162.2, 160.5, 160.3, 160.1, 159.7, 153.7, 136.3, 134.9, 137.7, 134.6, 130.7, 130.4, 130.3, 130.1, 128.3, 127.7, 127.6, 127.4, 127.1, 126.7, 126.1, 110.2, 108.4, 108.4, 108.0, 107.2, 99.6, 69.1, 68.2, 68.2, 68.1, 68.1, 65.8, 64.0, 63.8, 60.2, 58.7, 52.6, 49.0, 47.3, 45.3, 43.6, 41.4, 39.6, 39.3, 24.4, 24.3, 24.1, 24.0, 23.9, 23.8, 22.9, 20.8, 18.3, 14.0, -1.5, -1.6; high resolution mass spectrum (ES+) *m/z* 1349.6782 [$(M+Na)^+$; calcd for $C_{76}H_{98}N_6O_{11}Si_2Na$: 1349.6729].



(–)-**S7**

Aldehyde (–)-**S7.** A solution of pentapyrrolinone (–)-**10** (1.24 g, 0.94 mmol) in wet CH_3CN (150 mL, 1 % H_2O) was cooled to 0 °C and treated wih a 1 M solution of $LiBF_4$ in CH_3CN (56 mL). The reaction mixture was allowed to warm to room temperature and stir for an additional 45 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL), diluted with EtOAc (50

mL), and then the aqueous layer was further extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with water and brine (50 mL each), dried over Na_2SO_4, and then concentrated *in vacuo*. Flash chromatography (EtOAc/hexanes 2:3 → 9:1) provided aldehyde (–)-**S7** (0.77 g, 74%) as a colorless glass: $[\alpha]_D^{23}$ –5.1 (*c* 0.43, $CHCl_3$); IR (film) 3341 (s), 3030 (w), 2954 (m), 1720 (m), 1637 (s), 1571 (s), 1496 (m), 1454 (m), 1365 (w), 1217 (w), 1157 (s), 912 (w), 733 (m), 699 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.43 (s, 1 H), 8.24 (apparent s, 1 H), 8.14 (apparent s, 1 H), 7.87 (apparent s, 1 H), 7.78 (apparent s, 1 H), 7.70 (apparent s, 1 H), 7.47 (apparent s, 1 H), 7.02-7.37 (m, 25 H), 5.05 (d, *J* = 12.4 Hz, 1 H), 4.91 (d, *J* = 12.4 Hz, 1 H), 3.62 (s, 3 H), 3.23 (d, *J* = 13.7 Hz, 1 H), 3.16 (d, *J* = 13.5 Hz, 1 H), 2.99 (d, *J* = 14.4 Hz, 2 H), 2.96 (d, *J* = 13.8 Hz, 1 H), 2.91 (d, *J* = 13.5 Hz, 1 H), 2.76 (d, *J* = 17.4 Hz, 1 H), 2.57 (d, *J* = 17.4 Hz, 1 H), 2.04-2.11 (m, 1 H), 1.75-1.80 (m, 1 H), 1.47 (dd, *J* = 14.3, 4.7 Hz, 1 H), 1.35-1.40 (m, 1 H), 1.05-1.27 (m, 4 H), 1.01 (dd, *J* = 14.3, 6.8 Hz, 1 H), 0.74-0.80 (m, 12 H), 0.64-0.67 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 201.8, 200.6, 200.1, 198.9, 198.5, 173.4, 162.3, 161.3, 160.9, 160.8, 159.8, 154.0, 136.3, 134.8, 134.7, 134.1, 130.5, 130.4, 130.1, 128.5, 128.0, 127.9, 127.8, 127.5, 127.4, 127.1, 126.8, 126.2, 110.1, 108.3, 107.7, 107.3, 107.2, 68.5, 68.3, 68.0, 66.1, 60.3, 52.7, 49.1, 48.6, 47.3, 45.2, 43.8, 41.5, 41.1, 24.5, 24.4, 24.2, 24.1, 23.9, 23.8, 23.2, 23.0, 22.9, 21.0, 14.1; high resolution mass spectrum (ES+) *m/z* 1131.5150 [$(M+Na)^+$; calcd for $C_{66}H_{72}N_6O_{10}Na$: 1131.5207].

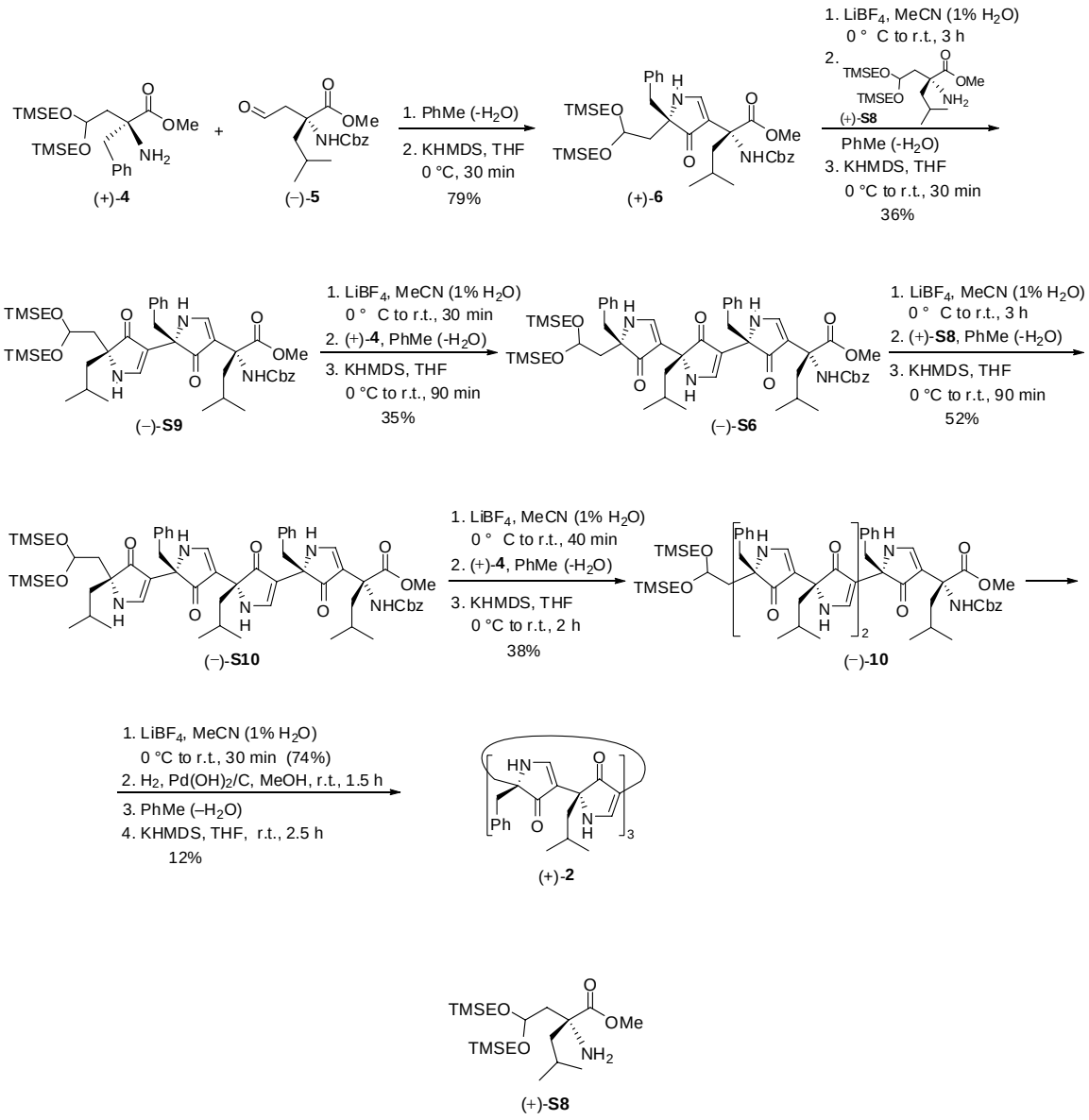


(+)-**2**

Macrocyclic Hexapyrrolinone (+)-**2.** Pd-hydroxide/C (20% Pd, wet, Degussa E101 NE/W, 0.162 g) was added to a solution of pentapyrrolinone aldehyde (–)-**S7** (0.93 g, 0.84 mmol) in MeOH (40 mL). The resulting mixture was stirred under H_2 (1 atm) at room temperature for 2 h. The catalyst was removed by filtration through celite and the resulting clear solution was concentrated *in vacuo*. The resulting product was azeotropically dehydrated with benzene (3 x 100 mL) and then stored for 1 h under high vacuum. The crude imine was dissolved in THF (280

mL) and treated at room temperature with a 0.5 M solution of KHMDS in toluene (25.2 mL, 12.6 mmol). The reaction mixture was stirred for an additional 3 h, before being quenched with saturated aqueous NH_4Cl (30 mL) and diluted with EtOAc (50 mL). The aqueous layer was further extracted with EtOAc (3 x 50 mL), and the combined organic extracts were washed with water and brine (30 mL each), dried over Na_2SO_4, and concentrated *in vacuo*. The product was purified by preparative thin-layer chromatography using CH_2Cl_2/MeOH 10:1 as eluent to afford the macrocyclic hexapyrrolinone (+)-**2** (0.093 g, 12%) as a white solid: $[\alpha]_D^{23}$ +82.5 (*c* 0.20, $CHCl_3$); IR (film) 3315 (s), 3029 (w), 2953 (m), 2869 (w), 1636 (s), 1576 (s), 1455 (m), 1162 (m), 965 (w), 745 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 4.1 Hz, 3 H), 7.82 (d, *J* = 4.0 Hz, 3 H), 7.50-7.51 (m, 6 H), 7.11-7.18 (m, 9 H), 7.10-7.11 (m, 6 H), 3.00 (d, *J* = 13.5 Hz, 3 H), 2.96 (d, *J* = 13.5 Hz, 3 H), 1.42 (dd, *J* = 13.5, 3.6 Hz, 3 H), 1.12-1.20 (m, 6 H), 0.78 (d, *J* = 6.2 Hz, 9 H), 0.72 (d, *J* = 6.4 Hz, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 201.1, 161.7, 161.5, 134.8, 130.2, 127.7, 126.7, 108.6, 107.4, 69.1, 69.1, 46.7, 44.3, 24.5, 24.2, 23.4; high resolution mass spectrum (ES+) *m/z* 947.4472 [$(M+Na)^+$; calcd for $C_{57}H_{60}N_6O_6Na$: 947.4483].

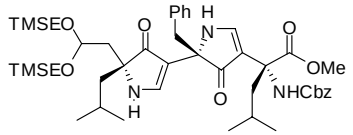
Scheme S1. Iterative Synthesis of Macrocyclic Hexapyrrolinone (+)-**2**



Amine (+)-**S8.** A solution of aldehyde (–)-**5** (5.6 g, 17.5 mmol), 2-(trimethylsilyl)-ethanol (7.0 mL, 48.8 mmol, 2.8 equiv.), and camphorsulfonic acid (0.050 g, 0.22 mmol, 0.013 equiv.) in benzene (30 mL) was heated to reflux using a Dean-Stark trap over a period of 2 h. After cooling to room temperature, the reaction mixture was treated with Et_3N (0.5 mL) and the solution was diluted with EtOAc (20 mL), washed with H_2O, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (EtOAc/hexanes 1:10 → 1:5) yielded the intermediate TMSE acetal (8.6 g, 91%)

as a colorless oil: $[\alpha]_D^{23}$ –26.5 (*c* 0.90, $CHCl_3$); IR (film): 3418 (m), 2954 (s), 2896 (m), 1726 (s), 1499 (s), 1443 (m), 1368 (m), 1323 (m), 1248 (s), 1056 (s), 860 (s), 836 (s), 756 (m), 697 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.30-7.37 (m, 5 H), 6.11 (s, 1 H), 5.09 (s, 3 H), 4.34 (dd, *J* = 8.3, 2.8 Hz, 1 H), 3.72 (s, 3 H), 3.57-3.63 (m, 1 H), 3.42-3.53 (m, 2 H), 3.30-3.34 (m, 1 H), 2.68 (dd, *J* = 14.1, 2.8 Hz, 1 H), 2.31 (dd, *J* = 14.2, 5.7 Hz, 1 H), 2.09 (dd, *J* = 14.1, 8.4 Hz, 1 H), 1.65 (dd, *J* = 14.2, 6.7 Hz, 1 H), 1.49-1.53 (m, 1 H), 0.76-0.89 (m, 9 H), 0.00 (s, 9 H), 0.00 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.4, 153.9, 136.8, 128.4, 128.0, 127.9, 100.0, 66.1, 65.0, 93.7, 60.9, 52.3, 43.9, 40.6, 24.2, 23.7, 22.9, 22.3, 18.3, 18.0, , –1.58, –1.64; high resolution mass spectrum (ES+) *m/z* 562.2978 [$(M+Na)^+$; calcd for for $C_{27}H_{49}NO_6NaSi_2$: 562.2996].

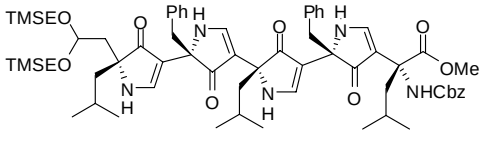
Pd/C (10% wt, 0.800 g) was added to a solution of the above acetal (8.55 g, 15.8 mmol) in EtOAc (100 mL). The resulting mixture was stirred under H_2 at room temperature for 5 h. The catalyst was removed by filtration through celite and the resulting clear solution was concentrated to yield amine (+)-**S8** (6.4 g, 99%) as a colorless oil: $[\alpha]_D^{23}$ +16.7 (*c* 1.04, $CHCl_3$). IR (film): 3390 (w), 2954 (s), 1734 (s), 1603 (w), 1436 (w), 1367 (w), 1249 (s), 1199 (m), 1135 (m), 1118 (m), 1054 (s), 940 (w), 860 (s), 836 (s), 758 (w), 693 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.52 (app. t, *J* = 5.6 Hz, 1 H), 3.69 (s, 3 H), 3.68-3.58 (m, 2 H), 3.50-3.43 (m, 2 H), 2.12 (dd, *J* = 14.0; 5.5 Hz, 1H), 1.89 (s br., 2 H), 1.84 (dd, *J* = 14.0, 5.5 Hz, 1 H), 1.69 (m, 2 H), 1.52 (m, 1 H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.85-092 (m, 4 H), 0.82 (d, *J* = 6.0 Hz, 3 H), 0.01 (s, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.9, 100.2, 63.7, 63.4, 51.7, 50.0, 44.4, 24.7, 23.8, 22.8, 18.3, 18.2, –1.50, –1.52; high resolution mass spectrum (ES+) *m/z* 428.2628 [$(M+Na)^+$; calcd for $C_{19}H_{43}NO_4NaSi_2$: 428.2628].



(–)-**S9**

Bispyrrolinone (–)-**S9.** A mixture of amine (+)-**S8** (1.28 g, 3.15 mmol) and aldehyde (–)-**8** (1.55 g, 3.15 mmol) was azeotropically dehydrated with toluene and then stored for 1 h under high vacuum. The resulting crude imine was dissolved in THF (60 mL), cooled to 0 °C, and treated

with a 0.5 M solution of KHMDS in toluene (38 mL, 19 mmol, 6 equiv.). After stirring at 0 °C for 10 min, the ice bath was removed and stirring was continued for 30 min. The reaction was quenched with saturated NH_4Cl and diluted with EtOAc and H_2O. The organic phase was separated, washed with H_2O and brine, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (EtOAc/hexanes 1:3 → 2:5) yielded bispyrrolinone (–)-**S9** (2.02 g, 76%) as a colorless glassy solid: $[\alpha]_D^{23}$ –125.7 (*c* 1.08, $CHCl_3$); IR (film): 3293 (s), 2953 (s), 1733 (s), 1636 (s), 1559 (s), 1506 (s), 1433 (m), 1249 (s), 1112(m), 1054 (m), 859 (s), 734 (m), 699 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, *J* = 3.9 Hz, 1 H), 7.83 (s, 1 H), 7.14-7.36 (m, 11 H), 6.40 (d, *J* = 4.0 Hz, 1 H), 5.03 (d, *J* = 12.4 Hz, 1 H), 4.93 (d, *J* = 12.4 Hz, 1 H), 4.65 (dd, *J* = 8.4, 3.5 Hz, 1 H), 3.74-3.80 (m, 1 H), 3.66 (s, 3 H), 3.45-39 (m, 3 H), 3.17 (d, *J* = 13.4 Hz, 1 H), 3.01 (d, *J* = 13.4 Hz, 1 H), 2.12-2.17 (m, 1 H), 1.93-1.99 (m, 1 H), 1.90 (dd (*J* = 14.4, 3.5 Hz, 1 H), 1.68 (dd, *J* = 13.9, 5.5 Hz, 1 H), 1.58 (dd, *J* = 14.0, 6.5 Hz, 1 H), 1.39-1.47 (m, 2 H), 1.10-1.15 (m, 1 H), 0.93-0.98 (m, 2 H), 0.83-0.93 (m, 8 H), 0.72 (d, *J* = 6.6 Hz, 3 H), 0.65 (d, *J* = 6.7 Hz, 3 H), 0.05 (s, 9 H), 0.00 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.4, 199.1, 173.4, 162.5, 160.4, 154.2, 136.9, 134.8, 130.3, 128.3, 127.7, 126.5, 110.1, 108.9, 100.0, 69.4, 68.7, 65.9, 64.9, 63.9, 60.2, 52.5, 43.8, 42.1, 42.0, 41.1, 24.4, 24.3, 24.2, 24.2, 23.8, 23.2, 18.6, 18.4, –1.46, –1.52; high resolution mass spectrum (ES+) *m/z* 870.4485 [$(M+H)^+$; calcd for $C_{46}H_{69}N_3O_8NaSi_2$: 870.4521].

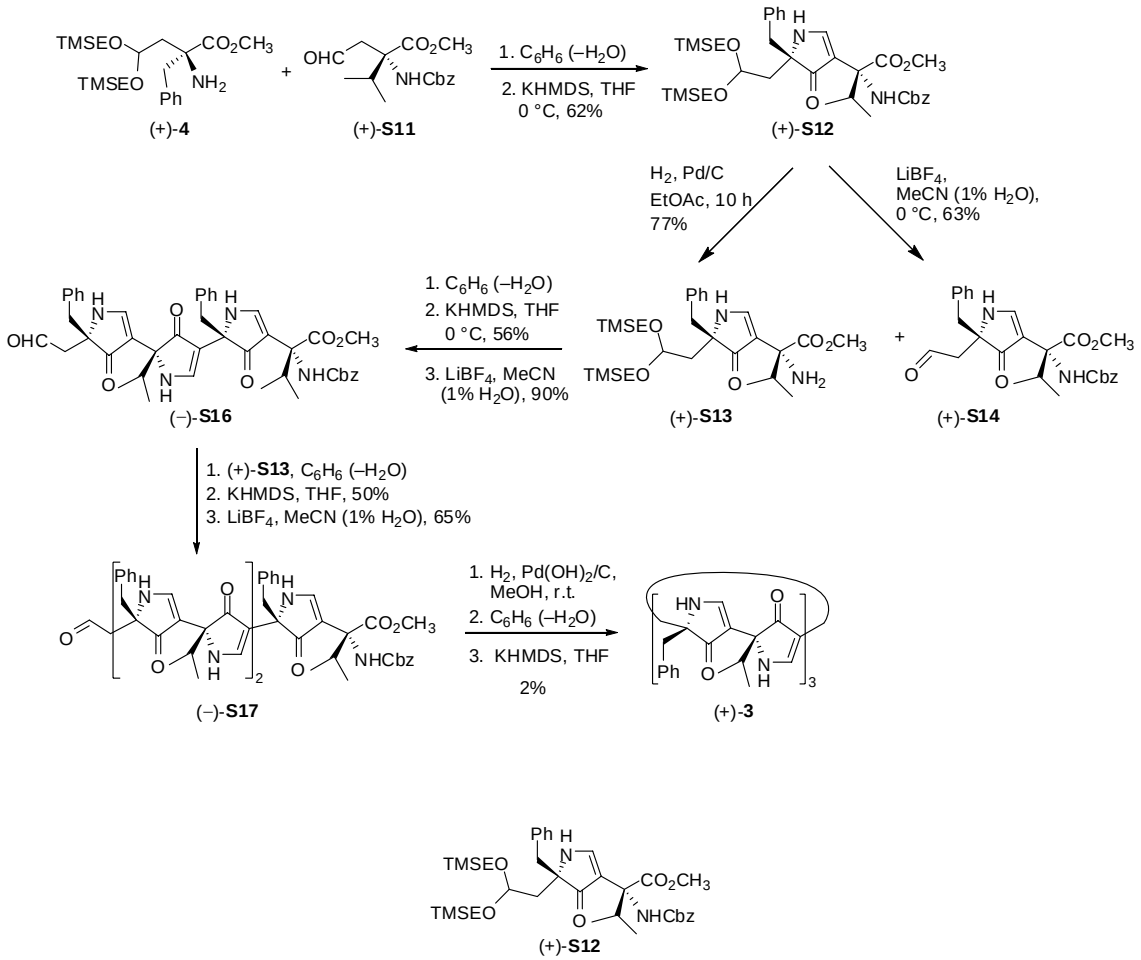


(–)-**S10**

Tetrapyrrolinone (–)-**S10.** A mixture of aldehyde (–)-**9** (0.603 g, 0.753 mmol) and amine (+)-**S8** (0.367 g, 0.905 mmol, 1.20 equiv.) was azeotropically dehydrated with toluene and then stored for 1 h under high vacuum. The resulting crude imine was dissolved in THF (60 mL) and a 0.5 M solution of KHMDS in toluene (30 mL, 15 mmol, 8 equiv.) was added over a period of 2 min at room temperature. After stirring for 90 min, the reaction was quenched with saturated NH_4Cl and diluted with EtOAc and H_2O. The organic phase was separated, washed with H_2O and brine, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (EtOAc/hexanes 2:3

→ 1:1) yielded tetrapyrrolinone (–)-**S10** (0.626 g, 72%) as a colorless glassy solid: $[\alpha]_D^{23}$ –86.7 (*c* 0.79, $CHCl_3$); IR (film): 3335 (s), 3063 (w), 3031 (w), 2953 (s), 2869 (m), 1728 (m), 1634 (s), 1568 (s), 1497 (m), 1455 (m), 1432 (m), 1365 (w), 1339 (w), 1249 (m), 1218 (m), 1153 (s), 1067 (m), 1028 (m), 974 (w), 915 (w), 860 (m), 836 (m), 734 (w), 699 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, concentration dependent, ~5 mg / 0.7 mL): δ 8.18 (d, *J* = 4.1 Hz, 1 H), 8.06 (d, *J* = 3.9 Hz, 1 H), 7.93 (d, *J* = 4.0 Hz, 1 H), 7.81 (app. s, 1 H), 7.10-7.38 (m, 19 H), 6.54 (d, *J* = 3.9 Hz, 1 H), 5.01 (d, *J* = 12.4 Hz, 1 H), 4.92 (d, *J* = 12.4 Hz, 1 H), 4.66 (dd, *J* = 8.8, 3.1 Hz, 1 H), 3.68-3.78 (m, 1 H), 3.62 (s, 3 H), 3.43-3.61 (m, 3 H), 3.23 (d, *J* = 13.3 Hz, 1 H), 3.14 (d, *J* = 13.4 Hz, 1 H), 2.97 (d, *J* = 13.3 Hz, 1 H), 2.95 (d, *J* = 13.4 Hz, 1 H), 2.05-2.15 (m, 1 H), 1.90-1.97 (m, 1 H), 1.84-1.89 (m, 1 H), 1.70 (dd, *J* = 14.0, 5.1 Hz, 1 H), 1.66 (dd, *J* = 14.0, 6.5 Hz, 1 H), 1.39-1.45 (m, 1 H), 1.26-1.36 (m, 2 H), 0.91-1.11 (m, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.84 (d, *J* = 6.7 Hz, 3 H), 0.79-0.90 (m, 1 H), 0.72 (d, *J* = 6.6 Hz, 9 H), 0.69 (d, *J* = 6.6 Hz, 3 H), 0.63 (d, *J* = 6.7 Hz, 3 H), 0.04 (s, 9 H), –0.02 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.4, 202.4, 200.7, 199.1, 173.4, 162.26, 160.6, 160.5, 160.2, 136.9, 134.7, 134.5, 130.3, 130.3, 128.3, 127.8, 127.7, 126.9, 126.5, 108.9, 108.3, 107.9, 100.2, 69.3, 68.6, 68.3, 68.2, 65.9, 65.2, 64.4, 60.3, 52.7, 47.9, 44.7, 43.9, 42.2, 41.8, 41.1, 24.5, 24.4, 24.3, 24.2, 24.0, 23.9, 23.7, 23.1, 18.6, 18.4, –1.46, –1.54; high resolution mass spectrum (ES+) *m/z* 1178.6044 [$(M+Na)^+$; calcd for $C_{65}H_{89}N_5O_{10}NaSi_2$: 1178.6046].

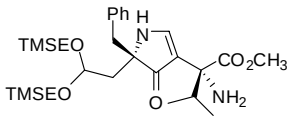
Scheme S2. Synthesis of Macrocyclic Hexapyrrolinone (+)-**3**.



Monopyrrolinone (+)-**S12.** A mixture of amine (+)-**4** (6.6 g, 15 mmol) and aldehyde (+)-**S11**[4] (4.6 g, 15 mmol) was azeotropically dehydrated with benzene (4 x 100 mL) and then stored for 1 h under high vacuum. The resulting crude imine was dissolved in ether (200 mL), cooled to 0 °C, and treated with a 0.5 M solution of KHMDS in toluene (120 mL, 60 mmol). The reaction mixture was stirred for an additional 1 hr, maintaining the internal temperature below 10 °C, before being quenched with 10% aqueous $NaHSO_4$ (100 mL) and diluted with EtOAc (200 mL). The aqueous layer was further extracted with EtOAc (3 x 50 mL), and the combined organic extracts were washed with a saturated $NaHCO_3$ aqueous solution and brine (100 mL each), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 20%

(4) Smith III, A. B. *et al. Org. Lett.* **2005**, *7*, 399.

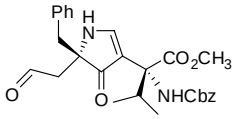
ethyl acetate in hexanes as eluent to afford monopyrrolinone (+)-**S12** (6.5 g, 62% yield) as a light yellow oil, containing some impurities as visualized by NMR: $[\alpha]_D^{23}$ +34.5 (*c* 1.5, $CHCl_3$); IR (film) 3308 (m), 2952 (s), 1734 (s), 1635 (m), 1506 (s), 1249 (s), 1049 (m), 860 (s), 836 (s), 698 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.99 (d, *J* = 2.5 Hz, 1 H), 7.09-7.34 (m, 11 H), 6.02 (d, *J* = 2.5 Hz, 1 H), 5.17 (d, *J* = 12.6 Hz, 1 H), 5.11 (d, *J* = 12.6 Hz, 1 H), 4.68 (apparent t, *J* = 5.3 Hz, 1 H), 3.73-3.80 (m, 2 H), 3.59-3.65 (m, 2 H), 3.54 (s, 3 H), 3.09 (d, *J* = 13.2 Hz, 1 H), 2.93 (d, *J* = 13.2 Hz, 1 H), 2.80-2.83 (m, 1 H), 2.22 (dd, *J* = 14.3, 5.3 Hz, 1 H), 2.16 (dd, *J* = 14.3, 5.3 Hz, 1 H), 0.98-1.17 (m, 4 H), 0.82 (d, *J* = 6.8 Hz, 3 H), 0.79 (d, *J* = 6.8 Hz, 3 H), 0.11 (s, 9 H), 0.10 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 201.6, 172.3, 164.0, 155.8, 138.0, 136.3, 131.2, 129.0, 128.9, 128.5, 128.5, 127.3, 110.1, 100.6, 69.7, 66.7, 65.3, 64.6, 64.2, 52.2, 42.1, 41.5, 34.3, 19.1, 19.0, 18.8, 18.1, -0.9, -0.9; high resolution mass spectrum (ES+) *m/z* 719.3545 $[(M+Na)^+$; calcd for $C_{34}H_{56}N_2O_7Si_2Na$: 719.3523].



(+)-**S13**

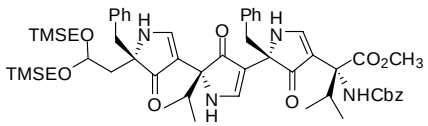
Amine (+)-**S13.** Pd/C (10% wt, 1.0 g) was added to a solution of monopyrrolinone (+)-**S12** (6.5 g, 9.3 mmol) in EtOAc (100 mL). The resulting mixture was stirred under H_2 (1 atm) at room temperature overnight. The catalyst was removed by filtration through celite and the resulting clear solution was concentrated *in vacuo*. The crude product was purified by flash chromatography using ethyl acetate-hexanes (1:1) as eluent to afford amine (+)-**S13** (4.0 g, 77%) as a white solid: mp 89-91°C, $[\alpha]_D^{23}$ +50.2 (*c* 0.61, $CHCl_3$); IR (film) 3244 (m), 2952 (s), 1734 (s), 1635 (m), 1558 (s), 1457 (m), 1249 (s), 1115 (m), 1054 (m), 859 (s), 835 (s), 699 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.82 (d, *J* = 4.1 Hz, 1 H), 7.21 - 7.09 (m, 5 H), 6.34 (d, *J* = 4.1 Hz, 1 H), 4.66 (dd, *J* = 4.1, 7.1 Hz, 1 H), 3.78 - 3.69 (m, 1 H), 3.64 - 3.62 (s, 3 H), 3.61 - 3.57 (m, 1 H), 3.54 - 3.45 (m, 2 H), 2.98 - 2.94 (m, 1 H), 2.93 - 2.89 (m, 1 H), 2.21 (spt, *J* = 6.8 Hz, 1 H), 2.07 (dd, *J* = 4.3, 14.3 Hz, 1 H), 2.03 (br. s, 2 H), 1.77 (dd, *J* = 7.1, 14.5 Hz, 1 H), 1.02 - 0.96 (m, 2 H), 0.89 (ddd, *J* = 1.7, 7.2, 9.4 Hz, 2 H), 0.66 (d, *J* = 6.7 Hz, 3 H), 0.53 (d, *J* = 6.7 Hz, 3 H), 0.05 (s, 9 H),

0.01 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5, 175.4, 162.0, 135.2, 130.2, 127.8, 126.6, 112.8, 99.9, 69.2, 64.4, 63.8, 62.8, 51.9, 40.5, 39.9, 34.7, 18.5, 18.4, 16.9, 16.2, -1.5, 1.5; high resolution mass spectrum (ES+) *m/z* 563.3346 [$(M+H)^+$; calcd for $C_{29}H_{51}N_2O_5Si_2$: 563.3336].



(+)-**S14**

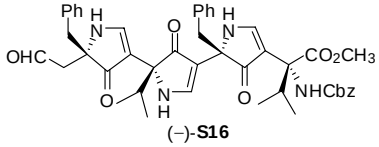
Aldehyde (+)-**S14.** A solution of monopyrrolinone (+)-**S12** (5.5 g, 7.9 mmol) in wet CH_3CN (160 mL, 1 % H_2O) was cooled to 0 °C and treated with a 1 M solution of $LiBF_4$ in CH_3CN (64 mL). After stirring for 2-3 h (0^oC-10^oC), the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL), diluted with EtOAc (100 mL), and then the aqueous layer was further extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with water and brine (100 mL each), dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was re-dissolved in EtOAc and filtered to remove inorganic salts. Flash chromatography (EtOAc/hexanes 1:4 $\rightarrow$ 1:1) yielded aldehyde (+)-**S14** (2.4 g, 63%) as a light yellow foam: $[\alpha]_D^{23}$ +29.4 (*c* 0.68, $CHCl_3$); IR (film) 3309 (m), 3031 (w), 2965 (s), 1718 (s), 1646 (m), 1507 (m), 1257 (m), 1235 (s), 739 (m), 700 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (s, 1 H), 7.89 (d, *J* = 3.0 Hz, 1 H), 7.40 - 7.00 (m, 10 H), 6.69 (br. s., 1 H), 5.24 (d, *J* = 12.3 Hz, 1 H), 5.13 - 5.00 (m, 2 H), 3.54 (br. s., 3 H), 2.90 - 2.72 (m, 3 H), 2.33 - 2.20 (m, 2 H), 0.86 (d, *J* = 7.1 Hz, 3 H), 0.79 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 199.5, 171.3, 163.9, 154.8, 136.7, 134.5, 130.1, 128.4, 128.2, 127.8, 127.7, 127.0, 109.3, 67.7, 66.2, 63.9, 52.2, 49.1, 41.3, 32.6, 18.0, 17.2; high resolution mass spectrum (ES+) *m/z* 501.2012 [$(M+Na)^+$; calcd for $C_{27}H_{30}N_2O_6Na$: 501.2002].



(–)-**S15**

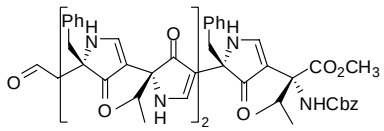
Trispyrrolinone (–)-**S15.** A mixture of amine (+)-**S13** (1.74 g, 3.1 mmol) and aldehyde (+)-**S14** (1.43 g, 3.0 mmol) was dissolved in 100 mL benzene and left at room temperature overnight.

The mixture was azeotropically dehydrated with benzene (4 x 50 mL) and then stored for 1 h under high vacuum. The resulting crude imine was dissolved in THF/Et_2O (1:3, 100 mL total), cooled to 0 °C, and treated with a 0.5 M solution of KHMDS in toluene (50 mL, 25 mmol). The reaction mixture was stirred at 0 °C for 30 min and was then allowed to warm to room temperature for an additional 1.5 h, before being quenched with 10% aqueous $NaHSO_4$ (100 mL) and diluted with EtOAc (200 mL). The aqueous layer was further extracted with EtOAc (3 x 50 mL), and the combined organic extracts were washed with saturated $NaHCO_3$ aqueous solution and brine (100 mL each), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography using ethyl acetate-hexanes (1:4 $\rightarrow$ 1:1) as eluent to afford trispyrrolinone (–)-**S15** (1.66 g, 56% yield) as a light yellow solid: mp 105-110°C; $[\alpha]_D^{23}$ –41.2 (*c* =0.87, $CHCl_3$); IR (film) 3300 (m), 3031 (s), 2953 (m), 1711 (m), 1640 (s), 1572 (s), 1496 (m), 1454 (m), 1250 (s), 1169 (s), 857 (m), 836 (m), 699 (m) cm^{-1}; ^1H NMR (500 MHz ,C_6D_6) δ 8.04 (d, *J* = 4.1 Hz, 1 H), 7.77 (d, *J* = 3.7 Hz, 1 H), 7.52 (d, *J* = 3.7 Hz, 1 H), 7.41 - 7.31 (m, 3 H), 7.26 - 6.96 (m, 15 H), 5.92 (br. s., 1 H), 5.11 (d, *J* = 12.3 Hz, 1 H), 5.04 (d, *J* = 12.3 Hz, 1 H), 4.49 (dd, *J* = 3.9, 7.3 Hz, 1 H), 3.72 - 3.64 (m, 1 H), 3.57 - 3.49 (m, 1 H), 3.48 - 3.28 (m, 6 H), 3.14 (d, *J* = 13.0 Hz, 1 H), 3.02 (d, *J* = 13.8 Hz, 1 H), 2.92 (d, *J* = 12.7 Hz, 1 H), 2.70 (spt, *J* = 7.1 Hz, 1 H), 2.09 (dd, *J* = 3.7, 14.5 Hz, 1 H), 1.83 (spt, *J* = 6.8 Hz, 1 H), 1.71 (dd, *J* = 7.3, 14.3 Hz, 1 H), 0.92 - 0.86 (m, 2 H), 0.81 (m, 2 H), 0.73 - 0.67 (m, 6 H), 0.65 - 0.61 (m, 6 H), 0.01 (s, 9 H), 0.01 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 203.7, 202.7, 200.0, 172.3, 163.4, 162.6, 161.9, 155.5, 137.9, 136.3, 136.3, 131.5, 131.2, 129.1, 128.9, 128.7, 128.5, 128.3, 127.6, 127.1, 110.2, 109.0, 108.1, 100.5, 72.0, 70.0, 69.2, 66.8, 65.2, 64.2, 64.1, 52.3, 44.0, 40.9, 40.8, 37.9, 33.7, 19.1, 19.0, 18.9, 18.2, 17.2, 16.9, -0.8, -1.0; high resolution mass spectrum (ES+) *m/z* 1013.4899 [$(M+Na)^+$; calcd for $C_{55}H_{74}N_4O_9Si_2Na$: 1013.4892].



(–)-**S16**

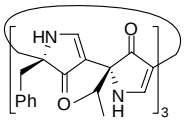
Aldehyde (–)-**S16.** A solution of trispyrrolinone (–)-**S15** (2.0 g, 2.0 mmol) in wet CH_3CN (160 mL, 1 % H_2O) was cooled to 0 °C and treated with a 1 M solution of $LiBF_4$ in CH_3CN (42 mL). The reaction mixture was then allowed to warm to room temperature and stir for an additional 50 min before being quenched with saturated aqueous $NaHCO_3$ (50 mL) and diluted with EtOAc (100 mL). The aqueous layer was further extracted with EtOAc (3 x 50 mL) and the combined organic extracts were washed with water and brine (50 mL each), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting residue was re-dissolved in EtOAc and filtered to remove inorganic salts. Flash chromatography (EtOAc/hexanes 1:1 $\rightarrow$ 5:1) provided aldehyde (–)-**S16** (1.4 g, 90%) as a white solid: mp > 125 °C; $[\alpha]_D^{23}$ –108.1 (*c* 1.2, $CHCl_3$); IR (film) 3300 (m), 3031 (w), 2964 (s), 1723 (s), 1640 (s), 1571 (s), 1496 (s), 1454 (m), 1172 (s), 733 (m), 699 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.37 (s, 1 H), 8.05 (s, 1 H), 7.84-7.87 (m, 2 H), 7.73 (d, J = 3.3 Hz, 1 H), 7.02-7.42 (m, 17 H), 6.56 (s, 1 H), 5.01 (d, *J* = 12.4 Hz, 1 H), 4.87 (d, *J* = 12.4 Hz, 1 H), 3.67 (s, 3 H), 3.30 (d, *J* = 13.5 Hz, 1 H), 3.08 (d, *J* = 13.5 Hz, 1 H), 2.96 (d, *J* = 13.4 Hz, 1 H), 2.91 (d, *J* = 13.4 Hz, 1 H), 2.57-2.69 (m, 3 H), 1.81-1.83 (m, 1 H), 0.58-0.68 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2, 200.1, 199.1, 197.7, 171.7, 162.9, 162.6, 162.1, 154.1, 136.4, 135.4, 134.2, 130.5, 130.1, 128.5, 128.5, 128.1, 128.0, 127.6, 127.3, 126.2, 109.8, 108.7, 107.0, 71.7, 68.3, 67.9, 66.1, 63.4, 52.2, 49.4, 42.7, 41.3, 37.4, 31.5, 18.2, 17.1, 16.6, 16.1; high resolution mass spectrum (ES+) *m/z* 773.3526 [$(M+H)^+$; calcd for $C_{45}H_{49}N_4O_8$: 773.3550].



(–)-**S17**

Aldehyde (–)-**S17.** A mixture of amine (+)-**S13** (1.04 g, 2.2 mmol) and aldehyde (–)-**S16** (1.4 g, 1.8 mmol) was dissolved in 100 mL benzene (ultrasonication) and left at room temperature overnight. The mixture was then azeotropically dehydrated with benzene (6 x 50 mL) and then stored for 1 h under high vacuum. The resulting crude imine was dissolved in THF (160 mL), cooled to 0 °C, and treated with a 0.5 M solution of KHMDS in toluene (56 mL, 28 mmol). The

reaction mixture was allowed to warm to room temperature and stir for an additional 1-2 h before being quenched with 10% aqueous $NaHSO_4$ (100 mL) and diluted with EtOAc (200 mL). The aqueous layer was further extracted with EtOAc (3 x 50 mL), and the combined organic extracts were washed with saturated $NaHCO_3$ solution and brine (50 mL each), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography using ethyl acetate-hexanes (1:4 $\rightarrow$ 2:1) as eluent to afford the resultant pentapyrrolinone (1.17 g, 50% yield) as a light yellow solid containing a small quantity of amine (+)-**S13.** This mixture was then used directly in the next step. A solution of crude pentapyrrolinone (1.17 g, 0.9 mmol) in wet CH_3CN (120 mL, 1% H_2O) was cooled to 0 °C and treated with a 1 M solution of $LiBF_4$ in CH_3CN (60 mL). The reaction mixture was allowed to warm to room temperature and stir for an additional 45 min before being quenched with saturated aqueous $NaHCO_3$ (50 mL) and diluted with EtOAc (100 mL). The aqueous layer was further extracted with EtOAc (3 x 50 mL) and the combined organic extracts were washed with water and brine (50 mL each), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was re-dissolved in EtOAc and filtered to remove inorganic salts. Flash chromatography (EtOAc/hexanes 1:1 $\rightarrow$ 5:1) provided aldehyde (–)-**S17** (0.62 g, 65%) as a white solid: mp >150°C; $[\alpha]_D^{23}$ –45.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (s, 1 H), 8.09 (d, *J* = 3.2 Hz, 1 H), 8.02 (d, *J* = 3.0 Hz, 1 H), 7.90-7.92 (m, 2 H), 7.79 (apparent s, 1 H), 7.69 (apparent s, 1 H), 7.01-7.40 (m, 24 H), 6.39 (apparent s, 1 H), 4.98 (d, *J* = 12.5 Hz, 1 H), 4.87 (d, *J* = 12.5 Hz, 1 H), 3.64 (s, 3 H), 3.42 (br s, 1 H), 3.13 (d, *J* = 13.5 Hz, 1 H), 3.01 (d, *J* = 13.5 Hz, 1 H), 2.93 (d, *J* = 13.4 Hz, 1 H), 2.90 (s, 2 H), 2.66 (br s, 2 H), 2.21-2.23 (m, 1 H), 1.87-1.90 (m, 1 H), 1.77-1.80 (m, 1 H), 0.63 (d, *J* = 6.8 Hz, 3 H), 0.61 (d, *J* = 6.8 Hz, 3 H), 0.54-0.57 (m, 6 H), 0.46 (d, *J* = 6.7 Hz, 3 H), 0.34 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6, 201.9, 200.5, 200.4, 199.8, 198.9, 171.9, 163.2, 162.6, 161.8, 161.7, 161.5, 155.6, 136.6, 135.2, 134.7, 134.3, 130.5, 130.4, 130.2, 128.5, 128.5, 128.1, 127.9, 127.6, 127.5, 127.2, 126.9, 126.5, 109.3, 108.7, 107.2, 106.7, 106.7, 71.9, 70.9, 68.5, 68.4, 68.1, 66.3, 64.8, 52.2, 49.0, 43.2, 41.9, 41.2, 36.3, 36.1, 34.4, 17.4, 17.2, 16.7, 16.3, 16.1, 15.8; high resolution mass spectrum (ES+) *m/z* 1089.4710 $[(M+Na)^+$; calcd for $C_{63}H_{66}N_6O_{10}Na$: 1089.4738].



(+)-**3**

Macrocyclic Hexapyrrolinone (+)-**3.** Pd-hydroxide/C (20% Pd, wet, Degussa E101 NE/W, 120 mg) was added to a solution of pentapyrrolinone aldehyde (–)-**S17** (0.62 g, 0.58 mmol) in MeOH (40 mL). The resulting mixture was stirred under H_2 (1 atm) at room temperature for 2 h. The catalyst was removed by filtration through celite and the resulting clear solution was concentrated *in vacuo*. The crude product was then azeotropically dehydrated with benzene (4 x 100 mL) and stored for 1 h under high vacuum. The crude imine was dissolved in THF (240 mL) and treated at room temperature with a 0.5 M solution of KHMDS in toluene (20 mL, 10 mmol). The reaction mixture was stirred for an additional 3 h before being quenched with 10% aqueous $NaHSO_4$ (60 mL) and diluted with EtOAc (200 mL). The aqueous layer was further extracted with EtOAc (3 x 50 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine (60 mL each), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was first purified by silica gel column, using 2:1 EtOAc/Hexanes as eluent, and then purified further by preparative thin-layer chromatography, using EtOAc/Hexanes 2:1 as eluent, to afford the macrocyclic hexapyrrolinone (+)-**3** (9 mg, 2%) as a white solid: $[\alpha]_D^{23}$ +40.6 (*c* 0.14, $CHCl_3$); IR (film) 3309 (s), 2961 (m), 2923 (s), 2852 (m), 1645 (s), 1559 (s), 1456 (s), 1261 (m), 1162 (s), 745 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 3.8 Hz, 3 H), 7.98 (d, *J* = 3.9 Hz, 3 H), 7.72 (d, *J* = 3.9 Hz, 3 H), 7.47 (d, *J* = 3.8 Hz, 3 H), 7.11-7.17 (m, 15 H), 2.99 (d, *J* = 13.6 Hz, 3 H), 2.94 (d, *J* = 13.6 Hz, 3 H), 1.66 (hep, *J* = 6.8 Hz, 3 H), 0.53 (d, *J* = 6.8 Hz, 9 H), 0.52 (d, *J* = 6.8 Hz, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4, 201.4, 162.7, 162.5, 134.8, 130.3, 127.8, 126.8, 108.5, 107.6, 72.3, 69.4, 44.6, 36.9, 29.6, 16.7, 16.2; high resolution mass spectrum (ES+) *m/z* 905.4031 [$(M+Na)^+$; calcd for $C_{54}H_{54}N_6O_6Na$: 905.4003].

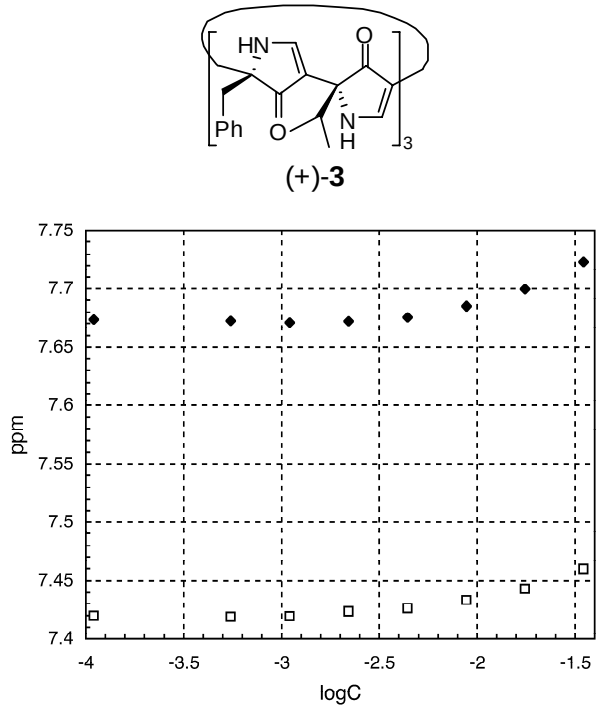
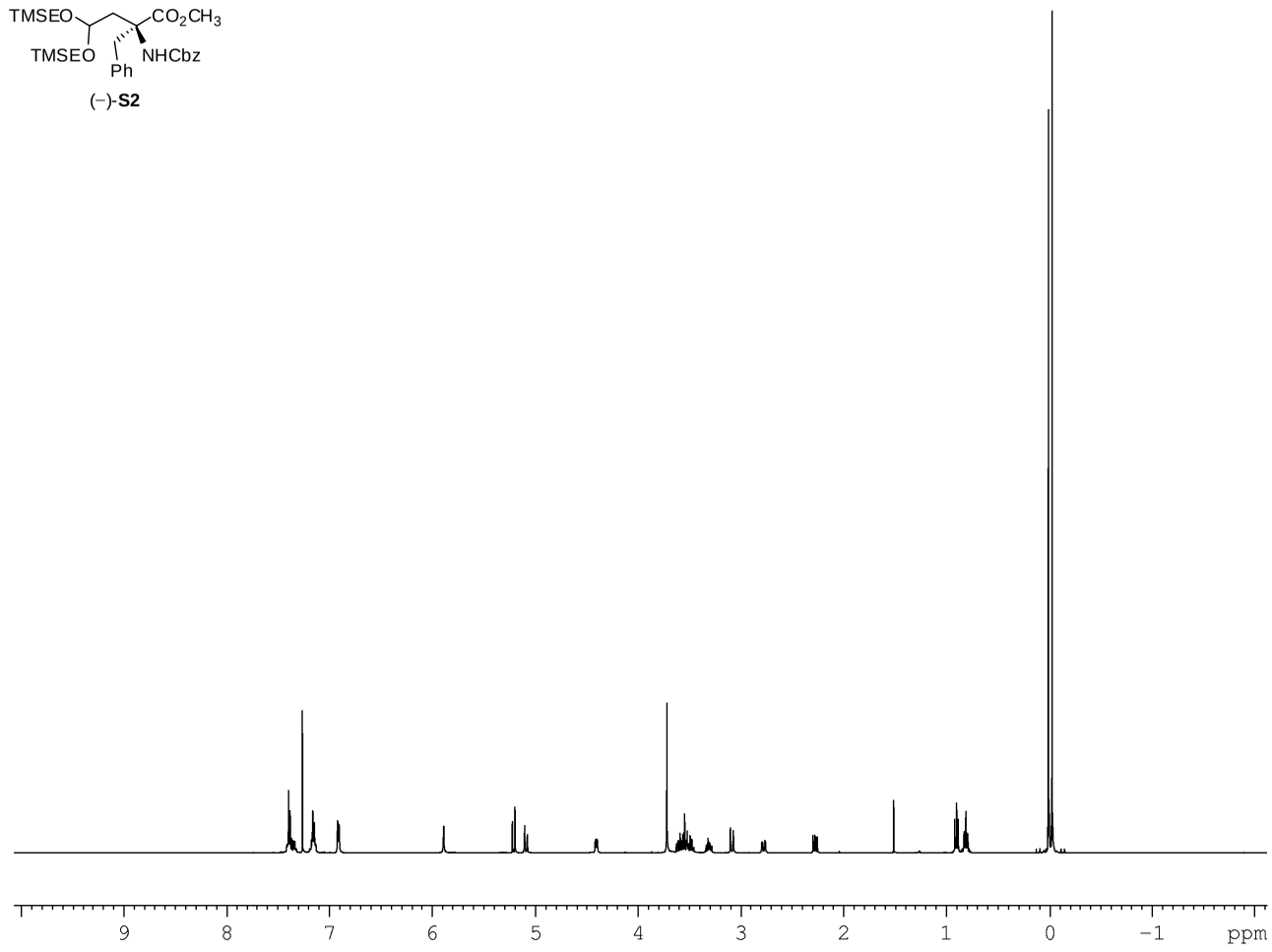


Figure S1. Concentration dependence of the ^{1}H NMR chemical shift of the N-H protons of (+)-**3**.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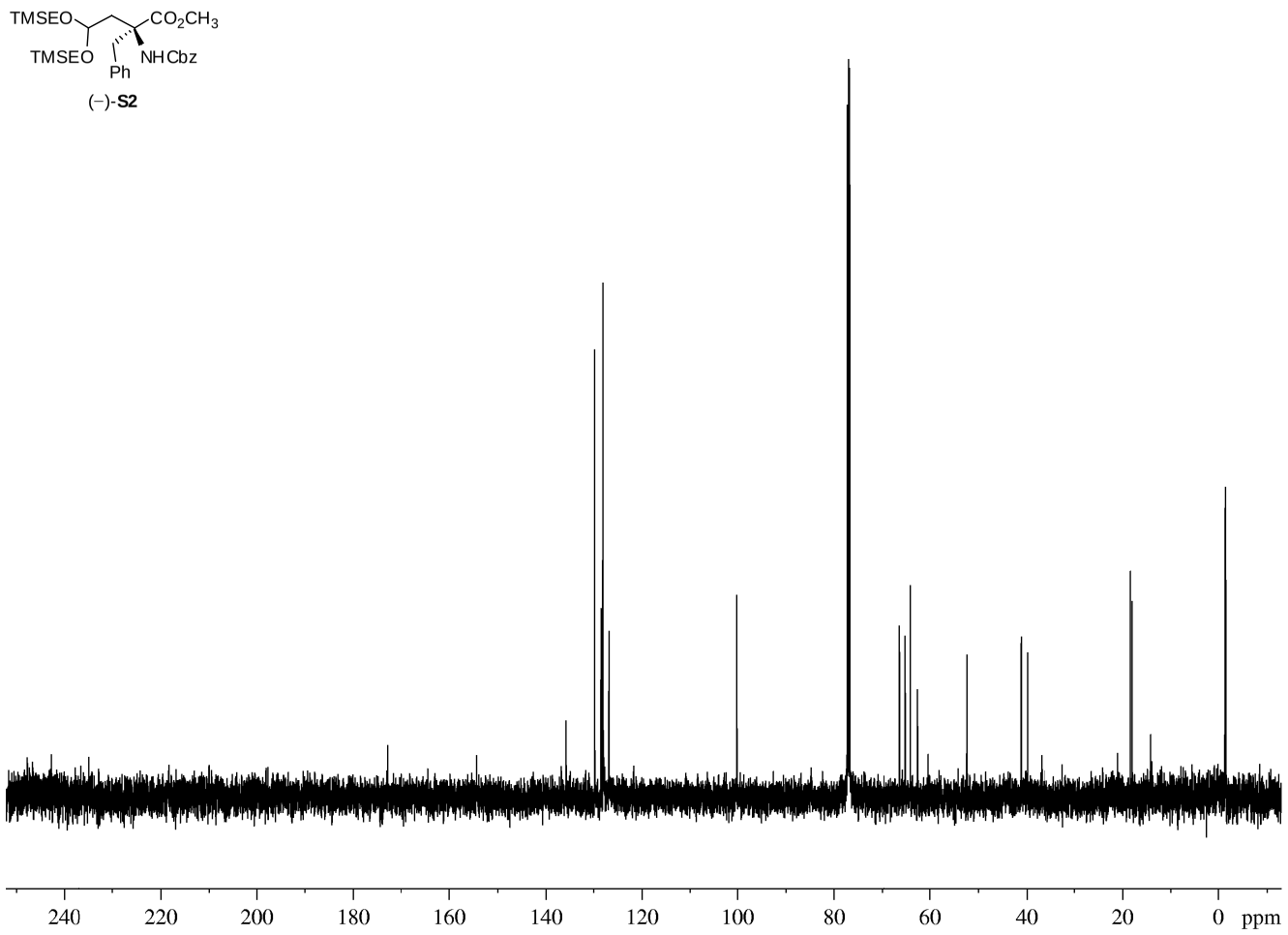
ppm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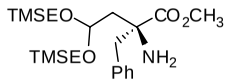
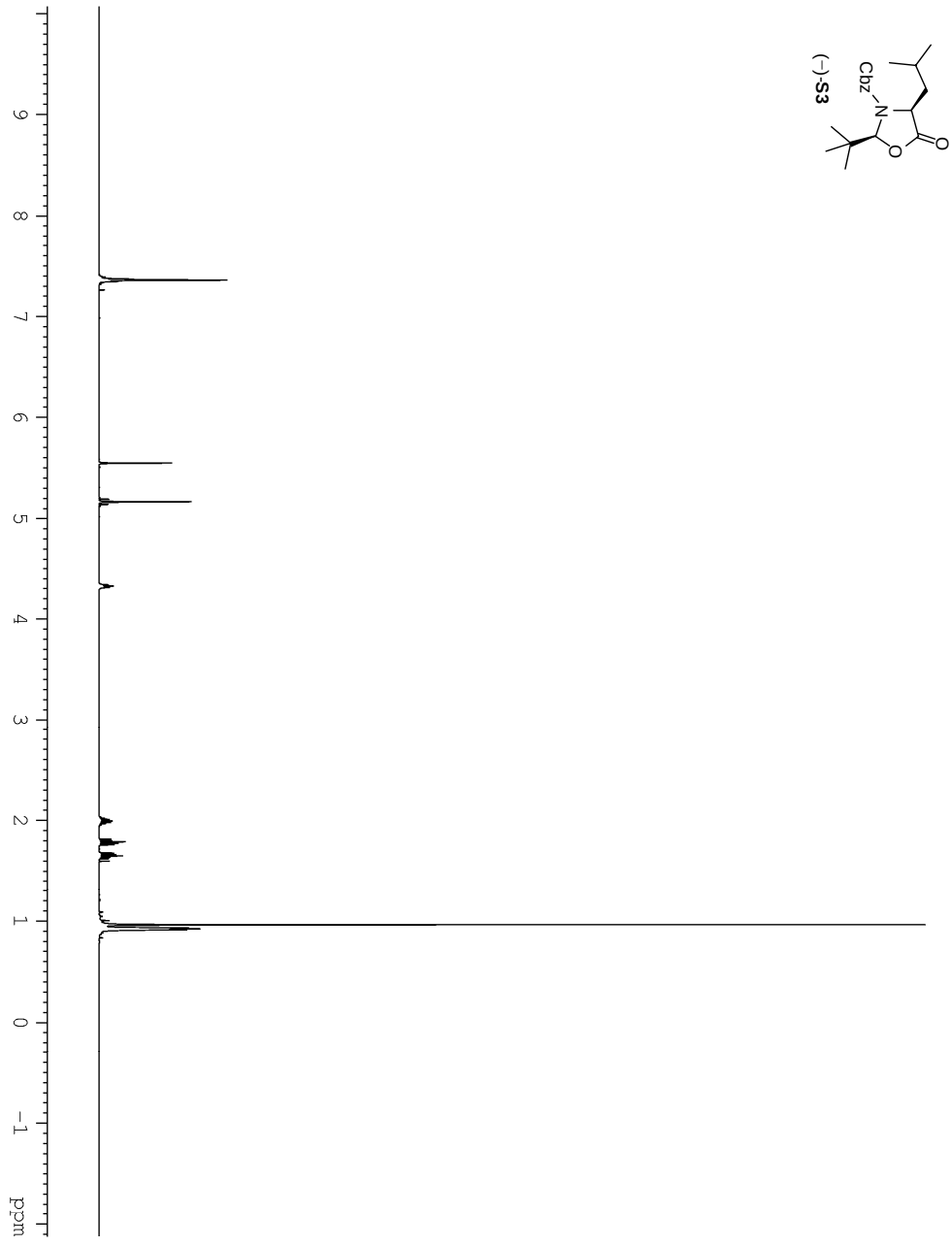
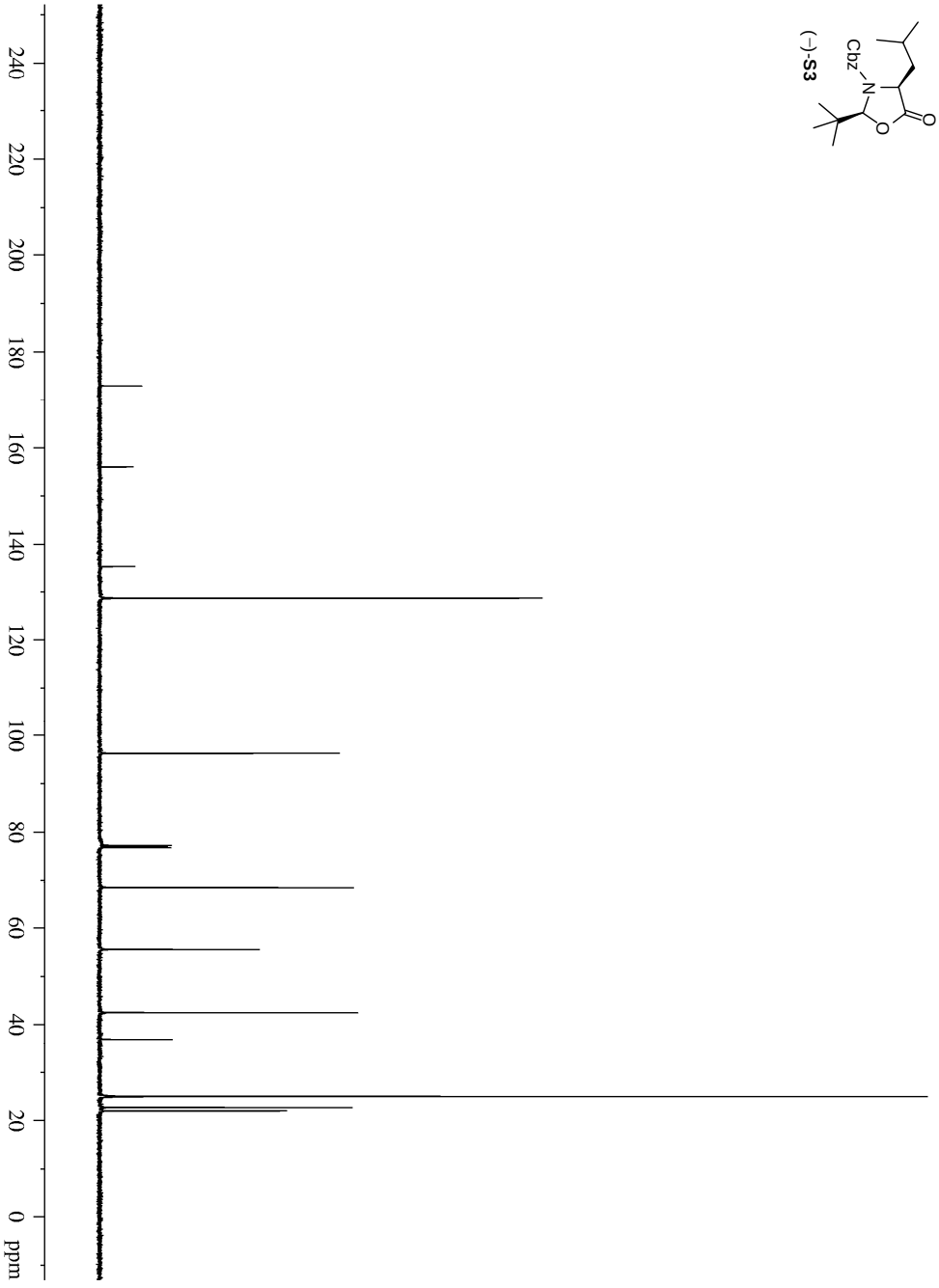


(+)-**4**



(−)-**S3**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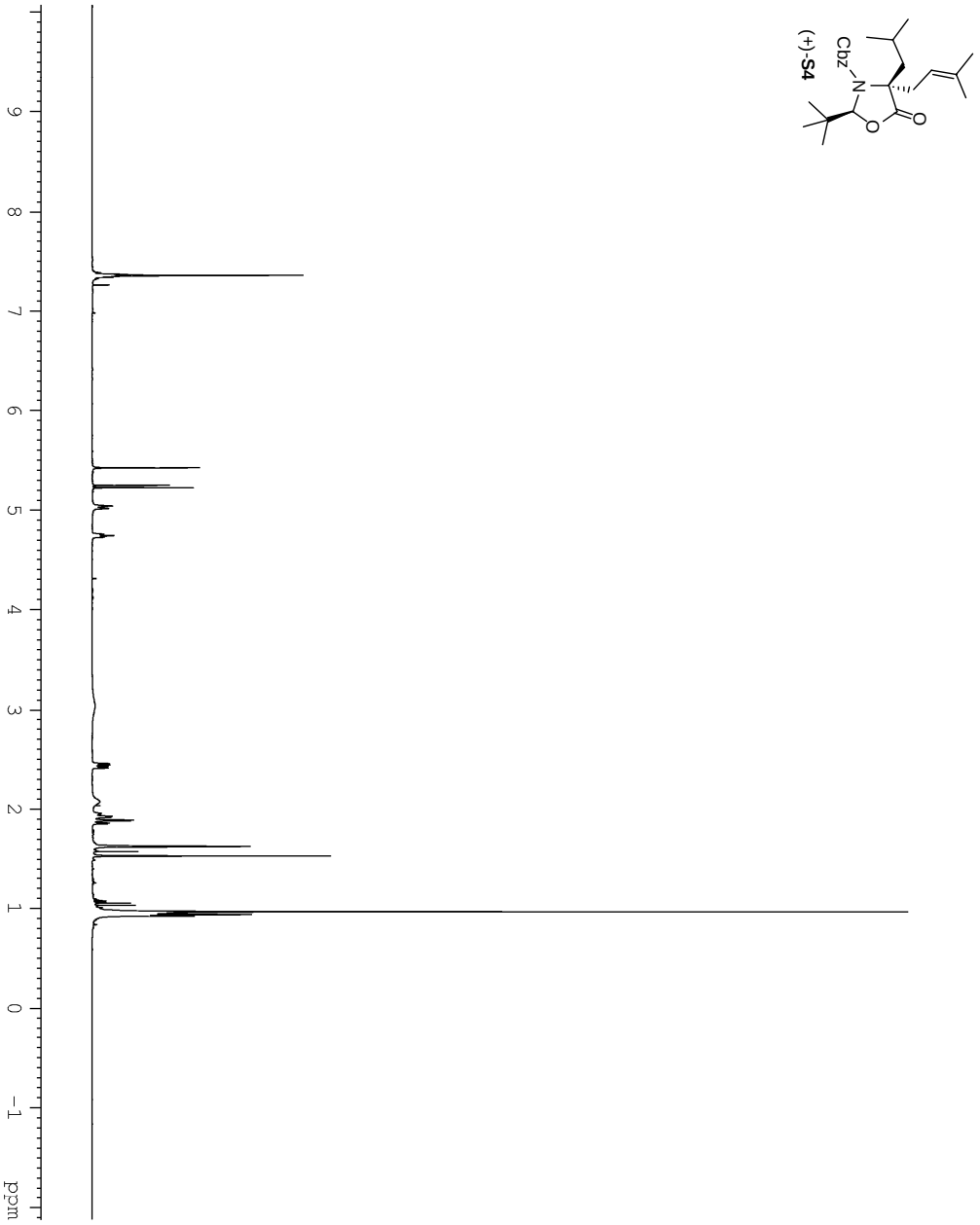
(–)-S3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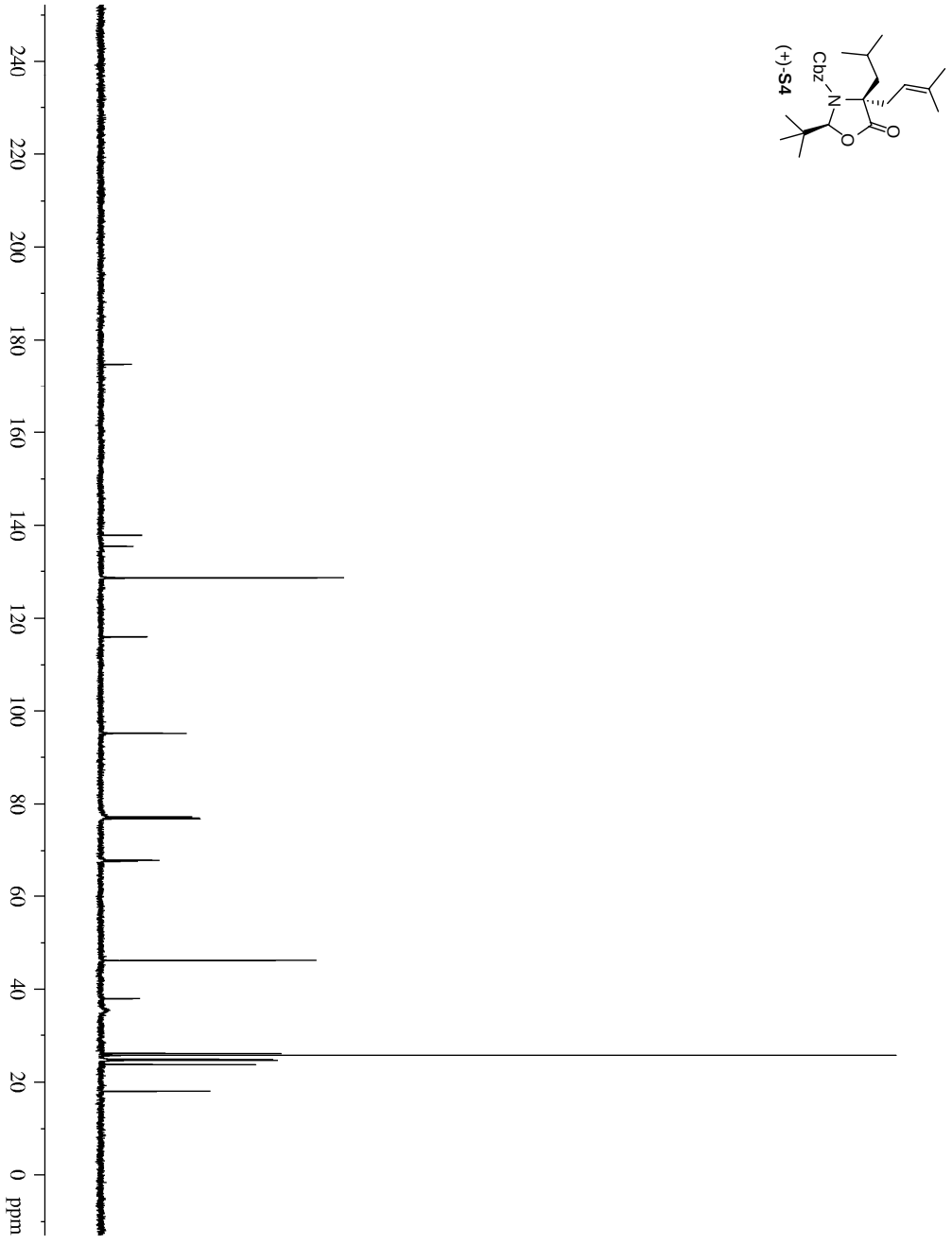
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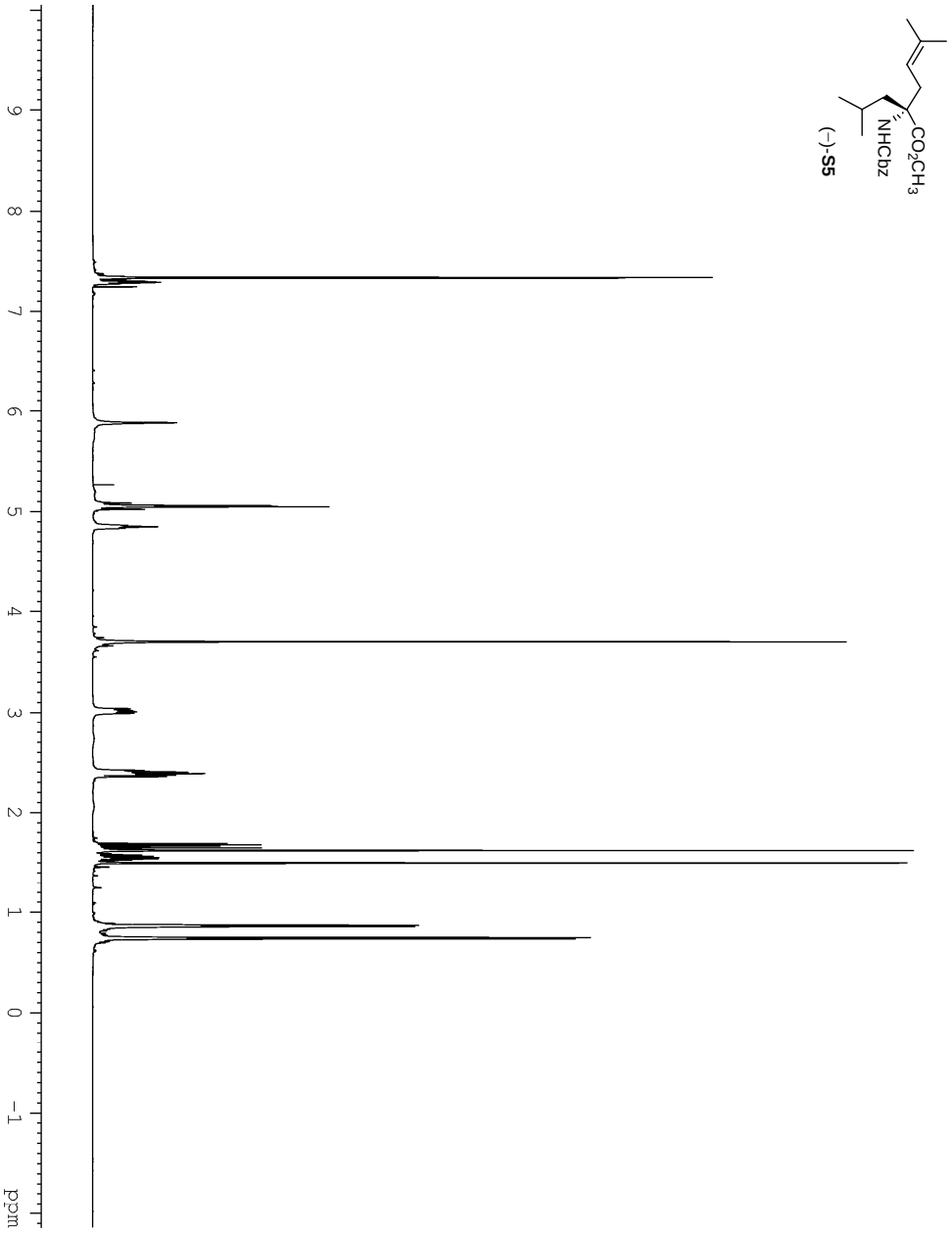
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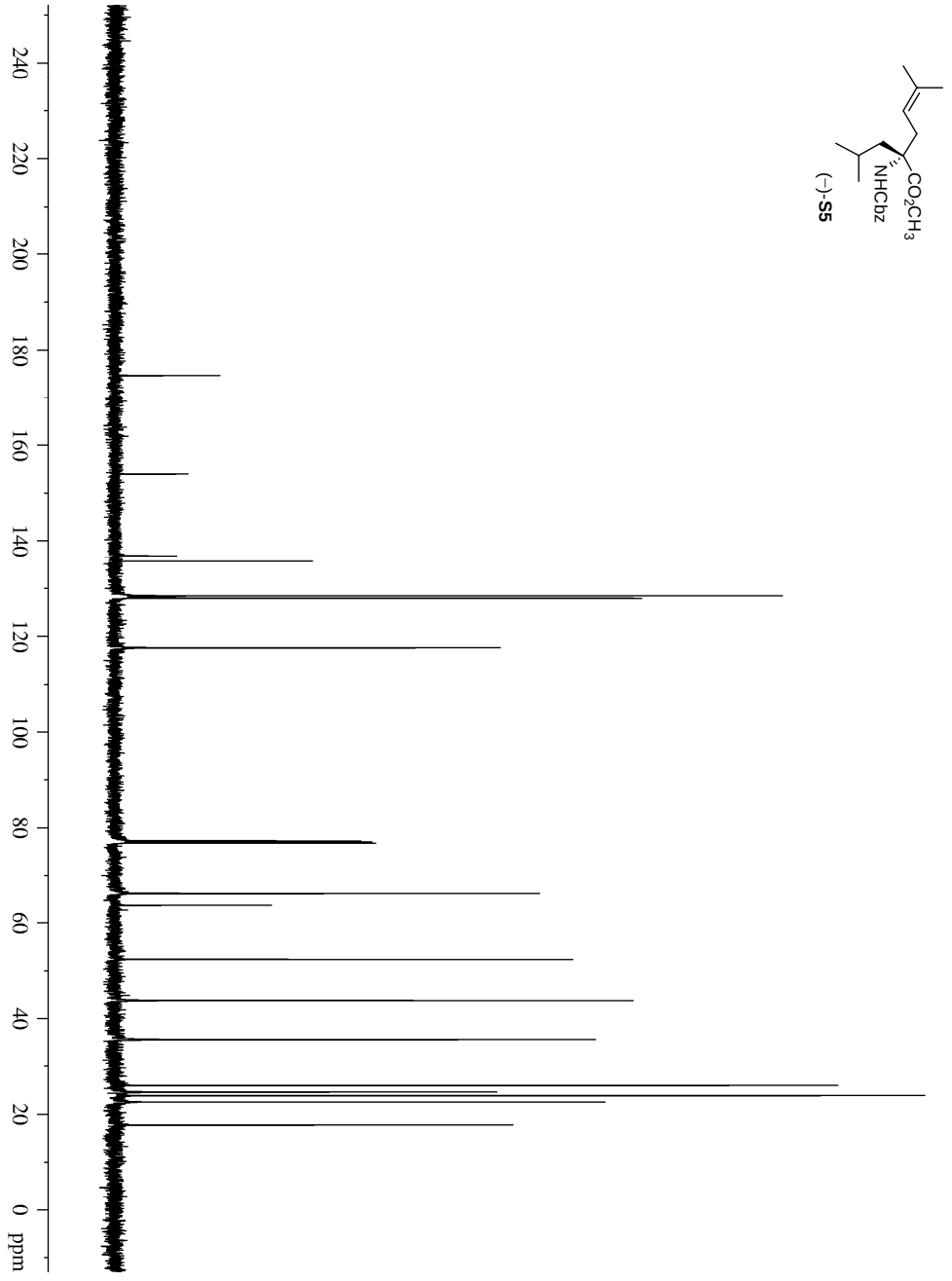
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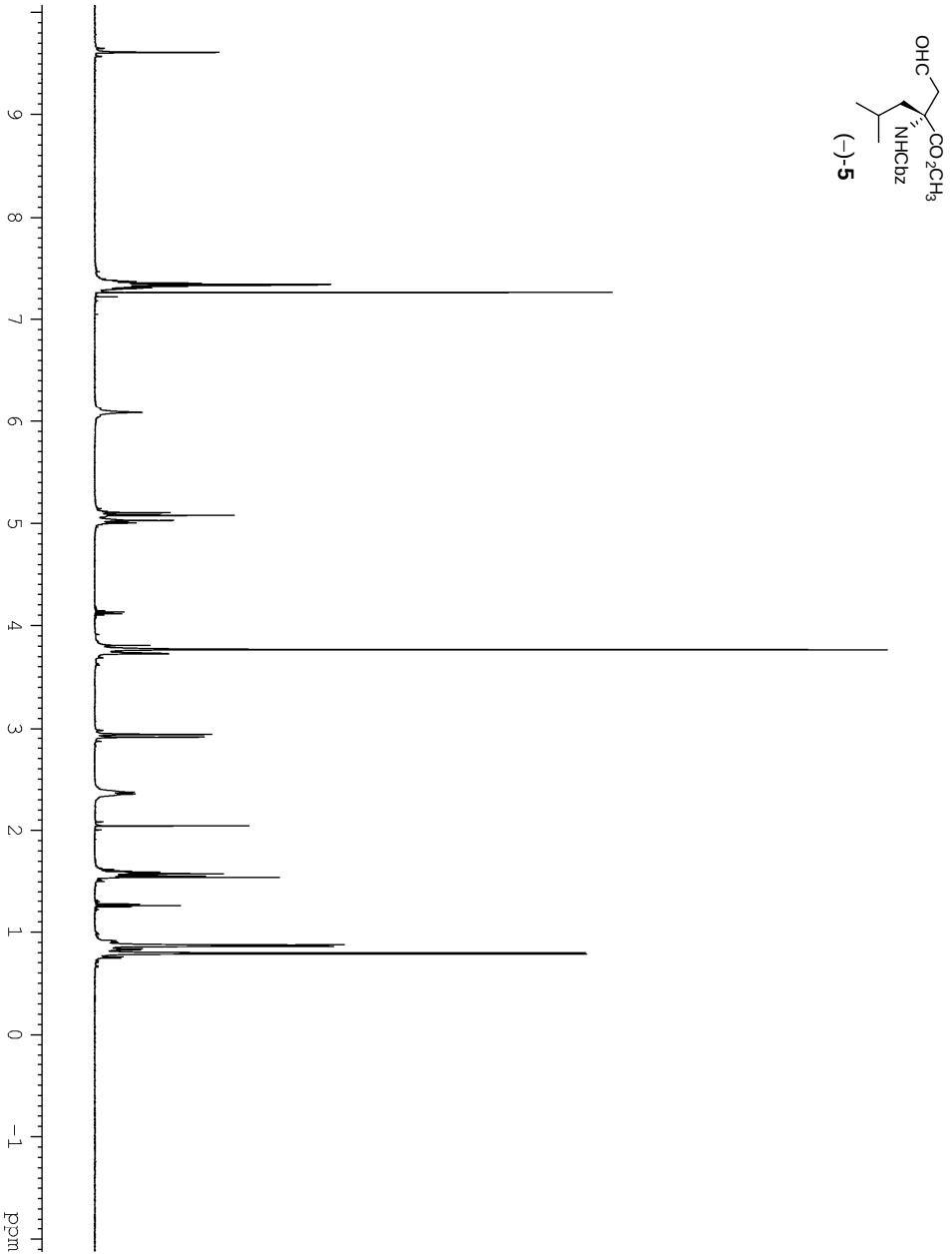
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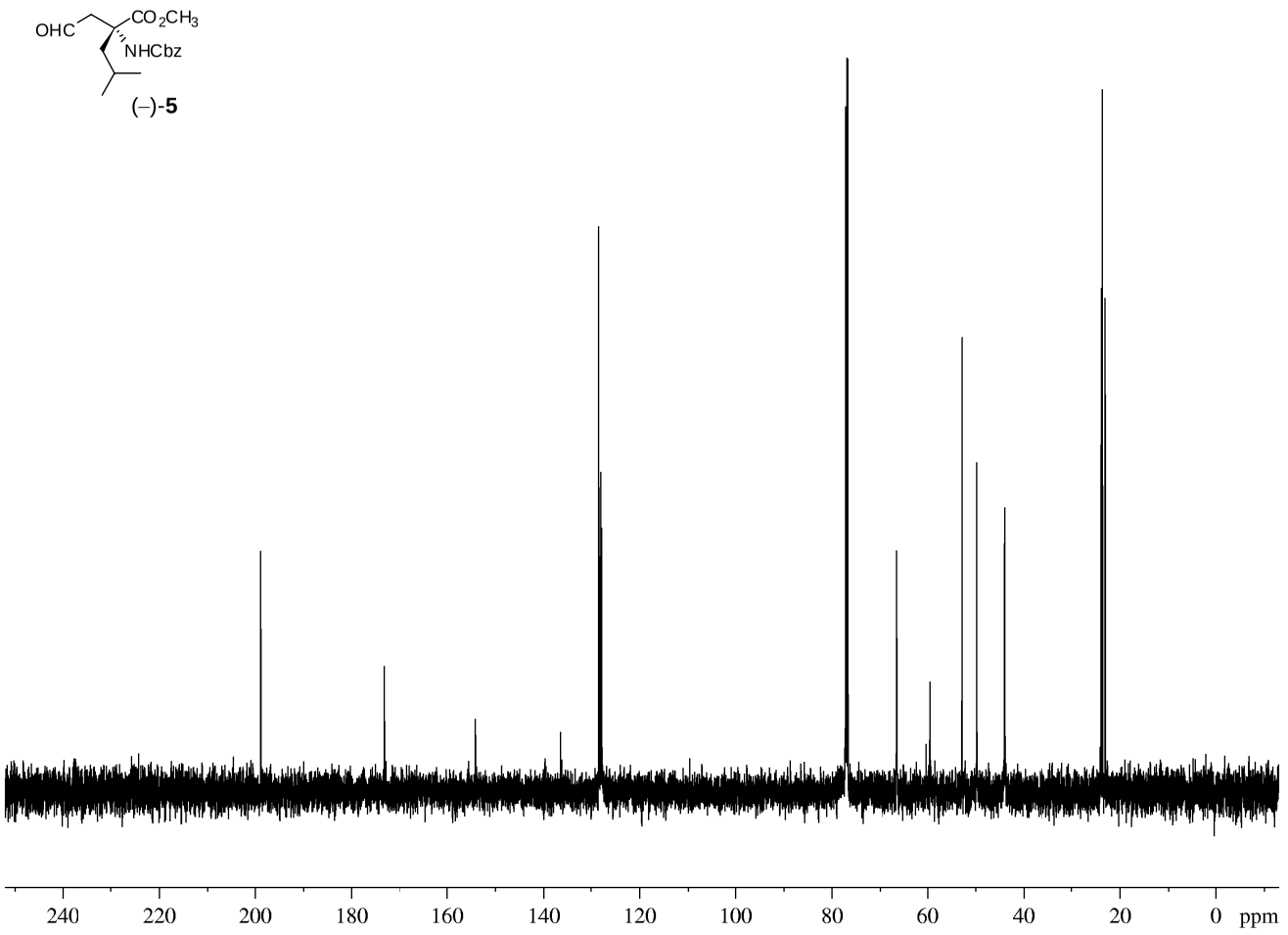
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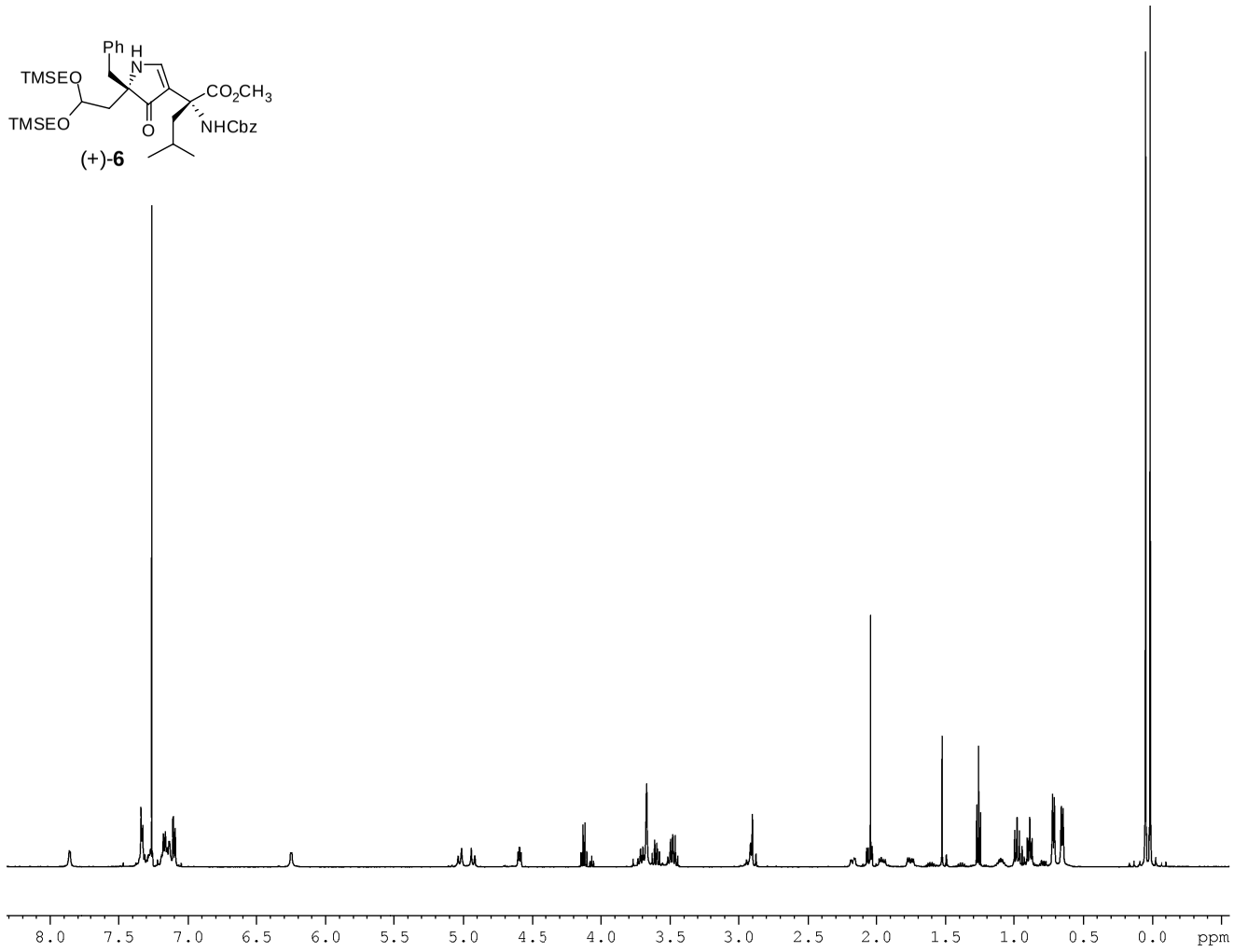
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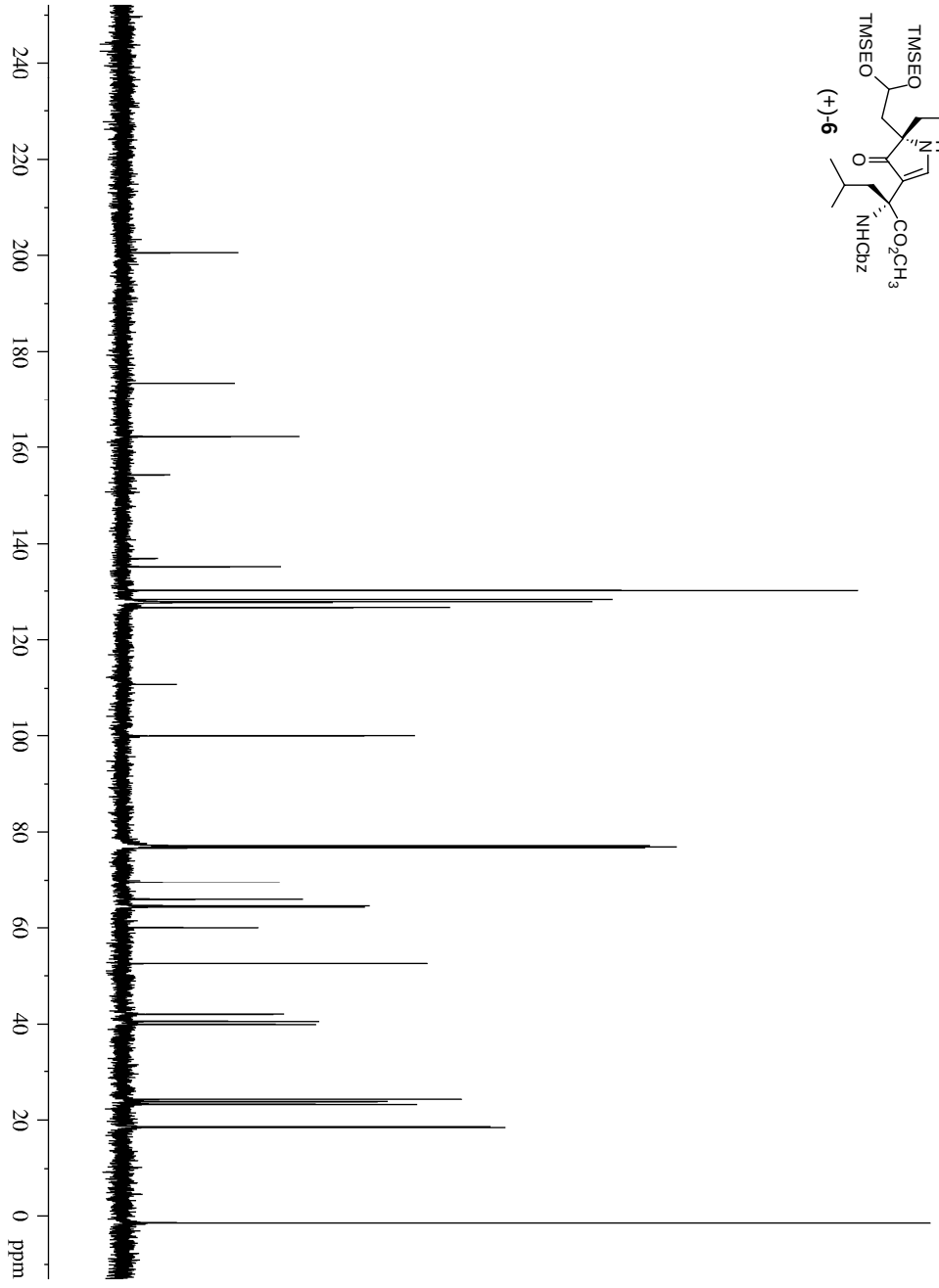
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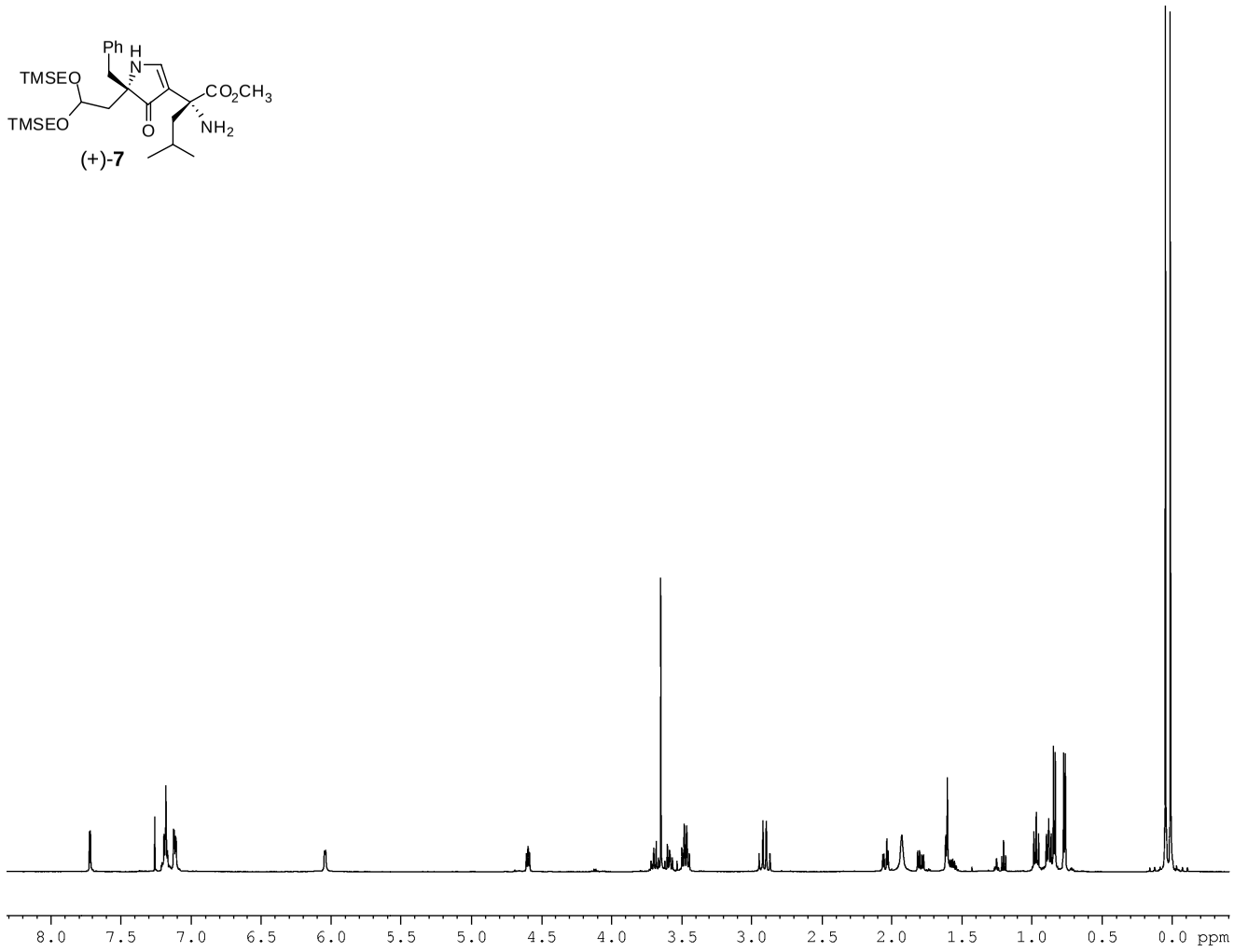
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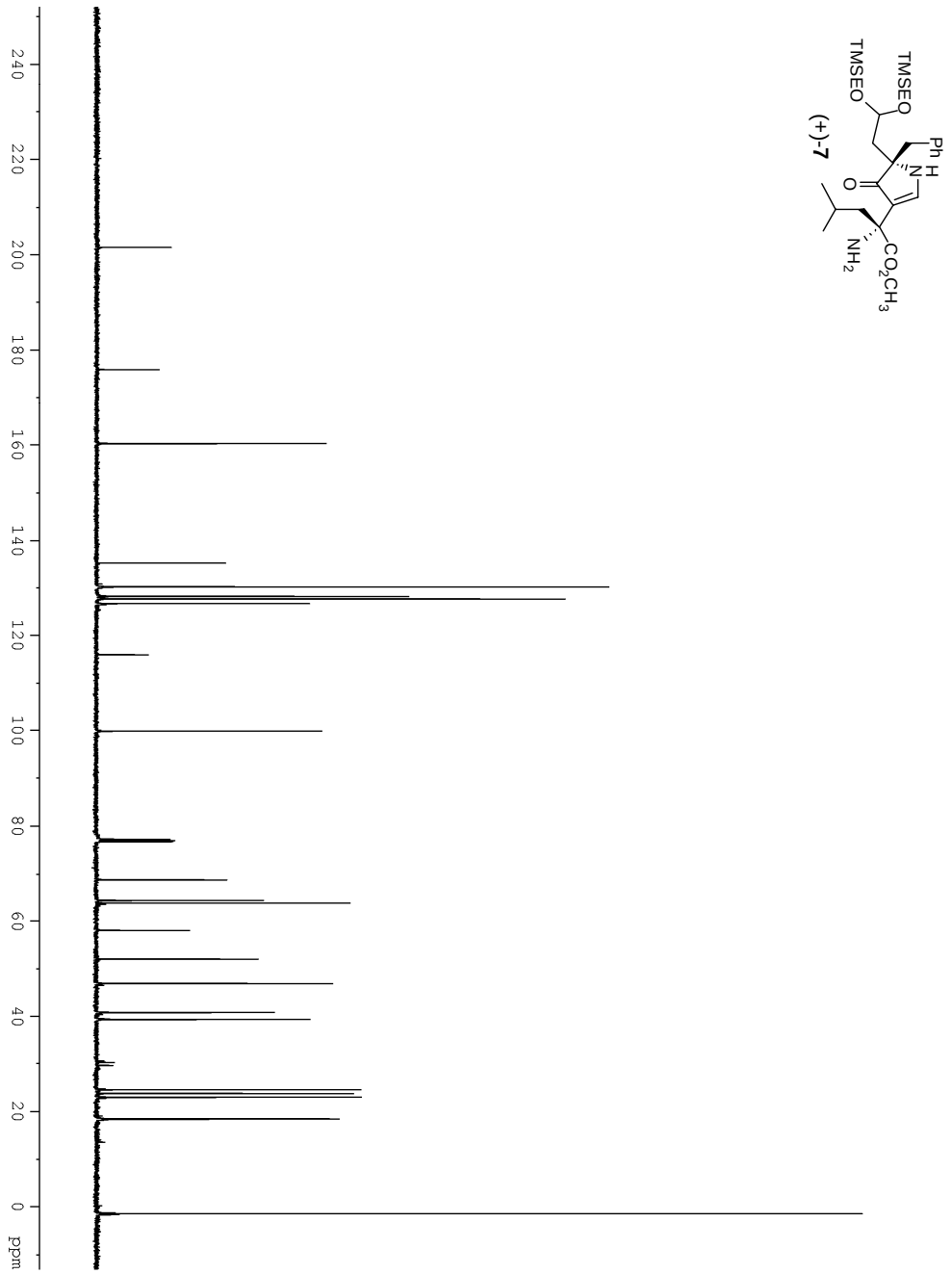
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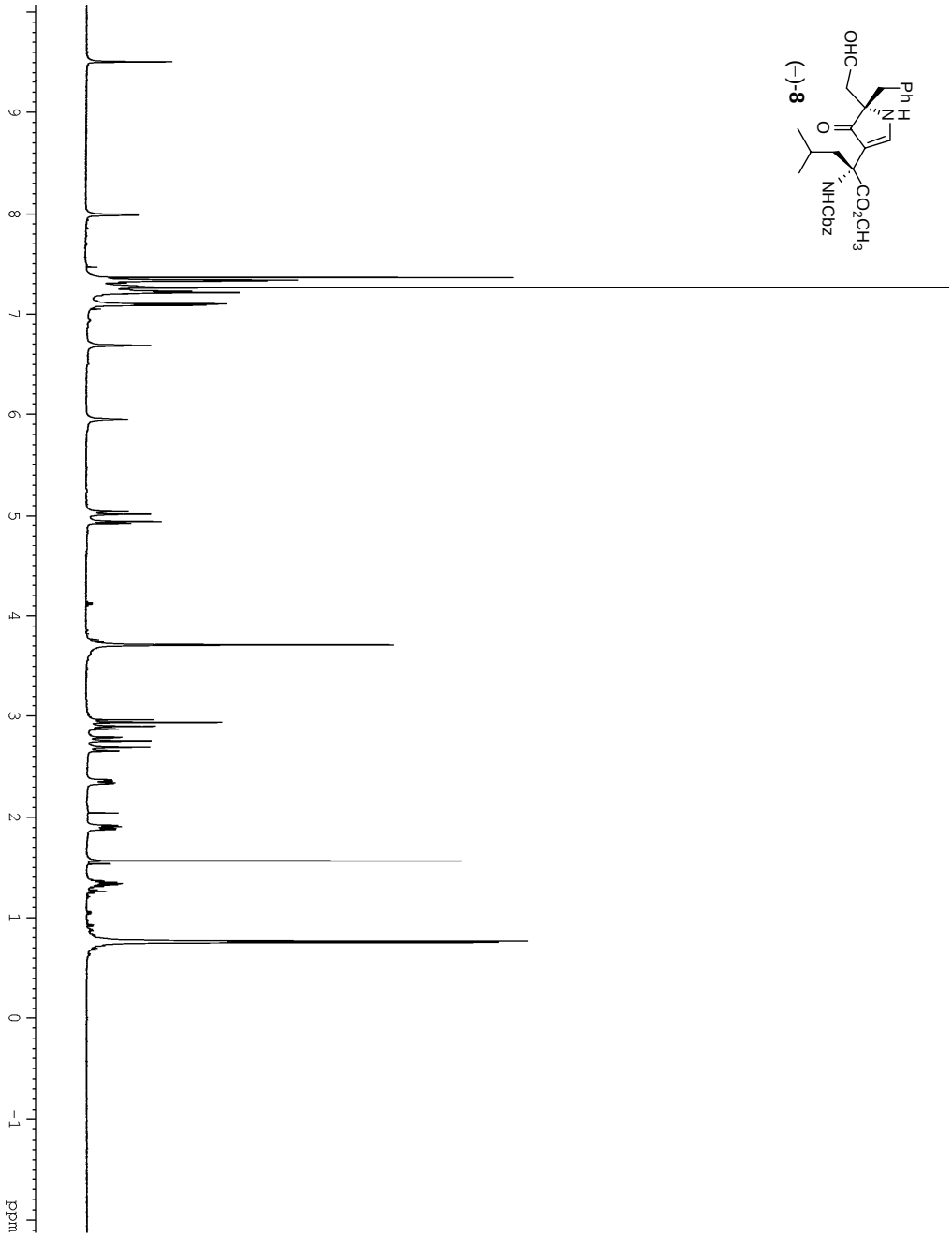
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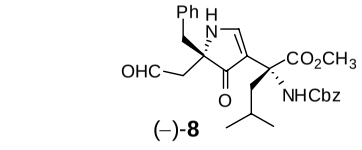
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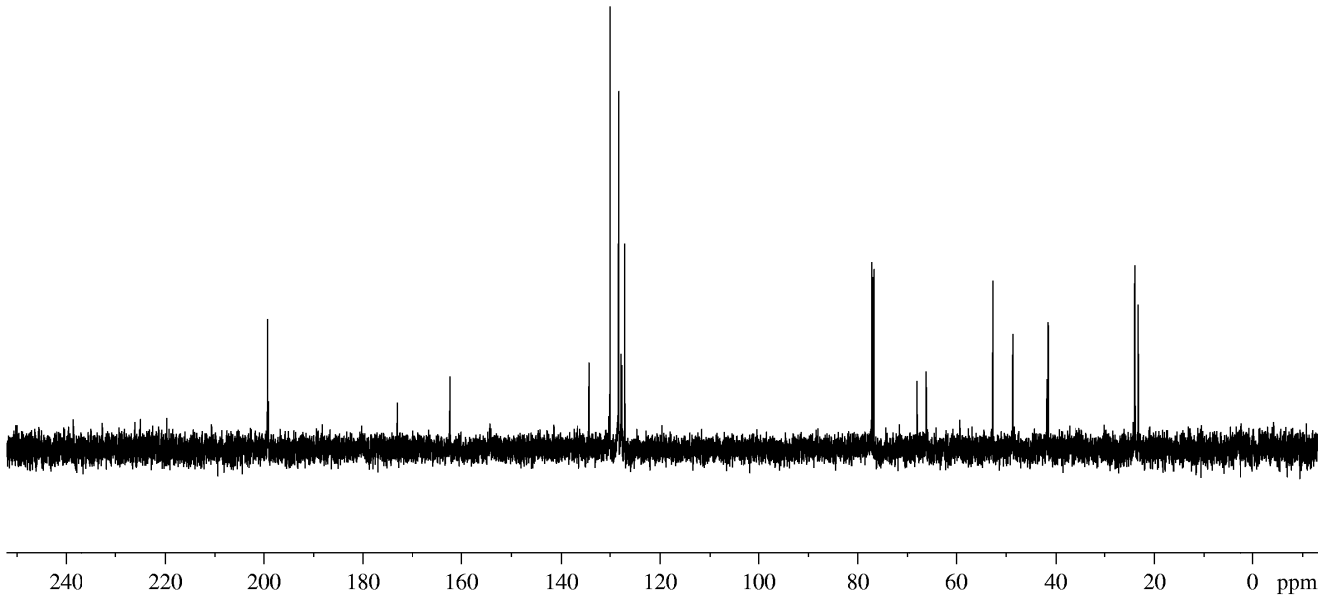
(–)-**8**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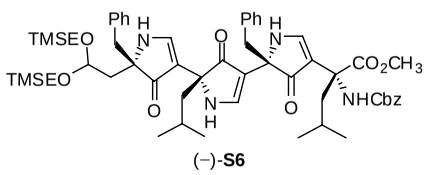
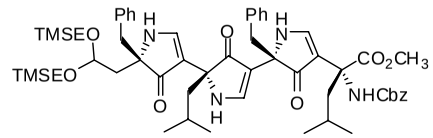


(–)-**S6**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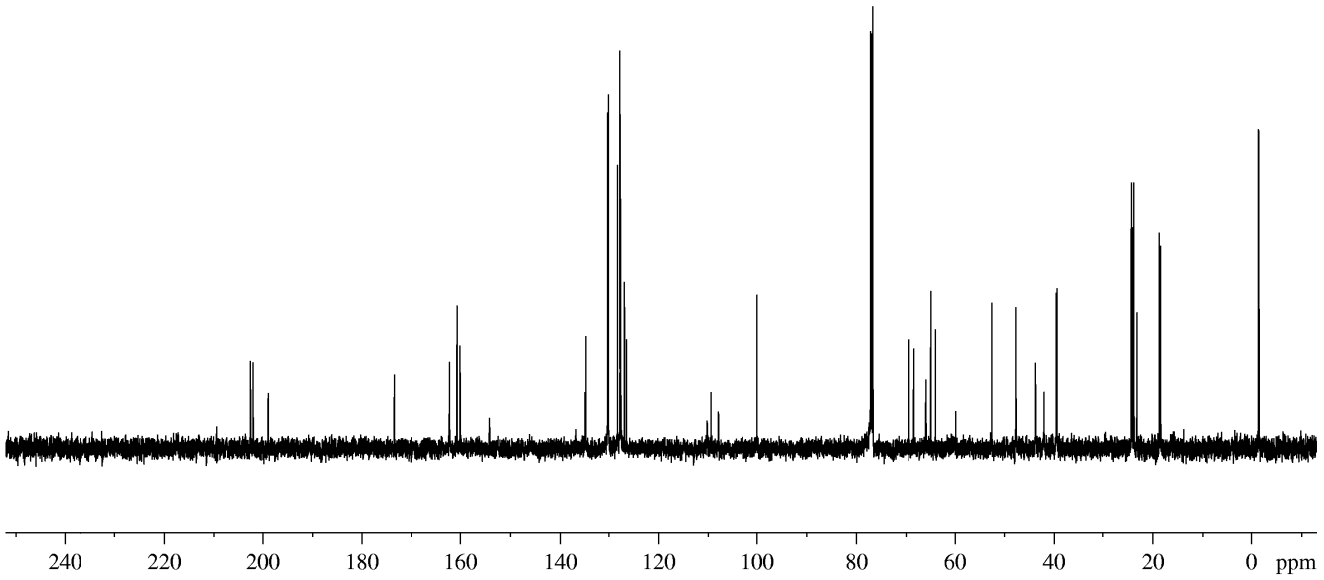
CO2CH3
NHCbz

(–)-**S6**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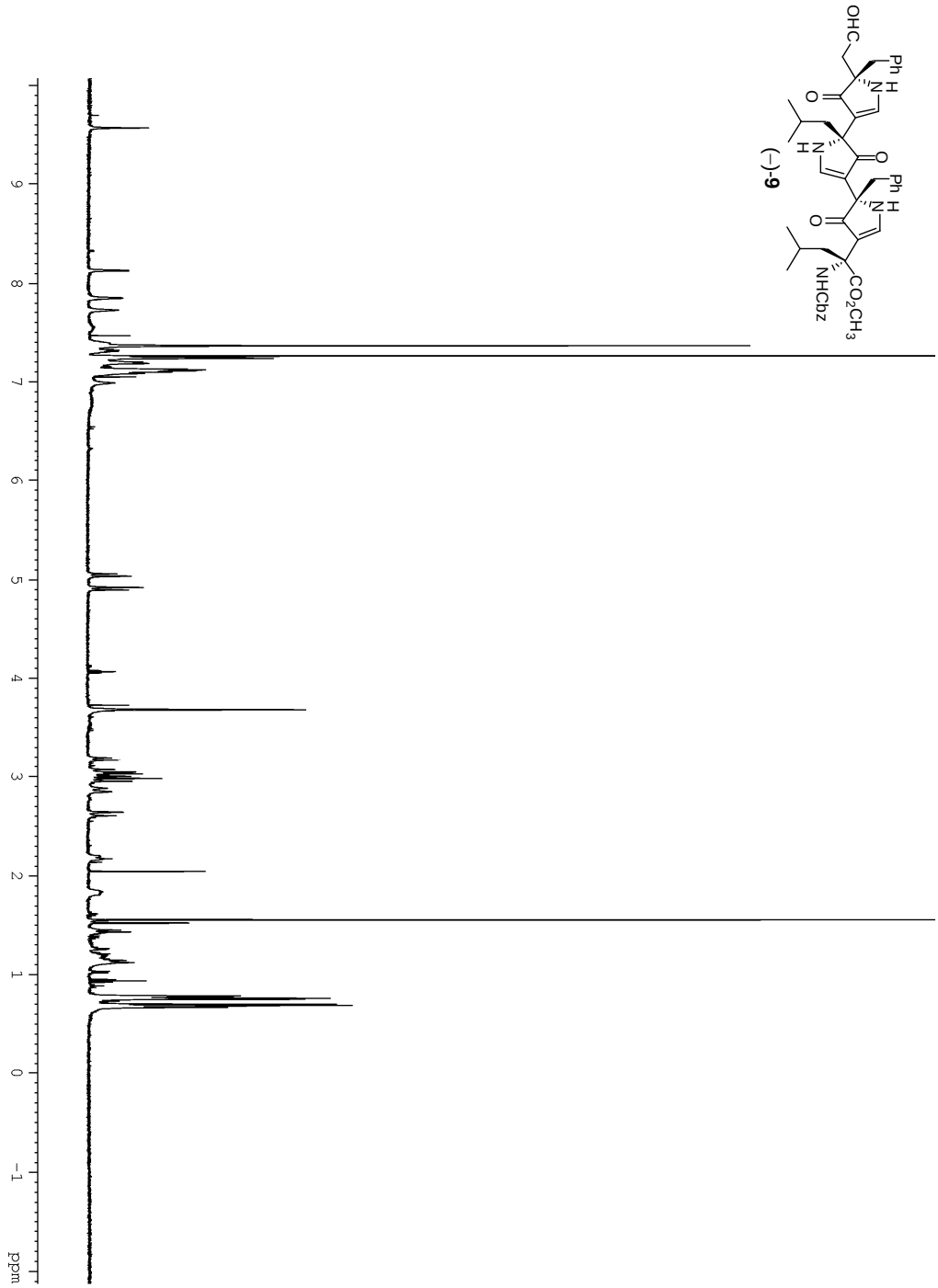
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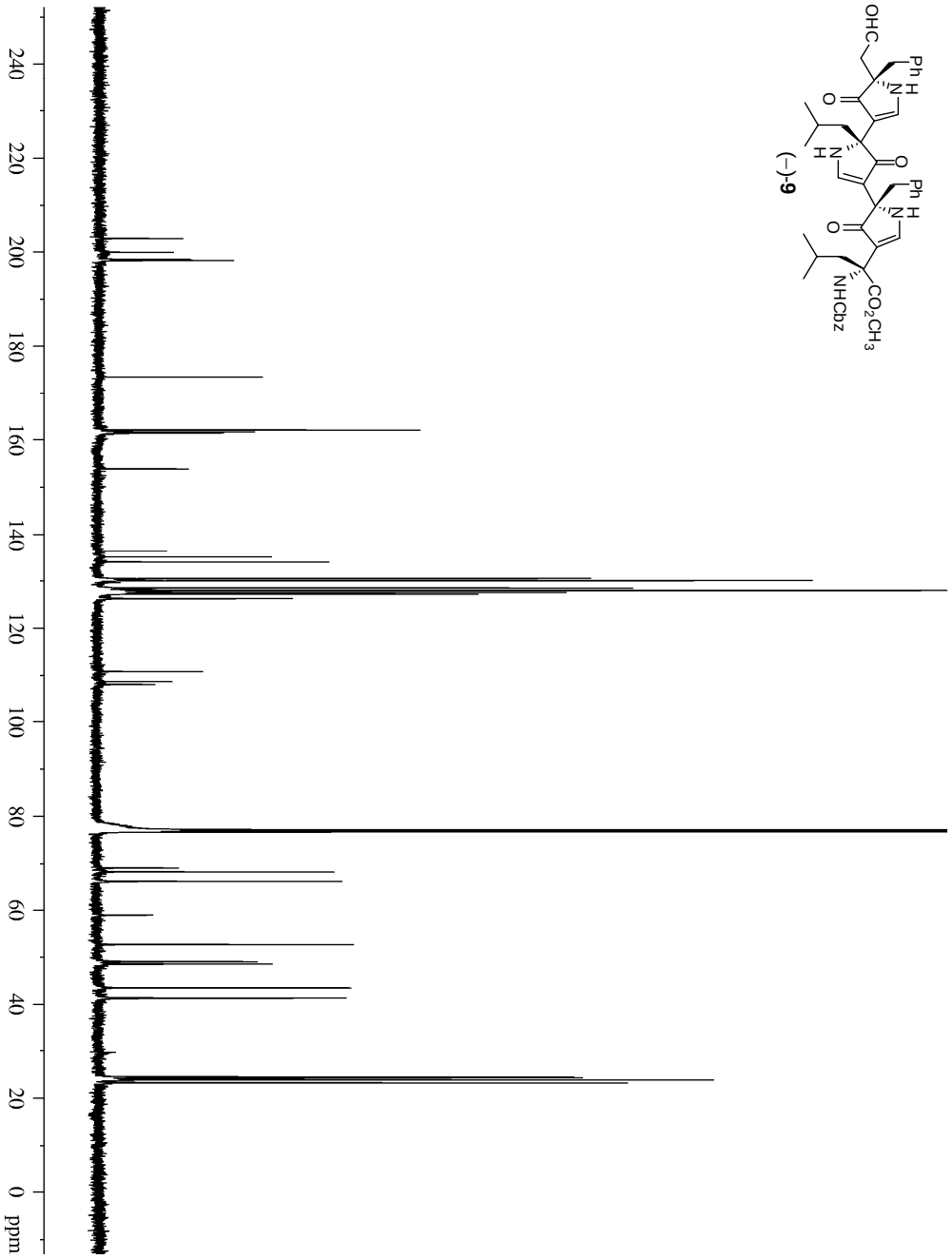
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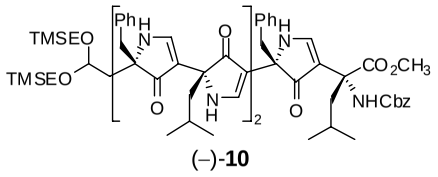
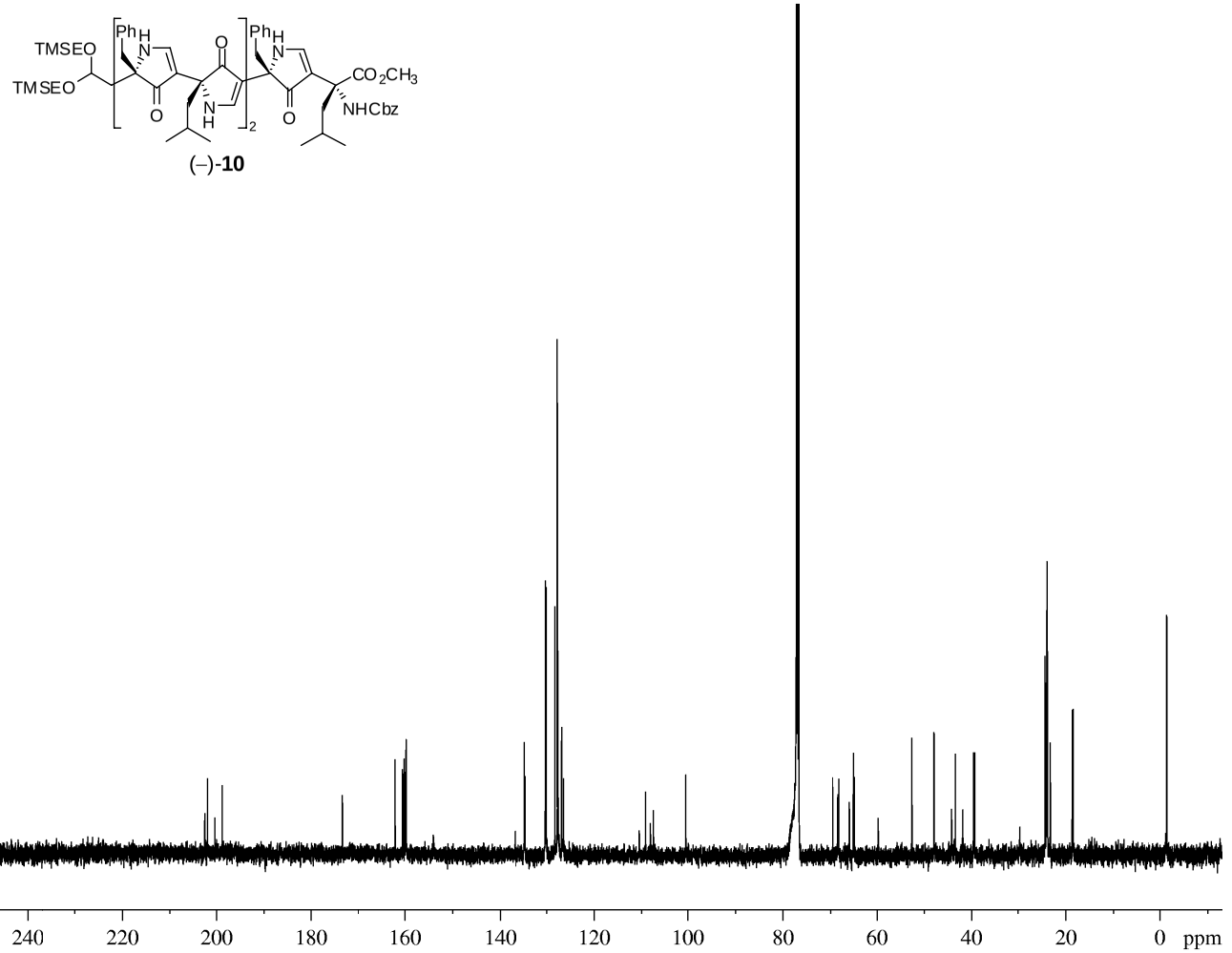


(–)-**10**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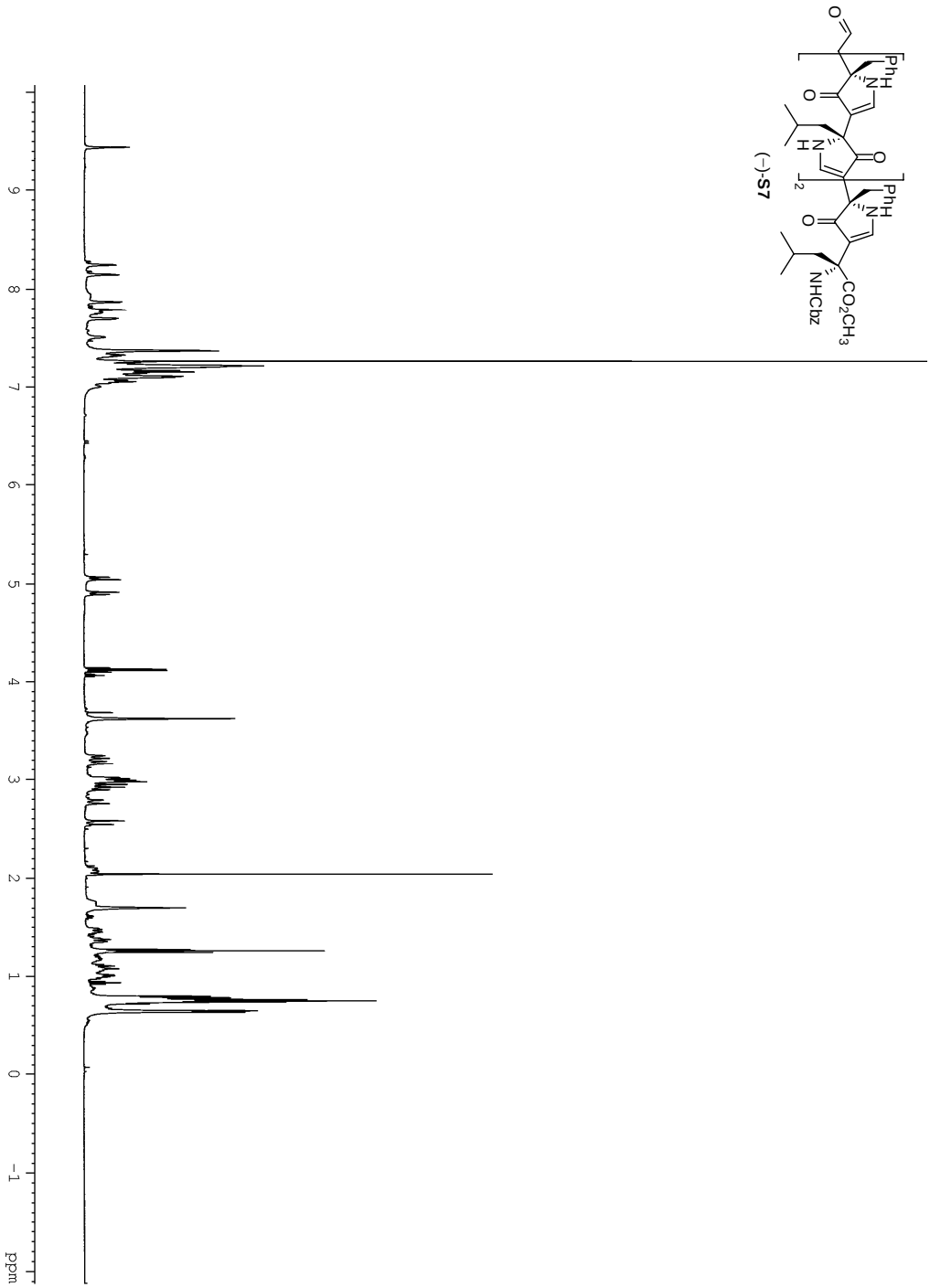
(–)-**10**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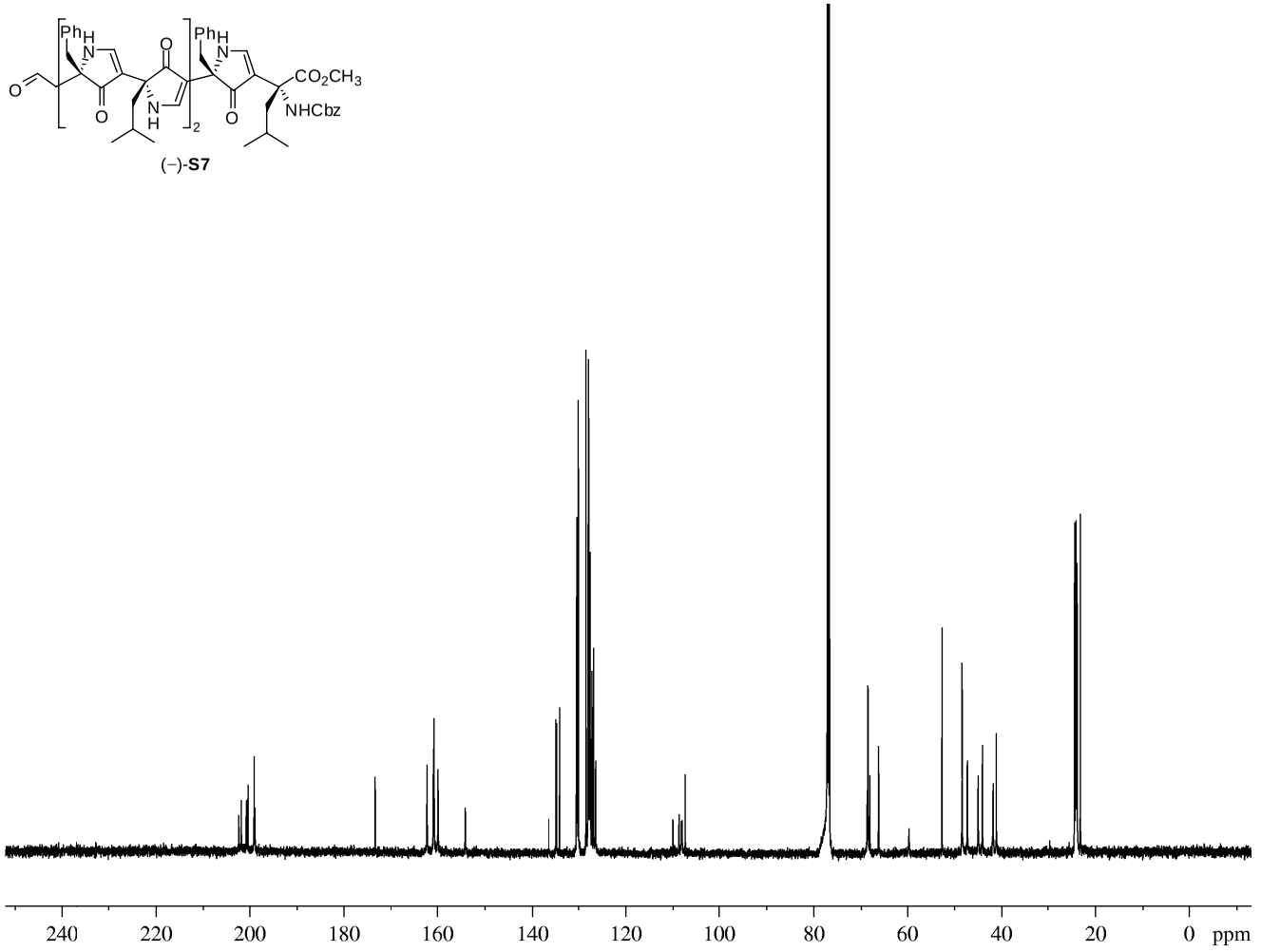
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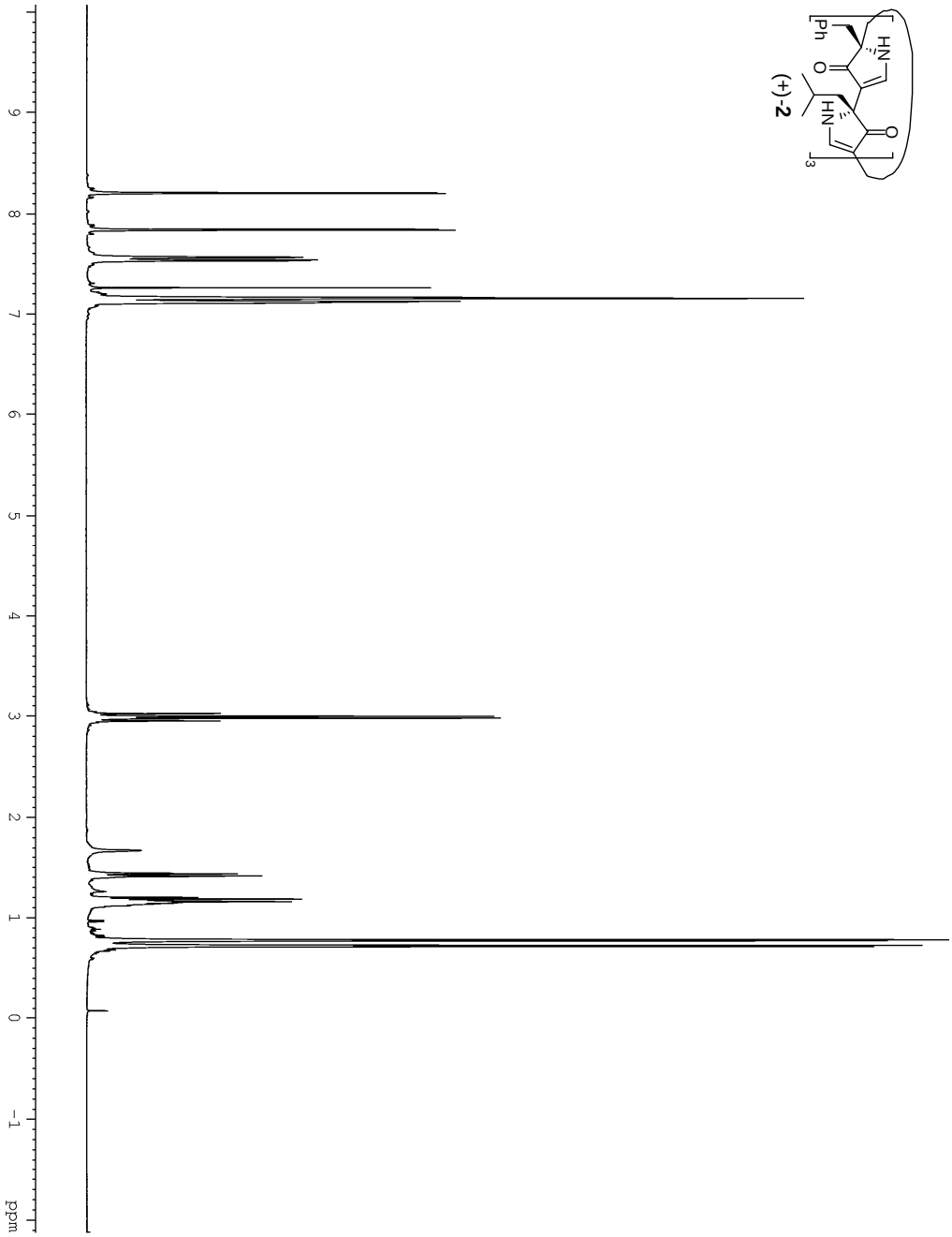
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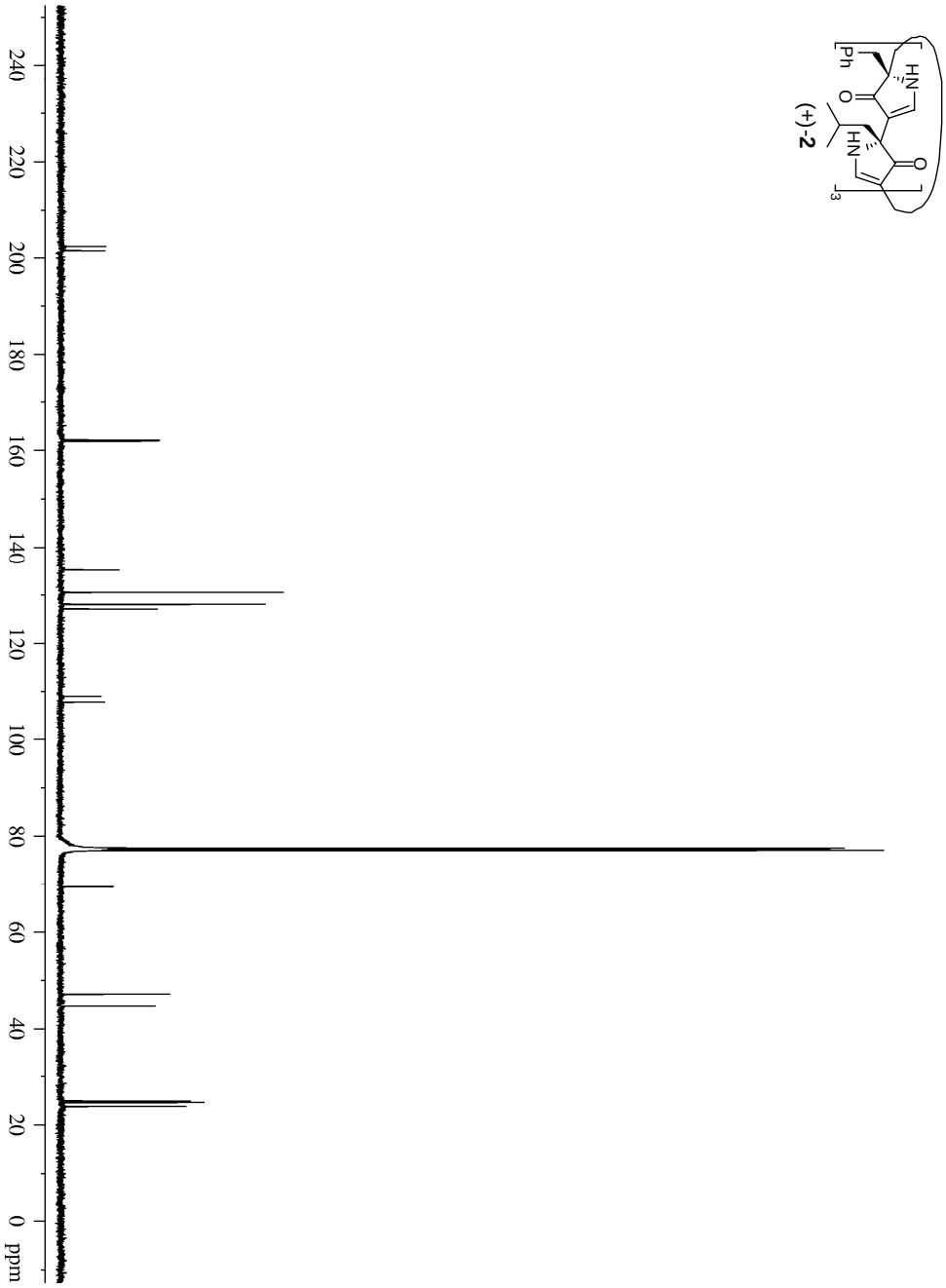
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ppm
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O
HN
O
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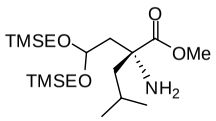
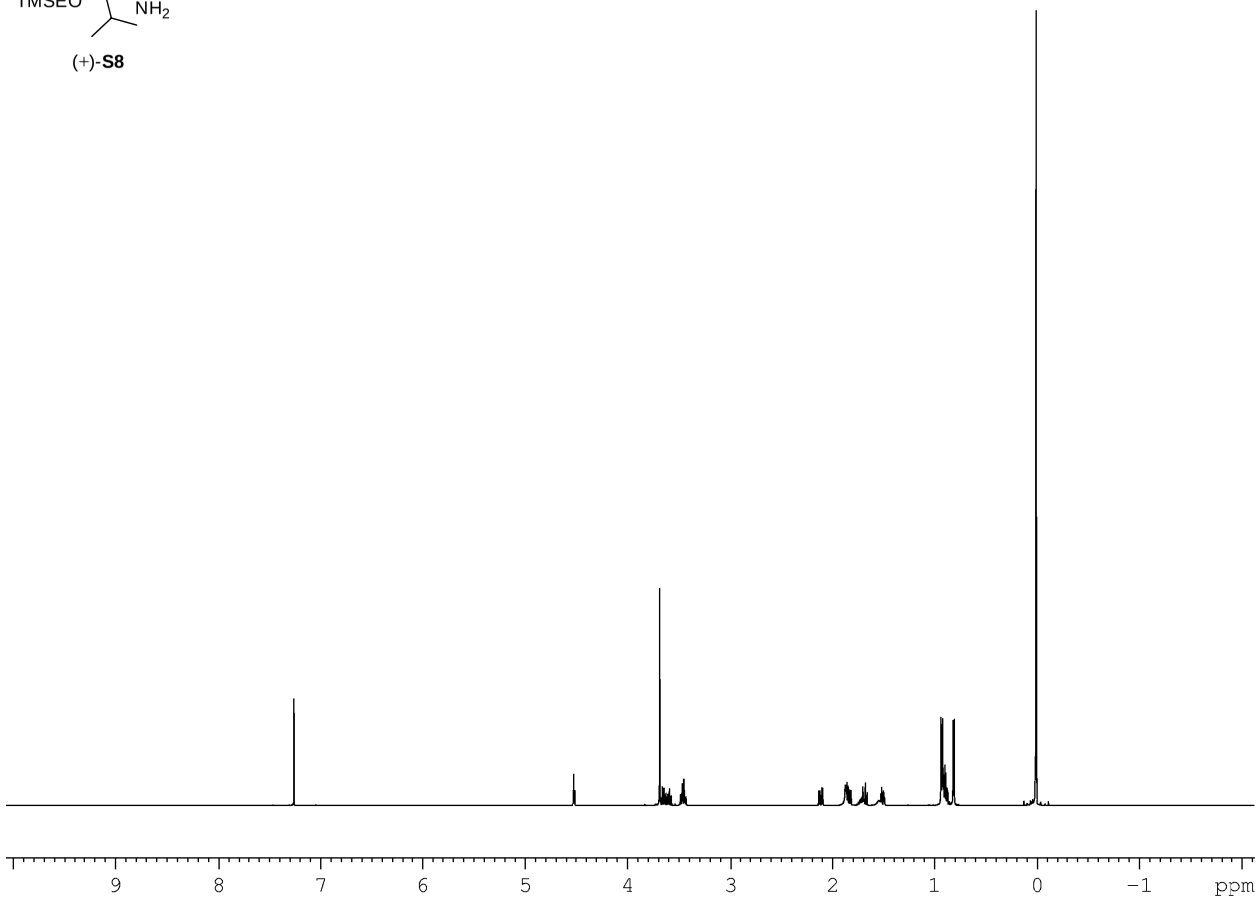
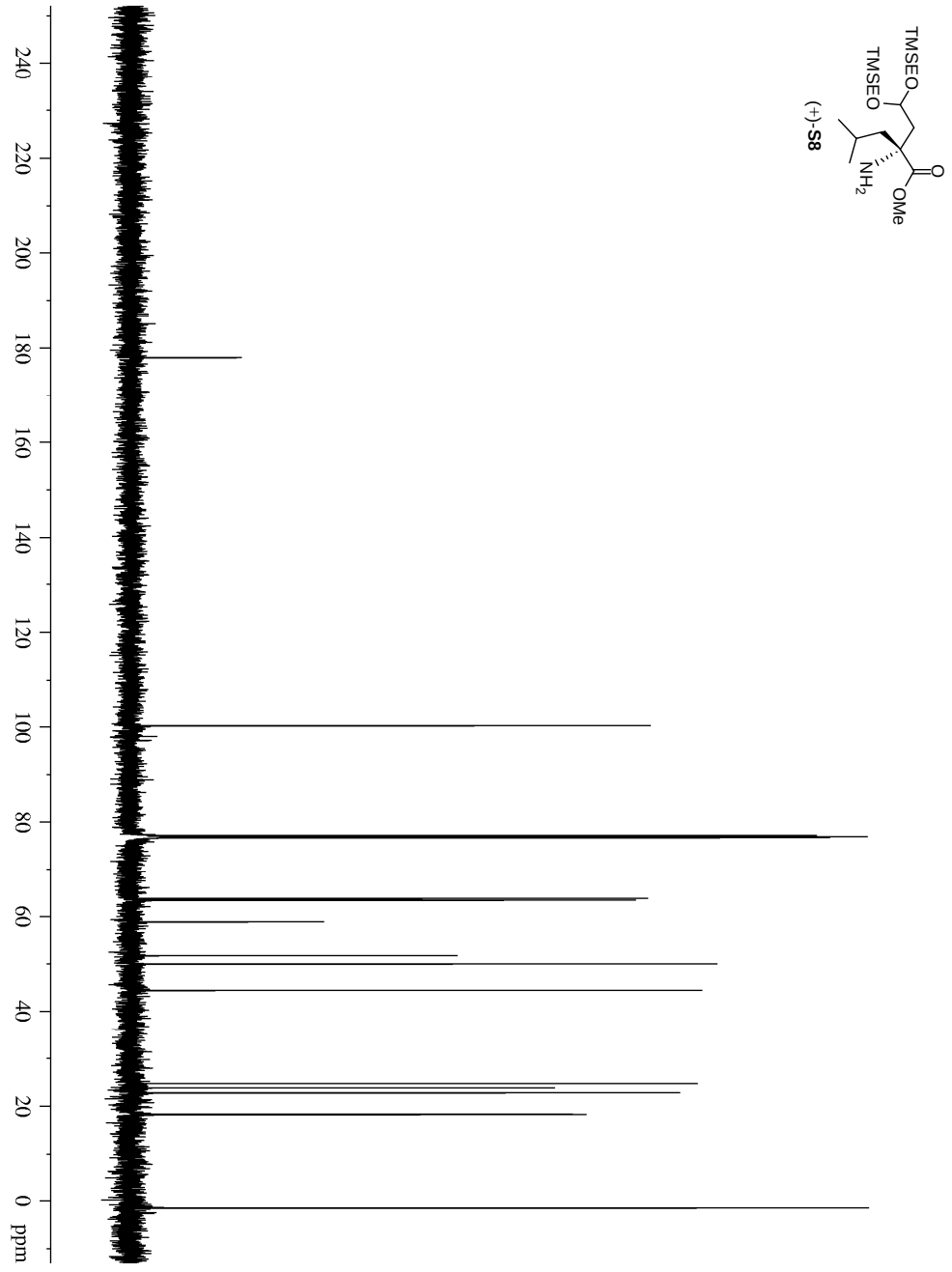
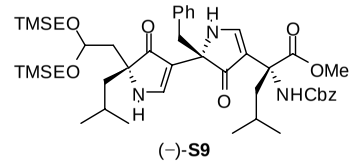


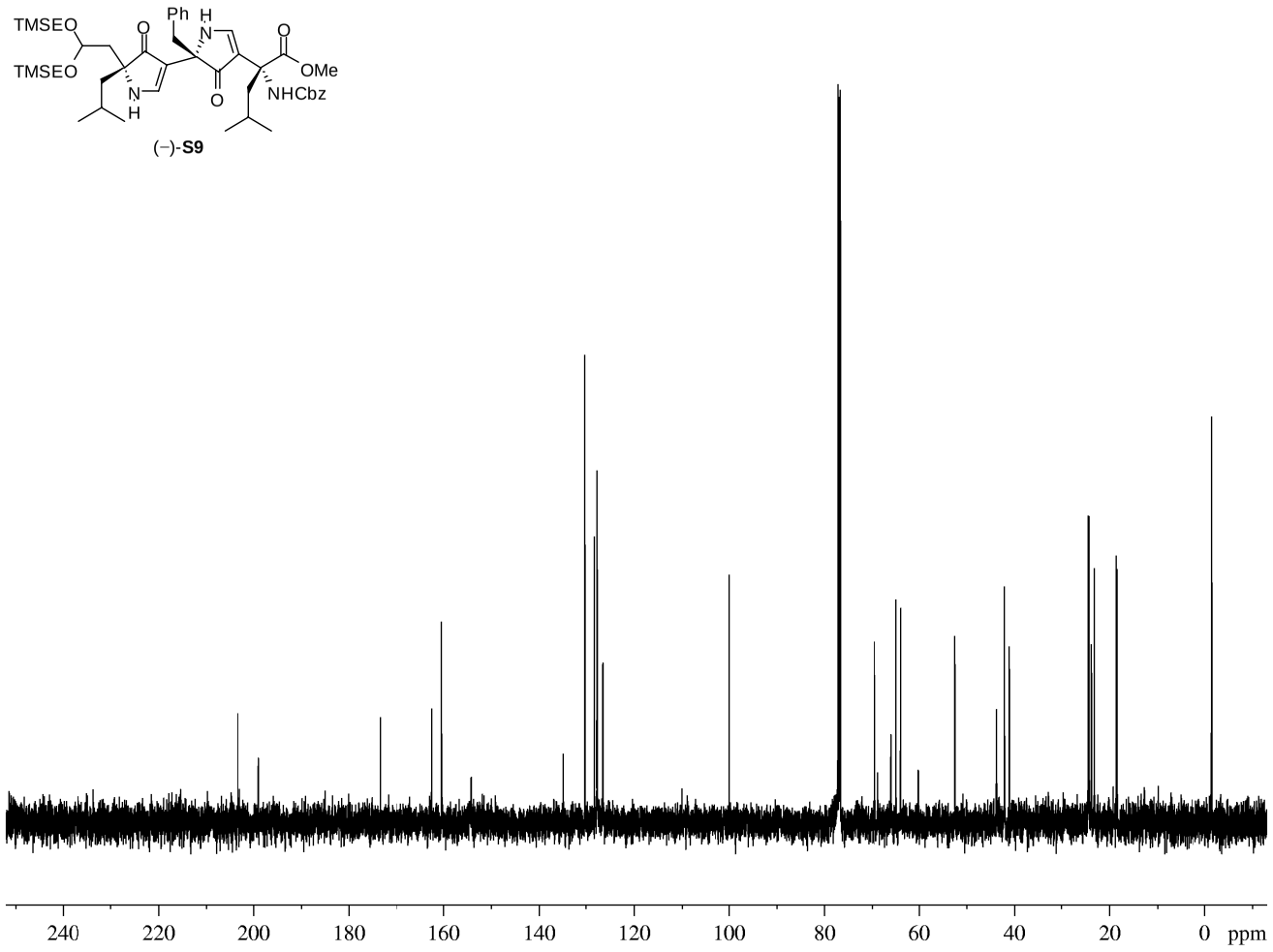
(+)-**S8**



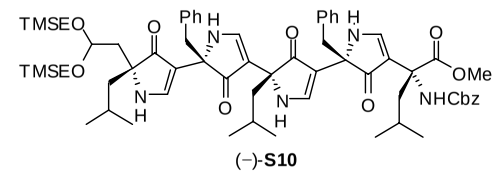

TMSEO
TMSEO
NH2
OMe
O
(+)-S8
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm



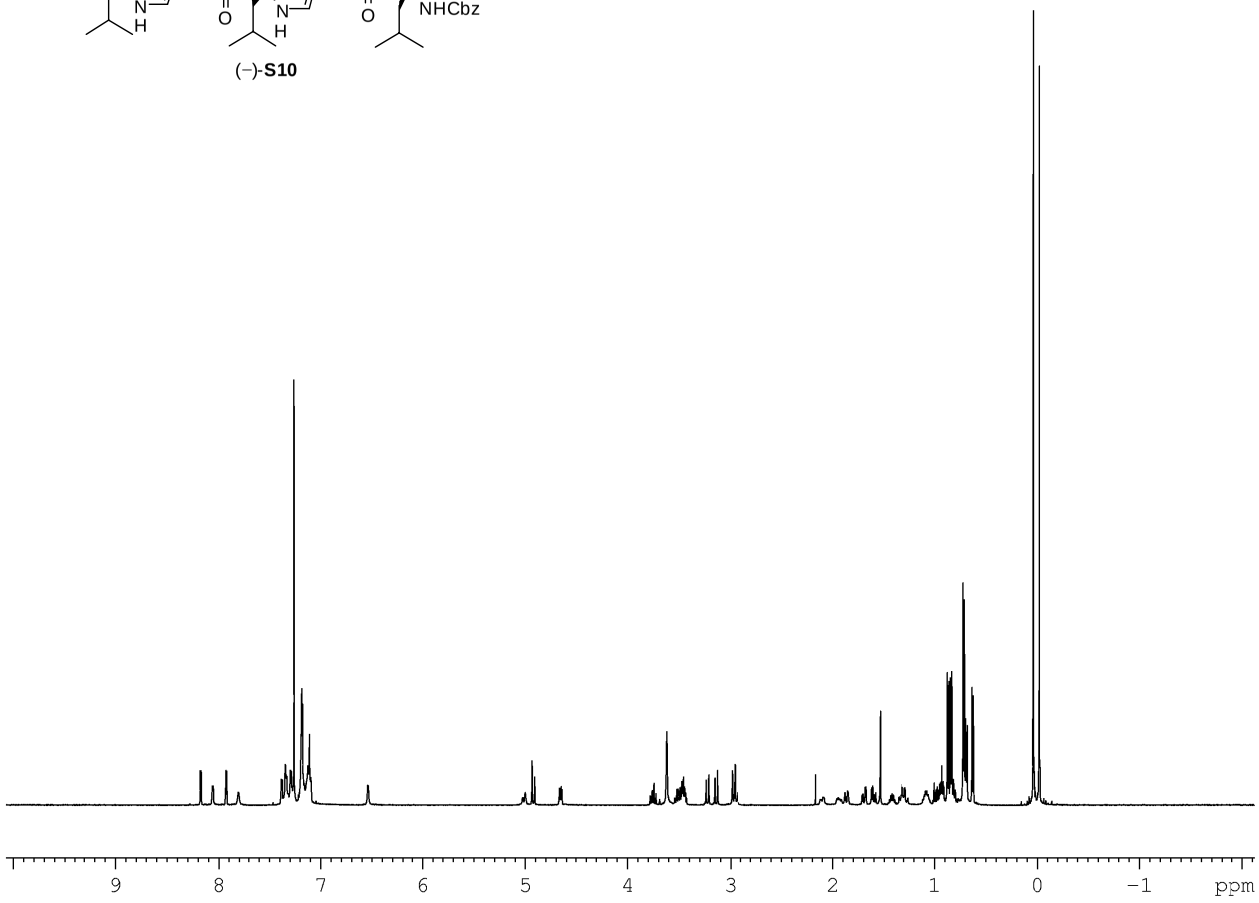
(−)-**S9**

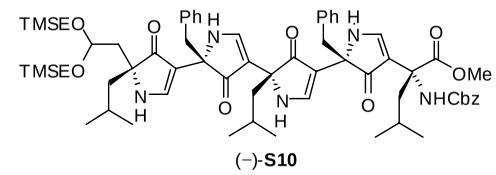

TMSEO
TMSEO
Ph
H
N
O
O
OMe
NHCbz
N
H
O
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(−)-**S9**



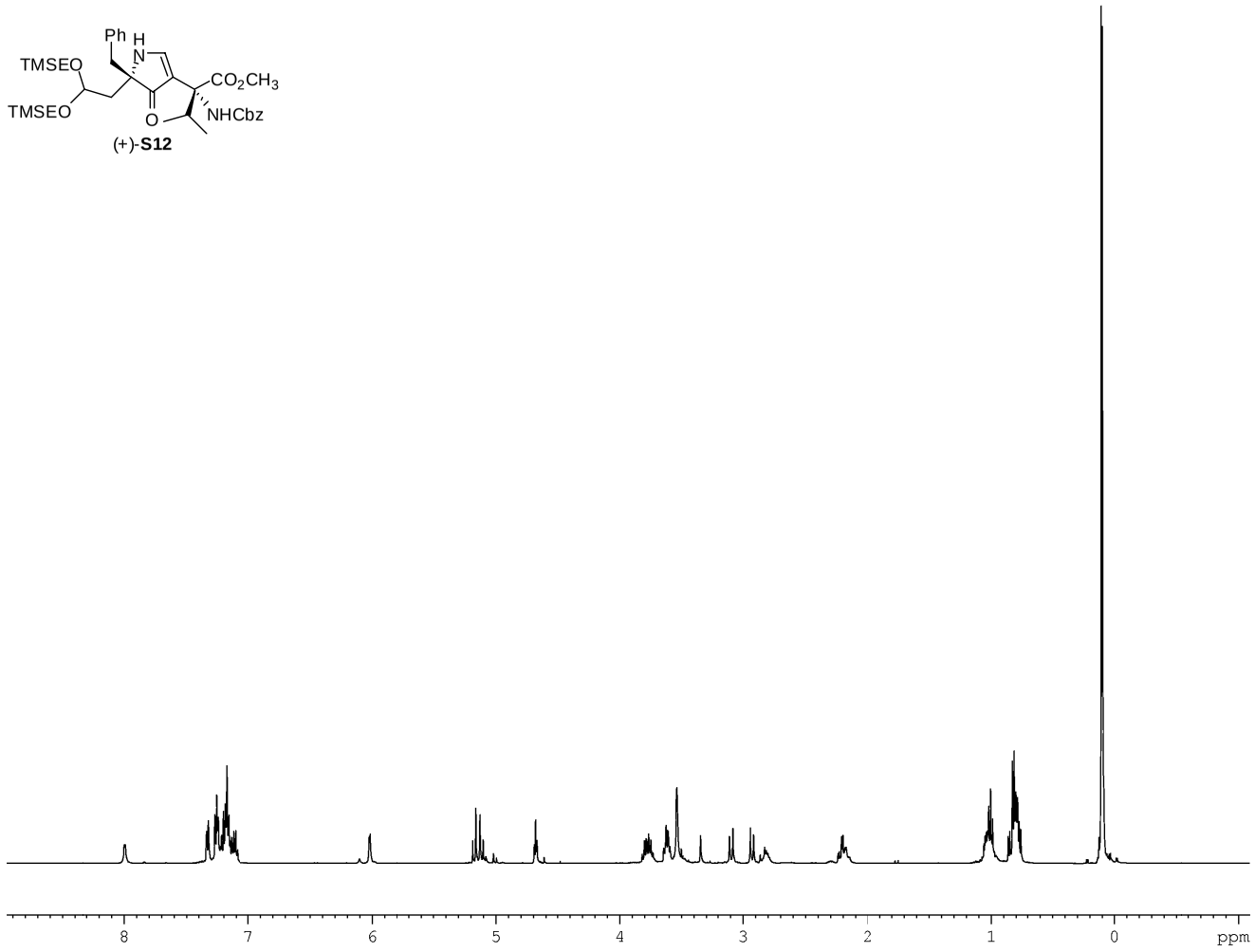
(−)-**S10**

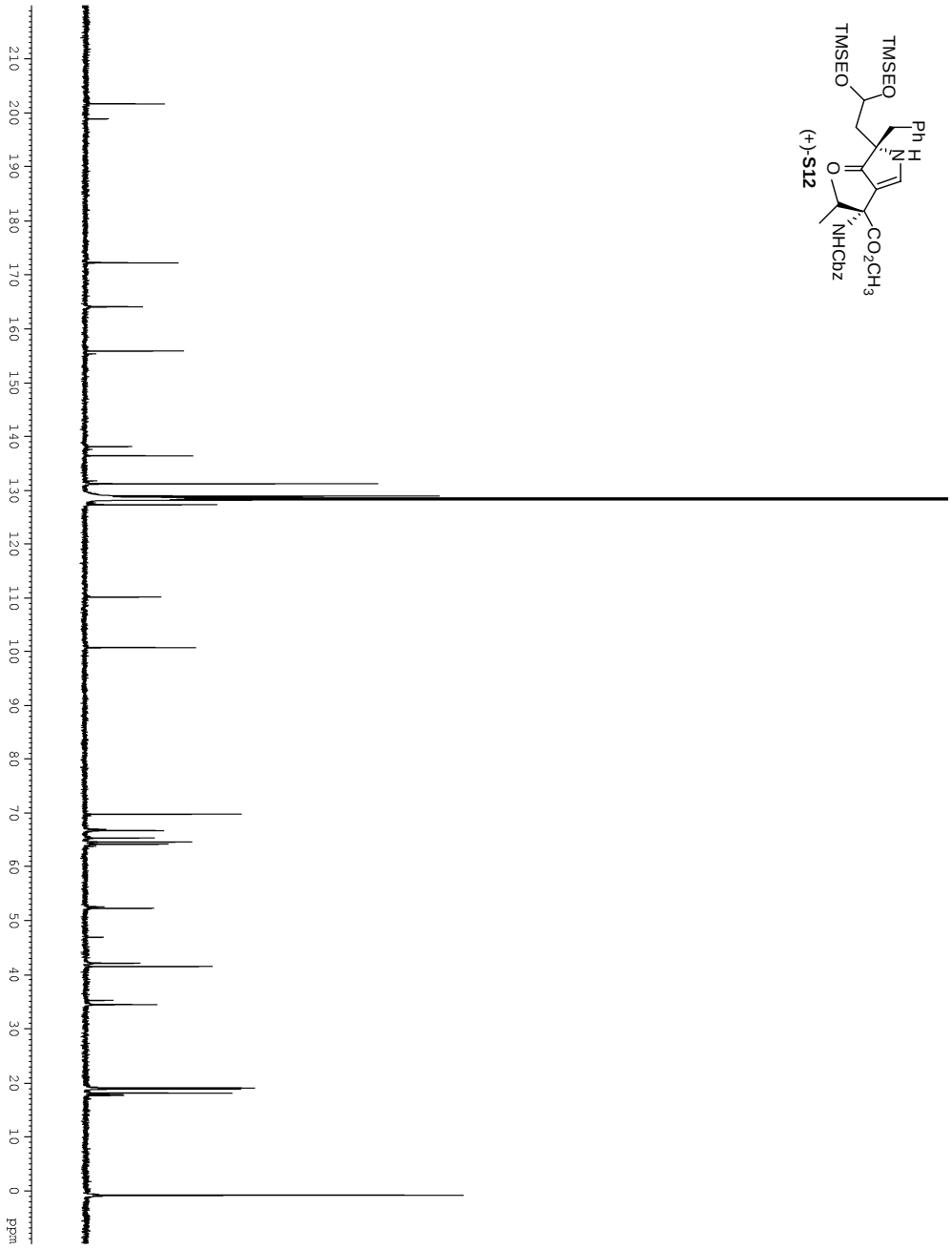


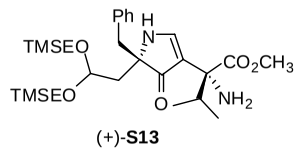

TMSEO
TMSEO
Ph
H
N
O
N
H
O
Ph
H
N
O
N
H
O
O
OMe
NHCbz

(−)-**S10**

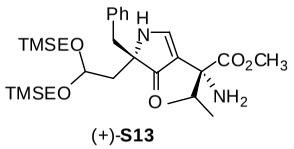
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Ph
H
N
TMSEO
TMSEO
CO2CH3
O
NHCbz
(+)-S12
8
7
6
5
4
3
2
1
0
ppm

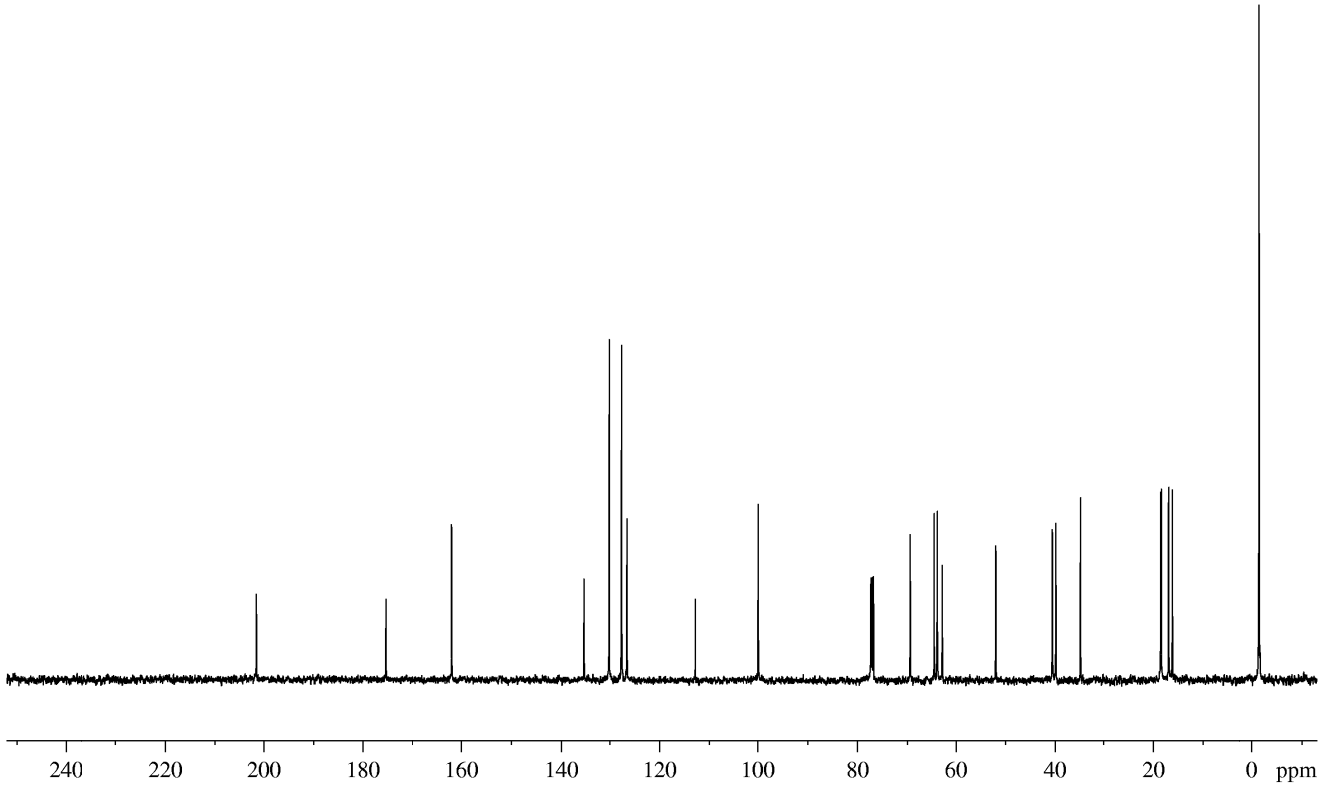

TMSEO
TMSEO
Ph
H
N
O
NHCbz
CO2CH3
(+)-S12
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

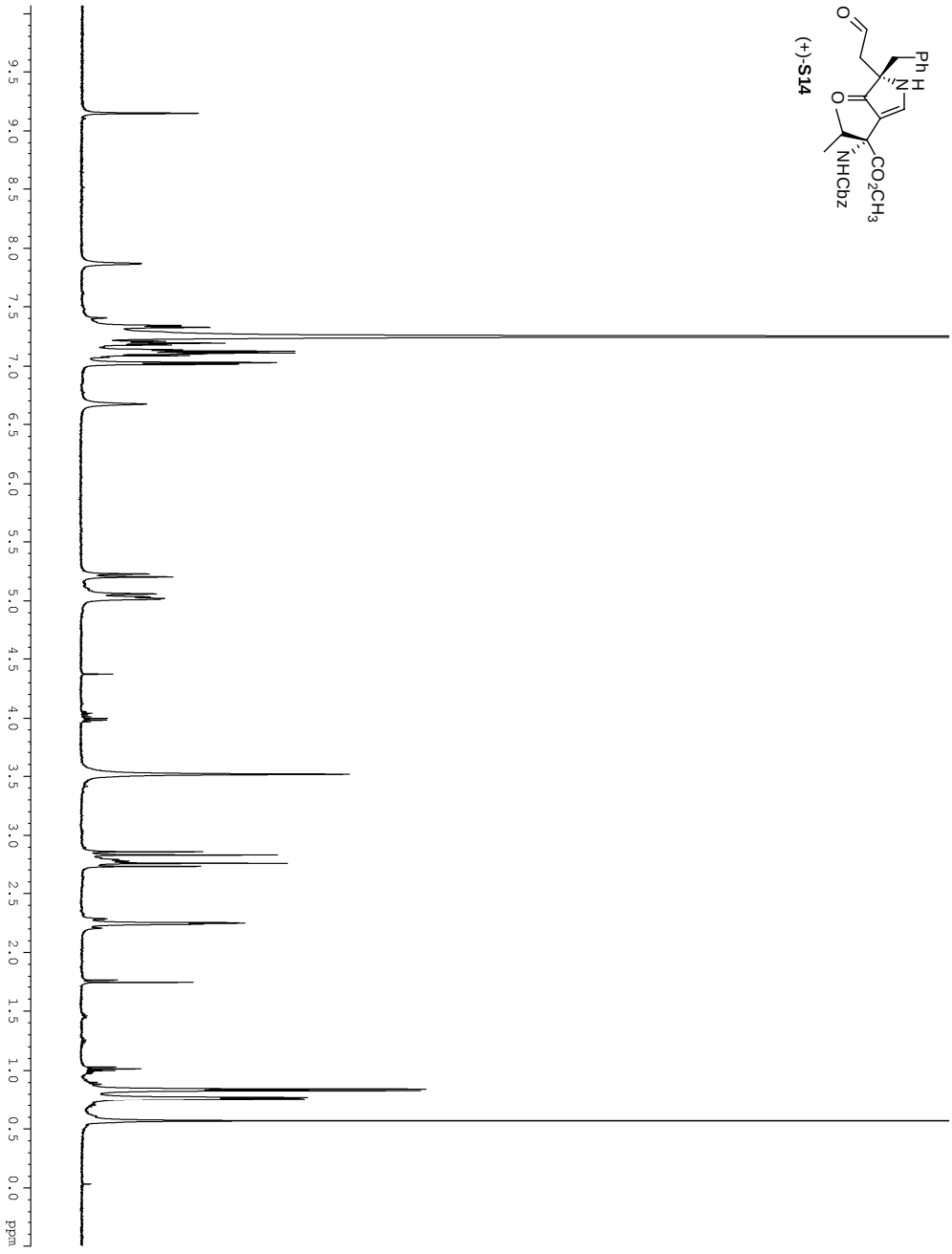


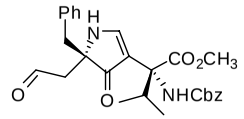
(+)-**S13**


Ph
H
N
TMSEO
TMSEO
CO2CH3
NH2
O

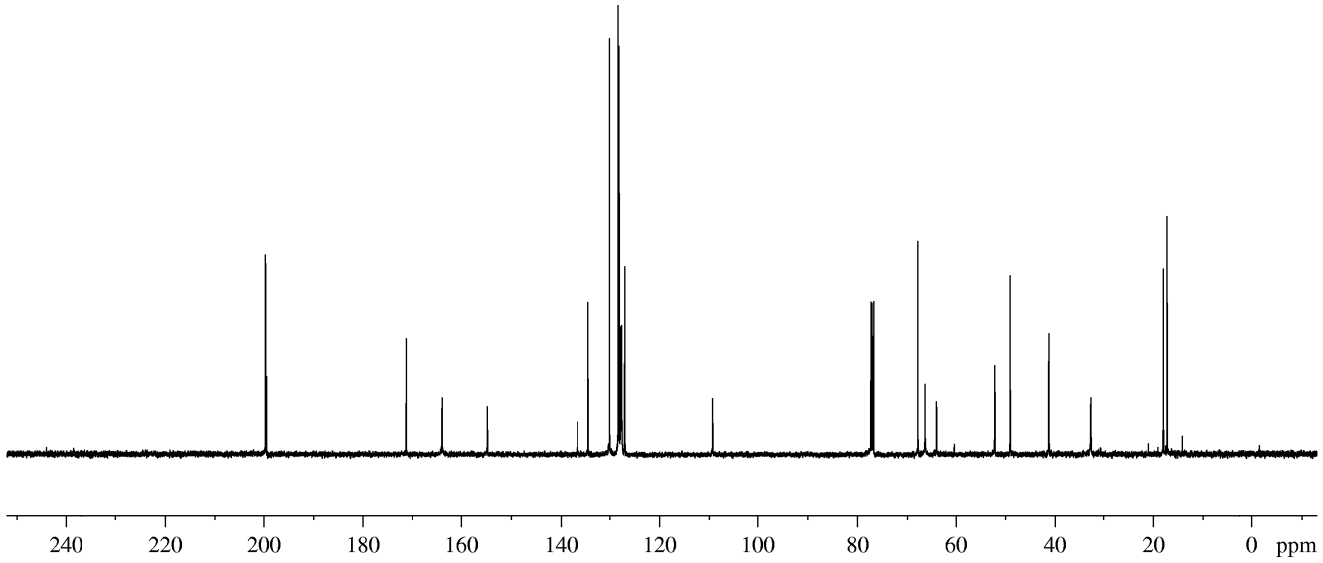
(+)-**S13**

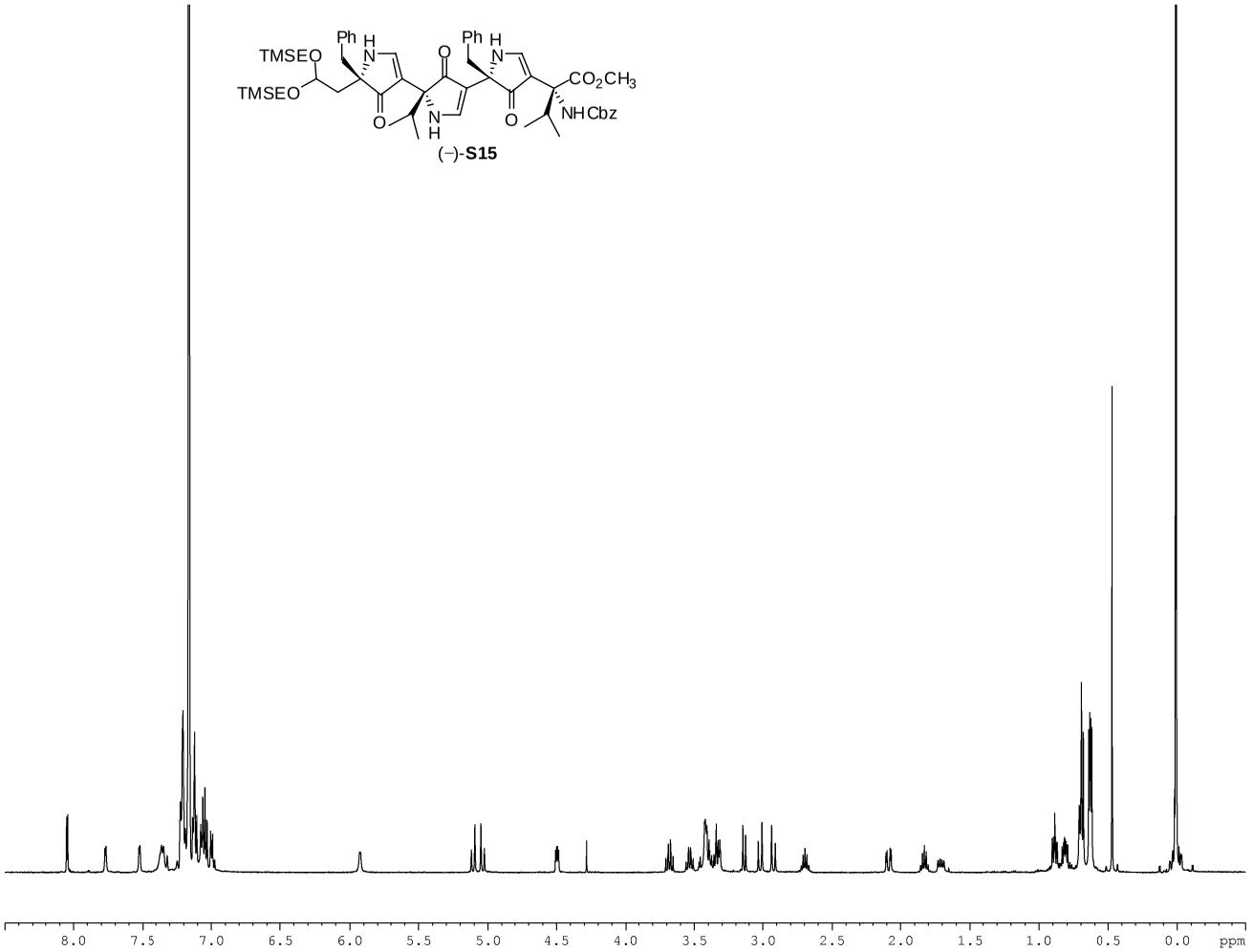

240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Ph
H
N
O
O
NHCbz
CO2CH3
(+)-S14
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

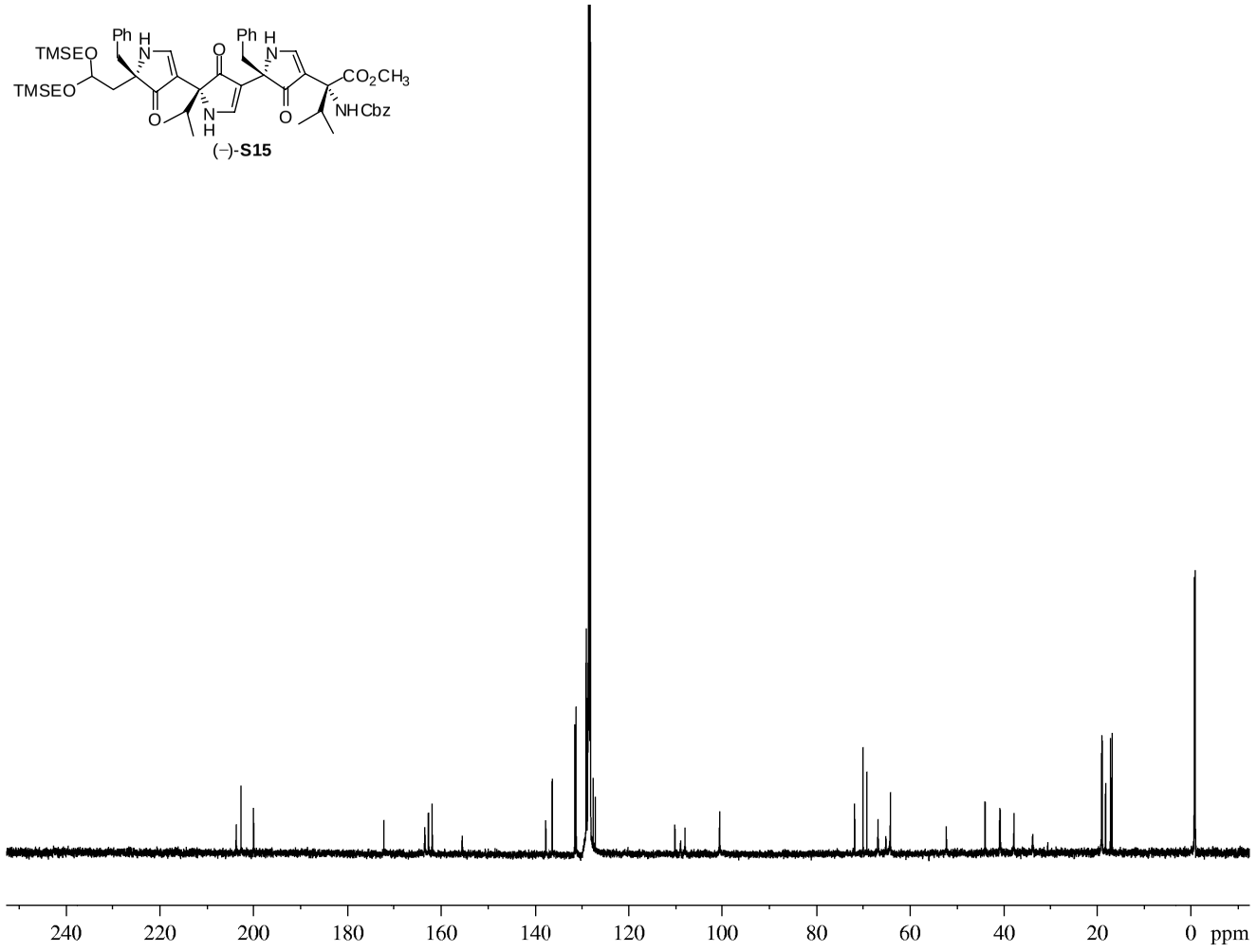

Ph
H
N
CO2CH3
O
O
NHCbz

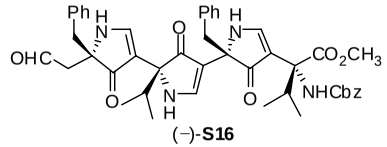
(+)-**S14**


240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

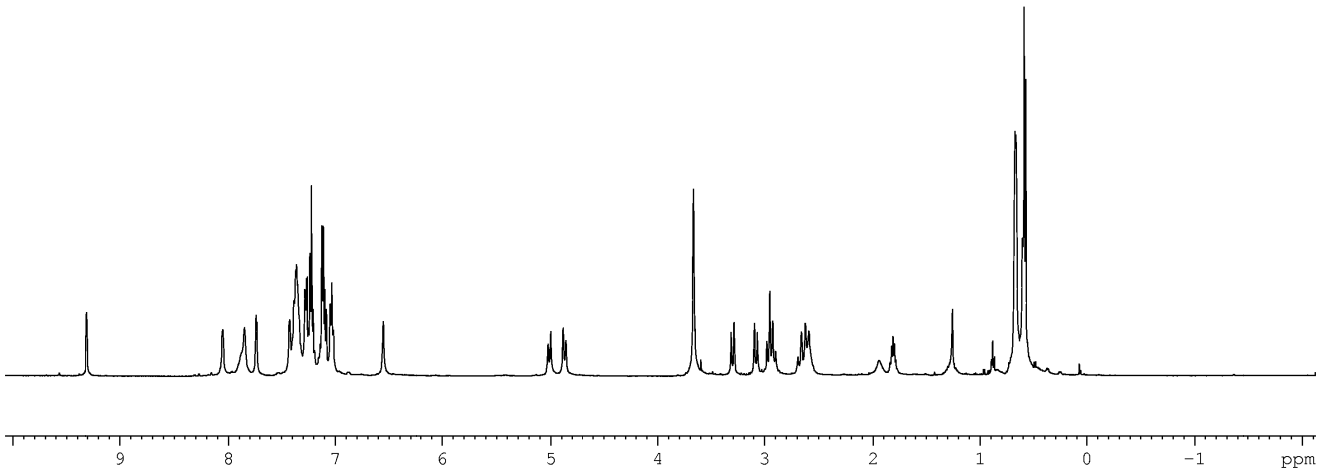

TMSEO
TMSEO
Ph
H
N
O
N
H
O
Ph
H
N
O
CO2CH3
NHCbz
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

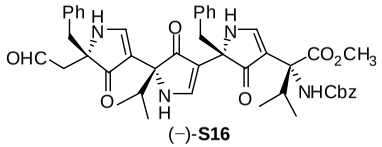
(–)-**S15**


TMSEO
TMSEO
Ph
H
N
O
N
H
Ph
H
N
O
O
CO2CH3
NHCbz
(–)-S15
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

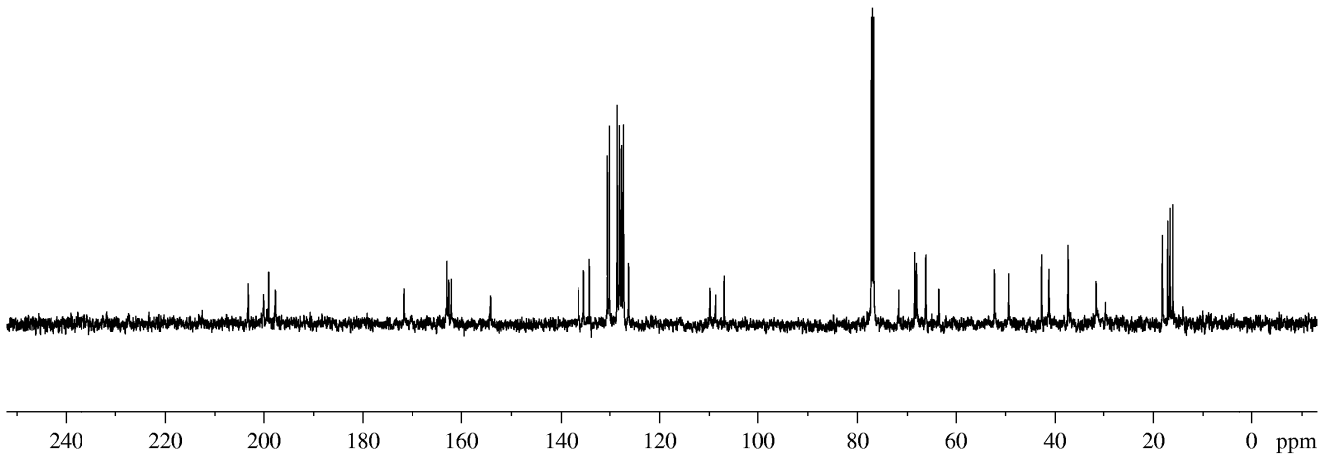


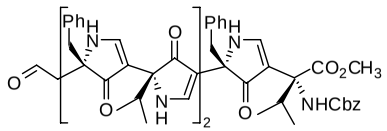
(–)-**S16**



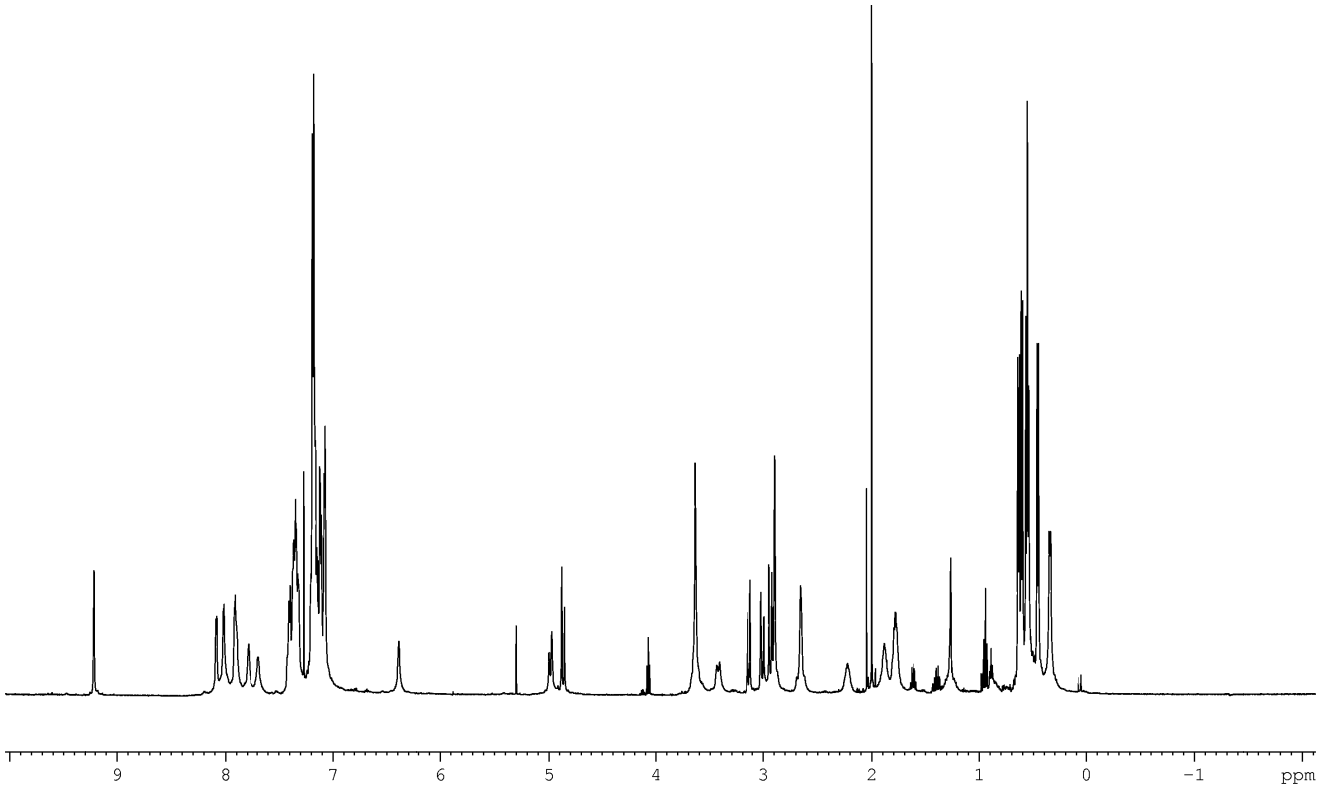

Ph
H
N
O
Ph
H
N
OHC
CO2CH3
O
N
H
O
NHCbz

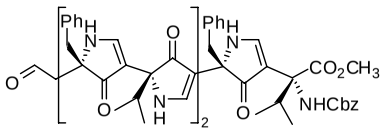
(−)-**S16**


240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

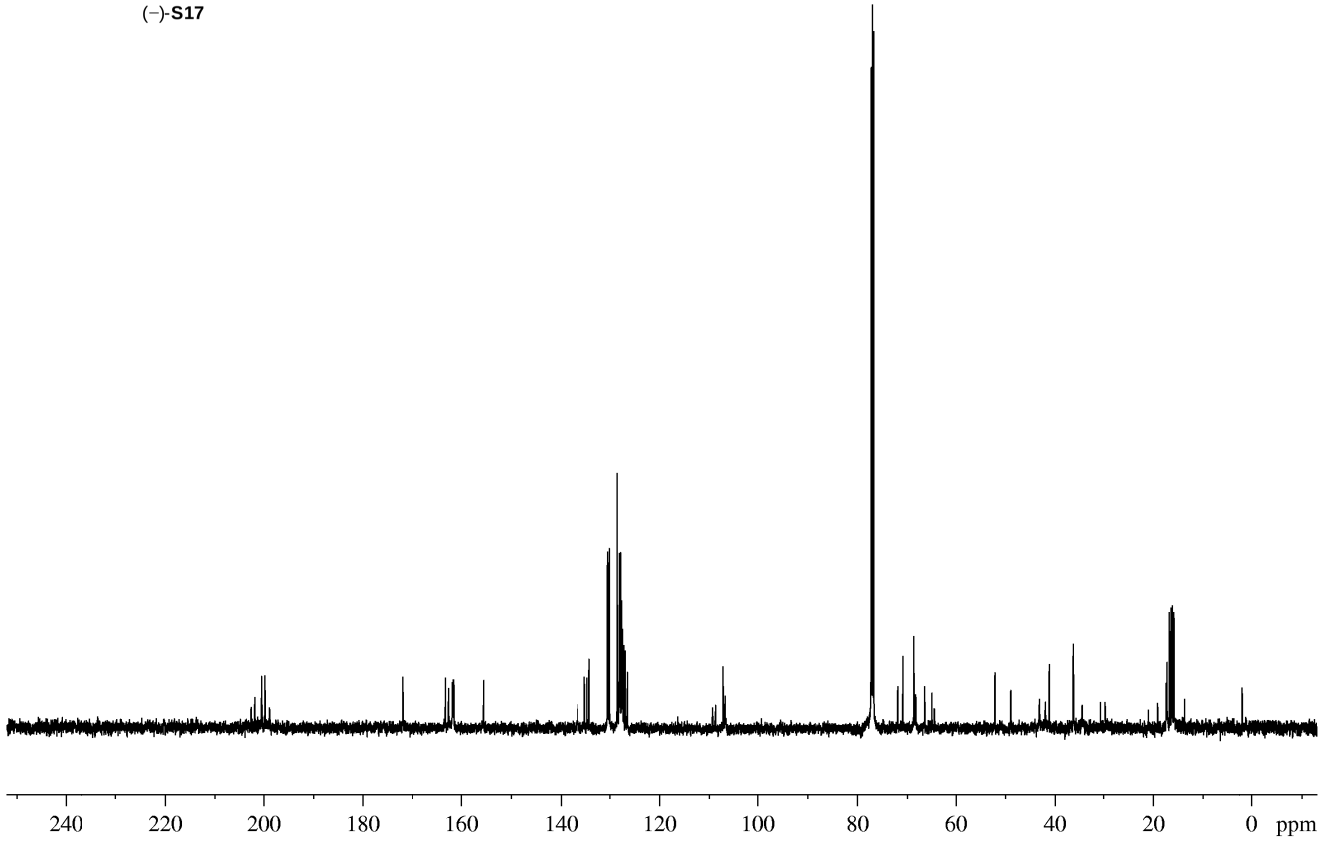


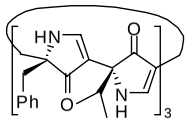
(−)-**S17**



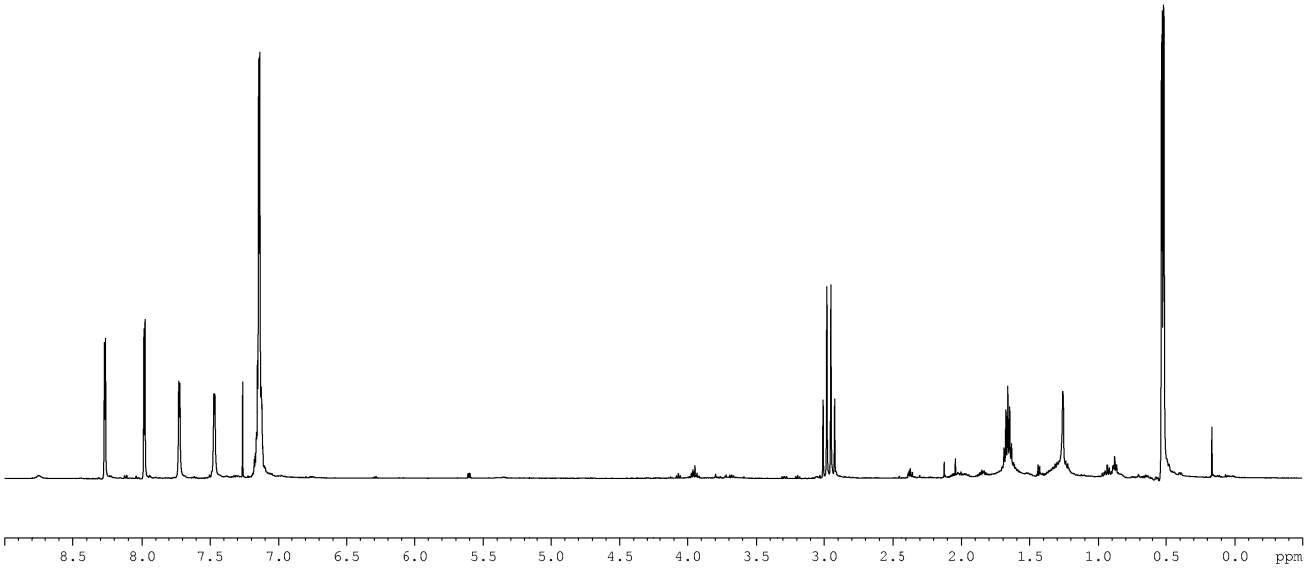

Ph
H
N
O
O
N
H
2
Ph
H
N
O
O
CO2CH3
NHCbz

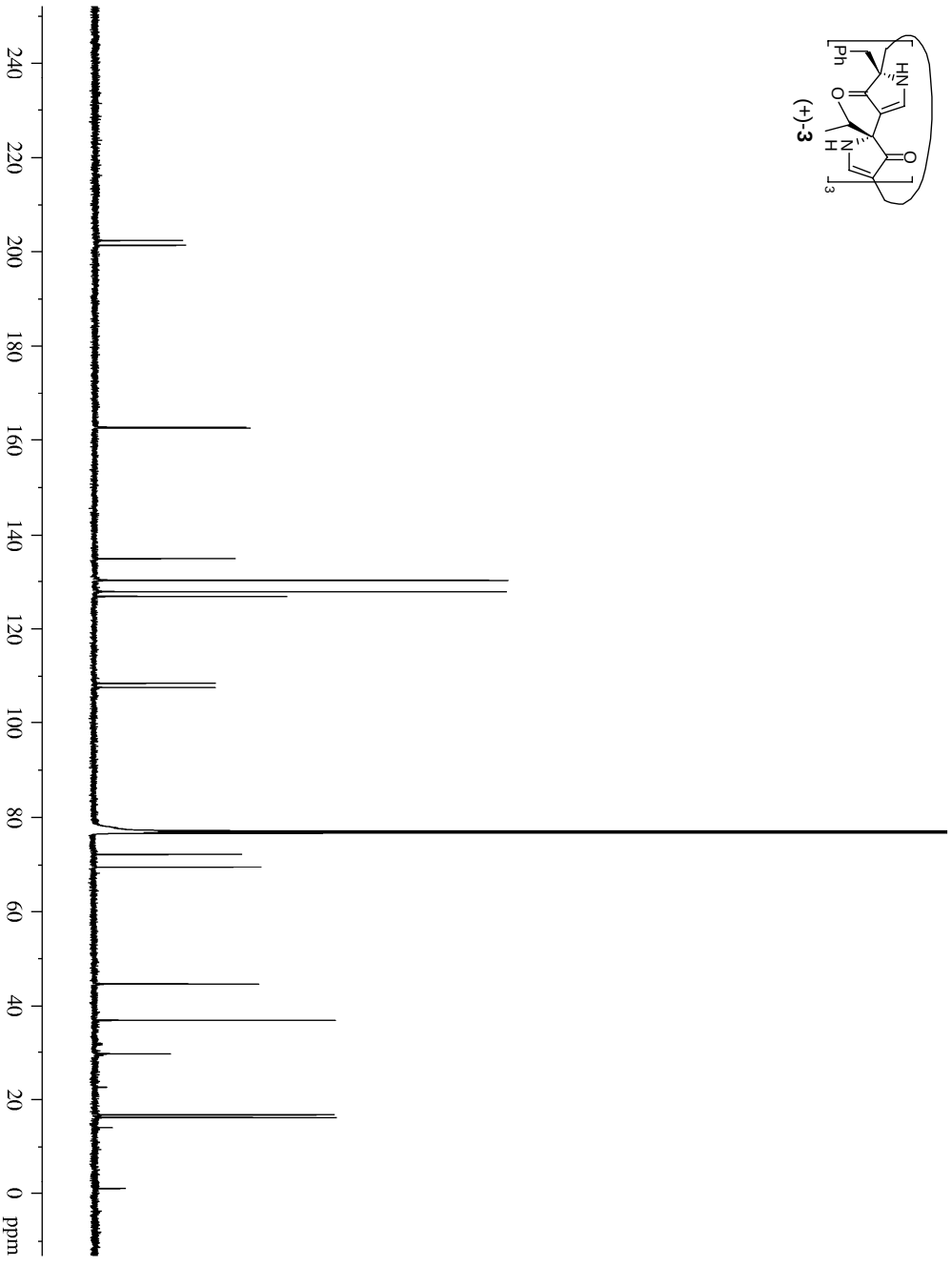
(−)-**S17**


240
220
200
180
160
140
120
100
80
60
40
20
0
ppm



(+)-**3**




240
220
200
180
160
140
120
100
80
60
40
20
0
ppm
Ph
HN
O
N
H
O
3
(+)-3