Electronic Supporting Information

Total Synthesis of Epicoccin G

K. C. Nicolaou,* Sotirios Totokotsopoulos, Denis Giguère, Ya-Ping Sun, and David Sarlah

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093

E-mail: kcn@scripps.edu

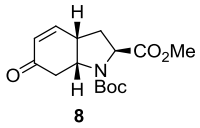
Supporting Information Available

I. Experimental Section

General Methods

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, benzene, diethyl ether (Et_2O), *N*,*N*′-dimethylformamide (DMF), and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. E. Merck silica gel (60, particle size 0.040 – 0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-500 or DRX-600 instruments and calibrated using residual undeuterated solvent ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.0 ppm) as an internal reference. Boc-protected compounds show ^{1}H spectra for two rotamers. The chemical shift of the peak of the major rotamer is listed and coupling constants are given in Hz only for the major rotamer. In ^{13}C spectra, peaks listed together in parentheses are assigned to rotamers. The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Infrared (IR) spectra were recorded on a Perkin–Elmer 100 FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on an Agilent ESI-TOF (time of flight) mass spectrometer using MALDI (matrix-assisted laser desorption ionisation) or ESI (electrospray ionization). Melting points are uncorrected and were recorded on a Thomas-Hoover Unimelt capillary melting point apparatus. Optical rotations were recorded on a Perkin-Elmer Model 343 polarimeter at 589 nm, and are reported in units of 10^{-1} (deg cm^2 g^{-1}).

Enone (**8**). To a stirred solution of compound **10**[1] (41.75 g, 134 mmol, 1.0 equiv) in CH_2Cl_2 (400 mL) at 0 °C was added Et_3N (54.8 mL, 402 mmol, 3.0 equiv), 4-DMAP (3.2 g, 26.8 mmol, 0.2 equiv) and Ac_2O (25.2 mL, 268 mmol, 2.0 equiv). The mixture was stirred at 25 °C for 4 h. The reaction was then quenched with a sat. aq. $NaHCO_3$ solution (200 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with brine (2 × 150 mL), dried over $MgSO_4$ and concentrated. The obtained crude yellow residue was used in the next step without further purification. An analytically pure sample of acetate was obtained by flash column chromatography (silica gel, EtOAc:hexanes, 1:1). Acetate: Light yellow foam; R_f = 0.37 (silica, EtOAc:hexanes, 1:2); $[\alpha]_D^{25}$ = –159.7 (*c* = 1.85, $CHCl_3$); IR ν_{max} (film): 2977w, 1740m, 1690s, 1367s, 1174m, 1132s, 770w cm^{-1}; ^1H NMR: ($CDCl_3$, 500 MHz) δ = 1.48 (s, 9 H), 2.00 (s, 3 H), 2.41 – 2.31 (m, 1 H), 2.55 – 2.45 (m, 1 H), 2.80 (d, *J* = 14.1 Hz, 1 H), 3.20 (dd, *J* = 16.9, 6.7 Hz, 1 H), 3.73 (s, 3 H), 4.59 (dd, *J* = 9.4, 1.5 Hz, 1 H), 4.70 (dd, *J* = 9.8, 6.7 Hz, 1 H), 6.06 (dd, *J* = 10.4, 4.5 Hz, 1 H), 6.91 (dd, *J* = 18.8, 10.4 Hz, 1 H) ppm; ^{13}C NMR: ($CDCl_3$, 125 MHz) δ = 195.2, (171.6, 170.9), (170.0, 169.9), (153.3, 152.8), (144.9, 144.1), (129.9, 129.5), (82.3, 81.8), (81.4, 80.9), (61.3, 60.8), (58.2, 57.9), (52.3, 52.2), (42.6, 41.1), (39.2, 38.4), (28.3, 28.2, 28.2), 21.5 ppm; HRMS calcd for $C_{17}H_{23}NO_7Na^+$ [*M*+Na^+] 376.1367 found 376.1367.

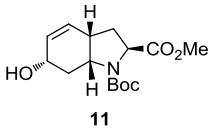


8

The crude acetate was dissolved in MeOH (600 mL), and activated Zn (69.7 g, 1072 mmol, 8.0 equiv) was added followed by glacial acetic acid (16.1 mL, 268 mmol, 2.0 equiv) at 25 °C. The resulting mixture was stirred under reflux for 30 min, then cooled down to ambient temperature. The mixture was filtered through a short pad of Celite® and the filtrate was concentrated under reduced pressure. The obtained residue was used for the next step without further purification. An analytically pure sample of ketone was obtained by flash column chromatography (silica gel, EtOAc:hexanes, 1:1). Ketone: light yellow foam; R_f = 0.48 (silica, EtOAc:hexanes, 1:2); $[\alpha]_D^{25}$ = –158.7 (*c* = 1.0, $CHCl_3$); IR ν_{max} (film): 2977w, 1747m, 1697s, 1391s, 1365s, 1172m, 1128s, 774w cm^{-1}; ^1H NMR: ($CDCl_3$, 500 MHz) δ = 1.41 (s, 9 H), 2.30 – 2.15 (m, 1 H), 2.75 – 2.65 (m, 1 H), 2.90 – 2.77 (m, 2 H), 3.05 – 2.90 (m, 1 H), 3.58 (dd, *J* = 15.4, 4.6 Hz, 1 H), 3.74 (s, 3 H), 4.59 – 4.37 (m, 2 H), 5.74 (br s, 1 H) ppm; ^{13}C NMR: ($CDCl_3$, 125 MHz) δ = (208.5, 208.0), (173.4, 173.0),

(154.5, 153.8), (139.6, 138.8), (81.3, 80.8), (60.1, 59.9), (56.9, 56.3), 52.3, (46.0, 45.0), (39.0, 38.9), (33.6, 33.1), (28.3, 28.2) ppm; HRMS calcd for $C_{15}H_{21}NO_5Na^+$ [*M*+Na^+] 318.1312 found 318.1321. The crude ketone was dissolved in toluene (600 mL), and DBU (100 mL, 670 mmol, 5.0 equiv) was added at ambient temperature. The resulting mixture was stirred at 65 °C for 3 h, and then it was allowed to cool to 25 °C and concentrated under reduced pressure. The crude mixture so-obtained was purified by flash column chromatography (silica gel, EtOAc:hexanes 1:2 → 1:1) to give enone **8** as a white foam (20.18 g, 68.34 mmol, 51% yield for the three steps). The NMR spectra of this compound exhibited signals corresponding to two carbamate rotamers (ca. 1.2:1) that did not coalesce on heating to 60 °C. **8**: R_f = 0.29 (silica, EtOAc:hexanes, 1:1); $[\alpha]_D^{25}$ = –110.9 (*c* = 0.28, $CHCl_3$); IR ν_{max} (film): 2976w, 1744m, 1681s, 1381s, 1365s, 1203m, 1164s, 1125s, 917w, 771m cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, signals for major rotamer) δ = 1.46 (s, 9 H), 2.29 – 2.22 (m, 2 H), 2.38 (dd, *J* = 16.4, 11.3 Hz, 1 H), 2.95 (dd, *J* = 16.3, 6.0 Hz, 1 H), 3.22 – 3.13 (m, 1 H), 3.74 (s, 3 H), 4.46 – 4.41 (m, 1 H), 4.48 (t, *J* = 5.4 Hz, 1 H), 6.03 (d, *J* = 10.0 Hz, 1 H), 6.79 (dd, *J* = 10.2, 5.0 Hz, 1 H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz, signals for both rotamers) δ = (197.0, 196.8), (173.0, 172.7), (153.6, 152.9), (146.5, 146.1), (129.9, 129.7), (80.9, 80.6), (59.6, 59.2), (56.0, 55.9), (52.3, 52.2), (40.9, 40.1), (37.3, 36.5), (33.9, 32.9), (28.3, 28.2) ppm; HRMS calcd for $C_{15}H_{21}NO_5Na^+$ [*M*+Na^+] 318.1312 found 318.1323.

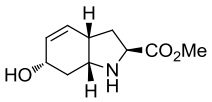
Alcohol (**11**). To a stirred solution of enone **8** (12.0 g, 40.6 mmol, 1.0 equiv) in MeOH (350 mL) was added $CeCl_3 \cdot 7H_2O$ (15.1 g, 40.6 mmol, 1.0 equiv) at ambient temperature. The resulting mixture was cooled to –78 °C and $NaBH_4$ (1.68 g, 44.7 mmol, 1.1 equiv) was added portionwise over 1 min. The reaction mixture was stirred for 1 h, while it was allowed to gradually warm to 0 °C. The resulting mixture was carefully quenched with sat. aq. NH_4Cl (200 mL), and then EtOAc (200 mL) was added and stirring was continued for a few minutes. The organic layer was separated and the aqueous phase was extracted with EtOAc (4 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo, and the residue so obtained was purified by flash column chromatography (silica gel,



11

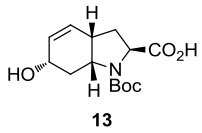
EtOAc:hexanes, 1:1) to give alcohol **11** as a white foam (11.1 g, 37.3 mmol, 92% yield). The NMR spectra of this product showed signals corresponding to two carbamate rotamers (ca. 1.5:1) that did not coalesce on heating at 60 °C. **11**: R_f = 0.21 (silica, EtOAc:hexanes, 1:1); $[\alpha]_D^{25}$ = –83.7 (*c* = 0.11, $CHCl_3$); IR ν_{max} (film): 3420s, 2974m, 1746m, 1694s, 1392s, 1367s, 1167s, 1125s, 742w cm^{-1}; ^1H NMR: ($CDCl_3$, 600 MHz, signals for major rotamer) δ = 1.36 – 1.23 (m, 1 H), 1.41 (s, 9 H), 2.05-1.97 (m, 1 H), 2.16 – 2.06 (m, 1 H), 2.60 – 2.53 (m, 1 H), 2.90 – 2.80 (m, 1 H), 3.72 (s, 3 H), 4.33 (d, *J* = 8.6 Hz, 2 H), 5.64 (br s, 1 H), 5.77 (t, *J* = 10.1 Hz, 1 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz, signals for both rotamers) δ = (173.4, 173.1), (154.2, 153.5), (133.3, 133.1), (127.0, 126.6), (80.3, 80.2), (66.6, 66.4), (59.7, 59.3), 55.2, (52.2, 52.0), (36.8, 35.9), (35.4, 34.8), (34.7, 33.8), (28.4, 28.3) ppm; HRMS calcd for $C_{15}H_{23}NO_5Na^+$ [*M*+Na^+] 320.1468 found 320.1468.

Amine (**12**). To a stirred solution of alcohol **11** (6.0 g, 20.2 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) at 0 °C was added dropwise TFA (50 mL, 649 mmol, 32 equiv), and the resulting mixture was stirred at room temperature for 0.5 h. The solvent was concentrated in vacuo and the resulting crude product was purified by flash column chromatography (silica gel, EtOAc; then MeOH:EtOAc, 1:9 → 2:8) to give amine **12** as an orange foam (3.92 g, 19.9 mmol, 99% yield). **12**: R_f = 0.42 (silica, MeOH:EtOAc, 1:5); $[\alpha]_D^{25}$ = –38.9 (*c* = 0.08, $CHCl_3$); IR ν_{max} (film): 3348w, 2961w, 1746m, 1670s, 1176s, 1127s, 799m, 720s cm^{-1}; ^1H NMR: ($CDCl_3$, 600 MHz) δ = 1.90 (d, *J* = 15.2 Hz, 1 H), 2.32 (dd, *J* = 12.9, 7.3 Hz, 1 H), 2.46 – 2.39 (m, 1 H), 2.51 (d, *J* = 15.1 Hz, 1 H), 3.04 (br s, 1 H), 3.80 (s, 3 H), 4.42 – 4.24 (m, 1 H), 4.53 (dd, *J* = 10.5, 7.5 Hz, 1 H), 5.67 (dd, *J* = 10.0, 2.2 Hz, 1 H), 6.19 (dd, *J* = 9.4, 4.6 Hz, 1 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz) δ = 169.1, 131.3, 127.9, 61.0, 57.9, 57.6, 53.3, 37.5, 34.8, 29.1 ppm; HRMS calcd for $C_{10}H_{15}NO_3H^+$ [*M*+H^+] 198.1125 found 198.1133.



12

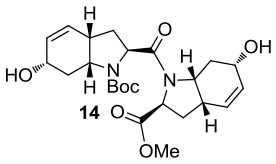
Carboxylic acid (**13**). To a stirred solution of alcohol **11** (6.0 g, 20.2 mmol, 1.0 equiv) in THF (10 mL) at 0 °C was added LiOH (1.0 M aq., 50 mL) in one portion, and the resulting mixture was stirred at ambient temperature for 3 h. The reaction was then quenched with aq. $KHSO_4$ solution



13

(1 M) until pH = 3, and then extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting crude product was purified by flash column chromatography (silica gel, MeOH:EtOAc, 2:8) providing pure carboxylic acid **13** as a white foam (5.66 g, 19.9 mmol, 99% yield). The NMR spectra of this compound exhibited signals corresponding to two carbamate rotamers (ca. 1.1:1) that did not coalesce on heating at 65 °C. **13**: R_f = 0.40 (silica, MeOH:CH_2Cl_2, 1:9); $[\alpha]_D^{25}$ = –78.2 (*c* = 0.15, $CHCl_3$); IR ν_{max} (film): 3383s, 2976m, 1673s, 1401s, 1367s, 1166s, 1130s, 1057m, 736m cm^{-1}; ^1H NMR: ($CDCl_3$, 600 MHz, signals for major rotamer) δ = 1.31 (dd, *J* = 22.9, 11.6 Hz, 1 H), 1.41 (s, 9 H), 2.05 – 1.96 (m, 1 H), 2.23 – 2.13 (m, 1 H), 2.56 – 2.45 (m, 1 H), 2.81 (dd, *J* = 15.4, 10.8 Hz, 1 H), 4.05 – 3.97 (m, 1 H), 4.35 – 4.29 (m, 1 H), 4.42 (d, *J* = 8.9 Hz, 1 H), 5.62 – 5.58 (m, 1 H), 5.77 (t, *J* = 11.1 Hz, 1 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz, signals for both rotamers) δ = (126.8, 126.3), (81.3, 80.8), (66.6, 66.2), (59.5, 59.4), (55.5, 55.2), (36.9, 35.9), (34.8, 34.6), (33.2, 29.1), (28.4, 28.2) ppm; HRMS calcd for $C_{14}H_{21}NO_5Na^+$ [*M*+Na^+] 306.1312 found 306.1309.

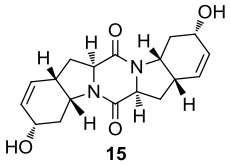
Amide (**14**). To a stirred solution of the above amine **12** (3.92 g, 19.9 mmol, 1.0 equiv) and carboxylic acid **13** (5.66 g, 19.9 mmol, 1.0 equiv) in CH_2Cl_2 (180 mL) at 0 °C was added Et_3N (8.3 mL, 60.6 mmol, 3.0 equiv) in one portion, followed by BOP-Cl (5.1 g, 20.2 mmol, 1.0 equiv) portionwise over 1 min. The resulting mixture was stirred at 25 °C for 15 h. The solvent was concentrated in vacuo and the crude mixture was purified by flash column chromatography (silica gel, EtOAc) to give amide **14** as white foam (7.91 g, 17.11 mmol, 86% yield). The NMR spectra of this compound showed signals corresponding to two carbamate rotamers (ca. 1.2:1) that did not coalesce on heating at 60 °C. [2] **14**: R_f = 0.60 (silica, MeOH:CH_2Cl_2, 1:9); $[\alpha]_D^{25}$ = –54.0 (*c* = 0.06, $CHCl_3$); IR ν_{max} (film): 3406s, 2955m, 1741m, 1677m, 1643s, 1393s, 1366s, 1169s, 1054m, 733s cm^{-1}; ^1H NMR: ($CDCl_3$, 600 MHz) δ = 1.34 – 1.22 (m, 1 H), 1.45 (m, 9 H), 2.14 – 1.95 (m, 4 H), 2.53 – 2.41 (m, 2 H), 2.95 – 2.87 (m, 2 H), 3.69 (s, 3 H), 4.13 – 3.99 (m, 2 H), 4.40 – 4.25 (m, 2 H), 4.51 (d, *J* = 8.8 Hz, 2 H), 4.65 – 4.60 (m, 2 H), 5.83 – 5.60 (m, 4 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz) δ = (172.7, 172.5),



14

(171.1, 170.9), (154.3, 153.7), 133.1, (133.0, 132.8), (127.4, 127.0), (126.5, 126.2), (80.3, 80.0), (66.6, 66.4), (66.3, 66.3), 59.1, (58.7, 58.5), (55.7, 55.6), (55.1, 54.9), (52.3, 52.2), 37.5, (36.3, 36.2), 35.7, (35.3, 35.1), (34.3, 33.4), 32.8, 28.5 ppm; HRMS calcd for $C_{24}H_{34}N_2O_7H^+$ [M+H^+] 463.2439 found 463.2449.

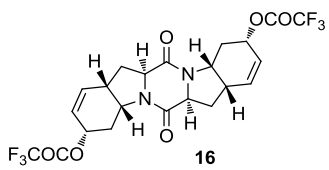
Diketopiperazine (**15**). To a stirred solution of amide **14** (11.0 g, 23.8 mmol, 1.0 equiv) in CH_2Cl_2 (150 mL) at 0 °C was added TFA (50 mL, 649 mmol, 32 equiv) dropwise, and then the resulting mixture was stirred at ambient temperature for 1.5 h. The solvent was removed in vacuo and the residue was coevaporated with toluene (2 × 25 mL) to remove all traces of TFA.



15

The crude product was dissolved in CH_2Cl_2 (150 mL) and Et_3N (16.2 mL, 119 mmol, 5.0 equiv) was added dropwise at 0 °C. The resulting mixture was stirred at ambient temperature for 15 h. The solvent was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel, EtOAc; then MeOH:EtOAc, 1:20) to give diketopiperazine **15** as a white solid (6.05 g, 18.34 mmol, 77% yield). **15**: R_f = 0.16 (silica, MeOH:EtOAc, 1:9); m.p. = 137.0 °C (EtOH); $[\alpha]_D^{25}$ = –171.6 (*c* = 0.06, MeOH); IR ν_{max} (film): 3355s, 1637s, 1435m, 1190s, 1136s cm^{-1}; ^1H NMR: ($CDCl_3$, 600 MHz) δ = 2.15 – 2.01 (m, 6 H), 2.69 – 2.63 (m, 2 H), 2.75 – 2.71 (m, 2 H), 3.49 (br s, 2 H), 4.35 – 4.27 (m, 6 H), 5.73 (dd, *J* = 10.1, 2.2 Hz, 2 H), 5.87 (d, *J* = 10.1 Hz, 2 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz) δ = 166.6, 131.3, 128.6, 64.5, 59.3, 54.9, 36.3, 31.9, 31.4 ppm; HRMS calcd for $C_{18}H_{22}N_2O_4H^+$ [M+H^+] 331.1652 found 331.1650.

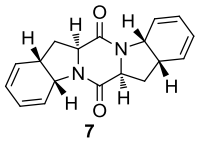
***bis*-Trifluoracetate** (**16**). To a stirred solution of diketopiperazine **15** (120 mg, 0.36 mmol, 1.0 equiv), Et_3N (0.3 mL, 2.2 mmol, 6.0 equiv), and 4-DMAP (14 mg, 0.108 mmol, 0.3 equiv) in MeCN (4 mL) at –40 °C was added trifluoroacetic anhydride (0.2 mL, 1.44 mmol, 4.0 equiv). The reaction mixture was stirred for 1 h while allowed to warm to ambient temperature. The reaction mixture was concentrated in vacuo, and the residue was purified by flash column chromatography (silica gel,



16

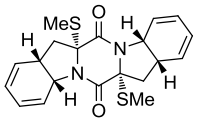
EtOAc) to give *bis*-trifluoracetate **16** as white needles (129.6 mg, 0.248 mmol, 69% yield). **16**: R_f = 0.46 (silica, MeOH:EtOAc, 1:9); m.p. = 93.5 °C (CH_2Cl_2/hexanes); $[\alpha]_D^{25}$ = –249.4 (*c* = 0.30, $CHCl_3$); IR ν_{max} (film): 2909w, 1762s, 1653s, 1435m, 1223m, 1145s, 880m cm^{-1}; ^1H NMR: ($CDCl_3$, 600 MHz) δ = 1.97 (m, 2 H), 2.14 (ddd, *J* = 13.0, 6.6, 2.3 Hz, 2 H), 2.35 (ddd, *J* = 13.0, 10.2, 7.6 Hz, 2 H), 2.98 (t, *J* = 6.8 Hz, 2 H), 3.09 (dt, *J* = 15.4, 3.6 Hz, 2 H), 4.15 (dd, *J* = 9.8, 6.7 Hz, 2 H), 4.30 – 4.25 (m, 2 H), 5.47 (d, *J* = 4.1 Hz, 2 H), 5.97 (dd, *J* = 10.2, 2.9 Hz, 2 H), 6.01 (dd, *J* = 10.2, 4.7 Hz, 2 H) ppm; ^{13}C NMR: ($CDCl_3$, 125 MHz) δ = 166.3, 156.8 [d, $J(^{13}C, ^{19}F)$ = 43 Hz], 134.6, 124.1, 114.4 [q, $J(^{13}C, ^{19}F)$ = 286 Hz], 69.6, 59.0, 53.7, 36.3, 32.3, 26.6 ppm; HRMS calcd for $C_{22}H_{20}F_6N_2O_6H^+$ [*M*+H^+] 523.1298 found 523.1315.

***bis*-Diene** (**7**). To a stirred solution of *bis*-trifluoracetate **16** (2.87 g, 5.5 mmol, 1.0 equiv) in degassed dioxane (55 mL) were added K_2CO_3 (1.6 g, 11.55 mmol, 2.1 equiv) and $Pd(PPh_3)_4$ (635 mg, 0.55 mmol, 0.1 equiv) at ambient temperature. The resulting mixture was stirred at 65 °C for 0.5 h, and then allowed to cool down to ambient temperature. EtOAc (100 mL) and water (100 mL) were added and the organic layer was separated. The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The so-obtained residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:1) to give *bis*-diene **7** as a yellow solid (1.45 g, 4.95 mmol, 90% yield). **7**: $[\alpha]_D^{25}$ = –379.3 (*c* = 0.10, $CHCl_3$); R_f = 0.26 (silica, EtOAc:hexanes, 1:1); m.p. = 137.5 °C (CH_2Cl_2/hexanes); IR ν_{max} (film): 3040w, 2937w, 1646s, 1418, 728m, 694m cm^{-1}; ^1H NMR: ($CDCl_3$, 600 MHz) δ = 2.25 (ddd, *J* = 12.9, 7.4, 5.6 Hz, 2 H), 2.60 (dt, *J* = 12.9, 7.8 Hz, 2 H), 3.05 – 2.99 (m, 2 H), 4.22 (t, *J* = 7.6 Hz, 2 H), 4.77 (dd, *J* = 9.8, 3.7 Hz, 2 H), 5.68 (dd, *J* = 9.5, 3.9 Hz, 2 H), 5.99 – 5.87 (m, 6 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz) δ = 165.4, 128.1, 124.3, 123.3, 123.1, 59.3, 55.2 35.1, 34.0 ppm; HRMS calcd for $C_{18}H_{18}N_2O_2H^+$ [*M*+H^+] 295.1441 found 295.1443.

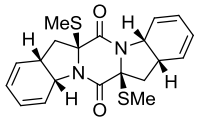


7

***bis*-(Methylthio)diketopiperazines** (**18**) and (2,2′-*epi*-**18**). To a suspension of sulfur (436 mg, 13.58 mmol, 8.0 equiv) in THF (8.5 mL) at 25 °C under argon was added NaHMDS (0.6 M in PhMe, 8.49 mL, 5.09 mmol, 3.0 equiv) dropwise over 2 min. During the addition the insoluble yellow S_8, turned to homogeneous dark blue, then dark orange, and finally light orange solution. This solution was stirred for an additional 1 min and *bis*-diene **7** (500 mg, 1.69 mmol, 1.0 equiv) dissolved in THF (8.5 mL) was added dropwise at ambient temperature over 2 min, at which time the reaction mixture turned light brown. The mixture was stirred for an additional 1 min, then more NaHMDS (0.6 M in PhMe, 5.66 mL, 2.0 equiv) was added and the resulting mixture was stirred 0.5 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL). The mixture was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting brownish residue was used for the next step without further purification.



18



2,2'-*epi*-18

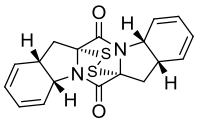
To the above crude product dissolved in a mixture of degassed THF/EtOH (1:1, 17 mL) at 0 °C was added $NaBH_4$ (1.61 g, 42.47 mmol, 25 equiv) in small portions over 1 min. The resulting mixture was stirred for 45 min while it was allowed to warm up to 25 °C. After this time, MeI (5.26 mL, 84.5 mmol, 50 equiv) was added and the mixture was stirred for 15 h at ambient temperature. The reaction was quenched by addition of sat. aq. NH_4Cl solution (50 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 40 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue so-obtained was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:4 → EtOAc:hexanes, 1:1) to afford pure *bis*-(methylthio)diketopiperazine **18** (222 mg, 0.575 mmol, 34% yield) and its diastereoisomer 2,2′-*epi*-**18** (158 mg, 0.410 mmol, 24% yield) (**18**:2,2′-*epi*-**18** ca. 1.4:1 *dr*).

bis-(methylthio)diketopiperazine **18**: light yellow foam; R_f = 0.44 (silica, EtOAc:hexanes, 1:1); $[\alpha]_D^{25}$ = –483.2 (*c* = 0.40, CH_2Cl_2); IR ν_{max} (film): 2918w, 1657s, 1391s, 1182m, 905m, 701m, 666m cm^{-1}; ^1H NMR: ($CDCl_3$, 600 MHz) δ = 2.22 (s, 6 H), 2.59 (dd, *J* = 13.9, 2.8 Hz, 2 H), 2.72 (dd, *J* = 13.9, 9.7 Hz, 2 H), 3.25 – 3.18 (m, 2 H), 5.00 (dd, *J* = 12.3, 3.7 Hz, 2 H), 5.77 (dd, *J* = 9.7, 3.7 Hz, 2

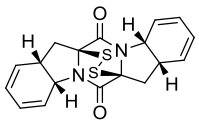
H), 5.92 – 5.84 (m, 2 H), 6.03 – 5.95 (m, 4 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz) δ = 164.1, 128.5, 124.4, 122.1, 121.3, 70.0, 55.7, 42.1, 33.6, 15.4 ppm; HRMS calcd for $C_{20}H_{22}N_2O_2S_2Na^+$ [*M*+Na^+] 409.1015 found 409.1017.

bis-(methylthio)diketopiperazine 2,2′-*epi*-**18**: light yellow foam; R_f = 0.60 (silica, EtOAc:hexanes, 1:1); $[\alpha]_D^{25}$ = –236.9 (*c* = 1.1, CH_2Cl_2); IR ν_{max} (film): 3045w, 2921w, 1664s, 1389m, 1370m, 1156w, 727m, 693m cm^{-1}; ^{1}H NMR: ($CDCl_3$, 600 MHz) δ = 2.11 (t, *J* = 8.3 Hz, 2 H), 2.27 (s, 6 H), 2.59 (dd, *J* = 13.0, 5.6 Hz, 2 H), 3.40 – 3.31 (m, 2 H), 5.01 (d, *J* = 11.5 Hz, 2 H), 5.86 – 5.81 (m, 2 H), 5.95 – 5.86 (m, 4 H), 6.07 – 6.02 (m, 2 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz) δ = 165.3, 126.6, 122.8, 122.4, 120.7, 67.9, 57.3, 39.9, 32.5, 15.0 ppm; HRMS calcd for $C_{20}H_{22}N_2O_2S_2Na^+$ [*M*+Na^+] 409.1015 found 409.1015.

Epidithiodiketopiperazines (**19**) and (2,2′-*epi*-**19**). To a suspension of sulfur (436 mg, 13.58 mmol, 8.0 equiv) in THF (8.5 mL) at 25 °C under argon was added NaHMDS (0.6 M in PhMe, 8.49 mL, 5.09 mmol, 3.0 equiv) dropwise over 2 min. During the addition, the insoluble yellow S_8, turned to homogeneous dark blue, then dark orange, and finally light orange solution. This solution was stirred for an additiona l1 min, and *bis*-diene **7** (500 mg, 1.69 mmol, 1.0 equiv) dissolved in THF (8.5 mL) was added dropwise at ambient temperature over 2 min, at which time the reaction mixture turned light brown. The mixture was stirred for an additional 1 min, then more NaHMDS (0.6 M in PhMe, 5.66 mL, 2.0 equiv) was added and the resulting mixture was stirred 0.5 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL). The mixture was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting brownish residue was used for the next step without further purification.



19



2,2'-*epi*-19

To the above crude product dissolved in a mixture of degassed THF/EtOH (1:1, 17 mL) at 0 °C was added $NaBH_4$ (1.61 g, 42.47 mmol, 25 equiv) in small portions over 1 min. The resulting mixture was stirred for 45 min while it was allowed to warmed up to 25 °C. After this time, the solution was cooled to 0 °C, and quenched by careful addition of sat. aq. NH_4Cl solution (50 mL). The resulting

mixture was extracted with EtOAc (3 × 40 mL) and to the combined organic extracts was added an aq. solution of KI_3 (15 mL, 1.4 M). This mixture was stirred for 10 min and then quenched by the addition of sat. aq. $Na_2S_2O_3$ solution (60 mL). The resulting mixture was extracted with EtOAc (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The so-obtained residue was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:4 → EtOAc:hexanes, 1:1) to afford pure bridged dithiodiketopiperazine **19** (193 mg, 0.542 mmol, 32 % yield) and its diastereoisomer 2,2′-*epi*-**19** (138 mg, 0.387 mmol, 23 % yield) (**19**: 2,2′-*epi*-**19** ca. 1.4:1 *dr*).

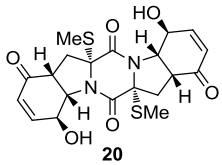
Epidithiodiketopiperazine **19**: light yellow foam; R_f = 0.49 (silica, EtOAc:hexanes, 1:1); $[\alpha]_D^{25}$ = –471.0 (*c* = 0.30, CH_2Cl_2); IR ν_{max} (film): 3042w, 1686s, 1369m, 699w cm^{-1}; ^1H NMR: ($CDCl_3$, 500 MHz) δ = 2.27 (dd, *J* = 13.9, 8.6, 2 H), 3.09 – 3.01 (m, 2 H), 3.46 (dd, *J* = 13.8, 8.4 Hz, 2 H), 4.97 – 4.92 (m, 2 H), 5.91 – 5.87 (m, 4 H), 6.04 – 5.95 (m, 4 H) ppm; ^{13}C NMR: ($CDCl_3$, 125 MHz) δ = 163.2, 127.0, 124.1, 122.9, 121.7, 73.9, 56.9, 38.3, 36.0 ppm; HRMS calcd for $C_{18}H_{16}N_2O_2S_2H^+$ [*M*+H^+] 357.0726 found 357.0777.

Epidithiodiketopiperazine 2,2′-*epi*-**19**: light yellow foam; R_f = 0.60 (silica, EtOAc:hexanes, 1:1); $[\alpha]_D^{25}$ = –236.4 (*c* = 0.10, $CHCl_3$); IR ν_{max} (film): 2922w, 1690s, 1360m, 720m cm^{-1}; ^1H NMR: ($CDCl_3$, 500 MHz) δ = 2.51 (dd, *J* = 7.2, 6.8 Hz, 2 H), 2.90 (dd, *J* = 14.4, 12.4 Hz, 2 H), 3.37 – 3.30 (m, 2 H), 5.11 (dt, *J* = 11.1, 2.2 Hz, 2 H), 5.74 – 5.69 (m, 2 H), 5.97 – 5.88 (m, 6 H) ppm; ^{13}C NMR: ($CDCl_3$, 125 MHz) δ = 163.2, 125.9, 123.1, 122.8, 122.0, 75.0, 57.6, 38.4, 35.2 ppm; HRMS calcd for $C_{18}H_{16}N_2O_2S_2H^+$ [*M*+H^+] 357.0726 found 357.0737.

bis-(Methylthio)diketopiperazines (**18**) from epidithiodiketopiperazine (**19**). To a mixture of pure epidithiodiketopiperazine **19** (100 mg, 0.281 mmol) in a degassed THF/EtOH (1:1, 2.8 mL) at 0 °C was added $NaBH_4$ (21 mg, 0.561 mmol, 2 equiv) in small portions over 1 min. The resulting mixture was stirred for 45 min while it was allowed to warm up to 25 °C. After this time, MeI (0.874 mL, 14.1 mmol, 50 equiv) was added and the mixture was stirred for 15 h at ambient temperature. The reaction was quenched by addition of sat. aq. NH_4Cl solution (50 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 40 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The

residue so-obtained was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:4 → EtOAc:hexanes, 1:1) to afford pure *bis*-(methylthio)dikeropiperazines **18** (71 mg, 0.183 mmol, 65% yield).

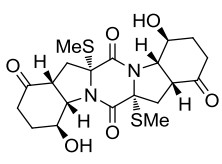
***bis*-(Hydroxy enone)** (**20**). To a solution of dimethylthiodiketopiperazine **18** (23.0 mg, 0.06 mmol) in CH_2Cl_2 (20 mL) was added tetraphenylporphyrin (0.7 mg, 0.0012 mmol, 0.02 equiv).



20

Oxygen was bubbled through the solution at –45 °C and the flask was irradiated with a 400 W (Philips-MH400/U) sunlamp for 40 min. DBU (0.09 mL, 0.6 mmol, 10 equiv) was added dropwise at –45 °C and the mixture was stirred for 1 h at 0 °C. The reaction was quenched by an aq. 1 M HCl solution (10 mL), and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic phase was washed with an aq. sat. $NaHCO_3$ solution (1 × 10 mL), and dried over Na_2SO_4. The solvent was removed in *vacuo* and the residue was purified by flash column chromatography (silica gel, Acetone:CH_2Cl_2, 1:1) to give *bis*-(hydroxy enone) **20** as a white foam (14.0 mg, 0.031 mmol, 52% yield). **20**: R_f = 0.40 (silica, acetone:CH_2Cl_2 1:1); $[\alpha]_D^{25}$ = –130.0 (*c* = 0.10, CH_2Cl_2); IR ν_{max} (film): 3432s, 2927w, 1666s, 1392m, 1249m, 1041m cm^{-1}; ^1H NMR: ($CDCl_3$, 600 MHz) δ = 2.15 (s, 2 H), 2.35 (dd, *J* = 14.1, 9.4 Hz, 1 H), 3.14 (t, *J* = 10.2 Hz, 1 H), 3.33 (d, *J* = 14.1 Hz, 1 H), 4.62 (br s, 1 H), 4.69 (dd, *J* = 11.1, 3.4 Hz, 1 H), 6.22 (d, *J* = 10.4 Hz, 1 H), 6.85 (d, *J* = 10.5 Hz, 1 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz) δ = 192.2, 165.5, 147.2, 128.0, 70.5, 70.2, 64.4, 41.8, 33.9, 14.5 ppm; HRMS calcd for $C_{20}H_{22}N_2O_6S_2H^+$ [*M*+H^+] 451.0992 found 451.009.

Epicoccin G (**1**): To a solution of *bis*-(hydroxy enone) **20** (14.0 mg, 0.031 mmol) in MeOH (6.0 mL) was added $Pd(OH)_2/C$ (20% w/w, 9 mg, 0.013 mmol, 0.4 equiv). The mixture was stirred



1: epicoccin G

under a hydrogen atmosphere (balloon) at 25 °C for 1 h. The solution was filtered through Celite®, and the residue was rinsed with EtOAc. The solution was concentrated in vacuo and the crude product was purified by PTLC (silica gel, acetone:CH_2Cl_2, 1:1) to give epicoccin G (**1**) as a white foam (12 mg, 0.026 mmol, 86% yield). **1**: R_f

= 0.38 (silica, Acetone:CH_2Cl_2, 1:1); $[\alpha]_D^{25}$ = –141.0 (*c* = 0.10, MeOH), lit.[3b] $[\alpha]_D^{25}$ = –141.5 (*c* = 0.10, MeOH); IR ν_{max} (film): 3403w, 1701s, 1643s, 1399m, 1327s, 1074m, 996s cm^{-1}; ^1H NMR: (DMSO-d_6, 600 MHz) δ = 1.88 (m, 2 H), 1.90 (s, 6 H), 2.14 (m, 2 H), 2.20 (m, 2 H), 2.27 (dd, *J* = 13.5, 8.1 Hz, 2 H), 2.59 (ddd, *J* = 17.4, 11.4, 6.0 Hz, 2 H), 2.75 (d, *J* = 13.8 Hz, 2 H), 2.94 (dd, *J* = 8.4, 7.8 Hz, 2 H), 4.28 (br d, *J* = 7.8 Hz, 2 H), 4.31 (m, 2 H), 5.32 (d, *J* = 3.0 Hz, 2 H) ppm; ^{13}C NMR: (DMSO-d_6, 150 MHz) δ = 207.7, 165.5, 71.5, 64.6, 63.3, 44.0, 34.1, 33.8, 25.8, 14.2 ppm; HRMS calcd for $C_{20}H_{27}N_2O_6S_2^+$ [M+H^+] 455.1305, found 455.1322.

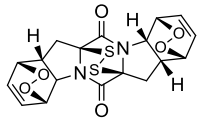
Table 1. ^1H NMR (DMSO-d_6) Spectroscopic Data Comparison of Natural[3b] and Synthetic Epicoccin G (**1**).

Position	**Natural** δ ^1H [ppm, mult, *J* (Hz)] 500 MHz	**Synthetic** δ ^1H [ppm, mult, *J* (Hz)] 600 MHz
3a, 3′a	2.76 (br d, 13.5)	2.75 (d, 13.8)
3b, 3′b	2.27 (dd, 13.5, 8.0)	2.27 (dd, 13.5, 8.1)
4, 4′	2.94 (br dd, 8.0, 8.0)	2.94 (dd, 8.4, 7.8)
6a, 6′a	2.59 (ddd, 17.0, 11.5, 5.5)	2.59 (ddd, 17.4, 11.4, 6.0)
6b, 6′b	2.19 (m)	2.20 (m)
7a, 7′a	2.14 (m)	2.14 (m)
7b, 7′b	1.88 (m)	1.88 (m)
8, 8′	4.31 (m)	4.31 (m)
9, 9′	4.29 (br d, 8.0)	4.28 (br d, 7.8)
2, 2′-SCH_3	1.90 (s)	1.90 (s)
8, 8′-OH	5.32 (s)	5.32 (d, 3.0)

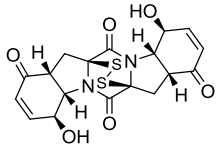
Table 2. ^{13}C NMR (DMSO-d_6) Spectroscopic Data Comparison of Natural[3b] and Synthetic Epicoccin G (**1**).

Position	**Natural** δ ^{13}C (ppm) 125 MHz	**Synthetic** δ ^{13}C (ppm) 150 MHz
1, 1′	165.5	165.5
2, 2′	71.5	71.5
3, 3′	34.1	34.1
4, 4′	44.0	44.0
5, 5′	207.7	207.7
6, 6′	33.8	33.8
7, 7′	25.8	25.8
8, 8′	63.4	63.3
9, 9′	64.7	64.6
2, 2′-SCH_3	14.2	14.2

***bis*-Endoperoxide** (**21**) and ***bis*-(hydroxy enone)** (**22**)**.** To a solution of epidithiodiketopiperazine 2,2′-*epi*-**19** (106 mg, 0.2988 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added tetraphenylporphyrin (3.0 mg, 0.005 mmol, 0.016 equiv). Oxygen was bubbled through the solution at 0 °C and the flask was irradiated with a 400 W (Philips-MH400/U) sunlamp for 2 h. Concentration of the solution provided crude *bis*-endoperoxide **21**, which was used for the next step without further purification. An analytically pure sample of **21** was obtained by flash column chromatography (silica gel, EtOAc:hexanes, 1:1). **21**: light yellow foam; R_f = 0.31 (silica, EtOAc:hexanes, 1:1); $[\alpha]_D^{25}$ = +79.4 (*c* = 0.10, $CHCl_3$); IR ν_{max} (film): 3020w, 1686s, 1364m, 924m, 749s, 723m cm^{-1}; ^1H NMR: ($CDCl_3$, 400 MHz) δ = 2.41 (dd, *J* = 15.6, 10.1 Hz, 2 H), 2.63 (dd, *J* = 15.6, 7.3 Hz, 2 H), 3.41 – 3.32 (m, 2 H), 4.62 (dd, *J* = 8.6, 4.5 Hz, 2 H), 4.81 (ddt, *J* = 6.0, 4.2, 1.6 Hz, 2 H), 5.36 (ddt, *J* = 6.2, 4.5, 1.7 Hz, 2 H), 6.45 (ddd, *J* = 6.1, 3.8, 1.0 Hz, 2 H), 6.72 (ddd, *J* = 7.9, 6.2, 1.5 Hz, 2 H) ppm; ^{13}C NMR: ($CDCl_3$, 100 MHz) δ = 161.1, 132.4, 130.6, 77.3, 72.1, 69.8, 57.1, 36.6, 34.3 ppm; HRMS calcd for $C_{18}H_{16}N_2O_6S_2H^+$ [*M*+H^+] 421.0523 found 421.0525.



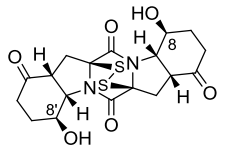
21



22

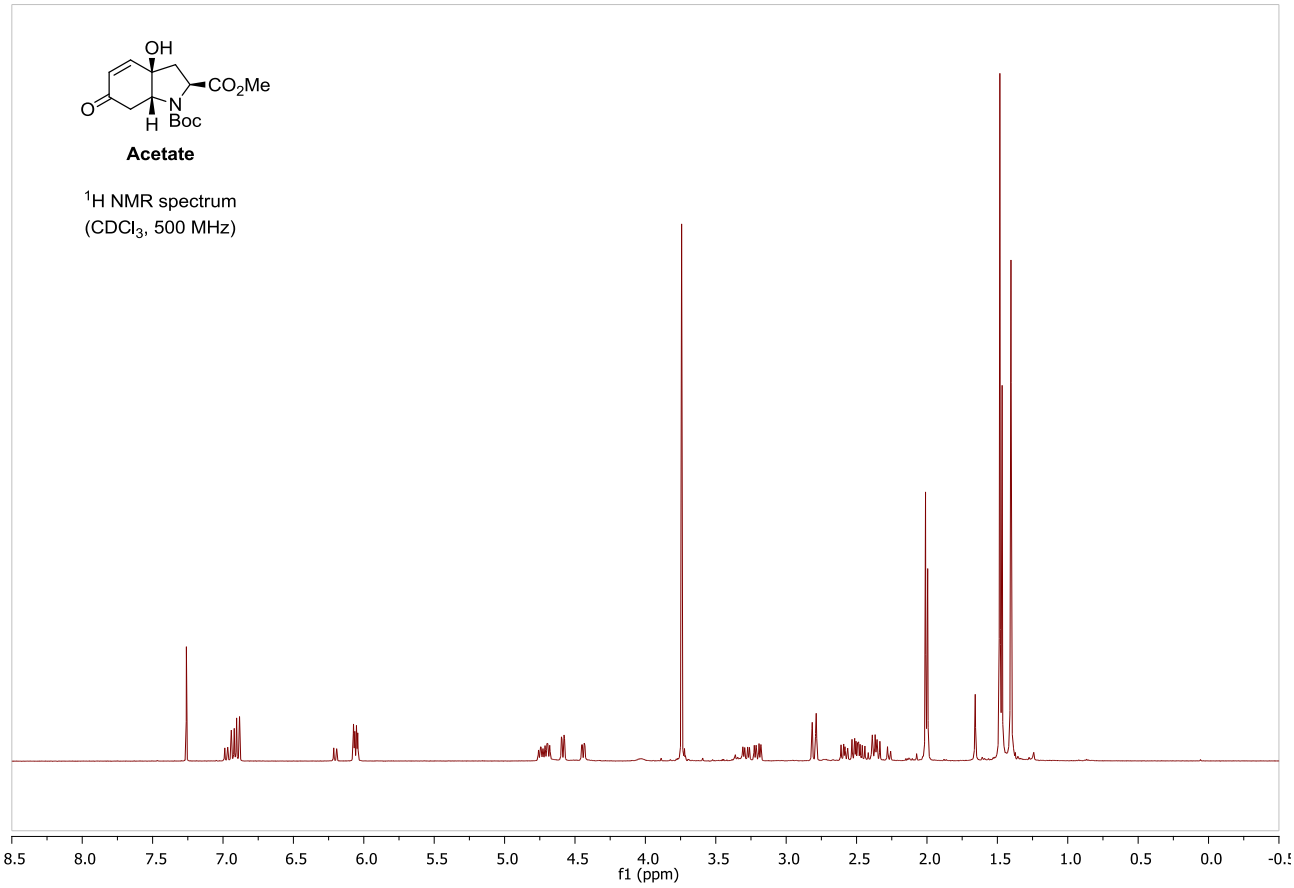
To a solution of the crude *bis*-(endoperoxide) **21** in CH_2Cl_2 (2.98 mL, 0.1 M) at 0 °C was added Et_3N (0.21 mL, 1.49 mmol, 5.0 equiv) dropwise. The resulting mixture was stirred at ambient temperature for 3 h, the solvent was removed in vacuo, and the residue was purified by flash column chromatography (silica gel, EtOAc) to give *bis*-(hydroxy enone) **22** as a white solid (69 mg, 0.164 mmol, 55% yield over two steps). **22**: R_f = 0.39 (silica, EtOAc); $[\alpha]_D^{25}$ = –16.1 (*c* = 0.60, CH_2Cl_2); m.p. = 142.5 (EtOH); IR ν_{max} (film): 3401s, 2926w, 1667s, 1375m, 1358m, 1245m, 1070m, 732s cm^{-1}; ^1H NMR: ($CDCl_3$, 400 MHz) δ = 2.79 (dd, *J* = 14.9, 7.7 Hz, 2 H), 3.00 – 2.93 (m, 2 H), 3.71 (ddd, *J* = 13.3, 9.7, 7.8 Hz, 2 H), 4.56 – 4.49 (m, 2 H), 4.63 (dd, *J* = 9.7, 7.4 Hz, 2 H), 6.16 (dd, *J* = 10.4, 2.5 Hz, 2 H), 6.89 (dd, *J* = 10.4, 1.9 Hz, 2 H) ppm; ^{13}C NMR: ($CDCl_3$, 100 MHz) δ = 193.0, 164.6, 149.6, 128.0, 75.8, 69.4, 65.9, 44.1, 34.0 ppm; HRMS calcd for $C_{18}H_{16}N_2O_6S_2H^+$ [*M*+H^+] 421.0523 found 421.0509.

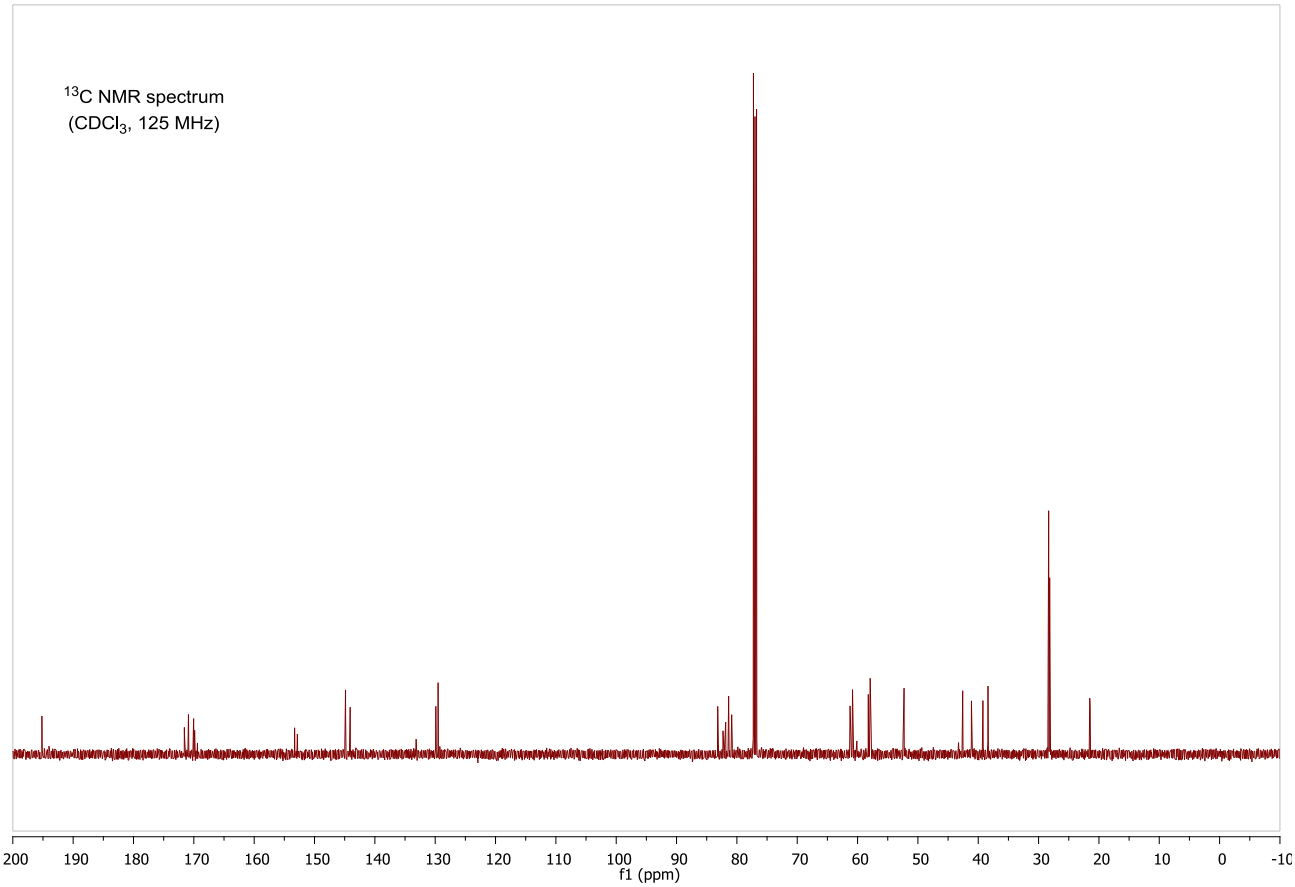
8,8′-*epi*-*ent*-Rostratin B (**4**). To a stirred solution of *bis*-(hydroxy enone) **22** (22 mg, 0.052 mmol) in benzene (1.0 mL) at ambient temperature was added $[CuH(PPh_3)]_6$ (0.5 M in benzene, 1.05 mL, 0.523 mmol),[4] and the resulting mixture was stirred at 25 °C for 0.5 h, then EtOAc (20 mL) was added followed by an aq. solution of KI_3 (15 mL, 1.4 M). This mixture was stirred for 10 min and then quenched by the addition of sat. aq. $Na_2S_2O_3$ solution (30 mL). The resulting mixture was extracted with EtOAc (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of **4** by PTLC (silica gel, EtOAc:hexanes, 4:1) gave 8,8′-*epi*-*ent*-rostratin B (**4**) as a colorless oil (18 mg, 0.043 mmol, 82% yield). **4**: R_f = 0.23 (silica, EtOAc:hexanes, 4:1); $[\alpha]_D^{25}$ = +19 (*c* = 0.27, $CHCl_3$); IR ν_{max} (film): 3417s, 2926w, 1699s, 1668s, 1451w, 1373m, 1074m, 771w cm^{-1}; ^1H NMR: ($CDCl_3$, 600 MHz) δ = 2.02 – 1.91 (m, 2 H), 2.27 – 2.20 (m, 2 H), 2.54 – 2.46 (m, 4 H), 2.59 (br d, *J* = 16.6 Hz, 2 H), 3.22 (dd, *J* = 15.2, 11.2 Hz, 2 H), 3.59 (dd, *J* = 19.7, 10.0, Hz, 2 H), 3.92 (ddd, *J* = 11.8, 8.2, 3.8 Hz, 2 H), 4.49 (dd, *J* = 9.6, 8.3 Hz, 2 H), 4.93 (s, 2 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz) δ = 206.2, 164.8, 76.5, 70.8, 67.7, 47.6, 35.7, 33.7, 28.1 ppm; HRMS calcd for $C_{18}H_{20}N_2O_6S_2H^+$ [M+H^+] 425.0836 found 425.0834.

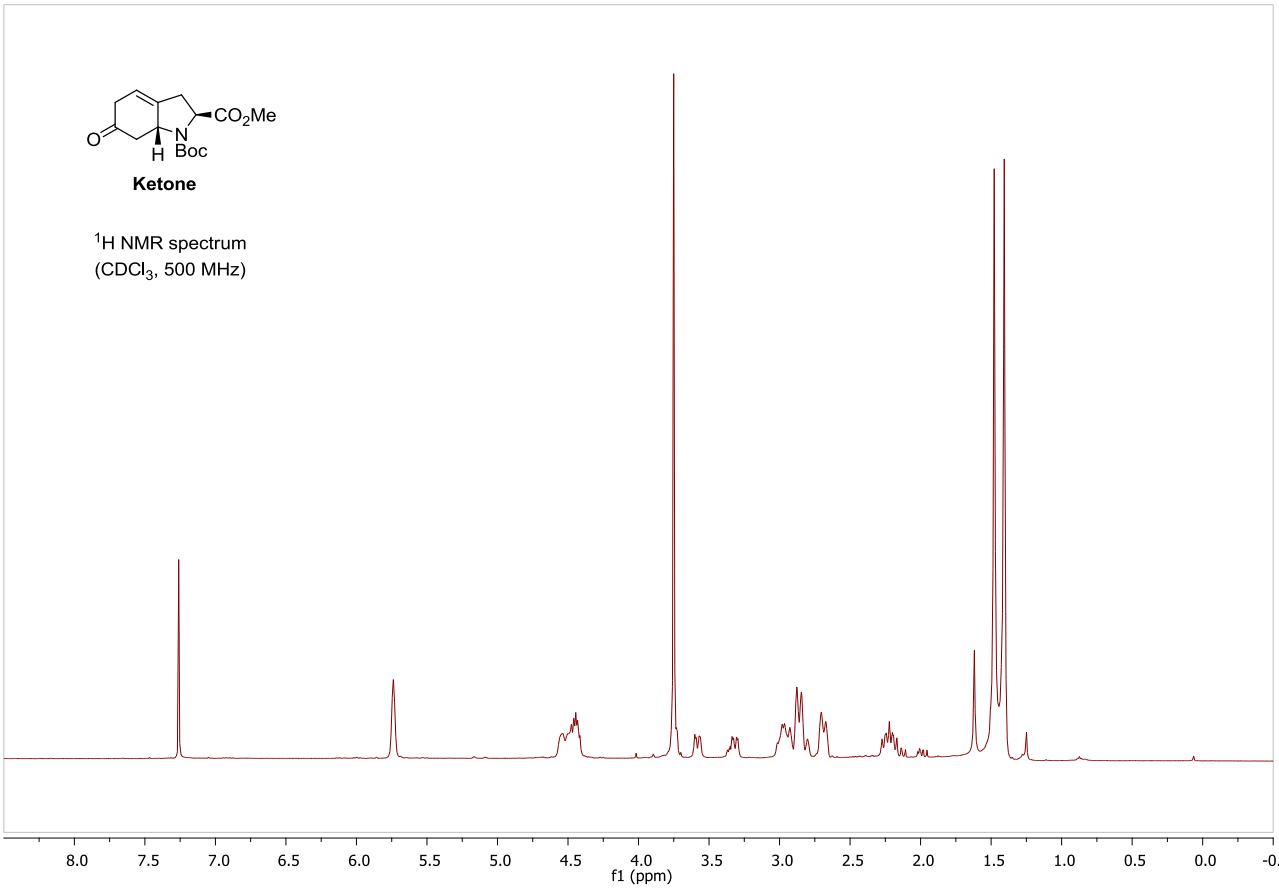


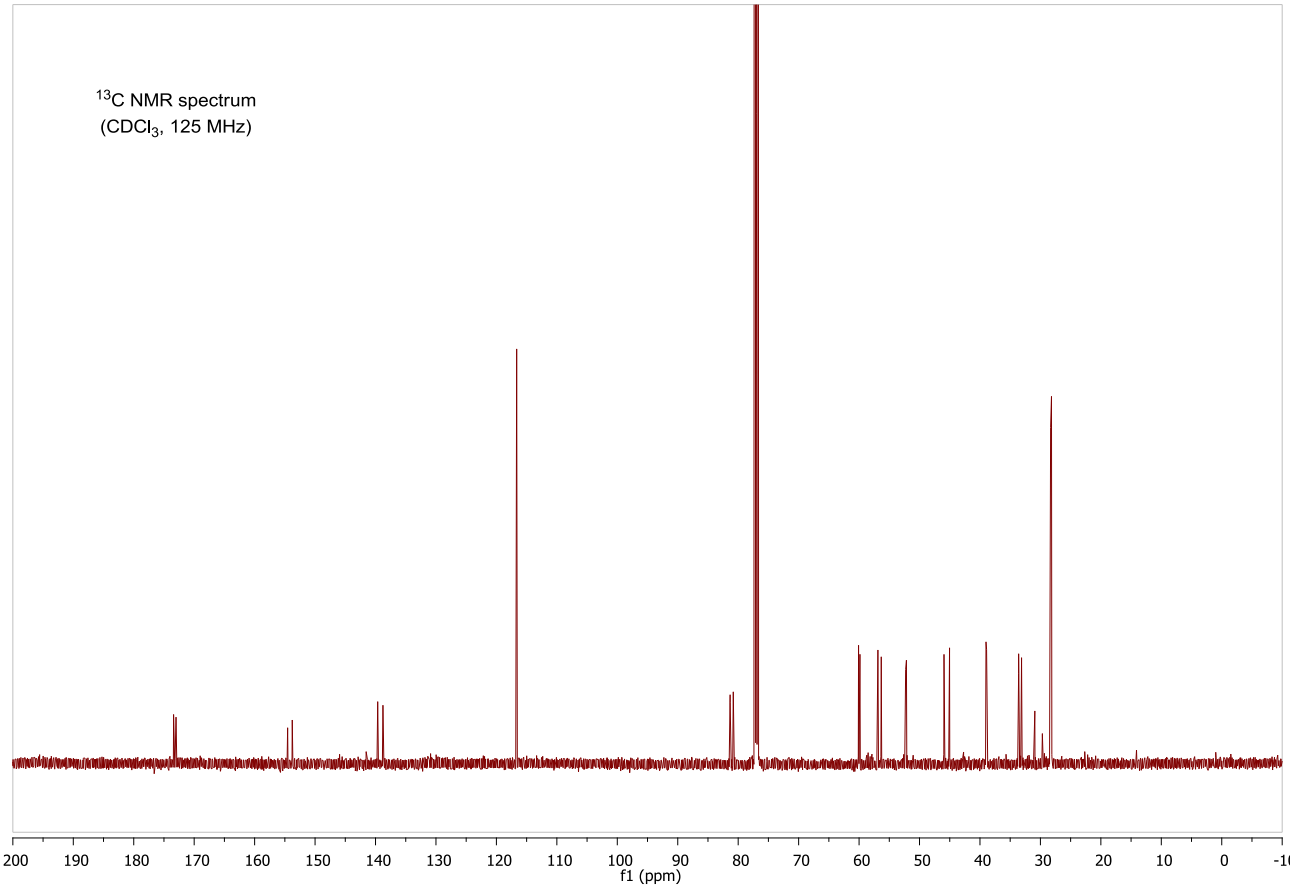
4: 8,8'-*epi*-*ent*-rostratin B

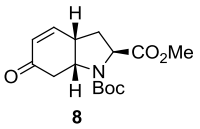
II. ^{1}H and ^{13}C NMR Spectra of Compounds






CO2Me
O
N
H
Boc
Ketone
1H NMR spectrum
(CDCl3, 500 MHz)
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
f1 (ppm)

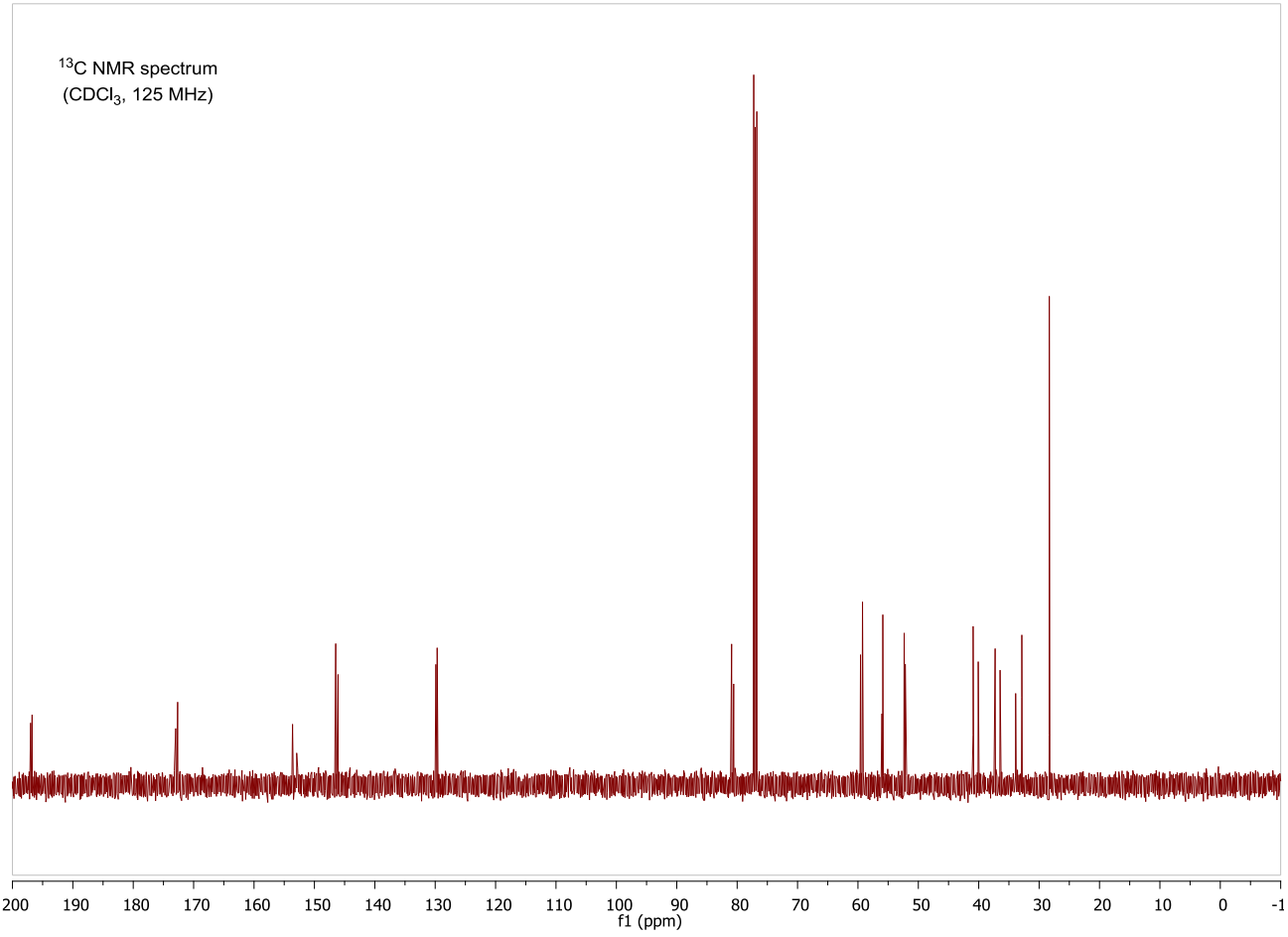

13C NMR spectrum
(CDCl3, 125 MHz)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

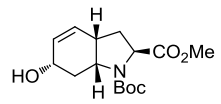


8

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

^{13}C NMR spectrum
($CDCl_3$, 125 MHz)

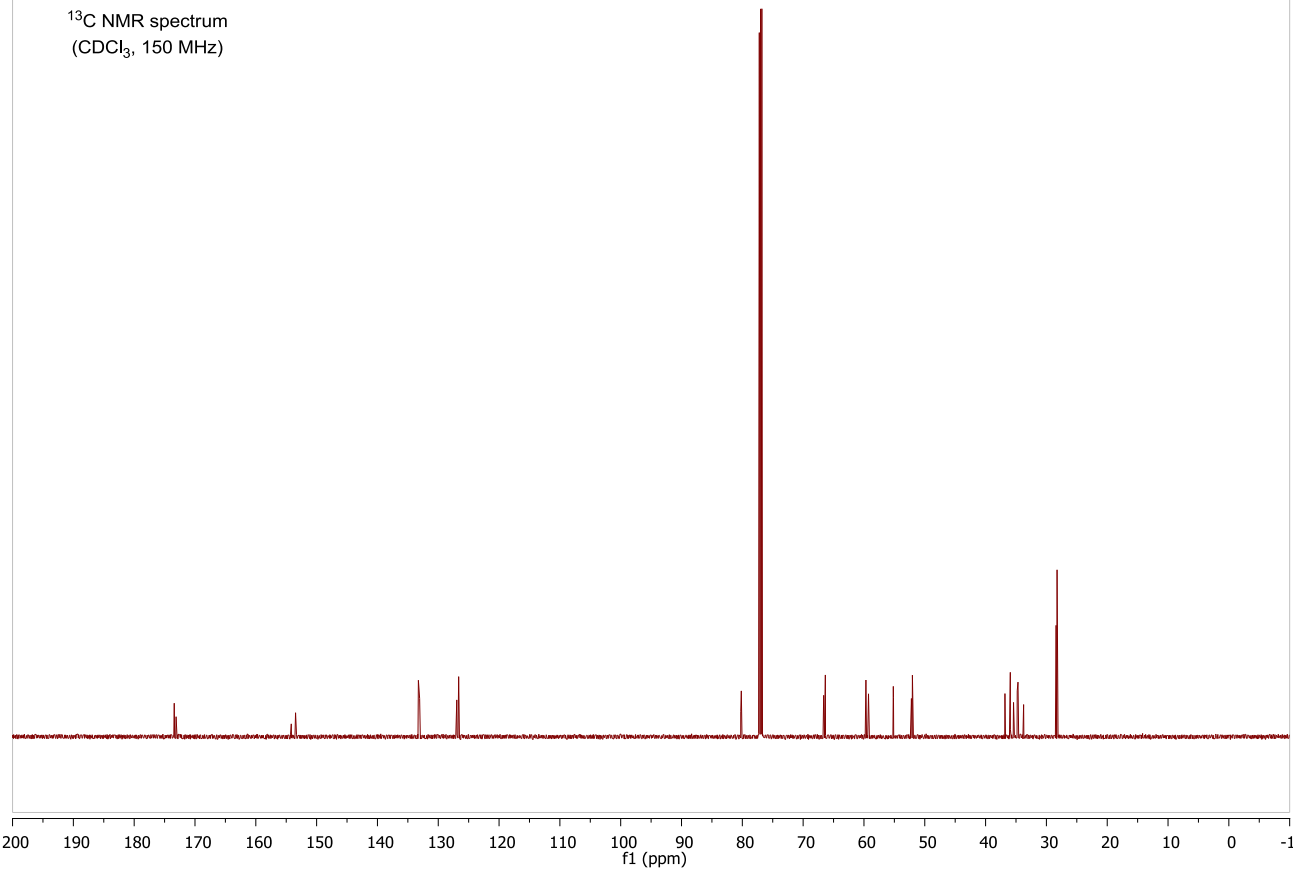


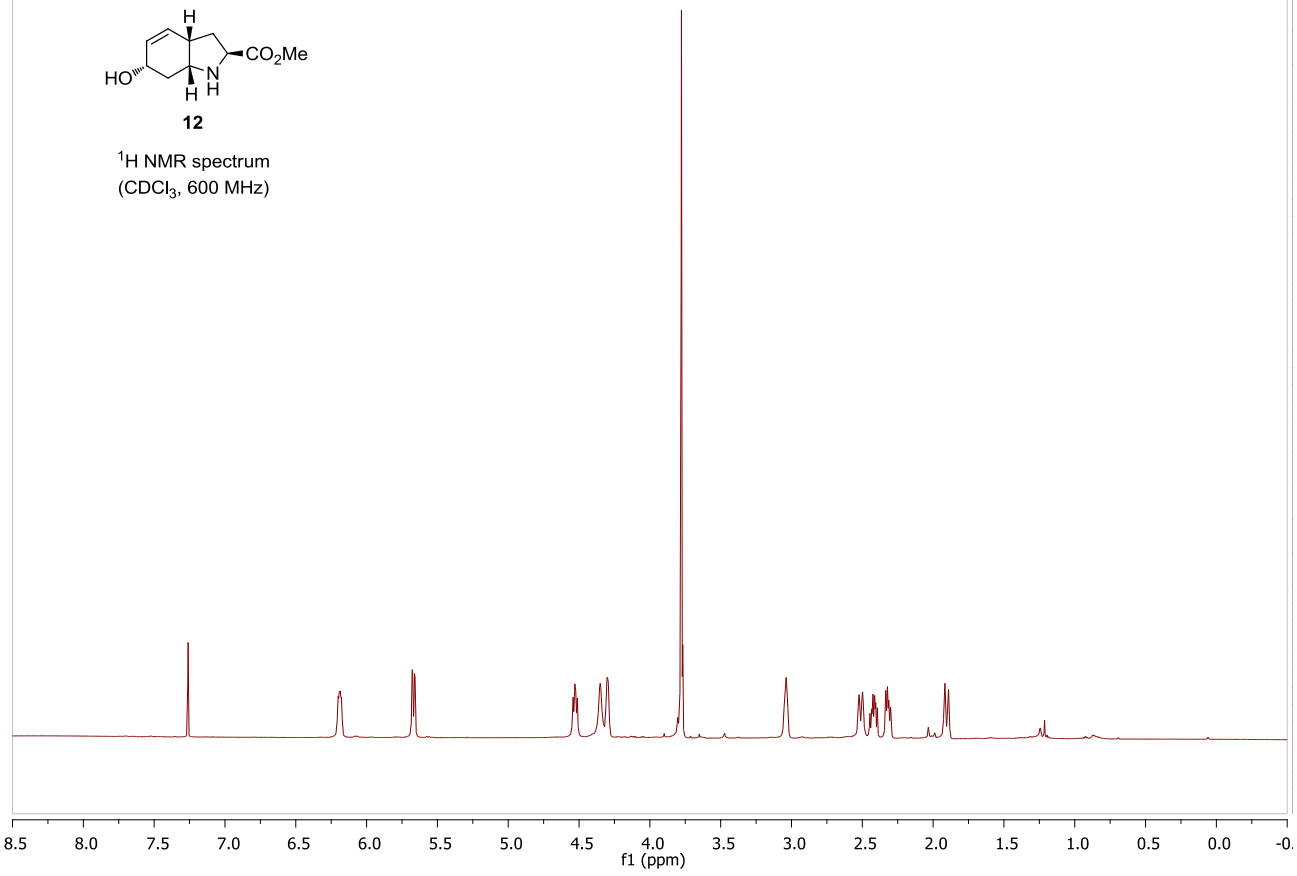


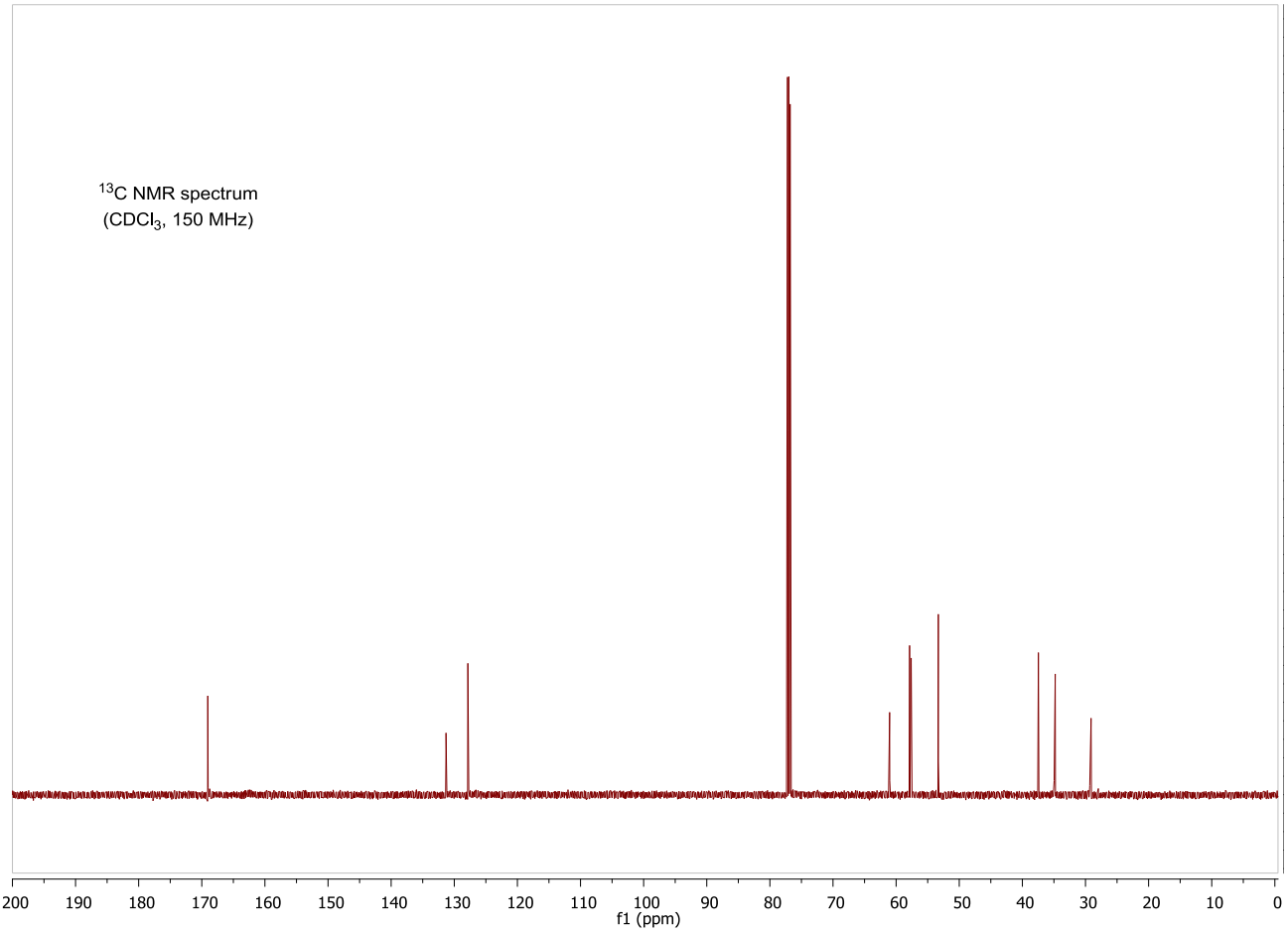
11

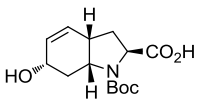
^{1}H NMR spectrum
($CDCl_3$, 600 MHz)

^{13}C NMR spectrum
($CDCl_3$, 150 MHz)




H
CO2Me
HO
N
H
H
12
1H NMR spectrum
(CDCl3, 600 MHz)
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
f1 (ppm)

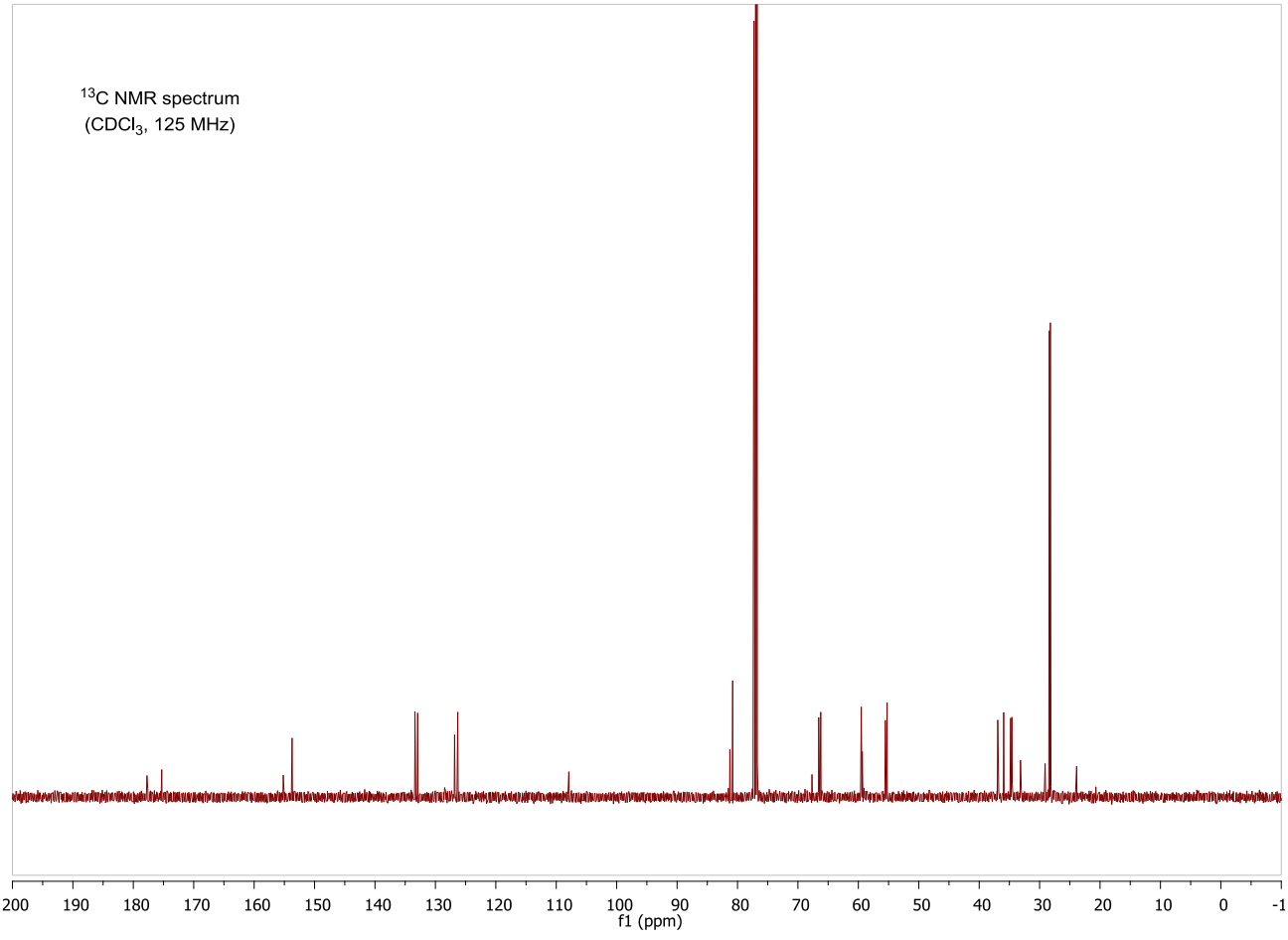

13C NMR spectrum
(CDCl3, 150 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

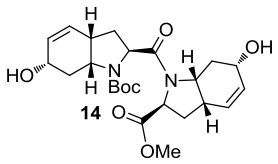


13

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

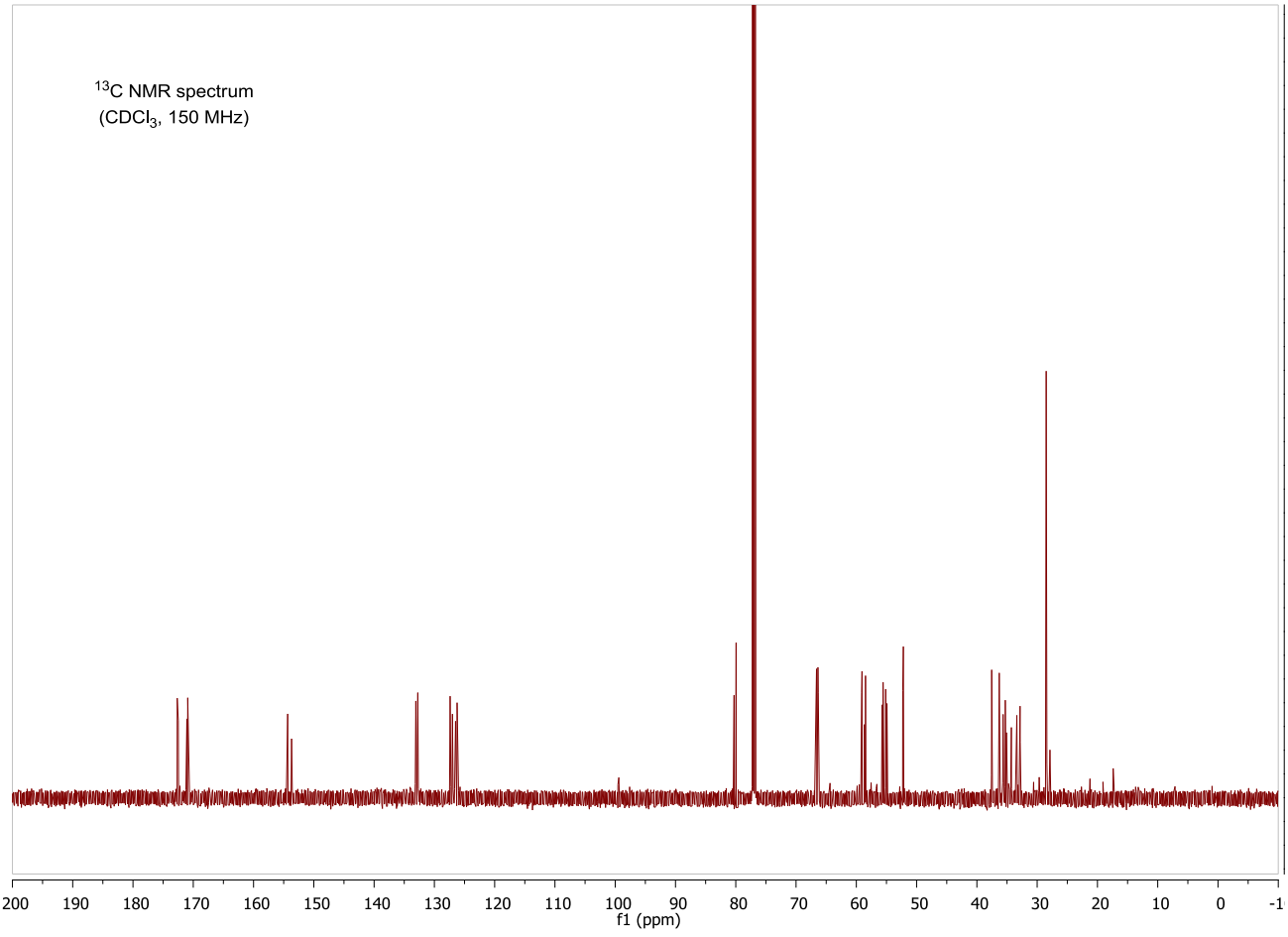
^{13}C NMR spectrum
($CDCl_3$, 125 MHz)

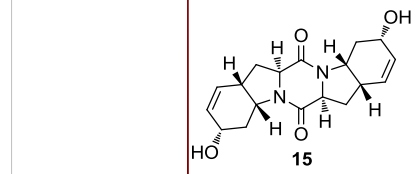




^{1}H NMR spectrum
($CDCl_3$, 600 MHz)

^{13}C NMR spectrum
($CDCl_3$, 150 MHz)

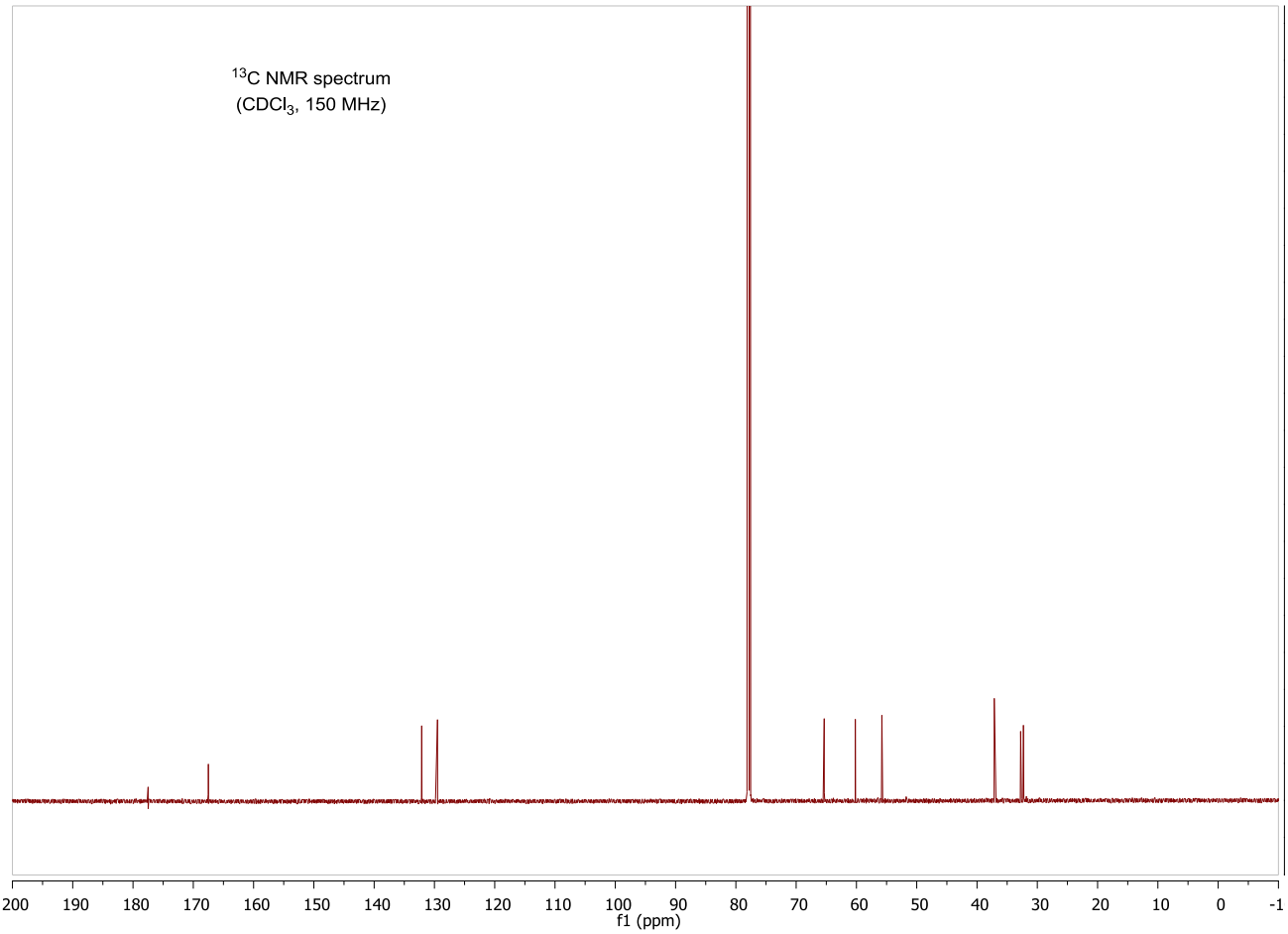


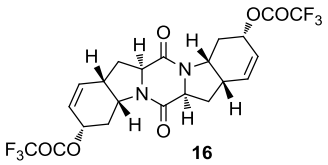


15

^{1}H NMR spectrum
($CDCl_3$, 600 MHz)

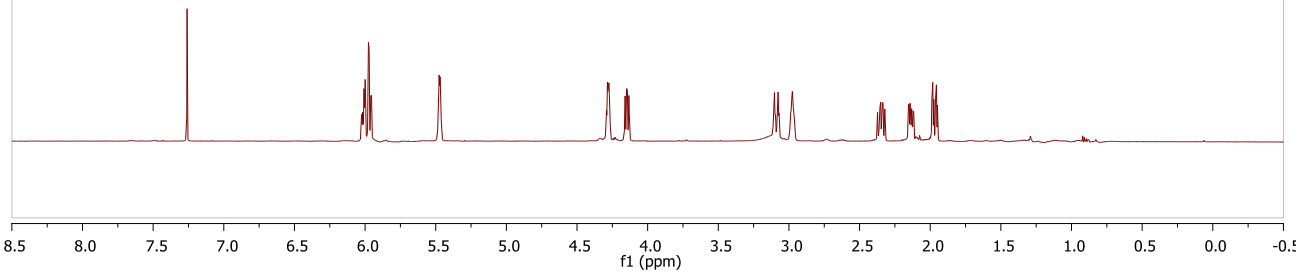
^{13}C NMR spectrum
($CDCl_3$, 150 MHz)



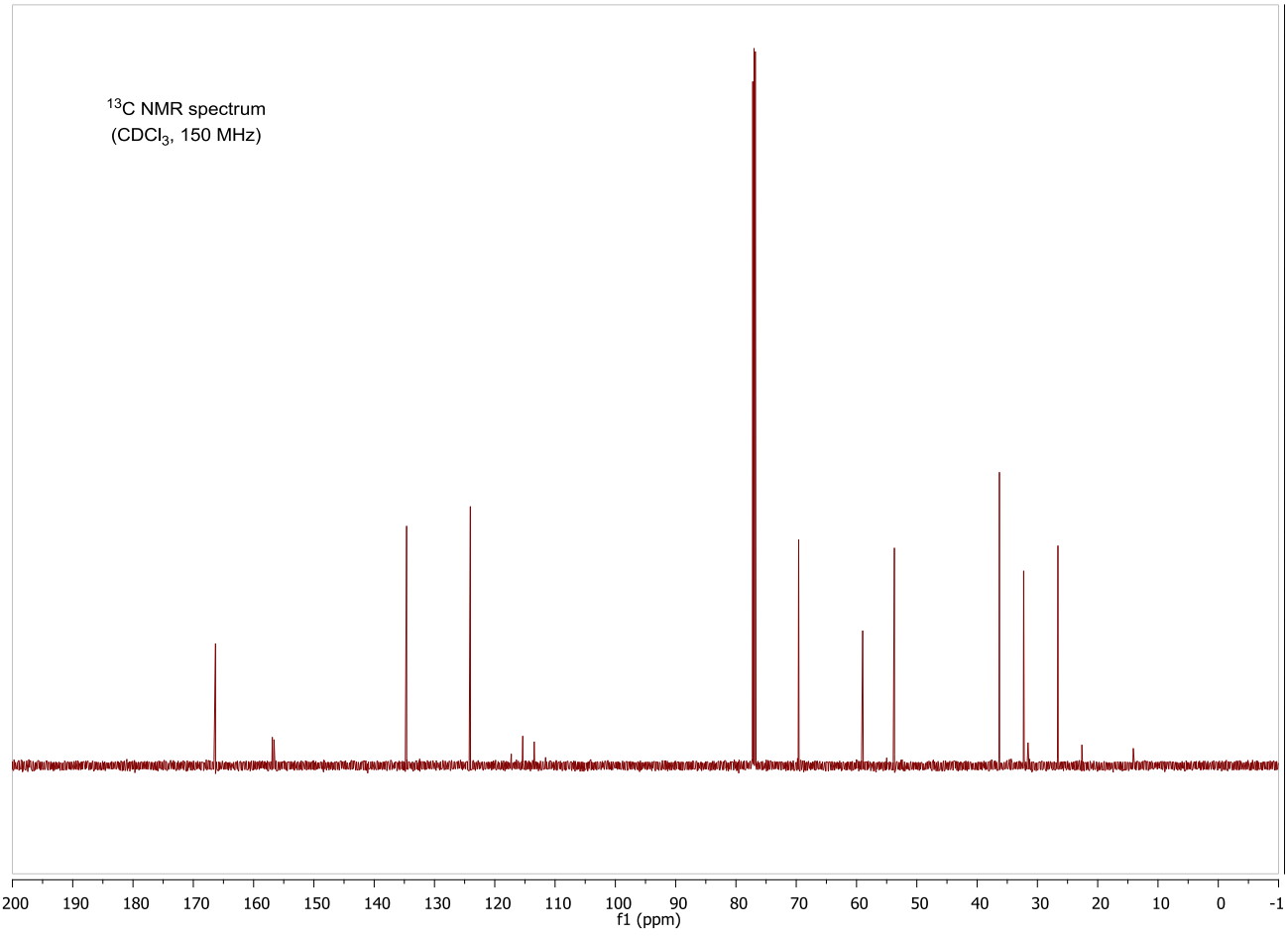


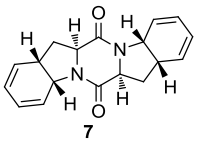
16

^{1}H NMR spectrum
($CDCl_3$, 600 MHz)



^{13}C NMR spectrum
($CDCl_3$, 150 MHz)

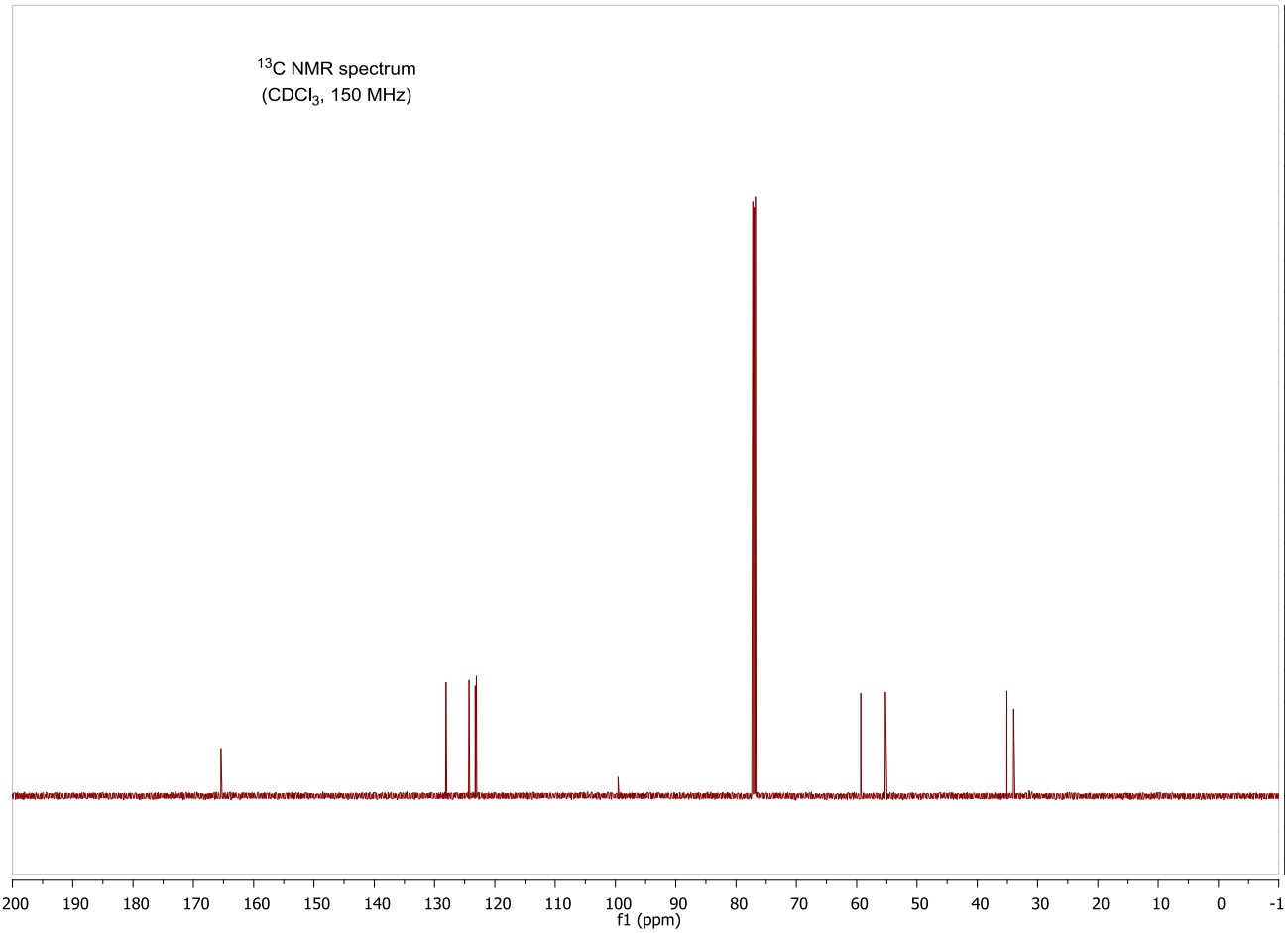


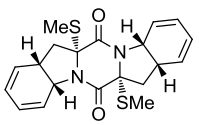


7

^{1}H NMR spectrum
($CDCl_3$, 600 MHz)

^{13}C NMR spectrum
($CDCl_3$, 150 MHz)

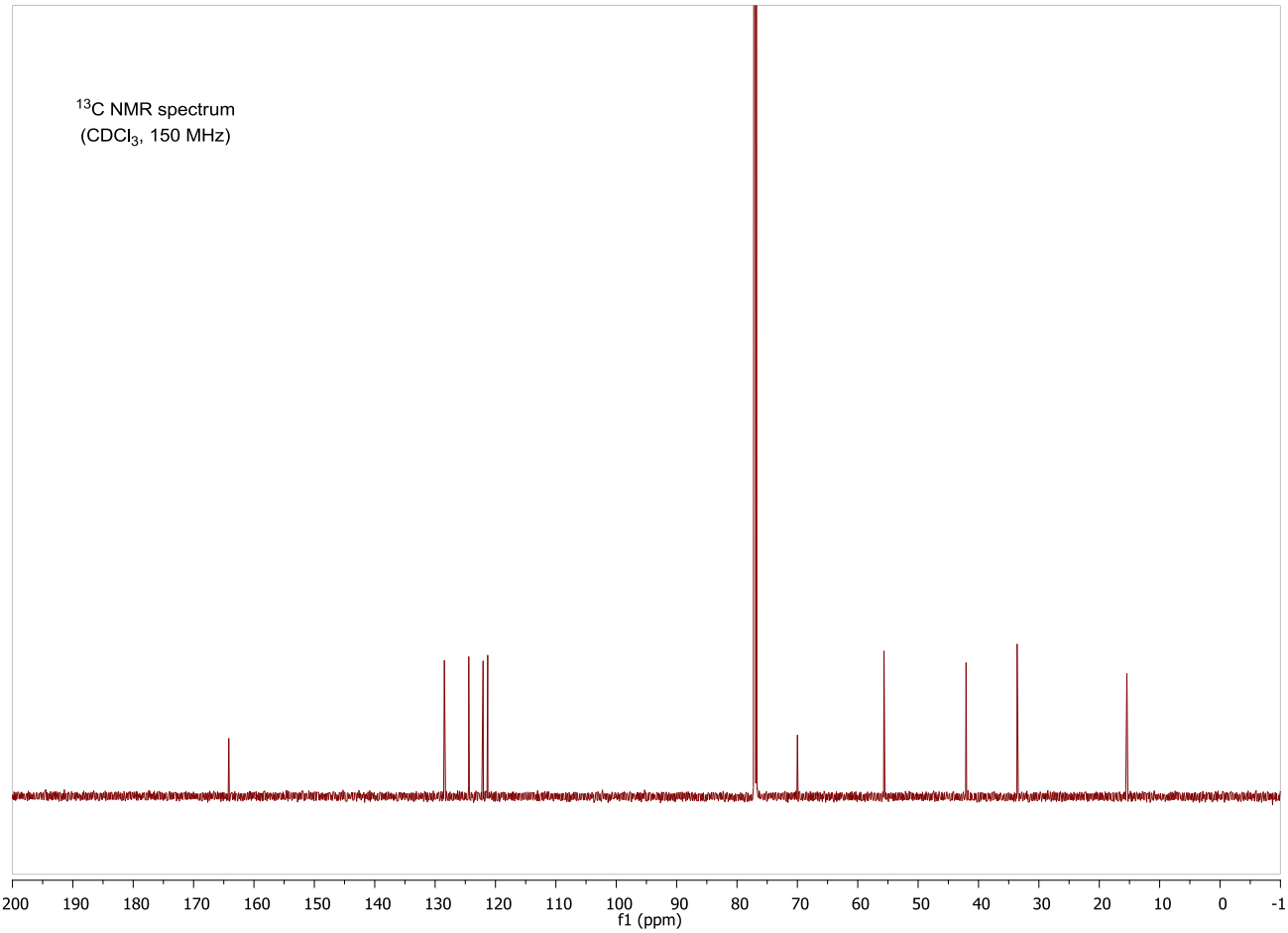


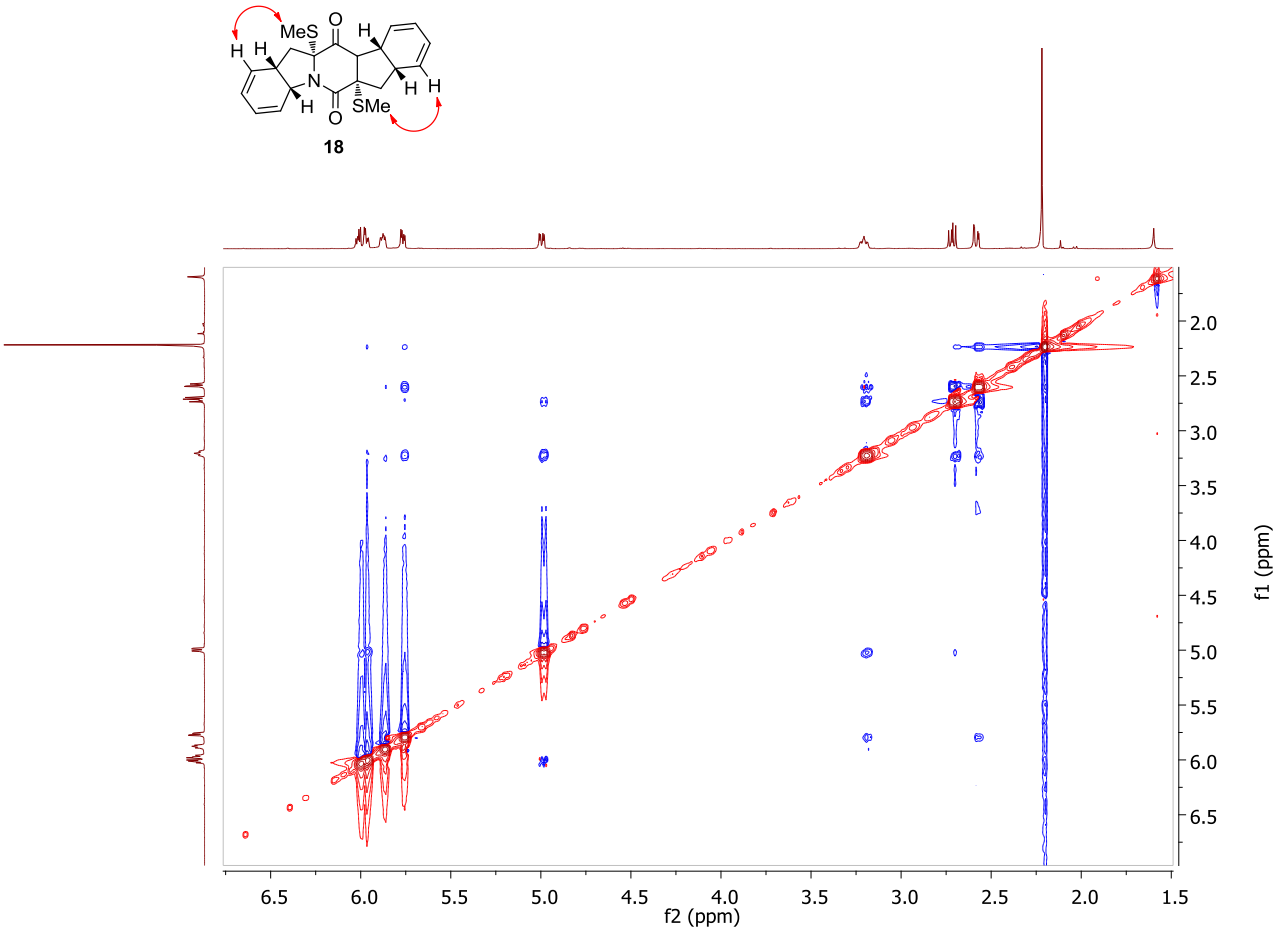


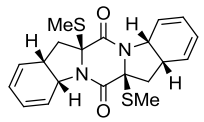
18

^{1}H NMR spectrum
($CDCl_3$, 600 MHz)

^{13}C NMR spectrum
($CDCl_3$, 150 MHz)



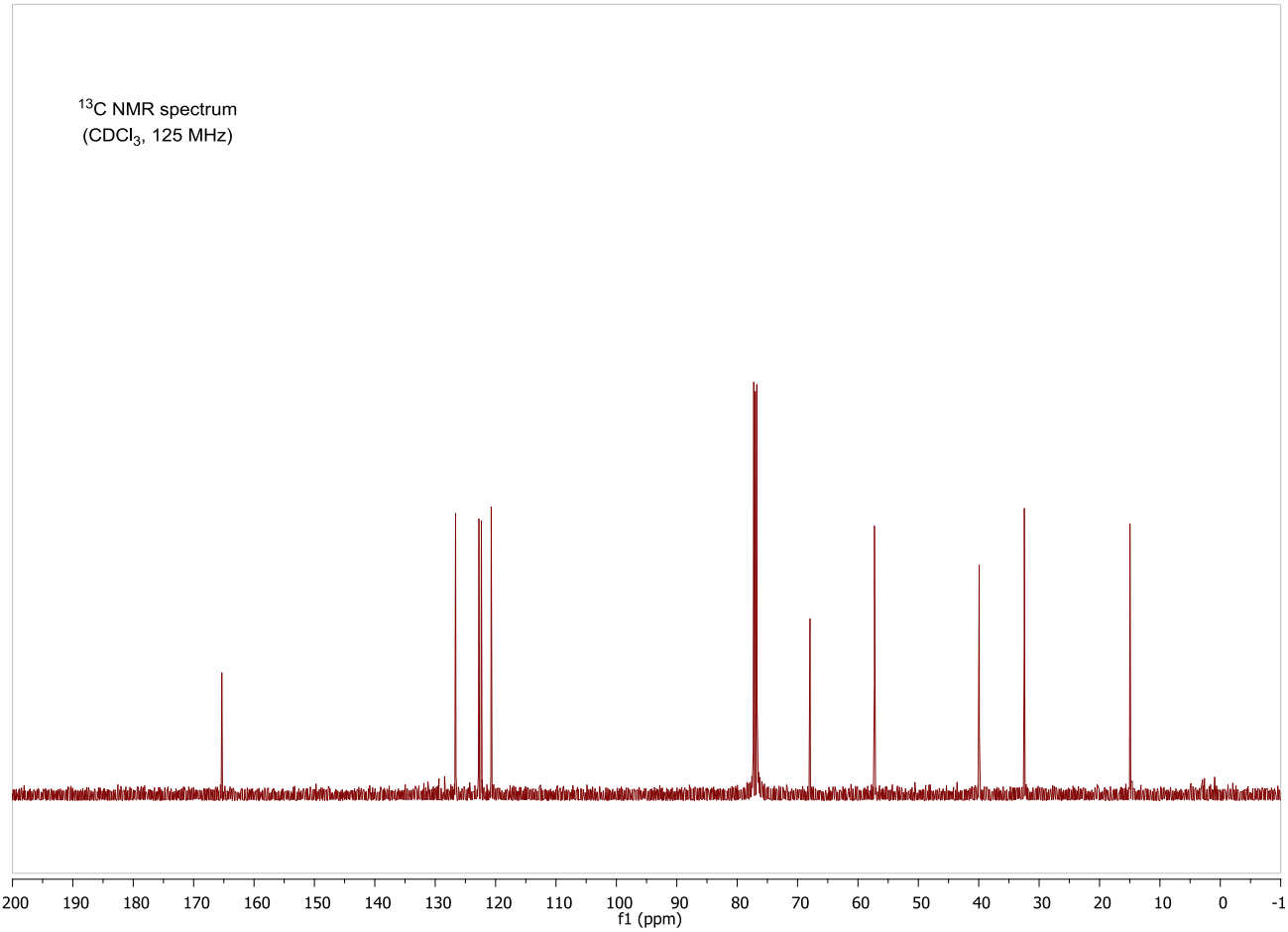

MeS
O
H
H H
N
H H
H
O
SMe
18
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
f1 (ppm)
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)

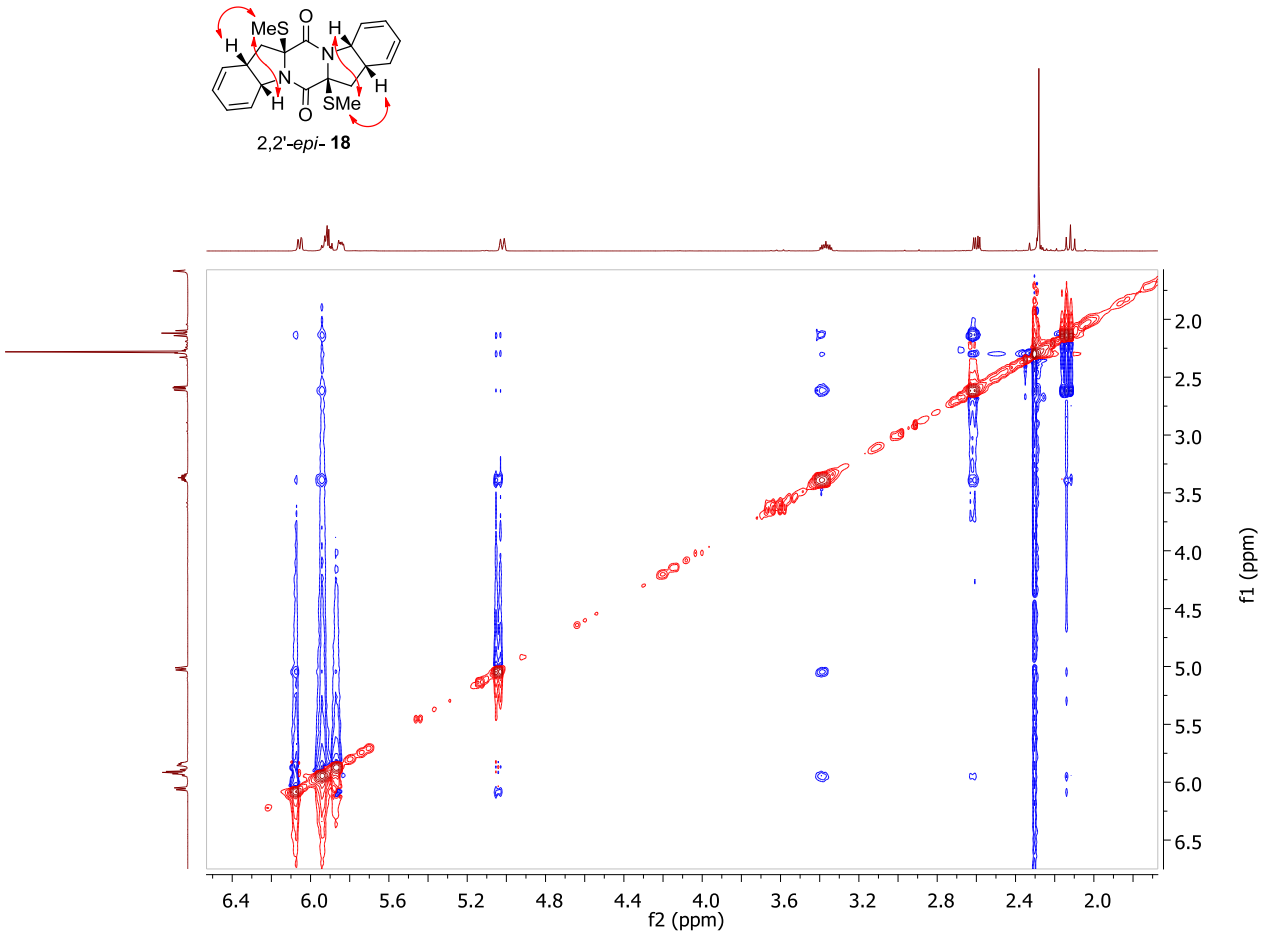


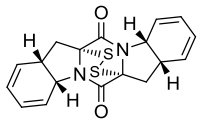
2,2'-*epi*-**18**

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

^{13}C NMR spectrum
($CDCl_3$, 125 MHz)

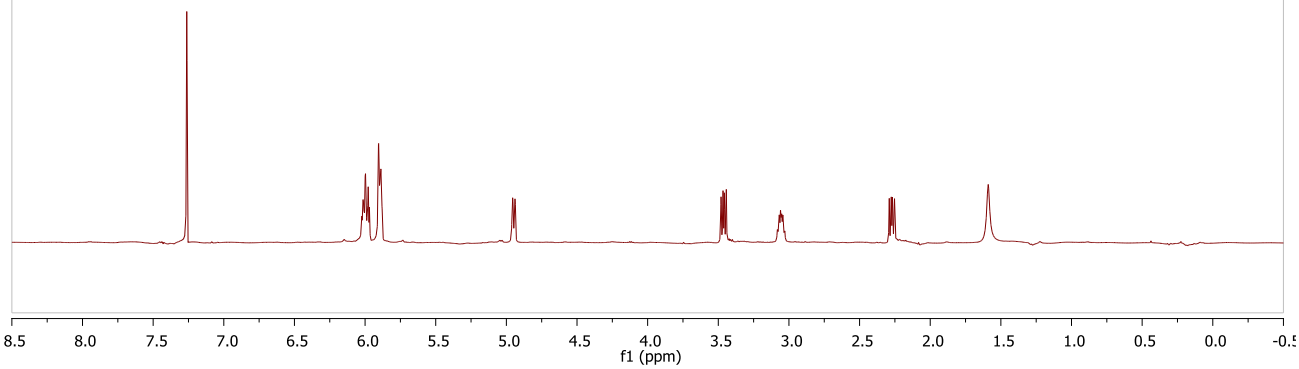



MeS
O
H
H
N
N
H
H
O
SMe
2,2'-epi- 18
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
f1 (ppm)
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
f2 (ppm)

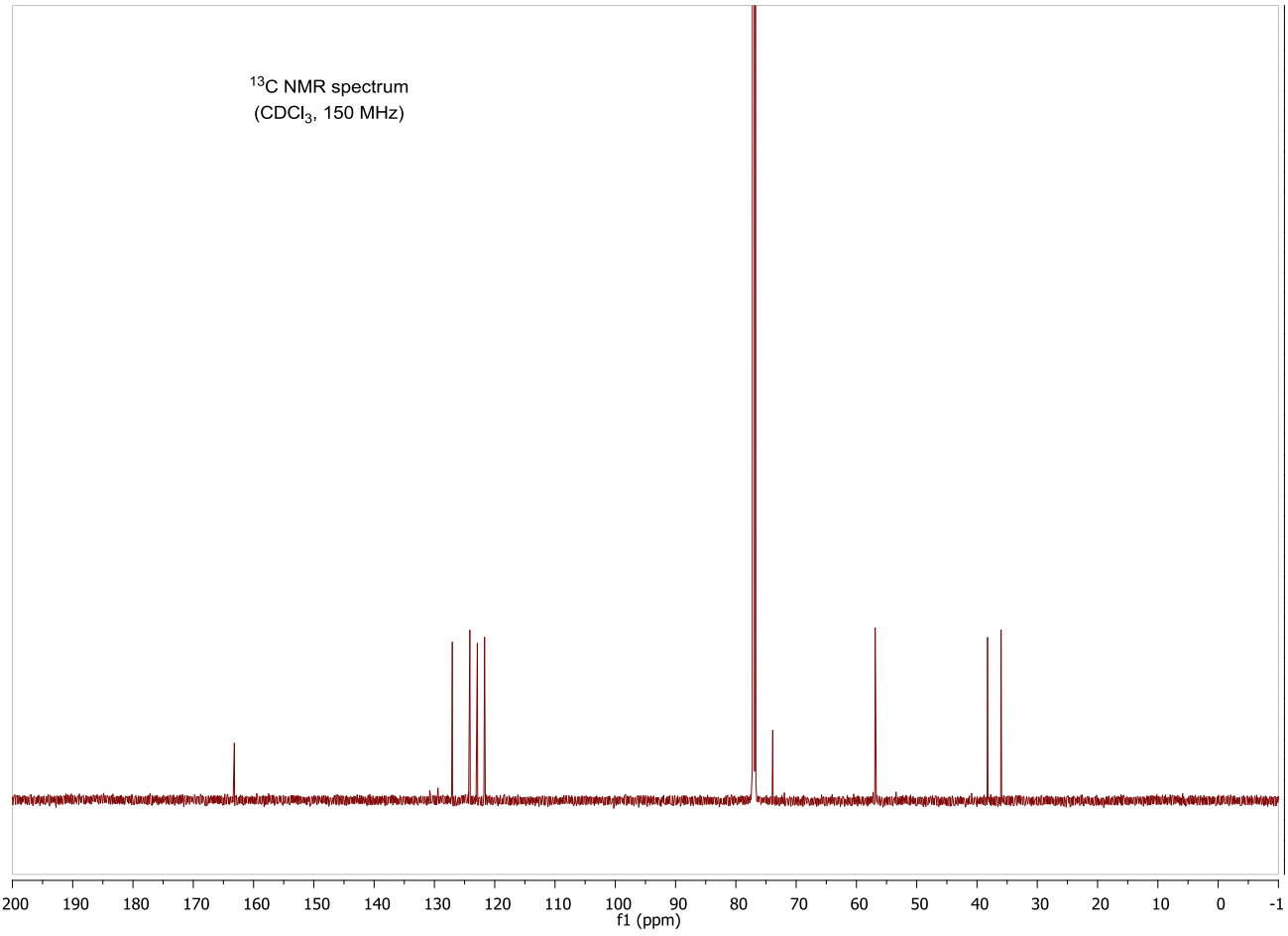


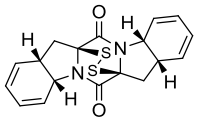
19

^{1}H NMR spectrum
($CDCl_3$, 600 MHz)



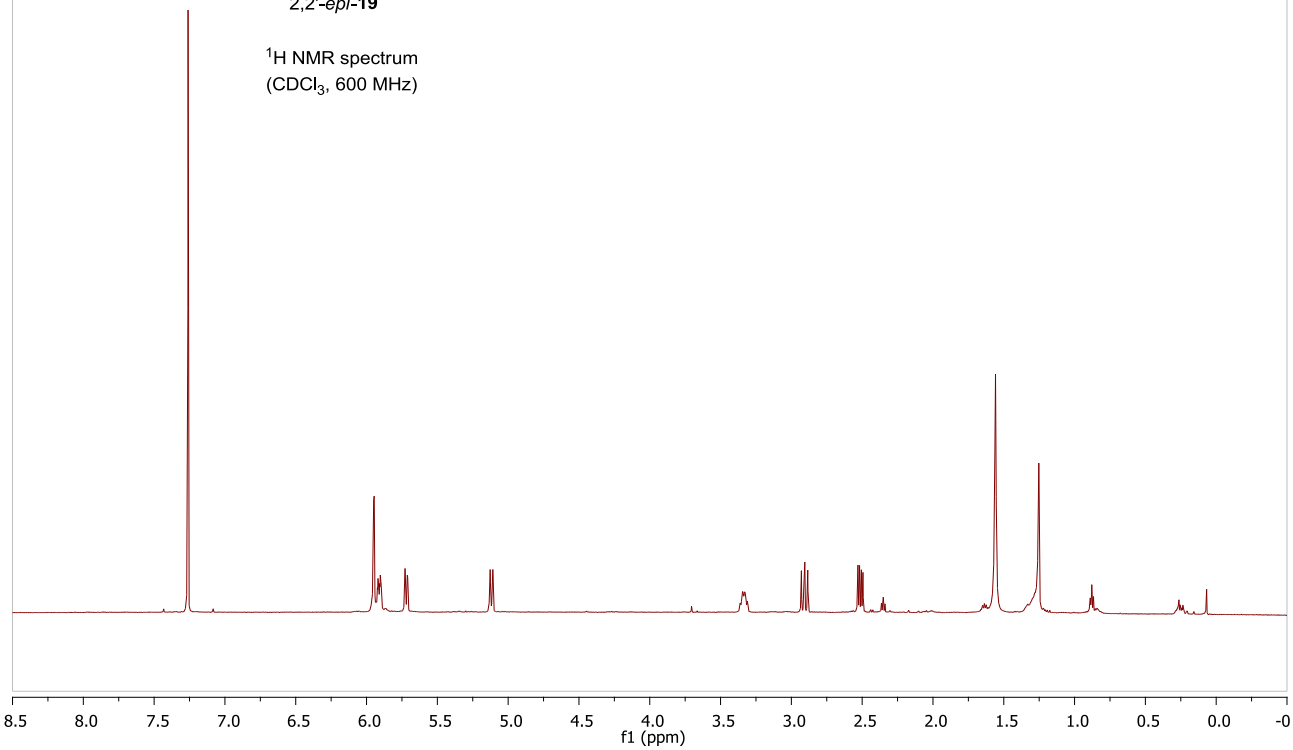
^{13}C NMR spectrum
($CDCl_3$, 150 MHz)



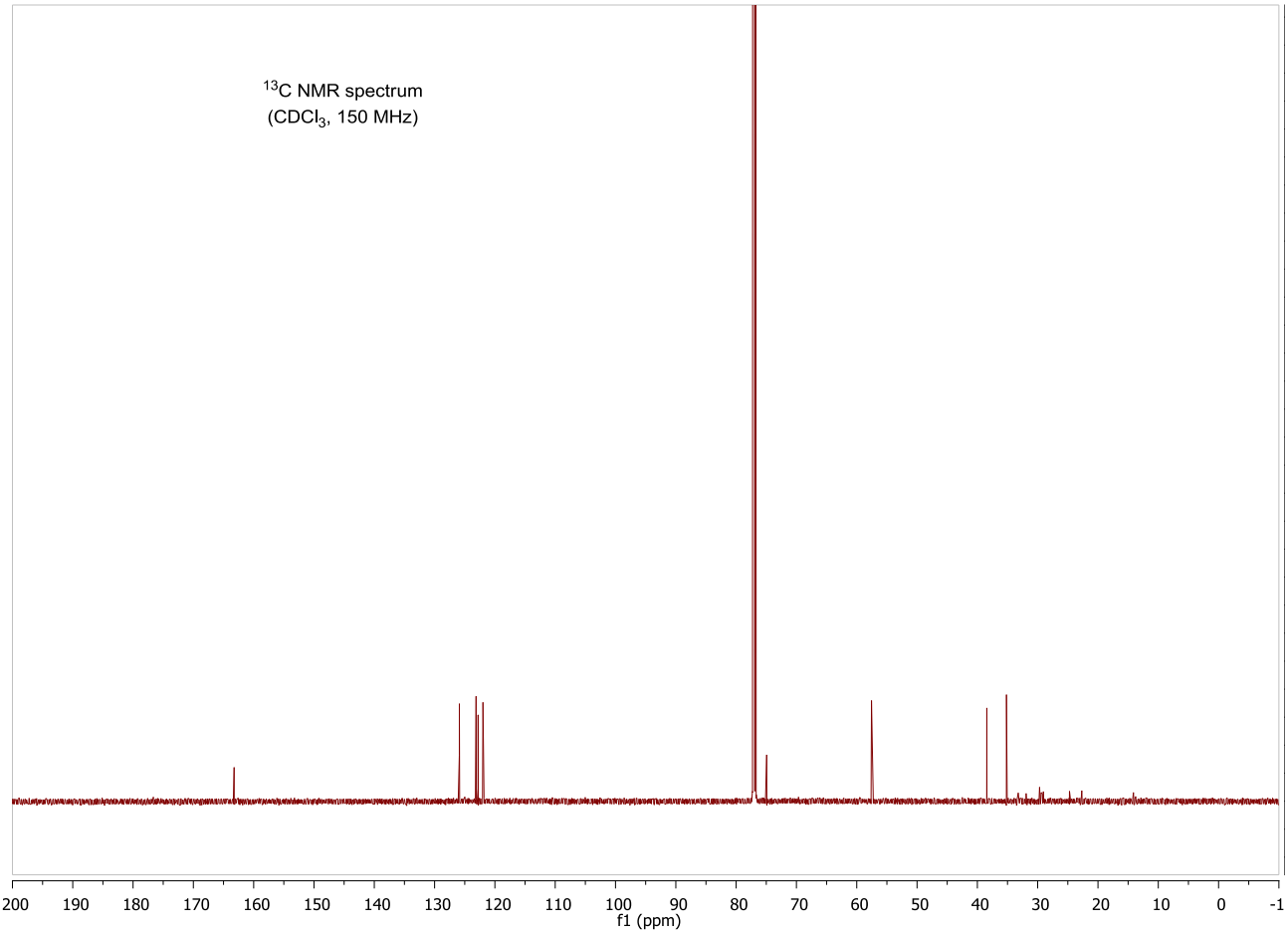


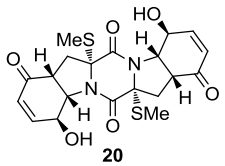
2,2'-*epi*-**19**

^{1}H NMR spectrum
($CDCl_3$, 600 MHz)



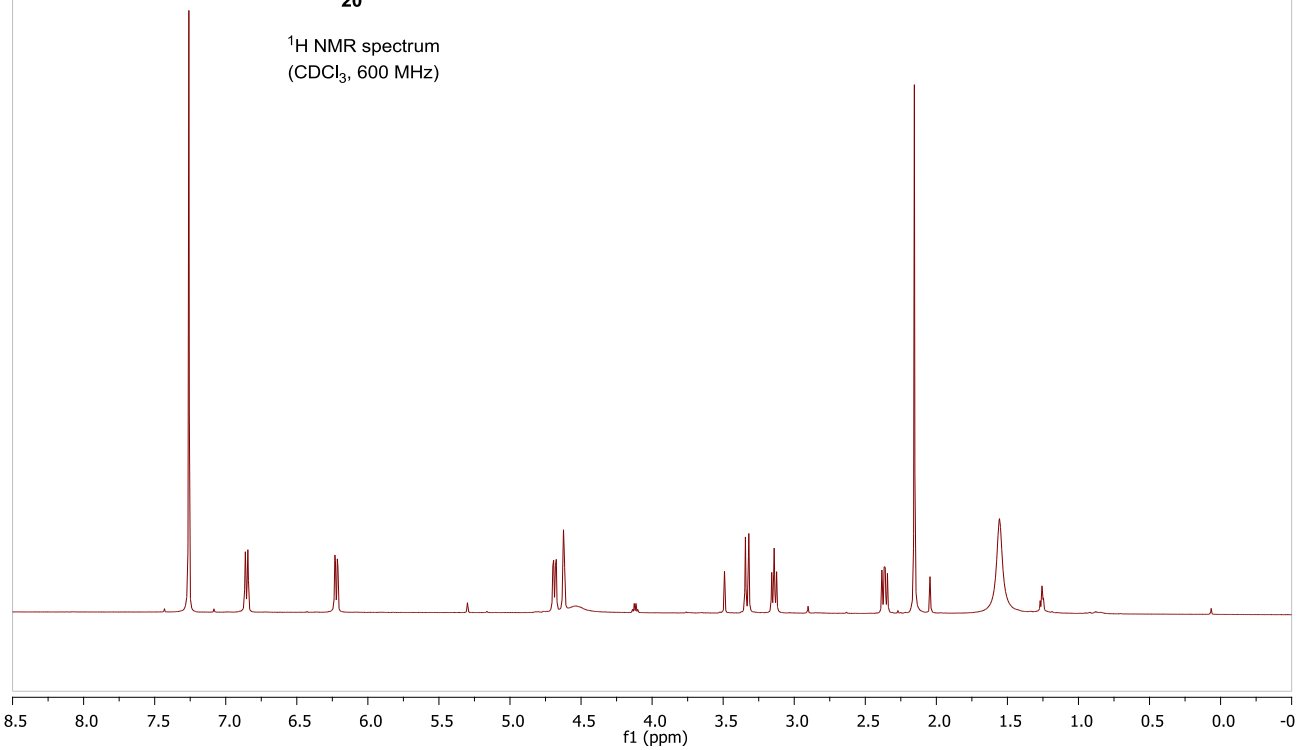
^{13}C NMR spectrum
($CDCl_3$, 150 MHz)



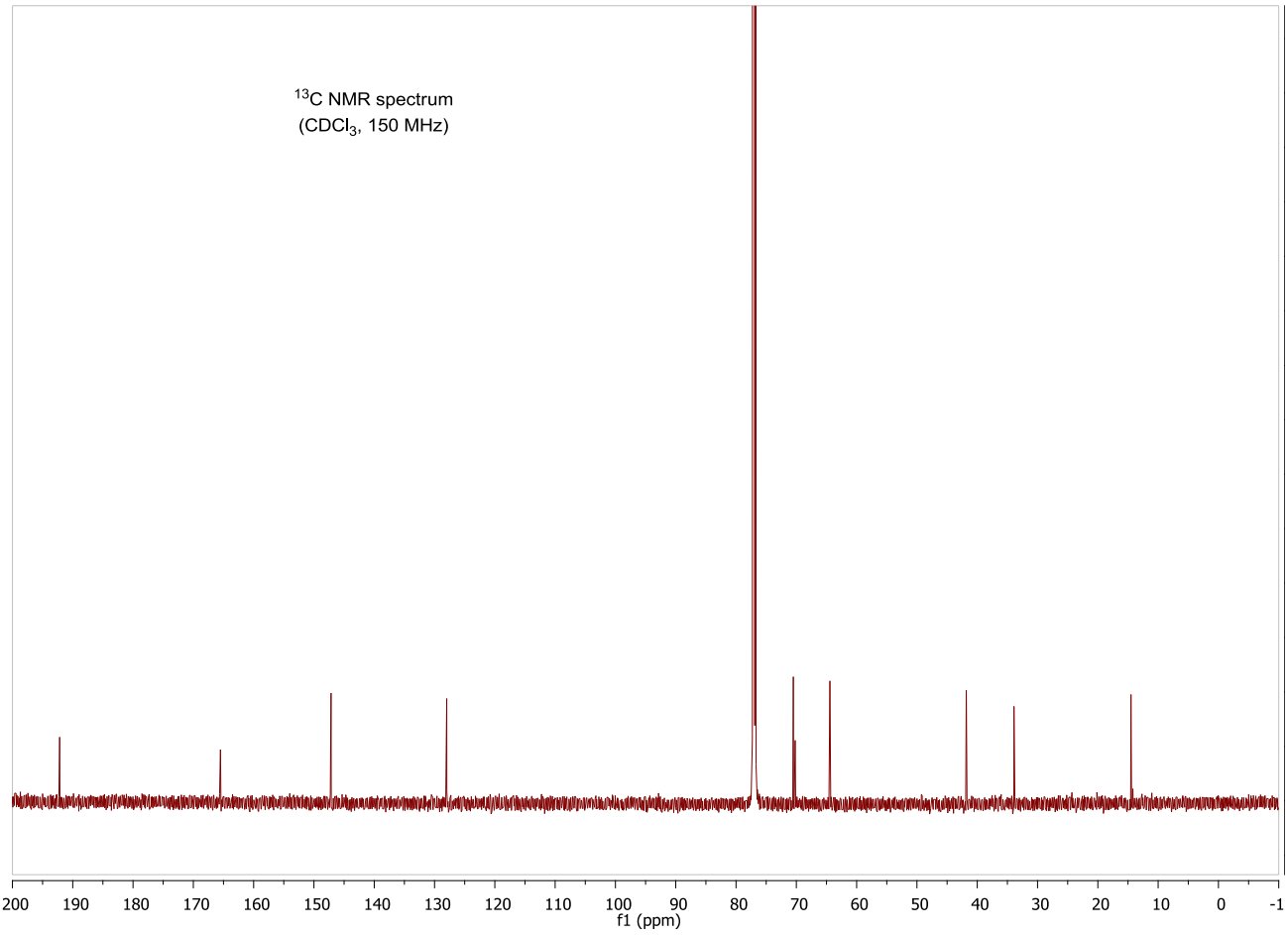


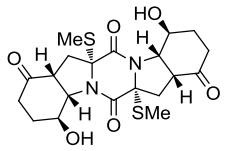
20

^{1}H NMR spectrum
($CDCl_3$, 600 MHz)



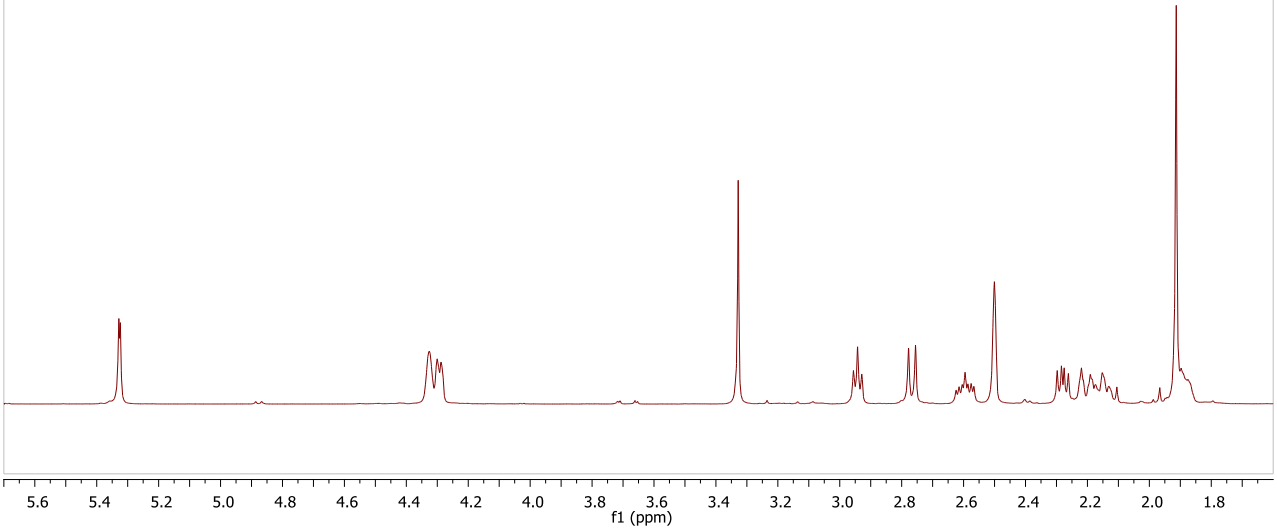
^{13}C NMR spectrum
($CDCl_3$, 150 MHz)



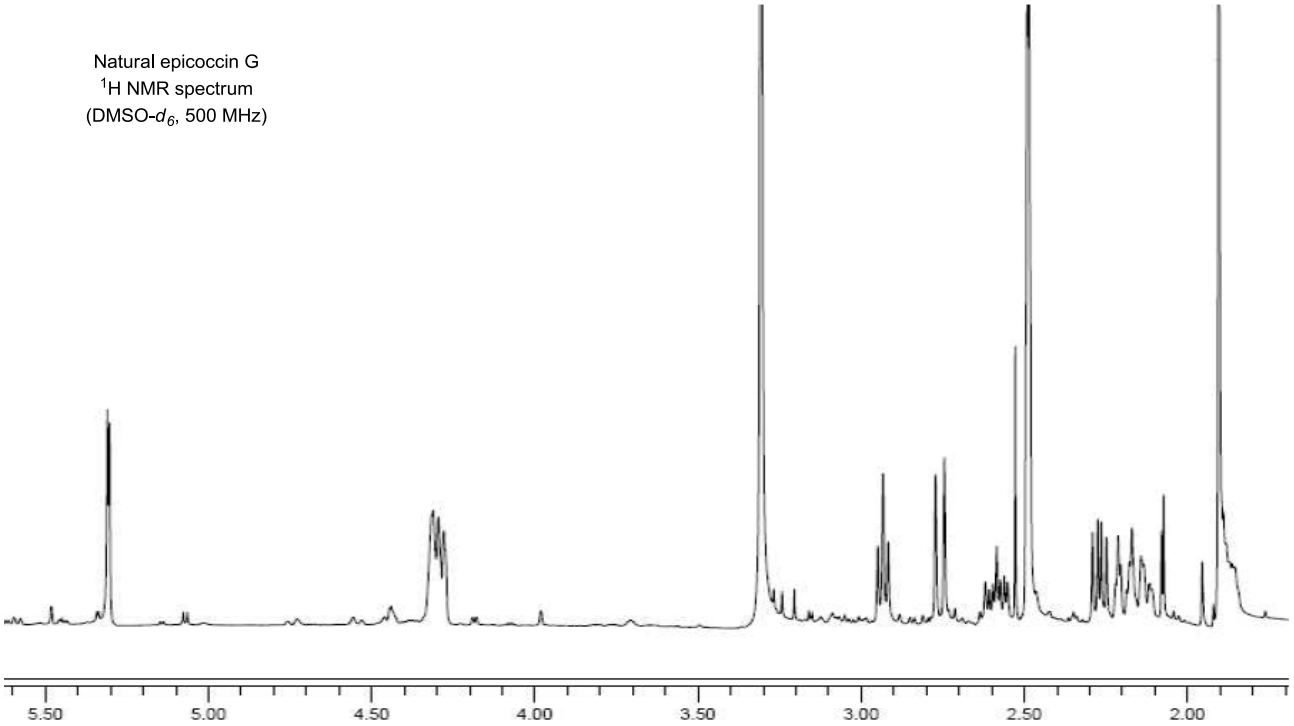


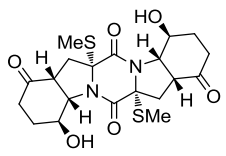
1: epicoccin G

Synthetic epicoccin G
^{1}H NMR spectrum
(DMSO-d_6, 600 MHz)



Natural epicoccin G
^{1}H NMR spectrum
(DMSO-d_6, 500 MHz)

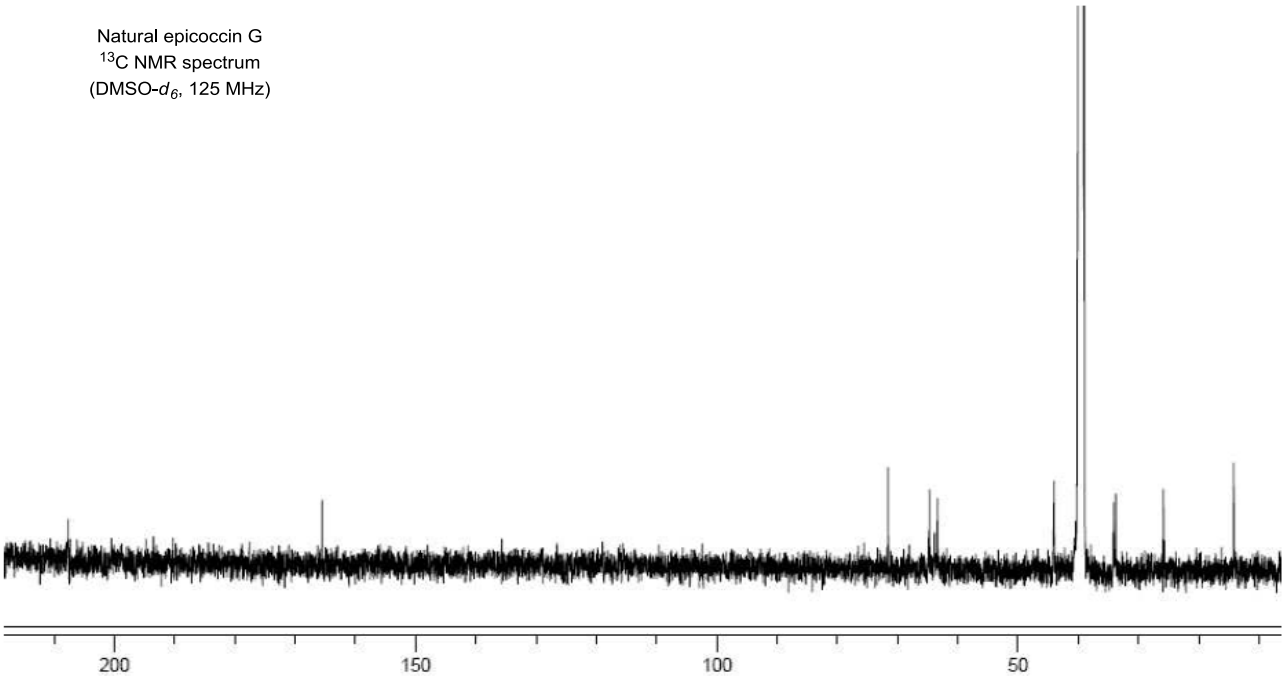


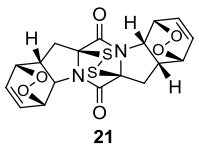


1: epicoccin G

Synthetic epicoccin G
^{13}C NMR spectrum
(DMSO-d_6, 150 MHz)

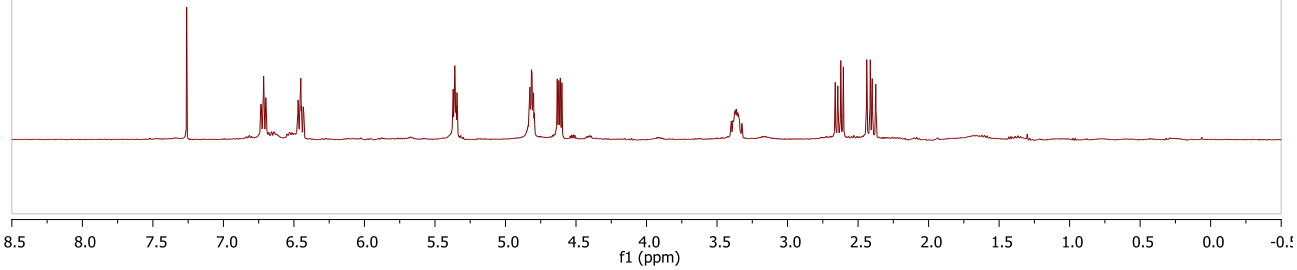
Natural epicoccin G
^{13}C NMR spectrum
(DMSO-d_6, 125 MHz)



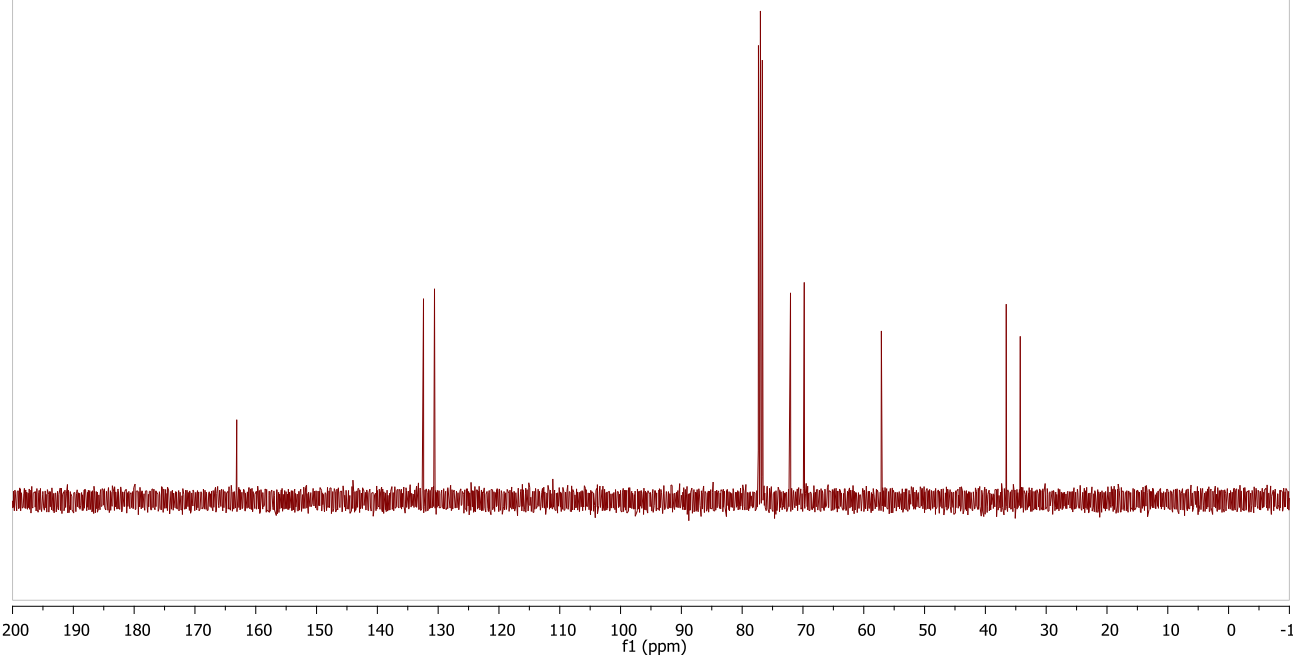


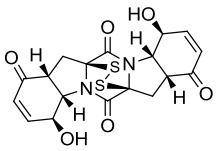
21

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



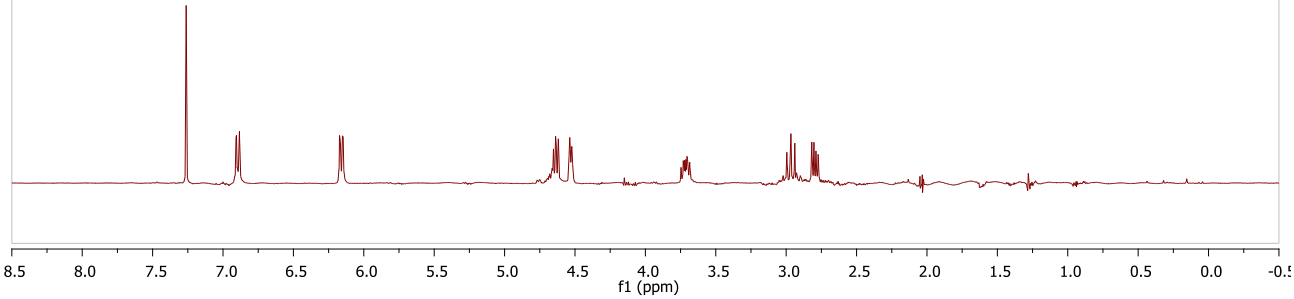
^{13}C NMR spectrum
($CDCl_3$, 125 MHz)



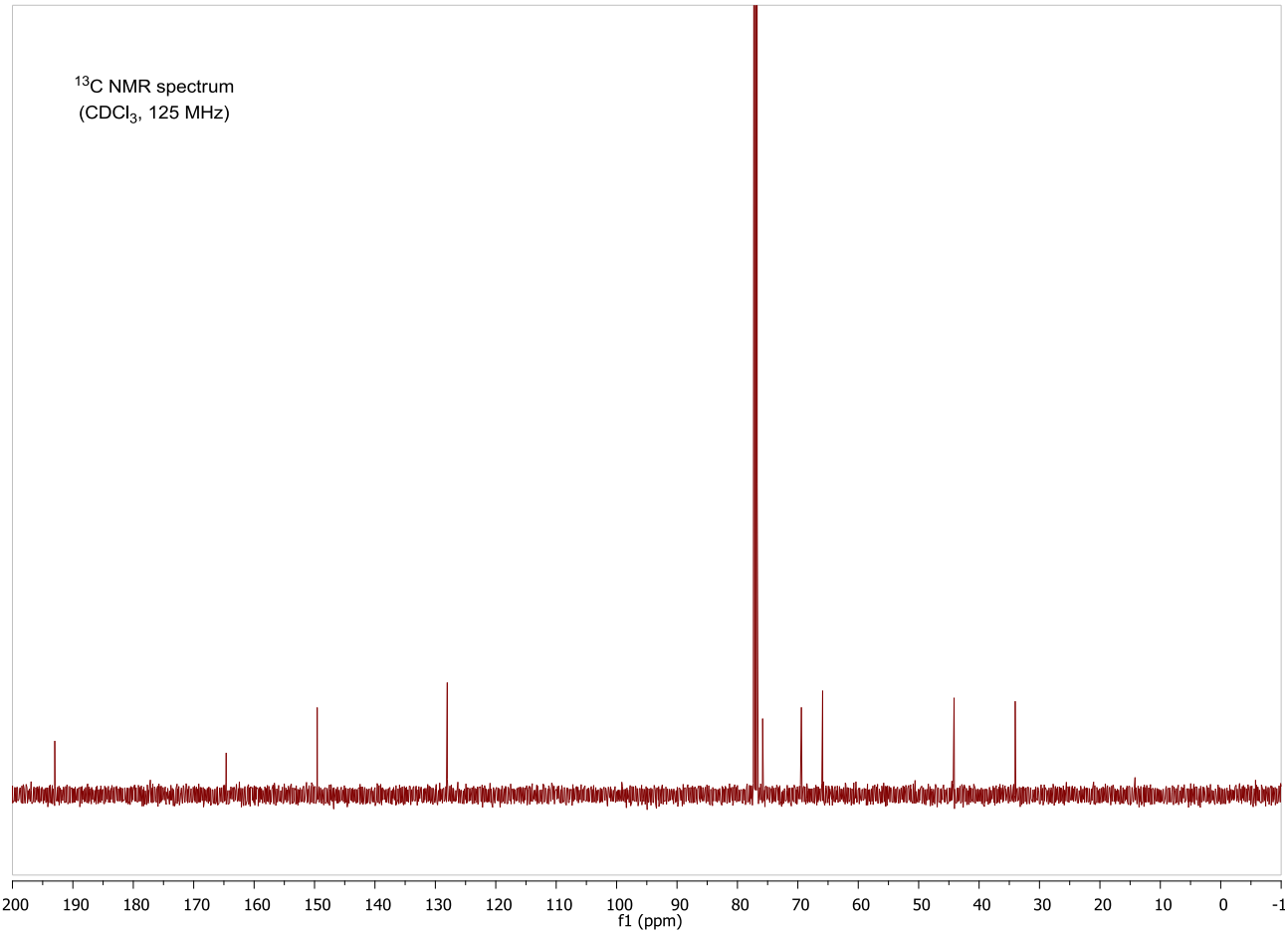


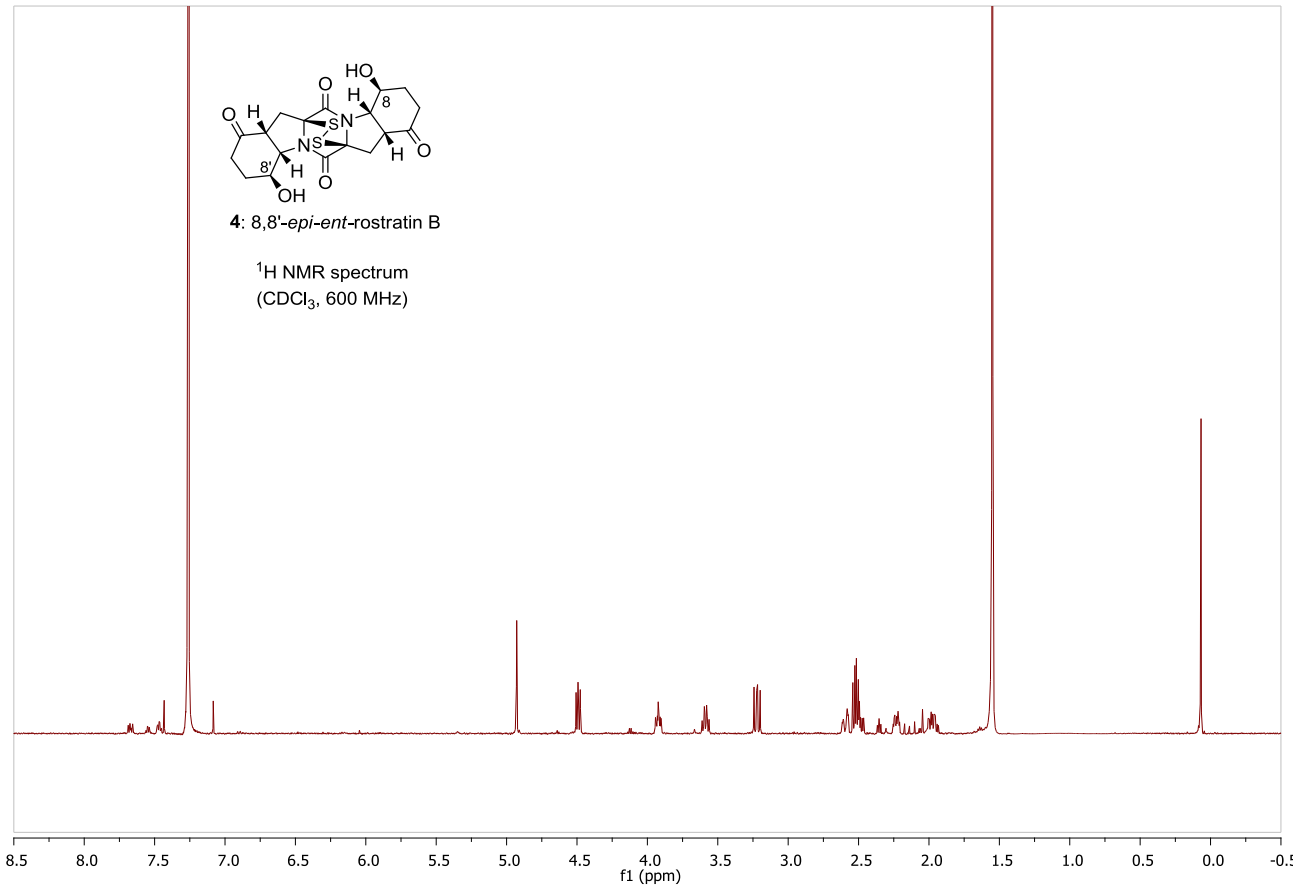
22

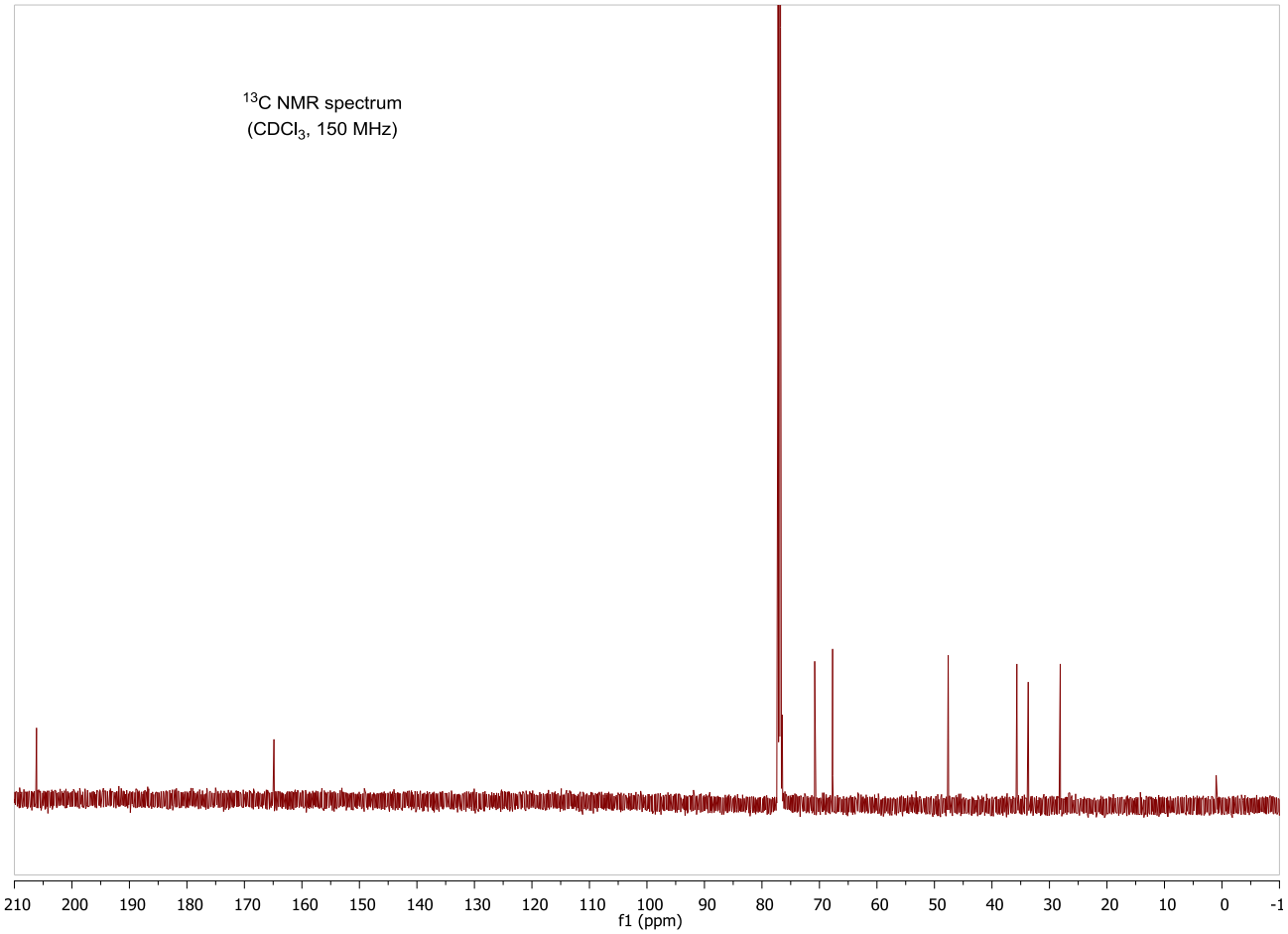
^{1}H NMR spectrum
($CDCl_3$, 500 MHz)



^{13}C NMR spectrum
($CDCl_3$, 125 MHz)




HO
H
8
O
H
O
S
N
N
S
H
O
8'
H
O
OH
4: 8,8'-epi-ent-rostratin B
1H NMR spectrum
(CDCl3, 600 MHz)
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
f1 (ppm)


13C NMR spectrum
(CDCl3, 150 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

III. References

(1) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477–5480.

(2) Middleton, M. D.; Peppers, B. P.; Diver, S. T. *Tetrahedron* **2006**, *62*, 10528–10540.

(3) (a) Guo, H.; Sun, B.; Gao, H.; Chen, X.; Liu, S.; Yao, X.; Liu, X.; Che, Y. *J. Nat. Prod.* **2009**, *72*, 2115–2119. (b) Wang, J.-M.; Ding, G.-Z.; Fang, L.; Dai, J.-G.; Yu, S.-S.; Wang, Y.-H.; Chen, X.-G.; Ma, S.-G.; Qu, J.; Xu, S.; Du, D. *J. Nat. Prod.* **2010**, *73*, 1240–1249.

(4) Lee, D.-W.; Yun, J. *Tetrahedron Lett.* **2005**, *46*, 2037–2039.