Supporting Information for:

The Total Synthesis of (+)-Dragmacidin F

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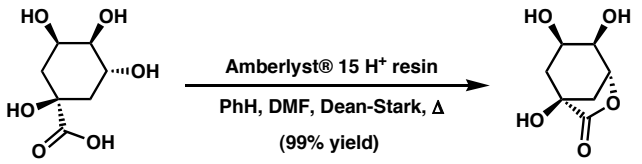
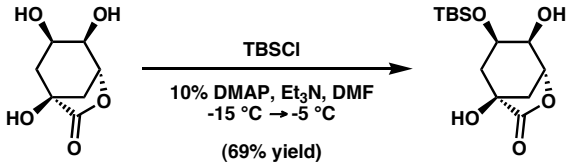
Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received. Reaction temperatures were controlled using an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, and potassium permanganate staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. Disposable Sep-Pak C_{18} Vac Cartridges were purchased from Waters and used for all reversed-phase filtrations. HPLC analysis was performed on a Beckman Gold system using a Rainin C_{18}, Microsorb MV, 5μm, 300 x 4.6 mm reversed-phased column in 0.1% (w/v) TFA with acetonitrile as eluent and a flow rate of 1.0 mL/min, gradient elution of 1.25% acetonitrile/min. Preparatory reversed-phase HPLC was performed on a Beckman HPLC with a Waters DeltaPak 25 x 100 mm, 100 μm C_{18} column equipped with a guard, 0.1% (w/v) TFA with acetonitrile as eluent, and gradient elution of 0.50% acetonitrile/min. For all reversed-phase purifications, water (18MΩ) was obtained from a Millipore MiliQ water purification system and TFA from Halocarbon, Inc. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz), a Varian Inova 500 (at 500 MHz), or a Varian Inova 600 (at 600 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz), or a Varian Inova 500 (at 125 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported

in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-1010 polarimeter. High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.



9 ***SM1***

Lactone SM1. A mixture of D-(–)-quinic acid (**9**) (50.0 g, 260.2 mmol), Amberlyst® 15 ion-exchange resin (7 g, 35 mmol), benzene (500 mL) and DMF (125 mL) was refluxed under a Dean-Stark trap for 16 h. The reaction mixture was cooled to 23 °C and filtered over a pad of Celite. The filtrate was then evaporated under reduced pressure to afford a thick oil, which was diluted with CH_2Cl_2 (150 mL). Hexanes (250 mL) was added and the resulting mixture was allowed to sit at 23 °C for 2 h. The product was collected by vacuum filtration, and was further dried *in vacuo* to afford lactone **SM1** (44.9 g, 99% yield) as a white powder. R_f 0.40 (3:1 EtOAc:acetone); characterization data for this compound have been previously reported.[1]

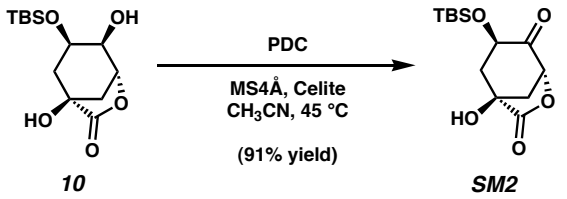


SM1 ***10***

TBS Lactone 10. To a mixture of lactone **SM1** (90.0 g, 517 mmol), DMAP (6.31 g, 51.7 mmol), triethylamine (90 mL, 646 mmol), and DMF (345 mL) at –15 °C was added TBSCl (84.9 g, 563 mmol) in 3 equal portions over 30 min. The temperature was maintained between –20 °C and –15 °C during the addition. The reaction mixture was allowed to warm to –5 °C over 3 h, quenched by the addition of 5% aq. citric acid (120 mL), and then warmed to 23 °C. The solvent was removed *in vacuo*, and the crude product was diluted with 5% aq. citric acid (350 mL) and extracted with Et_2O (1 x 500 mL, 2 x 400 mL). The combined organic layers were washed with H_2O (2 x 400 mL) and brine (400 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The product was triturated with hexanes (750 mL) and collected by vacuum filtration. It was further dried under vacuum to afford TBS lactone **10** (102.8 g, 69% yield) as a dry white

[1] Philippe, M.; Sepulchre, A. M.; Gero, S. D.; Loibner, H.; Streicher, W.; Stutz, P. *J. Antibiot.* **1982**, *35*, 1507-1512.

solid. R_f 0.48 (1:1 hexanes:EtOAc); R_f 0.28 (2:1 Et_2O:hexanes); characterization data for this compound have been previously reported.[2]



10 *SM2*

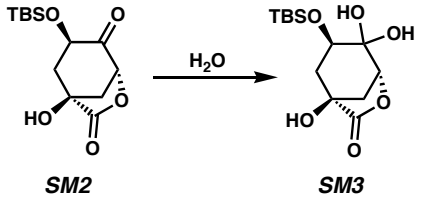
Keto Lactone SM2. A mixture of TBS lactone **10** (3.72 g, 12.90 mmol), powdered 4Å activated molecular sieves (2.79 g), Celite (2.79 g), pyridinium dichromate (12.13 g, 32.2 mmol), and acetonitrile (185 mL) was heated to 45 °C for 24 h. The reaction was allowed to cool to 23 °C, and then was filtered over a plug of silica gel topped with Celite (EtOAc eluent). The solvent was removed under reduced pressure to afford a brown oil, which was further purified by passage over a plug of silica gel (1:1 hexanes:EtOAc). Evaporating the solvent *in vacuo* afforded keto lactone **SM2** (3.35 g, 91% yield) as a pale yellow oil.

Alternate Procedure. Powdered 4Å activated molecular sieves (184.6 g) were agitated and flame-dried under vacuum for approximately 30 min until a fine, powder-like consistency was obtained. Upon cooling to 23 °C, CH_2Cl_2 (540 mL) was introduced and the slurry was cooled to 0 °C. Freshly prepared pyridinium dichromate[3] (148.7 g, 395.3 mmol) was added, and the resulting heterogeneous orange mixture was treated with TBS lactone **10** (70.04 g, 242.8 mmol) portionwise over 4 min. After the addition was complete, the reaction was stirred for 5 min and then freshly distilled AcOH (49.0 mL, 856.0 mmol) was added dropwise over a 20 min period. The reaction temperature was maintained at 0 °C for 15 min after the addition was complete, and was then stirred at 23 °C. After 10 h, the reaction was judged complete by ^{1}H NMR. The dark mixture was evenly divided into 3 portions, each of which was filtered over a pad of silica gel (10 cm diameter x 7.5 cm height, EtOAc eluent). The filtrates were combined and evaporated *in vacuo* to afford a dark liquid, and this residue was further coevaporated with toluene (3 x 150 mL). The crude product was diluted in a mixture of hexanes:EtOAc (10:1; 250 mL) and filtered over a pad of powdered Na_2SO_4 to remove insoluble impurities. The filtrate was evaporated, and dried *in vacuo*, to afford keto lactone **SM2** (55.27 g, 80% yield) as a brown,

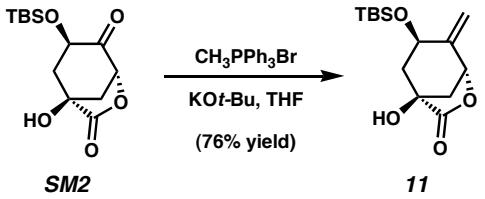
[2] Manthey, M. K.; González-Bello, C.; Abell, C. *J. Chem. Soc., Perkin Trans. 1*, **1997**, *5*, 625-628.
[3] Xiao, W. *Huaxue Shiji* **1992**, *14(6)*, 363-366.

waxy solid. This material was used immediately in the next step without further purification. *Unstable to TLC conditions*; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.71 (d, *J* = 6.6 Hz, 1H), 4.52 (dd, *J* = 10.3 Hz, 8.9 Hz, 1H), 2.95 (s, 1H), 2.88-2.79 (m, 1H), 2.57-2.47 (m, 1H), 2.39 (d, *J* = 12.4 Hz, 1H), 2.13 (dd, *J* = 12.4 Hz, 10.5 Hz, 1H), 0.88 (s, 9H), 0.11 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.6, 177.4, 79.0, 72.0, 70.6, 43.2, 42.6, 25.8 (3C), 18.5, -4.6, -5.3; IR (film): 3444 (br), 2931, 2858, 1799, 1753, 1254, 1144, 1111 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{13}H_{23}O_5Si$, 287.1315; found, 287.1316; $[\alpha]^{19}_D$ -96.47° (*c* 1.0, C_6H_6).

*NOTE: Exposure of keto lactone **SM2** to water (e.g. aqueous workup, or prolonged exposure to silica gel) led to the formation of hydrate **SM3**, as a white powder.*



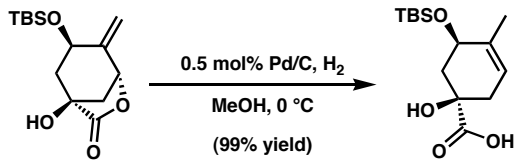
Unstable to TLC conditions; mp 104-6 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 4.46 (d, *J* = 5.8 Hz, 1H), 3.75 (dd, *J* = 10.7 Hz, 7.0 Hz, 1H), 2.48-2.31 (comp. m, 2H), 2.10-2.00 (m, 1H), 1.76 (app. t, *J* = 11.4 Hz, 1H), 0.93 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD): δ 179.4, 93.2, 81.8, 73.0, 72.3, 41.5, 40.9, 26.5 (3C), 19.1, -4.3, -4.7; IR (KBr): 3440 (br), 3374 (br), 2929, 2858, 1782, 1256, 1108, 1070 cm^{-1}; HRMS-CI (*m/z*): $[M + H]^+$ calc'd for $C_{13}H_{24}O_6Si$, 304.1342; found, 304.1336; $[\alpha]^{19}_D$ -54.29° (*c* 1.0, MeOH).



Methylene Lactone 11. To CH_3PPh_3Br (105 mg, 0.293 mmol) in THF (2.8 mL) at 0 °C was added potassium *t*-butoxide (31.3 mg, 0.279 mmol). The mixture was warmed to 23 °C and stirred for an additional 10 min. Keto lactone **SM2** (40 mg, 0.140 mmol) in THF (1 mL) was added and stirring was continued at 23 °C for 15 min. The reaction mixture was then refluxed for 2 h and cooled to 23 °C. The solvent was removed under reduced pressure and the residue was partitioned between Et_2O (3 mL) and brine (1.5 mL). The layers were separated and the aqueous

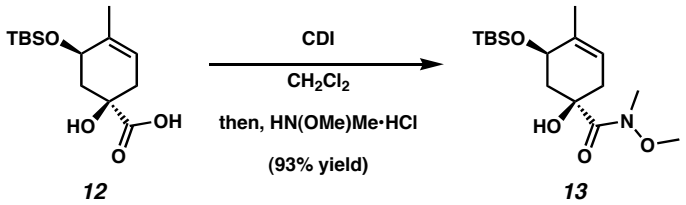
layer was further extracted with Et_2O (3 x 1 mL). The combined organic layers were washed with brine (1.5 mL), dried by passage over a plug of silica gel (Et_2O eluent, then 2:1 hexanes:EtOAc eluent), and evaporated under reduced pressure. The crude product was purified by flash chromatography (2:1 hexanes:EtOAc) to afford methylene lactone **11** (30 mg, 76% yield) as a white solid.

Alternate Procedure. To CH_3PPh_3Br (82.9 g, 232.1 mmol) in THF (1.10 L) at 23 °C was added potassium *t*-butoxide (23.8 g, 212.1 mmol) in one portion. The mixture was stirred for 2 h, then cooled to 0 °C. Keto lactone **SM2** (54.5 g, 190.3 mmol) in THF (240 mL) was added dropwise over a 30 min period. The reaction was allowed to warm slowly to 23 °C over 9 h, then quenched by the addition of ice-cold 15% aq. NH_4Cl (500 mL). The solvent was evaporated under reduced pressure, and the residue was partitioned between Et_2O (500 mL) and H_2O (100 mL). The aqueous phase was extracted with Et_2O (3 x 250 mL) and the combined organics were washed with H_2O (100 mL) and brine (100 mL), and dried over $MgSO_4$. Evaporation of the solvent afforded a crude yellow oil, which was filtered over a plug of silica gel (4:1 pentane:Et_2O → 3:2 pentane:Et_2O eluent). After evaporating the solvent *in vacuo*, the residue was triturated with ice-cold pentane (40 mL). The white solid was filtered, and washed with ice-cold pentane (2 x 2 mL). A second crop was collected from the filtrate after concentrating its volume to 15 mL. Drying the collected material *in vacuo* afforded methylene lactone **11** (22.1 g, 41% yield) as a white solid. R_f 0.59 (1:1 hexanes:EtOAc); mp 87-88 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.25-5.23 (m, 1H), 5.13-5.10 (m, 1H), 5.07 (d, J = 6.0 Hz, 1H), 4.38-4.29 (m, 1H), 2.85 (s, 1H), 2.67-2.59 (m, 1H), 2.31-2.21 (m, 1H), 2.09 (d, J = 11.5 Hz, 1H), 1.86 (app. t, J = 11.3 Hz, 1H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.1, 144.8, 111.0, 79.4, 73.1, 67.1, 44.7, 44.7, 26.0 (3C), 18.5, -4.5, -4.7; IR (film): 3426 (br), 2956, 2931, 2858, 1791, 1254, 1120, 1071 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{14}H_{25}O_4Si$, 285.1522; found, 285.1519; $[\alpha]^{19}_D$ -101.71° (*c* 1.0, $CHCl_3$).



11 *12*

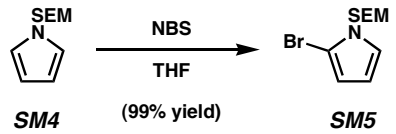
Acid 12. A mixture of methylene lactone **11** (4.0 g, 14.1 mmol) and 10% Pd/C (80 mg, 0.075 mmol) in methanol (120 mL) was cooled to 0 °C. The reaction vessel was evacuated and back-filled with H_2 (3x). After 7 h at 0 °C, the mixture was filtered over a pad of Celite (MeOH eluent) and the solvent was evaporated under reduced pressure to afford a colorless oil. Residual solvent was removed by holding the crude product under vacuum for 10 h, providing acid **12** (4.0 g, 99% yield), which was used immediately without further purification. R_f 0.28 (1:1 hexanes:EtOAc;1% acetic acid); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (s, 1H), 5.53-5.48 (m, 1H), 4.16-4.11 (m, 1H), 2.71-2.60 (m, 1H), 2.36-2.22 (m, 1H), 2.18 (dd, *J* = 14.3 Hz, 3.9 Hz, 1H), 2.08-2.01 (m, 1H), 1.79-1.76 (m, 3H), 0.89 (s, 9H), 0.15-0.13 (comp. m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.4, 133.2, 121.1, 73.6, 68.6, 37.9, 35.9, 25.8 (3C), 21.4, 18.0, -4.5, -4.7; IR (film): 3356 (br), 2956, 2931, 2858, 1768 (br), 1718 (br), 1255, 1063 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{14}H_{27}O_4Si$, 287.1679; found, 287.1675; $[\alpha]^{19}_D$ +37.58° (*c* 1.0, C_6H_6).



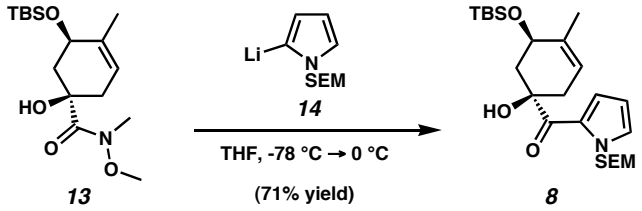
12 *13*

Weinreb Amide 13. To acid **12** (4.0 g, 14.1 mmol) in CH_2Cl_2 (70 mL) at 23 °C was added 1,1'-carbonyldiimidazole (3.65 g, 22.5 mmol) in equal portions over 15 min. After the final addition, stirring was continued for 10 min, then *N,O*-dimethylhydroxylamine • HCl (3.43 g, 35.16 mmol) was added in one portion. The reaction was allowed to stir at 23 °C for 3 h. Et_2O was added (50 mL) and the reaction mixture was filtered. The filtrate was evaporated, diluted with Et_2O (125 mL), washed with 5% aq. citric acid (2 x 50 mL) and brine (50 mL), and dried over $MgSO_4$. The crude product was purified by flash chromatography (3:1 hexanes:EtOAc) to afford Weinreb amide **13** (4.29 g, 93% yield) as a colorless oil. R_f 0.42 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.43 (m, 1H), 4.72 (s, 1H), 4.17-4.11 (m, 1H), 3.71 (s, 3H), 3.22 (s,

3H), 2.59-2.24 (comp. m, 3H), 2.03 (dd, J = 14.6 Hz, 4.1 Hz, 1H), 1.75-1.71 (m, 3H), 0.86 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 15/16 C): δ 133.5, 121.5, 74.3, 69.4, 61.2, 38.1, 35.9, 26.0, 25.9 (3C), 21.3, 18.1, -4.3, -4.7; IR (film): 3463 (br), 2956, 2932, 2858, 1655, 1362, 1254 cm^{-1}; HRMS-EI (*m/z*): $[M + H]^+$ calc'd for $C_{16}H_{32}NO_4Si$, 330.2101; found, 330.2085; $[\alpha]^{19}_D$ +41.13° (*c* 1.0, $CHCl_3$).



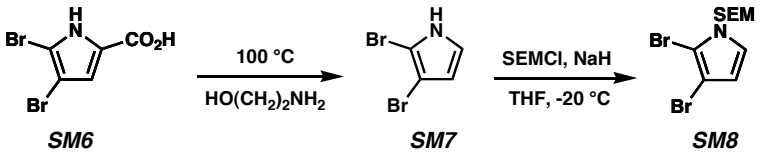
Bromopyrrole SM5. To SEM pyrrole **SM4**[4] (1.25 g, 6.33 mmol) in THF (125 mL) at 23 °C was added freshly recrystallized NBS (1.127 g, 6.33 mmol) in one portion. After stirring for 5 min, additional NBS was added (15 mg, 0.084 mmol) and the reaction was immediately judged complete by TLC. The reaction mixture was poured into saturated aq. $NaHCO_3$ (100 mL) and extracted with Et_2O (1 x 100 mL, 2 x 50 mL). The combined organic layers were washed with brine (75 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by passage over a plug of silica gel (CH_2Cl_2 eluent) to afford bromopyrrole **SM5** (1.73 g, 99% yield) as a pale yellow oil. R_f 0.53 (1:1 CH_2Cl_2:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.83 (app. t, J = 2.5 Hz, 1H), 6.18-6.16 (comp. m, 2H), 5.22 (s, 2H), 3.53-3.46 (m, 2H), 0.92-0.85 (m, 2H), -0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 122.9, 111.9, 110.1, 102.0, 76.7, 66.0, 17.9, -1.2 (3C); IR (film): 2953, 2895, 1264, 1249, 1108, 1085 cm^{-1}; HRMS-EI (*m/z*): $[M + H]^+$ calc'd for $C_{10}H_{18}NOSiBr$, 275.0341; found, 275.0331.



Acyl Pyrrole 8. To bromopyrrole **SM5** (1.73 g, 6.26 mmol) in THF (42 mL) at –78 °C was added *n*-BuLi (2.25 M in hexanes, 2.7 mL, 6.16 mmol) dropwise over 1 min. After 10 min at –78 °C, Weinreb amide **13** (655 mg, 1.99 mmol) in THF (5 mL) was added dropwise over 1 min.

[4] Muchowski, J. M.; Solas, D. R. *J. Org. Chem*. **1984**, *49*, 203-205.

The reaction vessel was immediately warmed to 0 °C, stirred for 25 min, and cooled to –78 °C. The reaction mixture was quenched with saturated aq. NH_4Cl (10 mL), then warmed to 23 °C. The volatiles were removed under reduced pressure. The residue was partitioned between Et_2O (75 mL) and H_2O (50 mL) and the layers were separated. The aqueous layer was further extracted with Et_2O (2 x 40 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (23:1 hexanes:EtOAc, then 15:1 hexanes:EtOAc) to afford acyl pyrrole **8** (656 mg, 71% yield) as a colorless oil. R_f 0.30 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (dd, *J* = 4.0 Hz, 1.7 Hz, 1H), 7.06 (dd, *J* = 2.5 Hz, 1.7 Hz, 1H), 6.19 (dd, *J* = 4.0 Hz, 2.5 Hz, 1H), 5.71 (d, *J* = 10.4 Hz, 1H), 5.67 (d, *J* = 10.0 Hz, 1H), 5.52-5.47 (m, 1H), 4.90 (s, 1H), 4.19 (app. t, *J* = 3.1 Hz, 1H), 3.51 (t, *J* = 8.3 Hz, 2H), 2.52-2.46 (comp. m, 2H), 2.19-2.16 (comp. m, 2H), 1.80-1.78 (m, 3H), 0.92-0.88 (comp. m, 11H), 0.13 (s, 6H), -0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 22/24 C): δ 193.7, 133.5, 129.9, 128.0, 123.8, 121.7, 109.0, 78.2, 69.4, 66.3, 38.6, 38.3, 26.0 (3C), 21.5, 18.1, -1.2 (3C), -4.2, -4.7; IR (film): 3476, 2954, 2931, 2859, 1639, 1412, 1310, 1251, 1085 cm^{-1}; HRMS-EI (*m/z*): $[M + H]^+$ calc'd for $C_{24}H_{44}NO_4Si_2$, 466.2809; found, 466.2822; $[\alpha]^{19}_D$ +34.25° (*c* 1.0, C_6H_6).



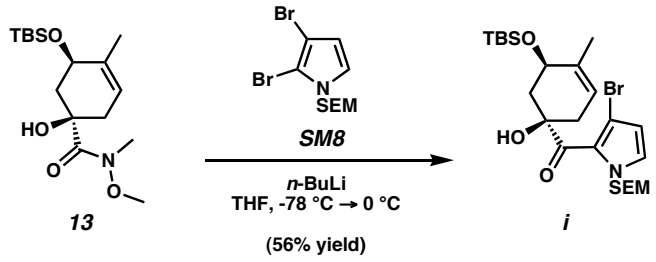
Dibromopyrrole SM8. A solution of 4,5-dibromopyrrole carboxylic acid (**SM6**)[5] (6.05 g, 22.5 mmol) in ethanolamine (36 mL) was heated to 100 °C for 2 h, cooled to 23 °C, and poured into a mixture of Et_2O (200 mL) and 0.5 N aq. HCl (300 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 250 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, and concentrated to 100 mL. The solution was diluted with hexanes (100 mL), filtered over a plug of silica gel (2:1 hexanes:Et_2O), and concentrated to 150 mL. THF (100 mL) was added, and the solution was concentrated to 100 mL. This solvent exchange procedure was repeated 2 additional times (2 x 100 mL THF) to

[5] Bailey, D. M.; Johnson, R. E. *J. Med. Chem.* **1973**, *16*, 1300-1302.

afford 2,3-dibromopyrrole (**SM7**) as a solution in THF which was used immediately in the subsequent reaction.

> *CAUTION: Concentrating the above described solutions to dryness or near-dryness leads to rapid decomposition of 2,3-dibromopyrrole (**SM7**).*[6]

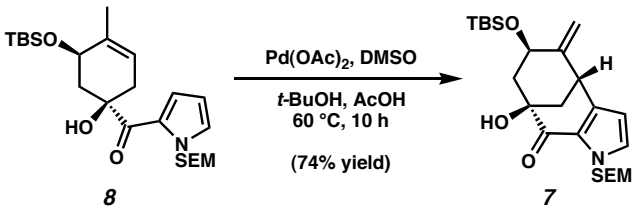
To 2,3 dibromopyrrole (**SM7**) in THF at –20 °C was added NaH (60% dispersion in mineral oil, 1.51 g, 37.8 mmol) in 3 equal portions over 3 min. After 10 min at –20 °C, SEMCl (4.8 mL, 27.1 mmol) was added dropwise over 1 min. The reaction mixture was allowed to warm to –8 °C over 40 min and was then quenched with saturated aq. NH_4Cl (30 mL). After warming to 23 °C, the reaction mixture was diluted with Et_2O (75 mL) and H_2O (20 mL) and the layers were separated. The aqueous layer was further extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (6:1 hexanes:CH_2Cl_2, then 4:1 hexanes:CH_2Cl_2) to afford dibromopyrrole **SM8** (6.25 g, 79% yield) as a yellow oil. R_f 0.17 (6:1 hexanes:CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.82 (d, J = 3.6 Hz, 1H), 6.25 (d, J = 3.3 Hz, 1H), 5.21 (s, 2H), 3.48 (t, J = 8.1 Hz, 2H), 0.88 (t, J = 8.1 Hz, 2H), -0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 123.1, 112.3, 103.7, 99.8, 77.8, 66.2, 17.9, -1.2 (3C); IR (film): 2953, 2896, 1514, 1470, 1279, 1250, 1109, 1084 cm^{-1}; HRMS-EI (*m/z*): [M + H]$^+$ calc'd for $C_{10}H_{17}NOSiBr_2$, 352.9446; found, 352.9435.



Bromo Acyl Pyrrole i. To dibromopyrrole **SM8** (6.02 g, 17.06 mmol) in THF (114 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 6.7 mL, 16.8 mmol) dropwise over 1 min. After 10 min at –78 °C, Weinreb amide **13** (1.58 g, 4.80 mmol) in THF (15 mL) was added dropwise over 30 seconds. The reaction vessel was immediately warmed to 0 °C, stirred for 90 min, and cooled to –78 °C. The reaction was quenched with saturated aq. NH_4Cl (15 mL), then warmed to 23 °C. The volatiles were removed *in vacuo*, and the residue was partitioned between Et_2O (75

[6] Audebert, P.; Bidan, G. *Synthetic Metals* **1986**, *15*, 9-22.

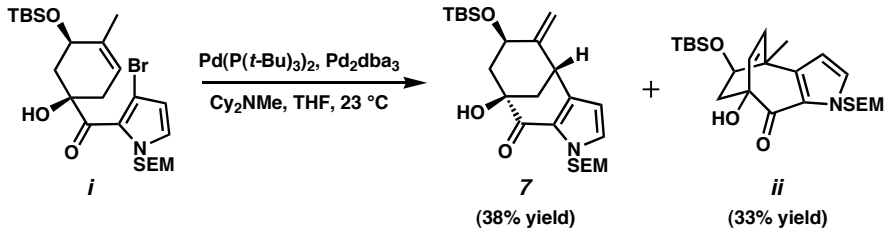
mL) and H_2O (30 mL). The layers were separated, and the aqueous layer was further extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (11:9 CH_2Cl_2:hexanes) to afford bromo acyl pyrrole **i** (1.47 g, 56% yield) as a colorless oil. R_f 0.29 (11:9 hexanes:CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.77 (d, *J* = 2.9 Hz, 1H), 6.20 (d, J= 2.7 Hz, 1H), 5.53-5.47 (m, 1H), 5.35 (d, *J* = 10.4 Hz, 1H), 5.29 (d, *J* = 10.4 Hz, 1H), 4.72 (s, 1H), 4.18-4.14 (m, 1H), 3.31 (t, *J* = 8.2 Hz, 2H), 2.65-2.53 (m, 1H), 2.53-2.41 (m, 1H), 2.32 (dt, *J* = 14.3 Hz, 1.7 Hz, 1H), 2.15 (dd, *J* = 14.2 Hz, 4 Hz, 1H), 1.79-1.76 (m, 3H), 0.87 (s, 9H), 0.81 (t, *J* = 8.2 Hz, 2H), 0.12 (s, 6H), -0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.9, 133.2, 129.6, 125.0, 121.6, 112.5, 101.8, 78.9, 78.6, 68.9, 66.2, 38.6, 37.4, 26.0 (3C), 21.5, 18.1, 17.8, -1.2 (3C), -4.1, -4.7; IR (film): 3477 (br), 2953, 1664 (br), 1400, 1253, 1101 cm^{-1}; HRMS-EI (*m/z*): $[M + H]^+$ calc'd for $C_{24}H_{43}NO_4Si_2Br$, 544.1914; found, 544.1903; $[\alpha]^{19}_D$ +1.64° (*c* 1.0, $CHCl_3$).



8 *7*

[3.3.1] Bicycle 7. To acyl pyrrole **8** (106.0 mg, 0.227 mmol) was added $Pd(OAc)_2$ (51.1 mg, 0.227 mmol), DMSO (32.3 μL, 0.455 mmol), *t*-BuOH (18.2 mL), and AcOH (4.5 mL). The mixture was heated to 60 °C for 10 h, cooled to 23 °C, and filtered over a plug of silica gel (3:1 hexanes:EtOAc). The solvent was evaporated, and the residue was again filtered over a plug of silica gel (3:1 hexanes:EtOAc). After removal of solvent *in vacuo*, the product was purified by flash chromatography on silica gel (6:1 hexanes:EtOAc) to afford [3.3.1] bicycle **7** (78.4 mg, 74% yield) as a pale yellow oil. R_f 0.20 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07 (d, *J* = 2.7 Hz, 1H), 6.05 (d, *J* = 2.7 Hz, 1H), 5.71 (d, *J* = 9.9 Hz, 1H), 5.58 (d, *J* = 9.9 Hz, 1H), 5.09-5.05 (m, 2H), 4.00 (s, 1H), 3.99-3.90 (m, 1H), 3.84 (app. t, *J* = 3.0 Hz, 1H), 3.55-3.47 (m, 2H), 2.39 (app. dt, *J* = 7.4 Hz, 3.8 Hz, 1H), 2.13-2.03 (comp. m, 2H), 1.73 (app. t, *J* = 11.8 Hz, 1H), 0.98-0.76 (comp. m, 11H), -0.04 (s, 9H), -0.11 (s, 6H); ^{1}H NMR (300 MHz, C_6D_6): δ 6.53 (d, *J* = 2.5 Hz, 1H), 5.77 (d, *J* = 2.8 Hz, 1H), 5.55 (d, *J* = 10.2 Hz, 1H), 5.32 (app. t, *J* = 1.9

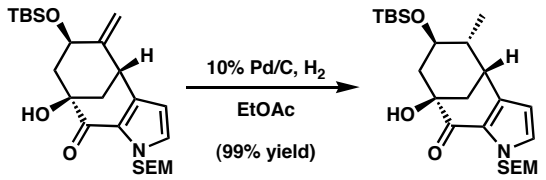
Hz, 1H), 5.26 (d, *J* = 10.2 Hz, 1H), 5.01-4.97 (m, 1H), 4.29 (s, 1H), 4.27-4.19 (m, 1H), 3.59-3.47 (comp. m, 3H), 2.45-2.31 (comp. m, 2H), 2.16 (dd, *J* = 12.1 Hz, 3.0 Hz, 1H), 2.07 (app. t, *J* = 11.8 Hz, 1H), 0.92-0.89 (comp. m, 11H), 0.01 (s, 9H), -0.06 (s, 3H), -0.07 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 191.5, 149.4, 141.8, 132.0, 125.5, 108.5, 107.4, 76.8, 75.8, 68.4, 66.3, 48.9, 45.5, 40.7, 26.3 (3C), 18.8, 18.2, -0.8 (3C), -4.4, -4.7; IR (film): 3480, 2953, 2858, 1651, 1420, 1318, 1251, 1100, 1077 cm^{-1}; HRMS-FAB (*m/z*): $[M]^+$ calc'd for $C_{24}H_{41}NO_4Si_2$, 463.2574; found, 463.2577; $[\alpha]^{23}_D$ -275.07° (*c* 1.0, $CHCl_3$).



Alternate Procedure. Bromo acyl pyrrole **i** (52.0 mg, 0.0955 mmol), Pd_2dba_3 (21.9 mg, 0.0239 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (24.4 mg, 0.0477 mmol), THF (1.2 mL), and Cy_2NMe (24.3 μL, 0.115 mmol) were combined under a glovebox atmosphere and stirred at 23 °C for 10 h. The reaction vessel was removed from the glovebox, diluted with 3:1 hexanes:EtOAc (2 mL), and filtered over a plug of silica gel topped with Celite (3:1 hexanes:EtOAc eluent). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (CH_2Cl_2, then 3:1 hexanes:EtOAc). The crude product was further purified by flash chromatography (6:1 hexanes:EtOAc) to afford [3.3.1] bicycle **7** (16.7 mg, 38% yield) and [3.2.2] bicycle **ii** (14.4 mg, 33% yield), both as pale yellow oils.

*[3.2.2] Bicycle **ii**:* R_f 0.42 (5:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.98 (d, *J* = 2.7 Hz, 1H), 6.15 (d, *J* = 2.7 Hz, 1H), 6.02 (d, *J* = 9.3 Hz, 1H), 5.98 (d, *J* = 8.8 Hz, 1H), 5.69 (d, *J* = 9.9 Hz, 1H), 5.62 (d, *J* = 9.9 Hz, 1H), 4.93 (s, 1H), 3.81 (d, *J* = 7.7 Hz, 1H), 3.50 (t, *J* = 8.0 Hz, 2H), 2.36 (dd, *J* = 14.3 Hz, 7.7 Hz, 1H), 1.94 (dd, *J* = 14.3 Hz, 1.6 Hz, 1H), 1.55 (s, 3H), 0.91-0.83 (comp. m, 11H), 0.02 (s, 3H), 0.01 (s, 3H), -0.07 (s, 9H); ^{1}H NMR (300 MHz, C_6D_6): δ 6.55 (d, *J* = 2.7 Hz, 1H), 6.23 (d, *J* = 8.8 Hz, 1H), 5.96 (d, *J* = 3.3 Hz, 1H), 5.94 (d, *J* = 9.2 Hz, 1H), 5.59 (d, *J* = 10.4 Hz, 1H), 5.40 (d, *J* = 9.9 Hz, 1H), 5.32 (s, 1H), 3.82-3.75 (m, 1H), 3.46 (t, *J* = 7.7 Hz, 2H), 2.46 (dd, *J* = 13.7 Hz, 7.7 Hz, 1H), 2.25 (dd, *J* = 13.7 Hz, 1.6 Hz, 1H), 1.52 (s, 3H),

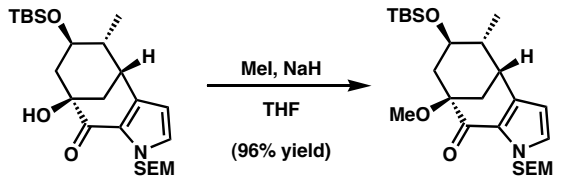
0.92 (s, 9H), 0.82 (t, *J* = 8.0 Hz, 2H), -0.03 (s, 3H), -0.08 (s, 3H), -0.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.7, 144.1, 139.4, 134.5, 129.1, 121.8, 107.7, 78.2, 77.8, 73.3, 66.4, 45.7, 45.0, 26.0 (3C), 22.2, 18.2, 18.0, -1.25 (3C), -4.1, -4.6; IR (film): 3432, 2955, 2858, 1645, 1250, 1081 cm^{-1}; HRMS-EI (*m/z*): $[M + H]^+$ calc'd for $C_{24}H_{42}NO_4Si_2$, 464.2652; found, 464.2665; $[\alpha]^{19}_D$ +19.22° (*c* 1.0, C_6H_6).



7 ***SM9***

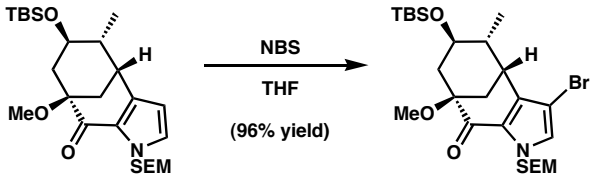
Reduced [3.3.1] Bicycle SM9. [3.3.1] bicycle **7** (360 mg, 0.78 mmol), 10% Pd/C (130 mg, 0.12 mmol), and EtOAc (8 mL) were combined, and the reaction vessel was evacuated and back-filled with H_2 (1 atm). The reaction mixture was stirred under H_2 for 30 min, then filtered over a plug of silica gel topped with Celite (EtOAc eluent) to afford reduced [3.3.1] bicycle **SM9** as a colorless oil (358 mg, 99% yield). R_f 0.28 (5:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.55 (d, *J* = 2.5 Hz, 1H), 5.74 (d, *J* = 2.5 Hz, 1H), 5.56 (d, *J* = 10.2 Hz, 1H), 5.30 (d, *J* = 10.2 Hz, 1H), 4.27 (s, 1H), 3.59-3.45 (m, 2H), 3.19 (ddd, *J* = 12.9 Hz, 7.7 Hz, 3.3 Hz, 1H), 2.58 (dd, *J* = 6.5 Hz, 3.2 Hz, 1H), 2.37-2.20 (comp. m, 2H), 2.06-1.90 (comp. m, 2H), 1.63-1.50 (m, 1H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.94-0.89 (comp. m, 11H), -0.02 (s, 9H), -0.06 (s, 3H), -0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.8, 140.4, 131.3, 125.2, 110.1, 76.6, 75.6, 71.8, 66.1, 46.8, 44.3, 40.0, 37.3, 25.9 (3C), 18.1, 17.9, 16.5, -1.2 (3C), -4.0, -4.6; IR (film): 3473 (br), 2953, 2931, 2857, 1651, 1420, 1249, 1079 cm^{-1}; HRMS-EI (*m/z*): $[M + H]^+$ calc'd for $C_{24}H_{44}NO_4Si_2$, 466.2809; found, 466.2804; $[\alpha]^{19}_D$ -166.30° (*c* 1.0, C_6H_6).

> *NOTE: In some instances, trace phosphine contaminants from the Heck reaction (i.e.* ***i*** *→* ***7****) prevented the reduction from occurring. Simply working up the reaction and re-exposing it to the identical reaction conditions (as described above) allowed the reduction to proceed.*



SM9 ***15***

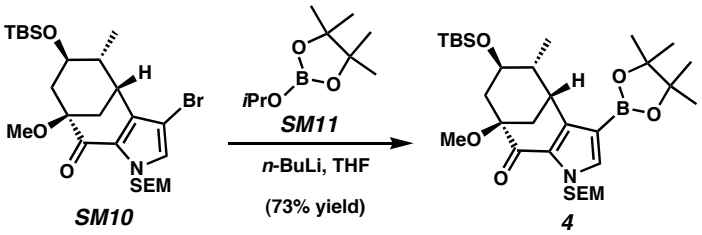
Methyl Ether 15. To reduced [3.3.1] bicycle **SM9** (358 mg, 0.77 mmol) in THF (7.7 mL) at 23 °C was added NaH (60% dispersion in mineral oil, 123 mg, 3.08 mmol). After stirring for 2 min at 23 °C, MeI was added (335 μL, 5.38 mmol). The resulting mixture was stirred for 1 h, cooled to 0 °C, and quenched with saturated aq. NH_4Cl (4 mL), then warmed to 23 °C. Et_2O (10 mL) and H_2O (5 mL) were added, and the layers were separated. The aqueous layer was further extracted with Et_2O (2 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (4:1 hexanes:EtOAc) to afford methyl ether **15** (354 mg, 96% yield) as a colorless oil. R_f 0.34 (5:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.58 (d, *J* = 2.8 Hz, 1H), 5.78 (d, *J* = 2.5 Hz, 1H), 5.57 (d, *J* = 10.2 Hz, 1H), 5.54 (d, *J* = 10.2 Hz, 1H), 3.65-3.50 (m, 2H), 3.37 (s, 3H), 3.22 (ddd, *J* = 12.9 Hz, 7.9 Hz, 3.1 Hz, 1H), 2.68 (dd, *J* = 6.5 Hz, 3.2 Hz, 1H), 2.59-2.49 (comp. m, 2H), 1.86 (dd, *J* = 12.4 Hz, 11.3 Hz, 1H), 1.72-1.56 (m, 2H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.93-0.85 (comp. m, 11H), -0.02 (s, 9H), -0.07 (s, 3H), -0.10 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6, 24/25 C): δ 189.4, 138.3, 130.4, 109.7, 81.9, 76.9, 72.4, 66.2, 51.8, 45.9, 41.3, 41.2, 37.6, 26.4 (3C), 18.5, 18.3, 17.0, -0.9 (3C), -3.6, -4.4; IR (film): 2954, 1657, 1421, 1250, 1085 cm^{-1}; HRMS-EI (*m/z*): [M + H]$^+$ calc'd for $C_{25}H_{46}NO_4Si_2$, 480.2965; found, 480.2970; $[\alpha]^{19}_D$ -172.9° (*c* 1.0, C_6H_6).



15 ***SM10***

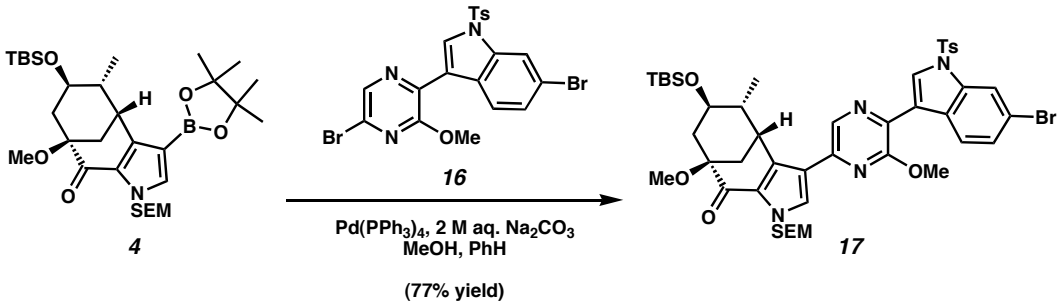
Bromide SM10. To methyl ether **15** (305 mg, 0.64 mmol) in THF (6 mL) at 0 °C was added freshly recrystallized NBS (147 mg, 0.83 mmol). After stirring for 10 min at 0 °C, the reaction mixture was warmed to 23 °C and additional NBS (30 mg, 0.17 mmol) was added. After 5 min, the reaction was quenched with saturated aq. $Na_2S_2O_3$, diluted with H_2O (15 mL)

and extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (5:1 hexanes:EtOAc) to afford bromide **SM10** (340 mg, 96% yield) as a colorless oil. R_f 0.55 (3:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.57 (s, 1H), 5.46 (d, *J* = 10.2 Hz, 1H), 5.34 (d, *J* = 10.2 Hz, 1H), 3.57-3.41 (m, 2H), 3.32-3.20 (m, 4H), 2.88 (dd, *J* = 6.5 Hz, 3.2 Hz, 1H), 2.46 (ddd, *J* = 12.2 Hz, 5.1 Hz, 2.5 Hz, 1H), 2.28 (app. dt, *J* = 7.4 Hz, 4.0 Hz, 1H), 1.78 (app. t, *J* = 11.8 Hz, 1H), 1.69-1.57 (m, 1H), 1.52 (dd, *J* = 11.8 Hz, 3.0 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 3H), 0.91-0.80 (comp. m, 11H), -0.05 (s, 9H), -0.09 (s, 3H), -0.12 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 189.6, 147.2, 137.2, 130.1, 98.4, 81.8, 77.0, 72.1, 66.6, 51.8, 45.8, 42.4, 41.0, 35.9, 26.3 (3C), 18.5, 18.3, 17.8, -0.9 (3C), -3.7, -4.3; IR (film): 2954, 2930, 1664, 1249, 1089 cm^{-1}; HRMS-EI (*m/z*): $[M + H]^+ - H_2$ calc'd for $C_{25}H_{43}NO_4Si_2Br$, 556.1914; found, 556.1928; $[\alpha]^{19}_D$ -98.22° (*c* 1.0, C_6H_6).



Boronic Ester 4. To bromide **SM10** (116 mg, 0.21 mmol) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**SM11**) (847 μL, 4.15 mmol) in THF (10.4 mL) at -78 °C was added *n*BuLi (2.3 M in hexanes, 1.35 mL, 3.11 mmol) dropwise over 2 min. After stirring for 15 min at -78 °C, the reaction mixture was quenched with saturated aq. NH_4Cl, warmed to 23 °C, and diluted with H_2O (10 mL). The mixture was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (4:1 hexanes:EtOAc with 0.5% Et_3N) to afford boronic ester **4** (92 mg, 73% yield) as a white powder which was used immediately in the next step. R_f 0.50 (3:1 hexanes:EtOAc); mp 143-145 °C; ^{1}H NMR (300 MHz, C_6D_6): δ 7.42 (s, 1H), 5.55 (d, *J* = 10.1 Hz, 1H), 5.51 (d, *J* = 9.8 Hz, 1H), 3.74-3.68 (m, 1H), 3.60-3.50 (m, 2H), 3.43-3.36 (m, 1H), 3.33 (s, 3H), 2.65-2.53 (comp. m, 2H), 1.91 (app. t, *J* = 11.8 Hz, 1H), 1.89-1.80 (m, 1H), 1.68 (dd, *J* = 11.8 Hz, 2.8 Hz, 1H), 1.34 (d, *J* = 6.6 Hz, 3H), 1.15 (s, 6H), 1.14 (s, 6H), 0.94-0.81 (comp. m, 11H), -0.04 (s, 3H), -0.05 (s, 9H), -0.07 (s, 3H);

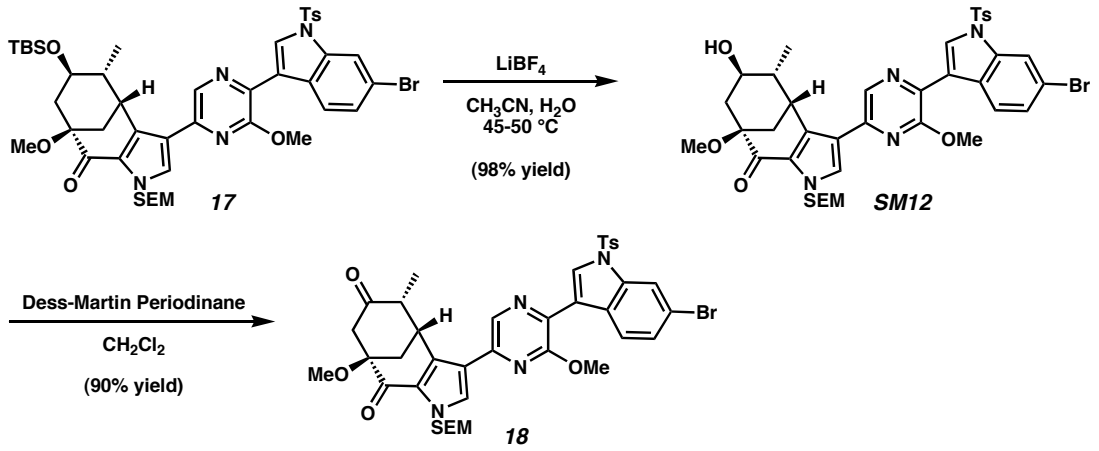
^{13}C NMR (75 MHz, C_6D_6, 30/31 C): δ 190.1, 145.1, 139.3, 130.2, 83.5 (2C), 82.0, 77.2, 72.6, 66.5, 51.7, 46.1, 42.0, 41.6, 36.8, 26.4 (3C), 25.4 (2C), 25.2 (2C), 18.5, 18.3, 16.9, -0.9 (3C), -3.6, -4.3; IR (film): 2953, 2931, 2858, 1658, 1543, 1249, 1141, 1085 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{31}H_{57}BNO_6Si_2$, 606.3818; found, 606.3805; $[\alpha]^{19}_D$ -98.84° (*c* 1.0, C_6H_6).



Suzuki Adduct 17. Bromopyrazine **16**[7] (46.5 mg, 0.087 mmol), boronic ester **4** (35 mg, 0.058 mmol), benzene (1.15 mL), methanol (231 μL), 2 M aq. Na_2CO_3 (96 μL), and tetrakis(triphenylphosphine)palladium(0) (6.7 mg, 0.0058 mmol) were combined and deoxygenated by sparging with argon for 5 min. The reaction vessel was evacuated, purged with N_2, sealed, heated to 50 °C for 65 h, cooled to 23 °C, then quenched by the addition of Na_2SO_4 (200 mg). Following filtration over a pad of silica gel (2:1 hexanes:EtOAc eluent) and evaporation to dryness under reduced pressure, the remaining residue was purified by flash chromatography (3:1 hexanes:EtOAc) to afford Suzuki adduct **17** (41.5 mg, 77% yield) as a yellow oil. R_f 0.43 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (d, *J* = 8.5 Hz, 1H), 8.45 (s, 1H), 8.44 (s, 1H), 8.16 (d, *J* = 1.5 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.59 (s, 1H), 7.40 (dd, *J* = 8.5 Hz, 1.8 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 2H), 5.85 (d, *J* = 10.0 Hz, 1H), 5.78 (d, *J* = 10.0 Hz, 1H), 4.27-4.21 (m, 1H), 4.19 (s, 3H), 3.72-3.59 (m, 2H), 3.34 (s, 3H), 3.13-3.02 (m, 1H), 2.87-2.77 (m, 1H), 2.32 (s, 3H), 2.22-2.12 (m, 1H), 1.98-1.89 (m, 1H), 1.82-1.72 (m, 1H), 1.67 (app. t, *J* = 11.7 Hz, 1H), 1.04-0.83 (m, 2H), 0.78 (s, 9H), 0.72 (d, *J* = 6.7 Hz, 3H), -0.02 (s, 9H), -0.09 (s, 3H), -0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 44/45 C): δ 190.0, 156.2, 145.7, 143.6, 136.9, 135.7, 135.5, 135.0, 132.7, 130.3 (2C), 130.2, 129.3, 128.8, 128.5, 127.3, 127.1 (2C), 125.3, 120.5, 119.0, 116.9, 116.4, 81.3, 77.2, 71.4, 66.7, 54.3, 51.6, 44.8, 41.8, 40.2, 34.8, 25.9 (3C), 21.8, 18.1, 16.1, -1.1 (3C), -4.0, -4.7; IR (film): 2952, 1660, 1555, 1372, 1372, 1190,

[7] Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179-13184.

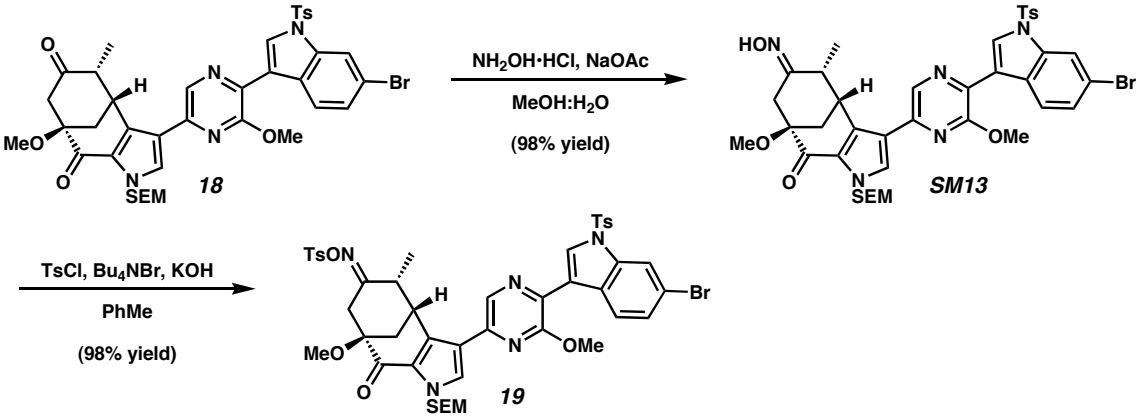
1140, 1089 cm^{-1}; HRMS-FAB (*m/z*): $[M]^+$ calc'd for $C_{45}H_{59}N_4O_7Si_2SBr$, 934.2826; found, 934.2829; $[\alpha]^{21}_D$ +51.73° (*c* 1.0, $CHCl_3$).



Ketone 18. Suzuki adduct **17** (113 mg, 0.121 mmol), $LiBF_4$ (113 mg, 1.21 mmol), acetonitrile (6 mL), and water (600 μL) were heated to 45–50 °C. After 9 h, additional $LiBF_4$ (30 mg, 0.32 mmol) was introduced and heating was continued. After 6 h, additional $LiBF_4$ (35 mg, 0.32 mmol) was introduced and heating was continued for 16 h. The reaction mixture was cooled to 23 °C, quenched with 10% aq. citric acid (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash chromatography (3:1 EtOAc:hexanes) to yield alcohol **SM12** (96.9 mg, 98% yield) as a yellow oil which was used in the subsequent step without further purification. R_f = 0.44 (3:1 EtOAc:hexanes).

To alcohol **SM12** (96 mg, 0.117 mmol) in CH_2Cl_2 (2.0 mL) at 23 °C was added Dess-Martin Periodinane (74.3 mg, 0.175 mmol). The mixture was stirred for 3 min, quenched with a solution of saturated aq. $NaHCO_3$ and saturated aq. $Na_2S_2O_3$ (1:1, 5 mL), stirred for 5 min, and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (1:1 hexanes:EtOAc) to yield ketone **18** (86 mg, 90% yield) as a yellow foam. R_f = 0.48 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (d, *J* = 8.5 Hz, 1H), 8.45 (s, 1H), 8.42 (s, 1H), 8.18 (d, *J* = 1.7 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.56 (s, 1H), 7.42 (dd, *J* = 8.7 Hz, 1.8 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 2H), 5.77 (d, *J* = 10.5 Hz, 1H), 5.72 (d, *J* = 10.2 Hz, 1H), 4.62-4.56 (m, 1H), 4.20 (s, 3H), 3.57 (app. dt, *J* = 8.2 Hz, 1.8 Hz, 2H), 3.43 (s, 3H),

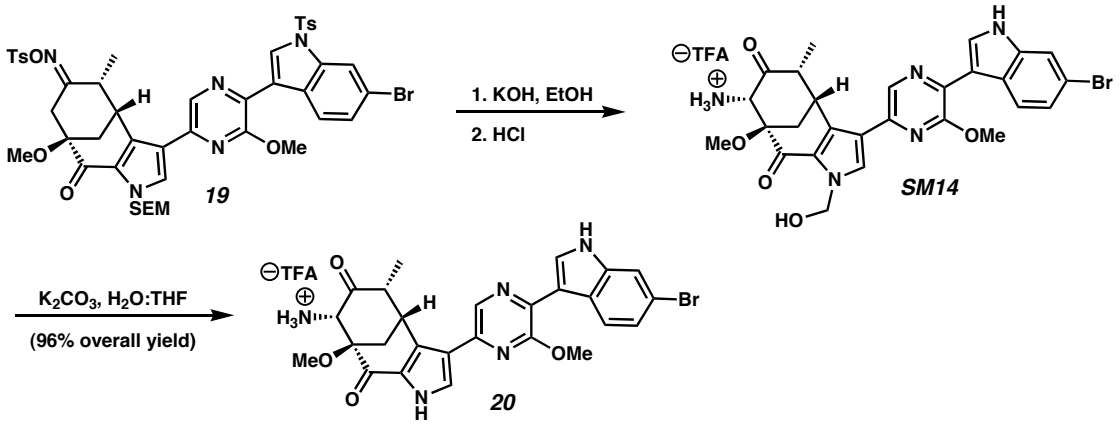
3.14-3.06 (m, 1H), 2.91-2.81 (m, 1H), 2.74 (s, 2H), 2.40 (dd, J = 12.5 Hz, 2.9 Hz, 1H), 2.34 (s, 3H), 0.96-0.88 (m, 2H), 0.78 (d, J = 6.6 Hz, 3H), -0.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 37/39 C): δ 207.2, 188.0, 156.1, 145.7, 143.2, 136.3, 135.7, 134.9, 132.6, 130.7, 130.3 (2C), 128.8, 128.4, 127.3, 127.1 (2C), 125.4, 120.5, 119.0, 116.8, 116.3, 82.4, 77.1, 66.9, 54.3, 52.2, 52.0, 49.2, 40.2, 35.2, 21.8, 18.1, 12.2, -1.2 (3C); IR (film): 2950, 1716, 1664, 1557, 1373, 1190, 1178, 1090 cm^{-1}; HRMS-FAB (*m/z*): $[M]^+$ calc'd for $C_{39}H_{43}N_4O_7SiSBr$, 818.1805; found, 818.1836; $[\alpha]^{21}_D$ +71.61° (*c* 1.0, $CHCl_3$).



Tosyl Oxime 19. To ketone **18** (50.0 mg, 0.061 mmol), NH_2OH•HCl (85 mg, 1.22 mmol), and NaOAc•3H_2O (125 mg, 0.915 mmol) was added methanol (2.5 mL), followed by H_2O (350 μL), then additional methanol (5 mL). The homogeneous solution was stirred at 23 °C for 8 h and the solvent was removed under reduced pressure. H_2O (15 mL) was added, and the resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was further purified by filtration over a plug of silica gel (EtOAc eluent) to yield oxime **SM13** (50.1 mg, 98% yield) as a yellow foam which was used without purification in the subsequent reaction. R_f = 0.46 (1:1 hexanes:EtOAc).

To a solution of oxime **SM13** (20.0 mg, 0.0240 mmol), TsCl (14.0 mg, 0.0734 mmol), and Bu_4NBr (1.0 mg, 0.0031 mmol) in toluene (2.0 mL) at 0 °C was added 50% aq. KOH (310 μL). The reaction mixture was stirred at 0 °C for 2 h, quenched with ice-cold H_2O (1.5 mL) and extracted with ice-cold EtOAc (5 x 1 mL). The combined organic layers were washed with brine (1 mL), dried by passage over a plug of silica gel (EtOAc eluent), and evaporated under reduced

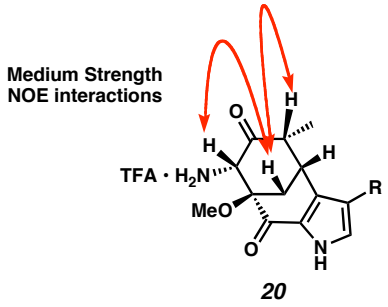
pressure. The crude product was purified by flash chromatography (1:1 hexanes:EtOAc) to yield tosyl oxime **19** (23.3 mg, 98% yield) as a yellow foam. R_f = 0.48 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (d, *J* = 8.5 Hz, 1H), 8.46 (s, 1H), 8.41 (s, 1H), 8.19 (d, *J* = 1.4 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.51 (s, 1H), 7.44 (dd, *J* = 8.7 Hz, 1.5 Hz, 1H), 7.28-7.19 (comp. m, 4H), 5.87 (d, *J* = 10.2 Hz, 1H), 5.42 (d, *J* = 10.2 Hz, 1H), 4.45-4.43 (m, 1H), 4.20 (s, 3H), 3.67-3.53 (comp. m, 3H), 3.38 (s, 3H), 2.98-2.89 (m, 1H), 2.87-2.77 (m, 1H), 2.42 (s, 3H), 2.35 (s, 3H), 2.12 (d, *J* = 14.0 Hz, 2H), 1.05-0.85 (m, 2H), 0.78 (d, *J* = 6.6 Hz, 3H), -0.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.2, 165.8, 156.3, 145.8, 144.8, 143.5, 135.8, 135.7, 135.3, 135.0, 132.9, 132.6, 130.4 (2C), 129.9, 129.4 (2C), 129.1 (2C), 128.9, 128.4, 128.0, 127.5, 127.2 (2C), 125.3, 120.3, 119.2, 116.8, 116.5, 80.8, 77.4, 67.2, 54.4, 52.2, 42.5, 40.3, 36.5, 36.2, 21.9, 21.9, 18.1, 13.7, -1.1 (3C); IR (film): 2946, 1665, 1555, 1373, 1191, 1178, 1140 cm^{-1}; HRMS-FAB (*m/z*): $[M]^+$ calc'd for $C_{46}H_{50}N_5O_9SiS_2Br$, 987.2002; found, 987.2038; $[\alpha]^{20}_D$ +139.01° (*c* 1.0, $CHCl_3$).



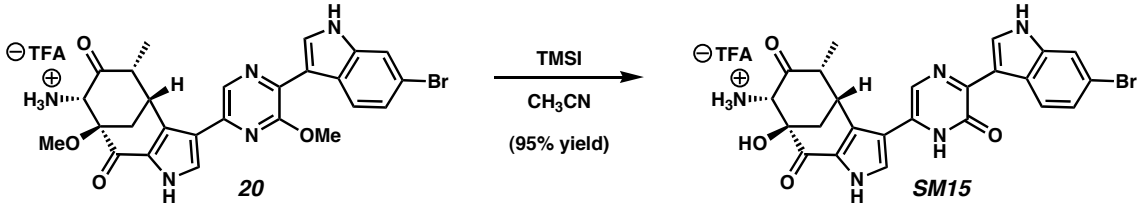
Amino Ketone 20. To a stirred solution of tosyl oxime **19** (23.3 mg, 0.0236 mmol) in EtOH (3.5 mL) at 0 °C was added 50% aq. KOH (450 μL) dropwise over 1 min. The reaction mixture was stirred at 0 °C for 3 h, then 6 N aq. HCl (5 mL) was added. The reaction mixture was heated to 60 °C for 10 h, cooled to 23 °C, and purified by reversed-phase filtration through a Sep-Pak column: loaded with water containing 0.1% (w/v) TFA, washed with 15% acetonitrile:water containing 0.1% (w/v) TFA to remove salts, then 70% acetonitrile:water containing 0.1% (w/v) TFA to collect the crude product. The solvents were removed under reduced pressure to afford hemiaminal **SM14**, which was used immediately in the subsequent reaction.

Hemiaminal **14** and K_2CO_3 (60 mg, 0.434 mmol) in THF (2 mL) at 23 °C was added H_2O (200 μL). The reaction mixture was stirred for 10 min, then purified by reversed-phase filtration through a Sep-Pak column: loaded with water containing 0.1% (w/v) TFA, washed with 10% acetonitrile:water containing 0.1% (w/v) TFA to remove salts, then 70% acetonitrile:water containing 0.1% (w/v) TFA to collect the crude product. After removal of solvents under reduced pressure, the crude material was further purified by reversed-phased HPLC. Concentration under reduced pressure provided amino ketone **20** (15.0 mg, 96% yield) as an orange/red oil. ^{1}H NMR (300 MHz, CD_3OD): δ 8.60 (d, J = 8.5 Hz, 1H), 8.53 (s, 1H), 8.23 (s, 1H), 7.81 (s, 1H), 7.61 (d, J = 1.4 Hz, 1H), 7.25 (dd, J = 8.7 Hz, 1.8 Hz, 1H), 4.82-4.78 (m, 1H), 4.46 (s, 1H), 4.21 (s, 3H), 3.47 (s, 3H), 3.41-3.30 (m, 1H), 3.26 (dd, J = 12.9 Hz, 3.9 Hz, 1H), 2.61 (dd, J = 12.9 Hz, 3.0 Hz, 1H), 0.88 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD, 25/26 C): δ 203.5, 183.3, 156.8, 142.4, 139.9, 139.1, 136.3, 133.4, 130.7, 129.9, 129.6, 126.9, 125.5, 124.5, 123.1, 116.9, 115.4, 112.6, 84.3, 66.0, 54.5, 52.9, 40.4, 36.6, 12.2; IR (film): 3156 (br), 2935, 1674, 1531, 1447, 1409, 1203, 1135 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{26}H_{25}N_5O_4Br$, 550.1090; found, 550.1071; $[\alpha]^{20}_D$ +99.19° (*c* 0.87, MeOH).

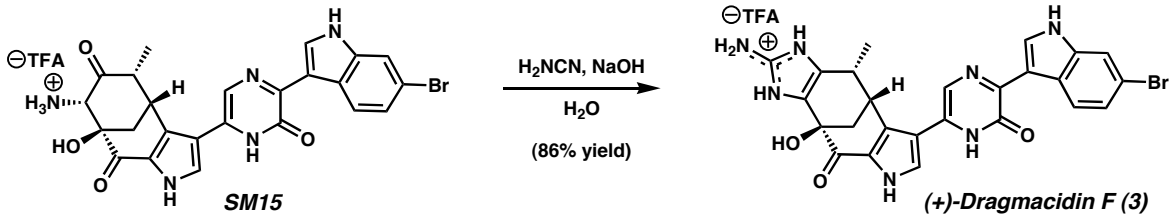
The relative stereochemistry of deprotected amino ketone **20** was determined by NOE experiments. Medium strength NOE interactions were observed as indicated below. Analogous NOE interactions were observed for hemiaminal **SM14** and deprotected amino ketone **SM15**.



20



Deprotected Amino Ketone SM15. To a stirred solution of amino ketone **20** (7.5 mg, 0.0113 mmol) in MeCN (1 mL) at 0 °C was added TMSI (500 μL, 3.51 mmol) dropwise over 30 sec. The reaction mixture was heated to 60 °C for 48 h, cooled to 0 °C, then transferred dropwise into a chilled solution (0 °C) of saturated aqueous sodium metabisulfite (5 mL). The mixture was diluted with 6 N HCl (15 mL), stirred at 0 °C for 20 min, then purified by reversed-phase filtration through a Sep-Pak column: loaded with water containing 0.1% (w/v) TFA, washed with 1 N HCl, 10% acetonitrile:water containing 0.1% (w/v) TFA to remove salts, then 60% acetonitrile:water containing 0.1% (w/v) TFA to collect the crude product. After removal of solvents under reduced pressure, the crude material was further purified by reversed-phase HPLC. Concentration under reduced pressure provided deprotected amino ketone **SM15** (6.8 mg, 95% yield) as an orange/red oil. ^{1}H NMR (300 MHz, CD_3OD): δ 8.69 (s, 1H), 8.59 (d, J = 8.5 Hz, 1H), 7.69 (s, 1H), 7.61 (d, J = 1.7 Hz, 1H), 7.57 (s, 1H), 7.27 (dd, J = 8.5 Hz, 1.7 Hz, 1H), 4.40 (s, 1H), 4.06-3.98 (m, 1H), 3.31-3.21 (m, 1H), 2.87 (dd, J = 13.2 Hz, 3.3 Hz, 1H), 2.79 (dd, J = 13.1 Hz, 2.9 Hz, 1H), 0.85 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD, 23/24 C): δ 203.4, 186.0, 157.4, 139.1, 136.3, 132.5, 132.4, 130.2, 130.1, 128.2, 126.7, 126.7, 125.6, 124.9, 117.1, 115.4, 113.6, 79.3, 67.1, 49.6, 45.5, 36.7, 12.3; IR (film): 3164 (br), 2927, 1674, 1451, 1207, 1143 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{24}H_{21}N_5O_4Br$, 522.0777; found, 522.0783; $[\alpha]^{22}_D$ +86.88° (*c* 0.33, MeOH).



(+)–Dragmacidin F (3). To deprotected amino ketone **SM15** (3.6 mg, 0.0056 mmol) and cyanamide (120 mg, 2.86 mmol) in H_2O (2 mL) at 23 °C was added 10% aq. NaOH (80 μL). The reaction mixture was heated to 60 °C for 2 h, cooled to 23 °C, then purified by reversed-phase

filtration through a Sep-Pak column: loaded with water containing 0.1% (w/v) TFA, washed with 10% acetonitrile:water containing 0.1% (w/v) TFA to remove salts, then 60% acetonitrile:water containing 0.1% (w/v) TFA to collect the crude product. After removal of solvents under reduced pressure, the product was further purified by reversed-phase HPLC. Concentration under reduced pressure afforded (+)–Dragmacidin F (**3**, 3.2 mg, 86% yield) as an orange/red oil. ^{1}H NMR (600 MHz, CD_3OD): δ 8.69 (s, 1H), 8.59 (d, J = 8.7 Hz, 1H), 7.68 (s, 1H), 7.60 (s, 1H), 7.47 (s, 1H), 7.26 (d, J = 8.7 Hz, 1H), 4.12 (br s, 1H), 3.40-3.34 (m, 1H), 2.73 (dd, J = 12.0 Hz, 2.9 Hz, 1H), 2.45 (d, J = 11.6 Hz, 1H), 0.92 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD, 22/25 C): δ 188.5, 157.5, 149.6, 139.1, 132.6, 132.4, 128.5, 128.4, 126.7, 126.2, 125.6, 124.9, 124.8, 123.3, 117.1, 115.4, 113.7, 72.8, 45.3, 36.9, 33.3, 15.9; IR (film): 3175 (br), 2925, 1679, 1637, 1205, 1141 cm^{-1}; UV (MeOH) λ_{max} 283, 389 nm; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{25}H_{21}N_7O_3Br$, 546.0889; found, 546.0883; $[\alpha]^{23}_D$ +146.21° (*c* 0.45, MeOH).

(+)–Dragmacidin F NMR Comparison Table[8]

^{1}H ppm (CD_3OD)			
Natural (600 MHz)		*Synthetic* (600 MHz)	
8.73	s	8.69	s
8.61	d, *8.3*	8.59	d, *8.7*
7.74	s	7.68	s
7.65	s	7.60	s
7.56	s	7.47	s
7.27	dd, *8.3, 1.8*	7.26	d, *8.7*
4.16	br s	4.12	br s
3.38	q, *7.0*	3.37	m
2.76	dd, *11.8, 3.50*	2.73	dd, *12.0, 2.9*
2.49	br d, *11.8*	2.45	d, *11.6*
0.93	d, *7.0* (3H)	0.92	d, *7.0* (3H)

^{13}C ppm (CD_3OD)	
Natural (150 MHz)	*Synthetic* (125 MHz)
189.0	188.5
157.2	157.5
149.6	149.6
149.4	–
138.8	139.1
133.0	132.6
132.2	132.4
128.8	128.5
128.1	128.4
126.4	126.7
125.9	126.2
125.3	125.6
125.0	124.9
124.6	124.8
123.1	123.3
117.2	117.1
116.8	–
115.3	115.4
113.3	–
113.3	113.7
73.1	72.8
45.0	45.3
36.8	36.9
33.1	33.3
15.8	15.9

[8] Natural ^{13}C- and ^{1}H-NMR data have been reproduced from the isolation paper, see: Cutignano, A.; Bifulco, G.; Bruno, I.; Casapullo, A.; Gomez-Paloma, L.; Riccio, R. *Tetrahedron* **2000**, *56,* 3743-3748.

(+)–Dragmacidin F NMR Comparison Table[8]

^{1}H ppm (DMSO-d_6)[9]						^{13}C ppm (DMSO-d_6)		
Natural (600 MHz)		*Synthetic* (500 MHz)		*Synthetic* + D_2O[10] (500 MHz)		*Natural* (150 MHz)	*Synthetic* (125 MHz)	Δ[11]
8.71	s	8.77	s	8.71	s	188.9	187.0	1.9
8.54	d, *8.6*	8.56	d, *8.3*	8.54	d, *8.5*	156.9	155.1	1.8
7.68	s	7.67	d, *2.3*	7.68	d, *1.8*	149.6	147.6	2.0
7.52	s	7.57	br s	7.59	br s	149.6	–	
7.52	s	7.54	br s	7.52	br s	139.0	137.2	1.8
7.25	br d, *8.6*	7.28	dd, *8.8, 2.0*	7.28	dd, *8.2, 1.5*	132.9	131.2	1.7
6.09		6.00	br s	–	see [12]	132.3	130.7	1.6
4.01	br s	4.03	br s	4.03	br s	132.3	–	
3.27	q, *7.0*	–	see [13]	3.28	m	128.8	127.1	1.7
2.53	br d, *10.9*	2.57	dd, *12.2, 3.9*	2.57	dd, *11.9, 3.7*	128.7	126.9	1.8
2.26	br d, *10.9*	2.28	dd, *12.0, 2.2*	2.28	dd, *12.1, 2.0*	126.7	124.9	1.8
0.78	d, *6.7* (3H)	0.78	d, *7.3* (3H)	0.75	d, *7.0* (3H)	126.0	124.2	1.8
						125.1	123.9	1.2
						124.8	123.1	1.7
						122.7	121.2	1.5
						117.2	–	
						116.5	114.8	1.7
						116.2	114.3	1.9
						113.4	111.7	1.7
						110.9	–	
						72.9	71.1	1.8
						45.1	43.5	1.6
						36.4	34.6	1.8
						33.0	31.2	1.8
						16.8	14.9	1.9
						Avg. Difference (ppm):		1.7

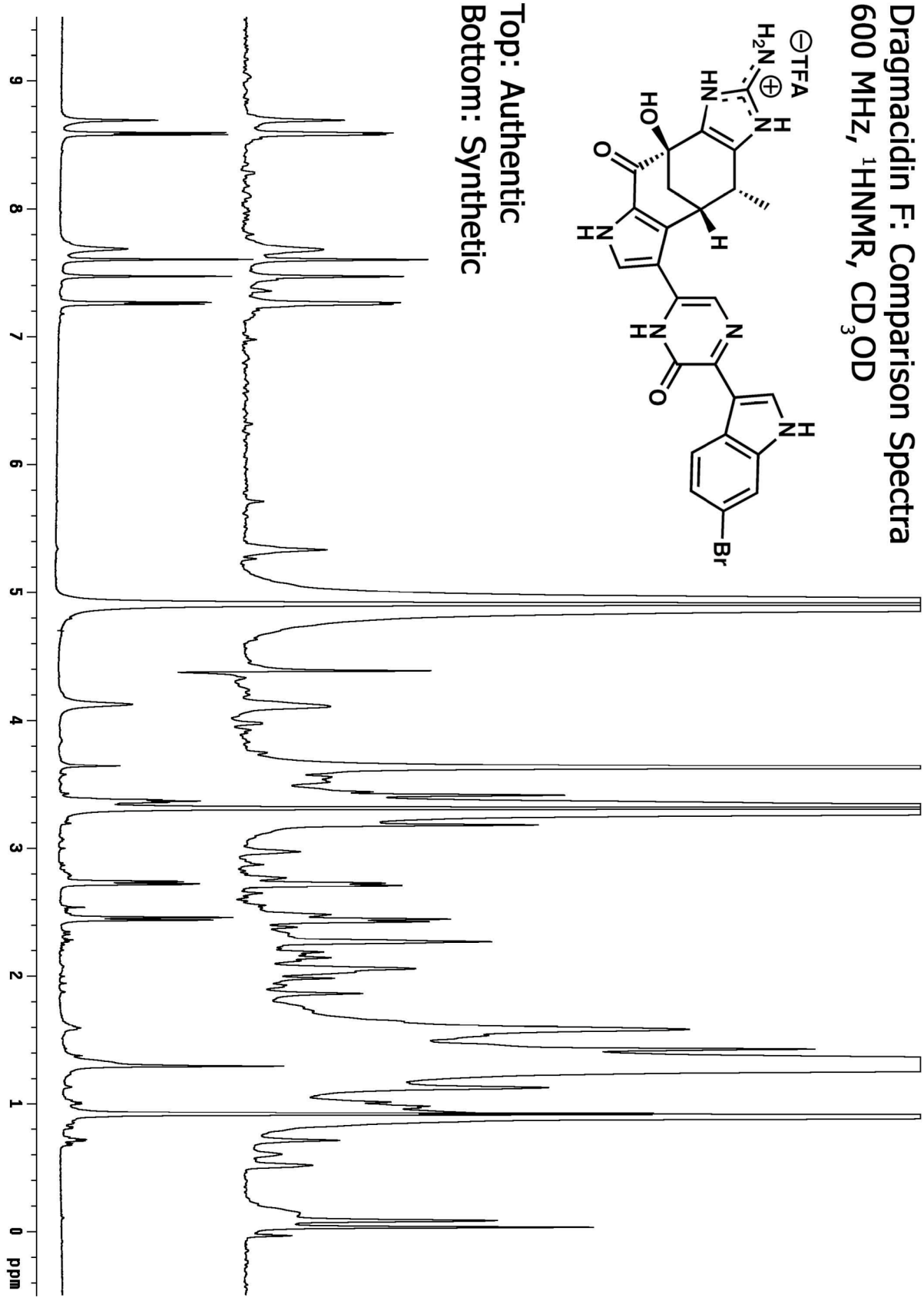
[9] NH protons have been omitted from the table. See attached spectra in DMSO-*d6*. *Note:* NH protons appear at slightly different δ (ppm) than reported by the isolation chemists.[8] We attribute this to differences in sample concentrations, and counterion effects (*natural*: counterion = unknown; *synthetic*: counterion = TFA).

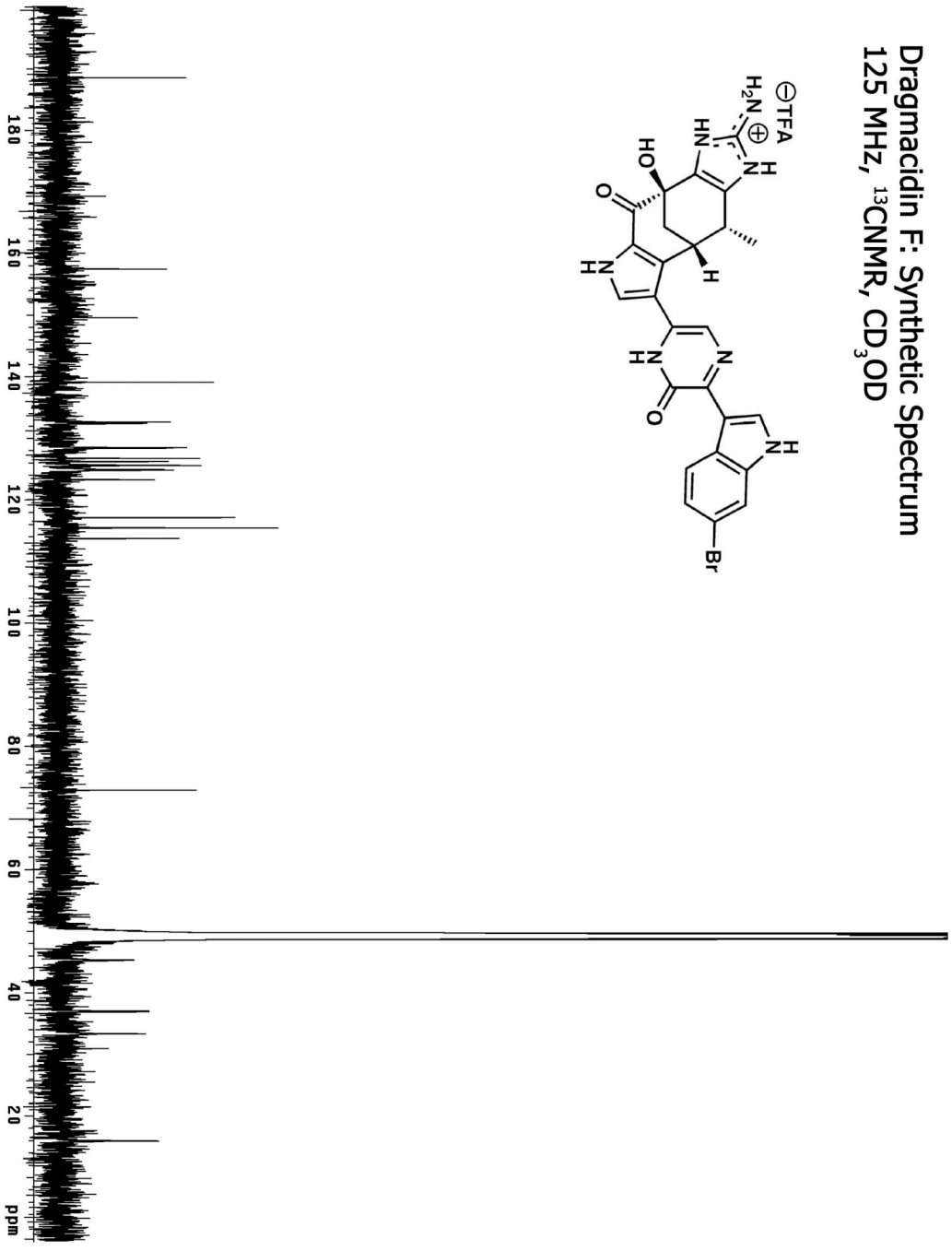
[10] One drop of D_2O was added to an NMR tube containing synthetic (+)–dragmacidin F in DMSO-d_6 and the sample was allowed to stand for 30 minutes at 23 °C.

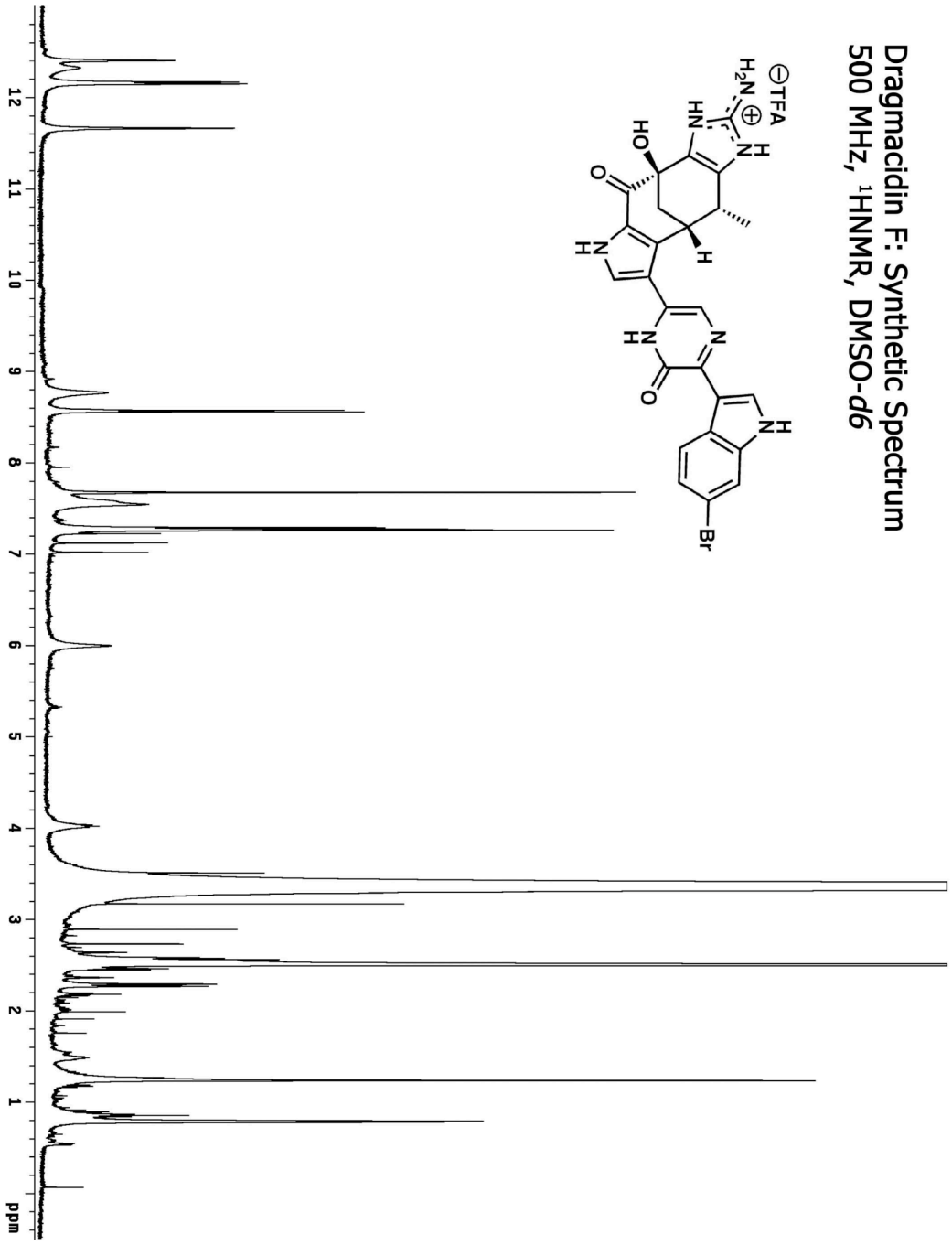
[11] There is clearly a discrepancy of ~1.7 ppm in the ^{13}C NMR data between the synthetic and natural samples of dragmacidin F. This is likely due to the differences in the deuterium referencing values. The deuterium signal for the synthetic sample of dragmacidin F (in DMSO-d_6) was referenced to 39.51 ppm in accord with Cambridge Isotope Laboratories, Inc.

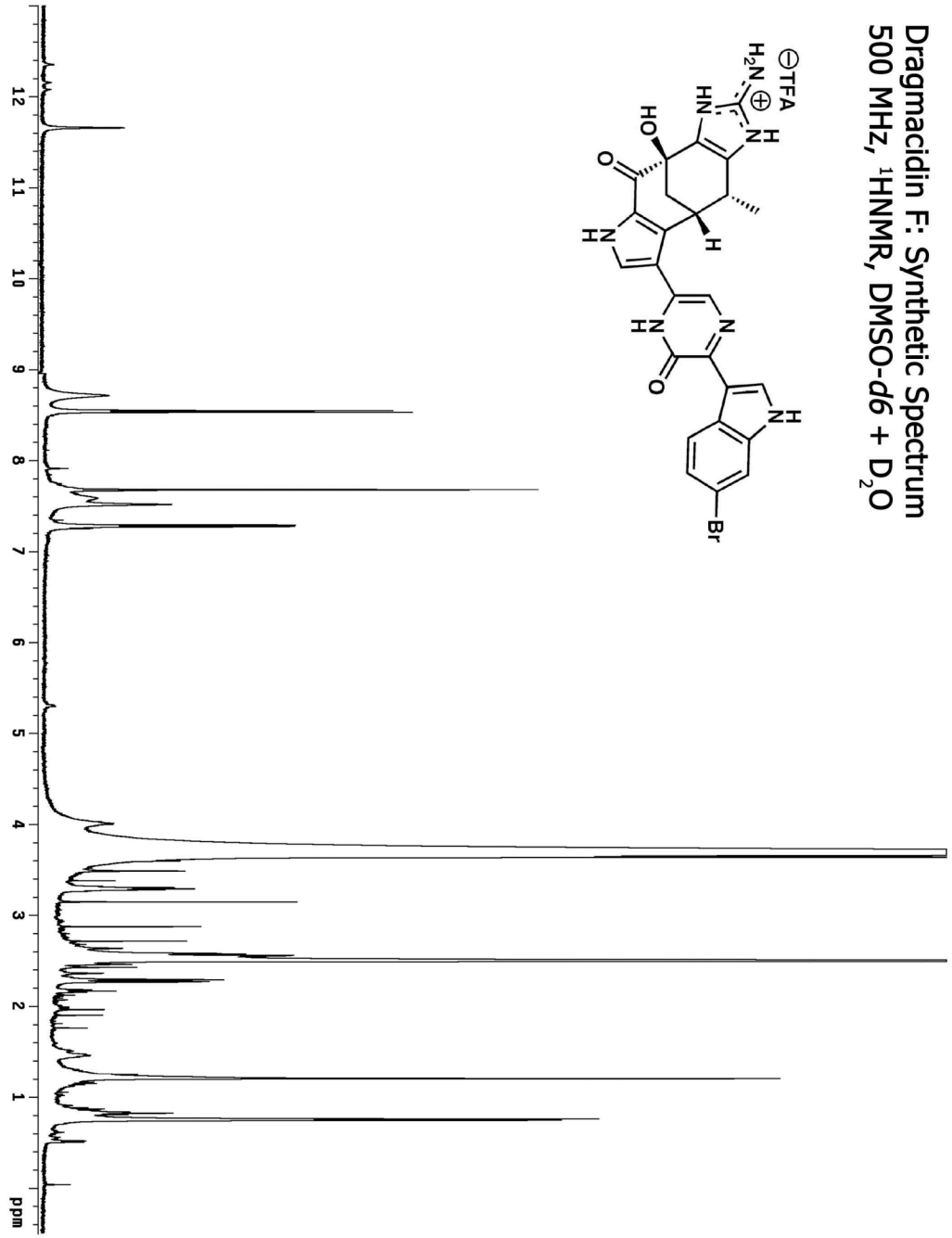
[12] Proton exchanged for deuterium (OH → OD).

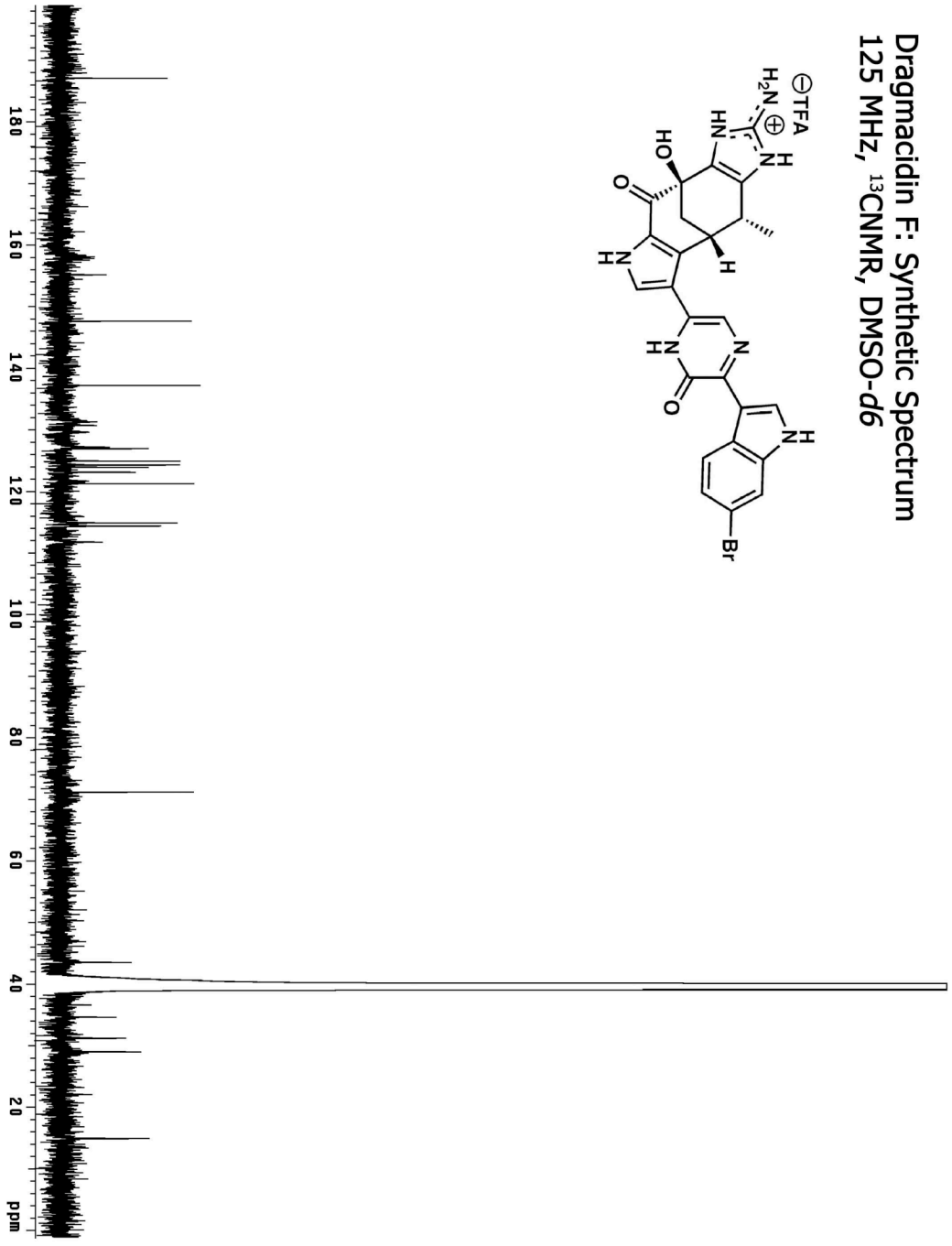
[13] Signal obscured by H_2O.


Dragmacidin F: Comparison Spectra
600 MHz, ^{1}HNMR, CD_3OD
⊖TFA
Top: Authentic
Bottom: Synthetic
9
8
7
6
5
4
3
2
1
0
ppm


Dragmacidin F: Synthetic Spectrum
125 MHz, ^{13}CNMR, CD_3OD
⊖TFA
H_2N
HN
HO
O
N
H
N
H
N
H
N
O
N
H
Br
180
160
140
120
100
80
60
40
20
ppm


Dragmacidin F: Synthetic Spectrum
500 MHz, ^{1}HNMR, DMSO-*d6*
⊖TFA
H_2N ⊕
HN
N
H
HO
O
H
N
H
N
N
H
O
N
H
Br
12
11
10
9
8
7
6
5
4
3
2
1
ppm

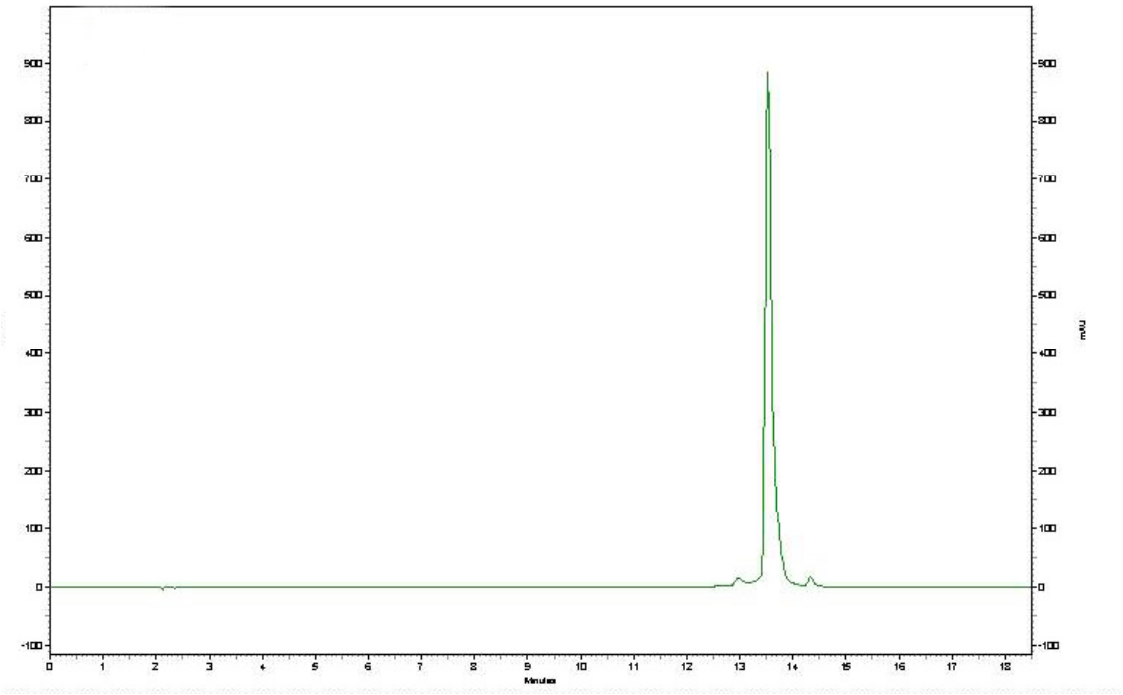

Dragmacidin F: Synthetic Spectrum
500 MHz, 1HNMR, DMSO-d6 + D2O
⊖TFA
ppm


Dragmacidin F: Synthetic Spectrum
125 MHz, ^{13}CNMR, DMSO-*d6*
⊖TFA
H_2N
HN
N
H
HO
O
N
H
H
N
H
N
N
O
N
H
Br
180
160
140
120
100
80
60
40
20
ppm

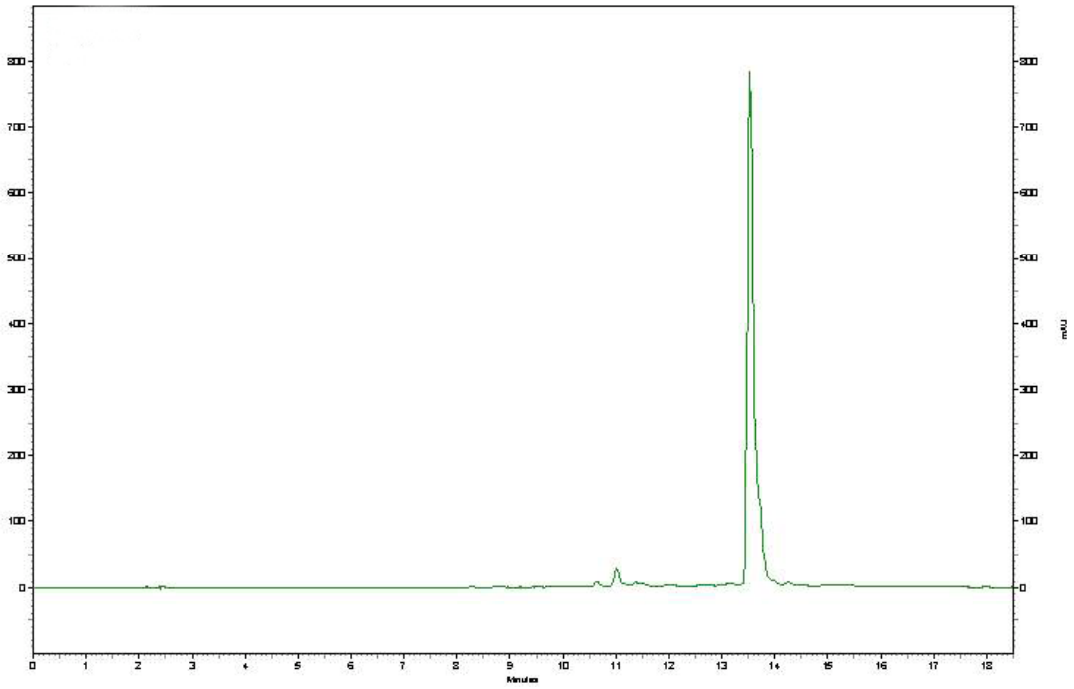
Dragmacidin F Analytical HPLC Comparison:

Analytical HPLC analysis for synthetic and natural dragmacidin F was performed on a Beckman Gold system using a Rainin C_{18}, Microsorb MV, 5μm, 300 x 4.6 mm reversed-phased column in 0.1% (w/v) TFA with acetonitrile as eluent, flow rate of 1.0 mL/min, gradient elution of 1.25% acetonitrile/min, 10% acetonitrile → 60% acetonitrile over 17 minutes, UV detection λ = 389 nm.

Synthetic (+)-Dragmacidin F; retention time = 13.53 minutes:



Authentic (–)-Dragmacidin F; retention time = 13.53 minutes:



Co-injection of Synthetic (+)-Dragmacidin F & Authentic (–)-Dragmacidin F;

retention time = 13.52 minutes: