Supplemental materials for:

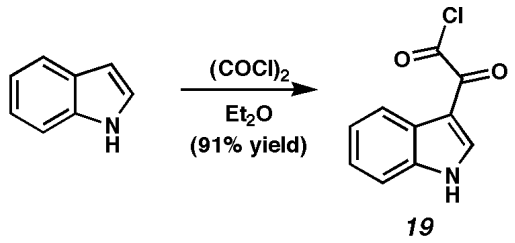
The First Total Synthesis of Dragmacidin D

Neil K. Garg, Richmond Sarpong, Brian M. Stoltz*

The Arnold and Mabel Beckman Laboratories of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, USA

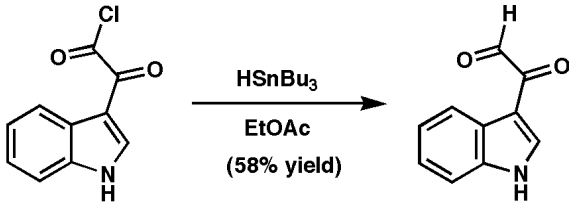
Material and Methods. Unless stated otherwise, reactions were performed in flame-dried glassware under a nitrogen or argon atmosphere using dry, deoxygenated solvents. All other commercially obtained reagents were used as received. Solvents were dried by passage through an activated alumina column under argon. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV or anisaldehyde staining. ICN Silica gel (particle size 0.032-0.063 mm) was used for flash 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, 5mm, 300 x 4.6 mm reversed-phased column in 0.1% (wt/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 mm C_{18} column equipped with a guard, 0.1% (wt/v) TFA with acetonitrile as eluent, and gradient elution of 0.50% acetonitrile/min. For all reversed-phase purifications, water (18MW) was obtained from a Millipore MiliQ water purification system and TFA from Halocarbon, Inc. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian Mercury 300 (at 300 MHz and 75 MHz respectively), Varian Mercury 500 (at 500 MHz and 125 MHz respectively), or on a Varian Mercury 600 (600 MHz for proton only) spectrometer 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. 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}). UV spectra were measured on a Hewlett-Packard Model 8452A diode array spectrophotometer. High resolution mass spectra were obtained from the UC Irvine Mass Spectral Facility. Analytic chiral HPLC was performed on a chiralcel AD column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd.



19

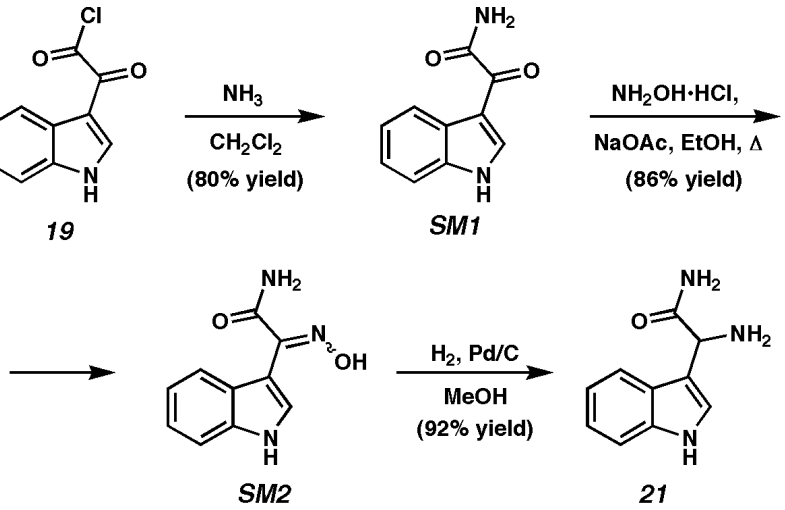
Acid chloride 19. To a solution of indole (20.0 g, 171 mmol) in anhydrous diethyl ether (340 mL) at 0 ˚C, oxalyl chloride (17.3 mL, 198 mmol) was added dropwise over 30 min. The reaction mixture was stirred at 0 ˚C for 3 h, then allowed to warm to 23 ˚C over 1 h. The resulting yellow crystals were collected by filtration, washed with cold anhydrous ether (100 mL), and dried under vacuum to yield **19** (32.52 g, 92% yield) which was used without further purification.



19 *20*

Ketoaldehyde 20. To a suspension of **19** (22.0 g, 106 mmol) in EtOAc (106 mL) at 0 ˚C, was added a solution of tributyltin hydride (28.5 mL, 106 mmol) in EtOAc (158 mL). The reaction mixture was stirred at 0 ˚C for 30 min, warmed to 23 ˚C, then stirred for an additional 15 h. Hexane (150 mL) was added and the resulting yellow powder was collected by filtration. Washing with copious amounts of hexanes (1 L) and drying under vacuum, gave ketoaldehyde **20**

(10.6 g, 58% yield): R_F 0.76 (13:7 chloroform/methanol eluent); ^{1}H NMR (300 MHz, acetone-d_6) δ 9.54 (s, 1H), 8.65 (s, 1H), 8.36-8.33 (comp.m, 1H), 7.61-7.58 (comp.m, 1H), 7.33-7.29 (comp.m, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 192.9, 183.2, 138.1, 125.3, 124.6, 124.1, 123.5, 123.1, 113.6, 113.3; IR (film) 3117, 1628, 1580, 1518, 1234 cm^{-1}; HRMS (NH_3Cl) *m/z* calc'd for $[C_{10}H_7NO_2+H]^+$: 174.0555, found 174.0555.

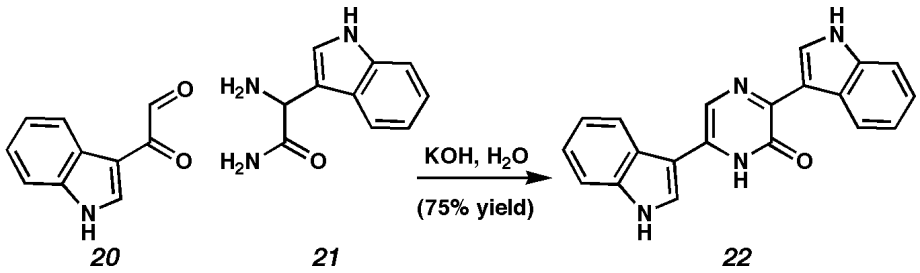


Amino-amide 21. Gaseous ammonia was bubbled through a suspension of **19** (12.4 g, 59.7 mmol) in CH_2Cl_2 (300 mL) for 10 min. After stirring for 30 min, the solvent was removed under reduced pressure. Addition of H_2O (600 mL) was followed by extraction of the resulting heterogeneous mixture with EtOAc (2 x 600 mL). The combined organic layers were washed with brine (300 mL), dried over magnesium sulfate, and evaporated under reduced pressure to afford the crude amide **SM1** (9.0 g, 80% yield) which was used without further purification.

To a suspension of amide **SM1** (500 mg, 5.32 mmol) in methanol (7.8 mL) was added hydroxylamine hydrochloride (2.0 g, 39.9 mmol) in H_2O (3.8 mL) and sodium acetate (1.64 g, 39.9 mmol) in H_2O (3.8 mL). The resulting heterogeneous mixture was heated under reflux for 10 h and allowed to cool to 23 ˚C. The solvent was removed under reduced pressure and the remaining crude residue extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL) and dried over sodium sulfate. After removal of solvent under

reduced pressure, the crude residue was purified by flash chromatography (3:1 CH_2Cl_2/hexanes eluent) to afford oxime **SM2** (454 mg, 86% yield) which was used without further purification.

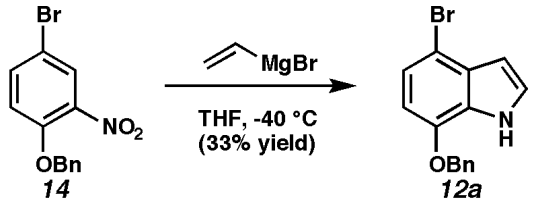
To a solution of oxime **SM2** (4.07 g, 20 mmol) in methanol in a stainless steel bomb calorimeter was added 10% palladium on charcoal (450 mg). The bomb was then purged with hydrogen and pressurized to 450 psi. After stirring for 14 h at 23 ˚C, the palladium on carbon was removed via filtration and the solvent was removed under reduced pressure. Passage through a plug of silica gel (methanol eluent) afforded the desired aminoamide **21** (3.5 g, 92% yield) as a yellow oil: R_F 0.10 (5:1 EtOAc/methanol eluent); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.93 (s, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.43 (s, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.23 (s, 1H), 7.07-6.93 (comp.m, 3H), 4.56 (s, 1H), 2.38 (bs, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.9, 136.2, 125.7, 122.8, 120.9, 119.5, 118.2, 116.2, 111.3, 52.5; IR (film) 3176, 1660, 1592 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{10}H_{11}N_3O+H]^+$: 190.0980, found 190.0978.



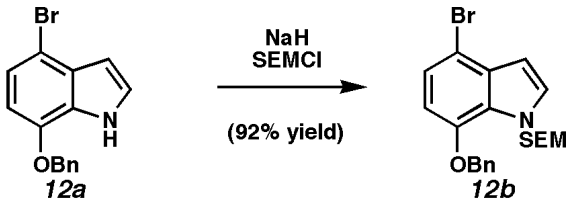
20 *21* *22*

Pyrazinone 22. To a solution of ketoaldehyde **20** (300 mg, 1.73 mmol) and aminoamide **21** (321 mg, 1.73 mmol) in H_2O (17 mL) at 70 ˚C was added powdered potassium hydroxide (487 mg, 8.67 mmol). After stirring at 70 ˚C for 5 h, the reaction mixture was allowed to cool to 23 ˚C, poured into saturated aqueous ammonium chloride (75 mL), and extracted with EtOAc (4 x 75 mL). The combined organic layers were dried briefly over sodium sulfate and concentrated under reduced pressure to afford the desired pyrazinone **22** (423 mg, 75% yield) as an orange/red solid: R_F 0.57 (5:1 dichloromethane/methanol eluent); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.23 (s, 1H), 11.75 (s, 1H), 11.52 (s, 1H), 8.75 (s, 1H), 8.69 (d, *J* = 7.3 Hz, 1H), 8.11 (d, *J* = 2.6 Hz, 1H,), 8.40-7.82 (comp.m, 2H), 7.51-7.45 (comp.m, 2H), 7.25-7.12 (comp.m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.5, 147.2, 136.8, 136.2, 130.1, 126.3, 125.9, 124.1, 122.7, 122.2, 122.0,

120.6, 120.1, 119.7, 112.2, 111.9, 111.6, 106.8; IR (film) 3307, 1633, 1602, 1421 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[C_{20}H_{15}N_4O+Na]^+$: 349.1065, found 349.1070.

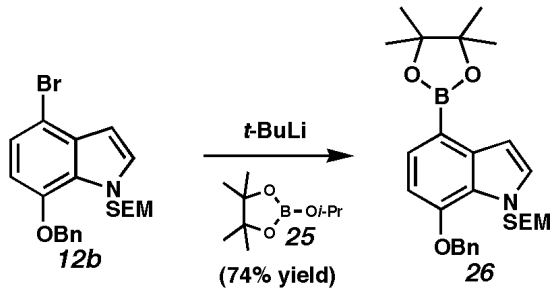


Indole 12a. To a solution of **14** (14.0 g, 45.5 mmol) in THF (455 mL) at -40 ˚C was added vinylmagnesium bromide (1.0 M in THF, 159 mL, 159 mmol) in a dropwise fashion. The reaction mixture was stirred at -40 ˚C for 4 h and then poured into a saturated aqueous solution of ammonium chloride (350 mL). The reaction mixture was extracted with ether (2 x 200 mL) and the combined organic layers were washed with brine (1 x 200 mL), dried over magnesium sulfate, and evaporated under reduced pressure. Dichloromethane (50 mL) was added and the resulting suspension was filtered over a pad of silica gel topped with celite. Removal of solvent under reduced pressure afforded the crude product as a red oil, which was further purified by flash chromatography (8:1 hexanes/ether eluent) to yield 7-benzyloxy-4-bromoindole **12a** (4.54 g, 33% yield) as a yellow oil: R_F 0.30 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (bs, 1H), 7.50-7.40 (comp.m, 5H), 7.20 (d, *J* = 8.2 Hz, 1H), 7.16 (app.t, *J* = 2.7 Hz, 1H), 6.61-6.58 (comp.m, 2H), 5.17 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 136.8, 129.7, 128.8, 128.5, 128.1, 126.9, 124.4, 122.6, 106.1, 104.4, 103.4, 70.6; IR (film) 3426, 1228 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{15}H_{12}BrNO]^+$: 301.0101, found 301.0102.



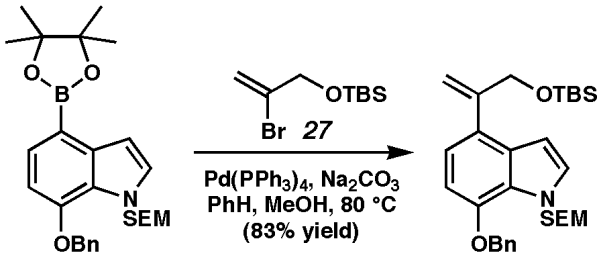
Indole 12b. To a stirred suspension of NaH (60% dispersion in mineral oil, 154 mg, 4.0 mmol) in THF (15 mL) at 0 ˚C was added a solution of **12a** (930 mg, 3.08 mmol) in THF (15 mL). The reaction mixture was allowed to warm to 23 ˚C and stirred for 30 min. The solution

was cooled to 0 ˚C, SEMCl (600 µL, 3.4 mmol) was added, and the mixture was stirred at 23 ˚C for 6 h. The reaction mixture was poured into saturated aqueous ammonium chloride (20 mL) and extracted with ether (2 x 30 mL). The combined organic layers were washed with brine (1 x 20 mL), dried over magnesium sulfate, and evaporated under reduced pressure. The crude residue was purified by flash chromatography (14:1 hexanes/EtOAc eluent) to afford **12b** (1.22 g, 92% yield) as a yellow oil: R_F 0.51 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.50 (comp.m, 2H), 7.46-7.37 (comp. m, 3H), 7.21 (d, *J* = 3.3 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 6.59 (d, *J* = 3.3 Hz, 1H), 5.73 (s, 2H), 5.20 (s, 2H), 3.45 (t, *J* = 8.2 Hz, 2H), 0.84 (t, *J* = 8.2 Hz, 2H), -0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 136.8, 131.6, 129.8, 128.8, 128.3, 127.8, 126.2, 123.0, 106.4, 105.7, 103.6, 77.7, 70.8, 65.5, 17.9, -1.2; IR (film) 1244, 1054 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{21}H_{26}BrNO_2Si]^+$: 431.0916, found 431.0919.



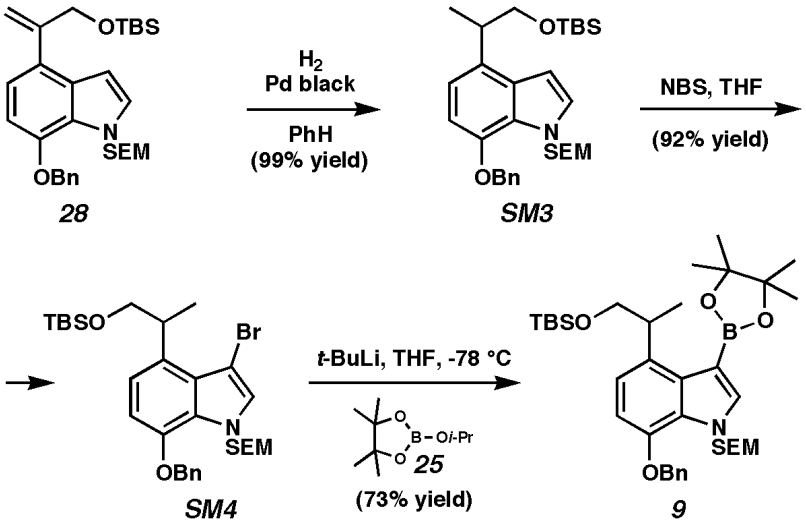
Boronic ester 26. To a solution of **12b** (3.81 g, 8.8 mmol) in THF (147 mL) at -78 ˚C was added *t*-BuLi (1.7 M in pentane, 11.4 mL, 19.4 mmol). Following addition, the reaction mixture was stirred for 15 min at -78 ˚C then borane **25** (3.6 mL, 17.6 mmol) was added. The mixture was stirred at -78 ˚C for 1.5 h, allowed to warm to 23 ˚C, then quenched with saturated aqueous ammonium chloride (75 mL). The layers were separated and the aqueous portion was extracted with ether (3 x 75 mL). The combined organic layers were washed with brine (100 mL), briefly dried over magnesium sulfate, and evaporated under reduced pressure. The crude residue was purified by flash chromatography (14:1 hexanes/EtOAc eluent) to give boronic ester **26** (3.11 g, 74% yield) as a yellow oil: R_F 0.32 (9:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.67 (d, *J* = 7.7 Hz, 1H), 7.59-7.56 (comp.m, 2H), 7.48-7.39 (comp.m, 3H), 7.25 (d, *J* = 3.3 Hz, 1H), 7.12 (d, *J* = 3.3 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 5.81 (s, 2H), 5.28 (s, 2H), 3.49 (t, *J* = 8.2 Hz, 2H), 1.44 (s, 12H), 0.87 (t, *J* = 8.2 Hz, 2H), -0.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 137.0, 136.5, 129.9, 129.7, 128.7, 128.1, 127.8, 125.2, 105.1, 104.2, 83.2, 77.5, 70.3, 65.2, 25.1, 17.9, -1.3; IR (film) 1371, 1330, 1251 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{27}H_{38}BNO_4Si]^+$: 479.2668, found 479.2673.



Olefin 28. A solution containing boronic ester **26** (3.17 g, 6.62 mmol) and bromide **27** (3.32 g, 13.2 mmol) in benzene (130 mL), methanol (30 mL), and aqueous sodium carbonate (2 M, 11 mL) was deoxygenated by bubbling a stream of argon through the reaction mixture for 5 min. Tetrakis(triphenylphosphine)palladium(0) (1.15 g, 0.99 mmol) was then added and the flask was equipped with a reflux condenser. The mixture was heated to 80 ˚C for 2 h and allowed to cool to 23 ˚C. To the reaction vessel was added sodium sulfate (10 g), which was allowed to stand for 30 min. After filtration over a pad of silica gel (CH_2Cl_2 eluent) and concentrating to dryness under reduced pressure, the resulting residue was purified by flash chromatography (1:1 CH_2Cl_2/hexanes eluent) to provide olefin **28** (2.87 g, 83% yield) as a yellow oil: R_F 0.53 (9:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.53 (comp.m, 2H), 7.46-7.37 (comp.m, 3H), 7.18 (d, *J* = 3.3 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.67 (d, *J* = 3.3 Hz, 1H), 5.78 (s, 2H), 5.62 (m, 1H), 5.40 (m, 1H), 5.24 (s, 2H), 4.55 (s, 2H), 3.48 (t, *J* = 8.2 Hz, 2H), 0.99 (s, 9H), 0.85 (t, *J* = 8.2 Hz, 2H), 0.15 (s, 6H), -0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 146.3, 137.2, 130.0, 129.3, 128.8, 128.2, 127.8, 126.3, 126.0, 118.9,

111.9, 104.2, 103.0, 77.6, 70.6, 65.6, 65.4, 26.2, 18.7, 18.0, -1.2, -5.1; IR (film) 1250, 1088 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[C_{30}H_{45}NO_3Si_2+H]^+$: 524.3016, found 524.3019.

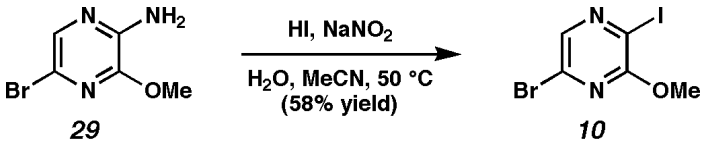


Boronic ester 9. To a solution of olefin **28** (545 mg, 1.04 mmol) in benzene (12 mL), saturated with hydrogen, was added palladium black (35 mg, 0.33 mmol). The reaction vessel was purged with hydrogen and kept under a hydrogen atmosphere (1 atm) with vigorous stirring for 1 h. Palladium black was removed via filtration through a pad of silica gel (benzene eluent) to afford the reduced silyl ether **SM3** (542 mg, 99% yield) as a yellow oil: R_F 0.53 (9:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.50 (comp.m, 2H), 7.43-7.34 (comp.m, 3H), 7.16 (d, *J* = 3.3 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 6.60 (d, *J* = 3.3 Hz, 1H), 5.75 (s, 2H), 5.20 (s, 2H), 3.87 (dd, *J* = 9.9, 4.9 Hz, 1H), 3.62 (app.t, *J* = 9.3 Hz, 1H), 3.45 (t, *J* = 8.2 Hz, 2H), 3.30 (m, 1H), 1.40 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.82 (t, *J* = 8.2 Hz, 2H), 0.00 (s, 6H), -0.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 137.3, 130.7, 129.5, 128.8, 128.7, 128.1, 127.8, 125.7, 117.3, 104.4, 101.7, 77.6, 70.6, 69.0, 65.4, 39.1, 26.3, 18.7, 18.0, 17.5, -1.1, -4.99, -5.04; IR (film) 1249, 1076 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[C_{30}H_{47}NO_3Si_2+Na]^+$: 548.2992, found 548.2997.

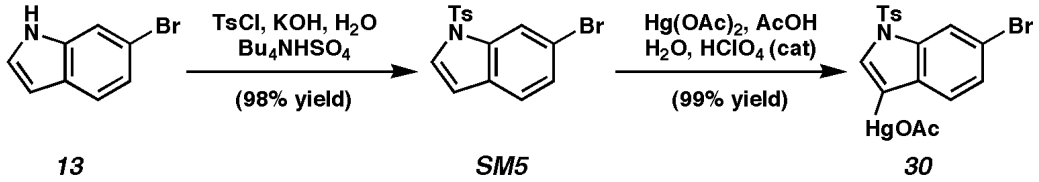
To a solution of the crude silyl ether **SM3** (270 mg, 0.51 mmol) in THF (5 mL), was added *N*-bromosuccinimide (922 mg, 0.51 mmol). After stirring for 5 min, the reaction mixture was poured into a saturated aqueous solution of sodium metabisulfite (3 mL), extracted with

ether (3 x 2 mL), and dried by passage through a plug of silica gel (ether eluent). After concentrating to dryness under reduced pressure, the crude residue was purified by flash chromatography (1:1 CH_2Cl_2/hexanes eluent) to furnish the 3-bromoindole derivative **SM4** (285 mg, 92% yield) as a yellow oil: R_F 0.47 (1:1 CH_2Cl_2/hexanes eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.54 (comp.m, 2H), 7.49-7.40 (comp.m, 3H), 7.24 (s, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 5.77 (d, *J* = 9.9 Hz, 1H), 5.73 (d, *J* = 10.4 Hz, 1H), 5.23 (s, 2H), 4.36 (m, 1H), 4.02 (dd, *J* = 9.6, 4.7 Hz, 1H), 3.65 (dd, *J* = 9.3, 8.3 Hz, 1H), 3.50 (t, *J* = 8.0 Hz, 2H), 1.46 (d, *J* = 7.1 Hz, 3H), 0.96 (s, 9H), 0.89 (t, *J* = 8.0 Hz, 2H), 0.08 (s, 3H), 0.06 (s, 3H), 0.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 136.9, 130.1, 129.6, 128.7, 128.2, 127.8, 126.1, 125.9, 118.7, 105.2, 90.1, 77.7, 70.7, 69.3, 65.6, 34.7, 26.2, 18.6, 18.0, -1.1, -5.0, -5.1; IR (film) 1250 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[C_{30}H_{46}BrNO_3Si_2+Na]^+$: 626.2097, found 626.2079.

To a solution of the 3-bromoindole derivative **SM4** (2.5 g, 4.1 mmol) in THF (69 mL) at -78 ˚C was added *t*-BuLi (1.7M in pentane, 5.4 mL, 9.1 mmol). The reaction mixture was stirred for 15 min at -78 ˚C and dioxaborolane **25** (1.69 mL, 8.3 mmol) was added. The mixture was stirred at -78 ˚C for 1 h, quenched with saturated aqueous ammonium chloride (20 mL), and allowed to warm to 23 ˚C. The layers were separated and the aqueous layer was extracted with ether (3 x 50 mL). The combined organic layers were washed with brine (75 mL), briefly dried over magnesium sulfate, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (14:1 hexanes/EtOAc eluent) to afford boronic ester **9** (1.96 g, 73% yield) as a moderately unstable colorless oil that was used immediately in the coupling reaction that follows: R_F 0.38 (9:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, C_6D_6) δ 7.79 (s, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.20-7.05 (comp.m, 5H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.50 (d, *J* = 10.6 Hz, 1H), 5.46 (d, *J* = 10.3 Hz, 1H), 4.86 (s, 2H), 4.70 (m, 1H), 4.09 (dd, *J* = 9.5, 4.8 Hz, 1H), 3.91 (dd, *J* = 9.5, 7.3 Hz, 1H), 3.28 (t, *J* = 7.7 Hz, 2H), 1.62 (d, *J* = 6.6 Hz, 3H), 1.21 (s, 6H), 1.19 (s, 6H), 0.98 (s, 9H), 0.64 (t, *J* = 7.7 Hz, 2H), 0.00 (s, 3H), -0.01 (s, 3H), -0.19 (s, 9H).



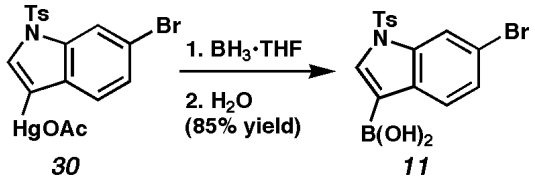
Iodopyrazine 10. To a thick-walled flask charged with **29** (100 mg, 0.49 mmol) was added acetonitrile (1.0 mL), H_2O (1.5 mL), and 48% aqueous HI (1.3 mL). The resulting solution was cooled in an ice bath, and a solution of sodium nitrite (600 mg, 8.7 mmol) in H_2O (1.0 mL) was added in a dropwise fashion. The reaction mixture was sealed, allowed to warm to 23 ˚C, then stirred at 50 ˚C for 30 h. After cooling, the solution was poured into 20% aqueous NaOH and extracted with ether (3 x 20 mL). The combined organic layers were washed with saturated aqueous sodium metabisulfite (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, then evaporated under reduced pressure. The crude product was then dissolved in a CH_2Cl_2/hexanes mixture (1:1) and filtered over silica gel (1:1 CH_2Cl_2/hexanes eluent) to provide iodopyrazine **10** (90 mg, 58% yield) as a white powder: R_F 0.52 (1:1 CH_2Cl_2/hexanes eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 4.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 139.2, 136.1, 104.4, 56.2; IR (KBr) 1357, 1150 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_5H_4BrIN_2O]^+$: 313.8552, found 313.8553.



Organomercurial 30. To a solution of **13** (4.35 g, 22.2 mmol) in toluene (22 mL) was added tetrabutylammonium hydrogensulfate (520 mg, 1.54 mmol), KOH (50% aqueous solution, 28 mL), and a solution of *p*-toluenesulfonyl chloride (5.08 g, 26.6 mmol) in toluene (44 mL). After stirring for 4 h, H_2O (40 mL) was added and the layers separated. The organic layer was washed with H_2O (2 x 20 mL) and brine (1 x 20 mL), dried over magnesium sulfate, and concentrated under reduced pressure to afford 6-bromo-*N*-tosylindole **SM5** (7.6 g, 98% yield) as an off-white powder: R_F 0.25 (9:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19

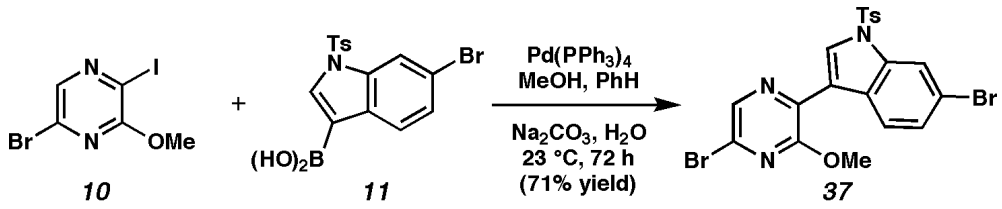
(s, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 3.3 Hz, 1H), 7.33 (comp.m, 2H), 7.21 (d, *J* = 7.7 Hz, 2H), 6.61 (d, *J* = 3.3 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 135.6, 135.1, 130.2, 129.7, 126.9, 126.8, 122.6, 118.3, 116.7, 108.9, 21.7; IR (film) 1364, 1169 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{15}H_{12}BrNO_2S]^+$: 348.9772, found 348.9773.

To a solution of 6-bromo-*N*-tosylindole **SM5** (7.6 g, 21.7 mmol) in acetic acid (145 mL), was added mercuric acetate (6.92 g, 21.7 mmol). After stirring at 23 ˚C for 15 min, perchloric acid (5 drops) was added. The mixture was stirred for 24 h, poured into H_2O (200 mL), then filtered. The resulting white solid was washed with copious amounts of water and dried under vacuum for 12 h to afford organomercurial derivative **30** (13.05 g, 99% yield) as an unstable white powder that was used immediately without further purification: R_F 0.57 (2:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.02 (d, *J* = 1.1 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.52 (s, 1H), 7.42-7.39 (comp.m, 3H), 2.32 (s, 3H), 1.96 (s, 3H).



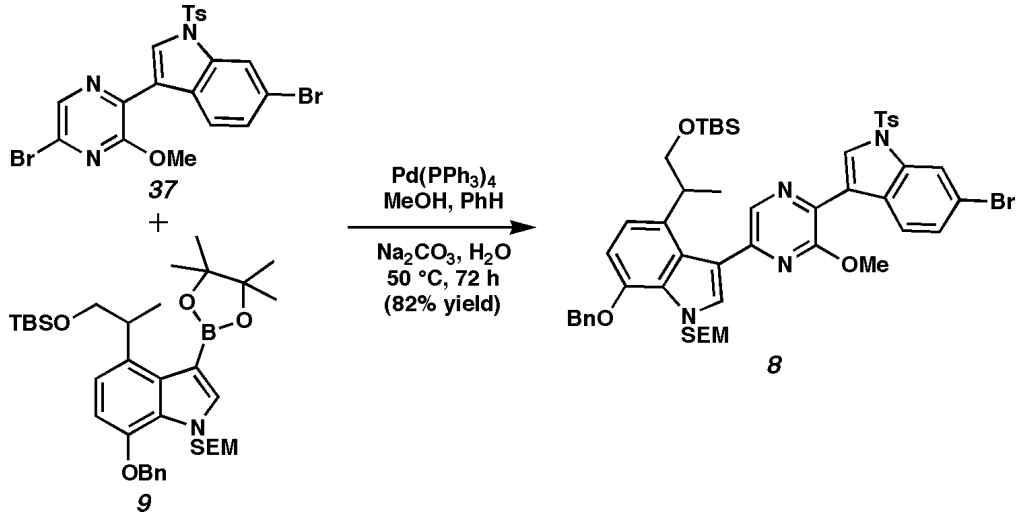
30 *11*

Boronic acid 11. To a solution of **30** (3.91 g, 6.4 mmol) in THF (128 mL) at 23 ˚C was added borane solution (1M in THF, 32 mL, 32 mmol). The resulting solution was stirred for 1 h, then H_2O (38 mL) was added very slowly. After filtration, the organic solvent was evaporated under reduced pressure and the residue was extracted with EtOAc (2 x 60 mL). The combined organic layers were washed with brine (1 x 30 mL) and concentrated under reduced pressure. Trituration of the crude product with hexanes (4x) afforded boronic acid **11** (2.15 g, 85% yield) as an unstable off-white solid that was used immediately without further purification.



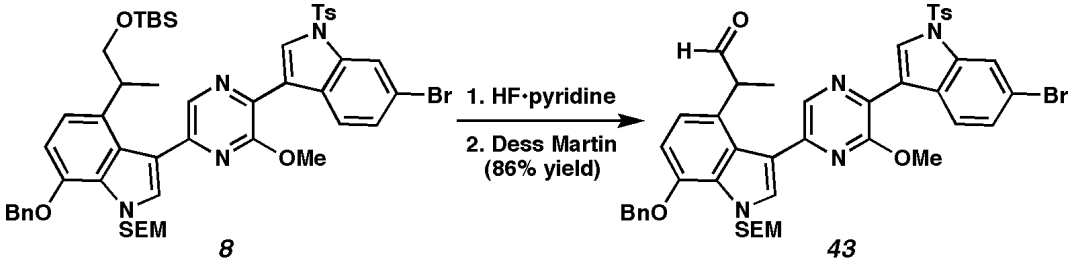
10 *11* *37*

Indolopyrazine 37. A solution containing iodopyrazine **10** (133 mg, 0.42 mmol) and boronic acid **11** (200 mg, 0.51 mmol) in benzene (10 mL), methanol (2 mL), and aqueous sodium carbonate (2 M, 0.70 mL) was deoxygenated by bubbling a stream of argon through the reaction mixture for 5 min. Tetrakis(triphenylphosphine)palladium(0) (73 mg, 0.06 mmol) was then added, the flask was evacuated, and purged with N_2. The reaction mixture was stirred at 23 ˚C for 72 h and quenched by addition of sodium sulfate (500 mg). Filtration over a pad of silica gel (CH_2Cl_2 eluent) and concentration to dryness under reduced pressure, followed by trituration of the remaining residue with ether (3x) and further purification by flash chromatography (CH_2Cl_2 eluent) afforded indolopyrazine **37** (161 mg, 71% yield) as an off-white powder: R_F 0.13 (3:1 hexanes/CH_2Cl_2 eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, *J* = 8.2 Hz, 1H), 8.45 (s, 1H), 8.33 (s, 1H), 8.18 (d, *J* = 2.2 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.43 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 2H), 4.19 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 145.9, 137.6, 137.0, 135.8, 135.1, 132.7, 130.4, 129.3, 128.2, 127.6, 127.2, 125.2, 119.3, 116.5, 116.1, 55.2, 21.8; IR (film) 1374, 1165 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[C_{20}H_{15}Br_2N_3O_3S+H]^+$: 535.9279, found 535.9272.



Bis-indole 8. In a Schlenk flask, a solution containing dibromide **37** (82 mg, 0.15 mmol) and boronic ester **9** (129 mg, 0.20 mmol) in benzene (4 mL), methanol (0.80 mL), and aqueous sodium carbonate (2 M, 0.25 mL) was deoxygenated by bubbling a stream of argon through the

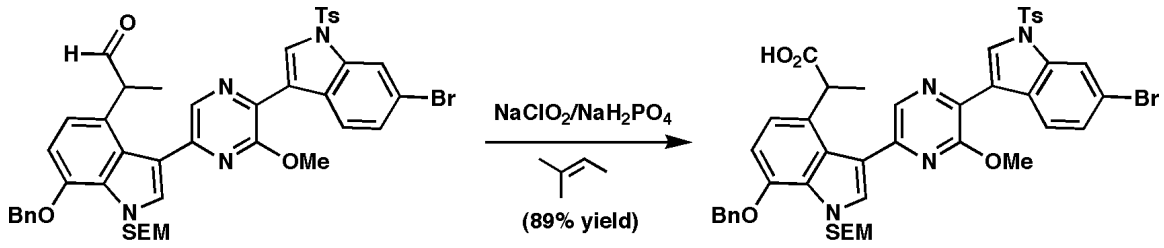
reaction mixture for 5 min. Tetrakis(triphenylphosphine)palladium(0) (27 mg, 0.02 mmol) was then added, the flask was evacuated, purged with N_2, and sealed. The reaction mixture was heated to 50 ˚C for 72 h, cooled to 23 ˚C, then quenched by addition of sodium sulfate (300 mg). Following filtration through a pad of silica gel (CH_2Cl_2 eluent) and evaporation to dryness *in vacuo*, the remaining residue was purified by flash chromatography (2:1 CH_2Cl_2/hexanes eluent) to give a crude product, which was further purified by flash chromatography (7:1 hexanes/EtOAc eluent) to afford bis-indole **8** (122 mg, 82% yield) as a yellow oil: R_F 0.2 (9:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, *J* = 8.4 Hz, 1H), 8.52 (s, 1H), 8.50 (s, 1H), 8.27 (d, *J* = 1.8 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.56-7.38 (comp.m, 7H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 5.84 (s, 2H), 5.25 (s, 2H), 4.25 (s, 3H), 4.07 (m, 1H), 3.62 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.55 (t, *J* = 8.1, 2H), 3.35 (app.t, *J* = 9.2 Hz, 1H), 2.37 (s, 3H), 1.33 (d, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 8.4 Hz, 2H), 0.69 (s, 9H), -0.04 (s, 9H), -0.16 (s, 3H), -0.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 145.7, 145.6, 145.4, 137.2, 135.8, 135.6, 135.5, 135.1, 131.3, 130.9, 130.3, 128.8, 128.7, 128.3, 127.8, 127.7, 127.3, 127.1, 127.0, 125.5, 119.0, 118.8, 117.3, 116.4, 115.6, 105.5, 78.0, 70.8, 69.2, 65.8, 54.2, 36.8, 25.9, 21.8, 18.2, 18.0, 17.7, -1.2, -5.5, -5.6; IR (film) 1374, 1178, 1087 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[C_{50}H_{61}BrN_4O_6SSi_2+H]^+$: 981.3112, found 981.3097.



Aldehyde 43. To a Falcon tube containing a THF (5 mL) solution of bis-indole **8** (70 mg, 0.07 mmol) at 0 ˚C, was added HF•pyridine (800 μL) in a dropwise fashion. The reaction mixture was stirred at 0 ˚C for 1.5 h until the reaction was judged complete by TLC. After dilution of the mixture with ether (10 mL), saturated aqueous sodium bicarbonate (10 mL) was added in a dropwise manner at 0 ˚C. The layers were separated and the organic portion was

further washed with saturated aqueous sodium bicarbonate (3 x 10 mL), dried over magnesium sulfate, and concentrated under reduced pressure.

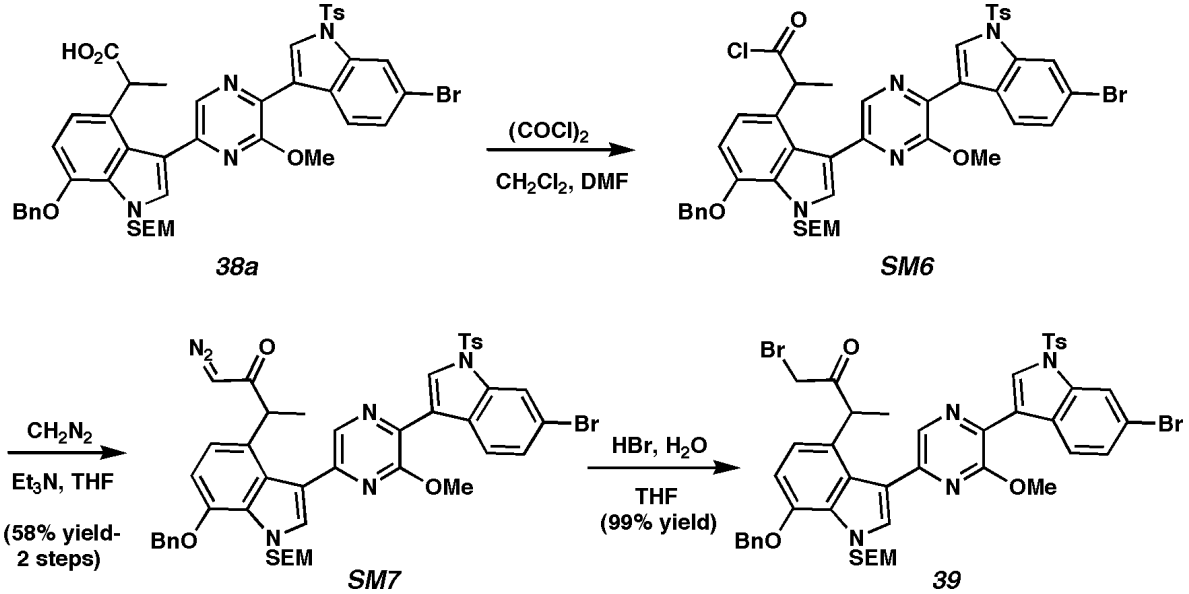
The crude residue prepared above was dissolved in anhydrous CH_2Cl_2 (5mL) and Dess-Martin periodinane (91 mg, 0.214 mmol) was introduced. The reaction mixture was stirred at 23 ˚C for 20 min, poured into a saturated aqueous solution of sodium bicarbonate/sodium thiosulfate (1:1, 5 mL), and extracted with CH_2Cl_2 (3 x 10mL). The organic layers were washed with brine (5 mL), dried over magnesium sulfate, and evaporated under reduced pressure to provide the crude product which was purified by flash chromatography (2:1 hexanes/EtOAc) to furnish aldehyde **43** (53 mg, 86% yield) as a yellow oil: R_F 0.67 (2:1 hexanes/EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.69 (d, *J* = 8.3 Hz, 1H), 8.52 (s, 1H), 8.46 (s, 1H), 8.24 (d, *J* = 1.5 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.56-7.39 (comp.m, 7H), 7.30 (d, *J* = 7.8 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 5.85 (s, 2H), 5.27 (s, 2H), 4.76 (q, *J* = 6.8 Hz, 1H), 4.18 (s, 3H), 3.55 (t, *J* = 8.0 Hz, 2H), 2.39 (s, 3H), 1.37 (d, *J* = 6.8 Hz, 3H), 0.89 (t, *J* = 8.0 Hz, 2H), -0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 156.1, 146.4, 145.7, 144.8, 136.8, 136.2, 135.8, 135.6, 135.0, 131.8, 130.4, 129.1, 128.9, 128.6, 128.5, 128.0, 127.9, 127.5, 127.4, 127.2, 125.4, 124.3, 121.0, 119.1, 116.9, 116.5, 115.2, 105.9, 78.2, 70.9, 66.0, 54.3, 48.5, 21.8, 18.0, 15.0, -1.2; IR (film) 1720, 1374, 1177, 1086 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[C_{44}H_{45}BrN_4O_6SSi+H]^+$: 865.2090, found 865.2103.



43 *38a*

Acid 38a. A solution of aldehyde **43** (53 mg, 0.061 mmol) in acetone (12 mL) was treated with a saturated solution of NaH_2PO_4 that had been acidified to pH 2 with 1 N HCl (1.4 mL) and cooled to 0 ˚C. After the addition of 2-methyl-2-butene (32.5 µL, 0.31 mmol), a solution of

$NaClO_2$ (13.9 mg, 0.123 mmol) in H_2O (1.4 mL) was added dropwise over 5 min. The reaction mixture was poured into cold H_2O (2 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried over magnesium sulfate and evaporated to dryness. The crude residue was passed through a short plug of silica gel (EtOAc eluent) and the solvent was evaporated to afford acid **38a** (49 mg, 89% yield): R_F 0.22 (2:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, *J* = 8.3 Hz, 1H), 8.52 (s, 1H), 8.44 (s, 1H), 8.23 (d, *J* = 1.5 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.53-7.37 (comp.m, 7H), 7.28 (d, *J* = 9.2 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 5.84 (d, *J* = 10.3 Hz, 1H), 5.78 (d, *J* = 10.3 Hz, 1H), 5.24 (s, 2H), 4.86 (q, *J* = 6.8 Hz, 1H), 4.20 (s, 3H), 3.53 (t, *J* = 8.3 Hz, 2H), 2.36 (s, 3H), 1.42 (d, *J* = 6.8 Hz, 3H), 0.86 (t, *J* = 8.3 Hz, 2H), -0.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 156.2, 146.2, 145.7, 145.0, 136.9, 136.2, 135.8, 135.7, 135.1, 131.7, 130.4, 129.1, 128.9, 128.6, 128.5, 128.4, 127.9, 127.5, 127.3, 127.2, 126.3, 125.4, 119.8, 119.1, 116.9, 116.5, 114.9, 105.8, 78.1, 70.9, 66.0, 54.5, 40.6, 21.8, 18.4, 18.0, -1.2; IR (film) 2948, 1703, 1373, 1177, 1139, 1088 cm^{-1}; HRMS (ESI) *m/z* calc'd for $(C_{44}H_{45}BrN_4O_7SSi+Na)^+$: 881.2040, found 881.2009.



Bromoketone 39. To a solution of carboxylic acid **38a** (49 mg, 0.0559 mmol) in CH_2Cl_2 (400 µL) at 0 ˚C, was added oxalyl chloride (6.3 µL, 0.0727 mmol), followed by DMF (1 µL). After stirring at 0 ˚C for 30 min, all solvents were removed in vacuo. The crude acid chloride

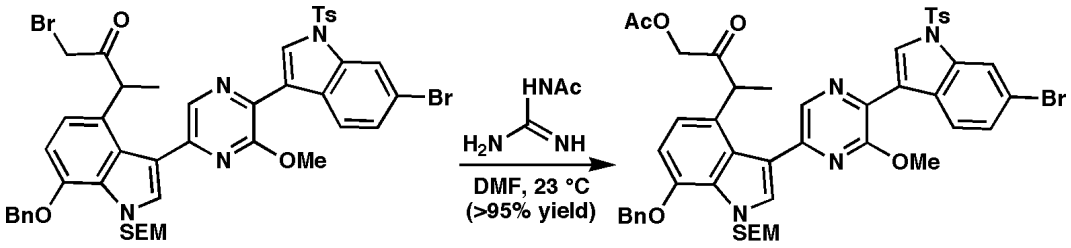
SM6 was allowed to dry in vacuo for an additional 1 h and was used in the next step without further purification.

Note: in the next step diazomethane was dried by storing the ethereal diazomethane solution over potassium hydroxide pellets for 3 h. Immediately before use, the diazomethane was further dried over sodium metal for approximately 15 min. ***Caution!*** *Diazomethane is toxic and explosive. Caution should always be used when preparing and handling diazomethane, particularly when drying over sodium. All reactions were carried out in a well-ventilated fume hood behind a blast shield. For the use of sodium to dry diazomethane, see:* Arndt, F. *Org. Synth*., **1943**, Coll. Vol. 2, 165.

To crude acid chloride **SM6** and Et_3N (23 μL, 0.168 mmol) in THF (400 μL) at 0 ˚C was added an ethereal solution of thoroughly dried diazomethane (1.5 mL) via a flamed glass pipette. The reaction mixture was allowed to warm to 23 ˚C, poured into saturated aqueous sodium bicarbonate (1 mL), and extracted with ether (3 x 3 mL). The combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. The crude residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to give diazoketone **SM7** (29.5 mg, 58% yield) as a yellow oil.

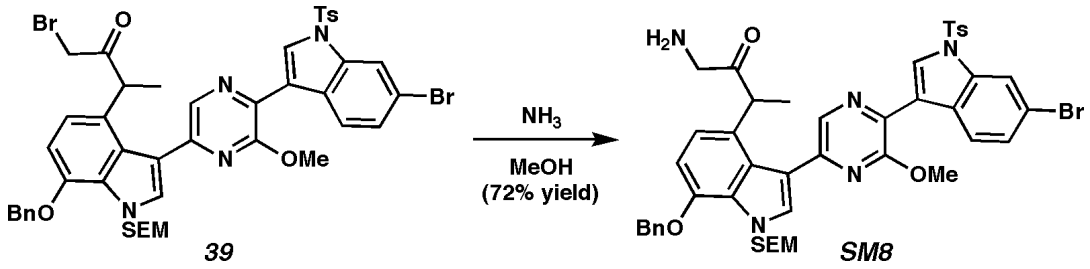
To **SM7** (19 mg, 0.021 mmol) in THF (2 mL) at 0 ˚C, 48% aqueous HBr (50 μL) was added slowly down the walls of the flask. After stirring for 5 min, the reaction mixture was poured into a saturated aqueous solution of sodium bicarbonate and extracted with ether (3 x 4 mL). The combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure to afford bromoketone **39** (20 mg, 99% yield) as a yellow oil: R_F 0.68 (2:1 hexanes/EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, *J* = 8.6 Hz, 1H), 8.53 (s, 1H), 8.47 (s, 1H), 8.24 (d, *J* = 1.5 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.55-7.38 (comp.m, 7H), 7.31 (d, *J* = 8.2 Hz, d), 6.85 (d, 2H), 5.83 (s, 2H), 5.25 (s, 2H), 5.01 (q, *J* = 6.7 Hz, 1H), 4.21 (s, 3H), 3.76 (d, *J* = 12.8 Hz, 1H), 3.67 (d, *J* = 13.1 Hz, 1H), 3.55 (t, *J* = 8.2 Hz, 2H), 2.39 (s, 3H), 1.48 (d, *J* = 6.7 Hz, 3H), 0.88 (t, *J* = 8.1 Hz, 2H), -0.052 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 146.5, 145.8, 144.8, 136.7, 136.5, 135.8, 135.7, 135.1, 140.0, 130.4, 129.2, 128.9, 128.6,

128.5, 128.0, 127.7, 127.5, 127.3, 127.2, 125.5, 125.4, 120.7, 119.1, 116.8, 116.5, 114.9, 106.0, 78.2, 71.0, 66.1, 54.3, 46.0, 34.2, 21.8, 18.0, 17.8, -1.2; IR (film) 2949, 1724, 1374, 1246, 1178, 1141, 1088 cm^{-1}; HRMS (ESI) *m/z* calc'd for $(C_{45}H_{46}Br_2N_4O_6SSi+H)^+$: 957.1353, found 957.1376.

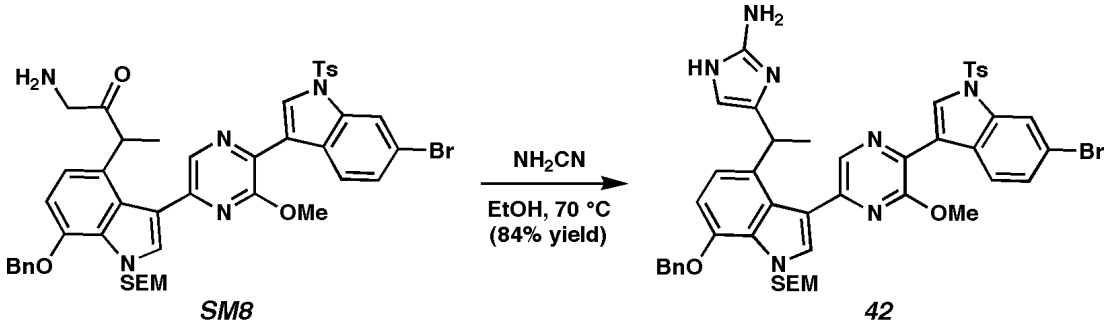


39 *41*

Acetoxyketone 41. To a solution of bromoketone **39** (10 mg, 0.0104 mmol) in DMF (350 μL) was added acetyl guanidine (32 mg, 0.316 mmol). After stirring at 23 ˚C for 48 h, H_2O (1 mL) and EtOAc (1 mL) were added. The layers were separated and the organic layer was washed with water (3 x 500 μL) and brine (1 x 500 μL), then dried by passage through a plug of silica gel (EtOAc eluent), and evaporated to afford acetoxyketone **41** (9.5 mg, 95% yield): R_F 0.53 (2:1 hexanes/EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, *J* = 8.5 Hz, 1H), 8.54 (d, *J* = 0.9 Hz, 1H), 8.46 (d, *J* = 1.2 Hz, 1H), 8.24 (s, 1H), 7.87 (d, *J* = 7.6 Hz, 2H), 7.55-7.39 (comp.m, 7H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.86 (s, 2H), 5.83 (s, 2H), 5.25 (s, 2H), 4.83 (q, *J* = 6.7 Hz, 1H), 4.47 (s, 2H), 4.21 (s, 3H), 3.54 (t, *J* = 8.2 Hz, 2H), 2.39 (s, 3H), 2.01 (s, 3H), 1.42 (d, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 8.2 Hz, 2H), -0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 156.3, 146.4, 145.8, 144.9, 136.8, 136.5, 135.9, 135.6, 135.1, 131.9, 130.4, 129.2, 128.9, 128.6, 128.5, 128.0, 127.6, 127.5, 127.3, 127.2, 125.7, 125.4, 120.6, 119.1, 116.9, 116.5, 114.9, 106.0, 78.2, 71.0, 67.2, 66.1, 54.3, 45.6, 21.9, 20.6, 18.1, 17.3, -1.2; IR (film) 2949, 1750, 1728, 1373, 1244, 1178, 1141, 1088 cm^{-1}; HRMS (ESI) *m/z* calc'd for $(C_{47}H_{49}BrN_4O_8SSi+H)^+$: 937.2302, found 937.2290.

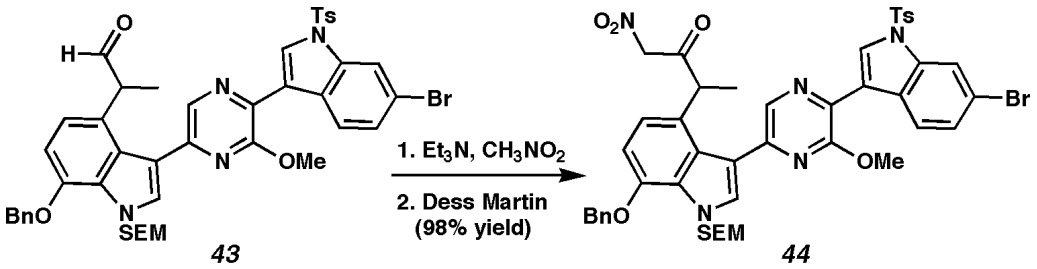


Aminoketone SM8. Bromoketone **39** (6 mg, 0.0062 mmol) was dissolved in a saturated solution of ammonia in methanol (1 mL). After stirring for 6 h at 23 ˚C, the reaction mixture was filtered through a plug of silica gel (methanol eluent) and the solvent was evaporated. The crude residue was then purified by preparative thin layer chromatography (7:1 CH_2Cl_2/methanol eluent) to afford aminoketone **SM8** (4 mg, 72% yield): R_F 0.67 (7:1 dichloromethane/methanol eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, 8.8, 1H), 8.53 (s, 1H), 8.46 (s, 1H), 8.23 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.54-7.37 (comp.m, 7H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.84-6.83 (comp.m, 2H), 5.82 (s, 2H), 5.24 (s, 2H), 4.71 (q, *J* = 6.6 Hz, 1H), 4.19 (s, 3H), 3.54 (t, *J* = 8.1 Hz, 2H), 3.31 (d, *J* = 19.3 Hz, 1H), 3.07 (d, *J* = 19.1 Hz, 1H), 2.38 (s, 3H), 1.44 (d, *J* = 7.0 Hz, 3H), 0.87 (t, *J* = 8.1 Hz, 2H), -0.06 (s, 9H).



Aminoimidazole 42. To a solution of aminoketone **SM8** (7 mg, 0.0078 mmol) in ethanol (700 µL) was added cyanamide (15 mg, 0.36 mmol). The reaction vessel was sealed, and heated to 70 ˚C for 10 h. After cooling to 23 ˚C, the reaction mixture was purified by reversed-phase filtration through a Sep-Pak column: first 10% acetonitrile, then 100% acetonitrile to collect the product. After removal of solvent under reduced pressure, **42** (6 mg, 84% yield) was isolated as an orange/red oil: R_F 0.27 (7:1 dichloromethane/methanol eluent); ^{1}H NMR (500

MHz, CD_3OD) δ 8.68 (d, *J* = 8.8 Hz, 1H), 8.52 (s, 1H), 8.38 (s, 1H), 8.16 (d, *J* = 1.5 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.60-7.33 (comp.m, 9H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.10 (s, 1H), 5.85 (s, 2H), 5.28 (s, 2H), 5.09 (q, *J* = 6.8 Hz, 1H), 4.19 (s, 3H), 3.57 (t, *J* = 7.9 Hz, 2H), 2.37 (s, 3H), 1.41 (d, *J* = 7.0 Hz, 3H), 0.82 (t, *J* = 7.9 Hz, 2H), -0.10 (s, 9H); HRMS (ESI) *m/z* calc'd for $(C_{46}H_{48}BrN_7O_5SSi+H)^+$: 918.2468, found 918.2467.

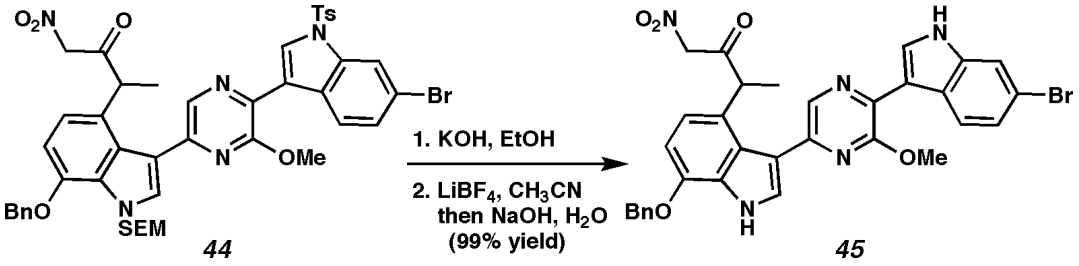


43 *44*

Ketone 44. To aldehyde **43** (20 mg, 0.023 mmol) in nitromethane (1 mL) was added triethylamine (75 μL, 0.54 mmol). The reaction mixture was stirred at 23 ˚C for 15 h. The excess nitromethane was removed by evaporation under reduced pressure to afford the crude nitroaldol product which was used without further purification.

The crude residue was dissolved in anhydrous CH_2Cl_2 (1.5 mL) and treated with Dess-Martin periodinane (15% solution in CH_2Cl_2, 200 μL, 0.099 mmol). The reaction mixture was stirred at 23 ˚C for 5 min and quenched by addition of a saturated aqueous solution of sodium bicarbonate/sodium thiosulfate (1:1, 2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (8 x 1mL). The combined organic layers were washed with brine (2 mL), dried by passage through a plug of silica gel (EtOAc eluent), and evaporated under reduced pressure to afford ketone **44** (21 mg, 98% yield) as a yellow oil: R_F 0.20 (3:1 hexanes/EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, *J* = 8.3 Hz, 1H), 8.44 (s, 1H), 8.39 (s, 1H), 8.18 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.49-7.33 (comp.m, 7H), 7.24 (d, *J* = 8.3 Hz, 2H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 5.77 (s, 2H), 5.21 (s, 2H), 5.03 (d, *J* = 14.6 Hz, 1H), 4.98 (d, *J* = 14.6 Hz, 1H), 4.90 (q, *J* = 6.8 Hz, 1H), 4.14 (s, 3H), 3.49 (t, *J* = 7.8 Hz, 2H), 2.32 (s, 3H), 1.44 (d, *J* = 6.8 Hz, 3H), 0.82 (t, *J* = 8.0 Hz, 2H), -0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.0, 156.3, 146.9, 145.8, 144.3, 136.9, 136.5, 135.8, 135.6, 135.0, 132.3, 130.4,

129.3, 129.0, 128.6, 128.5, 128.0, 127.6, 127.5, 127.4, 127.2, 125.4, 123.7, 121.0, 119.2, 116.7, 116.5, 114.6, 106.2, 82.2, 78.3, 71.0, 66.2, 54.4, 47.6, 21.8, 18.0, 16.9, -1.2; IR (film) 1732, 1559, 1376, 1178, 1080 cm^{-1}.

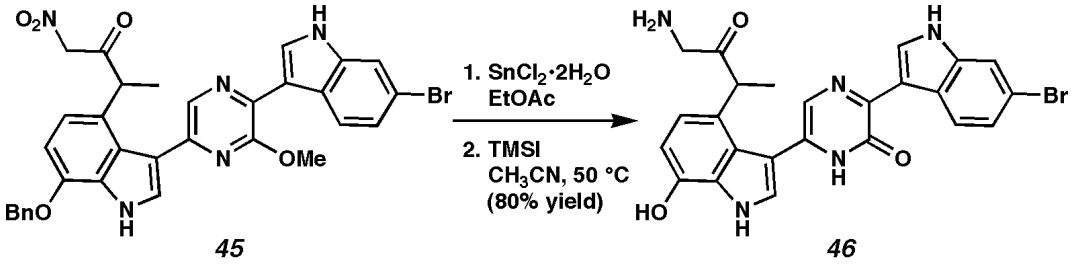


44 *45*

Nitroketone 45. To a suspension of ketone **44** (30 mg, 0.032 mmol) in EtOH (2 mL, deoxygenated by sparging with argon for 2 min), was added powdered KOH (100 mg, 1.8 mmol). The reaction vessel was equipped with a reflux condenser and heated to 40 ˚C for 2 h. After cooling to 23 ˚C, the reaction mixture was quenched with saturated aqueous ammonium chloride (2 mL) and extracted with EtOAc (8 x 1 mL). The combined organic layers were washed with brine (2 mL), dried by passage through a plug of silica gel (EtOAc eluent), and evaporated under reduced pressure to afford the crude detosylated ketone which was used without further purification.

To the crude detosylated ketone prepared above in acetonitrile (3 mL, deoxygenated by sparging with argon for 2 min) and water (30 μL), was added lithium tetrafluoroborate (120 mg, 0.13 mmol). The reaction vessel was equipped with a reflux condenser and heated to 70 ˚C for 1.5 h (TLC showed complete consumption of starting material). After cooling to 40 ˚C, sodium hydroxide (20% aqueous, 2 mL) was added. The resulting mixture was stirred for 10 min, allowed to cool to 23 ˚C, quenched with saturated aqueous ammonium chloride (2 mL), and extracted with EtOAc (8 x 1 mL). The combined organic layers were washed with brine (2 mL), dried by passage through a plug of silica gel (EtOAc eluent), and evaporated under reduced pressure to afford nitroketone **45** (20.5 mg, 99% yield) as a yellow oil: R_F 0.59 (1:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, acetone-d_6) δ 11.14 (bs, 1H), 10.86 (bs, 1H), 8.82 (d, J = 8.8 Hz, 1H), 8.54 (s, 1H), 8.43 (m, 1H), 7.75-7.72 (comp.m, 2H), 7.62-7.59 (comp.m,

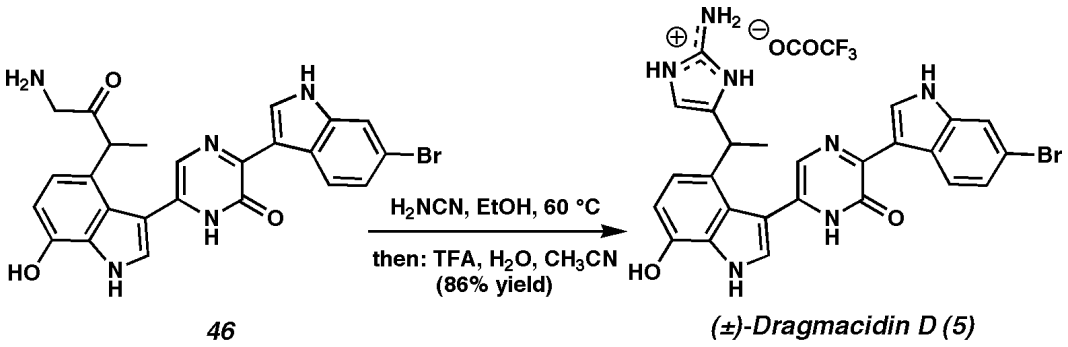
2H), 7.47-7.30 (comp.m, 4H), 6.95 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 5.41-5.22 (comp.m, 5H), 4.19 (s, 3H), 1.47 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 198.7, 156.2, 146.3, 143.6, 139.4, 138.6, 138.3, 136.1, 130.7, 129.4, 129.4, 128.9, 128.8, 128.3, 126.9, 126.8, 125.8, 124.9, 124.2, 120.5, 116.3, 116.0, 115.3, 112.5, 105.1, 83.4, 70.9, 54.1, 47.7, 17.3; IR (film) 3410 (broad), 1728, 1697, 1557, 1450 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[C_{32}H_{26}BrN_5O_5+H]^+$: 640.1196, found 640.1180.



Aminoketone 46. To a solution of deprotected ketone **45** (5.5 mg, 0.0086 mmol) in EtOAc (600 µL, deoxygenated by bubbling with argon for 1 min), was added $SnCl_2$•$2H_2O$ (30 mg, 0.13 mmol). The reaction vessel was equipped with a reflux condenser and heated at 80 ˚C for 3 h. After cooling to 23 ˚C, the solvent was removed under reduced pressure to leave an orange residue which was purified by reversed-phase filtration through a Sep-Pak column: first 10% acetonitrile containing 0.1% (wt/v) TFA to remove salts, then 90% acetonitrile containing 0.1% (wt/v) TFA to collect the crude product. After removal of solvent *in vacuo*, the compound was filtered through silica gel (5:1 CH_2Cl_2/methanol eluent) to provide the reduced compound which was used without further purification.

To the crude aminoketone in acetonitrile (700 µL) at 0 ˚C, in a Schlenk tube, was added iodotrimethylsilane (150 µL, 1.05 mmol). The reaction mixture was heated at 50 ˚C for 2 h, cooled to 0 ˚C, then quenched with a saturated aqueous solution of sodium metabisulfite. The reaction mixture was purified by reversed-phase filtration through a Sep-Pak column: first 10% acetonitrile containing 0.1% (wt/v) TFA to remove salts, then 90% acetonitrile containing 0.1% (wt/v) TFA to collect the crude product. After removal of solvent under reduced pressure, the compound was further purified by reversed-phase HPLC. Concentration under reduced pressure

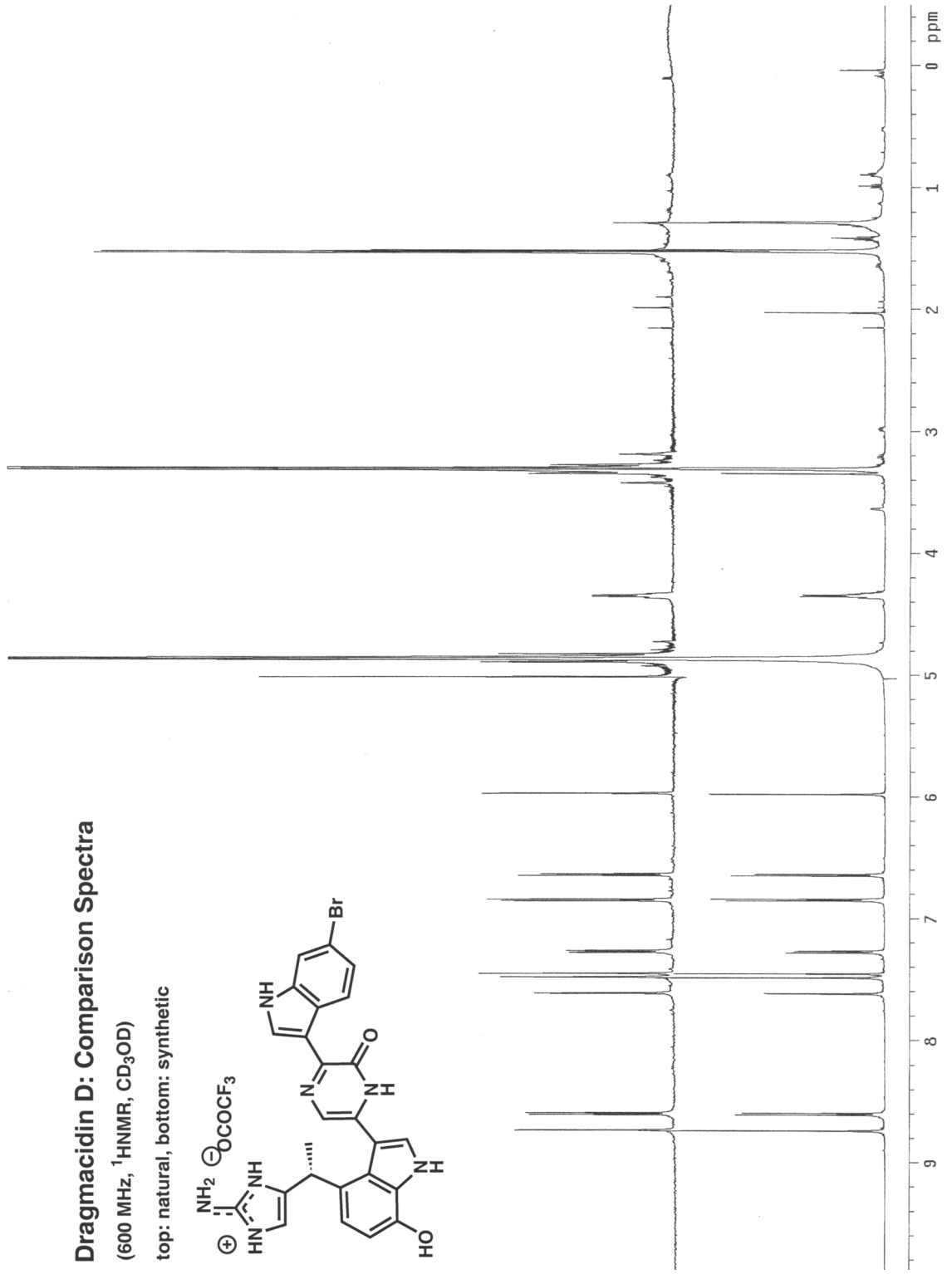
provided the fully deprotected aminoketone **39** (3.5 mg, 80% yield) as an orange/red oil: ^{1}H NMR (500 MHz, CD_3OD) δ 8.75 (s, 1H), 8.60 (d, *J* = 8.4 Hz, 1H), 7.67 (s, 1H), 7.62 (d, *J* = 1.7 Hz, 1H), 7.54 (s, 1H), 7.27 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.69 (d, *J* = 8.1 Hz, 1H), 6.63 (d, *J* = 7.7 Hz, 1H), 4.15 (q, *J* = 6.9 Hz, 1H), 3.64 (d, *J* = 1.7 Hz, 2H), 1.44 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 204.4, 157.4, 151.0, 145.3, 139.1, 132.6, 131.7, 129.0, 128.3, 127.7, 126.7, 126.1, 125.6, 124.9, 122.6, 121.0, 117.1, 115.5, 113.7, 108.5, 107.9, 46.8, 17.2; IR (film) 3140 (broad), 1671, 1200, 1140 cm^{-1}; HRMS (ESI) *m/z* calc'd for $[C_{24}H_{20}BrN_5O_3+H]^+$: 506.0828, found 506.0827.



46 *(±)-Dragmacidin D (5)*

Dragmacidin D (5). To a solution of aminoketone **46** (2 mg, 0.0039 mmol) in ethanol (700 μL, deoxygenated by bubbling with argon for 5 min) was added cyanamide (15 mg, 0.36 mmol). The reaction vessel was purged with argon, sealed, and heated to 60 ˚C for 3 h. After cooling to 23 ˚C, the reaction mixture was purified by reversed-phase filtration through a Sep-Pak column: first 10% acetonitrile containing 0.1% (wt/v) TFA to remove salts, then 60% acetonitrile containing 0.1% (wt/v) TFA to collect the product. After removal of solvent under reduced pressure, dragmacidin D (**5**, 1.8 mg, 86% yield) was isolated as an orange/red oil: ^{1}H NMR (600 MHz, CD_3OD) δ 8.74 (s, 1H), 8.6 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 1.8 Hz, 1H), 7.49 (s, 1H), 7.46 (s, 1H), 7.27 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 5.98 (s, 1H), 4.35 (q, *J* = 6.9 Hz, 1H), 1.52 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 157.1, 150.3, 148.7, 144.8, 139.1, 134.2, 132.4, 132.2, 128.7, 127.9, 127.3, 126.7, 126.3, 125.6, 124.8, 120.2, 117.1, 115.4, 113.7, 110.2, 108.9, 107.3, 33.2, 20.8; IR (film) 3200 (broad), 1667, 1204, 1138 cm^{-1}; UV λ_{max} (EtOH) 216, 274, 389 nm. After addition of 1 drop concentrated HCl

to 1 mL cell: λ_{max} (EtOH) 219, 277, 460 nm; HRMS (ESI) *m/z* calc'd for $[C_{25}H_{20}BrN_7O_2+H]^+$: 530.0940, found 530.0943. See Comparison ^1H NMR spectra:


Dragmacidin D: Comparison Spectra
(600 MHz, ^{1}HNMR, CD_3OD)
top: natural, bottom: synthetic
NH_2
$\ominus OCOCF_3$
HN
NH
NH
N
O
NH
Br
HO
9
8
7
6
5
4
3
2
1
0 ppm