(+)-Saxitoxin: A First and Second Generation Stereoselective Synthesis

Supplementary Information

(24 pages)

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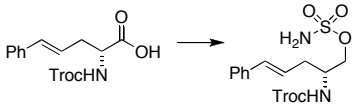
General. All reagents were obtained commercially unless otherwise noted. Reactions were performed using oven-dried glassware under an atmosphere of nitrogen. Air- and moisture sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated under reduced pressure (ca. 20 mm Hg) by rotary evaporation. Dichloromethane, tetrahydrofuran (THF), acetonitrile (MeCN) and *N,N*-dimethylformamide (DMF) were passed through two columns of activated alumina immediately prior to use. Hexamethyldisilazane was distilled from CaH_2 and trifluoroacetic acid was distilled from $MgSO_4$. *N*-[1-Chloro-1-methylsulfanylmethylidene]-4-methoxybenzenesulfonamide was prepared according to the procedure of Neidlain and Haussmann[1] and *N*-dichloromethylene-4-methoxybenzenesulfonamide was prepared according to the procedure of Gompper.[2,3] Boron tris(trifluoroacetate) was prepared as a 0.5 M solution in trifluoroacetic acid as described by Bauer[4] and stored in a Schlenk flask at 25 ºC. Chromatographic purification of products was accomplished using forced flow chromatography on Silicycle silica gel 60 (40–63 μm). Thin layer chromatography was performed on EM Science silica gel 60 F_{254} plates (250 μm). Visualization of the developed chromatogram was accomplished by fluorescence quenching and by staining with ethanolic anisaldehyde, aqueous potassium permanganate, or aqueous ceric ammonium molybdate (CAM) solution. High pressure liquid chromatography (HPLC) purification was performed using a Waters instrument with either a Novapac C_{18}, 7.8 x 300 mm, 6 μm column using MeCN/H_2O as eluent with 0.1% CF_3CO_2H buffer or 10 mM C_3F_7COOH (as indicated).

Nuclear magnetic resonance (NMR) spectra were acquired on a Varian Inova spectrometer operating at 400, 500, or 600 and 100, 125, or 150 MHz for ^1H and ^{13}C, respectively, and are referenced internally according to residual solvent signals. Data for ^1H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; br, broad), integration, coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Infrared (IR) spectra were recorded as either thin films using NaCl plates or as KBr pellets on a Thermo-Nicolet 300 FT-IR spectrometer and are reported in frequency of absorption. Optical rotation data were obtained from samples loaded into a 50 mm cell on a Jasco DIP-1000 digital polarimeter operating at the Na D-line. High resolution mass spectra were obtained from the Vincent Coates Foundation Mass Spectrometry Laboratory at Stanford University.

Experimental protocols and characterization data:

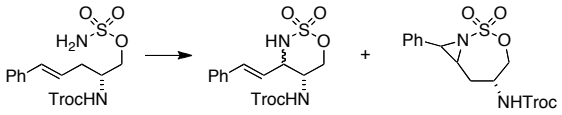


8

To a solution of (*R*)-2-(*N*-trichloroethoxycarbonyl)-5-phenyl-4-pentenoic acid[5] (6.43 g, 17.5 mmol) in 18 mL of DME cooled to –10 °C was added *N*-methylmorpholine (2.0 mL, 17.9 mmol, 1.02 equiv) and isobutylchloroformate (2.3 mL, 17.9 mmol, 1.02 equiv). The mixture was stirred for 5 min at –10 °C during which time a white precipitate formed. The slurry was filtered through a small pad of Celite, washing the flask and filter cake with 18 mL of DME. The combined filtrates were cooled to –10 °C and to this solution was added dropwise a solution of $NaBH_4$ (995 mg, 26.3 mmol, 1.5 equiv) in 10 mL of H_2O. After stirring the contents for 15 min at –10 °C, 50 mL of H_2O was added and the mixture was transferred to a separatory funnel containing 150 mL of EtOAc. The organic phase was collected and the aqueous layer was extracted with 3 x 50 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the oily residue by chromatography on silica gel (2:1 hexanes/EtOAc) afforded the corresponding 1° alcohol as a colorless oil (3.97 g, 64%): TLC R_f = 0.23 (2:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.18 (m, 5H), 6.49 (d, 1H, *J* = 15.9 Hz), 6.18 (ddd, 1H, *J* = 14.8, 7.3, 7.3 Hz), 5.26 (d, 1H, *J* = 7.2 Hz), 4.70 (d, 1H, *J* = 12.1 Hz), 4.73 (d, 1H, *J* = 12.1 Hz), 3.94-3.84 (m, 1H), 3.79 (dd, 1H, *J* = 11.0, 4.0 Hz), 3.73 (dd, 1H, *J* = 11.0, 4.9 Hz), 2.60-2.44 (m, 2H), 1.96 (br s, 1H) ppm.

To a flask containing $ClSO_2NCO$ (2.7 mL, 31.5 mmol, 3.0 equiv) in 15 mL of ice-cold CH_2Cl_2 was added via addition funnel a solution of HCO_2H (1.2 mL, 31.5, 3.0 equiv) in 15 mL of CH_2Cl_2. Vigorous gas evolution was witnessed immediately. The solution was warmed from 0° to 23 °C and stirred for 10 h. Following this period, the resulting white suspension was cooled to –10 °C and a solution of 1° alcohol (3.70 g, 10.5 mmol), Et_3N (5.1 mL,

36.7 mmol, 3.5 equiv) and DMAP (64 mg, 525 μmol, 0.05 equiv) in 40 mL of CH_2Cl_2 was added via cannula. An additional 10 mL of CH_2Cl_2 was used to ensure quantitative transfer of the alcohol. The homogeneous solution was warmed to 23 °C and stirred for 30 min. The reaction mixture was then concentrated under reduced pressure to ~1/3 the original volume and poured into a separatory funnel containing 300 mL of EtOAc and 150 mL of aqueous NaH_2PO_4/Na_2HPO_4 buffer (pH 7.5). The organic phase was collected and the aqueous layer was extracted with 3 x 50 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to an oily residue. Purification by chromatography on silica gel (2:1 hexanes/EtOAc) afforded sulfamate ester **8** as a colorless oil (3.60 g, 79%): TLC R_f = 0.28 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36-7.22 (m, 5H), 6.52 (d, 1H, *J* = 15.8 Hz), 6.14 (ddd, 1H, *J* = 15.6, 7.3, 7.3 Hz), 5.22 (d, 1H, *J* = 8.8 Hz), 4.93 (s, 2H), 4.73 (d, 1H, *J* = 12.1 Hz), 4.71 (d, 1H, *J* = 12.1 Hz), 4.35 (dd, 1H, *J* = 10.3, 4.0 Hz), 4.26 (dd, 1H, *J* = 10.4, 4.8 Hz), 4.19-4.10 (m, 1H), 2.62-2.50 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.5, 136.6, 133.9, 128.5, 127.6, 126.1, 123.9, 95.3, 74.4, 71.1, 50.2, 34.4 ppm; IR (thin film) ν 3373 (br), 3028, 2957, 1717, 1527, 1369, 1183 cm^{-1}; HRMS (ES$^+$) calcd for $C_{14}H_{17}Cl_3N_2O_5S$ 429.9924 found 452.9824 (MNa^+).



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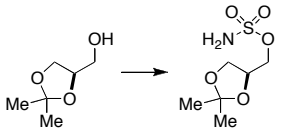
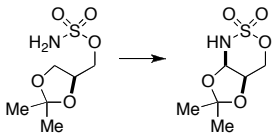
To a stirred suspension of sulfamate ester **8** (3.37 g, 7.81 mmol) and MgO (724 mg, 18.0 mmol, 2.3 equiv) in 55 mL of CH_2Cl_2 were added $PhI(OAc)_2$ (2.77 g, 8.59 mmol, 1.1 equiv) and $Rh_2(esp)_2$ (59 mg, 78 μmol, 0.01 equiv). After 9 h, the reaction mixture was filtered through a small pad of Celite, washing the flask and filter cake with 50 mL of CH_2Cl_2. The combined filtrates were concentrated under reduced pressure to an oily residue. Analysis of the unpurified material by ^{1}H NMR showed a product ratio of ~1.6:1.3:1.0 aziridine/*trans*-oxathiazinane/*cis*-oxathiazinane. Purification by chromatography on silica gel (gradient elution: 10:5:1→20:5:1 CH_2Cl_2/hexanes/Et_2O) afforded the desired *trans*-oxathiazinane as a white solid (760 mg, 23%): TLC R_f = 0.22 (20:5:1 CH_2Cl_2/hexanes/Et_2O); ^{1}H NMR (CD_3CN, 400 MHz) δ 7.40-7.25 (m, 5H), 6.73 (d, 1H, *J* = 15.9 Hz), 6.16 (d, 1H, *J* = 8.2 Hz), 6.12 (dd, 1H, *J* = 15.9, 7.8 Hz), 5.92 (d, 1H, *J* = 9.5 Hz), 4.77 (d, 1H, *J* = 12.2 Hz), 4.60 (d, 1H, *J* = 12.2 Hz), 4.31 (ddd, 1H, *J* = 9.5, 9.5, 9.5 Hz), 3.95 (dddd, 1H, *J* = 9.9, 9.9, 9.9, 5.9 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.2, 136.6, 135.8, 129.5, 129.2, 127.4, 123.9, 96.3, 74.7, 72.0, 61.3, 48.5 ppm; IR (thin film) ν 3356, 3263, 3031, 2960, 1718, 1531, 1437, 1368, 1286, 1229, 1179 cm^{-1}; HRMS (ES$^+$) calcd for $C_{14}H_{15}Cl_3N_2O_5S$ 427.9767 found 450.9660 (MNa^+).



9

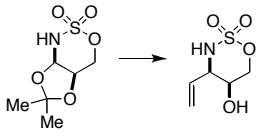
An oven-dried, 500-mL two-necked round bottom flask was fitted with a rubber septum and an oven-dried, 100-mL pressure equalizing addition funnel. The entire apparatus was flushed with N_2 gas through an inlet on the addition funnel and kept under positive pressure. The flask was cooled to 0 ºC in an ice-water bath and to the flask was added 60 mL of CH_2Cl_2, followed by $ClSO_2NCO$ (16.4 mL, 188 mmol, 2.5 eq). The addition funnel was charged with 35 mL of CH_2Cl_2 and HCO_2H (7.15 mL, 190 mmol, 2.5 eq). The contents of the addition funnel were added dropwise over 15 min and the addition was made quantitative by rinsing the addition funnel with 5 mL of CH_2Cl_2. The resulting clear, colorless solution was stirred at 0 ºC for 35 min then warmed to 23 ºC, and after stirring for 8 hr, the solution was cooled to –10 ºC with a methanol/ice bath. The addition funnel was charged with (*R*)-glycerol acetonide (10.0 g, 75 mmol, 1.0 eq), Et_3N (32 ml, 230 mmol, 3.0 eq) and 20 mL of CH_2Cl_2, and the contents of the addition funnel were added dropwise over 15 min. The bath was then removed and the resulting solution was stirred for 20 min, concentrated, and diluted with 300 mL of EtOAc. The contents were poured into a 1 L separatory funnel and washed with 200 mL of 1M aqueous K_2HPO_4 (pH 10). The aqueous layer was extracted with 2 x 100 mL of EtOAc and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The resulting colorless oil was purified by passing through a short pad of silica gel (6.5 cm x 3.5 cm) using 700 mL of 1:2 hexanes/EtOAc to give sulfamate ester **9** as a colorless oil (13.0 g, 81%): TLC R_f = 0.56 (1:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.12 (br s, 2H), 4.41 (quint, 1H, *J* = 5.6 Hz), 4.24 (dd, 1H, *J* = 10.7, 6.1 Hz), 4.18 (dd,

1H, *J* = 10.8, 4.9 Hz), 4.12 (dd, 1H, *J* = 8.8, 6.5 Hz), 3.82 (dd, 1H, *J* = 8.7, 5.3 Hz), 1.48 (s, 3H), 1.38 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 110.1, 72.8, 70.1, 65.3, 26.2, 24.8 ppm; IR (thin film) ν 3255, 2988, 1562, 1372, 1215, 1180, 1049, 984, 929 cm^{-1}.



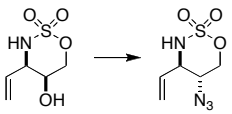
9 **10**

To a stirred suspension of sulfamate ester **9** (12.5 g, 59.2 mmol) and MgO (5.49 g, 136.2 mmol, 2.3 equiv) in 350 mL of CH_2Cl_2 were added successively $PhI(OAc)_2$ (20.97 g, 65.1 mmol, 1.1 equiv) and $Rh_2(esp)_2$ (0.135g, 0.178 mmol, 0.003 equiv). The pale red mixture gradually turned to light green and was stirred for 7 h. The contents were filtered through a pad of Celite using 300 mL of CH_2Cl_2 to rinse the filter cake. The combined filtrates were concentrated under reduced pressure and to the solid residue was added 40 mL of benzene followed by 5 mL of hexanes. After standing for 7 h the beige solid that had precipitated was collected in a sintered glass funnel and rinsed with cold benzene (10 mL) to give 8.45 g of the desired product **10** as a beige solid. The mother liquor was concentrated to a volume of ~10 mL and stored for 24 h in a –10 ºC freezer. Filtering this mixture gave an additional 1.00 g of product as a beige solid (9.45 g combined, 76%): TLC R_f = 0.48 (1:1 EtOAc/hexanes); mp 96–97 ºC; $[\alpha]_D$ –44.1º (c = 1.50, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 5.42 (d, 1H, *J* = 5.3 Hz), 4.59-4.58 (m, 2H), 4.31 (ddd, 1H, *J* = 5.3, 1.6, 1.6 Hz), 1.54 (s, 3H), 1.35 (s, 3H) ppm; ^{13}C NMR (CD_3OD, 125 MHz) δ 111.5, 85.6, 71.7, 71.5, 26.9, 25.6 ppm; IR (KBr pellet) ν 3260, 2997, 2979, 1456, 1390, 1379, 1354, 1245, 1180, 1071 cm^{-1}; HRMS (ES$^+$) calcd for $C_6H_{11}NO_5S$ 209.0358 found 232.0246 (MNa^+).



10 **12**

A 2-neck flask equipped with a rubber septum and glass stopper was charged with 194 mL of 0.80 M vinyl magnesium bromide (154.6 mmol, 4.2 equiv) in THF and placed in an ice bath. To this solution was added dropwise over 15 min, 80 mL of 1.0 M $ZnCl_2$ in THF (80.0 mmol, 2.2 mmol). The mixture was stirred for 15 min at 0 °C, then warmed to 23 °C and stirred for 30 min. After this time, the contents were cooled to 0 °C, the flask briefly unstoppered, and solid *N*,*O*-acetal **10** (7.70 g, 36.80 mmol) was added in five equal portions at 1 min intervals. The reaction mixture was stirred for 10 min at 0 °C, then warmed to 50 °C and stirred for 15 min. The solution was once again cooled to 0 °C and the reaction quenched by the slow addition of 150 mL of saturated aqueous NH_4Cl. The biphasic mixture was transferred to a separatory funnel with 300 mL of EtOAc and 100 mL of H_2O. The organic phase was collected and the aqueous phase was extracted with 3 x 100 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to a light orange, amorphous solid. Purification by chromatography on silica gel (gradient elution: 2:1→1:2 hexanes/EtOAc) afforded vinyl oxathiazinane **12** as a white solid (4.51 g, 68%): TLC R_f = 0.29 (1:1 hexanes/EtOAc); ^{1}H NMR (CD_3OD, 400 MHz) δ 5.90 (ddd, 1H, *J* = 17.2, 10.7, 5.5 Hz), 5.35 (ddd, 1H, *J* = 17.4, 1.7, 1.2 Hz), 5.28 (ddd, 1H, *J* = 10.7, 1.5, 1.5 Hz), 4.73 (dd, 1H, *J* = 12.2, 1.4 Hz), 4.32 (dddd, 1H, *J* = 5.6, 2.0, 2.0, 2.0 Hz), 3.62 (ddd, 1H, *J* = 1.7, 1.7, 1.7 Hz) ppm; ^{13}C NMR (CD_3OD, 100 MHz) δ 134.5, 117.9, 77.9, 63.7, 62.2 ppm; IR (thin film) ν 3523 (br), 3255, 1432, 1361, 1188 cm^{-1}; HRMS (ES$^+$) calcd for $C_5H_9NO_4S$ 179.0252 found 202.0159 (MNa^+).



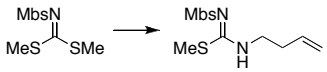
12 **13**

To a solution of vinyl oxathiazinane **12** (4.29 g, 23.9 mmol) in 80 mL of MeCN were added successively powdered, anhydrous K_2CO_3 (9.93 g, 71.8 mmol, 3.0 equiv), *p*-methoxybenzyl chloride (6.50 mL, 47.9 mmol, 2.0 equiv) and ^{n}Bu_4NI (1.33 g, 3.60 mmol, 0.15 equiv). The orange mixture was stirred at 23 ºC for 9 h, then filtered through a small pad of Celite. The flask and filter cake were rinsed with 200 mL of EtOAc and the combined filtrates were

transferred to a separatory funnel. The organic layer was washed with 2 x 60 mL of 1/2 saturated aqueous NaCl. The organic phase was collected and the aqueous layer was extracted with 2 x 50 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to a light orange oil. Purification of this material by chromatography on silica gel (gradient elution: 2:2:1 CH_2Cl_2/hexanes/EtOAc → neat EtOAc) afforded *N*-PMB-oxathiazinane as a colorless oil (5.07 g, 71%). A small portion of unreacted starting material **12** was also recovered as a white solid (708 mg): TLC R_f = 0.38 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.28-7.22 (m, 2H), 6.89-6.84 (m, 2H), 6.02 (ddd, 1H, *J* = 17.2, 10.4, 8.7 Hz), 5.48-5.44 (m, 1H), 5.44-5.39 (m, 1H), 4.71 (dd, 1H, *J* = 11.9, 2.4 Hz), 4.48 (dd, 1H, *J* = 11.8, 4.3 Hz), 4.35 (s, 2H), 4.23 (dd, 1H, *J* = 8.7, 2.9 Hz), 3.88-3.80 (m, 1H), 3.80 (s, 3H) 2.25 (br s, 1H) ppm.

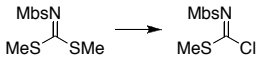
To a solution of *N*-PMB-oxathiazinane (5.68 g, 19.0 mmol), pyridine (13.0 mL, 159.4 mmol, 8.4 equiv) and DMAP (232 mg, 1.90 mmol, 0.10 equiv) in 25 mL of toluene at 0 °C was added dropwise over 15 min 28.0 mL of a 2.0 M toluene solution of trifluoromethanesulfonic anhydride (56.9 mmol, 3.0 equiv). The mixture was stirred at 0 °C for 10 min, then transferred to a separatory funnel containing 150 mL of ice cold 10% aqueous $NaHSO_4$ and 300 mL of EtOAc. The organic phase was collected and the aqueous layer was extracted with 3 x 50 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4 and filtered. Note: the triflate product appears to decompose when concentrated to dryness. Accordingly, 65 mL of DMF was added to the filtrate and the volatiles (EtOAc and toluene) were removed under reduced pressure. The DMF solution of unpurified triflate was cooled to –15 °C (MeOH/ice bath) and solid NaN_3 (6.17 g, 94.9 mmol, 5.0 equiv) was added in a single portion. The orange reaction mixture was warmed to –10 °C over 30 min, and poured into a separatory funnel containing 150 mL of 10% aqueous $NaHSO_4$, 300 mL of Et_2O, and 150 mL of EtOAc. The organic phase was collected and the aqueous layer was extracted with 2 x 100 mL of 2:1 Et_2O/EtOAc and 1 x 100 mL of 1:1 Et_2O/EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the oily residue by chromatography on silica gel (5:1 hexanes/acetone) afforded the desired azide as a colorless oil (474 mg, 8% over 2 steps): TLC R_f = 0.20 (5:1 hexanes/acetone); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.24 (m, 2H), 6.92-6.87 (m, 2H), 6.14 (ddd, 1H, *J* = 17.1, 10.4, 8.7 Hz), 5.45 (ddd, 1H, *J* = 10.4, 0.8, 0.8 Hz), 5.29 (ddd, 1H, *J* = 17.1, 0.9, 0.9 Hz) 4.87 (dd, 1H, *J* = 12.2, 2.8 Hz), 4.59 (d, 1H, *J* = 14.4 Hz), 4.51 (ddd, 1H, *J* = 12.2, 4.4, 1.5 Hz), 4.17 (d, 1H, *J* = 14.2 Hz), 3.98-3.93 (m, 1H), 3.82 (s, 3H), 3.43 (ddd, 1H, *J* = 4.3, 4.3, 2.9 Hz) ppm.

Azide (474 mg, 1.46 mmol) and $(NH_4)_2Ce(NO_3)_6$ (4.00 g, 7.31 mmol, 5.0 equiv) were combined in 10 mL of 4:1 ^{t}BuOH/CH_2Cl_2 and the resulting orange suspension was warmed to 55 ºC. After stirring at this temperature for 9 h, the reaction mixture was diluted with 60 mL of EtOAc and poured into a separatory funnel containing 40 mL of 1/2 saturated aqueous NaCl. The organic layer was separated and the aqueous phase was extracted with 2 x 20 mL of EtOAc. The combined organic extracts were washed with 30 mL of saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the oily residue by chromatography on silica gel (gradient elution: 6:1→4:1 hexanes/acetone) afforded the desired azido-oxathiazinane **13** as a pale yellow oil (275 mg, 92%): TLC R_f = 0.25 (3:1 hexanes/acetone); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.93 (ddd, 1H, *J* = 17.1, 10.5, 6.3 Hz), 5.51 (ddd, 1H, *J* = 17.2, 1.4, 0.3 Hz), 5.49 (ddd, 1H, *J* = 10.4, 1.2, 0.3 Hz), 4.58 (dd, 1H, *J* = 11.8, 5.0 Hz), 4.53 (d, 1H, *J* = 9.2 Hz), 4.48 (dd, 1H, *J* = 11.7, 9.9 Hz), 4.15 (ddddd, 1H, *J* = 9.3, 9.3, 6.3, 1.4, 1.4 Hz), 3.58 (ddd, 1H, *J* = 9.8, 9.8, 5.0 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 131.4, 121.1, 71.0, 60.4, 56.1 ppm; IR (thin film) ν 3271, 2115, 1434, 1368, 1189 cm^{-1}; HRMS (ES$^+$) calcd for $C_5H_8N_4O_3S$ 204.0317 found 227.0210 (MNa^+).

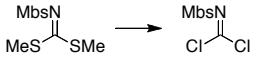


To a suspension of [(4-methoxyphenyl)sulfonyl]carbonimidodithioic acid dimethyl ester (258 mg, 885 μmol) in 2.0 mL of MeOH were added 3-butenylamine hydrochloride (100 mg, 0.93 mmol, 1.05 equiv) and Et_3N (0.14 mL, 0.97 mmol, 1.1 equiv). The reaction flask was equipped with a reflux condenser and the vessel was submerged in an oil bath pre-heated to 50 °C. The contents were stirred at this temperature for 30 min. The mixture was then cooled to 23 °C, the solution concentrated under reduced pressure to ~1/3 the original volume, and transferred to a separatory funnel with 50 mL of EtOAc and 25 mL of 10% aqueous $NaHSO_4$. The organic phase was collected and the aqueous layer was extracted with 3 x 10 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to an oily residue. Purification of this material by chromatography on silica gel (2:1 hexanes/EtOAc) afforded butenyl isothiourea as a colorless oil (259 mg, 93%): TLC R_f = 0.21 (2:1

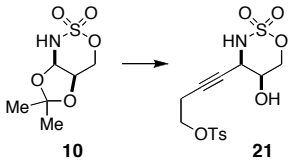
hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (br s, 1H), 7.87-7.79 (m, 2H), 6.97-6.90 (m, 2H), 5.74 (ddt, 1H, *J* = 16.7, 9.9, 6.8 Hz), 5.21-5.18 (m, 1H), 5.18-5.15 (m, 1H), 3.85 (s, 3H), 3.35 (dt, 2H, *J* = 6.6, 6.6 Hz), 2.39 (m, 2H), 2.36 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 162.2, 134.2, 133.4, 128.0, 118.4, 113.6, 55.3, 42.9, 33.0, 13.9 ppm; IR (thin film) ν 3292, 3079, 2932, 1574, 1498, 1257, 1138, 1089, 1079, 859, 834 cm^{-1}; HRMS (ES^+) calcd for $C_{13}H_{18}N_2O_3S_2$ 314.0759 found 337.0651 (MNa^+).



[(4-Methoxyphenyl)sulfonyl]carbonochloridimidothioic acid methyl ester. To a stirred solution of [(4-methoxyphenyl)sulfonyl]carbonimidodithioic acid dimethyl ester (7.40g, 25.4 mmol) in 75 mL of CH_2Cl_2 was added dropwise sulfuryl chloride (4.10 mL, 51.0 mmol, 2.0 equiv). The resulting yellow solution was warmed to 40 ºC and stirred for 3 h. After this time, the mixture was cooled to 23 °C and concentrated under reduced pressure. Purification of the solid residue by chromatography on silica gel (7:3 hexanes/EtOAc) gave the desired product (6.90 g, 97%) as a pale yellow solid: TLC R_f = 0.50 (7:3 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (m, 2H), 7.04 (m, 2H), 3.89 (s, 3H), 2.44 (s, 3H) ppm.

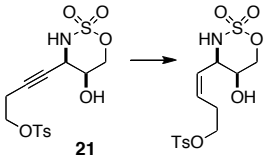


[(4-Methoxyphenyl)sulfonyl]carbonimidic dichloride. A 25 mL 2-neck flask equipped with a dropping funnel and a gas outlet was charged with $KMnO_4$ (4.00 g, 25.3 mmol). With the aid of the dropping funnel, commercial-grade, concentrated HCl (27 mL, 324 mmol, ~13 equiv) was slowly added to the solid mass. Evolution of Cl_2 gas immediately ensued. The gas was allowed to escape the vessel through the outlet and passed successively into solutions of H_2O and concentrated H_2SO_4 (note: Teflon tubing was used for this operation; the procedure for Cl_2 generation follows a reported method[6]). The purified Cl_2 gas was bubbled over ~1.5 h into a suspension of [(4-methoxyphenyl)sulfonyl]-carbonimidodithioic acid dimethyl ester (2.02 g, 6.93 mmol) in 20 mL of glacial AcOH held in an ice-H_2O bath at 12–14 ºC. After gas evolution ceased, the resulting pale green solution was stirred for 20 min at 12–14 °C then sparged briefly with N_2 and concentrated in vacuo. Purification of the resulting solid mass by sublimation (85–90 ºC, ~0.1 mm Hg) gave the desired dichloride as white needles (1.65 g, 89%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (m, 2H), 7.05 (m, 2H), 3.88 (s, 3H) ppm.



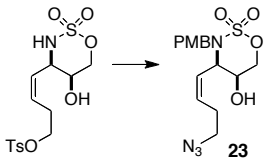
To a solution of 4-(*p*-toluylsulfonyloxy)-1-butyne (23.2 g, 103 mmol, 2.1 equiv) in 45 mL of THF at –78 °C was added dropwise a 2.5 M hexanes solution of *n*-BuLi (39.4 mL, 98.5 mmol, 2.0 equiv). The resulting viscous orange suspension was stirred for 20 min at –78 °C. A solution of $ZnCl_2$ (14.1 g, 103 mmol, 2.1 equiv) in 73 mL of THF was added dropwise via cannula. Transfer of the $ZnCl_2$ was made quantitative with an additional 5 mL of THF, and the resulting yellow mixture was warmed to 23 °C and stirred for 30 min at this temperature. Following this time, the solution was cooled to 0 °C, and neat BF_3•OEt_2 (18.7 mL, 148 mmol, 3.0 equiv) was added dropwise. The yellow homogeneous mixture was maintained at 0 ºC and stirred for 3 min before a solution of oxathiazinane **10** (10.1 g, 48.3 mmol) in 22 mL of THF was added via cannula. An additional 10 mL of THF was used to ensure quantitative transfer of the oxathiazinane. The reaction flask was then transferred from the 0 ºC ice/water bath to an oil bath preheated to 40 ºC. The light yellow mixture was stirred at 40 °C for 20 min then removed from the oil bath and quenched by the addition of 120 mL of saturated aqueous NH_4Cl. The biphasic contents were transferred to a separatory funnel containing 120 mL of Et_2O and 150 mL of saturated aqueous NH_4Cl. The organic phase was collected and the aqueous layer was extracted with 150 mL of Et_2O. The combined organic extracts were washed with 300 mL of a 1:1 saturated aqueous $NaHCO_3$/saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting orange solid was dissolved in 75 mL of boiling $CHCl_3$. Hexanes (50 mL) was added slowly (1 min), and the cloudy mixture was allowed to stand at 23 ºC for 1 h and then at 0 ºC for 1 h (if an oil results, trituration at 0 ºC will induce precipitation). The solid was collected on a Büchner funnel and washed with 75 mL of a 1:1 $CHCl_3$/hexanes mixture to give the desired product **21** as a beige powder

(14.1 g, 78%): TLC R_f = 0.34 (2:3 hexanes/EtOAc); mp = 112–114 ºC; $[\alpha]_D$ –10.4º (c = 2.40, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.85 (m, 2H), 7.50 (m, 2H,), 4.68 (dd, 1H, *J* = 12.3, 1.4 Hz), 4.56 (br d, 1H, *J* = 1.8 Hz), 4.42 (dd, 1H, *J* = 12.3, 2.2 Hz), 4.12 (t, 2H, *J* = 6.5 Hz), 3.61 (dd, 1H, *J* = 4.3, 1.8 Hz), 2.62 (dt, 2H, *J* = 6.5, 2.1 Hz), 2.50 (s, 3H) ppm; ^{13}C NMR (d_6-acetone, 125 MHz) δ 146.0, 133.9, 130.9, 128.7, 82.2, 77.2, 76.6, 68.7, 63.2, 53.3, 21.5, 20.0 ppm; IR (KBr pellet) ν 3477, 3220, 2260, 1380, 1353, 1175, 1012, 963 cm^{-1}; HRMS (ES$^+$) calcd for $C_{14}H_{17}NO_7S_2$ 375.0446 found 398.0334 (MNa^+).



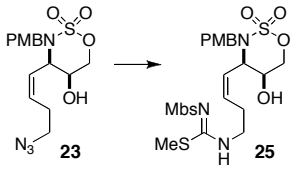
21

Alkyne **21** (10.25 g, 27.3 mmol) was dissolved in 140 mL of THF. Lindlar's catalyst (5 wt% Pd/$CaCO_3$/Pb, 3.49 g, 1.6 mmol, 0.06 equiv) and quinoline (546 mg, 4.4 mmol, 0.16 equiv) were added sequentially. The flask was fitted with a balloon of H_2 and the black suspension was stirred vigorously for 80 min. The reaction mixture was filtered through a pad of Celite (40 x 70 mm), and the filter cake was washed with ~100 mL of CH_2Cl_2. The combined filtrates were concentrated under reduced pressure to a pale yellow foam and the alkene product was used without further purification (> 95% yield, ~0.1 equiv of quinoline remaining). A sample of pure material was obtained by chromatography on silica gel (2:3 hexanes/EtOAc): TLC R_f = 0.34 (2:3 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78-7.76 (m, 2H), 7.38-7.38 (m, 2H), 5.72-5.62 (m, 2H), 4.90 (br s, 1H), 4.80 (dd, 1H, *J* = 12.4, 1.4 Hz), 4.56 (br d, 1H, *J* = 5.3 Hz), 4.51 (dd, 1H, *J* = 12.4, 2.0 Hz), 4.14-4.02 (m, 2H), 3.69 (dd, 1H, *J* = 3.2, 1.8 Hz), 2.62-2.50 (m, 1H), 2.49-2.42 (m, 1H), 2.46 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.3, 132.6, 130.6, 130.1, 127.9, 126.9, 76.7, 69.1, 63.1, 56.6, 28.0, 21.8 ppm; IR (thin film) ν 3523, 3261, 2960, 1598, 1427, 1356, 1188, 1175, 1020, 917 cm^{-1}; HRMS (ES$^+$) calcd for $C_{14}H_{19}NO_7S_2$ 377.0603 found 400.0500 (MNa^+).

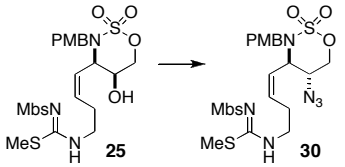


23

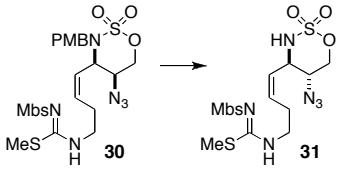
The starting tosylate was dissolved in 80 mL of DMF and to this solution was added NaN_3 (3.54 g, 54.5 mmol, 2.0 equiv) and ^{n}Bu$_4$NI (1.71 g, 5.5 mmol, 0.20 equiv). The light orange mixture was stirred for 7 h then poured into a separatory funnel with 350 mL of Et_2O and 250 mL of H_2O. The organic phase was collected and the aqueous layer was extracted with 2 x 150 mL of Et_2O and 2 x 150 mL of EtOAc. The combined organic extracts were washed successively with 2 x 100 mL of H_2O and 1 x 100 mL of saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The isolated material was purified by chromatography on silica gel (9:11 hexanes/EtOAc) to afford the desired azide with ~10 % of quinoline (as determined by ^{1}H NMR) remaining from the prior hydrogenation reaction. After re-dissolving the product azide in 100 mL of MeCN, powdered, anhydrous K_2CO_3 (10.2 g, 74.1 mmol, 3.0 equiv), *p*-methoxybenzyl chloride (6.70 mL, 49.4 mmol, 2.0 equiv), and ^{n}Bu$_4$NI (1.16 g, 3.7 mmol, 0.15 equiv) were added. The orange mixture was stirred for 10 h then filtered through a pad of Celite (40 x 70 mm) washing the filter cake with 200 mL of CH_2Cl_2. The combined filtrates were concentrated under reduced pressure to give an oily residue that was purified by chromatography on silica gel (3:2 hexanes/EtOAc). The desired product **23** was obtained as a pale yellow foam (7.40 g, 80% over 3 steps): TLC R_f = 0.62 (2:3 hexanes/EtOAc); $[\alpha]_D$ +54.1º (c = 2.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24-7.22 (m, 2H), 6.86-6.84 (m, 2H), 5.90 (dddd, 1H, *J* = 11.1, 9.6, 1.5, 1.5Hz), 5.80-5.75 (m, 1H), 4.71 (dd, 1H, *J* = 11.8, 2.4 Hz), 4.56 (dd, 1H, *J* = 9.5, 2.8 Hz), 4.48 (dd, 1H, *J* = 11.8, 4.4 Hz), 4.40 (d, 1H, *J* = 15.4 Hz), 4.31 (d, 1H, *J* = 15.4 Hz), 3.82-8.79 (m, 1H), 3.80 (s, 3H), 3.34-3.30 (m, 1H), 3.24 (ddd, 1H, *J* = 12.2, 8.2, 5.6 Hz), 2.45 (d, 1H, *J* = 8.7), 2.29-2.22 (m, 1H), 2.22-2.14 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1, 134.2, 129.6, 128.6, 124.6, 113.9, 75.2, 65.0, 59.0, 55.2, 50.3, 50.1, 27.6 ppm; IR (thin film) ν 3528, 2937, 2100, 1613, 1514, 1377, 1247, 1178, 1035, 969 cm^{-1}; HRMS (ES$^+$) calcd for $C_{15}H_{20}N_4O_5S$ 368.1154 found 391.1052 (MNa^+).



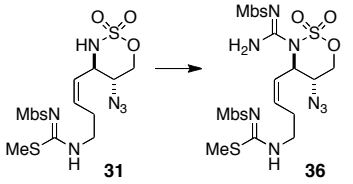
To a solution of azide **23** (7.00 g, 20.0 mmol) in 120 mL of a 5:1 THF/H_2O mixture was added a 1.0 M toluene solution of Me_3P (40.0 mL, 40.0 mmol, 2.0 equiv). The biphasic mixture was stirred for 9 h then concentrated under reduced pressure. The non-viscous, oily material was allowed to stand under high vacuum (~0.1 mm Hg) for 70 min. The resulting thick oil was dissolved in 300 mL of MeCN, and the solution was cooled to 0 ºC before $^{i}Pr_2NEt$ (5.05 mL, 29.0 mmol, 1.45 equiv) was added. To this mixture was then added dropwise via cannula over 5 minutes a solution of [(4-methoxyphenyl)sulfonyl]-carbonochloridimidothioic acid methyl ester in 50 mL of MeCN. Transfer of the sulfonamide reagent was made quantitative with an additional 5 mL of MeCN. This mixture was stirred for 70 min at 23 ºC then concentrated under reduced pressure. Purification of the oily residue by chromatography on silica gel (gradient elution: 2:1:0.3→3:1:0.5 EtOAc/hexanes/CH_2Cl_2) afforded the isothiourea **25** as a white foam (8.40 g, 72% over 2 steps): TLC R_f = 0.43 (1:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.95 (br s, 1H), 7.81-7.78 (m, 2H), 7.25-7.22 (m, 2H), 6.96-6.93 (m, 2H), 6.85-6.82 (m, 2H), 6.01 (dd, 1H, *J* = 10.7, 9.5 Hz), 5.70-5.65 (m, 1H), 4.70 (dd, 1H, *J* = 11.8, 2.4 Hz), 4.61 (dd, 1H, *J* = 9.0, 2.3 Hz), 4.50 (dd, 1H, *J* = 12.0, 4.6 Hz), 4.42 (d, 1H, *J* = 15.5 Hz), 4.36 (d, 1H, *J* = 15.6 Hz), 3.97-3.94 (br m, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.33 (ddd, 1H, *J* = 13.2, 10.8, 5.6 Hz), 3.20-3.14 (m, 1H), 2.95 (br d, 1H, *J* = 6.0 Hz), 2.39-2.28 (m, 1H), 2.35 (s, 3H), 2.13-2.09 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.1, 162.6, 159.1, 134.0, 132.8, 129.5, 129.0, 128.1, 126.4, 113.9, 113.8, 75.2, 64.0, 58.5, 55.6, 55.3, 50.6, 42.9, 27.6, 14.2 ppm; IR (thin film) ν 3453, 3301, 2936, 1571, 1513, 1498, 1376, 1258, 1180, 1137, 1079, 1031, 970 cm^{-1}; HRMS (ES$^+$) calcd for $C_{24}H_{31}N_3O_8S_3$ 585.1237 found 608.1185 (MNa^+).



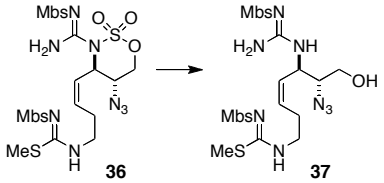
A solution of trifluoromethanesulfonic anhydride (12.3 g, 43.6 mmol, 3.0 equiv) in 20 mL of CH_2Cl_2 was added dropwise over 10 min to an ice-cold mixture of alcohol **25** (8.30 g, 14.2 mmol), pyridine (9.20 mL, 118.9 mmol, 8.4 equiv), and DMAP (440 mg, 3.60 mmol, 0.25 equiv) in 60 mL of CH_2Cl_2. The yellow solution was stirred for 30 min at 23 °C then loaded directly onto a column of silica gel (60 mm x 200 mm), pre-packed in 1:1 hexanes/EtOAc, and the product was eluted with 1:1 hexanes/EtOAc. The collected fractions were concentrated under reduced pressure to give an orange foam. The product was dissolved in 50 mL of DMF, cooled to –15 ºC in an ice/MeOH bath, and NaN_3 (4.14 g, 63.7 mmol, 5.0 equiv) was added in a single portion. The reaction mixture was stirred for 80 min at this temperature then poured into a separatory funnel containing 200 mL of Et_2O, 100 mL of EtOAc and 200 mL of H_2O. The organic phase was collected, and the aqueous phase was extracted with 2 x 150 mL of 1:1 Et_2O/EtOAc and 1 x 100 mL of EtOAc. The combined organic extracts were washed successively with 2 x 75 mL of H_2O and 1 x 75 mL of saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the oily residue by chromatography on silica gel (gradient elution: 11:9→9:11 hexanes/EtOAc) afforded the azide **30** as a pale yellow foam (5.90 g, 68% over 2 steps): TLC R_f = 0.33 (1:1 hexanes/EtOAc); $[\alpha]_D$ +93.5º (c = 2.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10-8.05 (br m, 1H), 7.85-7.82 (m, 2H), 7.31-7.28 (m, 2H), 6.98-6.95 (m, 2H), 6.92-6.89 (m, 2H), 6.05 (dd, 1H, *J* = 10.9, 10.0 Hz), 5.71 (dddd, 1H, *J* = 10.9, 8.7, 6.6, 1.0 Hz), 4.86 (dd, 1H, *J* = 12.3, 2.9 Hz), 6.88 (d, 1H, *J* = 14.4 Hz), 4.53 (ddd, 1H, *J* = 12.4, 4.8, 1.3 Hz), 4.30 (dd, 1H, *J* = 9.6, 4.6 Hz), 4.21 (d, 1H, *J* = 14.4 Hz), 3.88 (s, 3H), 3.83 (s, 3H), 3.54 (ddd, 1H, *J* = 4.6, 4.6, 2.9 Hz), 3.33-3.27 (m, 1H), 3.25-3.20 (m, 1H), 2.36 (s, 3H), 2.21-2.07 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.8, 162.5, 159.6, 134.2, 132.7, 130.3, 130.2, 128.2, 126.6, 114.1, 113.9, 71.2, 58.3, 56.1, 55.6, 55.3, 50.8, 42.8, 27.3, 14.1 ppm; IR (thin film) ν 3299, 2933, 2112, 1573, 1513, 1367, 1307, 1258, 1175, 1139, 1079, 1028, 834 cm^{-1}; HRMS (ES$^+$) calcd for $C_{24}H_{30}N_6O_7S_3$ 610.1338 found 633.1226.



Azide **30** (2.03 g, 3.32 mmol) and ceric ammonium nitrate (9.11 g, 16.6 mmol, 5.0 equiv) were combined in 25 mL of a 4:1 ^{t}BuOH/CH_2Cl_2 mixture, and the resulting orange suspension was warmed to 55 ºC. After stirring at this temperature for 8 h, the reaction mixture was diluted with 150 mL of EtOAc and poured into a separatory funnel containing 100 mL of a 1/2-saturated aqueous NaCl solution. The organic layer was collected, and the aqueous layer was extracted with 1 x 70 mL of EtOAc. The combined organic extracts were washed with 1 x 100 mL of saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the oily residue by chromatography on silica gel (9:1 CH_2Cl_2/EtOAc) afforded the desired product **31** as a pale yellow foam (1.20 g, 74%): TLC R_f = 0.42 (9:1 CH_2Cl_2/EtOAc); ^{1}H NMR ($CDCl_3$, 500MHz) δ 7.91-7.88 (m, 2H), 7.87 (br s, 1H), 6.99-6.96 (m, 2H), 5.87-5.82 (m, 1H), 5.69 (t, 1H, *J* = 9.5 Hz), 5.52 (d, 1H, *J* = 7.8 Hz), 4.57 (dd, 1H, *J* = 11.6, 5.1 Hz), 4.49 (dd, 1H, *J* = 11.6, 10.4 Hz), 4.39 (q, 1H, *J* = 8.5 Hz), 3.90 (s, 3H), 3.68 (ddd, 1H, *J* = 10.2, 10.2, 5.3), 3.60-3.54 (m, 1H), 3.35-3.31 (m, 1H), 2.86-2.78 (m, 1H), 2.42-2.38 (m, 1H), 2.40 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.3, 162.6, 133.9, 128.3, 128.2, 127.4, 113.9, 71.0, 56.3, 55.6, 55.5, 42.9, 27.7, 14.1 ppm; IR (thin film) ν 3299, 2932, 2114, 1572, 1498, 1433, 1370, 1258, 1189, 1139, 1080 cm^{-1}; HRMS (ES$^+$) calcd for $C_{16}H_{22}N_6O_6S_3$ 490.0763 found 513.0661(MNa^+).

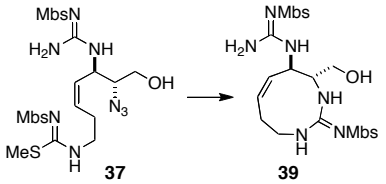


A solution of oxathiazinane **31** (570 mg, 1.16 mmol) in 2.5 mL of CH_2Cl_2 was added to a suspension of NaO^{t}Bu (125 mg, 1.30 mmol, 1.1 equiv) in 2 mL of CH_2Cl_2 at 0 °C. The mixture was stirred for 20 min then the flask was quickly unstoppered and solid [(4-Methoxyphenyl)sulfonyl]carbonimidic dichloride (467 mg, 1.74 mmol, 1.5 equiv) was added in a single portion. The colorless solution was stirred for 1 h before neat $(Me_3Si)_2NH$ (1.40 mL, 6.64 mmol, 5.7 equiv) was added dropwise; stirring was continued at 0 °C for 1.75 h. The reaction mixture was diluted with 75 mL of EtOAc and poured into a separatory funnel containing 50 mL of saturated aqueous NH_4Cl. The organic phase was collected, washed with 1 x 50 mL of saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the oily residue by chromatography on silica gel (gradient elution: 11:9:2→3:2:0 EtOAc/hexanes/CH_2Cl_2) afforded guanidine **36** as a white foam (560 mg, 69%, **note**: the product **36** is not stable to prolonged storage). Unreacted starting oxathiazinane **31** was also recovered (110 mg, 20%): TLC R_f = 0.37 (2:3 hexanes/EtOAc); $[\alpha]_D$ +71.0° (c = 3.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500MHz) δ 8.04 (br s, 1H), 7.88-7.82(m, 4H), 7.00-6.95 (m, 4H), 6.04 (t, 1H, *J* = 10.4 Hz), 5.99-5.93 (m, 1H), 5.70-5.64 (m, 1H), 5.04 (dd, 1H, *J* = 12.2, 1.6 Hz), 4.60 (dq, 1H, *J* = 12.3, 1.7 Hz), 3.99 (br d, 1H, *J* = 2.3 Hz), 3.88 (s 3H), 3.87 (s, 3H), 3.50-3.45 (m, 1H), 3.31-3.25 (m, 1H), 2.72-2.64 (m, 1H), 2.39-2.33 (m, 1H), 2.38 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.9, 162.8, 162.5, 151.9, 134.1, 133.7, 130.3, 128.3, 128.2, 125.3, 114.0, 113.9, 73.2, 57.5, 56.2, 55.6, 55.5, 42.8, 27.8, 14.1 ppm; IR (thin film) ν 3447, 3317, 2945, 2114, 1626, 1596, 1577, 1499, 1419, 1310, 1260, 1192, 1141, 1078, 1025 cm^{-1}.

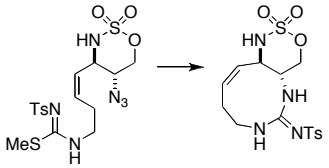


Guanidine **36** was dissolved in a mixture of 11:2 MeCN/H_2O, and the solution was stirred at 70 °C for 5 h. After this time, all volatiles were removed by concentration under reduced pressure. The isolated material was left to stand under vacuum (~0.1 mm Hg) for 1 h. Purification of the oily residue by chromatography on silica gel (10:5:1

EtOAc/CH_2Cl_2/MeOH) afforded alcohol **37** as a white foam (450 mg, 92%): TLC R_f = 0.36 (2:7 hexanes/EtOAc); $[\alpha]_D$ –103.3° (c = 2.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500MHz) δ 7.87-7.84 (m, 4H), 7.78 (br s, 1H), 6.98-6.93 (m, 4H), 6.70 (br s, 2H), 5.97 (br s, 1H), 5.71 (t, 1H, *J* = 9.3 Hz), 5.61-5.56 (m, 1H), 4.79-4.76 (br m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.73 (br s, 2H), 3.40 (br s, 1H), 3.27-3.22 (m, 2H), 2.36 (s, 3H), 2.26-2.22 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.5, 162.7, 162.3, 155.8, 134.9, 133.5, 132.0, 129.8, 128.1, 128.0, 114.0, 113.8, 65.4, 61.3, 55.6, 55.5, 47.3, 43.0, 27.5, 14.2 ppm; IR (thin film) ν 3444, 3338, 2944, 2103, 1596, 1577, 1533, 1499, 1258, 1133, 1083, 833 cm^{-1}; HRMS (ES$^+$) calcd for $C_{24}H_{32}N_8O_7S_3$ 640.1556 found 663.1437 (MNa^+).

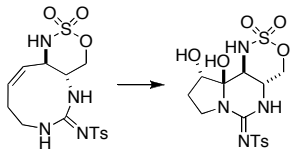


To a solution of alcohol **37** (440 mg, 0.688 mmol) in 9.6 mL of a 5:1 THF/H_2O mixture was added dropwise a 1.0 M toluene solution of PMe_3 (3.30 mL, 3.30 mmol, 4.8 equiv). The biphasic mixture was stirred for 23 h then transferred to a separatory funnel containing 50 mL of saturated aqueous $NaHCO_3$ with 80 mL of EtOAc. The organic layer was collected and the aqueous layer was extracted with 1 x 50 mL of EtOAc. The combined organic extracts were washed with 50 mL of saturated aqueous NaCl, dried over $MgSO_4$, and concentrated to a white solid. This material was dissolved in 80 mL of MeCN and added dropwise via syringe over 45 min to a solution of $AgNO_3$ (135 mg, 0.795 mmol, 1.3 equiv) and Et_3N (850 μL, 6.10 mmol, 10.0 equiv) in 120 mL of MeCN (**note**: the reaction vessel containing $AgNO_3$ was wrapped in aluminum foil to prevent exposure to light). The transfer was made quantitative with two 10 mL portions of MeCN. After stirring for an additional 20 min, the contents were filtered through a small pad of Celite using ~400 mL of CH_2Cl_2 to rinse the flask and filter cake. The combined filtrates were concentrated under reduced pressure to a light brown solid. Purification by chromatography on silica gel (97:3 CH_2Cl_2/MeOH) afforded the desired product **39** as a white solid (220 mg, 64% over two steps): TLC R_f = 0.28 (20:1 CH_2Cl_2/MeOH); mp 147–150 °C; $[\alpha]_D$ +91.0° (c = 2.60, MeOH); ^{1}H NMR (CD_3CN, 500 MHz, 70 °C) δ 7.81-7.75 (m, 4H), 7.07-7.01 (m, 4H), 6.73 (br s, 1H), 6.25 (br s, 2H), 5.76 (br s, 1H), 5.00 (br s, 1H), 4.87-4.83 (m, 1H), 4.69 (t, 1H, *J* = 10.0 Hz), 3.97-3.87 (br m, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.78 (br d, 1H, *J* = 11.7), 3.68 (br d, 1H, *J* = 11.9 Hz), 3.51-3.43 (m, 2H), 3.27 (br s, 1H), 2.49 (br s, 1H) 2.04-2.00 (br m, 1H) ppm; IR (KBr pellet) ν 3335, 2943, 1597, 1531, 1499, 1257, 1131, 1080, 834 cm^{-1}; HRMS (ES$^+$) calcd for $C_{23}H_{30}N_6O_7S_2$ 566.1617 found 589.1503 (MNa^+).

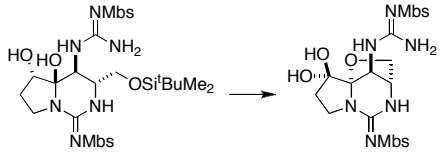


Azide (205 mg, 0.43 mmol) was dissolved in 10 mL of a 6:1 mixture of THF/MeOH and to this solution was added $SnCl_2$ (115 mg, 0.61 mmol, 1.4 equiv). The resulting pale yellow mixture was stirred for 6.5 h, after which time the reaction mixture was poured into a separatory funnel containing 50 mL of EtOAc and 25 mL of pH 6 aqueous NaOH. The organic phase was collected; the aqueous layer was adjusted to pH 9 by the addition of 1M NaOH and extracted with 2 x 20 mL of EtOAc. The combined organic fractions were washed with 20 mL of saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure to an oily residue. This material was re-dissolved in 50 mL of MeCN and 6 mL of CH_2Cl_2 and was added dropwise over 40 min to a solution of $AgNO_3$ (95 mg, 0.56 mmol, 1.3 equiv), and Et_3N (598 μL, 4.30 mmol, 10 equiv) in 65 mL of MeCN (**note**: the reaction vessel containing $AgNO_3$ was wrapped in aluminium foil to prevent exposure to light). The transfer of amine substrate was made quantitative with 15 mL of 2:1 MeCN/CH_2Cl_2. After stirring for an additional 20 min, the contents were filtered through a small pad of Celite using ~150 mL of CH_2Cl_2 to rinse the flask and filter cake. The combined filtrates were concentrated under reduced pressure to a beige solid. Purification by chromatograpy on silica gel (8:12:1 CH_2Cl_2/EtOAc/MeCN) gave the bicyclic product as a white solid (78 mg, 40%). TLC R_f = 0.38 (2:3 CH_2Cl_2/EtOAc); ^{1}H NMR ($CDCl_3$ + 10% CD_3CN, 500 MHz) δ 7.70 (d, 2H, *J* = 8.5 Hz), 7.25 (d, 2H, *J* = 8.5 Hz), 7.16 (br s, 1H), 5.46 (d, 1H, *J* = 10.5 Hz), 4.76 (br s, 1H), 4.65-4.54 (m, 3H), 4.47 (dd, 1H, *J* = 8.7, 4.9 Hz), 4.37-

4.29 (m, 1H), 4.05-3.95 (m, 1H), 3.46-3.38 (m, 1H), 3.38-3.30 (m, 1H), 2.86-2.74 (m, 1H), 2.38 (s, 3H), 2.21-2.16 (m, 1H).



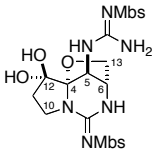
A 0.01 M aqueous solution of $RuCl_3$ (46 μL, 0.46 μmol, 0.02 equiv) was added to an ice cold mixture of $NaIO_4$ (7.5 mg, 0.035 mmol, 1.5 equiv) and 1.5 M aqueous H_2SO_4 (75 μL, 0.11 mmol, 5.0 equiv) in 100 μL of 1:1 MeCN/EtOAc. A solution of the starting alkene (10 mg, 0.023 mmol) in 300 μL of 1:1 MeCN/EtOAc was added via cannula. The transfer of this material was made quantitative with an additional 200 μL of 1:1 MeCN/EtOAc. After stirring for 2 h at 0 ºC, the pale yellow solution was warmed to 23 °C and stirred for an additional 2 h. The reaction was quenched by the successive addition of 1 mL of saturated aqueous $Na_2S_2O_3$ and 1 mL of saturated aqueous $NaHCO_3$. The contents were diluted with 20 mL of EtOAc and poured into a separatory funnel containing 5 mL of H_2O. The organic phase was collected, and the aqueous layer was extracted with 2 x 10 mL of EtOAc. The combined organic extracts were washed with 1 x 10 mL of saturared aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the solid residue by chromatography on silica gel (4:6:1 CH_2Cl_2/EtOAc/MeCN) gave the tricyclic hemi-aminal as a white solid (3.5 mg, 35%); TLC R_f = 0.28 (4:6:1 CH_2Cl_2/EtOAc/MeCN); ^{1}H NMR (CD_3CN, 500 MHz) δ 7.75 (m, 2H), 7.62 (s, 1H), 7.35 (m, 2H), 5.58 (d, 1H, *J* = 11.1 Hz), 4.83 (dd, 1H, *J* = 10.7, 4.6 Hz), 4.55 (s, 1H), 4.48 (dd, 1H, *J* = 10.6, 10.6 Hz), 4.12 (dd, 1H, *J* = 4.3, 4.3 Hz), 3.90 (dd, 1H, *J* = 11.2, 11.2 Hz), 3.82 (ddd, 1H. *J* = 10.9, 10.9, 4.5 Hz), 3.62-3.55 (m, 3H), 2.45 (s, 3H), 2.30 (dddd, 1H, *J* = 13.9, 9.9, 9.9, 4.0 Hz), 1.87 (ddd, 1H, *J* = 13.8, 7.0, 2.3 Hz) ppm; IR (thin film) ν 3310, 2925, 1578, 1519, 1382, 1261, 1193, 1129, 1077, 980, 860 cm^{-1}; HRMS (ES$^+$) calcd for $C_{15}H_{20}N_4O_7S_2$ 432.0073 found 455.0687 (MNa^+).



46 **48**

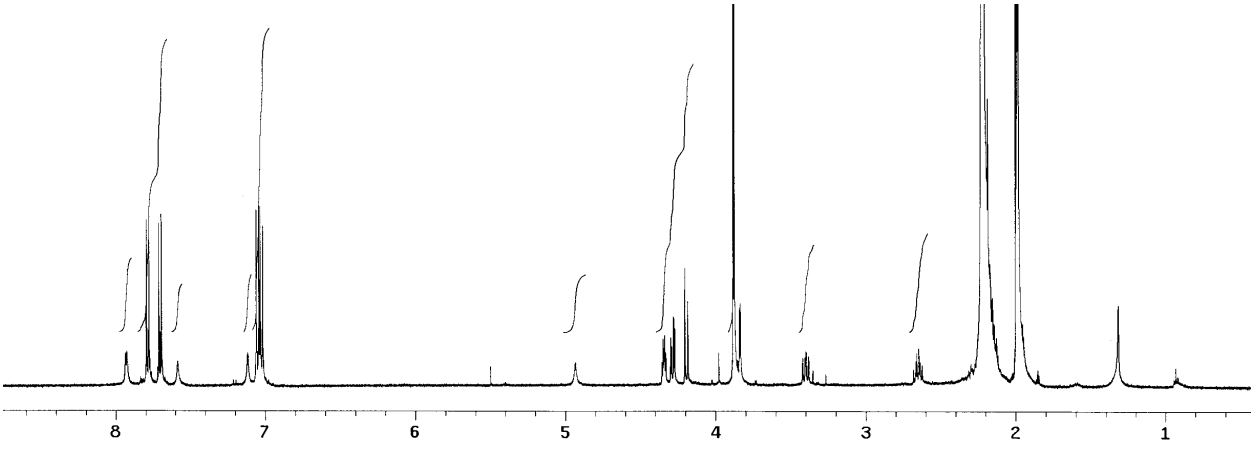
Hemi-aminal **46** (21 mg, 31 μmol) was dissolved in 6 mL of $CHCl_3$ and to this solution was added *p*-TsOH (6 mg, 35 μmol, 1.1 equiv). The resulting mixture was stirred for 10 h then concentrated under reduced pressure. Purification of the isolated residue by chromatography on silica gel (9:1 EtOAc/MeCN) furnished the intermediate product as a white solid (10 mg). This material was dissolved in 600 μL of a 5:1 mixture of CH_2Cl_2/DMSO, to which Et_3N (28 μL, 0.20 mmol, 12 equiv) and $C_5H_5N{\bullet}SO_3$ (16 mg, 0.10 mmol, 5.9 equiv) were then added successively. The resulting solution was stirred for 7.5 h then poured into a separatory funnel containing 20 mL of EtOAc. The solution was washed with 10 mL of half-saturated aqueous NH_4Cl and the organic phase was collected. The aqueous phase was extracted with 2 x 10 mL of EtOAc. The combined organic portions were washed with 10 mL of saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the oily residue by chromatography on silica gel (20:1 CH_2Cl_2/MeOH) gave *N,O*-acetal **48** as a white solid (6 mg, 36% over two steps): TLC R_f = 0.20 (9:1 EtOAc/MeCN); ^{1}H NMR (CD_3CN, 500 MHz) δ 7.93 (d, 1H, *J* = 4.9 Hz), 7.79-7.77 (m, 2H), 7.71-7.69 (m, 2H), 7.58 (br s, 1H), 7.11 (br s, 1H), 7.05-7.03 (m, 2H), 7.03-7.01 (m, 2H), 4.93 (br s, 1H), 4.34 (ddd, 1H, *J* = 5.5, 3.4, 3.4 Hz), 4.26 (dd, 1H, *J* = 9.5, 3.4 Hz), 4.19 (d, 1H, *J* = 9.4 Hz), 3.88 (s, 3H), 3.87 (s, 3H), 3.83 (dd, 1H, *J* = 3.7, 0.9 Hz), 3.40 (dd, 1H, *J* = 11.0, 8.1 Hz), 2.64 (ddd, 1H, *J* = 11.2, 11.2, 7.2 Hz), 2.26-2.10 (m, 2H) ppm; IR (thin film) ν 3313, 2922, 1596, 1566, 1499, 1257, 1134, 1081, 1004, 832 cm^{-1}; HRMS (ES$^+$) calcd for $C_{23}H_{26}N_6O_8S_2$ (ketone form) 578.1254 found 601.1151 (MNa^+).

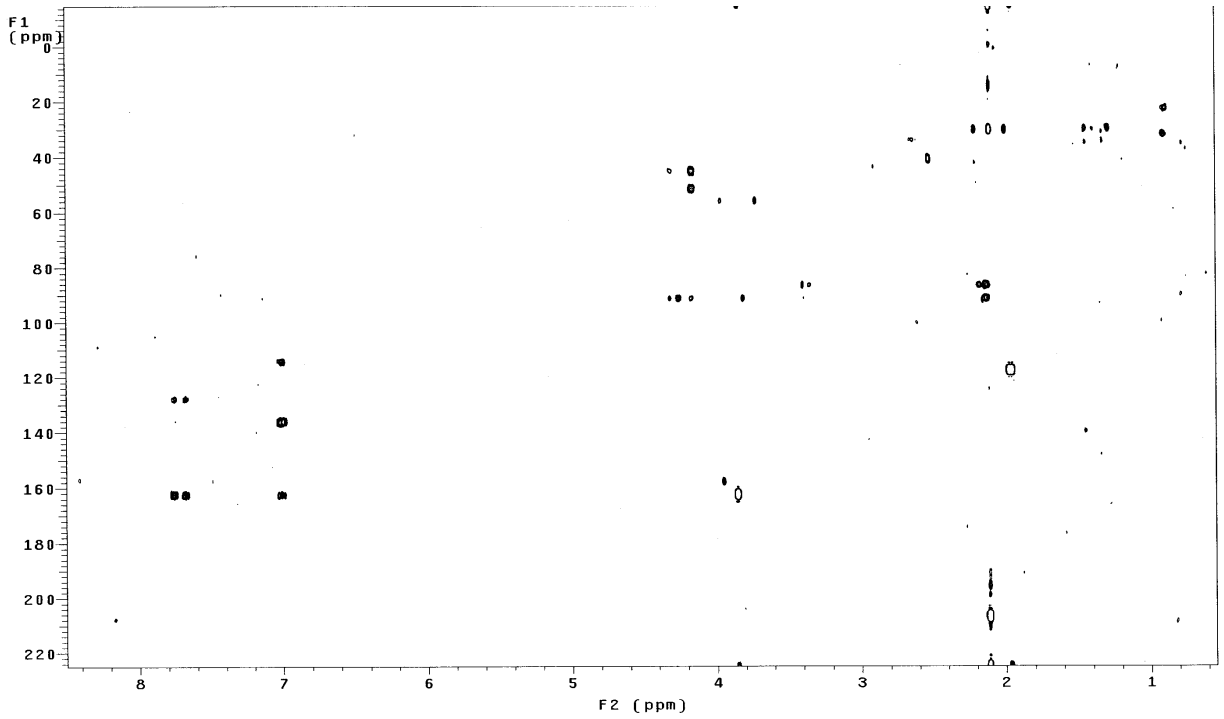
HMBC Correlations for **48** (CD_3CN, 600 MHz):
Note: ^{1}H and ^{13}C NMR signals associated with the Mbs groups have been omitted from the tabulated list.

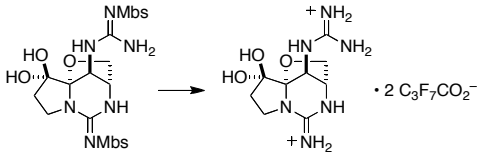


48

Position (STX numbering)	**^{1}H NMR δ** (ppm)	**^{13}C NMR δ** (ppm)
H5	4.32	C4 92.2; C6 46.1
H13a	4.26	**C4 92.2**
H13b	4.17	**C4 92.2**; C5 52.2; C6 46.1
H6	3.81	C4 92.2
H10a	3.40	C12 86.7
H10b	2.64	C11 35.8
H11a	2.18	C12 86.7
H11b	2.13	C12 86.7; C4 92.2

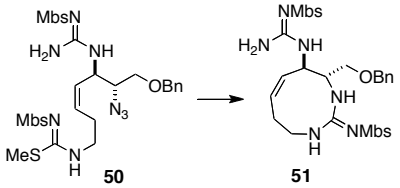






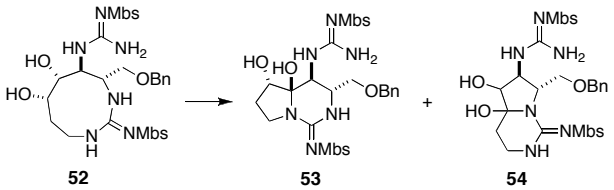
48 49

N,*O*-Acetal **48** (4.0 mg, 6.7 μmol) was dissolved in 400 μL of CF_3CO_2H and to this solution was added sequentially methanesulfonic acid (20 μL, 0.31 mmol, 46 equiv) and thioanisole (5 μL, 43 μmol, 6 equiv). After stirring for 28 h, the resulting colorless mixture was concentrated under reduced pressure. A portion of the obtained residue was purified by reverse-phase HPLC (Altima C18, 5 μm, 10 x 250 mm column, eluting with a gradient flow over 30 min of 10:90 MeCN/10 mM aqueous $C_3F_7CO_2H$ → 25:75 MeCN/10 mM aqueous $C_3F_7CO_2H$, 214 nm UV detection). At a flow rate of 6 mL/min, the bis-guanidinium salt **49** has a retention time of 15.0 min (~0.3 mg of pure **49** was isolated): ^{1}H NMR (D_2O, 500 MHz) δ 4.48 (d, 1H, *J* = 9.4 Hz), 4.44-4.40 (m, 2H), 4.02 (d, 1H, *J* = 3.5 Hz), 3.74 (ddd, 1H, *J* = 10.1, 6.3, 3.5 Hz), 3.31-3.25 (m, 1H), 2.49-2.46 (m, 2H); HRMS (ES^+) calcd for $C_9H_{14}N_6O_2$ (ketone form) 238.1178 found 239.1260 (MH^+). **Note:** The ^{1}H NMR spectrum of **49** shows clear differences from that of decarbamoyl STX • $2Cl^-$.[7]



50 51

To a solution of azide **50** (260 mg, 0.35 mmol) in 5.5 mL of 5:1 THF/H_2O was added dropwise a 1.0 M toluene solution of Me_3P (1.74 mL, 1.74 mmol, 5.0 equiv). The opaque mixture was stirred for 20 h then transferred to a separatory funnel containing 100 mL of EtOAc and 50 mL of saturated aqueous $NaHCO_3$. The organic layer was isolated and the aqueous layer was extracted with 50 mL of EtOAc. The combined organic fractions were washed with 50 mL of saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The oily residue was re-dissolved in 45 mL of MeCN and 5 mL of CH_2Cl_2 and this solution was added dropwise over 40 min to a mixture of $AgNO_3$ (77 mg, 0.45 mmol, 1.3 equiv), and Et_3N (485 μL, 3.48 mmol, 10 equiv) in 60 mL of MeCN (**note**: the reaction vessel containing $AgNO_3$ was wrapped in aluminium foil to prevent exposure to light). Transfer of the amine substrate was made quantitative with 15 mL of 2:1 MeCN/CH_2Cl_2. After stirring for an additional 20 min, the contents were filtered through a small pad of Celite using ~150 mL of CH_2Cl_2 to rinse the flask and filter cake. The combined filtrates were concentrated under reduced pressure to a beige solid. Purification of the solid residue by chromatography on silica gel (20:1 CH_2Cl_2/MeOH) gave cyclic guanidine **51** as a white solid (165 mg, 72% over 2 steps): TLC R_f = 0.20 (20:1 CH_2Cl_2/MeOH); ^{1}H NMR (CD_3CN, 500 MHz) δ 7.80-7.77 (m, 2H), 7.76-7.73 (m, 2H), 7.44-7.35 (m, 5H), 7.06-7.03 (m, 2H), 6.97-6.94 (m, 2H), 6.57 (br s, 1H), 6.23 (br s, 2H), 5.72 (br s, 1H), 5.17 (br s, 1H), 4.89-4.83 (m, 1H), 4.67-4.55 (m, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.72 (br d, 1H, *J* = 7.3 Hz), 3.65 (dd, 1H, *J* = 9.9, 2.4 Hz), 3.58 (br s, 1H), 3.46-3.37 (m, 1H), 3.05 (br s, 1H), 2.42 (br s, 1H) ppm; IR (thin film) 3327, 1595, 1498, 1309, 1255, 1130, 1080, 1026, 832 cm^{-1}; HRMS (ES^+) calcd for $C_{30}H_{36}N_6O_7S_2$ 656.2087 found 679.1957 (MNa^+).

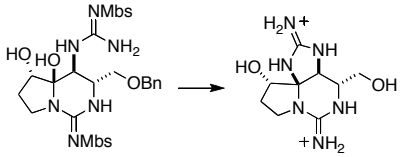


52 53 54

To a solution of diol **52** (41 mg, 59 μmol) in 3 mL of reagent-grade CH_2Cl_2 was added Dess–Martin periodinane (39 mg, 0.092 mmol, 1.5 equiv) in a single portion. The mixture became opaque over 20 min, and after stirring for 1.5 h, a second portion of Dess–Martin periodinane (10 mg, 0.024 mmol, 0.4 equiv) was added. Stirring was continued for 1.5 h then the reaction was quenched by the addition of 1 mL of 20:1 CH_2Cl_2/MeOH. The resulting white suspension was concentrated under reduced pressure, and the solid residue obtained was purified by chromatography

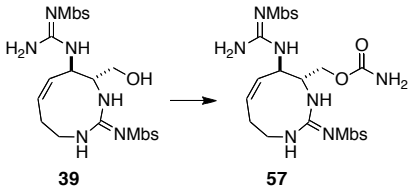
on silica gel (gradient elution: 25:1 CH_2Cl_2/MeOH → 20:1 CH_2Cl_2/MeOH). The minor, undesired product **54** was first to elute from the column and was isolated as a white solid (15 mg, 36%). The major product **53** was also obtained as a white solid (26 mg, 63%): TLC R_f = 0.60_{minor}, 0.53_{major} (93:7 CH_2Cl_2/MeOH); Minor isomer **54**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.78 (d, 2H, *J* = 8.9 Hz), 7.72 (d, 2H, *J* = 8.8 Hz), 7.67 (d, 1H, *J* = 4.9 Hz), 7.30-7.26 (m, 3H), 7.15-7.13 (m, 2H), 6.89-6.86 (m, 4H), 6.58 (br s, 3H), 4.35 (d, 1H, *J* = 11.5 Hz), 4.31-4.26 (m, 2H), 4.19 (br s, 1H), 4.12-4.11 (m, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.73 (br s, 1H), 3.67 (dd, 1H, *J* = 9.3, 3.5 Hz), 3.58 (br d, 1H, *J* = 9.0 Hz), 3.43 (ddd, 1H. *J* = 12.8, 12.8, 3.0 Hz), 3.35-3.33 (m, 1H), 2.10 (br d, 1H, *J* = 13.1 Hz), 1.44 (ddd, 1H, *J* = 13.3, 13.3, 4.9 Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.4, 162.3, 157.3, 151.4, 136.9, 135.6, 135.3, 128.6, 128.1, 128.0, 127.7, 127.6, 114.1, 114.0, 84.1, 80.8, 73.8, 68.7, 60.9, 55.5(2), 36.0, 29.8, 29.7 ppm; IR (thin film) ν 3339, 2944, 1624, 1581, 1521, 1499, 1386, 1258, 1133, 1023, 835 cm^{-1}; HRMS (ES^+) calcd for $C_{30}H_{36}N_6O_9S_2$ 688.1985 found 711.1891 (MNa^+). Major isomer **53**: ^{1}H NMR (CD_3CN, 500 MHz) δ 7.87 (br s, 1H), 7.78-7.76 (m, 2H), 7.76-7.73 (m, 2H), 7.43-7.33 (m, 5H), 7.01-6.98 (m, 2H), 6.97-6.94 (m, 2H), 6.41 (br s, 2H), 5.84 (br d, 1H, *J* = 8.0 Hz), 5.07 (br s, 1H), 4.45 (s, 2H), 4.25 (br s, 1H), 4.03-3.98 (m, 1H), 3.95 (dd, 1H, *J* = 3.4, 3.4 Hz), 3.86 (s, 3H), 3.85 (s, 3H), 3.64 (ddd, 1H, *J* = 10.7, 7.7, 2.9 Hz), 3.61-3.51 (m, 2H), 3.30 (dd, 1H, *J* = 9.8, 7.9 Hz), 2.26-2.19 (m, 1H), 1.86 (dd, 1H, *J* = 12.9, 6.5 Hz) ppm; IR (thin film) ν 3332, 1626, 1576, 1536, 1402, 1258, 1130, 1081, 833 cm^{-1}; HRMS (ES^+) calcd for $C_{30}H_{36}N_6O_9S_2$ 688.1985 found 711.1860 (MNa^+).

Boron tris(trifluoroacetate):[4] Neat CF_3CO_2H (620 μL, 8.04 mmol, 3.1 equiv) was added dropwise to a Schlenk flask containing a 1.0 M solution of BBr_3 (2.60 mL, 2.60 mmol) in CH_2Cl_2 cooled to 0 °C. The light brown solution was stirred for 40 min and was then concentrated *in vacuo* (~0.1 mm Hg) to a light brown powder. This material was dissolved in 5.2 mL of CF_3CO_2H and used in the subsequent transformation. The reagent appears to be stable to prolonged storage at 23 ºC.



53 **β-dcSTXol · 2Cl⁻**

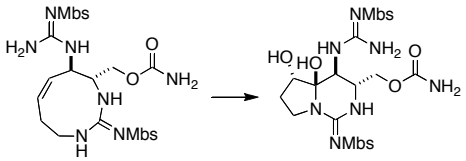
A 0.5 M CF_3CO_2H solution of $B(O_2CCF_3)_3$ (560 μL, 0.28 mmol, 30 equiv) was added dropwise to a 0 ºC solution of **53** (6.0 mg, 9.4 μmol) in 200 μL of CF_3CO_2H . The resulting light brown mixture was allowed to warm slowly to 23 ºC over 6 h. After stirring for 10.5 h the reaction was cooled in a cold-water bath and quenched by the dropwise addition of 1 mL of MeOH. The solution was concentrated under reduced pressure then twice was re-dissolved in 1 mL of MeOH and concentrated. Purification of the light brown residue was performed by ion-exchange chromatography (Dowex 1 x 8–200, $^-$OH form, H_2O eluent). The fractions containing product were combined and acidified to pH ~2 using 20 μL of 1M aqueous HCl. Lyophylization of this solution gave β-decarbamoylsaxitoxinol as a white solid (1.8 mg, 85%): $[\alpha]_D$ +116.2º (c = 0.25, MeOH); ^{1}H NMR (D_2O, 500 MHz) δ 4.67 (d, 1H, *J* = 1.5 Hz), 4.25 (d, 1H, *J* = 4.3 Hz), 3.71 (ddd, 1H, *J* = 10.2, 10.2, 2.2 Hz), 3.65-3.54 (m, 4H), 2.38 (dddd, 1H, *J* = 14.7, 9.8, 9.8, 4.3 Hz), 2.17 (ddd, 1H, *J* = 14.8, 8.3, 2.1 Hz) ppm; ^{13}C NMR (D_2O, 500 MHz) δ 157.1, 155.4, 82.9, 74.2, 60.9, 57.1, 55.0, 43.4, 28.3 ppm; HRMS (ES^+) calcd for $C_9H_{16}N_6O_2$ 240.1335 found 241.1417 (MH^+).



39 **57**

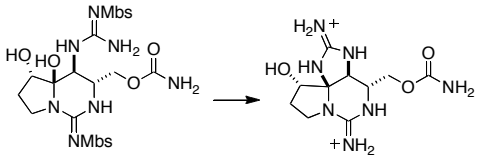
Cyclic guanidine **39** (87 mg, 0.163 mmol) was dissolved in 1.5 mL of an 8:1 THF/MeCN mixture, and the reaction vessel was cooled to –78 ºC. A 0.84 mM THF solution of trichloroacetyl isocyanate (440 μL, 0.369 mmol, 2.3 equiv) was added dropwise. The mixture was stirred for 1 h at –78 ºC after which time the reaction was quenched at this temperature by the slow addition of 1 mL of MeOH. The contents were warmed to 23 ºC and solid K_2CO_3 (15 mg, 0.11 mmol, 0.67 equiv) was added in a single portion. After stirring for 12 h, the mixture was concentrated under reduced pressure to a solid mass. Purification of this material by chromatography on silica gel (gradient

elution: 92:8→90:10 CH_2Cl_2/MeOH) furnished carbamate **57** as a white solid (81 mg, 82%): TLC R_f = 0.29 (10:1 CH_2Cl_2/MeOH); $[\alpha]_D$ +164.3º (c = 2.20, DMSO); ^{1}H NMR (d_6-DMSO, 500MHz, 80 ºC) δ 7.74-7.64 (m, 4H) 7.03-6.95 (m, 5H), 6.56 (br s, 2H), 6.34 (br s, 2H), 4.66-4.60 (br m, 1H), 4.57-4.53 (m, 2H), 4.04 (dd, 1H, *J* = 11.5, 3.3 Hz), 3.98 (dd, 1H, *J* = 11.4, 7.8 Hz), 3.84 (s, 3H), 3.82 (s, 3H), 3.81-3.79 (m, 1H), 3.42-3.33 (br m, 2H), 3.10-3.02 (m, 1H), 2.76 (br s, 1H), 2.04 (br s, 1H) ppm; ^{13}C NMR (d_6-DMSO, 125 MHz, 80 ºC) δ 161.5, 161.3, 159.1, 156.6, 156.0, 136.1, 134.9, 132.1, 128.9, 127.7, 127.6, 113.7, 113.3, 62.7, 56.6, 55.6, 55.5, 49.5, 40.0 (signal obscured by DMSO), 24.7 ppm; IR (thin film) ν 3436, 3347, 1734, 1597, 1529, 1258, 1133, 1082, 815 cm^{-1}; HRMS (ES$^+$) calcd for $C_{24}H_{31}N_7O_8S_2$ 609.1676 found 632.1580 (MNa^+).



57 **58**

Oxone (234 mg, 0.345 mmol, 7.0 equiv) was added in a single portion to a mixture of $OsCl_3$ (36 mM M solution in H_2O, 136 μL, 65 μmol, 0.10 equiv) and Na_2CO_3 (52 mg, 0.49 mmol, 10.0 equiv) in 2.2 mL of 11:11:2 EtOAc/MeCN/H_2O. Mild gas evolution was observed and the resulting yellow mixture was stirred for 2 min before carbamate **57** (30 mg, 49 μmol) was added. The contents were stirred vigorously for 48 h. The reaction was then quenched by the addition of 2 mL of saturated aqueous $Na_2S_2O_3$ and the mixture was transferred to a separatory funnel containing 6 mL of H_2O and 15 mL of EtOAc. The organic layer was collected and the aqueous phase was extracted with 1 x 15 mL of EtOAc. The combined organic extracts were washed with 1 x 5 mL of saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The solid residue was purified by chromatography on silica gel (92.5:7.5 CH_2Cl_2/MeOH) to give bicyclic guanidine **58** as a white solid (18 mg, 57%). This product was obtained as a 12:1 mixture (as determined by HPLC) with the undesired 5/6 bicyclic isomer **59** (see text). The sample could be purified further by reverse phase HPLC (NovaPak C_{18}, using 30:70 MeCN/H_2O + 1% CF_3CO_2H as eluent with a flow rate of 4 mL/min; 254 nm UV detection). Under these conditions the desired product eluted with a retention time of 12.5 min: TLC R_f = 0.21 (10:1 CH_2Cl_2/MeOH); $[\alpha]_D$ –120.2º (c = 2.00, MeOH); ^{1}H NMR (CD_3CN, 500 MHz) δ 7.82-7.77 (m, 4H), 7.73 (s, 1H), 7.06-7.01 (m, 4H), 6.46 (br s, 2H), 6.03 (br d, 1H, *J* = 6.1 Hz), 5.39 (br s, 2H), 4.33 (dd, 1H, *J* = 11.8, 2.5 Hz), 4.11-4.07 (m, 1H), 3.97 (d, 1H, *J* = 3.8 Hz), 3.89 (s, 3H), 3.88 (s, 3H), 3.76 (dd, 1H, *J* = 11.8, 5.7 Hz), 3.68 (ddd, 1H, *J* = 11.1, 5.6, 2.3 Hz), 3.60-3.50 (m, 2H), 2.26-2.18 (m, 1H), 1.86 (dd, 1H, *J* = 13.4, 7.0 Hz) ppm; ^{13}C NMR ($CDCl_3$ + 5% CD_3OD, 125 MHz) δ 162.4, 162.2, 156.9, 156.5, 151.3, 134.4, 133.8, 128.0, 127.9, 114.0, 113.9, 89.4, 74.7, 63.8, 55.4 (2), 49.8, 47.2, 46.0, 29.6 ppm; IR (thin film) ν 3334, 2924, 1678, 1579, 1536, 1499, 1410, 1260, 1132, 1081, 834 cm^{-1}; HRMS (ES$^+$) calcd for $C_{24}H_{31}N_7O_{10}S_2$ 641.1574 found 664.1500 (MNa^+).

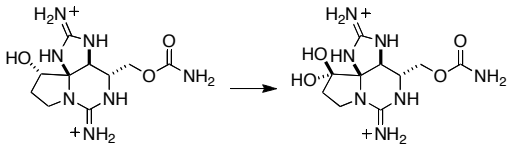


58 **β-STXol · 2Cl⁻**

A 0.5 M in CF_3CO_2H solution of $B(O_2CCF_3)$ (1.90 mL, 30 equiv) was added dropwise to a flask containing guanidine **58** (20 mg, 31 μmol) held in an ice-water bath. The light brown mixture was stirred vigorously as the contents warmed slowly over 5 h from 0 to 23 ºC. After stirring for 14 h at this temperature, the solution was cooled to 0 ºC, quenched by the dropwise addition of 1 mL of MeOH, and concentrated under reduced pressure. The solid residue was re-dissolved in 1 mL of MeOH and the solution was concentrated a second time. This process was repeated once. The isolated material was then dissolved in 0.5 mL of H_2O and passed through a 2 x 10 cm column of Dowex 1 x 8–200 ($^-$OH form). The fractions containing product, as determined by pH (~7.5–8.0), were collected and acidified to a pH of ~2 with 20 μL of 1 M aqueous HCl. The solution was lyophilized to give β-saxitoxinol•2Cl$^-$ as a white powder (9 mg, 84%): $[\alpha]_D$ +126.5º (c = 1.00, MeOH); ^{1}H NMR (D_2O, 500 MHz) δ 4.77 (d, 1H, *J* = 1.1 Hz), 4.32 (d, 1H, *J* = 4.3 Hz), 4.25 (dd, 1H, *J* = 11.5, 9.2 Hz), 4.00 (dd, 1H, *J* = 11.6, 5.5 Hz), 3.82 (ddd, 1H, *J* = 9.3, 5.4, 1.1 Hz), 3.75 (ddd, 1H, *J* = 10.2, 10.2, 2.0 Hz), 3.65 (q, 1H, *J* = 9.5 Hz), 2.40 (dddd, 1H, *J* =

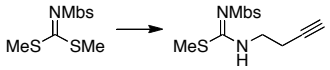
14.7, 9.9, 9.8, 4.4 Hz), 2.22 (ddd, 1H, J = 14.8, 8.0, 1.7 Hz) ppm; ^{13}C NMR (D_2O, 125 MHz)[8] δ 158.6, 157.3, 155.4, 83.0, 74.0, 62.7, 57.4, 52.5, 43.4, 28.4 ppm; HRMS (ES^+) calcd for $C_{10}H_{17}N_7O_3$ 283.1393 found 284.1472 (MH^+).

The following experimental protocol is based on the procedure reported by Schantz *et al*. for the oxidation of α-saxitoxinol:[9]



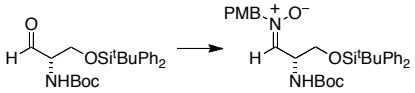
β-STXol · 2Cl⁻ **STX · 2($C_3F_7CO_2^-$)**

β-Saxitoxinol•2Cl^- (4.5 mg, 12 μmol) and powdered 3Å molecular sieves were combined in 500 μL of DMSO and stirred for 30 min. To this mixture were added dicyclohexylcarbodiimide (31 mg, 0.15 mmol, 12.0 equiv) and pyridinium trifluoroacetate (18 mg, 94 μmol, 7.5 equiv). A dense precipitate formed immediately and the resulting turbid suspension was stirred vigorously for 17 h. Lyophylization of the reaction mixture furnished a solid product that was suspended in 1 mL of H_2O and filtered. An additional 1 mL of H_2O was used to ensure quantitative transfer of the material. The combined filtrates were lypophylized and the obtained solid was purified by reverse-phase HPLC (Altima C18, 5 μm, 10 x 250 mm column, eluting with a gradient flow over 20 min of 12:88 MeCN/10 mM aqueous $C_3F_7CO_2H$ → 17:83 MeCN/10 mM aqueous $C_3F_7CO_2H$, 214 nm UV detection). At a flow rate of 6 mL/min, STX•2($C_3F_7CO_2^-$) had a retention time of 13.0 min and was isolated as a white, hygroscopic solid (4.0 mg, 60%): $[\alpha]_D$ +125 ± 3° (c = 0.13 (Cl^- salt)[10], H_2O); literature[11] (Cl^- salt) $[\alpha]_D$ +130 ± 5°; ^{1}H NMR (D_2O, 600 MHz, HOD referenced at 4.80 ppm) δ 4.77 (d, 1H, J = 1.2 Hz), 4.32 (dd, 1H, J = 11.7, 9.3 Hz), 4.05 (dd, 1H, J = 11.7, 5.4 Hz), 3.86 (ddd, 1H, J = 9.3, 5.2, 1.1 Hz), 3.83 (ddd, 1H, J = 10.0, 9.8, 2.0 Hz), 3.62-3.58 (m, 1H), 2.45 (ddd, 1H, J = 14.1, 8.2, 2.0), 2.37 (ddd, 1H, J = 14.0, 10.1, 10.0 Hz) ppm; ^{13}C NMR (D_2O, 600 MHz, determined by HMBC, appendix B) δ 159.7, 158.2, 156.5, 99.5, 83.1, 64.3, 57.6, 53.7, 43.8, 33.5 ppm; HRMS (ES^+) calcd for $C_{10}H_{15}N_7O_3$ 281.1236 (ketone form) found 282.1327 (MH^+).



63

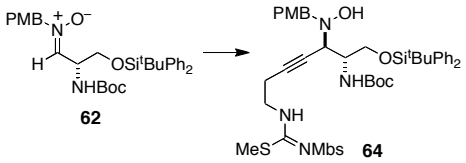
To a stirred suspension of [(4-methoxyphenyl)sulfonyl]carbonimidodithioic acid dimethyl ester (2.50 g, 8.61 mmol) in 20 mL of MeOH were added 3-butynylamine hydrochloride (1.00 g, 9.47 mmol, 1.1 equiv) and Et_3N (1.4 mL, 10.3 mmol, 1.2 equiv). The reaction flask was fitted with a reflux condenser and the mixture was stirred at 50 °C for 30 min. After cooling to 23 °C, the solution was concentrated under reduced pressure to ~1/3 the original volume and transferred to a separatory funnel with 50 mL of EtOAc and 25 mL of 10% aqueous $NaHSO_4$. The organic phase was collected and the aqueous layer was extracted with 3 x 10 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The amorphous solid obtained was dissolved in 8.0 mL of boiling 5:3 EtOAc/heptane, then cooled slowly to 23 °C. After allowing the mixture to stand for 2 h at 0 °C, the product was collected by filtration through a Büchner funnel, rinsed with ice-cold heptane, and dried in vacuo to give 2.22 g of the desired isothiourea **63** (83%). Following the same protocol, a second crop of material was collected from the mother liquor (164 mg, 6%): TLC R_f = 0.24 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.42 (br s, 1H), 7.87-7.81 (m, 2H), 6.95-6.90 (m, 2H), 3.83 (s, 3H), 3.44 (q, 2H, J = 6.4 Hz), 2.48 (td, 2H, J = 6.6, 2.6 Hz), 2.35 (s, 3H), 2.13-2.09 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.7, 162.2, 133.9, 128.0, 113.6, 79.5, 71.2, 55.3, 42.3, 19.0, 13.9 ppm; IR (thin film) ν 3290, 1574, 1258, 1140, 1080, 1024, 834 cm^{-1}; HRMS (ES^+) calcd for $C_{13}H_{16}N_2O_3S_2$ 312.0602 found 335.0497 (MNa^+).



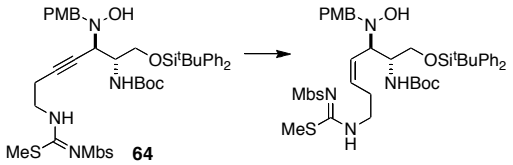
61 **62**

To a stirred solution of (*S*)-serinal **61** (5.30 g, 12.4 mmol) in 125 mL of CH_2Cl_2 were added *N*-(4-methoxybenzyl)hydroxylamine[12] (1.90 g, 12.4 mmol, 1.0 equiv) and $MgSO_4$ (2.24 g, 18.6 mmol, 1.5 equiv). The

resulting suspension was stirred for 5 h then poured through a sintered glass funnel. The flask and filter cake were washed with 3 x 10 mL of CH_2Cl_2, and the combined filtrates were concentrated under reduced pressure to an oily residue. This material was dissolved in 60 mL of boiling 3:1 hexanes/EtOAc and cooled slowly to 23 °C. After allowing the mixture to stand for 2 h at 0 °C, the product was collected by filtration through a Büchner funnel, rinsed with ice-cold hexanes, and dried in vacuo to furnish nitrone **62** as a white solid (4.89 g, 70%). Concentration of the mother liquor under reduced pressure and purification of the isolated residue by chromatography on silica gel (1:1 hexanes/EtOAc) afforded a second batch of **62** (420 mg, 6%). TLC R_f = 0.20 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60-7.53 (m, 4H), 7.46-7.32 (m, 6H), 7.31-7.25 (m, 2H), 6.92-6.85 (m, 2H), 6.71 (br s, 1H), 5.77 (br s, 1H), 4.78 (s, 2H), 4.76-4.68 (m, 1H), 4.00-3.95 (m, 1H), 3.95-3.86 (m, 1H), 3.80 (s, 3H), 1.40 (s, 9H), 1.02 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C) δ 160.3, 155.2, 136.0, 135.4, 135.4, 133.3, 133.2, 130.9, 129.7, 129.7, 127.7, 127.7, 124.7, 114.4, 79.6, 69.1, 62.7, 55.2, 50.5, 28.3, 26.8, 19.2 ppm; IR (thin film) ν 3270, 3072, 2961, 2933, 2858, 1710, 1514, 1252, 1175, 1113, 823 cm^{-1}; HRMS (ES$^+$) calcd for $C_{32}H_{42}N_2O_5Si$ 562.2863 found 585.2764 (MNa^+).

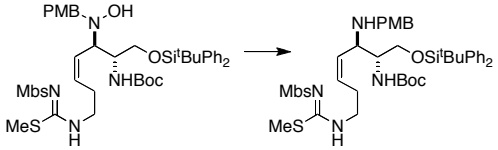


A 3-neck, 250 mL round bottom flask equipped with a rubber septum, internal thermometer, and a glass stopper was charged with isothiourea **63** (2.73 g, 8.74 mmol, 3.0 equiv) and 15 mL of THF. The vessel was cooled in a MeOH/ice bath to –15 °C, and to the solution was added dropwise 9.5 mL of 1.9 M ^{i}PrMgCl (17.9 mmol, 6.15 equiv) in THF. The contents were stirred at –15 °C for 5 min, then warmed to 0 °C. After 30 min, the mixture was cooled to –78 °C and a solution of nitrone **62** (1.64 g, 2.91 mmol) in 5.0 mL of THF was added dropwise via cannula. The internal temperature of the reaction did not rise above –65 °C during the addition process. An additional 3.0 mL of THF was used to ensure quantitative transfer of the nitrone. The resulting pale yellow suspension was stirred for 1 h at –78 °C, after which time the mixture was warmed to –50 °C. At this temperature, all solids had dissolved and stirring of the pale yellow solution was continued for 2 h. The reaction was then diluted with 150 mL of Et_2O and quenched with 75 mL of 2/3 saturated aqueous NH_4Cl. The contents were transferred to a separatory funnel, the organic phase was collected, and the aqueous layer was extracted with 3 x 25 mL of Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to an oily residue. Analysis of unpurified product by ^{1}H NMR showed a 4–5:1 diastereomeric ratio of products, as determined by integration of the *tert*-butyl signals. Purification by chromatography on silica gel (gradient elution: 2:2:1 CH_2Cl_2/hexanes/EtOAc → 1:1 hexanes/EtOAc) afforded the desired *anti*-diamine **64** as a white foam (1.98 g, 78%). A large portion of alkyne **63** was recovered as a white solid (1.27 g, 70%): TLC R_f = 0.23 (2:2:1 CH_2Cl_2/hexanes/EtOAc); ^{1}H ($CDCl_3$, 500 MHz, 50 °C) δ 8.40 (br s, 1H), 7.82 (d, 2H, J = 8.8 Hz), 7.67-7.59 (m, 4H), 7.44-7.33 (m, 6H), 7.29 (d, 2H, J = 8.5 Hz), 6.91-6.86 (m, 2H), 6.85-6.79 (m, 2H), 6.06 (br s, 1H), 5.17 (br s, 1H), 4.32-4.14 (m, 2H), 3.92-3.83 (m, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.74 (dd, 1H, J = 9.9, 6.5 Hz), 3.50-3.28 (m, 2H), 2.59-2.47 (m, 2H), 2.37 (s, 3H), 1.42 (s, 9H), 1.03 (s, 9H) ppm; ^{13}C ($CDCl_3$, 100 MHz, 50 °C) δ 168.7 (br), 162.4, 158.8, 156.9 (br), 135.5, 135.5, 134.5, 133.2, 133.1, 130.2, 129.6, 129.6, 128.2, 127.6, 127.6, 113.7, 113.6, 83.7 (br), 79.4, 78.1 (br), 63.3, 61.0, 60.1, 55.3, 55.1, 53.2, 42.7, 28.2, 26.7, 19.7, 19.1, 13.9 ppm; IR (thin film) ν 3376, 2932, 2857, 1697, 1575, 1512, 1253, 1139, 1111, 831 cm^{-1}; HRMS (ES$^+$) calcd for $C_{45}H_{58}N_4O_8S_2Si$ 874.3465 found 897.3357 (MNa^+).

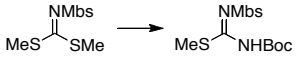


A thick-walled pressure tube was charged with diamine **64** (1.88 g, 2.15 mmol) and 15 mL of a 2:1 THF/H_2O solution. To this mixture were added *p*-toluenesulfonyl hydrazide (800 mg, 4.30 mmol, 2.0 equiv) and anhydrous sodium acetate (529 mg, 6.44 mmol, 3.0 equiv). After sealing the tube with a threaded Teflon stopper, the reaction vessel was submerged in an oil bath preheated to 100 °C. The reaction mixture was stirred for 1 h then cooled to 23

°C prior to removing carefully the Teflon plug. A second portion of *p*-toluenesulfonyl hydrazide (800 mg, 4.30 mmol, 2.0 equiv) and anhydrous sodium acetate (529 mg, 6.44 mmol, 3.0 equiv) were added, the reaction vessel was sealed, and the solution was stirred at 100 °C. Following a 1 h period, the contents were cooled to 23 °C and the Teflon stopper was carefully removed. A third portion of *p*-toluenesulfonyl hydrazide (800 mg, 4.30 mmol, 2.0 equiv) and anhydrous sodium acetate (529 mg, 6.44 mmol, 3.0 equiv) were added, the reaction vessel was sealed, and the solution was stirred at 100 °C for 1 h. Upon cooling to 23 °C, the flask was unstoppered and the contents were transferred to a separatory funnel with 50 mL of EtOAc and 20 mL of saturated aqueous $NaHCO_3$. The organic phase was collected and washed a second time with 20 mL of saturated aqueous $NaHCO_3$. The combined aqueous layers were extracted with 3 x 10 mL of EtOAc. The collected organic fractions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to an oily residue. Purification by chromatography on silica gel (5:2 toluene/Et_2O) afforded the desired *cis*-alkene as a white foam (1.47 g, 78%): TLC R_f = 0.40 (2:1 toluene/Et_2O); ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C) δ 8.17 (br s, 1H), 7.86-7.78 (m, 2H), 7.70-7.60 (m, 4H), 7.46-7.34 (m, 6H), 7.24-7.17 (m, 2H), 6.95-6.88 (m, 2H), 6.85-6.78 (m, 2H), 5.95 (br s, 1H), 5.76-5.57 (m, 2H), 4.75 (d, 1H, *J* = 9.5 Hz), 4.30-4.04 (m, 1H), 3.94 (d, 1H, *J* = 14.0 Hz), 3.83 (s, 3H), 3.78 (s, 3H), 3.73 (dd, 1H, *J* = 10.2, 5.2 Hz), 3.66 (dd, 1H, *J* = 9.5, 5.2 Hz), 3.58 (d, 1H, *J* = 13.6 Hz), 3.33-3.20 (m, 2H), 2.43-2.19 (m, 2H), 2.33 (s, 3H), 1.44 (s, 9H), 1.07 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C) δ 168.7, 162.4, 158.6, 156.2, 135.5, 135.5, 135.4, 134.7, 133.2, 133.1, 130.5, 129.8, 129.7, 129.6, 128.1, 127.7, 127.7, 113.8, 113.5, 79.3, 64.3, 63.1, 60.2, 55.3, 55.1, 53.6, 43.6, 28.3, 28.1, 26.8, 19.1, 13.9 ppm; IR (thin film) ν 3369, 2931, 2856, 1700, 1576, 1512, 1499, 1254, 1173, 1138, 1112, 1080, 859, 831 cm^{-1}; HRMS (ES$^+$) calcd for $C_{45}H_{60}N_4O_8S_2Si$ 876.3622 found 899.3510 (MNa^+).

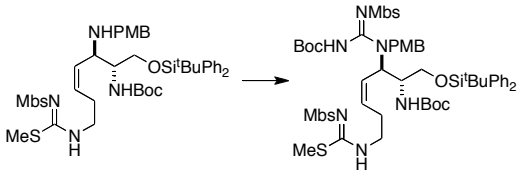


To a slurry of zinc dust (510 mg, 7.81 mmol, 5.0 equiv) in 3.0 mL of AcOH was added anhydrous $Cu(OAc)_2$ (28 mg, 156 μmol, 0.10 equiv). The gray suspension was stirred for 15 min following which time a solution of *cis*-alkene (1.37 g, 1.56 mmol) in 4.0 mL of AcOH was added via cannula. Transfer of this material was made quantitative with an additional 1.0 mL of AcOH and 2.0 mL of H_2O. The reaction vessel was sealed with a glass stopper, submerged in an oil bath, and the contents were stirred at 70 °C for 1 h. After cooling the reaction to 23 °C, 500 mg of solid Na_2EDTA was added in a single portion. The mixture was stirred vigorously for 5 min, then the solution was made basic (pH ~10) by the dropwise addition of 40 mL of 10% aqueous NaOH. Subsequent addition of 100 mL of EtOAc gave a biphasic solution, which was stirred vigorously for 1 min and then filtered through a small pad of Celite. The flask and the filter cake were rinsed with 100 mL of EtOAc and 50 mL of H_2O. After transferring the combined filtrates to a separatory funnel, the organic phase was collected and the aqueous phase was extracted with 3 x 20 mL of EtOAc. The combined organic fractions were washed successively with 1 x 30 mL of saturated aqueous EDTA and 1 x 30 mL of saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the foamy residue by chromatography on silica gel (gradient elution: 1:1→2:3 hexanes/EtOAc) afforded the desired 2° amine as a white foam (1.08 g, 81%): TLC R_f = 0.23 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30-8.20 (m, 1H), 7.87-7.79 (m, 2H), 7.68-7.57 (m, 4H), 7.46-7.32 (m, 6H), 7.25-7.17 (m, 2H), 6.95-6.88 (m, 2H), 6.86-6.78 (m, 2H), 5.61-5.50 (m, 1H), 5.45 (dd, 1H, *J* = 10.1 Hz), 5.36-5.20 (m, 1H), 3.91 (d, 1H, *J* = 10.2 Hz), 3.83 (s, 3H), 3.78 (s, 3H), 3.76 (d, 1H, *J* = 13.6 Hz), 3.71 (d, 1H, *J* = 10.8 Hz), 3.67-3.56 (m, 2H), 3.52 (d, 1H, *J* = 12.8 Hz), 3.33-3.16 (m, 2H), 2.41-2.21 (m. 2H), 2.32 (s, 3H), 1.56 (br s, 1H), 1.43 (s, 9H), 1.02 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.7, 162.2, 158.3, 155.4, 135.3, 135.3, 134.3, 133.4, 132.8, 132.8, 132.1, 129.6, 129.6, 129.1, 128.0, 127.8, 127.6, 127.6, 113.6, 113.5, 78.9, 63.5, 55.3, 55.1, 55.0, 54.3, 50.3, 43.7, 28.3, 27.4, 26.7, 19.0, 13.9 ppm; IR (thin film) ν 3294, 2931, 2856, 1708, 1575, 1512, 1498, 1255, 1173, 1138, 1111, 1080, 860, 831 cm^{-1}; HRMS (ES$^+$) calcd for $C_{45}H_{60}N_4O_7S_2Si$ 860.3673 found 861.3763 (MH^+).

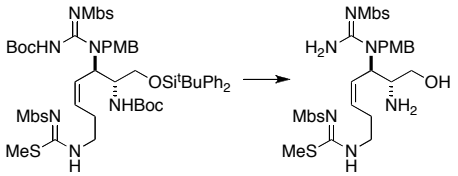


To a stirred suspension of *N*-[bis(methylthio)methylene]-4-methoxybenzenesulfonamide (2.00 g, 6.86 mmol) in 14 mL of MeOH was added 5.2 mL of 2.0 M methanolic NH_3 (10.3 mmol, 1.50 equiv). The reaction vessel was sealed with a glass stopper, submerged in an oil bath, and the mixture was stirred for 30 min at 50 °C. Following this time,

the reaction was cooled to 23 °C and all volatiles were removed under reduced pressure. The isolated, off-white amorphous solid was suspended in 20 mL of THF and the slurry was warmed gently with a heat gun to effect dissolution. To the resulting homogeneous medium was then added via cannula a solution of Boc_2O (1.57 g, 7.21 mmol, 1.05 equiv) in 10 mL of THF. An additional 5.0 mL of THF was used to ensure quantitative transfer of Boc_2O. The flask was quickly unstoppered and a single portion of DMAP (42 mg, 342 μmol, 0.05 equiv) was added. After stirring the reaction mixture for 12 h, the solution was concentrated under reduced pressure to a solid residue. Purification of this material by chromatography on silica gel (3:1 hexanes/EtOAc) afforded the desired isothiourea as a white powder (2.35 g, 95%): TLC R_f = 0.29 (3:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.3 (br s, 1H), 7.90-7.83 (m, 2H), 7.01-6.94 (m, 2H), 3.87 (s, 3H), 2.27 (s, 3H), 1.51 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.0, 162.9, 149.9, 132.7, 128.5, 114.0, 84.1, 55.5, 27.8, 14.7 ppm; IR (thin film) ν 3247, 2980, 1752, 1563, 1295, 1260, 1232, 1153, 1085, 847 cm^{-1}; HRMS (ES$^+$) calcd for $C_{14}H_{20}N_2O_5S_2$ 360.0814 found 383.0715 (MNa^+).

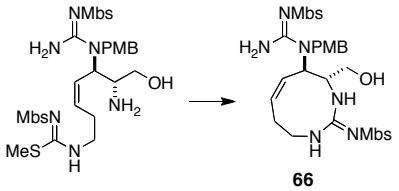


A solution of *N*-Boc-*N*'-Mbs isothiourea (500 mg, 1.39 mmol, 4.0 equiv) in 5.5 mL of CH_2Cl_2 was added to a rubber septum-stoppered, flame-dried 16 x 125 mm test tube containing anhydrous $HgCl_2$ (189 mg, 0.69 mmol, 2.0 equiv). The clear, colorless mixture was stirred rapidly while neat Et_3N (0.21 mL, 1.53 mmol, 4.4 equiv) was added dropwise. A white precipitate formed immediately; the resulting slurry was stirred vigorously for 15 min. After allowing the precipitate to settle, the test tube was placed in a centrifuge and spun at 1550 rpm for 5 min. With the aid of a syringe, 5.0 mL of the colorless supernatant was withdrawn and added dropwise to a solution of PMB-amine (299 mg, 347 μmol) in 1.5 mL CH_2Cl_2. The reaction vessel was equipped with a reflux condenser and the contents were stirred for 5 min at 40 °C. After cooling the suspension to 23 °C, the mixture was filtered through a small pad of Celite, rinsing the flask and filter cake with 50 mL of CH_2Cl_2. The combined filtrates was transferred to a separatory funnel and the organic solution was washed with 10% aqueous $NaHSO_4$. The organic layer was collected and the aqueous phase was extracted with 3 x 10 mL of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to an oily residue. Purification by chromatography on silica gel (gradient elution: 3:3:1→2:2:1 CH_2Cl_2/hexanes/EtOAc) afforded the desired *N*-Boc guanidine as a white foam (300 mg, 74%): TLC R_f = 0.36 (2:2:1 CH_2Cl_2/hexanes/EtOAc); ^{1}H NMR (CD_3CN, 400 MHz, 70 °C) δ 8.16 (br s, 1H), 7.86-7.79 (m, 2H), 7.71-7.65 (m, 4H), 7.65-7.53 (m, 2H), 7.49-7.34 (m, 6H), 7.06-6.95 (m, 4H), 6.88-6.82 (m, 2H), 6.82-6.76 (m, 2H), 5.70 (dd, 1H, *J* = 10.4, 10.4 Hz), 5.51 (ddd, 1H, *J* = 10.2, 7.3, 7.3 Hz), 5.24-4.98 (m, 1H), 5.00 (dd, 1H, *J* = 8.8 Hz), 4.42 (s, 2H), 4.15-4.02 (m, 1H), 3.86 (dd, 1H, *J* = 10.8, 3.8 Hz), 3.83 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.67 (dd, 1H, *J* = 10.7, 7.6 Hz), 3.40-3.13 (m, 2H), 2.42-2.28 (m, 2H), 2.33 (s, 3H), 1.40 (s, 9H), 1.39 (s, 9H), 1.06 (s, 9H) ppm; ^{13}C NMR (CD_3CN, 100 MHz, 70 °C) δ 163.9, 163.8, 160.6, 156.7, 153.6, 150.8, 136.8, 136.8, 136.0, 135.1, 134.9, 132.5 (br), 131.0, 131.0, 129.7, 129.4, 129.3, 129.2, 129.0, 129.0, 127.7 (br), 115.4, 115.3, 115.3, 84.2, 80.0, 64.6, 58.8, 56.7, 56.6, 56.3, 55.5 (br), 51.2 (br), 44.7, 29.0, 28.6, 27.8, 20.2, 14.8 ppm; IR (thin film) ν 3294, 2932, 1749, 1711, 1574, 1257, 1140, 1082, 1028, 869, 831, 805 cm$^{=1}$; HRMS (ES$^+$) calcd for $C_{58}H_{76}N_6O_{12}S_3Si$ 1172.4453 found 1195.4349 (MNa^+).



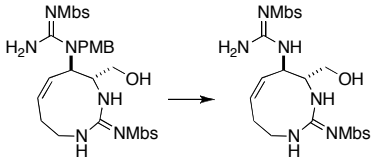
N-Boc guanidine (149 mg, 136 μmol) was dissolved in 3.0 mL of 1.0 M methanolic HCl, the reaction vessel was sealed with a glass stopper, and the solution was stirred at 40 °C for 12 h. Following this time, the reaction was cooled to 23 °C and all volatiles were removed under reduced pressure. The isolated off-white film was suspended in 3.0 mL of CH_2Cl_2 and to this mixture was added neat Et_3N (0.19 mL, 1.36 mmol, 10 equiv). After stirring for 15 min, the solution was concentrated under reduced pressure. Purification of the amorphous solid by chromatography

on silica gel (9:1 CH_2Cl_2/MeOH) afforded the amino alcohol as an opaque oil (52 mg, 52%): TLC R_f = 0.22 (93:7 CH_2Cl_2/MeOH); ^{1}H NMR (CD_3CN, 500 MHz, 70 °C) δ 7.83-7.88 (m, 2H), 7.77-7.72 (m, 2H), 7.60-7.20 (br s, 2H), 7.08-7.03 (m, 2H), 7.03-6.99 (m, 2H), 6.99-6.95 (m, 2H), 6.83-6.78 (m, 2H), 5.73 (dd, 1H, *J* = 10.6, 10.6 Hz), 5.51 (ddd, 1H, *J* = 10.7, 7.4, 7.4 Hz), 4.77-4.63 (m, 1H), 4.49 (ABq, 2H, *J* = 16.2 Hz, Δν = 33.2 Hz), 3.84 (s, 3H), 3.75 (s, 3H), 3.32 (dd, 1H, *J* = 11.1, 4.9 Hz), 3.29-3.17 (m, 2H), 3.25 (dd, 1H, *J* = 11.4, 5.1 Hz), 2.87 (ddd, 1H, *J* = 5.3, 5.3, 5.3 Hz), 2.36 (s, 3H), 2.31-2.21 (m, 1H), 2.13-2.04 (m, 1H) ppm; IR (thin film) ν 3339 (br), 3011, 2934, 1596, 1579, 1513, 1498, 1256, 1136, 1080, 833 cm^{-1}; HRMS (ES$^+$) calcd for $C_{32}H_{42}N_6O_8S_3$ 734.2226 found 757.2117 (MNa^+).



66

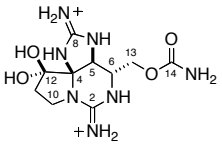
Amino alcohol (38 mg, 52 μmol) was dissolved in 6.0 mL of MeCN and added dropwise over 45 min to a solution of $AgNO_3$ (11 mg, 67 μmol, 1.3 equiv) and Et_3N (72 μL, 517 μmol, 10 equiv) in 10 mL of MeCN. Transfer of this material was made quantitative with 2 x 0.5 mL of MeCN. The reaction flask was wrapped in aluminum foil and the contents stirred in the dark for 20 min. The pale yellow suspension was then filtered through a small pad of Celite, rinsing the flask and filter cake with 40 mL of CH_2Cl_2. Concentration of the combined filtrates under reduced pressure gave an oily residue, which was purified by chromatography on silica gel (93:7 CH_2Cl_2/MeOH) to give the desired 9-membered ring guandine **66** as a white foam (26 mg, 73%): TLC R_f = 0.38 (93:7 CH_2Cl_2/MeOH); ^{1}H NMR (CD_3CN, 400 MHz, 70 °C) δ 7.86-7.63 (m, 4H), 7.04-6.95 (m, 2H), 6.95-6.87 (m, 2H), 6.91 (br s, 2H), 6.87-6.78 (m, 2H), 6.35 (br s, 2H), 4.90-4.66 (m, 1H), 4.66-4.45 (m, 1H), 4.45-4.08 (m, 2H), 3.85 (s, 3H), 3.78 (s, 3H), 3.72-3.50 (m, 4H), 3.48-3.33 (m, 2H) 2.22-1.50 (m, 5H) ppm; IR (thin film) ν 3336, 2930, 1596, 1515, 1498, 1258, 1134, 1081, 835, 811 cm^{-1}; HRMS (ES$^+$) calcd for $C_{31}H_{38}N_6O_8S_2$ 686.2193 found 709.2084 (MNa^+).



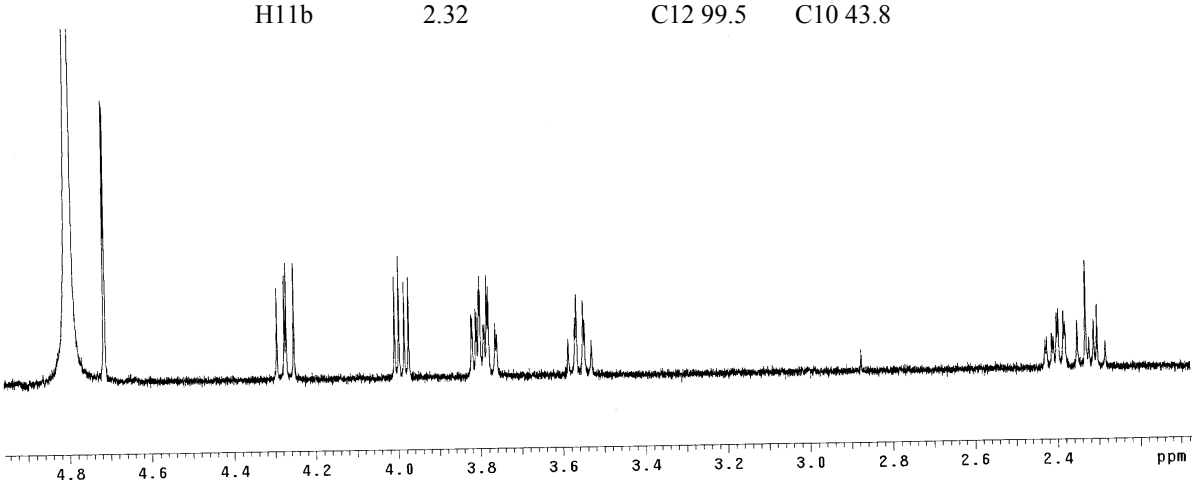
66 **39**

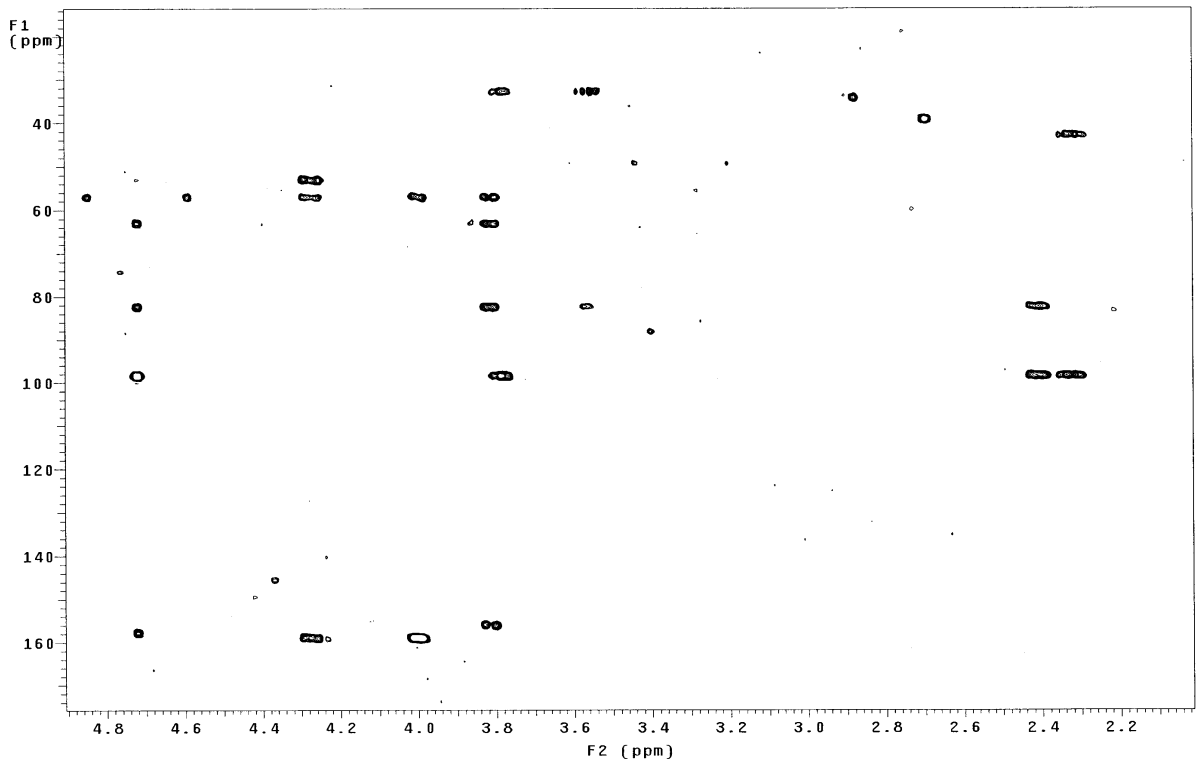
Cyclic guanidine **66** (13 mg, 19 μmol) was dissolved in 1.0 mL of TFA, the reaction vessel was sealed with a glass stopper, and the solution was stirred for 6 h at 60 °C. After cooling to 23 °C, the mixture was concentrated under reduced pressure to a solid residue. Purification by chromatography on silica gel (93:7 CH_2Cl_2/MeOH) afforded alcohol **39** as a white solid (10 mg, 91%): TLC R_f = 0.28 (20:1 CH_2Cl_2/MeOH); ^{1}H NMR (CD_3CN, 500 MHz, 70°C) δ 7.78-7.68 (m, 4H), 7.03-6.92 (m, 4H), 6.67 (br s, 1H), 6.20 (br s, 2H), 5.71 (br s, 1H), 4.98 (br s, 1H), 4.85-4.73 (m, 1H), 4.63 (t, 1H, *J* = 10.0 Hz), 3.85 (s, 3H), 3.84 (s, 3H), 3.72 (br d, 1H, *J* = 11.0 Hz), 3.62 (br d, 1H, *J* = 11.0 Hz), 3.50-3.35 (m, 2H), 3.23 (br s, 1H), 2.44 (br s, 1H), 2.04-1.99 (br m, 1H) ppm. HRMS (ES$^+$) calcd for $C_{23}H_{30}N_6O_7S_2$ 566.1617 found 589.1513 (MNa^+).

HMBC Correlations for Synthetic (+)-STX•2 $C_3F_7CO_2^-$ (D_2O, 600 MHz):

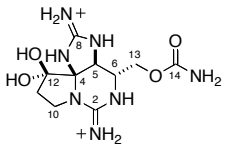


Position	^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)			
H5	4.72	C8 158.2	C12 99.5	C4 83.1	C13 64.3
H13a	4.27	C14 159.7	C5 57.6	C6 53.7	
H13b	3.99	C14 159.7	C5 57.6		
H6	3.80	C2 156.5	C4 83.1	C13 64.3	C5 57.6
H10a	3.76	C12 99.5	C11 33.5		
H10b	3.56	C4 83.1	C11 33.5		
H11a	2.41	C12 99.5	C4 83.1		
H11b	2.32	C12 99.5	C10 43.8		





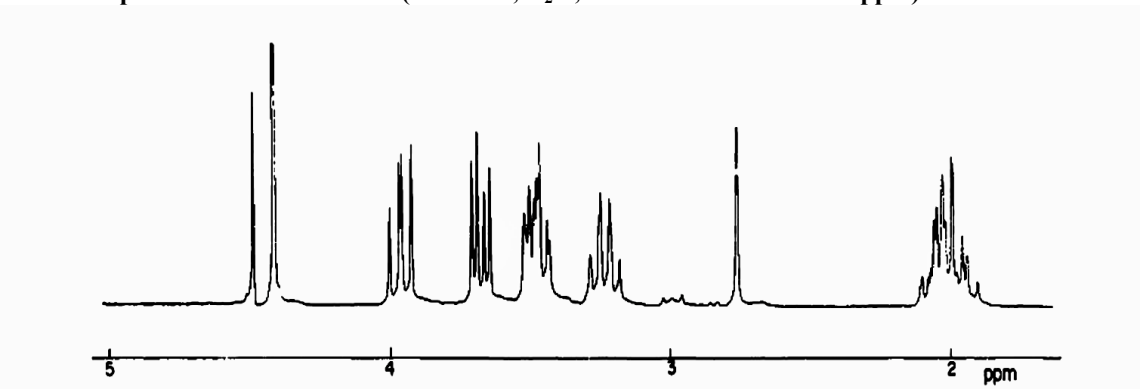
Comparison of Spectral Data for Synthetic and Natural (+)-Saxitoxin:



Position	Synthetic STX		Natural STX	
	^{13}C	^{1}H	^{13}C	^{1}H
2	156.5	–	156.8	–
4	83.1	–	83.2	–
5	57.6	4.33 (d, 1H, *J* = 1.2 Hz)	57.8	4.33 (d, 1H, *J* = 1.2 Hz)
6	53.7	3.42 (ddd, 1H, *J* = 9.3, 5.3, 1.2 Hz)	53.8	3.47 (ddd, 1H, *J* = 9, 6, 1.2 Hz)
8	158.2	–	158.5	–
10	43.8	2.02 (ddd, 1H, *J* = 13.9, 8.3, 2.0 Hz) 1.93 (ddd, 1H, *J* = 14.0, 9.9, 9.9 Hz)	43.8	2.00 (m, 1H) 1.99 (m, 1H)
11	33.5	3.40 (ddd, 1H, *J* = 10.1, 10.1, 2.0 Hz) 3.17 (ddd, 1H, *J* = 9.9, 9.9, 8.2 Hz)	33.8	3.40 (dd, 1H, *J* = 10, 3 Hz) 3.18 (ddd, 1H, *J* = 11, 10, 8 Hz)
12	99.5	–	99.4	–
13	64.3	3.88 (dd, 1H, *J* = 11.7, 9.4 Hz) 3.61 (dd, 1H, *J* = 11.7, 5.4, Hz)	64.0	3.88 (dd, 1H, *J* = 12, 9 Hz) 3.65 (dd, 1H, *J* = 12, 6 Hz)
14	159.7	–	159.7	–

- ^{1}H NMR of synthetic STX•2 $C_3F_7CO_2^-$ was recorded in D_2O and referenced internally to HOD at δ 4.40 ppm.
- ^{13}C NMR data for synthetic STX•2 $C_3F_7CO_2^-$ was obtained by HMBC analysis.
- Data for natural STX was reported by Koehn *et al*.[9]

^{1}H NMR Spectrum of Natural STX (270 MHz, D_2O, HOD referenced at 4.50 ppm):[13]



^{1}H NMR Spectrum of Synthetic STX (500 MHz, D_2O, HOD referenced at 4.50 ppm):

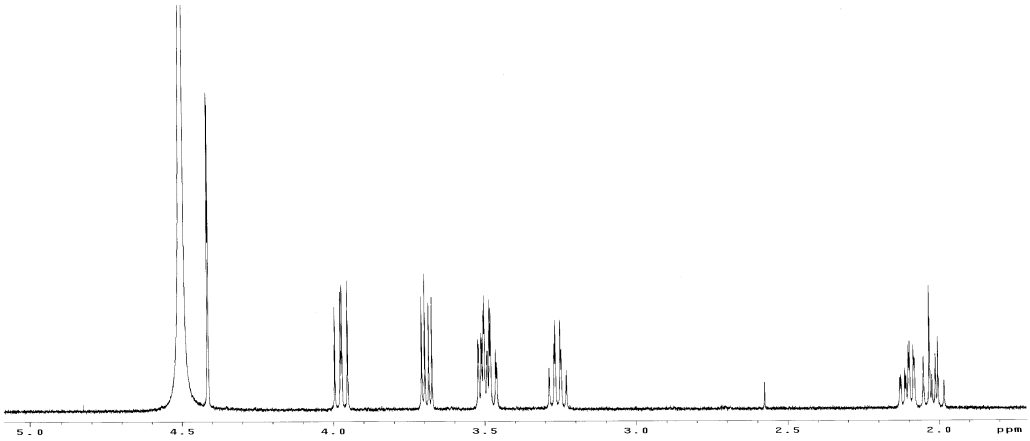
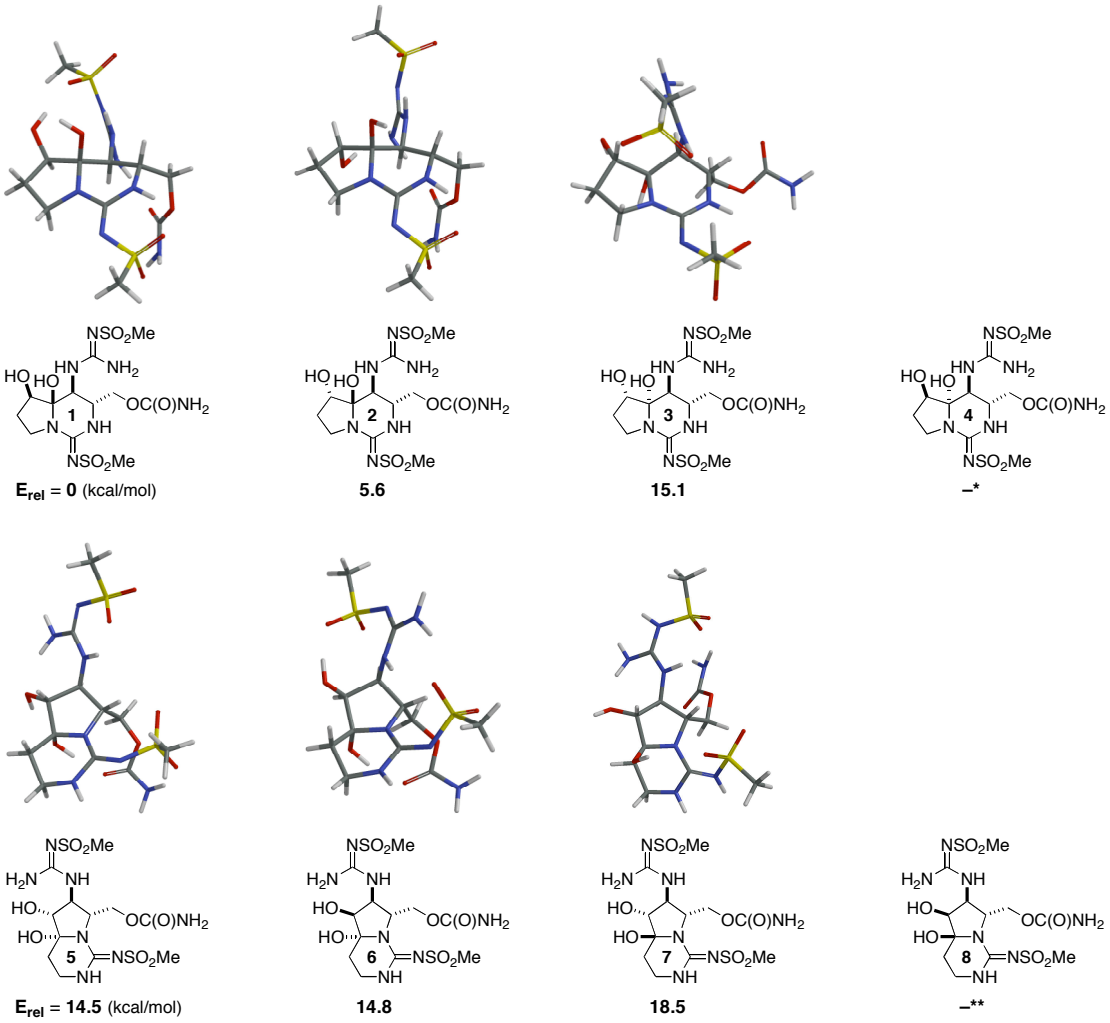


Table of Energies and Zero-Point Vibrational Corrections (ZPVE):[14]

isomer	E (hartree)	ZPVE (Hart)	E + ZPVE	E_{rel}(kcal/mol)
1	-2252.4936	0.411723	-2252.0819	0
2	-2252.4845	0.411595	-2252.0729	5.62060707
3	-2252.4669	0.409142	-2252.0578	15.1160884
4*	-2252.471	0.409498	-2252.0615	12.7861438
5	-2252.4699	0.411153	-2252.0587	14.523719
6	-2252.4696	0.411349	-2252.0582	14.8381015
7	-2252.463	0.410564	-2252.0524	18.4845621
8**	-2252.4691	0.412534	-2252.0566	15.8766305

* The minimized structure was found to be a second order saddle point on the energy surface and not a true local minimum.

** The minimized structure was found to be a first order saddle point on the energy surface and not a true local minimum.



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