Experimental

General

***General Procedures*:** All reactions were performed under a positive pressure of argon. The following solvents were distilled under a positive pressure of dry argon immediately before use: THF and ether from sodium-benzophenone ketyl and CH_2Cl_2 from CaH_2. All commercial materials were used without further purification, with the exception of *m*-CPBA [purified by extraction of a benzene solution with an aqueous solution buffered at pH 7.4 (NaH_2PO_4/NaOH)] and chlorotrimethylsilane (purified by distillation).

***Instrumentation and Protocols*:** ^{1}H NMR spectra were recorded on Bruker DPX-300 MHz, Bruker DRX-300 MHz, Bruker AMX-400 MHz, Bruker Advanced DMX-500 MHz, and Varian VXR-400 MHz spectrometers referenced to $CDCl_3$ (δ 7.26), CD_3OD (δ 3.30) or D_2O (δ 4.65). ^{13}C NMR spectra were recorded on either a Bruker DRX-300 MHz (75 MHz) or a Varian-VXR 300 MHz (75 MHz) spectrometer referenced to $CDCl_3$ (δ 77.0) or CD_3OD (δ 49.0). Data are reported as follows: chemical shift in ppm from internal standard tetramethylsilane on the δ scale, multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, dd=doublet of doublets, m=multiplet), coupling constant(s) in Hertz. Magnitude COSY and 1D nOe experiments were performed on a

Bruker Advanced DMX-500 MHz machine and nOe difference experiments were performed at Memorial Sloan-Kettering Cancer Center by Dr. George Sukenick. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FTIR spectrometer or a Perkin-Elmer 1420 Ratio Recording Infrared Spectrometer. Low and high resolution mass spectral analysis were performed with NermagR-10-10, JEOL-DX-303HF, and JEOL-HX110A mass spectrometers.

Preparation of Dithiane 9

Dithiane **7** (prepared according to the literature procedure)[1] was dissolved in anhydrous benzene and solvent was removed *in vacuo* (3 x). A solution of dithiane **7** (12.1 g, 45.7 mmol) in 500 mL anhydrous THF was cooled to –45 °C. *n*-BuLi (2.5 M, 23.8 mL) was added *via* syringe and solution was stirred 1.5 h at –50 °C. Bromide **8**[2] (15.0 g, 68.5 mmol) was added to this deep yellow solution slowly *via* cannula. The reaction mixture became pale yellow at the end of this addition. The solution warmed slowly to RT over 3 h and was quenched with H_2O. The organic solvent was removed *in vacuo*, and the residue was partitioned between EtOAc (500 mL) and H_2O (300 mL). The layers were separated and the organic layer was washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (5-10% ethyl acetate/hexanes) gave dithiane **9** (17.4 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (t, J= 6.71 Hz, 1H), 2.67-2.91 (m, 8H), 2.25 (t, J=6.93 Hz, 2H), 2.08-2.18 (m, 3H), 1.80-2.02 (m, 7H), 1.62-1.72 (m, 2H) 0.16 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 106.8, 85.2, 52.6, 47.3, 37.4, 35.1, 30.3, 30.2, 26.0, 25.9, 25.3, 23.2, 19.9, 18.9, 0.2; high resolution mass spectrum (EI) *m/z* calculated for $C_{18}H_{33}S_4Si$ 405.1234, found 405.1246.

Preparation of 4-Oxo-9-trimethylsilanylnon-8-ynal (10)

A solution of dithiane **9** (10 g, 24.7 mmol) in anhydrous CH_3CN (200 mL) and H_2O (25 mL) was cooled to 0 °C. Cerium ammonium nitrate (40.7 g, 74.2 mmol) was added, and the reaction mixture was stirred for 15 min at 0 °C. The reaction was diluted with H_2O (150 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated with care, due to the volatility of the product. Crude aldehyde **10** was not characterized, but upon subjection to the reaction conditions described below for aldol cyclization, cyclopentenone **4**, identical in all ways to the material produced by the other synthetic route, was obtained.

Preparation of α-Hydroxyketone mixture 23a/23b

A solution of α-hydroxyketone **19** in benzene (0.2 M) containing a few drops of 1 N NaOH was degassed (freeze/pump/thaw X 3) and heated to reflux for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica (15% ethyl acetate/ hexanes) to give a mixture (2:1) of hydroxyketones **23a** and **23b**. Yields ranged from 75% to 95%, and diosphenol **20b** was sometimes present.

^{1}H NMR (400 MHz, $CDCl_3$) 1.5:1 mixture of diastereomers; δ 4.84 (m, 2H), 4.38 (q, J = 6.0 Hz, 3.2 Hz, 0.6H), 4.16 (q, J= 10.8 Hz, 2.7 Hz, 0.4H), 3.57 (s, 0.6 H), 3.53 (s, 0.4H), 3.15 (s, 0.6H), 3.12 (s, 0.4H), 2.77 (t, J= 2.4 Hz, 0.6H), 1.20-2.33 (series of m, 10.4H), 0.94 (d, J= 7.0 Hz, 1.2 H), 0.86 (d, J=7.3 Hz, 1.8 H).

Preparation of Benzylamine 32

Imine formation with benzylamine and ketone **2** and subsequent reduction (imine = 2.0 mg) were carried out as described in the general procedure above. The product amine was purified by flash chromatography (10% ethyl acetate/ hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37- 7.24 (m, 5H), 3.77 (dd, J=32.8, 13.1 Hz, 2H), 2.89 (d, J=4.8 Hz, 1H), 2.05 (t, J=5.0 Hz, 1H), 1.84 (dd, J=12.7, 7.7 Hz, 1H), 1.72 (m, 2H), 1.25-1.65 (m, 10H), 1.13 (s, 3H), 1.19 (s, 3H), 0.83 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.4, 128.1, 127.0, 81.8, 80.1, 65.9, 52.7, 52.0, 44.2, 43.4, 43.3, 32.2,

29.4, 28.8, 27.3, 20.9, 20.3, 18.2, 14.1; high resolution mass spectrum (EI) *m/z* calculated for $C_{22}H_{32}NO$, 326.2484, found 326.2477.

Preparation of 1-Methoxy-3-trimethylsilanylbut-3-en-2-one (38). [8b]

Bromovinyltrimethylsilane (10.0 g, 56.0 mmol) was converted to the corresponding Grignard reagent with magnesium turnings (1.85 g, 76.2 mmol) and treated with methoxyacetaldehyde (8.3 g, 112.0 mmol). Usual workup gave crude allylic alcohol, which was treated with Jones reagent. Workup and chromatography on silica (10% ethyl acetate/ hexanes) gave enone **38** (4.6 g, 48% over 2 steps).

IR 2956(s), 2823, 1682(s), 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.40 (s, 1H), 6.12 (s, 1H), 4.35 (s, 2H), 3.43 (s, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 151.8, 135.2, 74.9, 59.1, -1.6.

Preparation of α-Methoxy Bicyclic Enone 39:

Robinson annulation was carried out as described for bicyclic ketone **4**. Cuprate addition was performed on cyclopentenone **5** (325 mg, 2.43 mmol) with copper iodide (554 mg, 2.9 mmol) and methyllithium (1.6 M in ether, 3.1 mL, 5.0 mmol), and then trapped with methoxymethylvinyl ketone **38** (836 mg, 4.86 mmol). Purification by flash chromatography on SiO_2 (25% ethyl acetate/hexane) gave 168 mg (30%) of methoxyenone **39** (3.5:1 mixture of diastereomers).

IR 3287, 2954 (s), 2875, 2835, 1682 (s), 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 3.5:1 mixture of diastereomers; δ 3.66 (s, 2.3 H), 3.64 (s, 0.7 H), 2.46-2.61 (m, 4H), 2.2-2.3 (m, 2H), 2.09 (m, 1H), 1.97 (m, 1H), 1.62-1.95 (m, 5H), 1.40-1.60 (m, 1H), 1.01 (d, J=7.0 Hz, 2.3 H), 0.84 (d, J=7.0 Hz, 0.7 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 158.9, 146.6, 84.0, 69.9, 59.5, 49.2, 47.5, 47.3, 38.8, 35.3, 34.5, 33.7, 33.1, 31.3, 30.5, 30.2, 25.9, 25.5, 16.9, 16.0, 14.6, 13.5; HRMS (EI) *m/z* calcd for $C_{15}H_{20}O_2K$ 271.1100, found 271.1098.

Preparation of analog 45

Reaction of adamantanone **44** (100 mg, 0.67 mmol) with amine **36** (150 mg, 0.8 mmol) was carried out as described in the general procedure above (reflux period for imine formation was 2 days). The product was ≥ 95% pure by proton NMR after aqueous workup, giving 144 mg (67%) of amine **45**.

IR 2904, 2845, 2785 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.70 (br s, 1H), 2.60 (br t, J=6.7 Hz, 2H), 2.35 (m, 4H), 2.27 (t, J=7.5 Hz, 2H), 2.22 (s, 9H), 1.94 (br d, J=12.0 Hz, 2H), 1.84 (m, 5H), 1.77 (br s, 1H), 1.60-1.70 (m, 7H), 1.47-1.53 (m, 6H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.5, 57.7, 57.5, 55.6, 46.7, 45.3, 42.1, 37.7, 37.4, 31.8, 31.3, 28.3, 27.6, 27.3, 25.4, 25.1; HRMS (EI) *m/z* calcd for $C_{20}H_{40}N_3$ 321.3144, found 322.3227.

Preparation of myoinositol analog 47

Reaction of ketone **43**[3] (200 mg, 0.54 mmol) with amine **36** (122 mg, 0.65 mmol) was carried out as described in the general procedure above (reflux period for imine formation was 1 day). The solvent was removed under reduced pressure and then diluted with water (5 mL). The solution was extracted with CH_2Cl_2 (3 X 5 mL), the combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure to give 225 mg (77%) of amine **47**.

IR 3351, 2946 (s, br) cm^{-1} ^1H NMR ($CDCl_3$, 400 MHz) δ 7.22–7.30 (m, 10H), 5.56 (s, 1H), 4.65 (s, 4H), 4.58 (m, 3H), 4.37 (m, 2H), 3.58 (br s, 1H), 2.64 (t, J=6.9H, 2H), 2.24-2.31 (m, 4H), 2.23 (s, 6H), 2.18 (t, J=7.4 Hz, 2H), 2.14 (s, 3H), 1.62 (m, 2H), 1.22-1.34 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 128.3, 127.7, 127.6, 103.2, 73.5, 71.8, 69.0, 68.3, 57.9, 57.7, 55.8, 47.0, 45.5, 42.0, 28.4, 25.6, 24.8; HRMS (EI) *m/z* calculated for $C_{31}H_{46}O_5N_3$ 540.3437, found 540.3425.

Preparation of myoinositol analog 48

Ammonia (20 mL) was condensed into a flame-dried 3-necked flask at –78 °C. Sodium (100 mg, 4.3 mmol) was added in small pieces to the stirring ammonia. The solution was stirred vigorously until it became deep blue (about 15 minutes). A solution of dibenzylated compound **47** (104 mg, 0.19 mmol) in 2 mL of anhydrous ether was added *via* cannula. The resultant mixture was allowed to warm to –35 °C over 10

minutes, and then stirred at –35 °C for 6 h. The blue color of the solution had dispersed after this period of time. Solid ammonium chloride (*ca.* 50 mg) was added carefully, and the solution slowly warmed to RT, with evaporation of the ammonia. The residue was taken up in methanol (10 mL), and filtered through a pad of Celite, rinsing the flask and repeatedly with methanol (6 X 2 mL), filtering each time through the Celite. The Celite was rinsed with additional methanol (10 mL). The combined filtrates were concentrated *in vacuo*, and subjected to high vacuum for 24 h to give diol **48** as the HCl salt of the triamine (83 mg, 92%). No further purification was necessary.

IR 3330 (br), 2949, 1467 cm^{-1}; ^1H NMR (D_2O, 500 MHz) δ 5.57 (s, 1H), 4.41 (s, 2H), 4.37 (s, 2H), 4.30 (s, 1H), 3.50 (s, 1H), 2.60 (t, J=6.6 Hz, 2H), 2.45 (br t, J=7.7 Hz, 4H), 2.39 (br t, J=7.7 Hz, 2H), 2.22 (s, 6H), 2.21 (s, 3H), 1.63 (m, 2H), 1.40 (m, 4H) ^{13}C NMR (75 MHz, D_2O containing MeOH) δ 103.0, 72.3, 70.9, 67.1, 57.6, 57.2, 56.1, 55.4, 47.0, 44.7, 41.8, 27.9, 24.3, 24.1; HRMS (EI) *m/z* calculated for $C_{17}H_{34}N_3O_5$ 360.2498, found 360.2481.

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