JOC*Note*

Synthesis of 1,2-Diamino-1,2-dideoxy-*myo*-inositol-Derived Ligands for the Investigation of Metal Complex Reactivity

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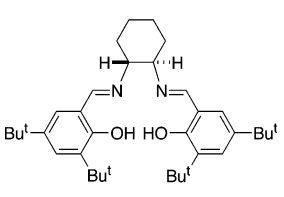
Abstract: A method for the synthesis of chiral 1,2-diamino-1,2-dideoxy-*myo*-inositol-based bis-pyridyl ligands **3a** and **3b** from the corresponding *myo*-inositol precursor is described. These highly functionalized inosamine-bis-pyridyl ligands are expected to provide a useful platform for exploring the relationship between chiral ligand structure and enantioselective olefin oxidation catalyzed by their metal complexes.

Metal-catalyzed asymmetric epoxidation of olefins remains a challenge for synthetic chemists. Despite impressive advances, methods for the highly enantioselective catalytic epoxidation of terminal, electron-deficient, or *cis*-olefins have not reached the same standards of efficiency, practicality, and predictability as for other classes of olefins. One limitation is the ready availability of a sufficient variety of chiral ligands to enable a broad structure−activity survey to identify so-called privileged structures.[1] The ligands derived from *trans*-cyclohexan-1,2-diamine, most notably salen ligand **1** and bis-pyridyl ligand **2** (*R*,*R*-mcp), have proven especially useful in producing effective asymmetric catalysts,[2] particularly as the Mn complexes.[3−5] Substituents on the cyclohexane ring of cyclohexan-1,2-diamine-derived ligands can significantly affect the efficacy of the catalysts.[6,7] To enable a comprehensive study of the effect of ring substitution, there is a need for synthetic methods to a variety of such substituted ligands. In this Note, we report the synthesis of *myo*-inositol-derived ligands **3a** and **3b**. The 1,2-diamino-1,2-dideoxy-*myo*-inositol scaffold is well suited to ligand development because (1) synthetic methods exist for selective modification of several of the hydroxyl groups, (2) unlike cyclohexan-1,2-diamine, the compound is chiral even with the cis disposition of the amino groups, and (3) differentially protected variants are available in either antipode via efficient enatioselective syntheses.



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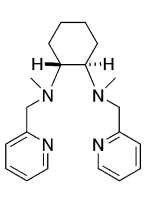

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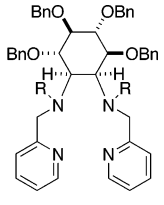

3a R=H
b R=CH$_3$

The synthesis of **3a** and **3b** began with 3,4,5,6-tetra-*O*-benzyl-*myo*-inositol **4** (Scheme 1). This precursor is readily available in racemic form,[8] or either enantiomer may be prepared[9] selectively from the appropriate enantiomer of xylose, both of which are commercially available. Furthermore, since differentially protected analogues of **4** have been prepared enantioselectively,[10−13] this method should allow the preparation of a variety of O-substituted analogues of **3**.

Conversion of diol **4** to diazide **5** followed the method of Guedat et al.[8] Dimesylation of **4** followed by nucleophilic substitutions with sodium azide afforded diazide **5** in 54% yield. In our hands, the hydrogenolysis of **5** to **7** was rather inconsistent, presumably due to poisoning of the catalyst by the product.[14] The crude diamine prepared in this way could be purified via its bis-trifluoroacetamide **10**. However, a better method was to circumvent the problem by addition of Boc_2O to the hydrogenolysis mixture[15] of **5** and $Pd/CaCO_3$ in EtOH/THF (1:5), thereby affording Boc-protected diamine **6** in 72% yield. Removal of the Boc groups (HCl, $MeOH/H_2O$) produced diamine **7** (99% yield). Acid-catalyzed imine formation from **7** and 2-pyridine carboxaldehyde, followed by reduction with BH_3·THF, and then acid hydrolysis produced ligand **3a** in 94% yield. Compound **3a** was converted to its ditosylate salt **11** for further characterization.

Unfortunately, we were unable to effectively dimethylate **3a** to produce **3b** despite a number of attempts, including formylation/reduction and direct methylation, either directly or with preliminary deprotonation of the amine nitrogens. Accordingly, we elected to install the methyl groups prior to the pyridyl component. Thus, diamine **7** was diformylated by treatment with trifluoroethyl formate (93% yield). This method was superior to formylation by heating in neat ethyl formate (75% yield) or with formic acetic anhydride, which gave a mixture of formylation and acetylation. Diamide **8** was reduced with BH_3·THF affording, after acid hydrolysis, bis(methylamino)cyclohexane **9** in 92% yield.

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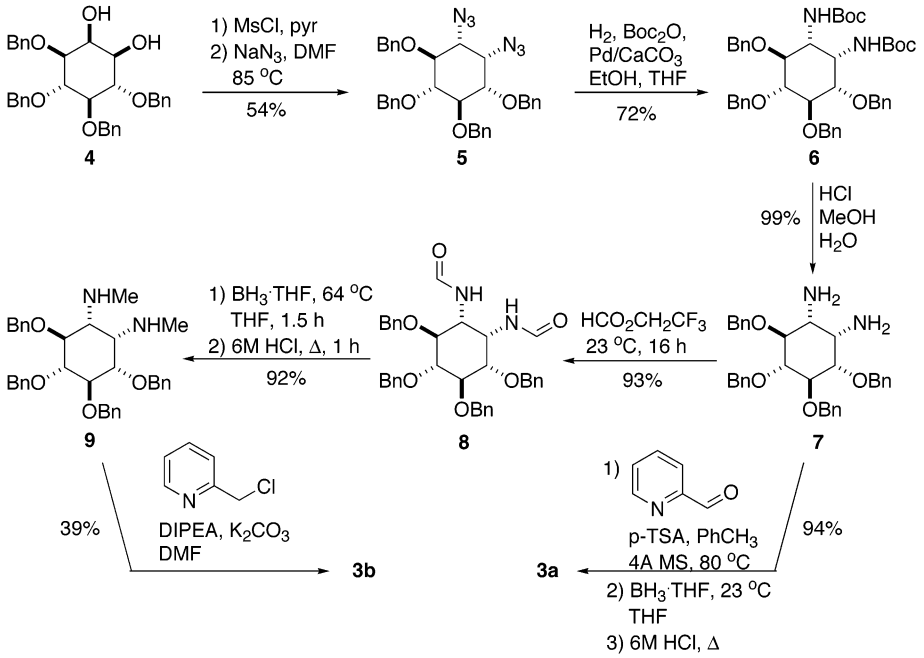
SCHEME 1



Attachment of the 2-methylpyridyl moiety to the nitrogens of **9** proved to be difficult. Acylation of **9** with picolinyl chloride produced the corresponding diamide (the ^{1}H NMR spectrum was very complex, presumably due to slowly interconcerting rotamers), but we were not able to find conditions for clean reduction of the diamide. The problem was ultimately solved, albeit in the modest yield of 39%, by direct alkylation of **9** with 2-chloromethylpyridine, thus providing the desired ligand **3b**.

With chiral complexes **3a** and **3b** in hand, we are now engaged in evaluating the catalytic activity of the corresponding metal ion complexes in olefin epoxidation. These data will be reported elsewhere.

Experimental Section

3,4,5,6-Tetra-*O*-benzyl-1,2-diazido-1,2-dideoxy-*myo*-inositol (5). A solution of **4**[8] (6.4 g, 11.9 mmol) in 50 mL of pyridine was cooled to 0 °C with stirring. Methylsulfonyl chloride (2.85 mL, 35.5 mmol) was added, and the reaction mixture was allowed to warm to 20 °C and stirred at this temperature for 20 h. The reaction mixture was then diluted with 200 mL of ethyl acetate and poured into ice−water (250 mL). The organic layer was washed with water (2 × 20 mL) and brine (2 × 25 mL) and dried over sodium sulfate. The solvent was evaporated, and the residue was coevaporated with 50 mL of heptane and then with 50 mL of toluene. Toluene (5 mL) was added, and then heptane was slowly added dropwise until no more precipitate formed. The precipitate was collected by filtration (7.3 g) and placed in a flask to which sodium azide (5.45 g, 83.8 mmol) was added followed by DMF (80 mL) via syringe. The reaction mixture was stirred and heated for 12 h at 110 °C behind a blast shield. The reaction mixture was cooled to 20 °C, and the DMF was removed by coevaporation with toluene; 50 mL of ethyl acetate were added, and the organic phase was separated and washed with water (2 × 20 mL) and brine (2 × 20 mL), dried with Na_2SO_4, and carefully evaporated. Flash chromatography (silica gel, 1:9 v/v EtOAc/hexane) gave 3.78 g of pure **5** (54% for two steps); R_f = 0.48 (silica gel, 1:5 v/v EtOAc/hexane). ^{1}H NMR ($CDCl_3$) and IR (CH_3Cl) are identical to those reported previously.[8]

3,4,5,6-Tetra-*O*-benzyl-1,2-di-(*N*-*t*-butoxycarbonylamino)-1,2-dideoxy-*myo*-inositol (6). Diazide **5** (60 mg, 102 μmol) was dissolved in a mixture of THF (1.5 mL) and EtOH (0.3 mL). Di-*tert*-butyl dicarbonate (111 mg, 510 μmol) and $Pd/CaCO_3$ (65 mg, 30.5 μmol) were added, and the reaction mixture was hydrogenated at 10−13 psig for 17 h. Completion of the reaction was confirmed by HPLC (see General Methods in Supporting Information); when the reaction was complete, the chromatogram showed a single peak at 6.95 min. (Starting material **5** has a retention time of 7.3 min.) The reaction mixture was diluted with toluene (40 mL), filtered through Celite, and evaporated. The residue was purified by flash chromatography (silica gel, 1:6 v/v EtOAc/hexane) to give 54 mg (72%) of white solid: R_f = 0.29 (1:5 v/v EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 18 H, O−C(C**H$_3$**)$_3$), 3.53 (ψt, J = 7.9 Hz, 1H, **H-6**), 3.59−3.75 (m, 3H, **H-3**, **H-4**, **H-5**), 3.90 (ψtd, J = 9.2, 3.3 Hz, 1H, **H-1**), 4.43 (dψt, J = 9.1, 3.7 Hz, 1H, **H-2**), 4.51 (d, J = 11.1 Hz, 1H, Ph**CH$_2$O**), 4.61 (d, J = 11.1 Hz, 1H, Ph**CH$_2$O**), 4.66−4.84 (m, 7H, Ph**CH$_2$O** (6H) + 2-N**H** (1H)), 5.31 (br, 1H, 1-N**H**), 7.2−7.35 (m, 20H, **Ph**CH$_2$O); {^{1}H}^{13}C NMR ($CDCl_3$) δ 138.72, 138.69, 138.1, 128.8, 128.75, 128.4, 128.3, 128.24, 128.21, 128.12, 128.1, 128.0, 82.0, 80.6, 80.2, 79.8, 79.4, 75.4, 75.35, 74.8, 72.5, 52.0, 49.5; LRMS m/z 761.5 (M + Na$^+$), calcd for $C_{44}H_{54}N_2O_8$ 738.91. Anal. Calcd for $C_{44}H_{54}N_2O_8$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.46; H, 7.35; N, 3.73.

3,4,5,6-Tetra-*O*-benzyl-1,2-di-(*N*-trifluoroacetylamino)-1,2-dideoxy-*myo*-inositol (10). A mixture of diazide **5** (660 mg, 1.12 mmol) and Lindlar catalyst (593 mg, 0.28 mmol) in 30 mL of THF and 6 mL of ethanol was hydrogenated at 10−13 psi for 7.5 h. Completion of the reaction was confirmed by HPLC (see General Methods in Supporting Information); when the reaction was complete, the chromatogram showed a single peak (2.5 min). The reaction mixture was diluted with toluene (70 mL), filtered through Celite, and evaporated to give 650 mg of dark brown oil. A similar experiment with 451 mg (0.763 mmol) of diazide **5** using 30 mol % Lindar catalyst gave 417 mg of light brown product in 3 h. The combined material (1.067 g) was dissolved in CH_2Cl_2 and chilled to −10 °C under Ar. Diisopropylethylamine (1.4 mL, 12 mmol) was added via syringe, followed by slow addition of trifluoroacetic anhydride (0.85 mL, 9.85 mmol, 3 equiv). The reaction mixture was allowed to warm to 23 °C, stirred for 12 h, and then chilled to 2 °C. Excess trifluoroacetic anhydride was quenched with cold (2 °C) sodium bicarbonate solution; the organic phase was washed with water (2 × 2 mL) and brine (2 × 2 mL), dried with Na_2SO_4, and evaporated. Flash chromatography (silica gel, 1:7 to 1:5 v/v EtOAc/hexane) gave 830 mg of pure **10** (58% for two steps): R_f = 0.17 (silica gel, 1:6 v/v EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 3.81−3.89 (m, 3H), 4.15

(dd, J = 4.2, 2.3 Hz, 1H), 4.22 (d, J = 11.1, 1H, Ph**CH$_2$**O), 4.37 (d, J = 11.4 Hz, 1H, Ph**CH$_2$**O), 4.44 (d, J = 11.4 Hz, 1H, Ph**CH$_2$**O), 4.48 (d, J = 11.8, 1H, Ph**CH$_2$**O), 4.54−4.68 (m, 4H), 4.71−4.81 (m, 2H), 6.64 (br d, J = 8.0, 1H, N**H**), 7.07−7.17 (m, 4H, **Ph**CH$_2$O), 7.22−7.36 (m, 20.8H, **Ph**CH$_2$O (16H) + C**H**Cl$_3$), 7.85 (br d, J = 10.2, 1H, N**H**); {^{1}H}^{13}C NMR ($CDCl_3$) δ 158.0, 157.5, 157.1, 157.0, 156.6, 156.5, 156.0, 137.2, 136.7, 136.2, 128.8, 128.6, 128.59, 128.56, 128.5, 128.3, 128.1, 127.95, 127.9, 121.4, 121.2, 117.6 117.4, 113.8, 113.6, 109.9, 109.8, 75.1, 74.2, 73.0, 72.8, 72.7, 72.4, 72.3, 48.8, 45.0; ^{19}F NMR ($CDCl_3$) δ −76.43, −76.47, −76.71, −76.74. Anal. Calcd for $C_{38}H_{36}F_6N_2O_6$: C, 62.46; H, 4.97; N, 3.83. Found: C, 62.33; H, 4.83; N, 3.73.

3,4,5,6-Tetra-*O*-benzyl-1,2-diamino-1,2-dideoxy-*myo*-inositol (7). Method A. Aqueous lithium hydroxide (2.2 mL of 1 M solution in water, 2.2 mmol) was added to a solution of diamide **10** (159 mg, 0.218 mmol) in 2.2 mL of methanol at 23 °C. The reaction mixture was heated at 45 °C for 24 h. Completion of the reaction was confirmed by HPLC (see General Methods in Supporting Information); when completed, the chromatogram showed a single peak (2.5 min). (Compound **10** has a retention time of 6.17 min.) Volatile materials were evaporated, and a mixture of toluene (3 mL) and water (3 mL) at 2 °C was added. The organic layer was separated, washed with water (2 × 1 mL) and brine (2 × 1 mL), dried with Na_2SO_4, and evaporated to give 116 mg (99%) of pure **7**.

Method B. Dicarbamate **6** (278 mg, 377 μmol) was suspended in methanol (12 mL). Aqueous HCl (0.25 mL of 6 M solution, 1.5 mmol) was added and the reaction mixture was heated at 55 °C for 13 h. Completion of the reaction was confirmed by HPLC (see General Methods in Supporting Information); when the reaction was complete, the chromatogram showed a single peak (2.5 min). Volatile materials were evaporated, and toluene (5 mL) was added to the residue. NaOH (2 mL of 1 M solution, 2 mmol) was added to the reaction mixture dropwise with chilling (ice bath). If precipitation of the diamine occured, methanol was added to the organic layer until the precipitate dissolved. The organic extract was washed with 1 M aqueous NaOH (2 × 2 mL), water (3 × 2 mL), and brine (1 × 2 mL) and evaporated to give 203 mg (99%) of pure **7**: ^{1}H NMR ($CDCl_3$) δ 2.67 (dd, J = 1.3, 5.2 Hz, 1H, **H**-1), 3.49 (m, 3H, **H**-2, **H**-3, **H**-5), 3.77 (ψt, J = 5.1 Hz, 1H, **H**-6), 3.74 (m, 1H, **H**-4), 4.64 (d, J = 11.2 Hz, 1H, Ph**CH$_2$O**), 4.67 (s, 2H, Ph**CH$_2$**O), 4.82 (d, J = 10.6 Hz, 1H, Ph**CH$_2$**O), 4.84 (d, J = 11.0 Hz, 1H, Ph**CH$_2$**O), 4.92 (d, J = 11.1 Hz, 1H, Ph**CH$_2$**O), 4.95 (d, J = 10.9 Hz, 1H, Ph**CH$_2$O**), 4.99 (d, J = 10.8 Hz, 1H, Ph**CH$_2$**O), 7.2−7.4 (m, 24.1H, **Ph**CH$_2$O (20H) + C**H**Cl$_3$); {^{1}H}^{13}C NMR ($CDCl_3$) δ 139.1, 139.05, 138.9, 138.6, 128.8, 128.75, 128.6, 128.58, 128.2, 128.0, 128.95, 128.90, 128.75, 128.65, 85.4, 82.12, 82.07, 82.0, 76.05, 75.94, 75.77, 72.5, 51.5, 53.7; LRMS *m/e* 539.5 (M + H$^+$) and 561.4 (M + Na$^+$), calcd for $C_{34}H_{38}N_2O_4$ 538.7.

For analytical purposes, the di-*p*-toluenesulfonate salt of **7** was prepared by reaction of *p*-toluenesulfonic acid (2 equiv) with **7** in CH_3OH for 2 days, collection of the resulting crystals, and recrystallization from methanol: ^{1}H NMR (d_4-MeOH + d_3-MeCN) δ 2.37 (s, 6H, **CH$_3$**C$_6$H$_4$SO$_3^-$), 3.90−3.95 (m, 2H), 4.02−4.09 (m, 2H), 4.11 (ψt, J = 4.7 Hz, 1H, **H**-6), 4.17 (ψt, J = 3.0 Hz, 1H, **H**-2), 4.55−4.73 (m, 8H, Ph**CH$_2$O**), 7.2−7.4 (m, 24H, **Ph**CH$_2$O (20H) + CH$_3$C$_6$**H$_4$**SO$_3^-$ (4H)), 7.68−7.75 (m, 4H, CH$_3$C$_6$**H$_4$**SO$_3^-$); {^{1}H}^{13}C NMR (d_4-MeOH + d_3-MeCN) 143.4, 142.0, 138.9, 138.6, 138.4, 137.7, 130.1, 130.0, 129.9, 129.8, 129.7, 129.65, 129.60, 129.5, 129.48, 129.2, 129.16, 129.10, 127.0, 76.9, 75.8, 74.9, 74.5, 74.2, 74.1, 51.3, 48.5 (hidden by CHD$_2$OD, extracted from HMQC), 21.4. Anal. Calcd for $C_{48}H_{54}N_2O_{10}S_2$: C, 65.28; H, 6.16; N, 3.17. Found: C, 64.88; H, 6.08; N, 3.19.

3,4,5,6-Tetra-*O*-benzyl-1,2-di-(*N*-pyridin-2-yl-methylamino)-1,2-Dideoxy-*myo*-inositol (3a). Crushed activated 4 Å molecular sieves (58 mg) and 0.6 mg (3.2 μmol, 0.1 equiv) of *p*-toluenesulfonic acid were added to a solution of diamine **7** (17 mg, 32 μmol) in 0.5 mL of toluene in a 10 mL flask fitted with a reflux condenser. The system was evacuated and flushed with Ar (five times). Pyridine-2-carbaldehyde (305 μL of 0.22 mM solution in toluene, 2.1 equiv) was introduced via syringe, and the reaction was heated at 80−85 °C for 5 h and then allowed to cool to 23 °C. The reaction mixture was filtered through Celite, and the solid was washed with toluene (6 × 0.5 mL). The combined filtrate was washed with 5% aqueous $NaHCO_3$ (3 × 0.5 mL) at 0 °C and brine (2 × 0.5 mL) and dried (Na_2SO_4). The solvent was evaporated, and the residue was coevaporated with toluene (5 mL). A reflux condenser was attached, and the system was evacuated and flushed with Ar (five times). Dry THF (0.5 mL) was introduced, and the reaction mixture was chilled to 2 °C. Borane−THF complex (320 μL of a 1 M solution in THF, 0.32 mmol) was added dropwise via a syringe, with stirring. The reaction mixture was allowed to warm to 23 °C. Completion of the reaction was confirmed by HPLC (see General Methods in Supporting Information); when the reaction was complete, the solution showed one peak (3.6 min). The reaction was carefully quenched with 6 M HCl (0.2 mL) at 2 °C. The reaction mixture was allowed to reach 23 °C, gently warmed at reflux for 1 h, and then allowed to cool to 23 °C. The solvent was evaporated, and the residue was dissolved in a mixture of 1 M NaOH (4 mL) and toluene (3 mL); the aqueous layer was extracted with toluene (3 × 0.5 mL), and the combined organic layers were washed with water (3 × 0.5 mL) and brine (2 × 1 mL). The organic phase was dried over Na_2SO_4 and evaporated to give 21.5 mg (94%) of a yellow oil, which slowly solidified: ^{1}H NMR ($CDCl_3$) δ 2.62 (dd, J = 10.1, 3.0 Hz, 1H, **H-1**), 2,67 (ψt, J = 6 Hz, 1H, N**H**), 2.75 (ψt, J = 7.3 Hz, 1H, N**H**), 3.38 (ψt, J = 2.9 Hz, 1H, **H-2**), 3.45 (dd, J = 9.7, 2.7 Hz, 1H, **H-3**), 3.59 (ψt, J = 9.2 Hz, 1H, **H-5**), 3.65 (dd, J = 14.2, 4.9 Hz, 1H, C**H$_2$**Py), 3.75 (dd, J = 14.2, 8.8 Hz, 1H, C**H$_2$**Py), 3.98 (ψt, J = 9.7 Hz, 1H, **H-6**), 4.1 (dd, J = 14.6, 6.8 Hz, 1H, C**H$_2$**Py), 4.27 (m, 1H, C**H$_2$**Py), 4.32 (ψt, J = 9.5 Hz, 1H, **H-4**), 4.62−4.76 (m, 3H, Ph**CH$_2$**O), 4.83 (d, J = 10.7 Hz, 2H, Ph**CH$_2$**O), 4.9−5.2 (m, 3H, Ph**CH$_2$**O), 7.05−7.15 (m, 2H, Py**H-5**), 7.16−7.4 (m, 31H, **Ph**CH$_2$ (20H) + C**H**Cl$_3$ + Py**H-3** (2H)), 7.56 (ψt, J = 7.7 Hz, 1H, Py**H-4**), 7.57 (ψt, J = 7.7 Hz, 1H, Py**H-4**), 8.47 (dq, J = 4.9, 0.9 Hz, 1H, Py**H-6**), 8.51 (dq, J = 4.8, 0.8 Hz, 1H, Py**H-6**); {^{1}H}^{13}C NMR ($CDCl_3$) δ 161.3, 159.8, 149.3, 139.12, 139.09, 138.9, 138.7, 136.5, 136.3, 128.63, 128.6, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 122.75, 122.16, 122.06, 121.8, 86.0, 84.1, 82.4, 81.1, 76.0, 75.81, 75.75, 73.2, 60.74, 55.3, 53.7, 52.9; LRMS *m/z* 721.3 (M + H$^+$) and 743.3 (M + Na$^+$), calcd for $C_{46}H_{48}N_4O_4$ 720.4.

3,4,5,6-Tetra-*O*-benzyl-1,2-di-(*N*-pyridin-2-yl-methylamino)-1,2-dideoxy-*myo*-inositol Ditosylate (11). Ditosylate **11** was prepared by mixing equivalent amounts of acetonitrile solutions of **3a** and *p*-toluenesulfonic acid, filtering the resulted solution through a 0.47 μ filter, and evaporating the filtrate until the final volume reached approximately 0.5 mL. The solution was kept at −20 °C for about 3 days and then filtered at 4 °C. The resulting solid was recrystallized from acetonitrile: ^{1}H NMR (d_4-MeOH) 2.32 (s, 6H, **CH$_3$**C$_6$H$_4$SO$_3^-$), 3.56 (dd, J = 8.9, 3.8 Hz, 1H, **H**-1), 3.78 (ψt, J = 7.5 Hz, 1H, **5**−H), 3.90−3.98 (m, 2H, **H**-2, **H**-3), 4.12 (dd, J = 8.9, 7.7 Hz, 1H, **H**-6), 4.16 (ψt, J = 7.5 Hz, 1H, **H**-4), 4.42 (d, J = 17 Hz, 1H, C**H$_2$**Py), 4.46 (d, J = 15.6 Hz, 1H, C**H$_2$**Py), 4.54 (d, J = 15.5 Hz, 1H, C**H$_2$**Py), 4.67−4.95 (m, 18.4H, C**H$_2$**Py (1H), Ph**CH$_2$O** (8H), N**H$_2^+$** (4H), RO**H** (5.4H), 7.14 (d, J = 7.9, 4H, CH$_3$C$_6$**H$_4$**SO$_3^-$), 7.17−7.39 (m, 20H, **Ph**CH$_2$O), 7.14 (m, 4H, CH$_3$C$_6$**H$_4$**SO$_3^-$), 7.42−7.49 (m, 2H, Py**H**-3 (1H), Py**H**-5 (1H)), 7.62−7.68 (m, 4H), 7.73−7.83 (m, 2H, Py**H**-3′ (1H), Py**H**-5′ (1H)), 7.94 (dt, J = 7.8, 1.7 Hz, 1H, Py**H**-4), 8.31 (dt, J = 7.9, 1.5 Hz, 1H, Py**H**-4′), 8.40 (dt, J = 7.8, 1.7 Hz, 1H, Py**H**-6), 8.72 (m, 1H, Py**H**-6′); ^{13}C{^{1}H} 156.3, 153.1, 148.5, 145.7, 144.1, 143.4, 142.0, 141.0, 139.8, 139.5, 139.5, 139.2, 130.1, 129.8, 129.6, 129.55, 129.5, 129.3, 129.0, 128.9, 127.1, 126.7, 126.4, 125.6, 124.8, 81.1, 80.0 (br), 77.4, 76.2, 76.0, 75.4, 74.5, 60.1, 55.6, 51.6, 49.5 (hidden by CHD$_2$OD, extracted from HMQC), 21.3. Anal. Calcd for $C_{48}H_{54}N_2O_{10}S_2$: C, 67.65; H, 6.06; N, 5.26. Found: C, 67.52; H, 6.14; N, 5.30.

3,4,5,6-Tetra-*O*-benzyl-1,2-di-(*N*-formylamino)-1,2-dideoxy-*myo*-inositol (8). Trifluoroethyl formate (0.5 mL) was slowly added to diamine **7** with stirring, and the solution was stirred for 16 h. Completion of the reaction was confirmed by HPLC (see General Methods in Supporting Information); when the reaction was complete, the chromatogram showed complete replacement of starting material (2.5 min) with product (2.95 min). Volatile materials were evaporated, and the residue was purified by preparative TLC (silica gel, 20:10:1 v/v EtOAc/

hexane/EtOH) to give 38 mg (93%) of a white solid. $R_f = 0.41$ (20:10:1 v/v EtOAc/hexane/EtOH). The ^{1}H NMR spectra were complex at 294 K, but coalesced above 390 K (DMSO-d_6), as expected for a diamide with restricted rotation: ^{1}H NMR (d_4-MeOH, 294 K) δ 3.51−3.7 (m, 2H), 3.7−3.84 (m, 2H), 4.07 (m, 0.1H), 4.18−4.3 (m, 0.9H), 4.5 (d, $J = 11$ Hz, 1H, Ph**CH$_2$**O), 4.6−4.98 (m, 14.8H, Ph**CH$_2$**O (7H) + Ins-H + CD_3O**H**), 7.2−7.4 (m, 20H, **Ph**CH_2O), 7.9 (s, 0.1H, N−C**H**O), 8.05−8.15 (m, 0.9 H, N−C**H**O), 8.16 (s, 0.1H, N−C**H**O), 8.3 (s, 0.9H, N−C**H**O); {^{1}H}^{13}C NMR (d_4-MeOH) 167.7, 165.2, 165.0, 164.0, 140.23, 140.15, 139.9, 139.6, 129.6, 129.5, 129.43, 129.41, 129.3, 129.2, 129.1, 129.0, 128.9, 128.83, 128.77, 128.75, 128.71, 84.9, 84.8, 82.4, 81.0, 79.9, 76.9, 76.6, 76.2, 73.3, 73.2, 55.3, 50.2, 47.9; LRMS m/z 595.5 (M + H$^+$) and 617.5 (M + Na$^+$), calcd for $C_{36}H_{38}N_2O_6$ 594.3. Anal. Calcd for $C_{36}H_{38}N_2O_6$: C, 72.71; H, 6.44; N, 4.71. Found: C, 73.05; H, 6.61; N, 4.72.

3,4,5,6-Tetra-*O*-benzyl-1,2-di-(*N*-methylamino)-1,2-dideoxy-*myo*-inositol (9). Dry THF (0.5 mL) was added to 22 mg (37 μmol) of diamide **8**, and the mixture was chilled to 2 °C. Borane−THF complex (300 μL of a 1 M solution in THF, 0.3 mmol) was added dropwise via a syringe with stirring. The reaction mixture was allowed to warm to 23 °C, gently warmed at reflux for 1.5 h, and allowed to cool to 23 °C. The reaction was carefully quenched with 6 M HCl (0.2 mL) at 2 °C. The reaction mixture was allowed to warm to 23 °C and then warmed at reflux for 1 h. After the mixture cooled back to 23 °C, the volatile materials were evaporated. The residue was dissolved in a mixture of 1 M NaOH (3 mL) and toluene (1.5 mL); the aqueous layer was extracted with toluene (3 × 0.5 mL), and the combined organic extracts were washed with water (3 × 0.5 mL) and brine (2 × 1 mL). The organic phase was dried over Na_2SO_4 and evaporated to give 19.3 mg (92%) of clear oil, which slowly crystallizes: ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H, N**CH$_3$**), δ 2.39 (dd, $J = 10.1$, 3.24 Hz, 1H, **H-1**), δ 2.62 (s, 3H, N**CH$_3$**), 3.38 (ψt, $J = 3.1$ Hz, 1H, **H-2**), 3.45 (dd, $J = 9.7$, 3.0 Hz, 1H, **H-3**), 3.57 (ψt, $J = 9.1$ Hz, 1H, **H-5**), 3.74 (ψt, $J = 9.7$ Hz, 1H, **H-6**), 4.15 (ψt, $J = 9.4$ Hz, 1H, **H-6**), 4.55 (d, $J = 11.1$, 1H, Ph**CH$_2$O**), 4.68 (d, $J = 11.5$, 1H, Ph**CH$_2$O**), 4.74−4.85 (m, 3H, Ph**CH$_2$O**), 4.9−5.2 (m, 3H, Ph**CH$_2$O**), 7.2−7.4 (m, 20H, **Ph**CH_2O); {^{1}H}^{13}C NMR ($CDCl_3$) δ 139.2, 139.1, 138.9, 138.7, 128.7, 128.53, 128.51, 128.3, 128.2, 128.0, 127.74, 127.68, 127.62, 127.55, 85.8, 84.3, 82.5, 81.0, 76.1, 75.7, 75.5, 72.6, 62.3, 56.0, 38.4, 34.3. LRMS m/z 566.4 (M + H$^+$), calcd for $C_{36}H_{42}N_2O_4$ 566.3. Anal. Calcd for $C_{36}H_{42}N_2O_4$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.17; H, 7.58; N, 4.96.

3,4,5,6-Tetra-*O*-benzyl-1,2-di-[*N*-pyridine-2-yl-methyl-*N*-methylamino]-1,2-dideoxy-*myo*-inositol (3b). Diamine **9** (14 mg, 24.7 μmol), finely powdered K_2CO_3 (34 mg, 247 μmol), diisopropylethylamine (53 μL, 247 μmol), anhydrous DMF (1 mL), and 80 μL of 0.68 M THF solution (494 μmol, 2 equiv) of 2-chloromethylpyridine (prepared by neutralization of the commercially available hydrochloride with K_2CO_3) were heated at 80 °C for 4 days under Ar. The mixture was cooled to 23 °C; an additional 40 μL of the 2-chloromethylpyridine solution was added, and heating was continued for another 3 days. The progress of the reaction was monitored by HPLC (see General Methods in Supporting Information). After 7 days, the only major peak in the chromatogram is the product (4.69 min). The reaction mixture was evaporated to dryness, and the residue was dissolved in 2 mL of toluene and 5 mL of water. The organic layer was washed with 1 M NaOH (6 × 1 mL), water (6 × 1 mL), and brine (2 × 1 mL) and evaporated. The residue was purified by preparative TLC (basic grade 1 alumina oxide, 50:200:3 v/v EtOAc/CH_2Cl_2/EtOH) to give 8 mg of pale yellow oil (~90% pure by NMR, 39%), $R_f = 0.53$ (50:200:3 v/v EtOAc/CH_2Cl_2/EtOH). The product was further purified by semi-preparative HPLC (see General Methods in Supporting Information for solvent gradient) on a C18 column (1.5 cm × 25 cm) with UV detection (217 nm) eluting at 8 mL min^{-1}: ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H, N−C**H$_3$**), 2.55 (s, 3H, N−C**H$_3$**), 2.95 (dd, $J = 4.9$, 10.3 Hz, 1H, **H**-1), 3.59 (ψt, $J = 4.3$ Hz, 1H, **H**-2), 3.64 (ψt, $J = 8.9$ Hz, 1H, **H**-5), 3.74 (dd, $J = 5.1$, 8.3 Hz, 1H, **H**-3), 4.09−4.37 (m, 6H, **H**-4, **H**-6, N**CH$_2$**Py (4H)), 4.68 (d, $J = 11.5$ Hz, 1H, Ph**CH$_2$**O), 4.72−4.86 (m, 4H, Ph**CH$_2$**O), 4.88−4.93 (m, 2H, Ph**CH$_2$**O), 5.04 (d, $J = 11.0$ Hz, 1H, Ph**CH$_2$**O), 7.04−7.12 (m, 2H, Py-**H**), 7.21−7.37 (m, 26.8H, **Ph**CH_2O (20H) + C**H**Cl_3), 7.38−7.53 (m, 4H, Py-**H**), 8.45−8.52 (m, 2H, Py-**H**); {^{1}H}^{13}C NMR ($CDCl_3$) δ 161.7, 161, 149, 139.1, 138.8, 138.79, 138.5, 136.4, 128.6, 128.5, 128.5, 128.1, 128.0, 127.94, 127.8, 127.7, 127.6, 127.5, 123.0, 122.6, 121.8, 121.7, 86.9, 83.8, 82.8, 79.4, 75.9, 75.3, 73.8, 73.4, 65.9, 65.3, 64.9, 62.9, 41.8, 40.5; LRMS m/z 749.6 (M + H$^+$) and 771.7 (M + Na$^+$); HRMS (ESI TOF) m/z 749.4057 (M + H$^+$), calcd for $C_{48}H_{53}N_4O_4$ 749.4067; error (ppm) 1.3.

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Supporting Information Available: General experimental methods and NMR spectra for all numbered compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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