Synthesis of 1,2-Diamino-1,2-dideoxy-myoinositol-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-myoinositol-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. 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, particularly as the Mn complexes. Substituents on the cyclohexane ring of cyclohexan-1,2-diamine-derived ligands can significantly affect the efficacy of the catalysts. 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-myoinositol 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 enantiopure via efficient enantioselective syntheses.

The synthesis of 3a and 3b began with 3,4,5,6-tetra-O-benzyl-myoinositol 4 (Scheme 1). This precursor is readily available in racemic form, or either enantiomer may be prepared selectively from the appropriate enantiomer of xyloose, both of which are commercially available. Furthermore, since differentially protected analogues of 4 have been prepared enantioselectively, 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. Dimesylation of 4 followed by nucleophilic substitutions with sodium azide afforded diazide 5 in 54% yield. In our hands, the hydrolysis of 5 to 7 was rather inconsistent, presumably due to poisoning of the catalyst by the product. The crude diamine prepared in this way could be purified via its bis-trifluoroacetamide. However, a better method was to circumvent the problem by addition of BocO to the hydrolysis mixture of 5 and Pd/CaCO3 in EtOH/THF (1:5), thereby affording Boc-protected diamine 6 in 72% yield. Removal of the Boc groups (HCl, MeOH/H2O) produced diamine 7 (99% yield). Acid-catalyzed imine formation from 7 and 2-pyrindine carbodimide, followed by reduction with BH3·THF, and then acid hydrolysis produced ligand 3a in 94% yield. Compound 3a was converted to its ditosylate salt 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 deuteration 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 trifluoroacetic anhydride (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 BH3·THF affording, after acid hydrolysis, bis(methylamino)cyclohexane 9 in 92% yield.

Attachment of the 2-methylpyridyl moiety to the nitrogen of 9 proved to be difficult. Acylation of 9 with picolinyl chloride produced the corresponding diamide (the 1H NMR spectrum was very complex, presumably due to slowly interconverting 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-chloro- methylpyridine, 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

**Scheme 1**

3,4,5,6-Tetra-O-benzyl-1,2-diazido-1,2-dideoxy-myo-inositol (5). A solution of 4 (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 2 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, and the organic phase was separated and washed with water (2 × 20 mL) and brine (2 × 20 mL), dried with Na2SO4, and evaporated. Flash chromatography (silica gel, 1:7 to 1:5 v/v EtOAc/hexane) gave 3.78 g of pure 3b, 92% 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.
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 NaHCO₃ (3 × 0.5 mL) at 0 °C and brine (2 × 0.5 mL) and dried (Na₂SO₄). 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 distilled 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 chromatogram showed a single 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 20 °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 Na₂SO₄ and evaporated to give 215 mg (94%) of a yellow oil, which slowly solidified: 1H NMR (CDCl₃) δ 2.67 (dd, J = 10.1, 3.0 Hz, 1H, H-1), 2.67 (t, J = 6.2 Hz, 1H, H-2), 2.67 (t, J = 6.2 Hz, 1H, H-3, 6.2 Hz, 1H, H-4), 4.28 (dd, J = 9.7, 2.7 Hz, 1H, H-5), 5.95 (J = 9.7, 2.7 Hz, 1H, H-5), 4.27 (J = 9.7, 2.7 Hz, 1H, H-5, 2.7 Hz, 1H, H-6), 4.27 (J = 9.7, 2.7 Hz, 1H, H-6, 4.62 (J = 9.7, 2.7 Hz, 1H, H-7) and the solid was purified by preparative TLC (silica gel, 20:10:1 v/v EtOAc/CH₂Cl₂/MeOH).
hexane/EtOH) to give 38 mg (93%) of a white solid. \(R_t = 0.41\) (20:10:1 v/v EtoAc/hexane/EtOH). The \(^1H\) NMR spectra were complex at 294 K, but coalesced above 390 K (DMSO-d6), as expected for a diamide with restricted rotation: \(^1H\) NMR (d8-THF, 294 K) \(\delta\) 3.51–3.7 (m, 2H), 4.27–4.3 (m, 0.9H), 4.41(d, \(J = 11\) Hz, 1H, PhCH2O).

4.6–4.98 (m, 14.8H, PhCH2O (7H) + Ins-H + CD3OH), 7.2–7.4 (m, 20H, PhCH2O), 7.99 (s, 0.1H, N–CHO), 8.05–8.15 (m, 0.9H, N–CHO), 8.16 (s, 0.1H, N–CHO), 8.3 (s, 0.9H, N–CHO); \(^{13}C\) NMR (d8-THF, 294 K) 167.7, 165.2, 165.0, 140.23, 140.15, 139.9, 139.6, 129.6, 129.5, 129.4, 129.1, 129.3, 129.2, 129.1, 128.9, 128.8, 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+), calcld for C36H38N2O6 594.3. Anal. Calcd for C36H38N2O6: C, 72.71; H, 6.44; N, 9.71. Found: C, 73.05; H, 6.61; N, 4.72.

3.4,5,6-Tetra-O-benzyl-1,2-dim-(N-methylamino)-1,2-dieoxy-myoo-inositol \(3b\). Dry THF (0.5 mL) was added to 22 mg (37 \(\mu\)m) of diamide \(8\), and the mixture was chilled to 2 °C. Borane–THF complex (300 \(\mu\)L of a 1 M solution in THF, 0.3 mmol) was added dropwise via a syringe to stir the mixture. 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 mixture was carefully quenched with 6 M NaOH (3 mL) at 2 °C. The volatile materials were evacuated. The residue was dissolved in a mixture of 1 M NaOH (3 mL) and toluene (1.5 mL); the volatile materials were evaporated. The residue was dissolved in water (80 °C for 4 days under Ar). The mixture was allowed to cool to 23 °C, and an additional 40 mL 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/CH3Cl/EtOH) to give 8 mg of pale yellow oil (~90% pure by NMR, 39%), \(R_t = 0.53\) (50:200:3 v/v EtoAc/CH3Cl/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 (CDCl3) \(\delta\) 2.55 (s, 3H, N–CHO), 2.95 (dd, \(J = 4.9, 10.3\) Hz, 1H, H-1), 3.59 (\(\gamma\)/t, \(J = 4.3\) Hz, 1H, H-2), 3.64 (\(\gamma\)/t, \(J = 8.9\) 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, NCH2Py (4H)). 4.68 (d, \(J = 11.5\) Hz, 1H, PhCH2O). 4.72–4.86 (m, 4H, PhCH2O), 4.88–4.93 (m, 2H, PhCH2O), 5.04 (dd, \(J = 3.0, 11.0\) Hz, 1H, H-2), 7.21–7.37 (m, 26.8H, Py-H), 8.45–8.52 (m, 2H, Py-H); \(^{13}C\) NMR (CDCl3) \(\delta\) 161.7, 161, 149, 139.1, 138.8, 138.7, 138.6, 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+), calcld for C36H38N2O6 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.