Synthesis of Unsymmetrical Chiral Triaza-18-crown-6 and Diaza-12-crown-4 with a Pendant Group

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The aza-crown compounds have received continued attention over the past years for their ability to form complexes of metal cations, halide anions, and small organic molecules.[1] Crown ethers bearing pendant groups are important intermediates for their immobilization on polymers[2] and transformation into more complex lariat crown ethers[3] such as ionizable crown ethers,[4] bis-crown ethers,[5] and chromogenic crown ethers.[6] Owing to Bradshaw and co-workers' extensive works, racemates of functionalized diaza-crown compounds[7] and symmetrical chiral crown compounds[8] have been well described. Unsymmetrical chiral aza-crown compounds, however, have not been prepared. Here we describe the synthesis of optically pure triaza-18-crown-6 and diaza-12-crown-4 with a hydroxymethyl pendant group as unsymmetrical chiral crown compounds.

The synthesis of triaza-18-crown-6 **9** was carried out using (*R*)-1-benzylglycerol **1** as the starting material, which was prepared from D-mannitol according to the literature (Scheme 1, 2).[9,10] The primary hydroxyl group of glycerol **1** was selectively protected from the secondary hydroxyl group with TBDPSCl and imidazole in DMF in 88% yield. Subsequent allylation of the secondary hydroxyl group gave fully protected glycerol **2** in 93% yield. Conversion of the allyl group to hydroxyethyl group was carried out in two stages: (i) dihydroxylation with OsO_4−NMO, and (ii) diol cleavage with $Pb(OAc)_4$ followed by in situ reduction with $NaBH_4$, producing alcohol **3a** in overall 81% yield. Alcohol **3a** was converted to the corresponding tosylate **3b** in 87% yield for the next chain extension. Treatment of tosylate **3b** with tosylamide **4**[11] in the presence of K_2CO_3 in DMF produced the coupled product **5a** in 65% yield. Debenzylation of the benzyloxy group in **5a** and mesylation of the corresponding diol **5b** gave dimesylate **6** in 98% yield for two steps. Finally, triaza-18-crown-6 **8** was obtained in 45% yield by the reaction of bis-sulfonamide **7** with dimesylate **6** in a two-phase system consisting of benzene, aqueous LiOH, and tetrabutylammonium iodide as phase-transfer catalyst. An attempt to increase the coupling yield using NaOH was not successful (12%). Deprotection of **8** with tetrabutylammonium fluoride (TBAF) in THF gave **9** in 91% yield.

The synthesis of diaza-12-crown-4 **12**, an analogue with smaller ring size, is described in Scheme 2. Initially, we studied the coupling between dimesylate **6** and benzylamine with Na_2CO_3 in refluxing acetonitrile, an apparently more direct approach to diaza-12-crown-4, but we could not obtain the desired product in any appreciable amounts. It was reasoned that the intramolecular cyclization at the sterically more-hindered mesylate site was hampered. Therefore, we modified the synthetic route to avoid this problem. Deprotection of the benzyl group of **3a** and subsequent tosylation gave ditosylate **10** in overall 78% yield. Coupling of this ditosylate with tosylamide **7** in a two-phase system consisting of benzene, aqueous LiOH, and tetrabutylammonium iodide as phase-transfer catalyst produced diaza-12-crown-4 **11** in 70% yield. In this case, the template effect of lithium cation presumably accounts for the good coupling yield. Deprotection of **11** with tetrabutylammonium fluoride (TBAF) in THF gave **12** in 99% yield. The absolute stereochemistry of **12** was confirmed by single-crystal X-ray crystallography.[12]

In summary, we have established a versatile synthetic route to chiral aza-crown ethers with a sidearm. The synthesized triaza-18-crown-6 and diaza-12-crown-4 are potentially useful intermediates for the synthesis of template-linked poly(aza-crown ethers) and related analogues, which would be interesting hosts for studying their amphi-ionophore properties.[13]

Experimental Section

General Procedures. All reagents were commercial products and were used without further purification. Flash column chromatography was performed on 230−400 mesh silica gel. Low

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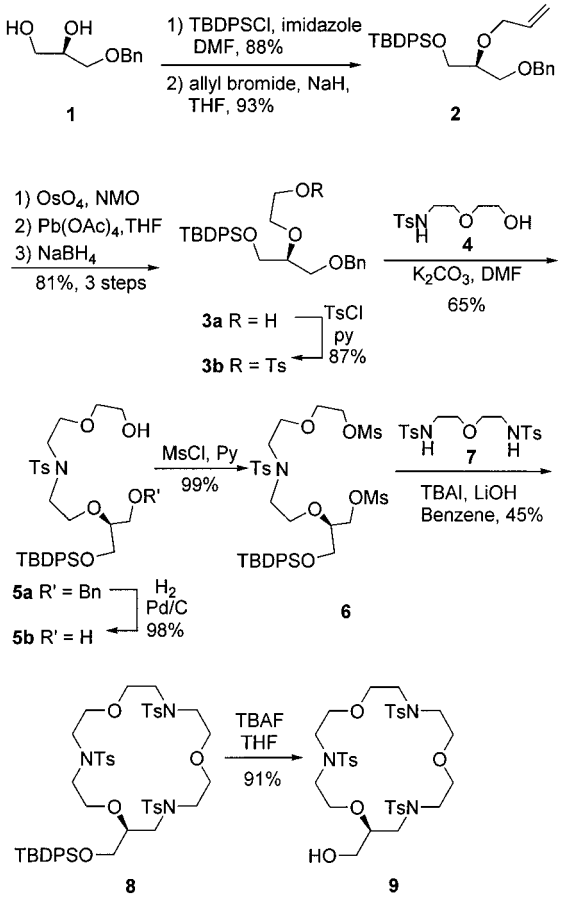
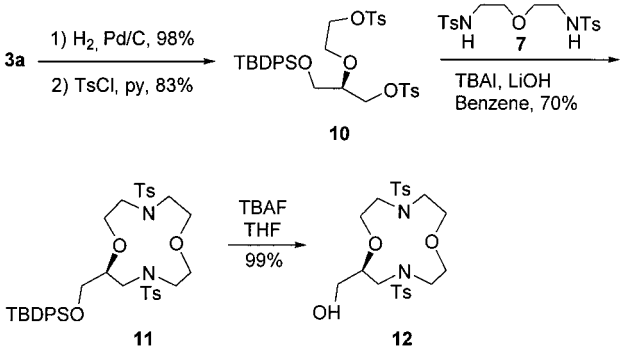
Scheme 1



Scheme 2



and high-resolution mass analyses were performed by Taejon Analytical Laboratory of Korea Basic Science Institute. ^{1}H NMR spectra were recorded on 300 MHz NMR spectrometer, and chemical shifts (δ) are in part per million relative to TMS.

***(S)*-1-*O*-Benzyl-3-*O*-(*tert*-butyldiphenylsilyl)-2-*O*-(2-hydroxyethyl)glycerol (3a).** To a solution of **2** (11.9 g, 25.9 mmol), *N*-methylmorpholine *N*-oxide (4.7 g, 40 mmol), THF (40 mL), *t*-BuOH (15 mL), and water (7 mL) at 0 °C was added OsO_4 (2.6 g, 2.5 wt % solution in *t*-BuOH, 0.26 mmol, 1 mol %), and the resulting mixture was stirred for 24 h at room temperature. The reaction mixture was treated with a saturated aqueous $NaHSO_3$ solution, and it was vigorously stirred for 1 h. The mixture was poured into water and then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give the corresponding diol, which was subjected to the next step without purification. To a THF (40 mL) solution of the above diol was added portionwise dry $Pb(OAc)_4$ (11.5 g, 25.9 mmol) while the temperature was kept below 10 °C. The reaction mixture was stirred for 30 min with an ice−water bath and additional 30 min without. After filtering through Celite and cooling in an ice bath, $NaBH_4$ (1.9 g, 50 mmol) in 4% aqueous NaOH (40 mL) solution was added dropwise with vigorous stirring while the temperature was kept below 10 °C. The reaction mixture was stirred 0 °C for 30 min and then at room temperature for 90 min. The pH of the reaction mixture was adjusted to about 8 by adding solid ammonium chloride, and it was extracted with ethyl acetate. The organic layer was washed with 5% aqueous NaOH solution and then brine. Drying over $MgSO_4$, concentration, and purification by flash chromatography (4:1, hexanes−ethyl acetate) afforded **3a** (9.8 g, 81%) as colorless oil. $[\alpha]^{23}_D$ −10.94 (*c* 10.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9H), 3.60−3.74 (m, 9H), 4.55 (s, 2H), 7.33−7.45 (m, 11H), 7.66−7.70 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.1, 26.7, 62.0, 63.7, 70.3, 71.9, 73.4, 80.0, 127.6, 127.7, 128.3, 129.7, 133.1, 133.2, 135.5, 137.7; FAB-MS *m*/*z* 465.1 ([M + H]$^+$, calcd 465.2).

(*S*)-1-Benzyloxy-2-[(*tert*-butyldiphenylsilyloxy)methyl]-6-*N*-(*p*-toluenesulfonyl)-6-aza-3,9-dioxa-11-undecanol (5a). A mixture of sulfonamide **4** (4.8 g, 18.3 mmol), tosylate **3b** (11.3 g, 18.3 mmol), and anhydrous K_2CO_3 (7.6 g, 55 mmol) in DMF (100 mL) was refluxed for 2 days with vigorous stirring. After being cooled to room temperature, the solid was removed by filtration, and the filtered solution was concentrated. The residue was purified by column chromatography (1:1, hexanes−ethyl acetate) to give **5a** (8.4 g, 65%) as colorless oil. $[\alpha]^{23}_D$ −3.93 (*c* 11.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H), 2.41 (s, 3H), 3.38−3.76 (m, 17H), 4.54 (s, 2H), 7.25−7.46 (m, 13H), 7.67−7.73 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 19.6, 21.9, 27.2, 49.0, 49.2, 62.1, 63.7, 69.8, 70.1, 70.4, 72.7, 73.8, 80.4, 127.6, 128.00, 128.04, 128.1, 128.8, 130.0, 130.1, 133.75, 133.79, 136.0, 137.3, 138.6, 143.6; FAB-MS *m*/*z* 706.3 ([M + H]$^+$, calcd 706.3); HRMS calcd 706.3234 for $C_{39}H_{52}NO_7SSi$ ([M + H]$^+$), found 706.3259.

(*S*)-2-[(*tert*-Butyldiphenylsilyloxy)methyl]-4,10,16-tris-(*p*-toluenesulfonyl)-4,10,16-triaza-1,7,13-trioxacyclooctadecane (8). Bis-sulfonamide **7**(0.1 g, 0.24 mmol) and dimesylate **6** (0.18 g, 0.24 mmol) in benzene (1.4 mL) are added to a refluxing mixture of tetra-*n*-butylammonium iodide (25% mol), 7% aqueous lithium hydroxide (1.4 mL), and benzene (9 mL). The vigorously stirred mixture is heated under reflux for 7 days, the organic layer is separated, and the solvent is removed under reduced pressure. The solid is washed with methanol and filtered off. Purification by flash chromatography on silica gel (2:1, hexanes−ethyl acetate) afforded **8** (0.1 g, 45%). $[\alpha]^{23}_D$ −15.7 (c 0.25: $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.0 (s, 9 H), 2.3 (s, 3H), 2.42 (d, 6H), 2.9−3.0 (m, 1H), 3.2−3.6 (m, 23 H), 3.7 (t, 1H) 7.3−7.4 (m, 12 H), 7.6 (q, 10 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.1, 21.4, 26.7, 45.9, 49.3, 49.5, 49.7, 51.4, 63.5, 66.0, 69.5, 70.0, 70.5, 70.6, 70.8, 77.4, 80.0, 126.9, 127.1, 127.7, 129.6, 129.7, 129.8, 133.0, 135.4, 136.0, 136.3, 136.5, 143.2, 143.3; FAB-MS *m*/*z* 991.39 ([M + H]$^+$, calcd 991.35).

[4,10,16-Tris(*p*-toluenesulfonyl)-4,10,16-triaza-1,7,13-trioxacyclooctadec-2-yl]methanol (9). A solution 58 mg (0.06 mmol) of **8** in 5 mL of THF was treated with 0.03 mL of a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran at room temperature for 3 h. The reaction mixture was dried over $MgSO_4$ and concentrated. Purification by flash chromatography on silica gel (1:1, hexanes−ethyl acetate) afforded **9** (40 mg, 91%): mp 69.0−70.3 °C; $[\alpha]^{23}_D$ −7.57 (*c* 0.81, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 9H), 3.24−3.40 (m, 12H), 3.53−3.80 (m, 13 H), 7.32 (t, 6H), 7.68 (q, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 29.6, 49.4, 49.6, 49.8, 50.0, 50.1, 60.6, 68.5, 70.4, 70.5, 70.6, 70.9, 79.1, 126.9, 127.0, 127.1, 129.7, 129.8, 135.6, 135.8, 136.3, 143.4, 143.5, 143.6; FAB-MS *m*/*z* 754.25 ([M + H]$^+$, calcd 753.25); HRMS calcd 754.2502 for $C_{34}H_{47}N_3O_{10}S_3$ ([M + H])$^+$, found 753.2511.

(*S*)-2-[(*tert*-Butyldiphenylsilyloxy)methyl]-4,10-bis(*p*-toluenesulfonyl)-4,10-diaza-1,7-dioxacyclododecane (11). Bis-sulfonamide **7** (1.0 g, 4 mmol) and ditosylate **10** (1.7 g, 25 mmol) in benzene (15 mL) are added to a refluxing mixture of tetra-*n*-butylammonium iodide (25% mol), 7% aqueous lithium hydroxide (15 mL), and benzene (90 mL). The vigorously stirred mixture is heated under reflux for 7 days, the organic layer is separated, and the solvent is removed under reduced pressure. The solid is washed with methanol and filtered off. Purification by flash chromatography on silica gel (3:1, hexanes−ethyl acetate) afforded **11** (1.3 g, 70%): mp 65.3−67.3 °C; $[\alpha]^{23}_D$ −16.7 (c 2.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 2.43 (s, 6H), 2.99−3.02 (m, 2H), 3.16−3.24 (m, 2H), 3.31−3.37 (m,

3H), 3.47−3.72 (m, 10H), 7.63−7.72 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) 19.0, 21.2, 26.6, 49.7, 50.3, 51.3, 52.7, 58.0, 64.0, 69.3, 69.7, 70.6, 78.0, 78.8, 127.1, 127.3, 127.5, 127.6, 129.5, 129.6, 133.0, 133.1, 134.7, 135.4, 135.6, 143.1, 143.2; FAB-MS *m*/*z* 751.2 ($[M + H]^+$, calcd 751.04).

[4,10-Bis(*p*-toluenesulfonyl)-4,10-diaza-1,7-dioxacyclododec-2-yl]methanol (12). A solution 0.4 g (0.5 mmol) of **11** in 15 mL of THF was treated with 0.3 mL of a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran at room temperature for 3 h. The reaction mixture was dried over $MgSO_4$ and concentrated. Purification by flash chromatography on silica gel (1:4, hexanes−ethyl acetate) afforded **12** (0.27 g, 99%): mp 175.2−177.0 °C; $[\alpha]^{23}_D$ +15.6 (c 0.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 6H), 3.04−3.36 (m, 7H), 3.53−4.09 (m, 10 H), 7.29−7.34 (m, 4H), 67.69 (d, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 50.7, 51.4, 51.5, 51.9, 62.7, 67.3, 70.5, 71.0, 78.3, 127.31, 127.33, 129.7, 129.8, 134.8, 134.9, 143.5, 143.6; FAB-MS *m*/*z* 513.17 ($[M + H]^+$, calcd 513.17); HRMS cacld 513.1729 for $C_{23}H_{32}N_2O_7S_2$ $([M + H])^+$, found 513.1744. Crystal Data: M_r = 512.63, monoclinic, $P2_1$, a = 6.0853(4) Å, α = 90°, b = 13.7666(9) Å, β = 95.5070(10)°, c = 14.4567(10) Å, γ = 90°, V = 1205.50(14) Å^3, Z = 2, D_{calcd} = 1.412 mg/m^3, $F(000)$ = 544, μ(Mo Kα) = 3.2 cm^{-1}, λ = 0.71073 Å, T = 243 K, R1 = 0.0417 and wR2 = 0.1121 for 2816 absorption corrected reflections with $I > 2\sigma(I)$.

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Supporting Information Available: The experimental procedure, copies of ^{1}H and ^{13}C NMR spectra of all compounds, and X-ray data for compound **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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