Alternative Routes to Functionalized Crown Ethers

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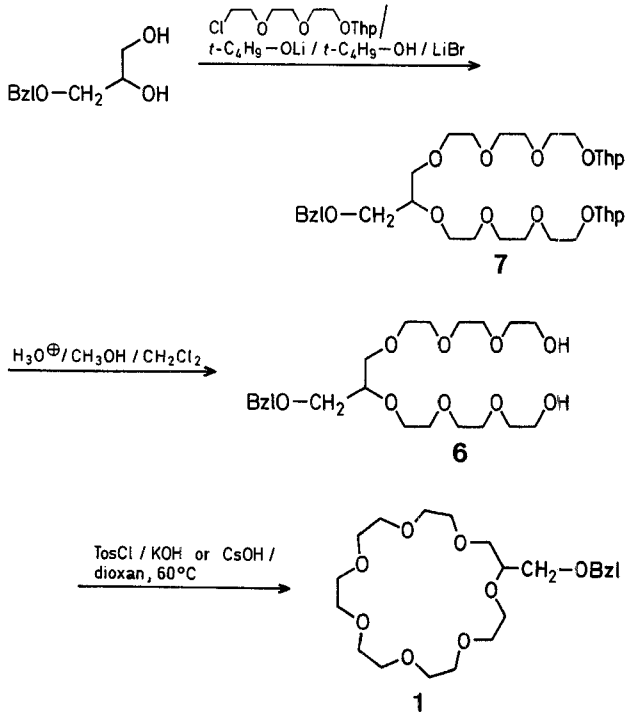
Although a variety of synthetic methods are available for the preparation of functionalized 12-crown-4[1,2,3], 15-crown-5[1-5], and 18-crown-6[2,3,5-9] compounds, accessibility to larger-ring crown ethers with pendant functional groups has been limited. Previously, we have reported the first syntheses

of hydroxymethyl-21-crown-7 and hydroxymethyl-24-crown-8[10] by reactions of benzyloxymethyl-substituted triethylene glycol[8,11] with ditosylates of tetraethylene and pentaethylene glycol, respectively, and cesium hydroxide in aqueous tetrahydrofuran followed by catalytic hydrogenolysis of the benzyl protecting group. More recently, we have described the synthesis of hydroxymethyl-27-crown-9 and hydroxymethyl-30-crown-10[12] in which a benzyloxymethyl-substituted pentaethylene glycol[13] was the key intermediate.

This communication reports more efficient synthetic routes to the known benzyloxymethyl derivatives of 21-crown-7 (**1**), 24-crown-8 (**2**), and 30-crown-10 (**3**) which are the immediate precursors to the corresponding large-ring hydroxymethyl-crowns. In addition, new, higher-yield routes to benzyloxymethyl-substituted benzo-18-crown-6 (**4**)[11,14] and 2,3-naphtho-18-crown-6 (**5**)[15] are described.

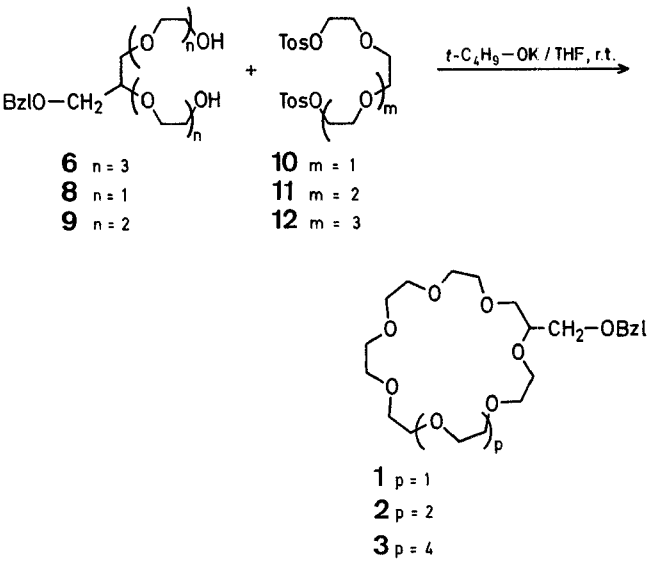
A key intermediate for the synthesis of benzyloxymethyl-21-crown-7 (**1**) and benzyloxymethyl-30-crown-10 (**3**), 3,6,9,12,15,18-hexaoxa-10-(benzyloxymethyl)-1,20-eicosandiol (**6**), was obtained in an overall yield of 52% by reaction of 3-*O*-benzylglycerol[16,17] with the tetrahydropyranyl ether of 2-[2-(2-chloroethoxy)]-ethanol[18] and lithium *t*-butoxide in *t*-butyl alcohol in the presence of lithium bromide monohydrate[2] followed by acid-catalyzed deprotection of the bis-tetrahydropyranyl ether **7**. The benzyloxymethyl-substituted heptaethylene glycol **6** was cyclized by the Okahara method[19] (which involves *in situ* monotosylation and subsequent cyclization) and gave 87 and 91% yields of benzyloxymethyl-21-crown-7 (**1**) with potassium and cesium hydroxides as the bases, respectively.



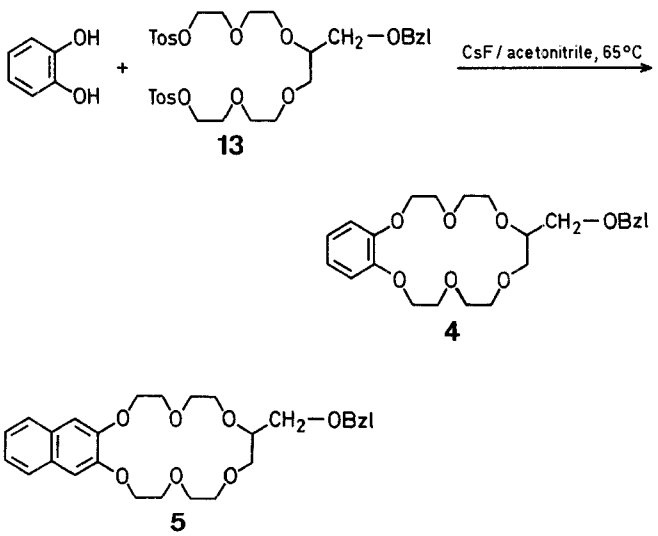
In an alternative approach to **1**, reaction of the benzyloxymethyl-substituted triethylene glycol **8** with the ditosylate of tetraethylene glycol (**11**) and potassium *t*-butoxide in tetrahydrofuran at room temperature afforded **1** in 44% yield. Compared with the reported[10] 27% yield of **1**, both methods are much more efficient.

Benzyloxymethyl-30-crown-10 (**3**) was prepared in 39% yield by reaction of the benzyloxymethyl-substituted heptaethylene glycol **6** with the ditosylate of triethylene glycol **10** and potassium *t*-butoxide in tetrahydrofuran at room temperature. This method offers a modest improvement in yield over that reported[12] for the reaction of protected diol **9** and ditosylate **12** under similar reaction conditions.

Benzyloxymethyl-24-crown-8 (**2**) was obtained in 35% yield from the room temperature reaction of the benzyloxymethyl-substituted triethylene glycol **8** with the ditosylate of pentaethylene glycol (**12**) and potassium *t*-butoxide in tetrahydrofuran. The analogous reaction of the benzyloxymethyl-substituted pentaethylene glycol **9** with the ditosylate of triethylene glycol (**10**) provided a 46% yield of **2**. In both cases, the yields far surpass that of 14% which was reported[10] for the preparation of **2** from **8** and **12** under other reaction conditions.



Cesium fluoride has been found to be an unusually efficient reagent for the conversion of catechol into benzocrowns[20,21]. Reaction of catechol with the ditosylate of benzyloxymethyl-substituted pentaethylene glycol **13** and cesium fluoride in acetonitrile afforded a 70% yield of the functionalized benzocrown **4**. Similarly, naphthocrown **5** was obtained from 1,2-dihydroxynaphthalene in 69% yield. These yields are substantially higher than those reported for the formation of **4** and **5** by cyclizations which involved different substrate and base combinations[11,14,15].



In summary, the reactions described above provide attractive alternative synthetic routes to the five known benzyloxymethyl-substituted crown ethers **1–5**. In each case, the product yields surpass those for the previously reported methods.

Bis-tetrahydropyranyl Ether of 10-Benzyloxymethyl-3,6,9,12,15,18-hexaoxa-1,20-eicosandiol (7):
To *t*-butyl alcohol (200 ml) is added lithium metal (0.80 g, 0.115 mol) and the mixture is refluxed for 2 h under nitrogen. Dropwise addition of 3-*O*-benzylglycerol[16,17] (7.00 g, 0.040 mol) to this solution, produces a white suspension. To this heterogeneous mixture is added the tetrahydropyranyl ether of 2-[2-(2-chloroethoxy)]-ethanol[18] (20.00 g, 0.080 mol), followed by lithium bromide monohydrate (4.10 g, 0.04 mol). After the mixture has been refluxed for 16 days, the solvent is evaporated under reduced pressure and water (100 ml) is added to the residue. The aqueous layer is extracted with dichloromethane (5 × 20 ml) and the combined organic layers are dried with magnesium sulfate. After filtration, the solvent is removed under reduced pressure to give an oil (25.4 g) which is chromatographed on alumina to give pure **7** as a viscous, colorless liquid; yield: 12.2 g (52%).

$C_{32}H_{54}O_{11}$ (614.8) calc. C 62.52 H 8.85 found 62.59 8.96

I.R. (neat): $\nu = 1114\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 1.2–2.1 (m, 12H); 3.2–4.2 (m, 33H); 4.4–4.9 (m, 4H); 7.30 ppm (s, 5H).

10-Benzyloxymethyl-3,6,9,12,15,18-hexaoxa-1,20-eicosanediol (6):
The bis-tetrahydropyranyl ether **7** (12.20 g, 0.020 mol) is dissolved in dichloromethane (60 ml) and methanol (60 ml) containing concentrated hydrochloric acid (1.2 ml). The solution is stirred for 2 h at room temperature. Solid sodium hydrogen carbonate (6 g) is added, the mixture is filtered, and the solvent is evaporated under reduced pressure to give diol **6** as a colorless oil; yield: 8.85 g (~ 100%).

$C_{22}H_{38}O_9$ (446.5) calc. C 59.18 H 8.58 found 59.06 8.74

I.R. (neat): $\nu = 3435, 1109\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 3.0–4.0 (m, 31H); 4.52 (s, 2H); 7.29 ppm (s, 5H).

Benzyloxymethyl-21-crown-7 (1):
Powdered potassium hydroxide (0.45 g, 8.0 mmol) is suspended in dioxan (10 ml) and the mixture is heated to 60°C under nitrogen. Very slowly, a solution of diol **6** (0.90 g, 2.0 mmol) and *p*-toluenesulfonyl chloride (0.39 g, 2.0 mmol) in dioxan (6 ml) is added and the mixture is stirred at 60°C for 42 h. The solvent is removed under reduced pressure and the residue is column-chromatographed on alumina using ethyl acetate/methanol (9/1) as the eluent to give product **1**; yield: 0.75 g (87%).

The spectral data of compound **1** thus prepared were identical with the reported data[10]. When cesium hydroxide was used as base the yield of isolated **1** was 91%.

Benzyloxymethyl-30-crown-10 (3); Typical Procedure:
Potassium *t*-butoxide (4.5 g, 40 mmol) is added to a solution of diol **6** (8.14 g, 18 mmol) in tetrahydrofuran (500 ml) and the mixture is stirred under nitrogen for 1 h. To this mixture a solution of triethylene glycol ditosylate (**10**; 8.53 g, 19 mmol) in tetrahydrofuran (200 ml) is added dropwise and the mixture is stirred for 9 days at room temperature. The solvent is removed under reduced pressure, the residue is dissolved in water (75 ml), and the solution is neutralized with 0.1 normal hydrochloric acid. The aqueous solution is extracted with dichloromethane (2 × 25 ml) and the combined extracts are dried with magnesium sulfate. Filtration and evaporation gives a residue which is chromatographed on an alumina column using ethyl acetate as the eluent to afford pure **3** as a colorless oil; yield: 3.95 (39%).

Compounds **1** and **2** were prepared under similar conditions.

Benzyloxymethyl-21-crown-7 (**1**) from **8** and **11**: 44% yield.

Benzyloxymethyl-24-crown-8 (**2**) from **8** and **12**: 35% yield; from **9** and **10**: 46% yield.

The spectral data of compounds **1**, **2**, and **3** thus prepared were identical with the reported data[10,12].

Ditosylate of 7-Benzyloxymethyl-3,6,9,12-tetraoxa-1,14-tetradecanediol (13):
A solution of *p*-toluenesulfonyl chloride (5.7 g, 30 mmol) in pyridine (10 ml) is added dropwise to a stirred solution of diol **9** (4.5 g, 12.5 mmol) in pyridine (10 ml) at −10°C[22]. After the addition is completed, the mixture is stirred at −5°C for 2 h and kept at 0°C overnight. The mixture is then poured over ice (~ 30 g), acidified with 6 normal hydrochloric acid and extracted with dichloromethane (2 × 20 ml). The combined extracts are washed with water (2 × 20 ml), dried with magnesium sulfate, and evaporated under reduced pressure to afford ditosylate **13** as a viscous, slightly yellow oil; yield: 8.1 g (96%).

$C_{32}H_{42}O_{11}S_2$ (666.8) calc. C 57.64 H 6.35 found 57.57 6.40

I.R. (neat): $\nu = 1357, 1190, 1178, 1097\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 2.41 (s, 6H); 3.3–3.8 (m, 17H); 4.30 (t, 4H); 4.48 (s, 2H); 7.0–7.9 ppm (m, 13H).

11-Benzyloxymethyl-2,3-benzo-18-crown-6 (4):
Anhydrous cesium fluoride (2.28 g, 15 mmol) is added in one portion to a stirred solution of catechol (0.33 g, 3.0 mmol) in dry acetonitrile (50 ml) under nitrogen. Vigorous stirring is continued for 1 h; then, a solution of ditosylate **13** (2.00 g, 3.0 mmol) in acetonitrile (20 ml) is added dropwise and the mixture is heated at 65°C for 20 h. After filtration, the solvent is removed under vacuum and the residue is column-chromatographed on alumina using ethyl acetate/30/60° petroleum ether (1/1) as the eluent to give product **4**; yield: 0.91 g (70%).

11-Benzyloxymethyl-2,3-(2',3'-naphtho)-18-crown-6 (**5**) is obtained under similar conditions in 69% yield.

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