7-Benzyloxymethyl-3,6,9,12-tetraoxa-1,14-tetradecanediol: A Versatile Intermediate in Crown and Azacrown Synthesis

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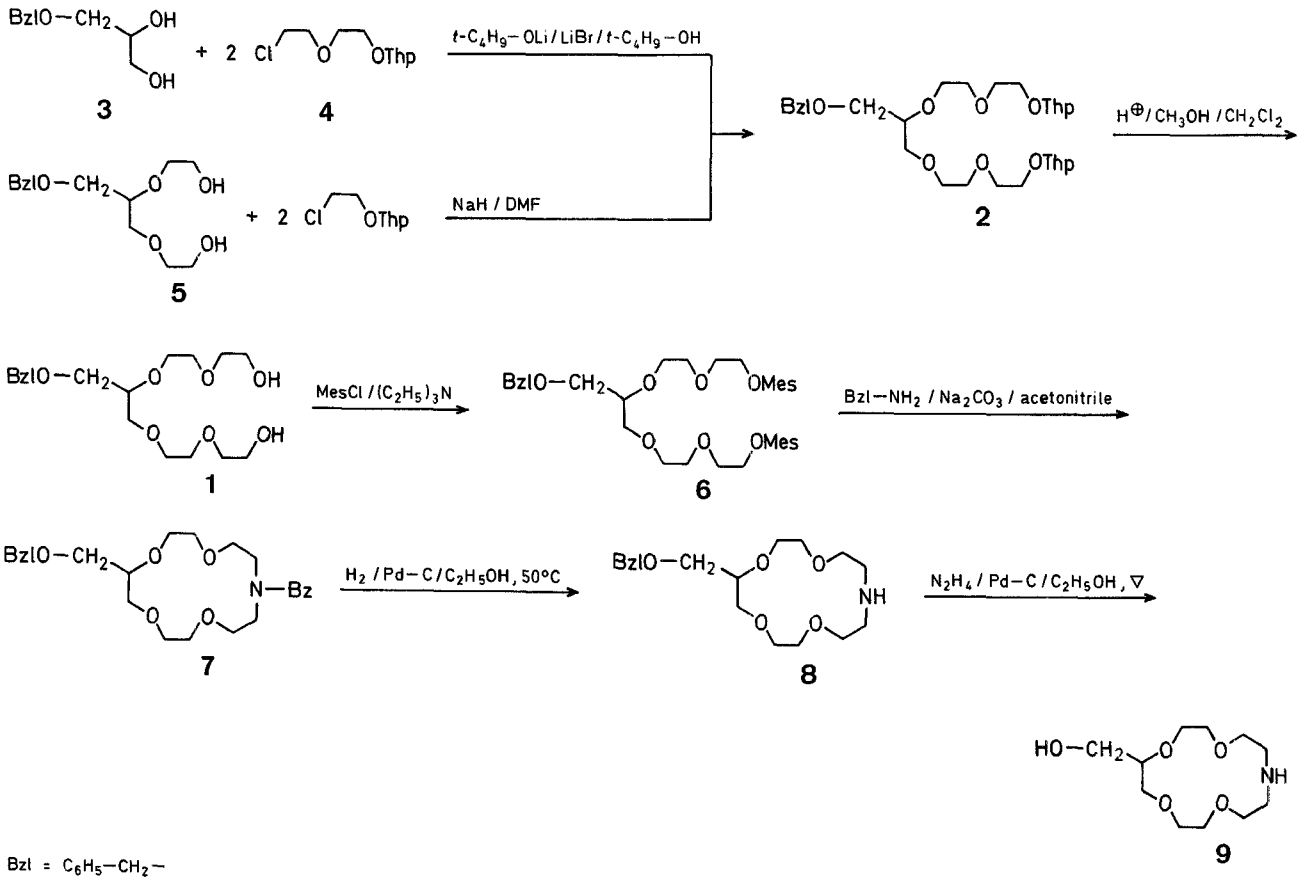
Functionalized crown compounds, particularly those which bear the hydroxymethyl group, serve as important intermediates for the synthesis of lariat crowns[1], bis-crowns[2], ionizable crowns[3], and polymer-supported catalysts with pendant crown units[4,5]. The synthesis of 7-benzyloxymethyl-3,6,9,12-tetraoxa-1,14-tetradecanediol (**1**) and its application in the preparation of functionalized crown and azacrown compounds is now described.

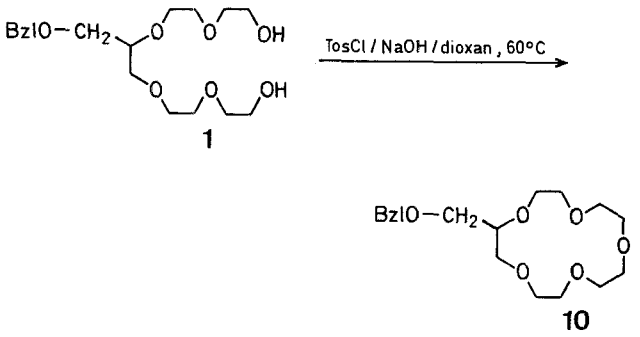
Three routes to the bis-tetrahydropyranyl derivative **2**, the immediate precursor to functionalized pentaethylene glycol **1**, were explored. In the most successful method, reaction of (3-O-benzyl)-glycerol[6,7] (**3**) with the *O*-tetrahydropyranyl derivative of 2-(2-chloroethoxy)-ethanol[8] (**4**) in the presence of lithium *t*-butoxide and lithium bromide in *t*-butyl alcohol[9] afforded **2** in 46% yield. A considerably lower yield (28%) of **2** was obtained when diol **3** was treated with **4** and sodium hydride in dimethylformamide. In this latter reaction, a 30% yield of 2-(2-vinyloxyethoxy)-tetrahydropyran was also isolated as the product of a competitive elimination reaction. An alternative route to compound **2** which involved the reaction of 4-benzyloxymethyl-3,6-dioxa-1,8-octanediol[10,11] (**5**) with the *O*-tetrahydropyranyl derivative of 2-chloroethanol[12] and sodium hydride in dimethylformamide provided a 29% yield of **2**. Acid-catalyzed deprotection of **2** produced the title diol **1** in almost quantitative yield.

Dimesylate **6** was obtained in 98% yield after treatment of **1** with methanesulfonyl chloride and triethylamine. Following Ref.[13], dimesylate **6** was reacted with benzylamine and solid sodium carbonate in acetonitrile to form the dibenzyl-protected monoazacrown **7** in 51% yield. Unexpectedly[14,15], hydrogenolysis of **7** using 10% palladium on carbon in ethanol at 50 °C selectivelty removed the *N*-benzyl group to afford a 76% yield of the *O*-benzyl-protected azacrown **8**. The addition of acid and/or the use of higher temperature and pressure were ineffectual for cleavage of the *O*-benzyl group of **8**. Ultimately, hydrogenolysis of the *O*-benzyl group in **8** was achieved using hydrazine and 10% palladium on carbon in ethanol at 80 °C to provide a 66% yield of the hydroxymethyl group-functionalized azacrown **9**.

Several preparative routes to benzyloxymethyl-15-crown-5 (**10**), the precursor of hydroxymethyl-15-crown-5, have been reported[16,17,18]. The benzyloxymethyl-substituted pentaethylene glycol **1** offers an alternative route to this important synthetic intermediate. Cyclization of **1** by the Okahara method[19] which involves *in situ* monotosylation and subsequent ring closure in the presence of sodium hydroxide, gave benzyloxymethyl-15-crown-5 (**10**) in 70% yield.

Compounds **9** and **10** clearly establish the utility of substituted pentaethylene glycol **1** in the synthesis of functionalized crowns and azacrowns.





1,14-Bis[tetrahydropyran-2-yloxy]-7-benzyloxymethyl-3,6,9,12-tetraoxatetradecane (2):

Method A: Lithium (2.20 g, 0.32 mol) is added to *t*-butanol (500 ml) and the mixture is refluxed for 2 h under nitrogen. Then, (3-*O*-benzyl)-glycerol[6,7] (19.10 g, 0.105 mol) is added dropwise whereupon a white suspension forms. To this heterogenous mixture is added the *O*-tetrahydropyranyl derivative of 2-(2-chloroethoxy)-ethanol[8] (44.0 g, 0.21 mol), followed by anhydrous lithium bromide (9.10 g, 0.105 mol) and water (1.0 ml). The mixture is refluxed for 15 days. The solvent is evaporated under reduced pressure and water (300 ml) is added to the residue. The aqueous layer is extracted with dichloromethane (6 × 100 ml) and the combined organic layers are dried with magnesium sulfate. The solvent is removed under vacuum and most of the impurities are distilled off under vacuum (up to 150 °C/1 torr). The residue is chromatographed on an alumina column using ether/ethanol (98/2) as eluent to give pure **2** as a viscous colorless liquid; yield: 25.3 g (46%).

$C_{28}H_{46}O_9$ (526.7) calc. C 63.86 H 8.80 found 63.84 8.83

I.R. (neat): ν = 1122 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 1.2–2.0 (m, 12H); 3.2–4.1 (m, 25H); 4.4–4.7 (m, 4H); 7.28 ppm (s, 5H).

Method B: Sodium hydride (2.00 g, 85 mmol) is added under nitrogen to a solution of 4-benzyloxymethyl-3,6-dioxa-1,8-octanediol[10,11] (**5**; 9.60 g, 35 mmol) in dry dimethylformamide (150 ml) and the mixture is stirred at 70 °C for 4 h. To this mixture, a solution of the *O*-tetrahydropyranyl derivative of 2-chloroethanol (11.70 g, 71 mmol) in dimethylformamide (150 ml) is added, and heating is continued for 3 days. Additional amounts of sodium hydride (2.00 g, 85 mmol) and the tetrahydropyranyl derivative (5.80 g, 35 mmol) are added and heating is continued for 3 days. The solvent is distilled off under vacuum, the residue is partitioned between water (400 ml) and dichloromethane (300 ml), and the organic layer is separated. The aqueous layer is extracted with dichloromethane (3 × 300 ml). The combined organic extracts are dried with magnesium sulfate and evaporated to produce 13.8 g of a brown oil. The crude product is column-chromatographed on alumina using ether as eluent; yield of **2**: 5.40 g (29%).

7-Benzyloxymethyl-3,6,9,12-tetraoxa-1,14-tetradecanediol (1):

The bis-tetrahydropyranyl derivative **2** (21.80 g, 41 mmol) is dissolved in dichloromethane (120 ml) and methanol (120 ml) containing concentrated hydrochloric acid (2.4 ml). The solution is stirred for 2 h at room temperature. Solid sodium hydrogen carbonate (12 g) is added, the mixture is filtered, and the solvent is evaporated under reduced pressure to give the diol **1** as a colorless oil; yield: 14.6 g (99%).

$C_{18}H_{30}O_7$ (358.4) calc. C 60.32 H 8.44 found 60.36 8.45

I.R. (neat): ν = 3410, 1100 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 3.3–4.1 (m, 23H); 4.50 (s, 2H); 7.28 ppm (s, 5H).

Dimesylate of 7-Benzyloxymethyl-3,6,9,12-tetraoxa-1,14-tetradecanediol (6):

A solution of methanesulfonyl chloride (2.6 ml, 34 mmol) in dichloromethane (60 ml) is added dropwise to a stirred solution of diol **1** (5.00 g, 14 mmol) and triethylamine (6.2 ml, 45 mmol) in dichloromethane (60 ml) which has been cooled to −10 °C. After the ad-

dition is completed, the mixture is stirred for 20 min, diluted with cold dichloromethane (100 ml), and subsequently washed with cold 5% aqueous hydrochloric acid (100 ml), cold saturated aqueous sodium hydrogen carbonate (100 ml), and cold water (2 × 100 ml). Drying and evaporation under reduced pressure affords dimesylate **6** as a viscous, slightly yellow oil; yield: 7.00 g (98%).

$C_{20}H_{34}O_{11}S_2$ calc. C 46.68 H 6.66
(514.6) found 46.39 6.82

I.R. (neat): ν = 1348, 1172, 1110 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 2.98 (s, 6H); 3.3–4.0 (m, 17H); 4.1–4.6 (m, 6H); 7.31 ppm (s, 5H).

N-Benzyl-8-benzyloxymethyl-4,7,10, 13-tetraoxa-1-azacyclopentadecane (7):
A solution of dimesylate **6** (3.50 g, 6.8 mmol) and benzylamine (0.80 g, 7.5 mmol) in dry acetonitrile (100 ml) containing powdered anhydrous sodium carbonate (3.5 g) is refluxed with stirring under nitrogen for 48 h. The mixture is then filtered and the solvent is evaporated under reduced pressure. The residue is partitioned between dichloromethane (100 ml) and water (200 ml). The aqueous layer is extracted with additional portions of dichloromethane (2 × 100 ml). The combined organic extracts are dried with magnesium sulfate and the solvent is removed to give 3.0 g of the crude product. Column chromatography on alumina using ether/acetone (9/1) as eluent affords pure **7** as a colorless oil; yield: 1.50 g (51%).

$C_{25}H_{35}NO_5$ calc. C 69.90 H 8.21
(429.6) found 69.75 8.26

I.R. (neat): ν = 1120 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 2.5–3.0 (m, 4H); 3.3–4.0 (m, 19H); 4.50 (s, 2H); 7.27 ppm (s, 10H).

8-Benzyloxymethyl-4,7,10,13-tetraoxa-1-azacyclopentadecane (8):
The azacrown **7** (1.39, 3.2 mmol) is hydrogenolyzed in ethanol (50 ml) over 10% palladium/carbon (0.14 g) at 50 °C for 18 h to give the crude product which is purified by column chromatography (silica gel, methanol/triethylamine, 49/1) to give **8** as a colorless oil; yield: 0.83 g (76%).

$C_{18}H_{29}NO_5$ calc. C 63.69 H 8.61
(339.4) found 63.46 8.87

I.R. (neat): ν = 3300, 1120 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 2.6–2.9 (m, 5H); 3.3–3.9 (m, 17H); 4.50 (s, 2H); 7.27 ppm (s, 5h).

8-Hydroxymethyl-4,7,10,13-tetraoxa-1-azacyclopentadecane (9):
To a solution of compound **8** (0.30 g, 0.90 mmol) in ethanol (50 ml) are added hydrazine hydrate (85%, 4 ml) and 10% palladium/carbon (0.06 g). The mixture is refluxed for 48 h, filtered through a layer of Celite 545, and the solvent is evaporated under reduced pressure. The residue is chromatographed on a silica gel column using ethanol/dichloromethane (1/1) as eluent to give pure **9** as a colorless, extremely hygroscopic oil which solidifies below room temperature; yield: 0.145 g (66%).

$C_{11}H_{23}NO_5$ (249.3) [satisfactory microanalysis could not be obtained due to the extremely hygroscopic character of the compound].

M.S.: m/e = 218 ($M^+ - CH_2OH$, 26%).

I.R. (neat): ν = 3390–3270, 1105 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 2.6–3.0 (m, 4H); 3.1–4.1 ppm (m, 19H).

Benzyloxymethyl-15-crown-5 (10):
Powdered sodium hydroxide (0.48 g, 12 mmol) is suspended in dioxan (15 ml) and a solution of diol **1** (1.08 g, 3 mmol) and *p*-toluenesulfonyl chloride (0.57 g, 3 mmol) in dioxan (9 ml) is added very slowly at 60 °C under nitrogen. The mixture is stirred at 60 °C for 24 h. The solvent is removed under reduced pressure and the residue is chromatographed on a short alumina column using ethyl acetate / 30/60 petroleum ether (1/1) as the eluent to give **10**; yield: 0.71 g (70%). [The spectral data of compound **10** thus obtained were identical with those reported[16,17,18]].

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