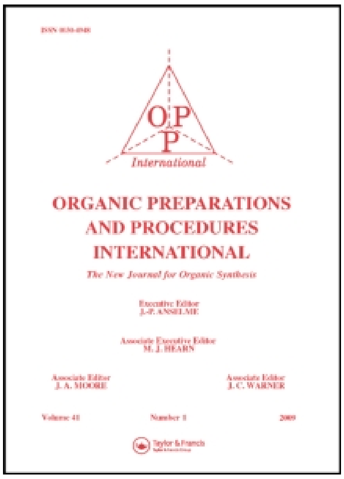

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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Bronislaw Czech[a]; David A. Babb[a]; Richard A. Bartsch[a]
[a] Department of Chemistry, Texas Tech University, Lubbock, Texas

To cite this Article Czech, Bronislaw , Babb, David A. and Bartsch, Richard A.(1983) 'PREPARATION OF 3,6-DIOXA-4-(BENZYLOXYMETHYL)-1,8-OCTANEDIOL, A VERSATILE INTERMEDIATE FOR THE SYNTHESIS OF FUNCTIONALIZED CROWN ETHERS', Organic Preparations and Procedures International, 15: 1, 29 — 34

To link to this Article: DOI: 10.1080/00304948309355427

URL: http://dx.doi.org/10.1080/00304948309355427

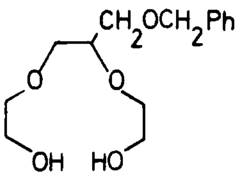
ORGANIC PREPARATIONS AND PROCEDURES INT. 15(1-2), 29-34 (1983)

PREPARATION OF 3,6-DIOXA-4-(BENZYLOXYMETHYL)-1,8-OCTANEDIOL, A VERSATILE INTERMEDIATE FOR THE SYNTHESIS OF FUNCTIONALIZED CROWN ETHERS[+]

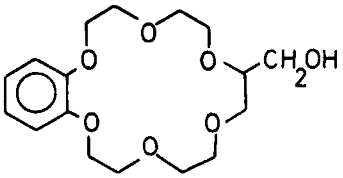
Bronislaw Czech, David A. Babb and Richard A. Bartsch[*]
Department of Chemistry, Texas Tech University, Lubbock, Texas 79409

Although convenient synthetic routes to a variety of cyclic polyethers (crown ethers) were reported by Pederson[1] nearly 15 years ago, the preparation of functionalized crown ethers has become a subject of intensive investigation only recently. In such compounds a functional group is attached to the crown ether moiety and may serve as a site for further structural modification such as immobilization on a polymer support[2-4] or introduction of an ionizable group[5]. Probably the most versatile of the functionalized crown ether compounds are ones in which a hydroxymethyl group is attached directly to the polyether ring. Several groups have reported preparative routes to hydroxymethyl crown ethers[6-11].

Recently, we have discovered that 3,6-dioxa-4-(benzyloxymethyl)-1,8-octanediol (I) is an accessible and very useful key compound for the synthesis of hydroxymethyl crown ethers. Although the use of this intermediate has been mentioned by others,[12] neither the experimental details for its synthesis nor characterization were provided. We now report a viable procedure for the preparation of I as well as its use in the



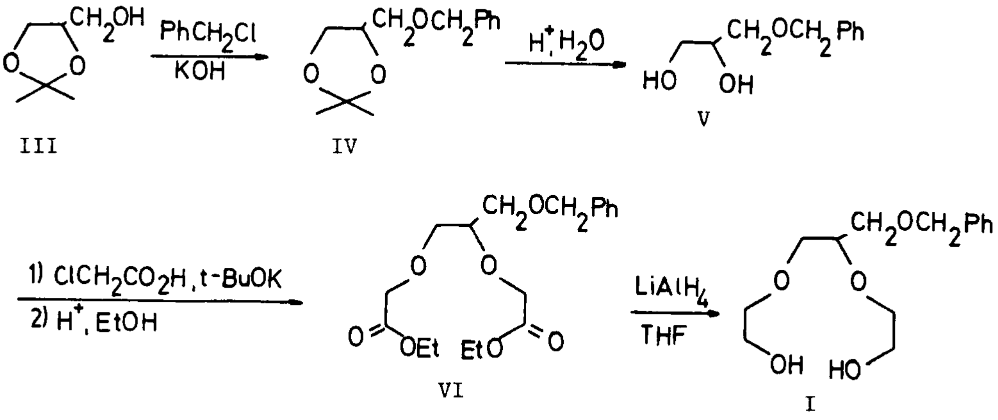
I



II

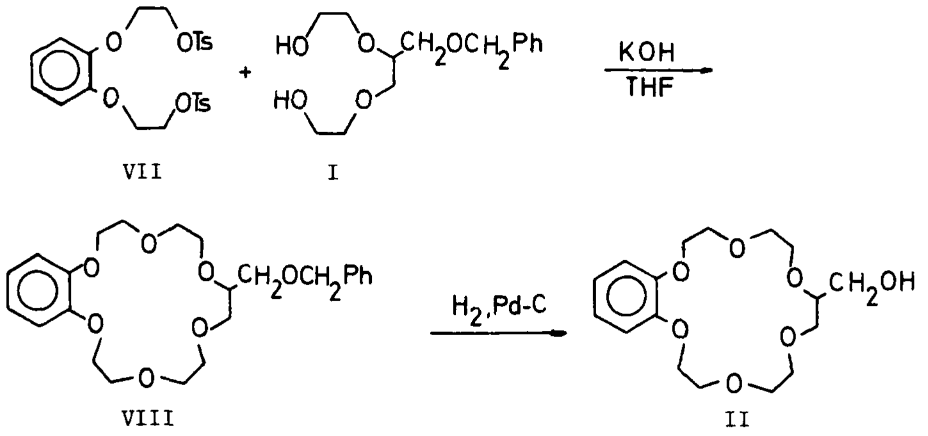
synthesis of 11-hydroxymethyl-2,3-benzo-18-crown-6 (II), an isomer of the known[13,14] 4'-(hydroxymethyl)-benzo-18-crown-6.

The key compound I was prepared by the 5 step synthesis outlined in Scheme 1. Using the literature procedure,[15,16] commercially-available 1,2-O-isopropylidene glycerol (III) was treated with benzyl chloride followed by acidic hydrolysis of the isopropylidene group to give the diol V. Reaction of V with chloroacetic acid in the presence of potassium tert-butoxide led to an intermediate which was converted without purification into diethyl 3,6-dioxa-4-(benzyloxymethyl)-1,8-octanedicarboxylate (VI). The diester was reduced with lithium aluminum hydride to afford the title compound I in 56% overall yield from V.



Scheme 1

An illustration of the utility of I in the formation of hydroxymethyl crown ethers is presented in Scheme 2. When diol I was treated with potassium hydroxide and 1,2-bis(2'-hydroxyethoxy)benzene ditosylate[17] (VII) the cyclization product 11-(benzyloxymethyl)-2,3-benzo-18-crown-6 (VIII)



Scheme 2

was isolated in 54% yield. Removal of the protecting group by hydrogenolysis yielded the previously unknown hydroxymethyl crown ether II.

EXPERIMENTAL SECTION

PMR spectra were determined in $CDCl_3$ with a Varian EM360 spectrometer and are reported in δ units. IR spectra were obtained using a Beckman Acculab 8 spectrophotometer and are given in cm^{-1}. Elemental analyses were performed by Galbraith Laboratories of Knoxville, Tennessee.

Diethyl 3,6-dioxa-4-(benzyloxymethyl)-1,8-octanedicarboxylate (VI).- A solution of chloroacetic acid (105.3 g, 1.11 mole) in 300 ml of t-BuOH was added slowly to a stirred and reluxing mixture of 3-(O-benzyl)glycerol[15,16] (V) (81.0 g, 0.44 mole) and t-BuOK (250 g, 2.23 mole) in 1.5 ℓ. of t-BuOH under nitrogen. After completion of the addition, stirring and refluxing were continued for 15 hrs. Following removal of the solvent by distillation under reduced pressure, the residue was dissolved in 500 ml of H_2O and then extracted with Et_2O (2 x 100 ml). The aqueous layer was acidified with 6 N HCl and extracted with EtOAc (3 x 100 ml). The combined EtOAc extracts were washed with brine and dried over $MgSO_4$. Evaporation of the solvent in vacuo afforded 138.0 g of the crude diacid which was dissolved in 1.4 ℓ. of a 1:1 (v/v) mixture of absolute EtOH and C_6H_6. p-Toluenesulfonic acid (8.0 g) was added and the mixture was refluxed for 5 hrs with continuous circulation of the condensing vapors through a Soxhlet thimble which contained anhydrous Na_2SO_4. The solvent was removed *in vacuo* and a solution of the residue in Et_2O was washed with aqueous $NaHCO_3$ and then with H_2O. After drying over $MgSO_4$ and evaporation of the solvent *in vacuo*, the residual liquid was distilled to afford 103.1 g (65.5%) of diester VI as a colorless liquid, b.p. 170-172/0.3 torr, $n_D^{24°}$ = 1.4810. IR (neat): 1745 (C=O), 1120 (C-O). PMR (δ): 1.26 (t, 6H), 3.56-4.45 (m, 13H), 4.53 (s, 2H), 7.28 (s, 5H).

Anal. Calcd for $C_{18}H_{26}O_7$: C, 61.00; H, 7.39; Found: C, 60.87; H, 7.37.

3,6-Dioxa-4-(benzyloxymethyl)-1,8-octanediol (I).-The diester VI (53.1 g, 0.15 mole) and 15.0 g (0.39 mole) of $LiAlH_4$ were refluxed in 450 ml of dry THF for 3 hrs. The reaction mixture was then stirred and cooled in an ice bath while the following additions were made slowly and consecutively: 90 ml of H_2O-THF (1:5, v/v); 15 ml of 15% aqueous NaOH; and, 150 ml of H_2O-THF (1:1, v/v). The resulting mixture was allowed to stand overnight at room temperature, after which the precipitated inorganic material was filtered and washed with hot THF. The combined filtrate and washings were evaporated *in vacuo* to yield 38.0 g of the crude diol. Distillation gave 35.0 g (86%) of I as a colorless, heavy, very hygroscopic liquid, b.p. 179-181°/0.4 torr ($n_D^{24°}$ = 1.5092. IR (neat): 3400 (O-H), 1100 (C-O). PMR: 3.40-4.30 (m, 15H), 4.53 (s, 2H), 7.31 (s, 5H).

Anal. Calcd for $C_{14}H_{22}O_5 \cdot 1/2\ H_2O$: C, 60.20; H, 8.30. Found: C, 60.08; H, 7.93.

11-(Benzyloxymethyl)-2,3-benzo-18-crown-6 (VIII).-A solution of diol I (5.60 g, 0.020 mole) and KOH (2.90 g, 0.050 mole) in 20 ml of THF and 2 ml of H_2O was stirred and heated to reflux. To this solution, 10.49 g (0.020 mole) of 1,2-bis(2'-hydroxyethoxy)benzene ditoxylate[17] (VII) was added in portions over 1 h. The mixture was refluxed for 3 hrs and allowed to cool. The solvent was removed *in vacuo* and CH_2Cl_2 (50 ml) was added to the semi-solid residue. The insoluble salt was removed by filtration and washed with CH_2Cl_2. Evaporation of the combined filtrate and washings *in vacuo* gave 13.4 g of the crude reaction product which was chromatographed on a neutral alumina column using a 1:1 (v/v) mixture of EtOAc and 30-60° pet. ether to yield 4.70 g (54%) of the title compound VIII as a colorless viscous liquid. IR (neat): 1120 (C-O). PMR: 3.40-4.43 (m, 12H), 4.52 (s, 2H), 6.89 (s, 4H), 7.30 (s, 5H).

Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.43; H, 7.47.

11-Hydroxymethyl-2,3-benzo-18-crown-6 (II).-The benzyl-protected crown ether VIII (7.20 g, 0.017 mole) was dissolved in 100 ml of EtOH and 0.75 g of 10% Pd-C was added. Hydrogenolysis was conducted for 18 hrs at room temperature with slightly more than one atmosphere pressure of hydrogen. The catalyst was removed by filtration and was washed with EtOH. Evaporation of the combined filtrate and washings *in vacuo* yielded 5.50 g (96%) of crown ether II as a heavy, colorless, hygroscopic liquid which appeared to be reasonably pure by TLC (alumina, EtOAc-30-60° pet. ether). An analytical sample was obtained by chromatography on a short column of neutral alumina using EtOAc and EtOAc-MeOH (10:1) as eluents. IR (neat): 3400 (O-H), 1130 (C-O). PMR: 2.40 (br s, 1H), 3.5-4.4 (m, 21H), 6.90 (s, 4H).

Anal. Calcd for $C_{17}H_{26}O_7$: C, 59.64; H, 7.65. Found: C, 59.29; H, 7.93.

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† Research supported by grant D-775 from the Robert A. Welch Foundation.

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(Received August 31, 1982; in revised form October 18, 1982)