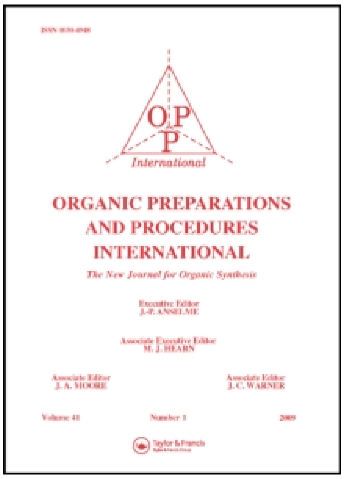

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SYNTHESIS OF NEW bis(*m*-PHENYLENE)-32-CROWN-10 DERIVATIVES

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SYNTHESIS OF NEW bis(*m*-PHENYLENE)-32-CROWN-10 DERIVATIVES

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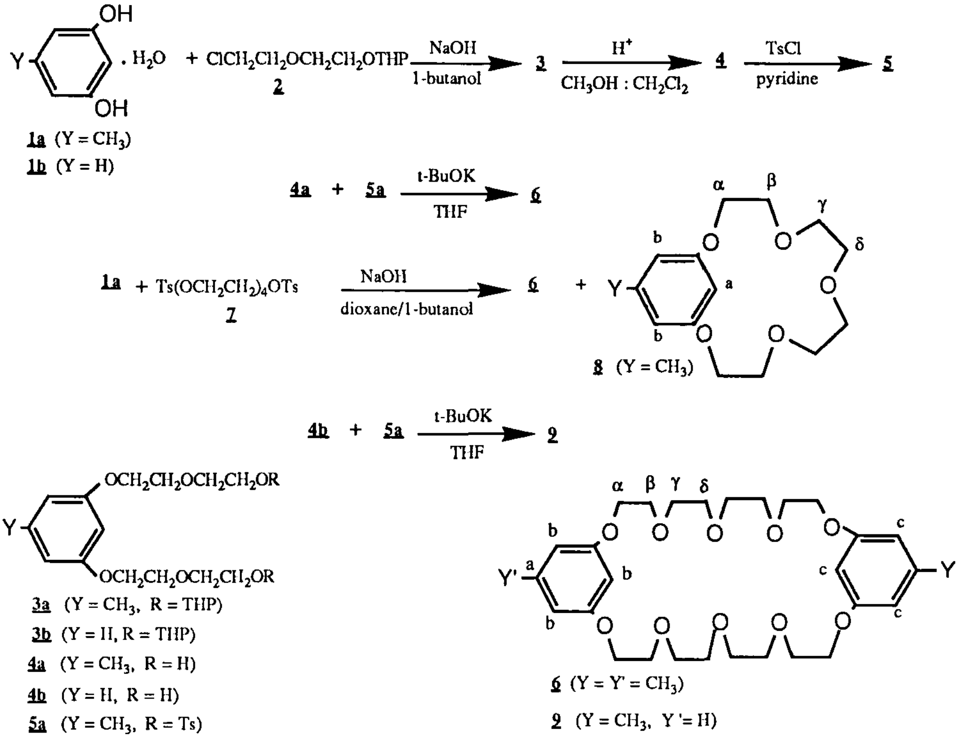
High yields are generally not obtained in the synthesis of macrocycles because of the formation of linear and cyclic oligomeric by-products. Although optimized procedures for the synthesis of crown ethers, especially in the range up to 18-membered rings, have been developed,[1] we were interested in synthesizing significant quantities of functionalized semi-rigid 30-40 membered rings; the objective of the present study was to develop a simple method for the preparation of mono- and difunctionalized bis(*m*-phenylene)-32-crown-10.

The new macrocycle bis(5-methyl-1,3-phenylene)-32-crown-10 (**6**) was prepared (21%) *via* **1a** and the series of new compounds **2a-5a** according to a four-step route (Scheme) used by Bartsch et al.[2] for another crown ether. A one-step method has been used by Cram et al.[3] as well as in our laboratory[4] to synthesize bis(*p*-phenylene)-34-crown-10. Thus orcinol monohydrate (**1a**) was treated with tetra(ethylene glycol) ditosylate (**7**)[5] in dioxane/1-butanol at reflux for 24 hrs to produce macrocycle **6**

(9%) as well as a second new compound 5-methyl-1,3-phenylene-16-crown-5 (**8**) (7%). Even though the four-step method gave a higher yield of **6** than the one-step route, the one-step route is much simpler, cheaper and less time consuming. The third new macrocycle 5-methyl-bis(1,3-phenylene)-32-crown-10 (**9**) was produced (20%) as shown in the Scheme from **5a** and **4b**, also both new compounds.



The ^{1}H NMR spectra allowed us to distinguish between **8** and **6**. The α-OCH$_2$ protons of crown **8** appeared at lower field than those in the larger macrocycle **6** ($\Delta\delta$ = 0.22 ppm). The methylene protons of the tetra(ethylene glycol) chain of the large macrocycle were magnetically more equivalent (three absorption peaks with 1:1:2 ratio) than in the smaller macrocycle (four distinct absorption peaks with 1:1:1:1 ratio). The size of the ring also affects the chemical shifts of the aromatic protons, i.e., in the 32-membered ring compound **6** the aromatic protons (H$_a$, H$_b$) showed one absorption while in the 16-membered ring **8** the intraannular aromatic proton (H$_a$) shifts 0.60 ppm to lower field.

EXPERIMENTAL SECTION

All melting points were taken in capillary tubes with a Haake-Buchler melting point apparatus and have been corrected. ^{1}H NMR spectra were obtained at ambient temperature in deuteriochloroform solutions with Me$_4$Si as internal standard (δ = 0 ppm) and recorded on a Bruker WP high resolution spectrometer operating at 270 MHz. Infrared spectra were determined on a Nicolet MX-1 FTIR spectrometer. Mass spectra were measured with a VGA 7070E Analytical mass spectrometer. Elemental analyses were performed by Atlantic Microlab of Norcross, Georgia. Tetrahydrofuran was refluxed over Na/benzophenone and was used immediately. The tetrahydropyranyl ether **2** of 2-(2'-chloroethoxy)ethanol was prepared by following a literature procedure.[6]

3,5-bis(5-Tetrahydropyranyloxy-3-oxa-1-pentyloxy)toluene (**3a**).- A literature procedure[7] was followed to produce this new compound as a viscous oil (95%). IR (neat): 1600 (C=C), 1129 (C-O-C) cm^{-1}; ^{1}H NMR: δ 1.3-1.9 (12H, m, CH_2), 2.25 (3H, s, Ph-CH_3), 3.5-4.1 (20H, m, OCH_2), 4.6 (2H, s, O-CH-O) and 6.35 (3H, s, Ph-H).

3,5-bis(5-Hydroxy-3-oxa-1-pentyloxy)toluene (**4a**).- 3,5-bis(5-Tetrahydropyranyloxy-3-oxa-1-pentyloxy)toluene (**3a**) was deprotected according to a literature procedure,[2] giving new compound **4a** as a liquid, bp. 195-197°/0.05 mm (92%). IR (neat): 3405 (O-H), 1600 (C=C), 1129 (C-O-C) cm^{-1}; ^{1}H NMR: δ 2.25 (3H, s, Ph-H), 2.8 (2H, br s, OH), 3.5-4.2 (16H, m, OCH_2) and 6.35 (3H, s, Ph-H).

3,5-bis(5-Toluenesulfonyloxy-3-oxa-1-pentyloxy)toluene (**5a**).- A literature procedure[5] was followed from **4a** to afford new compound **5a** as a viscous oil (97%). IR (neat): 1355, 1190 and 1175 (S=O), 1600 (C=C), 1129 (C-O-C) cm^{-1}; ^{1}H NMR: δ 2.25 (3H, s, Ph-H), 2.4 (3H, s, O-SO_2-Ph-CH_3), 3.7-4.3 (16H, m, OCH_2), 6.2-6.4 (3H, m, Ph-H), 7.55 (8H, AB q, O-SO_2-Ph-H).

bis(5-Methyl-1,3-phenylene)-32-crown-10 (**6**).- A literature procedure[2] was followed to produce **6** (25%) from **4a** and **5a** as a white solid, mp. 94-96°. IR (KBr): 1129 (C-O-C) cm^{-1}; ^{1}H NMR: δ 2.25 (6H, s, Ph-CH_3), 3.7 (16H, s, γ/δ-OCH_2), 3.82 (8H, t, β-OCH_2), 4.05 (8H, t, α-OCH_2), 6.32 (6H, s, Ph-H); m/z (CI^+): 565 (M^++1), 521 (M^+-OCH_2CH_2).

Anal. Calcd for $C_{30}H_{44}O_{10}$: C, 63.81; H, 7.85. Found: C, 63.74; H, 7.86

bis(5-Methyl-1,3-phenylene)-32-crown-10 (**6**) and 5-Methyl-1,3-phenylene-16-crown-5 (**8**).- Tetraethylene glycol ditosylate[5] (**7**) (50.23 g, 0.100 mol) in 500 mL dioxane/1-butanol (3:2 v/v) was added to 450 mL of 1-butanol containing orcinol monohydrate (**1a**) (16.40 g, 0.115 mol) and NaOH (9.10 g, 0.230 mol) in 8 mL of water. The solution was refluxed for 24 hrs under nitrogen, cooled, filtered and evaporated to give a brown viscous oil. A short column of silica gel (7 g per 1 g of crude products) with diethyl ether was then used. The smaller ring corand was the fast moving (R_f = 0.50) and the larger macrocycle was the slow moving fraction (R_f = 0.44, silica gel/ethyl acetate). This produced corand **6**, 2.5 g, 9% yield (mp and other characteristic data reported above) and the new macrocycle **8** as a needle-like crystalline solid, 1.6 g (7% yield), mp. 69-71°. ^{1}H NMR: δ 2.25 (3H, s, Ph-CH_3), 3.60 (4H, t, δ-OCH_2), 3.70 (4H, t, δ-OCH_2), 3.82 (4H, t, β-OCH_2), 4.27 (4H, t, α-OCH_2), 6.37 (2H, s, Ph-H_b) and 6.92 (1H, s, Ph-H_a) (for H_a and H_b see Scheme); m/z (EI^+): 282 (M^+), 195 [M^+-$(OCH_2CH_2)_3$], 168 [M^+-$CH_2CH_2(OCH_2CH_2)_2$], 151 [M^+-$(OCH_2CH_2)_3$], 124 [M^+-$CH_2CH_2(OCH_2CH_2)_3$].

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85; Found: C, 63.67; H, 7.86

1,3-bis(5-Hydroxy-3-oxa-1-pentyloxy)benzene (**4b**).- The same procedure was followed with resorcinol (**1b**) *via* **3b** as in the synthesis of **4a** to give the diol **4b** (91%), bp. 190-195°/0.1 mm, mp 36-38°. IR (neat): 3405 (O-H), 1600 (C=C), 1129 (C-O-C) cm^{-1}; ^{1}H NMR: δ 3.35 (2H, s, OH), 3.55-

4.3 (16H, m, OCH_2), 6.7-7.2 (4H, m, Ph-H); m/z (EI^+): 286 (M^+);

Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.72; H, 7.75. Found: C, 58.51; H, 7.77

5-Methyl-bis(1,3-phenylene)-32-crown-10 (**9**).- The same procedure as in four-step route of the synthesis of **6** was followed with **4b** and **5a** to produce the new macrocycle **9** (20%) as a white crystalline solid, mp. 66-68°. IR (KBr): 1600 (C=C), 1129 (C-O-C) cm^{-1}; ^1H NMR: δ 2.25 (3H, s, Ph-CH_3), 3.70 (16H, s, γ/δ-OCH_2), 3.82 (8H, t, β-OCH_2), 4.05 (8H, t, α-OCH_2), 6.32 (3H, s, Ph-H_c), 6.5 (3H, d, Ph-H_b), 7.12 (1H, t, Ph-H_a); m/z (EI^+): 550 (M^+), 283 [M^+-$(CH_2CH_2O)_2C_6H_4(OCH_2CH_2)_2OCH_2$].

Anal. Calcd for $C_{29}H_{41}O_{10}$: C, 63.37; H, 7.52. Found: C, 63.17; H, 7.71

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