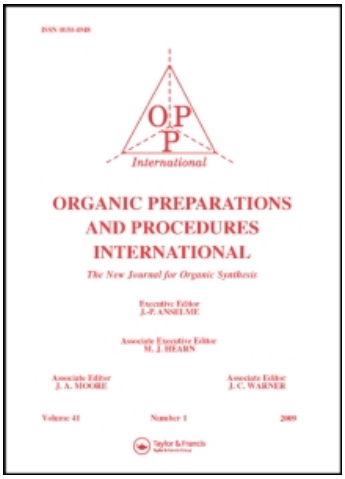

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IMPROVED SYNTHESES OF 20- AND 26-MEMBERED *bis*(5-CARBOMETHOXY-1,3-PHENYLENE) CROWN ETHERS

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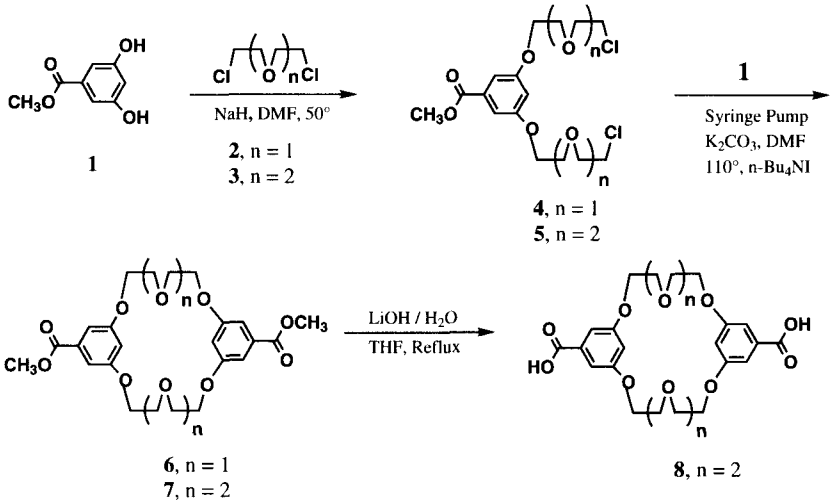
Recently a number of useful functionalized *bis*(*m*-phenylene) crown ethers were synthesized in a one step reaction of 5-substituted resorcinols with linear dihalides in DMF,[1-6] but this method gave relatively poor yields. Controlling the rates of *intra*- versus *inter*-molecular reactions during the condensation is a major problem in any single step cyclization,[7,8] although a number of other factors are known to affect yields.[8] Taking advantage of the preorganization effect, we achieved improved syntheses of these macrocycles *via* a two-step methodology.

The disodium salt of methyl 3,5-dihydroxybenzoate (**1**) in DMF was added slowly to a large excess of oligo(ethylene glycol) dichloride (**2** or **3**), which also acted as solvent. This reaction gave intermediate dichlorides **4** and **5** in 81 and 71% yields, respectively, after purification *via* column chromatography. Cyclization was accomplished with alkali metal salts in the presence of the phase transfer agent n-Bu_4NI. It is well known that crown ether yields are greatly dependent on the nature of the metal ion[9] and the ring size of the macrocycle, in addition to concentration.[10] The yields of macrocycles **6** and **7** were higher *via* the two-step method (Table). In the two-step method K_2CO_3 gave the highest yield for both macrocycles, much higher than NaH or CsF. Macrocycles **6** and **7** were purified by column chromatography.



The hydrolysis of *bis*(5-carbomethoxy-1,3-phenylene)-26-crown-8 (**7**) was achieved with LiOH in THF, affording the diacid **8**. The syntheses of polyesters and polyamides from the macrocyclic diesters and diacids are currently under investigation and will be reported elsewhere.

TABLE. Yields of Macrocycles **6** and **7** by One-step and Two-step Methods with Various Bases in DMF

Method	Base	Temp. (°C)	Yield of **6** (%)	Yield of **7** (%)
One-step	NaH	85	7.0[a]	6.0[c]
One-step	KH	85	18.0[a]	—
One-step	Cs_2CO_3	85	4.5[a]	—
Two-step	NaH	110	16.0[b]	—
Two-step	K_2CO_3	110	58.0[b]	46.0[d]
Two-step	CsF	110	26.0[b]	26.0[d]

a) One-step reaction[6] of **1** and **2**, 0.12 M each. b) Reaction of **1** and **4** under pseudo-high dilution with n-Bu_4NI as catalyst. c) One-step reaction[6] of **1** and **3**, 0.12 M each. d) Reaction of **1** and **5** under pseudo-high dilution with n-Bu_4NI as catalyst.

EXPERIMENTAL SECTION

Methyl 3,5-dihydroxybenzoate was synthesized according to the literature procedure.[1] Melting points were taken in capillary tubes with a Haake-Buchler apparatus and have been corrected. NMR spectra were obtained at 20° on a Varian Unity 400 MHz spectrometer using $CDCl_3$ unless otherwise noted and TMS as internal standard. Infrared spectra were recorded on a Nicolet MX-1 FTIR spectrometer. A Harvard syringe infusion pump. Model 22 was used to control the addition rates in the cyclization reactions. Mass spectroscopy was carried out at the Mass Spectrometry Center at the University of Nebraska-Lincoln. Elemental analysis was performed by Atlantic Microlabs of Norcross, GA.

Methyl 3,5-*bis*(5-Chloro-3-oxapentyloxy)benzoate (4).- Sodium hydride (2.92 g, 73 mmol, 60% in mineral oil) was added to a solution of methyl 3,5-dihydroxybenzoate (**1**, 6.06 g, 36 mmol) in DMF (30 mL). The mixture was stirred for 2 hrs at 110° and cooled to 25°; the resulting suspension of dianion was added to a solution of di(ethylene glycol) dichloride (**2**, 51.81 g, 362.3 mmol, 10 equiv.) in DMF (30 mL) over 6 hrs and then the mixture was stirred for five days at 50° and filtered to remove NaCl. DMF and excess dichloride **2** were removed *in vacuo*. Purification of the residue by flash column chromatography with 20:1 $CHCl_3$:EtOAc gave 11.1 g (81%) of **4**, an oil; IR (neat): 3100 (=CH), 2951 (-CH), 1716 (C=O), 1601 (C=C), 1126 (C-O-C); ^{1}H NMR: δ 7.21 (d, J = 2.2Hz, 2H), 6.53 (t, J = 2.2Hz, 1H), 4.16 (t, J = 4.6Hz, 4H), 3.88 (m, 7H), 3.83 (t, J = 5.8Hz, 4H), 3.66 (t, J = 5.8Hz, 4H); ^{13}C NMR: δ 42.64, 52.18, 67.67, 69.53, 71.45, 106.86, 108.02, 131.88, 159.56, 166.59; MS (EI) m/z: 380 (M^+, 3.8%), 349 [$(M-OCH_3)^+$, 3.5%], 274 [$(M-C_4H_7ClO)^+$, 5.3%], 106 [$(M-C_{12}H_{15}ClO_5)^+$, 53%], 63 ($C_2H_4Cl^+$, 100%).

Methyl 3,5-*bis*(8-Chloro-3,6-dioxaoctyloxy)benzoate (5).- The above procedure with **1** and **3** on a similar scale produced (71%) **5**, an oil: IR (neat): 3090 (=CH), 2884 (-CH), 1722 (C=O), 1596 (C=C), 1118 (C-O-C); ^{1}H NMR: δ 7.20 (d, J = 2.2Hz, 2H), 6.70 (t, J = 2.2Hz, 1H), 4.15 (t, J = 4.6Hz, 4H), 3.90 (s, 3H), 3.87 (t, J = 4.6Hz, 4H), 3.77 (t, J = 5.8Hz, 4H), 3.73 (m, 8H), 3.64 (t, J = 5.8Hz, 4H); ^{13}C NMR: δ 42.68, 52.19, 67.68, 69.60, 70.64, 70.77, 71.34, 106.87, 107.99, 131.84, 159.67, 166.70; MS (FAB) m/z: 469 [$(M+H)^+$, 57%] and 437 [$(M-OCH_3)^+$, 100%].

***bis*(5-Carbomethoxy-1,3-phenylene)-20-crown-6 (6)**.- A solution of methyl 3,5-*bis*(5-chloro-3-oxapentyloxy)benzoate (**4**, 6.04 g, 15.8 mmol) and methyl 3,5-dihydroxybenzoate (**1**, 2.66 g, 15.8 mmol) in DMF (total volume 22 mL) was added *via* a syringe pump at 0.75 mL/hr to a suspension containing K_2CO_3 (22.04 g, 159.5 mmol) and n-Bu_4NI (20 mg) in DMF (750 mL) at 110°. After complete addition, the mixture was stirred vigorously at 110° for five days, cooled and evaporated. The residue in CH_2Cl_2 was filtered to remove salts and subjected to flash column chromatography using Et_2O to give 4.36 g (58%) of pure **6**, mp. 185.9-187.5°, lit.[6] 179-181°; ^{1}H NMR: δ 7.09 (d, J = 2.4Hz, 4H), 6.67 (br s, 2H), 4.12 (br s, 8H), 3.83 (br s, 14H); ^{13}C NMR: δ 52.16, 68.03, 69.72, 108.27, 131.73, 159.68, 166.68.

***bis*(5-Carbomethoxy-1,3-phenylene)-26-crown-8 (7)**.- The above procedure with **1** and **5** on a similar scale produced (46%) pure **7**: mp. 131.4-132.9°, lit.[6] 131.2-133.2°; ^{1}H NMR: δ 7.16 (d, J = 2.2Hz, 4H), 6.68 (t, J = 2.2Hz, 2H), 4.11 (t, J = 4.6Hz, 8H), 3.87 (s, 6H), 3.85 (t, J = 4.6Hz, 8H), 3.74 (s, 8H); ^{13}C NMR: δ 52.16, 67.65, 69.50, 70.92, 107.06, 107.86, 131.74, 159.71, 166.73.

***bis*(5-Carboxy-1,3-phenylene)-26-crown-8 (8)**.- A solution of LiOH•H_2O (0.764g, 19.1 mmol), *bis*(5-carbomethoxy-1,3-phenylene)-26-crown-8 (**7**, 1.35 g, 2.39 mmol), water (10 mL) and THF (60 mL) was refluxed for 4 days. The solvent was removed and the residue was treated with H_2O (30 mL), and then filtered. The filtrate was acidified with 2N HCl to give a white precipitate. Filtration followed by drying gave 1.20 g (94%) of **8**, mp. 259.1-260.8°; ^{1}H NMR (DMSO-d_6): δ 7.05 (d, J = 1.6Hz, 4H), 6.71 (s, 2H), 4.10 (brs, 8H), 3.73 (br s, 8H), 3.60 (s, 8H); ^{13}C NMR (DMSO-d_6): δ 67.45, 68.72, 70.03, 106.29, 107.12, 132.85, 159.49, 166.93.

Anal. Calcd. for $C_{26}H_{32}O_{12}$: C, 58.21; H, 6.01. Found: 58.24; H, 6.04

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5-BENZYLOXYRESORCINOL, A MONOPROTECTED PHLOROGLUCINOL

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5-Benzyloxyresorcinol (**6**) is a key intermediate in our synthetic schemes directed toward di- and mono-functionalized *bis*(*m*-phenylene) crown ethers[1-7] and related cryptands. The previous one-step synthesis of 5-benzyloxyresorcinol (**6**) from phloroglucinol (**1**) gave only a 9% yield.[8] Although our attempts to improve this method failed, herein we report an alternative synthesis that affords an improved overall yield of the target compound.

Treatment of phloroglucinol (**1**) with two moles of benzoyl chloride produced a mixture of benzoates **2**, **3** and **4**. The monoester **4** was insoluble in $CHCl_3$ and hence could be easily removed from the mixture, since both **2** and **3** were soluble. Analysis of the soluble mixture *via* ^1H NMR spectroscopy revealed a 36:64 ratio of **2: 3**. Pure **3** was prepared as a reference material from pure **2**[9] by hydrolysis with Cs_2CO_3. It was also converted to the desired **6** (34% overall), but this route was less efficient than the one described here. The mixture of **2** and **3**, without further purification, was treated with NaH and one equivalent of benzyl bromide to give a mixture of **2** and **5**, which was hydrolyzed with aqueous methanolic KOH. Neutralization with acid, followed by removal of benzoic acid with saturated aqueous $NaHCO_3$ and removal of phloroglucinol (**1**) derived from **2** by washing with water afforded the desired 5-benzyloxyresorcinol (**6**) in 41% overall yield.

The application of 5-benzyloxyresorcinol (**6**) to the synthesis of monomeric macrocycles, cryptands and polymacrocycles is the subject of current research and will be reported elsewhere. We note that Büchi reported the dibenzyl ether and the monobenzenesulfonate of phloroglucinol.[10]