Desymmetrization of Disubstituted Aromatic Crown Ethers via Intramolecular Cannizzaro Reactions

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ARTICLE

Desymmetrization of Disubstituted Aromatic Crown Ethers via Intramolecular Cannizzaro Reactions

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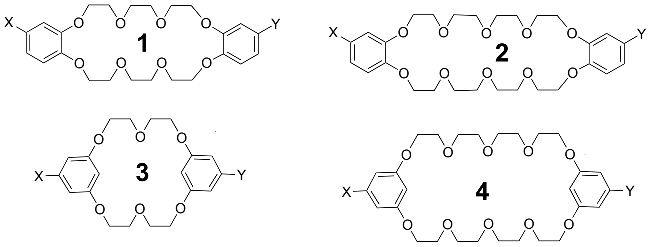
We report a high-yielding metal templated Cannizzaro reaction for converting symmetrical aromatic crown ether dialdehydes of various types [dibenzo and bis(*meta*-phenylene)] and sizes (20-32 atom rings) to acid-alcohol functionalized crown ethers in 70 – 98 % yields.

Since their discovery by Pedersen,[1] crown ethers have been employed as macrocyclic hosts for metal cations,[1,2] ammonium ions,[3] and N,N'-dialkyl-4,4'-bipyridinium salts (viologens).[4] In order to further the chemistry of crown ethers and incorporate them into more diverse and complex molecules, the incorporation of functional groups on the crown ethers is necessary. There are high-yielding methodologies for difunctional dibenzo crown ethers **1a**,[3d,5] **2a** [5] and reproducible, though less efficient, protocols for bis(*m*-phenylene) crown ethers **3a** [6] and **4a**;[7] from these diesters diols **1b**,[8] **2b** [5a] and **4b** [7] are available.



a. X = Y = $COOCH_3$ **b.** X = Y = CH_2OH **c.** X = Y = CHO

d. X = Y = COOH **e.** X =COOH, Y = CH_2OH

f. X = $COOCH_3$, Y = CH_2OH

However, the lack of unsymmetrical difunctional crown ethers reported in the literature is a testament to the often time consuming and inefficient methods of making them. Here we report a facile and high-yielding desymmetrization process to make unsymmetrical crown ethers from symmetrical derivatives resulting from the efficient crown syntheses noted above.

The Cannizzaro reaction, a diproportionation of an aldehyde to an alcohol and an acid,[9] is an ideal candidate for a desymmetrization process. Inspired by another intramolecular Cannizzaro reaction [10] based on earlier templation studies,[11] we sought to extend the utility of this reaction to crown ether systems

Previous studies established that crown ethers bind metal cations,[1,2] and from X-ray crystal structures it has been observed that crown ethers wrap around the cations,[2] and in the cases of dibenzo crown ethers, that the phenyl rings were spatially close to each other.[2c,12] A proper templating cation could force the crown into a conformation that keeps the two aldehyde groups in proximity of each other, which would allow the Cannizzaro reaction to take place through an intramolecular pathway.

We previously reported the syntheses of diols **1b**, **2b** and **4b** from the corresponding diesters.[5a,7,8] Here, bis(*m*-phenylene)-20-crown-6 (BMP20C6) diol **3b** was prepared by lithium aluminum hydride reduction of BMP20C6 diester **3a**. These four diols were readily oxidized to the corresponding dialdehydes **1c**, **2c**, **3c** and **4c** using pyridinium chlorochromate (PCC), all in >95% yield.

When aqueous 2M NaOH was used as the base with the DB30C10 dialdehyde **2c**, both the intermolecular (diol **2b** and diacid **2d**) and intramolecular (acid-alcohol **2e**) Cannizzaro products were observed in the electrospray ionization high-resolution mass spectrum (ESI HR MS; see ESI). The inability of NaOH to quantitatively template the intramolecular reaction may be due to the small size of the sodium cation in relation to the size of the crown, or differences between the conformation of the complex in the solution and crystalline states.

On this basis and prior reports [10] of its efficacy, we turned to use of barium as a templating ion. In the event by subjecting dialdehydes **1c, 2c**, **3c** and **4c** to refluxing aqueous 2M $Ba(OH)_2$ for 48 hours (**Scheme 1**) the unsymmetrical acid-alcohols **1e** and **2e** were each isolated in 97-98% yields and acid alcohols **3e** and **4e** in somewhat lower yields (70-77%) via the desired intramolecular pathway. The lower yields for the BMP acid-alcohols **3e** and **4e** were, at least in part, due to their small reaction scales. In the HR ESI MS of products **1e**, **2e** (**Figure 1**), **3e** and **4e** only the intramolecular Cannizzaro products were observed; the intermolecular Cannizzaro products (the diol and diacid) were not observed.

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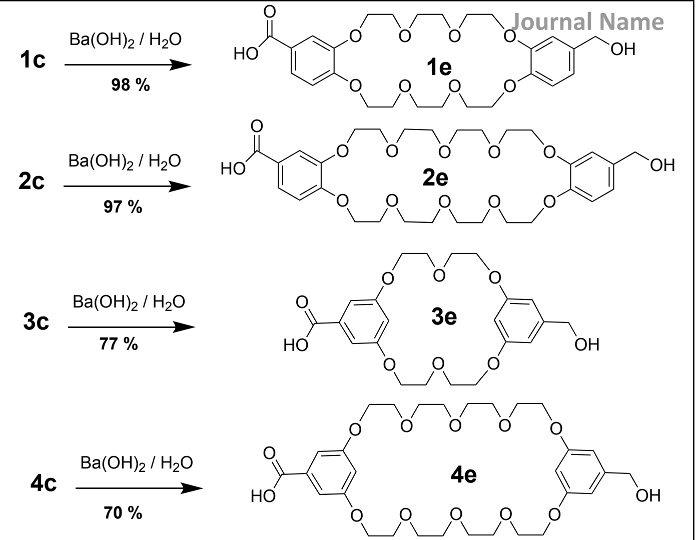
The association constant for the barium cation with DB30C10 (35 M^{-1} in H_2O @ 25 °C) is somewhat higher than that for sodium (13 M^{-1} in H_2O @ 25 °C).[12] Under these reaction conditions with dialdehyde concentrations of 3.6 mM the crown ethers are essentially completely (~99%) complexed with Ba^{+2}. Moreover, the larger size of the barium cation may limit the conformational freedom available to the crown ether, leading to the nearly quantitative conversion, whereas the inability of sodium to template the intramolecular reaction suggests that there is conformational freedom in the sodium complex which leads to intermolecular reaction products DB30C10 diol **1b** and diacid **1d**. The binding constants of Na^+ and Ba^{++} with dibenzo-24-crown-8 are the same within experimental error (12 M^{-1} in H_2O @ 25 °C).[12] It is likely that the binding constants for the bis(*m*-phenylene) crown ethers with Ba^{+2} are lower, hence the somewhat lower yields.

The unsymmetrical acid-alcohols **1e** and **3e** were converted to the ester-alcohol crown ethers **1f** and **3f** in quantitative yields by refluxing in acetonitrile containing DBU and methyl iodide. The products were confirmed by HR ESI MS and ^1H NMR.



Scheme 1. Conversion of crown ether dialdehydes **1c**, **2c**, **3c** and **4c** to the corresponding acid-alcohols **1e**, **2e**, **3e** and **4e** via Cannizzaro reactions using $Ba(OH)_2$.

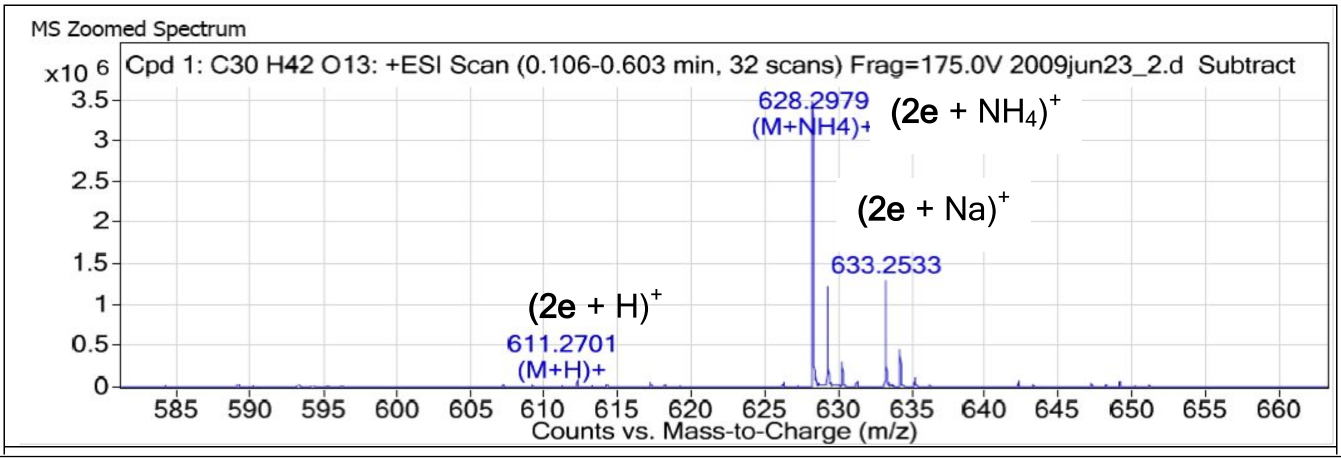
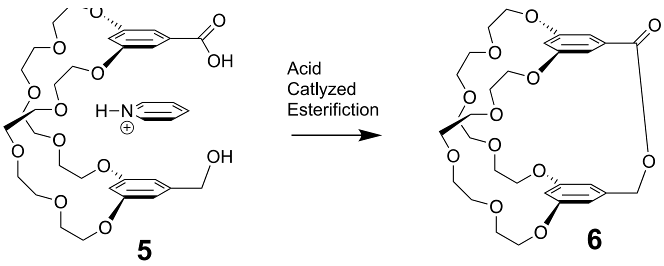


Figure 1. ESI HR MS of DB30C10 acid-alcohol product **2e** obtained using $Ba(OH)_2$ as the base and templating agent in the intramolecular Cannizzaro reaction of dialdehyde **2c**. Note the absence of starting dialdehyde **2c** [m/z 593.3 $(M + H)^+$], diol **2b** [m/z 614.3 and 619.3 $(M + NH_4)^+$]) and diacid **2d** [m/ 642.3 $(M + Na)^+$]), products that were formed when NaOH was used as the base.

In a somewhat surprising process, attempted oxidation of acid-alcohol **4e** with PCC led to the isolation of cryptand lactone **6** (HR ESI MS m/z 593.2607, calcd. for $C_{30}H_{41}O_{12}$ m/z 593.2598, error 2 ppm), which was prepared before in an unrelated manner.[7] We ascribe this to templation of **4e** by the pyridinium cation, forming intermediate **5**, as we have demonstrated in other useful syntheses of cryptands.[13]



Symmetrical crown ether dialdehydes of varying sizes and types were quantitatively converted to unsymmetrical acid-alcohol disubstituted crown ethers using aqueous $Ba(OH)_2$ as both a base and a templating agent for intramolecular Cannizzaro reactions. Use of the more common base NaOH led to a mixture of products formed by both intramolecular and intermolecular Cannizzaro pathways. The unsymmetrical bis(*m*-phenylene) acid-alcohol crowns **1e** and **3e** were converted to the ester alcohols **1f** and **3f**. Further transformations on these unsymmetrically substituted crown ethers are obviously possible, including polymerizations to polyesters.

EXPERIMENTAL

General

^1H NMR spectra were recorded on a 500 MHz EclipsePlus 500 JEOL spectrometer in $CDCl_3$ solution with TMS as an internal standard. High-resolution mass spectra were obtained on an Agilent LC-ESI-TOF at 70V. Melting points were determined on a

Mel-Temp II apparatus and are uncorrected. Crown ether diols **1b**,[8] **2b** [5a,14] and **4b** [7] were prepared according to the literature.

Bis(5-hydroxymethyl-1,3-phenylene)-20-crown-6 (3b). To a solution of bis(*m*-phenylene)-20-crown-6 diester **3a** [15] (0.32 g, 0.67 mmol) in dry 20 mL of THF was added $LiAlH_4$ (40 mg, 1.0 mmol). The suspension was stirred for 20 minutes, and water (10 mL) was added to quench remaining LAH. Aqueous NaOH (10 mL, 3M) was added and the mixture was filtered. The organic phase was collected, and the aqueous phase was washed 3x with CH_2Cl_2. The organic fractions were combined and dried over anhydrous Na_2SO_4, followed by removal of the solvent *in vacuo,* giving diol **3b** as a waxy colorless solid 0.26 g, 93%), mp 125-129 °C. ^1H NMR (500 MHz, DMSO-d_6) δ: 6.45 (d, *J* = 2 Hz, 4H), 6.35 (t, *J* = 2 Hz, 2H), 4.39 (s, 4H), 4.06 (t, *J* = 5 Hz, 8H), 3.76 (t, *J* = 5 Hz, 8H). ESI HR MS: *m/z* 858.3922, 100%, $[(\mathbf{2a})_2 + NH_4]^+$, calc. for $C_{44}H_{60}NO_{16}$ 858.3907, error 1.8 ppm; 859.3953, 51%, $[(\mathbf{2a})_2 + NH_4 +1]^+$, calc. for $C_{44}H_{60}NO_{16}$ 859.3940, error 1.5 ppm; 863.3487, 71%, $[(\mathbf{2a})_2 + Na]^+$, calc. for $C_{44}H_{56}NaO_{16}$ 863.3461, error 3.1 ppm; 864.3530, 36%, $[(\mathbf{2a})_2 + Na +1]^+$, calc. for $C_{44}H_{56}NaO_{16}$ 864.3495, error 4.1 ppm.

General Procedure for the Oxidation of Crown Ether Diols. To a solution of dibenzo-24-crown-8 diol **1b** (0.51 g, 1.0 mmol) in CH_2Cl_2 was added pyridinium chlorochromate (0.45g, 2.1 mmol). The mixture was allowed to stir at RT for 25 min and filtered. The filtrate was run through a neutral alumina plug, and the solvent was removed *in vacuo,* giving 4,4'-diformyldibenzo-24-crown-8 (**1c**) as a colorless solid (0.49 g, 98%), mp 133.8-135.4 °C (lit. [16] mp 134-136 °C). ^1H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 2H), 7.42 (dd, *J* = 8, 2 Hz, 1H), 7.36 (d, *J* = 2 Hz, 2H), 6.92 (d, *J* = 8 Hz, 1H), 4.24–4.15 (m, 8H), 3.98–3.81 (m, 16H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.8, 154.1, 149.0, 130.1, 126.7, 111.7, 110.8, 71.5, 71.4, 69.6, 69.5, 69.4, 69.2.

4,4'-Diformyldibenzo-30-crown-10 (2c): 97%, mp 122.3-123.7 °C (lit. [17] 123-124 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 2H), 7.43 (dd, *J* = 8, 2 Hz, 2H), 7.38 (d, *J* = 2 Hz, 2H), 6.94 (d, *J* = 8 Hz, 2H), 4.23 – 4.17 (m, 8H), 3.91 (dt, *J* = 9, 5 Hz, 8H), 3.78 (q, *J* = 5 Hz, 8H), 3.72 – 3.66 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.0, 154.3, 149.2, 130.3, 126.9, 112.2, 111.3, 71.1, 70.9, 69.7, 69.0.

Bis(5-formyl-1,3-phenylene)-20-crown-6 (3c): 98%, mp 150.5-153.0 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 9.83 (s, 2H), 6.97 (d, *J* = 8, 2 Hz, 4H), 6.77 (t, *J* = 2 Hz, 2H), 4.18 (m, 8H), 3.89 (m, 8H). ESI HR MS: *m/z* 417.1576, 13%, $[\mathbf{3c} + H]^+$, calc. for $C_{22}H_{25}O_8$ 417.1544, error 7.7 ppm; 434.1844, 100%, $[\mathbf{3c} + NH_4]^+$, calc. for $C_{22}H_{28}NO_8$ 434.1809, error 8.1 ppm; 435.1873, 23%, $[\mathbf{3c} + NH_4 + 1]^+$, calc. for $C_{22}H_{28}NO_8$ 435.1843, error 7.0 ppm; 439.1394, 36%, $[\mathbf{3c} + Na]^+$, calc. for $C_{22}H_{24}NaO_8$ 439.1363, error 7.1 ppm; 855.2864, 14%, $[(\mathbf{3c})_2 + Na]^+$, calc. for $C_{44}H_{48}NaO_{16}$ 855.2835, error 3.5 ppm; 856.2896, 6%, $[(\mathbf{3c}) + Na + 1]^+$, calc. for $C_{44}H_{48}NaO_{16}$ 856.2869, error 3.2 ppm.

Bis(5-formyl-1,3-phenylene)-32-crown-10 (4c): 97%, mp 92.6-95.9 °C (lit.[7] 92.3-95.8 °C).

Attempted Cannizzaro Desymmetrization of 2c with NaOH. To 250 mL of boiling aqueous 2 M NaOH was added DB30C10 dialdehyde **2c** (0.43 g, 0.73 mmol). The solution was refluxed under N_2 for 48 h and acidified with 1M HCl to pH <3. The mixture was extracted with CH_2Cl_2 5x and the combined organic fractions were washed with water 3x, dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo*, giving 0.40 g of a mixture of **2b**, **2d**, **2c**, and **2e** as a yellow solid. ESI HR MS: *m/z* 593.2632, 9% $[\mathbf{2c} + H]^+$, calc. for $C_{30}H_{41}O_{12}$ 593.2598, error 5.7 ppm; 614.3183, 31% $[\mathbf{2b} + NH_4]^+$, calc. for $C_{30}H_{48}O_{12}N$ 614.3177, error 1 ppm; 615.3212, 10% $[\mathbf{2b} + NH_4 + 1]^+$, calc. for $C_{30}H_{48}O_{12}N$ 615.3210, error 0.3 ppm; 619.2733, 11% $[\mathbf{2b} + Na]^+$, calc. for $C_{30}H_{44}O_{12}Na$ 619.2730, error 0.5 ppm; 628.2950, 100% $[\mathbf{2e} + NH_4]^+$, calc. for $C_{30}H_{46}O_{13}N$ 628.2969, error 3.0 ppm; 629.3009, 34% $[\mathbf{2e} + NH_4 +1]^+$, calc. for $C_{30}H_{46}O_{13}N$ 629.3003, error 1 ppm; 630.3036, 8%, $[\mathbf{2e} + NH_4 + 2]^+$, calc. for $C_{30}H_{46}O_{13}N$ 630.3036, error 0 ppm; 633.2532, 19%, $[\mathbf{2e} + Na]^+$, calc. for $C_{30}H_{42}O_{13}Na$ 633.2523, error 1 ppm; 634.2562, 6% $[\mathbf{2e} + Na +1]^+$, calc. for $C_{30}H_{42}O_{13}Na$ 634.2557, error 0.8 ppm; 642.2772, 5% $[\mathbf{2d} + NH_4]^+$, calc. for $C_{30}H_{40}O_{10}Na$ 642.2762, error 1.6 ppm.

General Procedure for the Cannizzaro Desymmetrization of Crown Dialdehydes with $Ba(OH)_2$, (Acid-alcohols 1e, 2e, 3e, and 4e). To 250 mL of boiling aqueous 2 M $Ba(OH)_2$ was added *cis*-DB24C8 dialdehyde **1c** (0.45 g, 0.89 mmol). The solution was refluxed under N_2 for 48 h, acidified with 1 M HCl to pH < 3, and extracted with CH_2Cl_2 5x. The combined organic fractions were washed with water 3x, dried over anhydrous Na_2SO_4, and desolvated *in vacuo*, yielding 4-carboxy-4'-hydroxymethyldibenzo-24-crown-8 (**1e**) as a colorless solid (0.46 g, 98%), mp 164.6-165.8 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 12.68 (s, 1H), 7.55 (t, *J* = 9 Hz, 1H), 7.45 (t, *J* = 9 Hz, 1H), 7.04 (t, *J* = 9 Hz, 1H), 6.91 (m, 2H), 6.82 (t, *J* = 9 Hz, 1H), 5.06 (s, 1H), 4.40 (s, 2H), 4.15-4.05 (m, 8H), 3.80-3.58 (m, 16H) . ESI HR MS: *m/z* 540.2442, 46% $[\mathbf{1e} + NH_4]^+$, calc. for $C_{26}H_{38}O_{11}N$ 540.2439, error 0.4 ppm; 541.2525, 15% $[\mathbf{1e} + NH_4 + 1]^+$, calc. for $C_{26}H_{38}O_{11}N$ 541.2473, error 9.6 ppm; 545.1999, 100% $[\mathbf{1e} + Na]^+$, calc. for $C_{26}H_{34}O_{11}Na$ 545.1993, error 1 ppm; 546.2030, 27% $[\mathbf{1e} + Na + 1]^+$, calc. for $C_{26}H_{34}O_{11}Na$ 546.2027, error 0.6 ppm.

4-Carboxy-4'-hydroxymethyldibenzo-30-crown-10 (**2e**): 97%, mp 123.3-125.4 °C. ^1H NMR (500 MHz, DMSO-d_6) 12.65 (s, 1H), 7.54 (dd, *J* = 9, 2 Hz, 1H), 7.43 (d, *J* = 2 Hz, 1H), 7.04 (d, *J* = 9 Hz, 1H), 6.90 (d, *J* = 2 Hz, 1H), 6.88, (d, *J* = 9 Hz, 1H), 6.81 (dd, *J* = 9, 2 Hz, 1H), 5.05 (t, *J* = 6 Hz, 1H), 4.39 (d, *J* = 6 Hz, 2H), 4.14 (t, *J* = 4 Hz, 2H), 4.10 (t, *J* = 4 Hz, 2H), 4.05 (m, 4H), 3.74 (m, 8H), 3.62 (m, 8H), 3.55 (m, 8H). ESI HR MS: *m/z* 628.2979, 100% $[\mathbf{2e} + NH_4]^+$, calc. for $C_{30}H_{46}O_{13}N$ 628.2964, error 2.4 ppm; 629.3013, 35%, $[\mathbf{2e} + NH_4 + 1]^+$, calc. for $C_{30}H_{46}O_{13}N$ 629.2997, error 2.5 ppm; 630.3039, 8% $[\mathbf{2e} + NH_4 + 2]^+$, calc. for $C_{30}H_{46}O_{13}N$ 630.3023, error 2.6 ppm; 633.2533, 38%, $[\mathbf{2e} + Na]^+$, calc. for $C_{30}H_{42}O_{13}Na$ 633.2518, error 2.5 ppm; 634.2566, 13%, $[\mathbf{2e} + Na + 1]^+$, calc. for $C_{30}H_{42}O_{13}Na$ 634.2552, error 2.3 ppm; 635.2594, 3%, $[\mathbf{2e} + Na + 2]^+$, calc. for $C_{30}H_{42}O_{13}Na$ 635.2577, error 2.6 ppm.

5-Carboxy-5'-hydroxymethylbis(1,3-phenylene)-20-crown-6 (**3e**): 77%, mp 162.3-164.0 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 13.01 (s, 1H), 7.03 (d, *J* = 3 Hz, 2H), 6.72 (t, *J* = 3Hz, 1H), 6.45 (d, *J* = 2 Hz, 2H), 6.36 (broad s, 1H), 6.30 (t, *J* = 2 Hz, 1H), 5.13 (q, *J* = 6 Hz, 2H), 4.39 (d, *J* = 5 Hz, 4H), 4.13 (t, *J* = 5 Hz, 4H), 4.05 (m, 8H). ESI HR MS: *m/z* 433.1486, 100%, $[\mathbf{3e} - H]^-$, calc. for $C_{22}H_{25}O_9$ 433.1504, error 4.2 ppm; 434.1518, 23%, $[\mathbf{3e} - H + 1]^-$, calc. for $C_{22}H_{25}O_9$ 434.1538, error 4.7 ppm; 435.1541, 5%, $[\mathbf{3e} - H + 2]^-$, calc. for $C_{22}H_{25}O_9$ 435.1562, error 5.0 ppm; 465.1741, 9%, $[\mathbf{3e} + OCH_3]^-$, calc. for $C_{23}H_{29}O_{10}$ 465.1766, error 5.5 ppm; 867.3071, 9%, $[(\mathbf{3e})_2 - H]^-$, calc. for $C_{44}H_{51}O_{18}$ 868.3081, error 5.1 ppm.

5-Carboxy-5'-hydroxymethylbis(1,3-phenylene)-32-crown-10 (**4e**): 70 %, mp 121.6-122.9 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 (s, 2H), 6.65 (s, 1H), 6.48 (s, 2H), 6.36 (s, 1H), 4.56 (s, 2H), 4.09 – 3.99 (m, 8H), 3.88 – 3.77 (m, 8H), 3.75 – 3.64 (m, 16H). ESI HR MS: *m/z* 628.2976, 100% $[\mathbf{4e} + NH_4]^+$, calc. for $C_{30}H_{46}O_{13}N$ 628.2964, error 1.9 ppm; 629.3008, 100% $[\mathbf{4e} + NH_4 + 1]^+$, calc. for $C_{30}H_{46}O_{13}N$ 629.2997, error 1.7 ppm; 630.3019, 9%, $[\mathbf{4e} + NH_4 + 2]^+$, calc. for $C_{30}H_{46}O_{13}N$ 630.3023, error -0.6 ppm; 633.2528, 82%, $[\mathbf{4e} + Na]^+$, calc. for $C_{30}H_{42}O_{13}Na$ 633.2518, error 1.6 ppm; 634.2562, 28%, [**4e** +

Na + 1]$^+$, calc. for $C_{30}H_{42}O_{13}Na$ 634.2552, error 1.6 ppm; 635.2581, 7%, [**4e** + Na + 2]$^+$, calc. for $C_{30}H_{42}O_{13}Na$ 635.2577, error 0.5 ppm.

General Procedure for Methyl Esters (1f). A solution of DB24C8 acid-alcohol **1e** (70 mg, 0.1 mmol) in acetonitrile (10 mL), DBU (1 mL, 6 mmol), and methyl iodide (0.5 mL, 8 mmol) was refluxed under N_2 for 16 h. The solvent and MeI were removed *in vacuo*, and the remaining material was partitioned between methylene chloride and water. The organic phase was washed with 1 M HCl solution 3x, water 3x, and dried over anhydrous Na_2SO_4 and concentrated. The crude product was dissolved in ethyl acetate and passed through a neutral alumina plug using ethyl acetate as the eluent to give 60 mg (84%) of 4-carbomethoxy-4'-hydroxymethyldibenzo-24-crown-8 (**1f**) as a white paste. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (td, *J* = 8, 2 Hz, 1H), 7.50 (dd *J* = 8, 2 Hz, 1H), 6.83 (m, 4H), 4.58 (s, 2H), 4.16 (m, 8H), 3.85 (m, 19H). HPLC ESI LR MS: *m/z* 554.18, 42%, [**1f** + NH_4]$^+$, calc. for $C_{27}H_{40}O_{12}N$ 554.26.

5-Carbomethoxy-5'-hydroxymethylbis(1,3-phenylene)-20-crown-6 (3f). Yield 82%, white paste. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 3 Hz, 2H), 6.77 (t, *J* = 3 Hz 1H), 6.50 (overlapping peaks, 3H), 4.36 (s, 2H), 4.25 – 4.08 (m, 16H). ESI HR MS: *m/z* 449.1766, 5%, [**3f** + H]$^+$, calc. for $C_{23}H_{29}O_9$ 449.1806, error 8.9 ppm; 466.2041, 100%, [**3f** + NH_4]$^+$, calc. for $C_{23}H_{32}O_9N$ 466.2072, error 6.6 ppm; 467.2069, 24%, [**3f** + NH_4 + 1]$^+$, calc. for $C_{23}H_{32}O_9N$ 467.2105, error 7.6 ppm; 468.2092, 5%, [**3f** + NH_4 + 2]$^+$, calc. for $C_{23}H_{32}O_9N$ 468.2129, error 7.9 ppm; 471.1589, 14%, [**3f** + Na]$^+$, calc. for $C_{23}H_{28}O_9Na$ 471.1626, error 7.6 ppm.

Conflicts of interest

There are no conflicts to declare.

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