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Multi-gram syntheses of four crown ethers using K^+ as template

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Multi-gram syntheses of four crown ethers using K⁺ as templating agent.

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ABSTRACT Dibenzo-30-crown-10 (**DB30C10**, **1c**), dibenzo-24-crown-8 (**DB24C8**, **1a**), 4-carbomethoxydibenzo-24crown-8 (**1b**) and a new crown ether, 4-carbomethoxydibenzo-30-crown-10 (**1d**), were synthesized by a simple, high yielding, three step method. Potassium ions from the highly soluble KPF₆ were employed to template the cyclization step, which resulted in very high isolated yields (80-90%).

Keywords: Crown ethers; templation; supramolecular chemistry; improved synthesis.

1. Introduction

DB30C10 and **DB24C8** are useful components in the construction of mechanically interlocked molecules such as pseudorotaxanes,¹ rotaxanes,^{1d,2} catenanes,^{2d,3} molecular shuttles,^{2b,4} and other molecular machines.^{2b,5} These crown ethers also have great utility as components in potentiometric sensors,⁶ in selective complexation and extraction of ions,⁷ in polymers,⁸ and other stimuli-responsive materials.⁹ **DB30C10** has anticoccidial activity.¹⁰ Functionalized **DB24C8** has been used extensively in more complicated supramolecular devices,^{1, 4-5, 11} supramolecular polymers,¹² and self-healing supramolecular gels.^{9b}

DB30C10 is commercially available at ~\$285/gram. Our research requires multiple grams of the material, which makes purchasing it cost prohibitive. A careful search of the literature revealed that most authors to date used the method published by Pederson in 1967 (**Scheme**

1).¹³ Pedersen did not isolate the **DB30C10** completely in his initial report, but claimed that his reaction mixture contained at least 6% of the desired crown.^{13a} To our knowledge, the highest cyclization yield that has been obtained using Pedersen's method to date is 25%.^{13b}

Scheme 1. DB30C10 synthesis as outlined by Pedersen.

None of the reports in the literature takes advantage of the fact that the final cyclization step in the syntheses of **DB30C10** and **DB24C8** can be templated with potassium ion, as was previously demonstrated in the syntheses of the *cis*-dicarbomethoxy derivatives.¹⁴ Association constants for complexation between **DB24C8** and potassium ion in acetonitrile as measured by conductivity and solubility average $7.6 (\pm 1.9) \times 10^3 \text{ M}^{-1}$.¹⁵ Similarly association constants for **DB30C10** with K^+ average $4.3 \times 10^4 \text{ M}^{-1}$.^{15d, 16} Given these association constants, we thought it reasonable to suppose that potassium would be an effective templation agent for formation of **DB24C8** and **DB30C10**.

K_2CO_3 is often employed as the base in such cyclizations; however, its solubility in the organic solvents normally used is quite low, minimizing the effect of templation. Furthermore, the synthesis that gave the highest yield for **DB30C10**^{13b} uses a benzyl protecting group to make the diphenolic intermediate shown in **Scheme 1**. Since this crown ether is symmetrical, the use of a protecting group is wholly unnecessary. We designed the synthetic route depicted in **Scheme 2** to take advantage of templation by potassium ion in the form of the highly organic-

soluble hexafluorophosphate and the symmetry of the desired **DB30C10**. Our route closely resembles that reported by Bruns et al. for the synthesis of 1,5-dinaphtho-38-crown-10 (28 or 33%, syringe pump addition),¹⁷ but with the exception that they did not use potassium ion templation in the form of KPF₆.

Knowing that the *cis*-dicarbomethoxy derivatives of both **DB30C10**^{14b} and **DB24C8**^{14a} can be templated with potassium, and that, unlike the dicarbomethoxy crown derivatives, the unsubstituted and monocarbomethoxy derivatives cannot form regio-isomers, we saw no reason that **DB24C8** and the 2-carbomethoxy derivatives of **DB30C10** and **DB24C8** could not be synthesized by the same route.

Indeed, this synthetic route requires only a single chromatographic step after the tosylation of **2a** and **2b**. The cyclization step essentially yields a single product: the crown ethers **1a-d**, which can easily be purified by washing or by ion exchange resin. In contrast, most untemplated cyclizations require two chromatography columns, or chromatography followed by recrystallization, to yield crown ethers of satisfactory purity.

Scheme 2. Improved syntheses of crown ethers.

2. Results and discussion

Known diols **2a**^{3a} and **2b**^{11c} were prepared via Williamson ether synthesis with the monotosylate of the appropriate glycol and catechol, in MeCN with K₂CO₃ as base. Tosylate **3a**^{3a} was formed by dropwise addition of tosyl chloride in DCM to a solution of diol **2a** in DCM at 0 °C. Likewise tosylate **3b**^{11a} was prepared by adding a solution of tosyl chloride in DCM to a cold solution of **2b**, trimethylamine and DMAP. **DB30C10** was prepared by Williamson ether synthesis of ditosylate **3b** with catechol. K₂CO₃ was used as the base, and 1.2 equivalents KPF₆ were added as a templating agent by simple mixing without the use of a syringe pump. The concentrations of the two components were 44 mM. After four days at reflux, the crude solution's ¹H NMR spectrum revealed no trace of the starting material and indicated almost exclusively the complex between **DB30C10** and K⁺ [as compared to the ¹H NMR of a sample of commercial **DB30C10** mixed with KPF₆ (Supplementary information, Figure S13)].

Removing the K⁺ from **DB30C10** proved unexpectedly challenging. When the diester derivative of **DB30C10** was prepared using KPF₆ as template, the K⁺ was removed by simply washing a DCM solution with water three times.^{14b} This was not the case with the parent **DB30C10**, as extensive water washing did not remove the K⁺. Eventually the template was removed by washing with pyridinium hydrochloride solution to displace the K⁺. The solution turned yellow, indicating the formation of a charge transfer complex between **DB30C10** and pyridinium hydrochloride. The solution was then washed with 10% (w/v) NaOH, which led to the deprotonation of the pyridinium salt and subsequent decomplexation. The resulting solid was reasonably pure, but had a slight brown color that was removed by treatment with

decolorizing carbon, followed by recrystallization from MeOH to yield **DB30C10** as a colorless solid in 86% yield. (The discoloration was only observed in one of the five batches prepared in this fashion. The recrystallization step was therefore omitted in the other batches).

The other crown ethers were prepared in a similar fashion. The carbomethoxy crown ethers **1b** and **1d** were washed with NaHCO₃, instead of 10% NaOH, to prevent hydrolysis of the esters. Both esters contained residual pyridine (¹H NMR), which was removed by drying under high vacuum or by passing the compound through a cation exchange resin.

The synthesis is amenable to multi-gram preparation of product, as up to 5 grams can be produced in a single reaction without undue difficulty, whereas multigram preparation is impractical for untemplated cyclizations. Note that, though syringe pump addition or high dilution is unnecessary, some attention should be paid to concentration. In more concentrated solutions (67 mM) some linear oligomers were formed. This led to a decrease in the yield of **1c** from 86% to 65%.

Since the templation of the reaction between ditosylate and catechol does not produce significant by-products (save for oligomers at high concentration), we tested the efficacy of the templation by attempting a one-pot preparation of the crown ethers. Typically this method produces very poor yields (6-15%), for example, the one pot preparation of bis(*m*-phenylene)-32-crown-10 and its derivatives.¹⁸ The one-pot procedure was attempted for **DB24C8**. Tri(ethylene glycol) ditosylate, catechol, KPF₆, and K₂CO₃ were combined and allowed to reflux in MeCN for several days. **DB24C8** was easily isolated from the mixture by column chromatography in 36% yield. Although a yield of 43% has been reported in the one-step

synthesis of **DB24C8**, that synthesis required much harsher conditions such as boiling DMSO and KOH.¹⁹

3. Conclusion

DB30C10, **DB24C8** and their corresponding 4-carbomethoxy derivatives were prepared by a facile, three step synthesis from relatively inexpensive starting materials using KPF₆ to template the cyclizations. The isolated yields of the final cyclization steps ranged from 80-90%. It is believed that the high yield and the lack of significant by-products is a result of the ethyleneoxy arms of the ditosylates (**3a** or **3b**) “wrapping around” the K⁺ ion. With the tosylated ends of the ethylene glycol arms positioned close together, the entropic barrier to ring closure by reaction with the catecholate anion is reduced. This arrangement favors ring closure over polymerization, the typical competing process in macrocyclizations of this kind. The method does not require special purification or syringe pump addition. The syntheses require only a single chromatographic purification of the ditosylates. Isolation of the crown ether is accomplished by washing or by treatment with ion exchange resin. This simple, economical, high yielding synthesis provides access to multiple grams of these valuable supramolecular building blocks.

4. Experimental

General: Compounds **2a**^{3a}, **2b**^{11c}, **3a**^{3a} and **3b**^{11a} were prepared according to literature procedures in yields of 88, 94, 62 and 71%, respectively. The diols were sufficiently pure to proceed, but the ditosylates were purified by column chromatography on silica (6:1 DCM:EtOAc). THF was dried by distillation over Na/benzophenone. DCM was dried by

distillation over CaH, and pyridine was dried by distillation over molecular sieves. All other chemicals were used as received. Melting points were measured with a Mel-Temp II device in capillary tubes and are uncorrected. ^1H , ^{19}F and ^{13}C NMR spectra were obtained at ambient temperature on JOEL Eclipse Plus 500 MHz, Varian Unity Plus or Varian MR 400 MHz spectrometers. ^1H NMR and ^{13}C spectra are corrected relative to residual solvent peaks. High-resolution mass spectra were obtained with an Agilent 6220 LCMS ESITOF spectrometer. Ion exchange was performed with Amberlite GC-120, strongly acid sulfonated cation exchange resin ($\text{RSO}^- \text{Na}^+$) 100-200 mesh. Column chromatography was performed with silica gel, 40-63 μm , 60 Å from Sorbent Technologies, or Flash Alumina-N from Agela Technologies.

Dibenzo-30-crown-10 (1c). Ditosylate **3b** (7.52 g, 9.75 mmol), catechol (7.07 g, 9.75 mmol) and KPF_6 (2.15 g, 11.7 mmol) were dissolved in MeCN (220 mL). N_2 (g) was bubbled through the solution for 20 min. The flask was wrapped in aluminium foil, and K_2CO_3 (8.08 g, 59 mmol) was added. The mixture was allowed to reflux under N_2 (g) for 4 days, allowed to cool to room temperature and evaporated under reduced pressure. The residue was partitioned between DCM and water. The DCM layer was washed with water 1x, pyridinium hydrochloride solution (1:1:1 pyridine: conc. HCl: water) (5x20 mL), 10% (w/v) NaOH (20 mL), and water (1x 20 mL). The organic layer was dried over Na_2SO_4 , filtered, and evaporated *in vacuo* to yield a white solid, (4.50 g, 86%), mp 102.0-103.6 °C; lit. mp 106.0 - 107.5 °C.^{13a} ^1H NMR (400 MHz, CDCl_3) δ 6.89 - 6.81 (m, 8H), 4.10 (t, J = 4 Hz, 8H), 3.82 (t, J = 4 Hz, 8H), 3.75-3.69 (m, 8H), 3.66-3.64 (m, 8H). ^{13}C NMR (101 MHz, CDCl_3) δ 149.1, 121.6, 114.6, 70.9, 70.7, 69.8, 69.2. ESI-TOF: $(\text{M}+\text{H})^+$ m/z 537.2691 (found), 537.2694 (calculated for $\text{C}_{28}\text{H}_{40}\text{O}_{10}$), error -0.5 ppm.

4-Carbomethoxydibenzo-30-crown-10 (1d). Ditosylate **3b** (1.30 g, 1.70 mmol), methyl 3,4-dihydroxybenzoate (0.28 g, 1.7 mmol) and KPF_6 (0.38 g, 2.1 mmol) were dissolved in MeCN (100 mL). The solution was degassed with N_2 (g) and the flask was wrapped in foil to exclude light. K_2CO_3 (0.96 g, 7.0 mmol) was added and the mixture was heated at reflux for 7 days, allowed to cool to room temperature and filtered to remove the solids. The solvent was removed by rotary evaporation. The residue was dissolved in DCM and washed with pyridinium hydrochloride (1:1:1 pyridine: conc. HCl: water) (12 x 15 mL), water (15 mL), NaHCO_3 (sat.) (4 x 15 mL), and water (1x 15 mL). The organic layer was dried over MgSO_4 , filtered, and the solvent was removed by rotary evaporation. The white solid still had some pyridinium peaks in the ^1H NMR spectrum. The solid was dissolved in acetone and passed through an ion exchange resin. The solvent was removed to yield a white solid (0.80 g, 80%), mp 76-78 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.64 (dd, J = 8, 2 Hz, 1H), 7.52 (d, J = 2 Hz, 1H), 6.88 (d, J = 2 Hz, 4H), 6.85 (d, J = 8 Hz, 1H), 4.19 (t, J = 4 Hz, 4H), 4.14 (t, J = 4 Hz, 4H), 3.92-3.86 (m, 11H), 3.80-3.75 (m, 8H), 3.70-3.66 (m, 8H). ^{13}C NMR (101 MHz, CDCl_3) δ 166.8, 152.9, 149.1, 148.3, 123.9, 122.9, 121.5, 114.7, 114.6, 112.4, 71.02, 70.98, 70.91, 70.7, 69.8, 69.6, 69.5, 69.18, 69.16, 69.15, 68.9, 51.9. ESI-TOF: $(\text{M}+\text{H})^+$ m/z 595.2753 (found), 595.2749 (calculated for $\text{C}_{30}\text{H}_{42}\text{O}_{12}$), error 0.6 ppm.

4-Carbomethoxydibenzo-24-crown-8 (1b). Ditosylate **3a** (2.40 g, 3.50 mmol), methyl 3,4-dihydroxybenzoate (0.59 g, 3.5 mmol) and KPF_6 (0.78 g, 4.2 mmol) were dissolved in MeCN (110 mL). The solution was degassed by bubbling N_2 (g) through it. The flask was wrapped in aluminium foil to exclude light, and K_2CO_3 (1.96 g, 14.0 mmol) was added. The mixture was heated at reflux under N_2 (g) for 5 days, allowed to cool to room temperature and the solids were filtered. The solvent was removed by rotary evaporation and the residue was dissolved in

DCM. The solution was washed with pyridinium hydrochloride (12 x 15 mL), water (15 mL), NaHCO₃ (sat.) (4 x 15 mL), and water (1 x 15 mL), dried over MgSO₄, filtered, and the solvent was removed by rotary evaporation to yield a white solid (1.61 g, 90%), mp 86.0-87.5 °C. Lit. yield 40% (12.5 g by pseudo-high dilution in 3.5 L of DMF using K₂CO₃ as base and syringe pump addition of the two reactants), mp 83-85 °C.²⁰ The analogous ethyl ester was reportedly prepared in 56% yield (2.6 g) by slow (12 h) addition of the ditosylate in 500 mL of MeCN to a mixture of K₂CO₃ and the catechol derivative and in 1 L of MeCN.^{11a} ¹H NMR (400 MHz, CDCl₃) δ 7.64 (dd, *J* = 8, 2 Hz, 1H), 7.51 (d, *J* = 2 Hz, 1H), 6.90-6.86 (m, 4H), 6.84 (d, *J* = 8 Hz, 2H), 4.21-4.17 (m, 4H), 4.16—4.13 (m, 4H), 3.95-3.90 (m, 8H), 3.87 (s, 3H), 3.84 (s, 4H), 3.83 (s, 4H). ¹³C NMR (101 MHz, CDCl₃) δ 166.8, 152.9, 148.95, 148.93, 148.3, 123.9, 122.9, 121.4, 114.3, 114.1, 112.0, 71.5, 71.4, 71.3, 69.95, 69.8, 69.6, 69.5, 69.4, 69.39, 69.32, 51.9. ESITOF: (M+H)⁺ *m/z* 507.2238 (found), 507.2225 (calculated for C₂₆H₃₄O₁₀), error 2.6 ppm.

Dibenzo-24-crown-8 (1a). Ditosylate **3a** (2.23 g, 3.2 mmol), catechol (0.36 g, 3.2 mmol) and KPF₆ (0.72 g, 3.9 mmol) were dissolved in MeCN (100 mL). Ar (g) was bubbled through the solution for 10 min. The flask was wrapped in aluminium foil to exclude light, and K₂CO₃ (1.78 g, 13 mmol) was added. The mixture was heated at reflux under Ar (g) for 3 days, allowed to cool to room temperature and the solids were filtered. The solvent was removed by rotary evaporation and the purple residue was partitioned between DCM and water. The organic layer was washed with 1:1:1 pyridine: HCl: H₂O (10 x 20 mL), water (1 x 20 mL), 10% (w/v) NaOH (3 x 20 mL) and water (1 x 20 mL). The purple solution turned bright red when it was washed with the pyridinium•HCl solution and back to purple again with the NaOH washings. The organic layer was dried over MgSO₄ and activated carbon was added. The solution was filtered through *Celite*®, filtered again and the solvent was removed. The residual pyridine was removed by drying under high vacuum to yield a white solid (1.27 g, 87%), mp 100-102 °C.

Lit. yield 43% (NaOH/DMSO), mp 102-103 °C.^{19,21} ¹H NMR (400 MHz CDCl₃, Figure S10) δ 6.88 (m, 8H), 4.15 (t, *J* = 4 Hz, 8H), 3.92 (t, *J* = 4 Hz, 8H), 3.83 (s, 8H). ¹³C NMR (101 MHz, CDCl₃) δ 149.1, 121.5, 114.2, 71.4, 70.1, 69.5 ESITOF: (M+H)⁺ *m/z* 449.2171 (found), 449.2174 (calculated for C₂₄H₃₂O₈), error 0.3 ppm.

One Step Synthesis of Dibenzo-24-crown-8. Catechol (1.01 g, 9.10 mmol), tri(ethylene glycol) ditosylate (4.16 g, 9.10 mmol) and KPF₆ (6.66 g, 36.0 mmol) were dissolved in MeCN (120 mL). N₂ (g) was bubbled through the solution for 20 min. The flask was wrapped in aluminium foil to exclude light, and K₂CO₃ (5.03 g, 36 mmol) was added. The mixture was heated at reflux under N₂ (g). After one week, the solution was allowed to cool to room temperature. The solvent was removed by rotary evaporation and the solid was partitioned between DCM and water (15 mL). The DCM layer was washed with water (3 x 15 mL), dried over Na₂SO₄, filtered, and the solvent was removed by rotary evaporation. The crude solid was purified by column chromatography (neutral alumina; 2:1 EtOAc:DCM, v:v). The fractions containing product were concentrated to yield a white solid (0.74 g, 36%), mp 100-102 °C; lit. mp 102-103 °C.^{19,21} ¹H NMR (500 MHz, CDCl₃) δ 7.01-6.96 (m, 4H), 4.24-4.20 (m, 4H), 3.80-3.76 (m, 4H), 3.73 (s, 4H). ¹³C NMR (101 MHz, CDCl₃) δ 150.1, 123.0, 118.1, 71.2, 70.0, 69.0.

ASSOCIATED CONTENT

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Author Contributions

The authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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