Tetrahedron 65 (2009) 2285–2289

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Regioselective synthesis of *syn* disubstituted dibenzo-30-crown-10 ethers

Piotr Piątek *, Aleksandra Litwin

Department of Chemistry, University of Warsaw, Pasteura 1, 02-093 Warsaw, Poland

ARTICLE INFO

Article history:
Received 4 November 2008
Received in revised form 17 December 2008
Accepted 9 January 2009
Available online 15 January 2009

Keywords:
Macrocycles
Crown compounds
Dibenzo-30-crown-10
Regioselectivity
Protecting groups

ABSTRACT

A practical and regioselective synthetic method for the synthesis of *syn* substituted dibenzo-30-crown-10 ethers is reported. This novel methodology is reported with the syntheses of dibenzo crown ethers bearing nitro, formyl and carbomethoxy groups. The synthesis of macrocyclization precursors was accomplished in three steps and featured an application of *para*-methoxybenzyl group (PMB) as protecting group of phenol moiety that is orthogonal to NO_2, CHO and COOMe groups. General non-high dilution macrocyclization conditions have been developed that allow for the effective preparation of substituted large crown ethers.

1. Introduction

The most recognizable member of crown ether family is unquestionably 18-crown-6 and its benzo and dibenzo counterparts. Their complexation properties are well documented and most commonly studied.[1] By comparison, comparatively less attention has been paid to crown ethers possessing large macrorings.[2] Those crown ethers display interesting properties that can be employed in variety of applications. Interestingly, very large crown ethers like dibenzo-24-crown-8 and dibenzo-30-crown-10 exhibit, similarly to dibenzo-18-crown-6, good selectivity for potassium cation.[3] This is a result of the ability of large, flexible crown ether to 'wrap around' the metal cation, effectively enclosing it almost entirely within an organic sheath. A similar binding mode is observed for the natural potassium ionophores valinomycin and nonactin.[4] Moreover, dibenzo-30-crown-10 encapsulates the flat bipyridinium derived herbicide diquat.[5] Furthermore, large crown ethers effectively form interlocked structures like: pseudorotaxanes,[6] rotaxanes,[7] polyrotaxanes[8] and canenanes.[9] However, for the construction of even more complex and functional supramolecular architectures substituted crown ethers are required.[10]

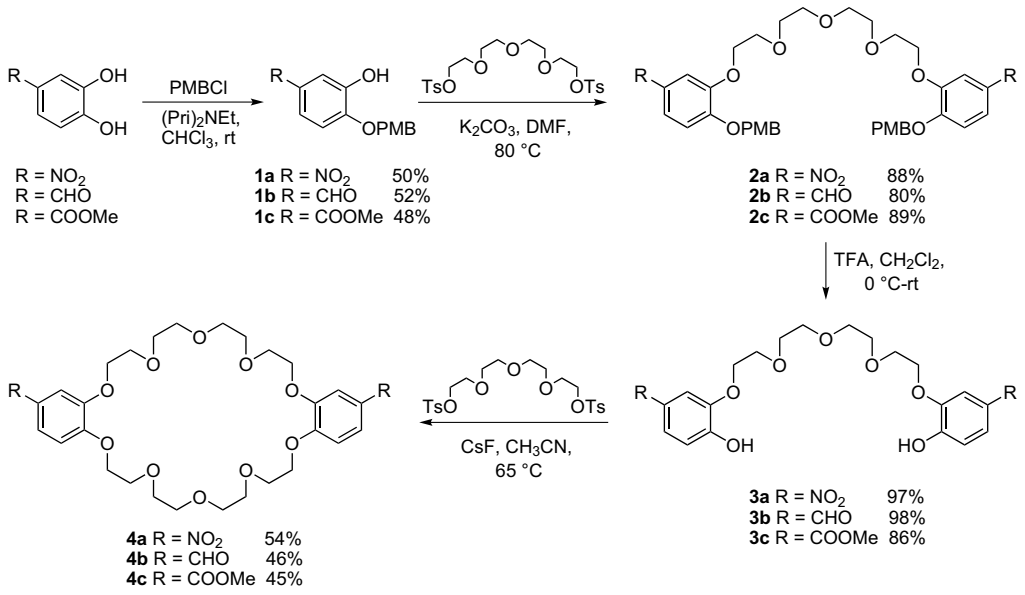
There are two main approaches for the synthesis of functionalized dibenzo crown ethers. One is based on electrophilic aromatic substitution of the catechol units of the parent macrocycle.[10a–d,11] Since this strategy requires only one step and many of dibenzo crown ethers are commercially available it is often applied for the synthesis of disubstituted macrocycles. Unfortunately this method leads to a mixtures of *syn* and *anti* regioisomers, which are, for large dibenzo crown ethers, inseparable. Nevertheless, a mixture of isomers is frequently used for the construction of supramolecular structures.[10a–d] This leads inevitably to complications since positional isomers of crown ethers possess different complexing and other physicochemical properties.

Another approach to disubstituted dibenzo crown ethers employed mono *O*-substituted-4-substituted catechols as starting materials for the regioselective synthesis of desired regioisomer of the macrocycle.[10f,12] Recently this method has been successfully used in the construction of *syn* and *anti* isomers of di(carbomethoxybenzo)-24-crown-6 and di(carbomethoxybenzo)-30-crown-10.[13,14]

Our interest in the preparation of substituted large crown ethers was stimulated by the observation that, in the 'wrap around' complex of dibenzo-30-crown-10 with a potassium ion, aromatic rings of the macrocycle are close to each other in near parallel alignment.[15] We envisioned that placing an anion binding group (i.e., amide, urea or thiourea) on those aromatic rings would create a molecular receptor that is able to bind simultaneously both cation and anion (salt). Thus dibenzo-30-crown-10 substituted with groups that are precursors of amine function are needed. In this paper we report a synthetic strategy, which allows for the efficient regioselective synthesis of *syn* disubstituted dibenzo-30-crown-10. The preparation of three different *syn* disubstituted dibenzo-30-crown-10 ethers bearing electron-withdrawing groups such as nitro, formyl and carbomethoxy is described.

* Corresponding author. Tel.: +48 22 822 0211x237; fax: +48 22 822 5996.
E-mail address: ppiatek@chem.uw.edu.pl (P. Piątek).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.01.039



2. Results and discussion

It is known that catechols possessing an EWG group at the 4-position could be *O*-alkylated predominantly at the 1-position.[16] This regioselectivity is believed to be dictated by the stabilization of the phenoxide ion in the position *para* to the EWG group. Using this information Stoddart et al. recently reported that in the reaction of triethyleneglycol bistosylate with 3,4-dihydroxybenzaldehyde only one pure *syn*-isomer of the triethyleneglycol linked catechols is formed.[10f] Macrocyclization of this product lead directly to *syn*-di(formylbenzo)-24-crown-8. Attracted by this very short synthetic pathway to substituted dibenzo crown ethers we reacted 4-nitrocatechol with tetraethyleneglycol bistosylate in the presence of K_2CO_3. Unfortunately, only 4-nitrobenzo-15-crown-5 was isolated from the reaction mixture.

Therefore, we turned our attention to the longer approach, which relied on the regioselective protection of one of hydroxyl group of 4-substituted catechol. This methodology has been previously applied by various research groups for the preparation of substituted crown ethers.[5,13,14] Those research groups employ benzyl group for the protection of 1-hydroxy group of catechol. Although for our purpose the benzyl group was not a suitable protecting group because for its deprotection, catalytic hydrogenolysis is required. Under those conditions nitro as well as formyl groups undergo reduction. Thus we sought an other protecting group that could be cleaved by a non-reductive method. The *para*-methoxybenzyl group (PMB) is a convenient alternative to the benzyl group that could be deprotected under a variety of non-reductive conditions.[17] Thus, 4-nitrocatechol was reacted with *para*-methoxybenzyl chloride in the presence of K_2CO_3 in actonitrile. Although, those conditions are most commonly employed in benzyl monoprotection of catechol derivatives, in our case a complicated mixture of isomeric monoprotected and diprotected products was formed. From this mixture 38% of pure crystalline **1a** was isolated. In order to increase the yield of mono-PMB product other reaction conditions were investigated. In particular, a variety of bases including: Na_2CO_3, $NaHCO_3$, Et_3N, $Pr^i{}_2NEt$, NaH, Bu^tOH in solvents like CH_3CN, DMF, CH_2Cl_2, THF have been tested. Unfortunately we found that none of the tested conditions allow for the synthesis of **1a** with yields much exceeded 50%. The procedure employing $Pr^i{}_2NEt$ as a base and CH_2Cl_2 as a solvent was selected for the synthesis of **1a** due to reasonable yield of desired compound and low yield of side products. The mono-PMB protected nitrocatechol **1a** was alkylated with tetraethyleneglycol bistosylate to give the diprotected acyclic polyether **2a** with a yield of 88%. The acid mediated PMB group deprotection readily afforded diphenol **3a**. With this product in hand we sought an efficient macrocyclization method. Two different approaches have been reported for the synthesis of dibenzo-30-crown-10 and its substituted derivatives.[18] The Stoddart group employed NaH in THF under non-high dilution conditions.[5] Whereas very recently a high dilution method for the preparation of di(carbomethoxybenzo)-30-crown-10 has been reported.[14] To avoid the high dilution method we screened numerous conditions and found that using CsF in acetonitrile allowed effective macrocyclization.[19] Thus diphenol **3a** was reacted with tetraethyleneglycol bistosylate in the presence of CsF to afford *syn*-di(nitrobenzo)-30-crown-10 ether in 54% yield. It is important to note that chromatographic purification is not required at any synthetic step leading to **4a**.

The analogous protocol was applied for the preparation of *syn*-di(formylbenzo)-30-crown-10 ether. Thus regioselective monoprotection of 4-formylcatechol afforded **1b** (52%).[20] The coupling of **1b** with tetraethyleneglycol bistosylate lead to diprotected compound **2b**. Removal of PMB groups under an acidic condition gave **3b** in nearly quantitative yield. In contrast, as reported in the literature, cleavage of benzyl groups from benzyl analogue of **3b** leads to the mixture of an aldehyde and alcohol.[13] Thus the PMB protective group is superior compared to the benzyl group and allows for the effective preparation of formyl groups containing precursors of dibenzo crown ethers. Finally the cyclization reaction of **3b** with tetraethyleneglycol bistosylate afforded *syn*-di(formylbenzo)-30-crown-10 ether **4b** (46%).

To compare the efficiency of our macrocyclization methodology with the high dilution technique we attempted to prepare *syn*-di(carbomethoxybenzo)-30-crown-10 the compound synthesized very recently by the Huang group.[14] Thus reaction of the 4-carbomethoxy catechol with PMBCl in the presence of $Pr^i{}_2NEt$ gave **1c**. Subsequent alkylation of free hydroxyl groups and removal of protective groups afforded diphenol **3c**. The macrocyclization of **3c** with tetraethyleneglycol bistosylate in the presence CsF in acetonitrile furnished di(carbomethoxybenzo)-30-crown-10 in a 45% yield. Although our macrocyclization method gave **4c** in a yield,

which is 10% lower than reported for high dilution conditions, it does not require elongated syringe pump reagent addition.

3. Conclusions

We have presented a simple synthetic method for the synthesis of *syn* disubstituted dibenzo-30-crown-10. The utility of this method was confirmed by the preparation of dibenzo-30-crown-10 substituted by nitro, formyl and carbomethoxy groups. We have demonstrated that application of PMB group for protection of phenol moiety allows for the synthesis of dibenzo-30-crown-10 derivatives bearing groups susceptible to reductive conditions. Moreover, we have successfully developed an effective non-high dilution protocol for the macrocyclization reaction. This methodology should be of general utility for the preparation of other substituted dibenzo crown ethers.

4. Experimental section

General methods: 4-nitrocatechol, 3,4-dihydroxybenzaldehyde and 3,4-dihydroxybenzoic acid were purchased from commercial sources and used as received. All other commercially available reagents were also used as received. Solvents were purified and dried prior to use following the guidelines of Perrin and Armarego.[21] Methyl 3,4-dihydroxybenzoate and tetraethyleneglycol bistosylate were prepared according to the literature.[13,22] All reactions were carried out under an argon atmosphere. Chromatographic purification of products was accomplished using column chromatography on Merck 60 silica gel 230–400 mesh. Thin layer chromatography (TLC) was done using Fluka silica gel matrix plates. The ^{1}H and ^{13}C NMR spectra were acquired with a Varian Unity Plus 200/50 MHz spectrometer. High resolution mass spectra (HRMS) were obtained on a Micromass Quattro LC spectrometer. Melting points were measured with a Kofler instrument and are uncorrected.

4.1. General method for the regioselective monoprotection of 4-substituted catechols

To a mixture of 4-substituted catechol (6.4 mmol), *N*,*N*-diisopropylethylamine (1.3 mL, 9.6 mmol, 1.5 equiv) and tetrabutylammonium iodide (0.36 g, 0.96 mmol, 0.15 equiv) in 60 mL of chloroform *para*-methoxybenzyl chloride (1.68 mL, 9.6 mmol 1.5 equiv) was added dropwise. The resulting mixture was stirred at room temperature for 2 days. Products were purified as described below.

*4.1.1. 2-(4-Methoxybenzyloxy)-4-nitrocatechol (**1a**)*

The reaction mixture was diluted with 40 mL of hexanes and filtered through short pad of silica gel (ϕ=85 mm, 3 cm). The silica gel was washed with CH_2Cl_2. The solvent was removed in vacuo to give the crude material, which was crystallized from EtOH to give the titled compound as yellow crystals (50%). Mp (EtOH)=136–138 °C; R_f (40% AcOEt/hexanes)=0.50; ^{1}H NMR ($CDCl_3$) 7.81–7.79 (m, 2H), 7.35 (d, *J*=8.8, 2H), 7.0–6.92 (m, 3H), 5.90 (s, 1H, –OH), 5.14 (s, 1H, $-CH_2-$), 3.83 (s, 1H, $-CH_3$); ^{13}C NMR ($CDCl_3$) 160.4, 151.2, 146.02, 142.0, 130.1, 117.0, 114.5, 111.0, 110.5, 71.7 ($-CH_2-$), 55.6 ($-CH_3$); HRMS (ESI): *m*/*z* calcd for $C_{14}H_{13}NO_5Na$: 298.0691; found: 298.0694 $[M+Na]^+$.

*4.1.2. 2-(4-Methoxybenzyloxy)-4-formylcatechol (**1b**)*

The solvent was removed in vacuo to give the crude material, which was purified by column chromatography (hexanes/CH_2Cl_2 1:4 then CH_2Cl_2) to give **1b** as a white solid (52%). Mp=124–127 °C; R_f (30% AcOEt/hexanes)=0.57; ^{1}H NMR ($CDCl_3$) 9.840 (s, 1H, –CHO), 7.45–7.34 (m, 4H), 7.05 (d, *J*=8.0, 1H), 6.97–6.92 (m, 2H), 5.78 (s, 1H, –OH), 5.13 (s, 2H, $-CH_2-$), 3.84 (s, 3H, $-OCH_3$).

*4.1.3. 2-(4-Methoxybenzyloxy)-4-methoxycarbonylcatechol (**1c**)*

The solvent was removed in vacuo to give the crude material, which was purified by column chromatography (hexanes/CH_2Cl_2 1:4 then CH_2Cl_2) to give **1c** as a white solid (48%). Mp=119–121 °C; R_f (40% AcOEt/hexanes)=0.44; ^{1}H NMR ($CDCl_3$) 7.61–7.56 (m, 2H), 7.36–7.32 (m, 2H), 6.96–6.90 (m, 3H), 5.79 (s, 1H, –OH), 5.07 (s, 2H, $-CH_2-$), 3.87 (s, 1H, $-OCH_3$), 3.82 (s, 1H, $-OCH_3'$); ^{13}C NMR ($CDCl_3$) 167.0 (C=O), 160.0, 149.9, 145.6, 129.9, 128.8, 127.8, 123.6, 122.9, 116.0, 114.4, 111.4, 71.1 ($-CH_2-$), 55.5 ($-CH_3$), 5.2 ($-COOCH_3$).

4.2. General method for the alkylation of monoprotected 4-substituted catechols

Monoprotected 4-substituted catechols **1a**–**c** (3–13.2 mmol) were dissolved in dry DMF (40–150 mL) in an oven-dried two neck round bottom flask equipped with a dropping funnel and a reflux condenser. To this solution, K_2CO_3 (9–39.6 mmol, 3 equiv) was added followed by the addition of a solution of tetraethyleneglycol bistosylate (1.5–6.6 mmol, 0.5 equiv) in dry DMF. The suspension was then stirred at 80 °C (oil bath temperature) overnight. DMF was removed in vacuo and the residue was dissolved in CH_2Cl_2 and washed with water. The aqueous layer was extracted twice witch CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through a cotton plug and concentrated. Details of further product purification are described below.

*4.2.1. Tetraethyleneglycol bis[2-(4-methoxybenzyloxy)-5-nitrobenzene] (**2a**)*

The crude product was purified by crystallization from hot CH_2Cl_2/Et_2O 1:1 to afford 88% of the title compound as a light-yellow solid. Mp=108–110 °C; R_f (50% AcOEt/hexanes)=0.26; ^{1}H NMR ($CDCl_3$) 7.85–7.77 (m, 4H), 7.34 (d, *J*=8.8, 4H), 6.95–6.88 (m, 6H), 5.13 (*s*, 4H, $-CH_2-$), 4.24–4.19 (m, 4H), 3.91–3.81 (m, 4H), 3.80 (s, 6H, $-OCH_3$), 3.71–3.67 (m, 4H), 3.65–3.56 (m, 4H); ^{13}C NMR ($CDCl_3$) 159.8, 154.4, 148.8, 141.6, 130.0, 129.3, 128.1, 127.9, 118.1, 114.2, 112.5, 109.0, 71.1 (2×$-CH_2-$), 70.9, 69.6, 69.4, 55.4 (2×$-OCH_3$). HRMS (ESI): *m*/*z* calcd for $C_{36}H_{40}N_2O_{13}Na$ 731.2428 found: 731.2424 $[M+Na]^+$.

*4.2.2. Tetraethyleneglycol bis[2-(4-methoxybenzyloxy)-5-formylbenzene] (**2b**)*

The crude material was purified by column chromatography (hexanes/AcOEt 1:1, then AcOEt) to give **2b** as an oil, which solidified upon standing (80%). R_f (80% AcOEt/hexanes)=0.22; ^{1}H NMR ($CDCl_3$) 9.81 (s, 2H, 2×–CHO), 7.42 (d, *J*=1.2, 2H), 7.39–7.33 (m, 6H), 7.0 (d, *J*=8.8, 2H), 6.91–6.87 (m, 4H), 5.12 (s, 4H, 2×$-CH_2-$), 4.20 (t, *J*=4.8, 4H), 3.87 (t, *J*=4.8, 4H), 3.70 (s, 6H, 2×$-OCH_3$), 3.71–3.70 (m, 4H), 3.68–3.60 (m, 4H); ^{13}C NMR ($CDCl_3$) 191.1 (2×–CHO), 159.7, 154.4, 149.6, 130.4, 129.1, 128.4, 126.7, 114.2, 113.3, 112.1, 71.1, 70.9, 69.7, 69.0, 55.5 (2×$-OCH_3$); HRMS (ESI): *m*/*z* calcd for $C_{38}H_{42}O_{11}Na$: 697.2625; found: 697.2618 $[M+Na]^+$.

*4.2.3. Tetraethyleneglycol bis[2-(4-methoxybenzyloxy)-5-carbomethoxybenzene] (**2c**)*

The crude material was purified by column chromatography (hexanes/AcOEt 1:1) to give **2c** as an oil, which solidified upon standing (89%). R_f (60% hexanes/AcOEt)=0.42; ^{1}H NMR ($CDCl_3$) 7.62 (dd, *J*=8.2, 1.8, 4H), 7.57 (d, *J*=1.8, 4H), 7.34 (d, *J*=8.8, 4H), 6.93–6.86 (m, 6H), 5.08 (s, 4H, 2×$-CH_2-$), 4.22–4.17 (m, 4H), 3.89–3.80 (m, 10H), 3.79 (s, 6H), 3.71–3.69 (m, 4H), 3.63–3.60 (m, 4H); ^{13}C NMR ($CDCl_3$) 167.0 (2×–C=O), 159.6, 152.9, 148.6, 129.2, 128.7, 124.0, 123.1, 114.9, 114.1, 113.4, 71.1, 70.8, 69.7, 69.0, 55.5 ($-OCH_3$), 52.0

(–$COOCH_3$). HRMS (ESI): *m*/*z* calcd for $C_{40}H_{46}O_{13}Na$: 757.2836; found: 757.2829 $[M+Na]^+$.

4.3. General method for the deprotection of monoprotected tetraethyleneglycol derivatives

To the solution of **2a–c** (1.2–5.2 mmol) in CH_2Cl_2 (3–10 mL) cooled to 4 °C trifluoroacetic acid (3–10 mL) was added. The cooling bath was removed and the reaction mixture was stirred for 1 h. The reaction mixture was then diluted with CH_2Cl_2 and water. The aqueous layer was neutralized with 1 M NaOH, and the organic phase was separated. The aqueous layer was extracted twice with CH_2Cl_2. All combined organic extracts were dried ($MgSO_4$), filtered and concentrated. The obtained residue was redissolved in hexanes/AcOEt 1:1 (40–100 mL) and filtered through short pad of silica gel. The filtrate was discharged. Next the silica gel was washed with acetone. The solvent was removed in vacuo to give diphenol of type **3**.

4.3.1. Tetraethyleneglycol bis(2-hydroxy-5-nitrobenzene) (**3a**)

Yellow solid. Yield 97%. Mp=81–82 °C; R_f (80% acetone/hexanes)=0.90; ^{1}H NMR ($CDCl_3$) 8.59 (br s, –OH), 7.87 (dd, *J*=8.2, 1.8, 2H), 7.79 (d, *J*=1.8, 2H), 6.93 (d, *J*=3.6, 2H), 4.26–4.25 (m, 4H), 3.91–3.89 (m, 4H), 3.77–3.72 (m, 8H); ^{13}C NMR ($CDCl_3$) 153.7, 145.9, 140.8, 119.8, 115.4, 110.0, 70.7, 70.4, 69.6, 69.2, 60.7; HRMS (ESI): *m*/*z* calcd for $C_{20}H_{24}N_2O_{11}Na$: 491.1278; found: 491.1282 $[M+Na]^+$.

4.3.2. Tetraethyleneglycol bis(2-hydroxy-5-formylbenzene) (**3b**)

White solid. Yield 98%. R_f(AcOEt)=0.25; ^{1}H NMR ($CDCl_3$) 9.79 (s, 2H, 2×–CHO), 8.44 (br s, 2H, 2×–OH), 7.44–7.40 (m, 4H), 7.0 (d, *J*=8.6, 2H), 4.27–4.23 (m, 4H), 3.92–3.88 (m, 4H), 3.76–3.69 (m, 8H); ^{13}C NMR ($CDCl_3$) 191.0 (2×–CHO), 153.6, 146.9, 130.2, 128.2, 115.9, 111.5, 70.4, 70.2, 69.3, 68.2; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{26}O_9Na$: 457.1475; found: 457.1475 $[M+Na]^+$.

4.3.3. Tetraethyleneglycol bis(2-hydroxy-5-carbomethoxybenzene) (**3c**)

White solid. Yield 86%. Mp 64–66 °C (lit[14] 62–63 °C); R_f (60% AcOEt/hexanes)=0.33; ^{1}H NMR ($CDCl_3$) 8.2 (br s, –OH), 7.58 (dd, *J*=8.2, 1.8, 2H, 2×H[5]), 7.49 (d, *J*=1.8, 2H), 6.85 (d, *J*=8.2, 2H), 4.19–4.14 (m, 4H), 3.84–3.79 (m, 4H), 3.82 (s, 6H, –OCH_3), 3.66–3.3.65 (m, 8H); ^{13}C NMR ($CDCl_3$) 167.1 (2×–C=O), 151.9, 145.9, 125.2, 121.8, 115.6, 115.2, 70.5, 70.33, 69.4, 68.9, 52.1 (2×–OCH_3).

4.4. General method for the crown ether formation

Diphenols **3a–c** (0.85–3.5 mmol) were dissolved in dry acetonitrile (50–150 mL) in an oven-dried two neck round bottom flask equipped with a dropping funnel and a reflux condenser. To this solution CsF (3.4–14 mmol, 4 equiv) was added followed by the addition of a solution of tetraethyleneglycol bistosylate (0.85–3.5 mmol, 1 equiv) in dry acetonitrile. The suspension was then stirred at 65 °C (oil bath temperature) for 3 days. The solution was allowed to cool to room temperature and water was added to dissolve any solids. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 and washed with water and saturated sodium bicarbonate. The organic layer was dried over $MgSO_4$, filtered through a cotton plug and concentrated. Details of further products purification are described below.

4.4.1. syn-Di(nitrobenzo)-30-crown-10 ether (**4a**)

The crude product was purified by crystallization from hot AcOEt to afford **4a** as a light-yellow solid. Yield 54%. Mp=119–123 °C; R_f (80% acetone/hexanes)=0.70; ^{1}H NMR ($CDCl_3$) 7.84–7.80 (m, 2H), 7.70–7.68 (m, 2H), 6.84 (dd, *J*=8.9, 1.2, 2H), 4.02–4.14 (m, 8H,), 3.91–3.85 (m, 8H), 3.75–3.64 (m, 16H); ^{13}C NMR ($CDCl_3$) 154.5, 148.6, 142.1, 118.2, 111.7, 108.7, 71.2, 70.9, 69.5, 68.0; HRMS (ESI): *m*/*z* calcd for $C_{28}H_{38}N_2O_{14}Na$: 649.2221; found: 649.2214 $[M+Na]^+$.

4.4.2. syn-Di(formylbenzo)-30-crown-10 ether (**4b**)

The crude material was purified by column chromatography (acetone/hexanes/1:1, then 7:3) to give a white solid, which was further purified by crystallization from EtOH to afford **4b** in 46% yield. Mp 123–124 °C; R_f (80% acetone/hexanes)=0.49; ^{1}H NMR ($CDCl_3$) 9.82 (s, 2H, CHO), 7.43 (dd, *J*=7.8, 1.8, 2H), 7.37 (d, *J*=1.8, 2H), 6.94 (d, *J*=8.0, 2H), 4.24–4.17 (m, 8H), 3.94–3.88 (m, 8H), 3.81–3.67 (m, 16H). ^{13}C NMR ($CDCl_3$) 191.0, 154.4, 149.3, 130.3, 126.9, 112.2, 111.4, 71.2, 71.1, 70.8, 69.6, 69.5, 69.2, 69.1. HRMS (ESI): *m*/*z* calcd for $C_{30}H_{40}O_{12}Na$: 615.2417; found: 615.2415 $[M+Na]^+$.

4.4.3. syn-Di(carbomethoxybenzo)-30-crown-10 ether (**4c**)

The crude material was purified by column chromatography (CH_2Cl_2 then 2% MeOH/CH_2Cl_2) to give a white solid, which was further purified by crystallization from EtOH to afford **4c** in 45% yield. Mp=114–115 °C; R_f (6% MeOH/CH_2Cl_2)=0.32; ^{1}H NMR ($CDCl_3$) 7.64 (dd, *J*=8.2, 2.0, 2H), 7.52 (d, *J*=2.0, 2H), 6.85 (d, *J*=8.6, 2H), 4.21–4.16 (m, 8H), 3.92–3.78 (m, 14H), 3.79–3.76 (m, 8H), 3.71–3.69 (m, 8H); ^{13}C NMR ($CDCl_3$) 167.0 (2×–C=O), 153.0, 148.4, 124.1, 123.1, 114.6, 112.4, 71.2, 71.0, 70.9, 69.8, 69.6, 69.2, 69.0, 52.1 (–OCH_3); HRMS (ESI): *m*/*z* calcd for $C_{32}H_{44}O_{14}Na$: 675.2629; found: 675.2237 $[M+Na]^+$.

Acknowledgements

Financial support from The State Committee for Scientific Research (project T09A-012-030) is gratefully acknowledged.

References and notes

1. (a) Izatt, R. M.; Bradshaw, J. S.; Nielsen, S.; Lamb, J. D.; Christensen, J. J. *Chem. Rev.* **1985**, *85*, 271–339; (b) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721–2085; (c) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1995**, *95*, 2529–2586.
2. Buschmann, H.-J.; Wego, A.; Schollmer, E. *Inorg. Chem. Commun.* **2001**, *4*, 9–11.
3. Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; John Wiley & Sons: Chichester, UK, 2000; pp 118–119.
4. Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; John Wiley & Sons: Chichester, UK, 2000; pp 38–42.
5. (a) Colquhoun, H. M.; Stoddart, J. F.; Williams, D. J.; Wolstenholme, J. B.; Zarzycki, R. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1051–1053; (b) Colquhoun, H. M.; Goodings, E. P.; Maud, J. M.; Stoddart, J. F.; Wolstenholme, J. B.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 2* **1985**, 607–625.
6. (a) Orda-Zgadzaj, M.; Abraham, M. *Tetrahedron* **2008**, *64*, 2669–2676; (b) Castillo, D.; Astudillo, P.; Mares, J.; Gonzalez, F. J.; Vela, A.; Tiburcio, J. *Org. Biomol. Chem.* **2007**, *5*, 2252–2256; (c) Ashton, P. R.; Glink, P. T.; Schiavo, C.; Stoddart, J. F.; Chrystal, E. J. T.; Menzer, S.; Williams, D. J.; Tasker, P. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1869–1871.
7. For selected examples, see: (a) Hirose, K.; Ishibashi, K.; Shiba, Y.; Doi, Y.; Tobe, Y. *Chem.—Eur. J.* **2008**, *14*, 5803–5811; (b) Li, S.; Liu, M.; Zhang, J.; Zheng, B.; Zhang, C.; Wen, X.; Li, N.; Huang, F. *Org. Biomol. Chem.* **2008**, *6*, 2103–2107; (c) Badjić, J. D.; Balzani, V.; Credi, A.; Lowe, J. N.; Silvi, S.; Stoddart, J. F. *Chem.—Eur. J.* **2004**, *10*, 1926–1935; (d) Orita, A.; Okano, J.; Tawa, Y.; Jiang, L.; Otera, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3724–3728; (e) Tokunaga, Y.; Akasaka, K.; Hisada, K.; Shimomura, Y.; Kakuchi, S. *Chem. Commun.* **2003**, 2250–2251; (f) Nikitin, K.; Long, B.; Fitzmmaurice, D. *Chem. Commun.* **2003**, 282–283; (g) Takata, T.; Kawasaki, H.; Kihara, N.; Furusho, Y. *Macromolecules* **2001**, *34*, 5449–5456; (h) Zehnder, D. W., II; Smithrud, D. B. *Org. Lett.* **2001**, *3*, 2485–2487.
8. (a) Chiu, S.-H.; Rowan, S. J.; Cantrill, S. J.; Ridvan, L.; Ashton, P. R.; Garrell, R. L.; Stoddart, J. F. *Tetrahedron* **2002**, *58*, 807–814; (b) Cao, J.; Fyfe, M. C. T.; Stoddart, J. F.; Cousins, G. R. L.; Glink, P. T. *J. Org. Chem.* **2000**, *65*, 1937–1946; (c) Gong, C.; Gibson, H. W. *Macromolecules* **1997**, *30*, 8524–8525; (d) Shen, Y. X.; Gibson, H. W. *Macromolecules* **1992**, *25*, 2058–2059.
9. For selected examples, see: (a) Tomcsi, M. R.; Stoddart, J. F. *J. Org. Chem.* **2007**, *72*, 9335–9338; (b) Halterman, R. L.; Pan, X.; Martyn, D. E.; Moore, J. L.; Long, A. T. *J. Org. Chem.* **2007**, *72*, 6454–6458; (c) Gibson, H. W.; Nagvekar, D. S.; Yamaguchi, N.; Bhattacharjee, S.; Wang, H.; Vergne, M. J.; Hercules, D. M. *Macromolecules* **2004**, *37*, 7514–7529; (d) D'Acerno, C.; Doddi, G.; Ercolani, G.; Mencarelli, P. *Chem.—Eur. J.* **2000**, *6*, 3540–3546; (e) Ashton, P. R.; Huff, J.; Menzer, S.; Parsons, I. W.; Preece, J. A.; Stoddart, J. F.; Tolley, M. S.; White, A. J. P.; Williams, D. J. *Chem.—Eur. J.* **1996**, *2*, 31–44.
10. (a) Smukste, I.; Smithrud, D. B. *J. Org. Chem.* **2003**, *68*, 2547–2558; (b) Sun, Q.; Wang, H.; Yang, C.; Li, Y. *J. Mater. Chem.* **2003**, *13*, 800–806; (c) Smukste, I.;

House, B. E.; Smithrud, D. B. *J. Org. Chem.* **2003**, *68*, 2559–2571; (d) Jung, J. H.; Kobayashi, H.; Masuda, M.; Shimizu, T.; Shinkai, S. *J. Am. Chem. Soc.* **2001**, *123*, 8785–8789; (e) Rowan, S. J.; Stoddart, J. F. *Polym. Adv. Technol.* **2002**, *13*, 777–787; (f) Elizarov, A. M.; Chang, T.; Chiu, S.-H.; Stoddart, J. F. *Org. Lett.* **2002**, *4*, 3565–3568; (g) Duggan, S. A.; Fallon, G.; Langford, S. J.; Lau, V.-L.; Satchell, J. F.; Paddon-Row, M. N. *J. Org. Chem.* **2001**, *66*, 4419–4426; (h) Ashton, P. R.; Baxter, I.; Cantrill, S. J.; Fyfe, M. C. T.; Glink, P. T.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1294–1297.

11. (a) Takashi, S.; Toshikazu, T. *Tetrahedron Lett.* **2007**, *47*, 2797–2801; (b) Deetz, M. J.; Shang, M.; Smith, B. D. *J. Am. Chem. Soc.* **2000**, *122*, 6201–6207; (c) Stott, P. E.; Bradshaw, J. S.; Parish, W. W.; Cooper, J. W. *J. Org. Chem.* **1980**, *45*, 4716–4720; (d) Barboiu, M.; Hovnanian, N.; Luca, C.; Popescu, G.; Cot, L. *Eur. J. Org. Chem.* **1998**, *8*, 1705–1708; (e) Barboiu, M.; Popescu, G.; Barboiu, C.; Supuran, C. T.; Luca, C. *Liebigs Ann.* **1996**, *6*, 959–963; (f) Xu, X.-H.; Fu, X.-G.; Wu, L.-Z.; Chen, B.; Zhang, L.-P.; Tung, C.-H.; Ji, H.-F.; Schanze, K. S.; Zhang, R.-Q. *Chem.—Eur. J.* **2006**, *12*, 5238–5245; (g) Chuit, C.; Corriu, R. J. P.; Dubois, G.; Reyé, C. *Chem. Commun.* **1999**, 723–724.
12. (a) Kohnke, F. H.; Stoddart, J. F.; Allwood, B. L.; Williams, D. J. *Tetrahedron Lett.* **1985**, *26*, 1681–1684; (b) Bourgeois, J.-P.; Echegoyen, L.; Fibboli, M.; Pretsch, E.; Diederich, F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2118–2121; (c) Bourgeois, J.-P.; Seiler, P.; Fibbioli, M.; Pretsch, E.; Diederich, F.; Echegoyen, L. *Helv. Chim. Acta* **1999**, *82*, 1572–1595.
13. Gibson, H. W.; Wang, H.; Bonrad, K.; Jones, J. W.; Slebodnick, C.; Zackharov, L. N.; Rheingold, A. L.; Habenicht, B.; Lobue, P.; Ratliff, A. E. *Org. Biomol. Chem.* **2005**, *3*, 2114–2121.
14. He, C.; Shi, Z.; Zhou, Q.; Li, S.; Li, N.; Huang, F. *J. Org. Chem.* **2008**, *73*, 5872–5880.
15. Bush, M. A.; Truter, M. R. *J. Chem. Soc., Perkin Trans. 2* **1972**, 345–350.
16. Reitz, A.; Avery, M. A.; Verlander, M. S.; Goodman, M. *J. Org. Chem.* **1981**, *46* 4859–4863.
17. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, NY, 1999; p 269.
18. Shortly before the submission of the present work, a report describing the very efficient, potassium ion templated, synthesis of *syn* di(carbomethoxybenzo)-30-crown-10 ether appeared: Pederson, A. M.-P.; Ward, E. M.; Schoonover, D. V.; Slebodnick, C.; Gibson, H. W. *J. Org. Chem.* **2008**, *73*, 9094–9101.
19. The benefit of employing CsF as a base in macrocyclization reactions is well documented: (a) Blesa, M.-J.; Zhao, B.-T.; Allain, M.; Le Derf, F.; Sallé, M. *Chem.—Eur. J.* **2006**, *12*, 1906–1914; (b) Martin, V. V.; Rothe, A.; Gee, K. R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1851–1855; (c) Kenmoku, S.; Urano, Y.; Kanda, K.; Kojima, H.; Kikuchi, K.; Nagano, T. *Tetrahedron* **2004**, *60*, 11067–11073; (d) Wasikiewicz, W.; Ślaski, M.; Rokicki, G.; Böhmer, V.; Schmidt, C.; Paulus, E. F. *New J. Chem.* **2001**, *25*, 581–587; (e) Stephan, H.; Gloe, K.; Paulus, E. F.; Saadioui, M.; Bohmer, V. *Org. Lett.* **2000**, *2*, 839–841; (f) Murashima, T.; Uchihara, Y.; Wakamori, N.; Uno, H.; Ogawa, T.; Ono, N. *Tetrahedron Lett.* **1996**, *37*, 3133–3136; (g) Pappalardo, S.; Parisi, M. F. *J. Org. Chem.* **1996**, *61*, 8724–8725; (h) Vichet, A.; Patellis, A.-M.; Galy, J.-P.; Galy, A.-M.; Barbe, J.; Elguero, J. *J. Org. Chem.* **1994**, *59*, 5156–5161; (i) De Boer, J. A. A.; Uiterwijk, J. W. H. M.; Geevers, J.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1983**, *48*, 4821–4830; (j) van der Leij, M.; Oosterink, H. J.; Hall, R. H.; Reinhoudt, D. N. *Tetrahedron* **1981**, *37*, 3661–3666.
20. A more efficient method for the preparation of **1b** has been reported: Plourde, G. L.; Spaetzel, R. R. *Molecules* **2002**, *7*, 697–705. Although in our hands this method lead to the mixture of monoprotected products, from which ~45% of **1b** was isolated by tedious column chromatography.
21. Perrin, D. D.; Armarego, W. L. F. *Purificaion of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford, 1996.
22. Chen, Y.; Baker, G. L. *J. Org. Chem.* **1999**, *64*, 6870–6873.