A NOVEL SYNTHESIS OF 2'-HYDROXY-1',3'-XYLYL CROWN ETHERS

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Abstract—Six novel 2' - hydroxy - 1',3' - xylyl crown ethers (8a-e and 13)[1] have been synthesized utilizing the allyl group to protect the OH function during the cyclization reaction. The macrocycles 6a-e were formed in yields of 26 to 52%, by intermolecular reaction of 4 - chloro - 2,6 - bis(bromomethyl) - 1 - (2 - propenyloxy)benzene (5) with polyethylene glycols; 6a was also obtained by an intramolecular cyclization reaction of monotosylate 14.

A 30-membered ring with a 2' - hydroxy - 1',3' - xylyl sub-unit was obtained in 87% yield by reaction of ditosylate 9 with bis [2 - (o - hydroxyphenoxy)ethyl]ether (11) in the presence of cesium fluoride. The synthesis of crown ethers with a 2' - hydroxy - 1',3' - xylyl sub-unit (1c-e, H for CH₃) by demethylation of the corresponding 2'-methoxy crown ethers 1c-e with lithium iodide were unsuccessful; it would appear that the demethylation reaction is restricted to 15- and 18-membered rings. One of the 2' - hydroxy - 1',3' - xylyl crown ethers 8d forms a crystalline 1:1-complex with water.

Proton transfer reactions in crown ether complexes have not been studied in detail. A complex of a chiral 2,2' - bis(carboxymethoxymethyl) - 1,1' - binapthyl crown ether with an amino acid in which one of the acid groups donates a proton to the amino group of the amino acid[3] and a crystalline complex of 2' - carboxy - 1',3' - xylyl - 18 - crown - 5 and t-butylamine[4,5] have been described. The complexation of 5' - nitro - 2' - hydroxy - 1',3' - xylyl crown ethers and ammonia[6] might also involve a proton transfer process.

In relation with our work on the complexation of urea[7] we are currently investigating proton transfer reactions in complexes of crown ethers with neutral molecules. For this work crown ethers of various ringsizes with intra-annularly placed acid groups are required.† Since the 1',3'-xylyl sub-unit provides the possibility of various substituents at the 2'-position in such a way that they point towards the crown ether cavity, we decided to investigate preparative routes to such crown ethers with OH functions at the 2'-position.

The preparation of several crown ethers with 1',3' - xylyl subunits and with additional functional groups either at the intraannular 2'-position or at the more remote 4'- or 5'-position have been described[4,10–13] and the mode of substitution has been shown to effect the complexing properties with alkali metal and ammonium salts.[4,11,14] Substitution at the 2'-position generally decreases the stability of the complexes with ammonium salts and this has been attributed to crowding of the crown ether cavity.[4,10] Substituents at the 5'-position have a considerable effect on complexation showing that the aryl ring is involved in this process.[11]

The preparation of 2' - hydroxy - 1',3' - xylyl crown ethers has been reported previously by two groups. In both cases the major problem in this synthesis was to find a suitable protecting group for the OH function that should be stable under the strongly basic conditions of the Williamson ether synthesis and that could be

removed selectively under conditions which do not cleave the benzylic ether bonds. Koenig et al.[15] reported a synthesis of 5' - methyl - 2' - hydroxy - 1',3' - xylyl crown ethers in nine steps from p-cresol utilizing the methoxymethyl group for the protection of the phenolic OH group. In their synthesis of 2' - hydroxy - 1',3' - xylyl - 15 - crown - 4 and 18 - crown - 5 (1a and 1b, H for CH₃) McKervey and Mulholland[6] protected the OH group by methylation and after the Williamson ether synthesis the selective cleavage of the methyl aryl ether bond was performed with anhydrous lithium iodide in pyridine at 100°. Under these conditions the benzylic ether bonds were found to be stable.

RESULTS AND DISCUSSION

To extend the Koenig multistep synthesis to a whole series of crown ethers was obviously not attractive and at the start of our work McKervey and Mulhollands method appeared to be suitable for the synthesis of crown ethers with ringsizes of 24 to 30 atoms. Therefore we prepared the crown ethers 1b-1e in yields of 27-71% by the reaction of 2,6 - bis(bromomethyl)anisole with tetra-, penta-, hexa- and heptaethylene glycol. However demethylation of 1c-1e with anhydrous lithium iodide in pyridine at 100° could not be realized under similar conditions to those reported for 1a and 1b.[6] Other methods that have been used for the cleavage of the methyl aryl ether bond similarly failed.[16] The different reactivities of the 15- and 18-membered rings 1a and 1b on one hand and the larger crown ethers 1c-1e on the other is probably due to the favourable "intramolecular" crown ether catalysis proposed by McKervey and Mulholland[6] for the smaller rings.
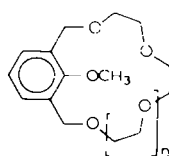
1a, n = 1
1b, n = 2
1c, n = 3
1d, n = 4
1e, n = 5

Since complexation of lithium salt usually decreases strongly with increasing ringsize[14] and since 2,6-dimethylanisole itself does not react with lithium iodide,[6] this crown ether catalysis cannot operate in larger rings.

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†CPK molecular models indicate that ringsizes of at least 27 atoms are required to encapsulate small organic polyfunctional molecules or ions and although full information about the structure is not available, complexation of guanidinium salts by benzo - 27 - crown - 9 supports this assumption.[8,9]

Therefore we decided to investigate the use of another protecting group that fulfills the conditions mentioned. The allyl group potentially meets these requirements since allyl ethers are stable in acid and base but readily isomerize on Pd–C to give the analogous vinyl ethers.[17] The latter readily are cleaved under dilute acidic conditions.

The starting material for the synthesis of the crown ethers 8, 4 - chloro - 2,6 - bis(bromomethyl) - 1 - (2 - propenyloxy)benzene (5), was prepared in three steps from 4-chlorophenol (Scheme 1). Bishydroxymethylation of 4-chlorophenol according to Openshaw[18] followed by reaction of the resulting 4 - chloro - 2,6 - bis(hydroxymethyl)phenol (3) with one equivalent of allylbromide gave 4 in an overall yield of 42%. Reaction of 4 with phosphorus tribromide gave the dibromide 5 in a yield of 90%. Reaction of 5 with one equivalent of tetra-, penta-,

hexa-, hepta- and octaethylene glycol respectively gave the corresponding crown ethers 6a-e. The yields of the crown ether prepared and the base used are given in Table 1.

In several cases (n = 3, 4, 5) the isolated products were shown to contain the analogous vinyl derivatives 7, indicating that some base-catalyzed isomerization had taken place.[19] The ^{1}H NMR spectrum of 6a showed that the benzylic protons were nonequivalent indicating that the intra-annular allyloxy group at the 2'-position of this 18-membered ring inhibits the conformational changes by which the two faces of the macroring become equivalent on the ^{1}H NMR time scale. This feature has been observed for other 2'-substituted 1',3'-xylyl crown ethers and there is a clear correlation between the size of substituents, the ringsize[4,6,15] and the rate of conformational changes.
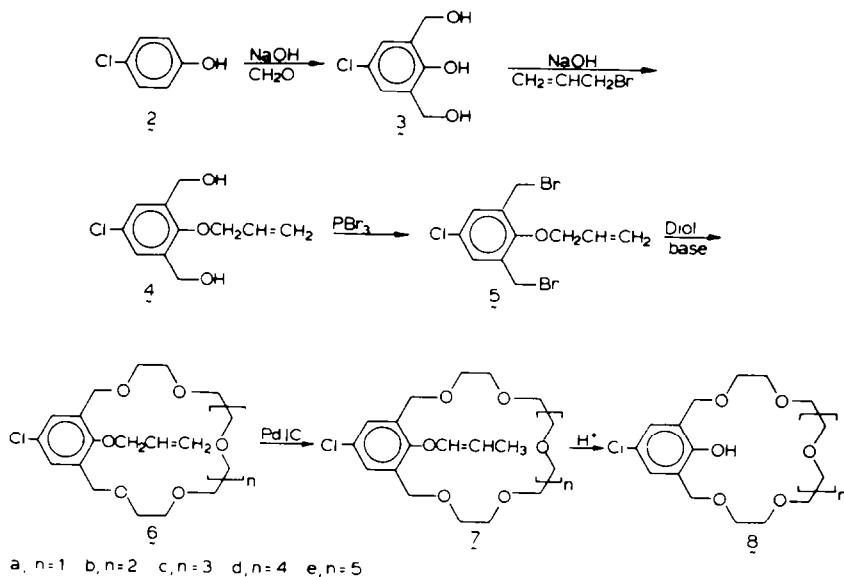
Scheme 1.

Table 1. Reactions of 5 with polyethylene glycols

CE	n	BASE	YIELD
6a	1	NaH	22[a]
6a	1	NaH	53[b]
6a	1	KOtBu	30[b]
6b	2	NaH	26
6c	3	KOtBu	52
6d	4	KOtBu	37
6e	5	KOtBu	47

[a] OVERALL YIELD OF PHENOL 8a

[b] OBTAINED BY INTRAMOL. CYCLIZATION OF MONOTOSYLATE 14
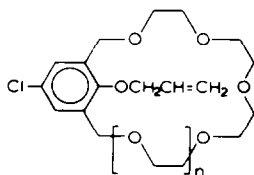
Crown ethers **6** were converted into **7**, using the procedure of Boss and Scheffold,[17] with Pd–C in aqueous ethanol and simultaneously the crown ethers **7** formed were hydrolyzed by *p*-toluenesulfonic acid to the 5' - chloro - 2' - hydroxy - 1',3' - xylyl crown ethers **8a-e**. The yields varied from 64 to 87%, calculated on **6**. The crown ethers **6** and **8** have been characterized by mass spectrometry, ^{1}H and ^{13}C NMR spectroscopy and by elemental analysis for crystalline crown ethers.

Crown ether **6a** was also obtained by an alternative synthetic route as indicated in Scheme 2. The intramolecular cyclization reaction of monotosylate **14**, that was obtained as a by-product of ditosylate **10** (see Scheme 3), was effected by sodium hydride or potassium t-butoxide, giving **6a** in 53 and 30% yield respectively.

1',3' - Xylyl - dibenzo - 30 - crown - 9 **12** has been prepared in a different way. It comprises a high yield synthesis of a 30-membered crown ether having nine O donor atoms in the macroring in addition to an intraannular phenolic group. The synthesis of the macrocycle **12** is outlined in Scheme 3. Dibromide **5** reacted with an excess of diethylene glycol in the presence of base to give in 70% yield the diol **9**, which gave with *p*-toluenesulfonyl chloride a mixture of the ditosylate **10** (58%) and the monotosylate **14** (9%). The two compounds were separated by chromatography. Reaction of ditosylate **10** with one equivalent of bis[2 - (*o* - hydroxyphenoxy)ethyl]ether (**11**)[9] in acetonitrile in the presence of four equivalents of cesium fluoride[20] gave the crown ether **12** in a yield of 87%. This result demonstrates again the remarkable template effect of the cesium cation in ringclosure reactions.[20,21]

The allyl group in **12** was also removed by reaction with Pd–C in the presence of *p*-toluenesulphonic acid to give crown ether **13**, that was readily characterized by the usual spectroscopic techniques. Its ^{1}H NMR spectrum with separate absorptions for the nonbenzylic ether protons at δ 3.70 (s, 8H), δ 3.88 (t, 8H), δ 4.17 (t, 8H) and an absorption at δ 7.81 for the OH proton confirmed the structure assignment. The complexation of various neutral molecules with crown ethers **8** and **13** is currently under investigation, and was already demonstrated by the selective complexation of **8d** with water. A crystalline 1:1 complex was obtained. Hitherto only two crystalline complexes of a crown ether and water had been reported.[13,22] An X-ray analysis in order to establish the nature of the binding will be carried out in the near future.

CONCLUSIONS

The synthesis of 2' - hydroxy - 1',3' - xylyl crown ethers utilizing the allyl group to protect the OH group during the Williamson ether cyclization reaction has been shown to be a general method.

We found no limitation due to steric hindrance in the ring-closure reaction for ringsizes that vary from 18- to 30-membered rings. Cleavage of the C–O bond in the crown ethers by isomerization of the C=C double bond followed by acid-catalyzed hydrolysis of the *cis*-enol ethers leaves the macrocyclic ring unaffected.

EXPERIMENTAL

M.ps were recorded on a Reichert m.p. microscope, the ^{1}H NMR-spectra on a Bruker WP 80-FT and the ^{13}C NMR-spectra
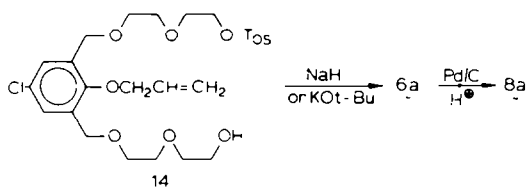
Scheme 2.
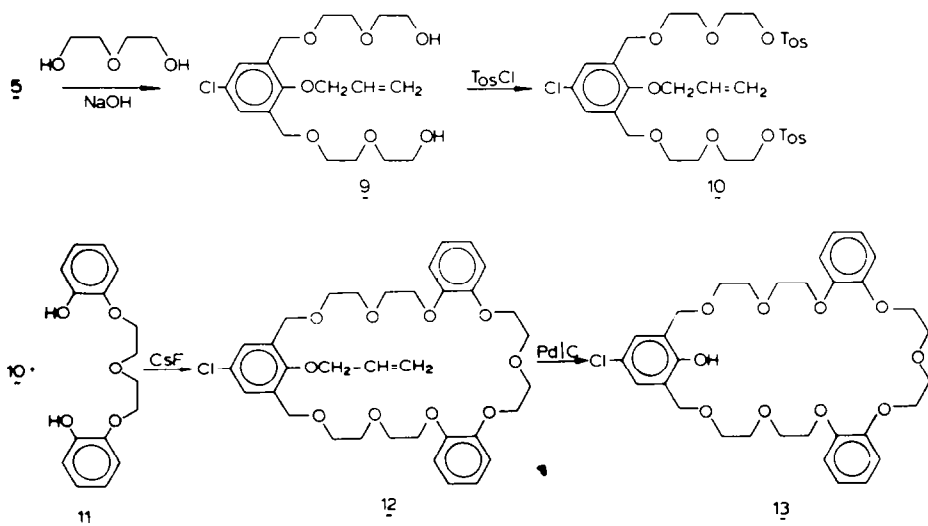
Scheme 3.

on a Varian XL-100-spectrometer in CDCl₃ with TMS as internal standard. Mass spectra were obtained with a Varian Mat 311A and IR spectra with a Perkin–Elmer 257 spectrometer. Elemental analyses were carried out by the Elemental Analytical Section of the Institute for Organic Chemistry TNO, Utrecht, the Netherlands, under the supervision of W. J. Buis.

Tetraethylene glycol refers to Aldrich reagent. Penta- and heptaethylene glycol were prepared as described by Krespan.[23] Hexa- and octaethylene glycol were prepared respectively from sodium diethylene glycol and diethylene glycol dichloride (Fluka) and from potassium diethylene glycol and bis[2 - (2 - chloroethoxy)ethyl]ether[24] by the same procedure with minor modifications. The glycols were distilled under vacuum until glc analysis showed that they were >95% pure. 2,6 - *Bis(bromomethyl)anisole*[25] and 4 - *chloro - 2,6 - bis(hydroxymethyl)phenol* (3)[18] were prepared according to known methods.

4 - Chloro - 2,6 - bis(hydroxymethyl) - 1 - (2 - propenyloxy)benzene (4) and 5 were prepared as follows: 5.2 ml (60.6 mmol) allylbromide was added dropwise to a refluxing soln of 12.5 g (60 mmol) Na salt of 3[18] in 100 ml MeOH. After the addition refluxing was continued for 6 hr, the soln was concentrated *in vacuo* and to the residue water and ether were added. Separation of the organic layer, drying and concentration *in vacuo* afforded a solid which on crystallization from chloroform, gave 4 (8.4 gr, 62%), m.p. 109–110°. IR (KBr): 1030, 1060, 1200, 1440, 2890 and 3300 cm⁻¹. ¹H NMR (CDCl₃): δ 4.24 (d, J = 6 Hz, OH, 2H); δ 4.43 (m, OCH₂, 2H); δ 4.72 (d, J = 6 Hz, ArCH₂, 4H); δ 5.24 (m of d, J = 1.5, 10 Hz, =CH₂, 1H); δ 5.42 (m of d, J = 1.5, 17 Hz, =CH₂, 1H); δ 6.14 (ddt, J = 1.5, 10 and 17 Hz, =CH–, 1H); δ 7.41 (s, ArH, 2H). ¹³C NMR (CDCl₃): δ 75.6 (t, OCH₂); δ 117.2 (t, =CH₂); δ 126.1 (s, C₄); δ 127.3 (d, C₃,₅); δ 134.8 (d, =CH–); δ 138.2 (s, C₂,₆); δ 154.6 (s, C₁). MS: M⁺ 228.055, Calc. 228.055. (Found: C, 57.81; H, 5.62; O, 15.16. Calc. for C₁₁H₁₃O₃Cl: C, 57.77; H, 5.74; O, 15.50%).

A soln of 18.0 gr (66 mmol) fresh distilled PBr₃ in 75 ml toluene was added dropwise to a suspension of 13.8 gr (60 mmol) diol 4 in 400 ml toluene/75 ml ether at RT. After stirring for 20 hr 10 ml water was added and stirring was continued for ½ hr. The soln was extracted with a sat NaHCO₃aq, washed with water, dried and concentrated *in vacuo*. The residue was crystallized from hexane to give 5 (19.0 gr, 90%), m.p. 88–89°. IR (KBr): 1205, 1220, 1240, 1255 and 1460 cm⁻¹. ¹H NMR (CDCl₃): δ 4.48 (s, ArCH₂, 4H); δ 4.63 (t of d, J = 1.5, 5.5 Hz, OCH₂, 2H); δ 5.34 (m of d, J = 10 Hz, =CH₂, 1H); δ 5.51 (m of d, J = 17 Hz, =CH₂, 1H); δ 6.17 (ddt, J = 5.5, 10 and 17 Hz); δ 7.36 (s, ArH, 2H). ¹³C NMR (CDCl₃): δ 75.3 (t, OCH₂); δ 118.1 (t, =CH₂); δ 129.7 (s, C₄); δ 131.6 (d, C₃,₅); δ 132.6 (d, =CH–); δ 133.7 (s, C₂,₆); δ 153.7 (s, C₁). MS: M⁺ 351.887, Calc. 351.887. (Found: C, 37.30; H, 3.05; Br, Cl, 8.55 meq/g. Calc. for C₁₁H₁₁OBr₂Cl: C, 37.27; H, 3.13; Br, Cl, 8.46 meq/g).

General procedure A. A soln of 10 mmol 2,6 - bis(bromomethyl)anisole and 10 mmol of the appropriate glycol in 100 mmol THF was added dropwise under N₂ to a refluxing suspension of 25 mmol NaH in 150 ml THF. After the addition was complete, refluxing was continued for 30 min. The mixture was allowed to cool to RT and stirred for 16 hr. The salt was removed by filtration and the solution was concentrated *in vacuo*.

General procedure B. A soln of 10 mmol of the appropriate glycol in 50 ml THF was added dropwise under N₂ to a suspension of 22 mmol NaH in 50 ml THF. After refluxing for ½ hr a soln of 10 mmol of 5 in 50 ml THF was added dropwise and the resulting mixture was heated at 60° for 2 hr. After cooling the mixture was filtered and the soln was concentrated *in vacuo*.

2' - Methoxy - 1',3' - xylyl - 18 - crown - 5 **1b** was prepared according to procedure A. Purification was accomplished by distillation (200–240°C, 3 × 10⁻² mm) and crystallization from hexane–ether; yield 69.5% (lit[6] 58%), m.p. 45–47°. IR (KBr): 775, 790, 1105, 1470, 1600 and 2870 cm⁻¹. ¹H NMR (CDCl₃): δ 3.48, 3.60 (2s, OCH₂CH₂O, 16H); δ 4.14 (s, OCH₃, 3H); δ 4.60 (s, ArCH₂, 4H); δ 6.90–7.40 (m, ArH, 3H). ¹³C NMR (CDCl₃): δ 64.9 (q, OCH₃); δ 122.8 (s, C₅); δ 131.7 (s, C₁,₃); δ 131.9 (d, C₄,₆); δ 159.4 (s, C₂). MS: M⁺ 326.173, Calc. 326.173. (Found: C, 62.59; H, 8.17. Calc. for C₁₇H₂₆O₆: C, 62.55; H, 8.04%).

2' - Methoxy - 1',3' - xylyl - 21 - crown - 6 **1c** was prepared

according to procedure A. The residue was dissolved in ether and the organic layer washed with water, dried and concentrated *in vacuo*. Purification of the solid material was accomplished by elution with MeOH; yield 27%, m.p. 82.5–83.5°. IR (KBr): 770, 790, 1100, 1465, 1600 and 2870 cm⁻¹. ¹H NMR (CDCl₃): δ 3.53, 3.56 and 3.67 (3s, OCH₂CH₂O, 20H); δ 4.01 (s, OCH₃, 3H); δ 4.58 (s, ArCH₂, 4H); δ 6.90–7.40 (m, ArH, 3H). ¹³C NMR (CDCl₃): δ 64.3 (q, OCH₃); δ 123.5 (s, C₅); δ 131.4 (s, C₁,₃); δ 131.4 (d, C₄,₆); δ 158.6 (s, C₂). MS: M⁺ 370.199, Calc. 370.199. (Found: C, 61.43; H, 8.02; O, 30.55. Calc. for C₁₉H₃₀O₇: C, 61.59; H, 8.18; O, 30.23%).

2' - Methoxy - 1',3' - xylyl - 24 - crown - 7 **1d** was prepared according to procedure A, with the modification that KO t-Bu was used as the base. The residue was purified by chromatography (ether–THF 9/1), yield 71% (referred to used dibromide 5). The oily compound crystallized after standing, m.p. 47–48°. IR (KBr): 775, 790, 1105, 1465, 1600 and 2870 cm⁻¹. ¹H NMR (CDCl₃): δ 3.57, 3.59 and 3.68 (3s, OCH₂CH₂O, 24H); δ 3.92 (s, OCH₃, 3H); δ 4.62 (s, ArCH₂, 4H); δ 7.00–7.50 (m, ArH, 3H). ¹³C NMR (CDCl₃): δ 63.3 (q, OCH₃); δ 123.7 (s, C₅); δ 130.5 (d, C₄,₆); δ 131.4 (s, C₁,₃); δ 157.5 (s, C₂). MS: M⁺ 414.225, Calc. 414.225. (Found: C, 60.99; H, 8.17; O, 30.84. Calc. for C₂₁H₃₄O₈: C, 60.84; H, 8.28; O, 30.88%).

2' - Methoxy - 1',3' - xylyl - 27 - crown - 8 **1e** was prepared according to procedure A, with the modification that KO t-Bu was used as the base. The residue was purified by chromatography on silicagel (CHCl₃) and distillation (b.p. 200–225°, 10⁻² mm), yield 30%. IR (neat): 770, 790, 1100, 1465, 1600 and 2870 cm⁻¹. ¹H NMR (CDCl₃): δ 3.50–3.75 (m, OCH₂CH₂O, 28H); δ 3.87 (s, OCH₃, 3H); δ 4.63 (s, ArCH₂, 4H); δ 7.00–7.50 (m, ArH, 3H). ¹³C NMR (CDCl₃): δ 62.8 (q, OCH₃); δ 123.8 (s, C₅); δ 129.9 (d, C₄,₆); δ 131.3 (s, C₁,₃); δ 157.0 (s, C₂). MS: M⁺ 458.248, Calc. 458.252. (Found: C, 59.39; H, 8.23. Calc. for C₂₃H₃₈O₉: C, 60.24; H, 8.35%).

5' - Chloro - 2' - (2 - propenyloxy) - 1',3' - xylyl - 18 - crown - 5 **6a** was prepared according to procedure B. An analytical sample was obtained on chromatography on silicagel (CHCl₃–EtOAc 6/4) and crystallization from CHCl₃–PE 60–80 at low temp, m.p. 96–97°. IR (KBr): 1100, 1245, 1350, 1450 and 2880 cm⁻¹. ¹H NMR (CDCl₃): δ 3.28–3.73 (m, OCH₂CH₂O, 16H); δ 4.13 (d, J = 10.5 Hz, ArCH₂, 2H); δ 4.53 + 4.75–4.92 (m, OCH₂, 2H); δ 4.92 (d, J = 10.5 Hz, ArCH₂, 2H); δ 5.25 (m of d, J = 10 Hz, =CH₂, 1H); δ 5.50 (m of d, J = 16 Hz, =CH₂, 1H); δ 6.21 (ddt, J = 5, 10 and 16 Hz, =CH–, 1H); δ 7.26, 7.27 (2s, ArH, 2H). ¹³C NMR (CDCl₃): δ 77.3 (t, OCH₂); δ 115.4 (t, =CH₂); δ 131.3 (s, C₄,₆); δ 133.3 (s, C₅); δ 133.8 (s, C₁,₃); δ 135.7 (d, =CH–); δ 156.9 (s, C₂). MS: M⁺386.150, Calc. 386.150. (Found: C, 59.07; H, 7.06. Calc. for C₁₉H₂₇O₆Cl: C, 58.99; H, 7.03%).

5' - Chloro - 2' - (2 - propenyloxy) - 1',3' - xylyl - 21 - crown - 6 **6b** was prepared according to procedure B. Purification was accomplished by chromatography on silicagel (EtOAc) and crystallization from heptane; yield 26%, m.p. 46–47°. IR (KBr): 1035, 1100, 1210, 1250, 1355, 1455 and 2870 cm⁻¹. ¹H NMR (CDCl₃): δ 3.53, 3.55 and 3.64 (3s, OCH₂CH₂O, 20H); δ 4.53 (s, ArCH₂, 4H); δ 4.66 (t of d, J = 1.5 and 5 Hz, OCH₂, 2H); δ 5.30 (m of d, J = 10 Hz, =CH₂, 1H); δ 5.54 (m of d, J = 17 Hz, =CH₂, 1H); δ 6.23 (ddt, J = 5, 10 and 17 Hz, =CH–, 1H); δ 7.32 (s, ArH, 2H). ¹³C NMR (CDCl₃): δ 76.9 (t, OCH₂); δ 116.2 (t, =CH₂); δ 128.4 (s, C₅); δ 130.6 (d, C₄,₆); δ 133.5 (s, C₁,₃); δ 134.6 (d, =CH–); δ 155.6 (s, C₂). MS: M⁺ 430.176, Calc. 430.176. (Found: C, 58.82; H, 7.14; Cl, 8.29; O, 25.75. Calc. for C₂₁H₃₁O₇Cl: C, 58.52; H, 7.27; Cl, 8.23; O, 25.99%).

5' - Chloro - 2' - (2 - propenyloxy) - 1',3' - xylyl - 24 - crown - 7 **6c** was prepared according to procedure B, however KO t-Bu was used as the base. Purification was accomplished by chromatography on silicagel (EtOAc). From spectral data it appeared that a 1:1 mixture of the allyl and vinylether was present, yield 52%. IR (neat): 1110, 1210, 1250, 1355, 1450 and 2880 cm⁻¹. ¹H NMR (CDCl₃): δ 1.77 (dd, J = 2 and 7 Hz, =CH–CH₃, 1.5H); δ 3.55, 3.60, 3.68 (3s, OCH₂CH₂O, 24H); δ 4.50 (t of d, J = 1.2 and 5 Hz, OCH₂, 1H); δ 4.58 (s, ArCH₂, 4H); δ 5.28 (m of d, J = 10 Hz, =CH₂, 0.5H); δ 5.46 (m of d, J = 17 Hz, =CH₂, 0.5H); δ 5.90–6.40 (m, =CH–, 1.5H); δ 7.37, 7.42 (2s, ArH, 2H). ¹³C NMR (CDCl₃): δ 76.1 (t, OCH₂); δ 102.8 (d, OCH=); δ 116.8 (t,

=CH$_2$); δ 128.8 (d, C$_{4,6}$); δ 128.8 (s, C$_5$); δ 129.7 (d, C$_{4,6}$); δ 129.7 (s, C$_5$); δ 133.0 (s, C$_{1,3}$); δ 133.5 (s, C$_{1,3}$); δ 133.9 (d, =CH–); δ 145.1 (d, =CH–); δ 151.7 (s, C$_2$); δ 154.4 (s, C$_2$). MS: M$^+$ 474.201, Calc. 474.202.

5' - *Chloro* - 2' - (2 - *propenyloxy*) - 1',3' - *xylyl* - 27 - *crown* - 8 **6d** was prepared according to procedure B, however KO t-Bu or KH were used as the base. Purification was accomplished by chromatography on silicagel (CHCl$_3$–MeOH, 7%), yield 37%. From spectral data it appeared that about 5% of vinylether **7d** was present. IR (neat): 1110, 1200, 1350, 1450 and 2860 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.62, 3.64, 3.69 (3s, OCH$_2$CH$_2$O, 28H); δ 4.41 (m of d, J = 5 Hz, OCH$_2$, 2H); δ 4.54 (s, ArCH$_2$, 4H); δ 5.20 (m of d, J = 10 Hz, =CH$_2$, 1H); δ 5.38 (m of d, J = 14 Hz, =CH$_2$, 1H); δ 6.08 (ddt, J = 5, 10 and 14 Hz, =CH–, 1H); δ 7.30 (s, ArH, 2H). ^{13}C NMR (CDCl$_3$): δ 75.9 (t, OCH$_2$); δ 117.2 (t, =CH$_2$); δ 128.4 (s, C$_5$); δ 129.2 (d, C$_{4,6}$); δ 133.5 (s, C$_{1,3}$); δ 133.6 (d, =CH–); δ 153.8 (s, C$_2$). MS: M$^+$ 518.233, Calc. 518.228.

5' - *Chloro* - 2' - (2 - *propenyloxy*) - 1',3' - *xylyl* - 30 - *crown* - 9 **6e** was prepared according to procedure B, however KO t-Bu was used as the base. Purification was accomplished by chromatography on silicagel (CHCl$_3$–MeOH, 7%), yield 47%. IR (neat): 1110, 1200, 1250, 1350, 1450 and 2870 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.64, 3.65, 3.66, 3.67 and 3.70 (5s, OCH$_2$CH$_2$O, 32H); δ 4.36 (m of d, J = 5 Hz, OCH$_2$, 2H); δ 4.56 (s, ArCH$_2$, 4H); δ 5.22 (m of d, J = 10 Hz, =CH$_2$, 1H); δ 5.40 (m of d, J = 14 Hz, =CH$_2$, 1H); δ 6.06 (ddt, J = 5, 10 and 14 Hz); δ 7.35 (s, ArH, 2H). ^{13}C NMR (CDCl$_3$): δ 75.7 (t, OCH$_2$); δ 117.4 (t, =CH$_2$); δ 128.6 (d, C$_{4,6}$); δ 129.3 (s, C$_5$); δ 133.3 (s, C$_{1,3}$); δ 133.3 (d, =CH); δ 153.3 (s, C$_2$). MS: M$^+$ 562.250, Calc. 562.245.

5' - *Chloro* - 2' - *hydroxy* - 1',3' - *xylyl* - 18 - *crown* - 5 **8a** was prepared from crude **6a** according to the procedure of Boss and Scheffold[17] with the difference that the reaction was carried out in EtOH. Purification was accomplished by chromatography on silicagel (CHCl–EtOAc 14), yield 22% (referred to dibromide **5**), m.p. 62–65°. IR (KBr): 1100, 1250, 1355, 1470, 2870 and 3350 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.68, 3.70 (2s, OCH$_2$CH$_2$O, 16H); δ 4.64 (s, ArCH$_2$, 4H); δ 7.10 (s, ArH, 2H); δ 8.0 (br s, OH, 1H). ^{13}C NMR (CDCl$_3$): δ 123.6 (s, C$_5$); δ 126.3 (s, C$_{1,3}$); δ 128.8 (d, C$_{4,6}$); δ 154.0 (s, C$_2$). MS: M$^+$ 346.119, Calc. 346.118. (Found: C, 55.49; H, 6.73. Calc. for C$_{16}$H$_{23}$O$_6$Cl: C, 55.41; H, 6.68%).

5' - *Chloro* - 2' - *hydroxy* - 1',3' - *xylyl* - 21 - *crown* - 6 **8b** was prepared from **6b** according to the procedure of Boss and Scheffold[17] with the difference that the reaction was carried out in EtOH. Purification was accomplished by chromatography on silicagel (CHCl$_3$–MeOH, 6%), yield 70%. IR (neat): 1100, 1250, 1350, 1460, 2860 and 3340 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.60, 3.68 and 3.70 (3s, OCH$_2$CH$_2$O, 20H); δ 4.66 (s, ArCH$_2$, 4H); δ 7.11 (s, ArH, 2H); δ 7.89 (br s, OH, 1H). ^{13}C NMR (CDCl$_3$): δ 123.6 (s, C$_5$); δ 126.1 (s, C$_{1,3}$); δ 127.9 (d, C$_{4,6}$); δ 153.1 (s, C$_2$). MS: M$^+$ 390.145, Calc. 390.145.

5' - *Chloro* - 2' - *hydroxy* - 1',3' - *xylyl* - 24 - *crown* - 7 **8c** was prepared from **6c** according to the procedure of Boss and Scheffold[17] with the difference that the reaction was carried out in EtOH. Purification was accomplished by chromatography on silicagel (CHCl$_3$–MeOH, 7%), yield 64%. IR (neat): 1100, 1252, 1352, 1465, 2870 and 3350 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.67, 3.69 and 3.72 (3s, OCH$_2$CH$_2$O, 24H); δ 4.66 (s, ArCH$_2$, 4H); δ 7.13 (s, ArH, 2H); δ 7.96 (br s, OH, 1H). ^{13}C NMR (CDCl$_3$): δ 123.9 (s, C$_5$); δ 126.0 (s, C$_{1,3}$); δ 127.8 (d, C$_{4,6}$); δ 152.6 (s, C$_2$). MS: M$^+$ 434.170, Calc. 434.171.

5' - *Chloro* - 2' - *hydroxy* - 1',3' - *xylyl* - 27 - *crown* - 8 **8d** was prepared from **6d** according to the procedure of Boss and Scheffold[17] with the modification that the reaction was carried out in EtOH. Purification was accomplished by chromatography on silicagel (CHCl$_3$–MeOH, 7%) and crystallization from wet ether-hexane; yield 87%, m.p. 55°. IR (KBr): 1100, 1260, 1350, 1460, 2880 and 3440 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 2.89 (br s, H$_3$O$^+$, 3H); δ 3.62, 3.65, 3.67 and 3.72 (4s, OCH$_2$CH$_2$O, 28H); δ 4.65 (s, ArCH$_2$, 4H); δ 7.14 (s, ArH, 2H). ^{13}C NMR (CDCl$_3$): δ 124.0 (s, C$_5$); δ 126.0 (s, C$_{1,3}$); δ 128.0 (d, C$_{4,6}$); δ 152.6 (s, C$_2$). MS: M$^+$ 478.197, Calc. 478.197. (Found: C, 52.86; H, 7.30; Cl, 7.21. Calc. for C$_{22}$H$_{35}$O$_9$Cl·H$_2$O: C, 53.16; H, 7.50; Cl, 7.13%).

5' - *Chloro* - 2' - *hydroxy* - 1',3' - *xylyl* - 30 - *crown* - 9 **8e** was prepared from **6e** according to the procedure of Boss and

Scheffold[17] with the difference that the reaction was carried out in EtOH. Purification was accomplished by chromatography on silicagel (CHCl$_3$–MeOH, 7%), yield 65%. IR (KBr): 1100, 1250, 1350, 1460, 2870 and 3340 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.65, 3.70 (2s, OCH$_2$CH$_2$O, 32H); δ 4.63 (s, ArCH$_2$, 4H); δ 7.14 (s, ArH, 2H); δ 7.37 (br s, OH, 1H). ^{13}C NMR (CDCl$_3$): δ 124.0 (s, C$_5$); δ 125.6 (s, C$_{1,3}$); δ 127.3 (d, C$_{4,6}$); δ 152.5 (s, C$_2$). MS: M$^+$ 522.227, Calc. 522.223.

4 - *Chloro* - 2,6 - *bis(hydroxyethoxyethoxymethyl)* - 1 - (2 - *propenyloxy*)*benzene* (**9**). A suspension of 7.1 gr (20 mmol) of **5** and 1.0 gr (25 mmol) NaOH in 30 ml diethylene glycol was kept at 110° for 2 hr. To the clear soln water and ether were added. The organic layer was separated and the water layer extracted with CHCl$_3$. The combined organic layers were dried and concentrated *in vacuo*, yielding almost pure **9** (5.6 gr, 70%). An analytical sample was obtained by chromatography on silicagel (CHCl$_3$–MeOH 5%). IR (neat): 1100, 1200, 1350, 1450, 2860 and 3420 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.04 (br s, OH, 2H); δ 3.60, 3.62 and 3.68 (3s, OCH$_2$CH$_2$O, 16H); δ 4.37 (t of d, J = 5 Hz, OCH$_2$, 2H); δ 4.57 (s, ArCH$_2$, 4H); δ 5.26 (m of d, J = 10 Hz, =CH$_2$, 1H); δ 5.41 (m of d, J = 16 Hz, =CH$_2$, 1H); δ 6.08 (ddt, J = 5, 10 and 16 Hz, =CH–, 1H); δ 7.37 (s, ArH, 2H). ^{13}C NMR (CDCl$_3$): δ 75.6 (t, OCH$_2$); δ 117.5 (t, =CH$_2$); δ 128.8 (d, C$_{3,5}$); δ 129.3 (s, C$_4$); δ 133.1 (d, =CH–); δ 133.2 (s, C$_{2,6}$); δ 153.4 (s, C$_1$). MS: (M$^-$-41); 363.121, Calc. 363.121. (Found: C, 55.35; H, 6.99; Cl, 8.80. Calc. for C$_{19}$H$_{28}$O$_7$Cl: C, 56.36; H, 7.22; Cl, 8.76%).

4 - *Chloro* - 2,6 - *bis(hydroxyethoxyethoxymethyl)* - 1 - (2 - *propenyloxy*)*phenyl mono and bis toluene* - p - *sulphonate* **14** resp. **10** were prepared from **9** according to the procedure of Pearson *et al.*[26] Purification was accomplished by chromatography on silicagel (CHCl$_3$–EtOAc 6/4).

Monotosylate **14**, yield 9%. IR (neat): 925. 1100, 1180, 1190, 1355, 1450, 2870 and 3490 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 2.17 (br s, OH, 1H); δ 2.43 (s, ArCH$_3$, 3H); δ 3.61 (s, OCH$_2$CH$_2$O, 4H); δ 3.69 (s, OCH$_2$CH$_2$O, 8H); δ 3.69 (t, J = 3 Hz, OCH$_2$CH$_2$Tos); δ 4.18 (t, J = 3 Hz, OCH$_2$CH$_2$Tos, 2H); δ 4.36 (d, J = 5 Hz, OCH$_2$, 2H); δ 4.53 (s, ArCH$_2$, 2H); δ 4.58 (s, ArCH$_2$, 2H); δ 5.25 (m of d, J = 10 Hz, =CH$_2$, 1H); δ 5.46 (m of d, J = 16 Hz, =CH$_2$, 1H); δ 6.10 (ddt, J = 5, 10 and 16 Hz, =CH–, 1H); δ 7.33 (d, J = 7 Hz, ArH, 2H); δ 7.37 (s, ArH, 2H); δ 7.80 (d, J = 7 Hz, ArH, 2H). ^{13}C NMR (CDCl$_3$): δ 75.6 (t, OCH$_2$); δ 117.4 (t, =CH$_2$); δ 127.7 (d, ArSO$_2$); δ 128.7 (d, C$_{3,5}$); δ 128.9 (s, ArSO$_2$); δ 129.3 (s, C$_4$); δ 129.6 (d, ArSO$_2$); δ 132.9 (d, =CH–); δ 133.2 (s, C$_{2,6}$); δ 153.4 (s, C$_1$). MS: (M$^+$-41): 517.132, Calc. 517.130.

Ditosylate **10**, yield 58%. IR (neat): 920, 1000, 1100, 1180, 1360, 1450 and 2880 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 2.42 (s, ArCH$_3$, 6H); δ 3.61 (s, OCH$_2$CH$_2$O, 8H); δ 3.67 (t, J = 5 Hz, OCH$_2$CH$_2$Tos, 4H); δ 4.16 (t, J = 5 Hz, OCH$_2$CH$_2$Tos, 4H); δ 4.35 (d, J = 5 Hz, OCH$_2$, 2H); δ 4.52 (s, ArCH$_2$, 4H); δ 5.24 (d, J = 9.5 Hz, =CH$_2$, 1H); δ 5.39 (d, J = 14.5 Hz, =CH$_2$, 1H); δ 6.08 (ddt, J = 5, 9.5 and 14.5 Hz, =CH–, 1H); δ 7.32 (d, J = 8 Hz, ArH, 4H); δ 7.32 (s, ArH, 2H); δ 7.97 (d, J = 8 Hz, ArH, 4H). ^{13}C NMR (CDCl$_3$): δ 75.8 (t, OCH$_2$); δ 117.3 (t, =CH$_2$); δ 127.7 (d, ArSO$_2$); δ 128.6 (d, C$_{3,5}$); δ 128.6 (s, ArSO$_2$); δ 129.2 (s, C$_4$); δ 129.6 (d, ArSO$_2$); δ 132.8 (d, =CH–); δ 133.3 (s, C$_{2,6}$); δ 144.6 (s, ArSO$_2$); δ 153.4 (s, C$_1$).

5' - *Chloro* - 2' - (2 - *propenyloxy*) - 1',3' - *xylyl* - *dibenzo* - 30 - *crown* - 9 (**12**). A suspension of 2.2 gr (3.1 mmol) **10**, 0.9 gr (3.1 mmol) bis[2 - (o - *hydroxyphenoxy*)*ethyl*]*ether*[9] and 1.9 gr (12.4 mmol) CsF in 40 ml acetonitrile was refluxed for 20 hr. The suspension was concentrated *in vacuo*, then water and CHCl$_3$ were added. Separation of the organic layer, drying and concentration *in vacuo* afforded 1.74 gr of oil, that on purification by chromatography on silicagel (CHCl$_3$–EtOH, 5%), gave **12** (yield 87%). IR (neat): 1050, 1120, 1200, 1250, 1450, 1500, 1590 and 2860 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.69 (s, OCH$_2$CH$_2$O, 8H); δ 3.89 (t, J = 5 Hz, OCH$_2$CH$_2$O, 8H); δ 4.17 (t, J = 5 Hz, OCH$_2$CH$_2$O, 8H); δ 4.33 (m of d, J = 5 Hz, OCH$_2$, 2H); δ 4.53 (s, ArCH$_2$, 4H); δ 5.20 (m of d, J = 9.5 Hz, =CH$_2$, 1H); δ 5.35 (m of d, J = 15 Hz, =CH$_2$, 1H); δ 5.75–6.34 (m, =CH–, 1H); δ 6.90 (s, ArH, 8H); δ 7.36 (s, ArH, 2H). ^{13}C NMR (CDCl$_3$): δ 75.6 (t, OCH$_2$); δ 115.0 (d, Ar); δ 117.3 (t, =CH$_2$); δ 121.5 (d, Ar); δ 128.6 (d, C$_{4,6}$); δ 129.3 (s, C$_5$); δ 133.3 (s, C$_{1,3}$); δ 133.3 (d, =CH–); δ 148.9 (s, Ar); δ 153.3 (s, C$_2$). MS: M$^+$ 658.258, Calc. 658.255.

5' - Chloro - 2' - hydroxy - 1',3' - xylyl - dibenzo - 30 - crown - 9 (13) was prepared from 12 according to the procedure of Boss and Scheffold[17] with the difference that the reaction was carried out in EtOH–5% THF. Purification was accomplished by chromatography on silicagel (CHCl$_3$–EtOH, 4%), yield 64%. IR (neat): 1100, 1250, 1350, 1450, 1600, 2900 and 3340 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.70 (s, OCH$_2$CH$_2$O, 8H); δ 3.88 (t, $J = 5$ Hz, OCH$_2$CH$_2$O, 8H); δ 4.17 (t, $J = 5$ Hz, OCH$_2$CH$_2$O, 8H); δ 4.58 (br s, ArCH$_2$, 4H); δ 6.90 (s, ArH, 8H); δ 7.27 (s, ArH, 2H); δ 7.81 (br s, OH, 1H). ^{13}C NMR (CDCl$_3$): δ 75.6 (t, OCH$_2$); δ 115.0 (d, Ar); δ 121.5 (d, Ar); δ 124.0 (s, C$_5$); δ 125.6 (s, C$_{1,3}$); δ 127.3 (d, C$_{4,6}$); δ 148.8 (s, Ar); δ 152.2 (s, C$_2$). MS: M$^+$ 618.231, Calc. 618.223.

5' - Chloro - 2' - (2 - propenyloxy) - 1',3' - xylyl - 18 - crown - 5 6a. A suspension of 414 mg (0.74 mmol) monotosylate 14 and 50 mg (2.2 mmol) NaH in 10 ml THF was refluxed for 1.5 hr; then water and ether were added. The organic layer was separated, dried and concentrated *in vacuo*. The residue was purified by chromatography on silicagel (CHCl$_3$–EtOAc 6–4), yield 151 mg (53%), m.p. 96–97°C. Spectral data were in agreement with the structure. 6a was obtained in 30% yield when KO t-Bu was used as the base.

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