Ion solutions were heated in tightly closed NMR sample tubes by using a thermostated bath at the temperatures indicated in the text.

Irradiations were carried out by placing the ion solutions into quartz tubes surrounding a centrally positioned quartz cooling jacket (external diameter 55 mm) containing a 125-W medium pressure mercury lamp. The temperature was kept below 30 °C by means of a water bath.

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Registry No. 1, 498-23-7; $1H^+$, 116664-83-6; 2, 498-24-8; 3, 97-65-4; $3H^+$, 116664-77-8; 4, 616-02-4; $4H^+$, 116664-78-9; $8H^+$, 116664-79-0; $9H^+$, 116664-84-7; $11H^+$, 116664-80-3; $13H^+$, 116664-81-4; $14H^+$, 116664-82-5; $CH_3CO_2H_2^+$, 18639-92-4.

Intraannular Functionalization of Macrocyclic Polyethers via Organolithium Intermediates

Maria Skowronska-Ptasinska,† Veronika M. L. J. Aarts,† Richard J. M. Egberink,† Johan van Eerden,‡ Sybolt Harkema,‡ and David N. Reinhoudt*,†

Laboratories of Organic Chemistry and Chemical Physics, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands

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1,3-Xylyl crown ethers substituted at the 2-position with an acidic (COOH, OH, SO_2H) or reactive (CHO) functional group can be synthesized from a common starting material by a generally applicable method that does not require the protection of these groups. 2-Bromo-1,3-xylyl crown ethers **1** react at −78 °C with *n*-butyllithium to yield the corresponding 2-lithio-1,3-xylyl crown ethers **2** without extensive cleavage of the polyether ring. Subsequent reaction with electrophilic reagents (dimethyl disulfide, *N,N*-dimethylformamide, CO_2, or SO_2) yielded the corresponding macrocycles **3–6**. Reaction of **2** with trimethyl borate, followed by hydrolysis and oxidation by hydrogen peroxide, provides an excellent alternative for the published synthesis of 2-hydroxy-1,3-xylyl crown ethers **8**. The single-crystal X-ray structures of 2-bromo-1,3-xylyl-18-crown-5 (**1b**) and 2-sulfino-1,3-xylyl-18-crown-5 (**6b**) reveal a restricted flexibility of the macroring in these 18-membered macrocycles. In **6b**, the macrocyclic cavity is filled by the SOH group, which is engaged in a bifurcated hydrogen bond with two ether oxygen atoms.

Introduction

Complexes of neutral molecules with macrocyclic receptors are thermodynamically much less stable than are complexes of crown ethers with charged guests.[1,2] One way to increase the complex stability would be the in situ conversion of a neutral guest into a (partially) charged species. This would provide additional electrostatic interactions in the complex between host and guest, as we have shown for the complexation of urea.[3] We have recently demonstrated that 1,3-xylyl crown ethers with an intraannular proton-donating group and a cavity large enough to encapsulate the guest molecule provide good ligands for the complexation of neutral guests such as urea or water via strong hydrogen bonds.[4] In an extension of this approach we were interested in developing a general and convergent synthetic procedure for the functionalization of crown ethers with different intraannular acidic substituents.

Various syntheses of crown ethers with intraannular acidic carboxyl or hydroxyl groups have been described previously. However, they all require the protection of the acidic substituent during the Williamson cyclization, which takes place under strongly basic conditions, and involve multistep processes with low overall yields. Various 2-carboxy-1,3-xylyl-3*n*-crown-(n − 1) ethers (n = 5–7 and 10) were obtained previously by Cram[5] starting from 2-(methoxycarbonyl)-1,3-bis(bromomethyl)benzene and this method was extended in our group for the preparation of larger macrocycles.[4]

The syntheses of 2-hydroxy-1,3-xylyl crown ethers have been also previously reported.[6] The major problem was finding a suitable protecting group for the hydroxyl function that would be stable under the strongly basic conditions of the Williamson macrocyclization and could be selectively removed under conditions that did not cleave the benzylic ether bonds. In the synthesis of 2-hydroxy-1,3-xylyl crown ethers, methoxymethyl,[6a] allyl,[6b] and methyl[6c] groups were reported for protection of hydroxyl function. The use of methoxymethyl and allyl groups was described for the synthesis of 2-hydroxy-1,3-xylyl crown ethers in which the 5-position was blocked by a methyl or a chloro substituent, respectively.[6a,b] Since substituents at the 5-position show a considerable effect on the complexation properties of the macrocycle and on the proton-donating ability of the OH group, 2-hydroxy-1,3-xylyl crown ethers with an unsubstituted 5-position are much more attractive, because they provide the possibility for

† Laboratory of Organic Chemistry.
‡ Laboratory of Chemical Physics.

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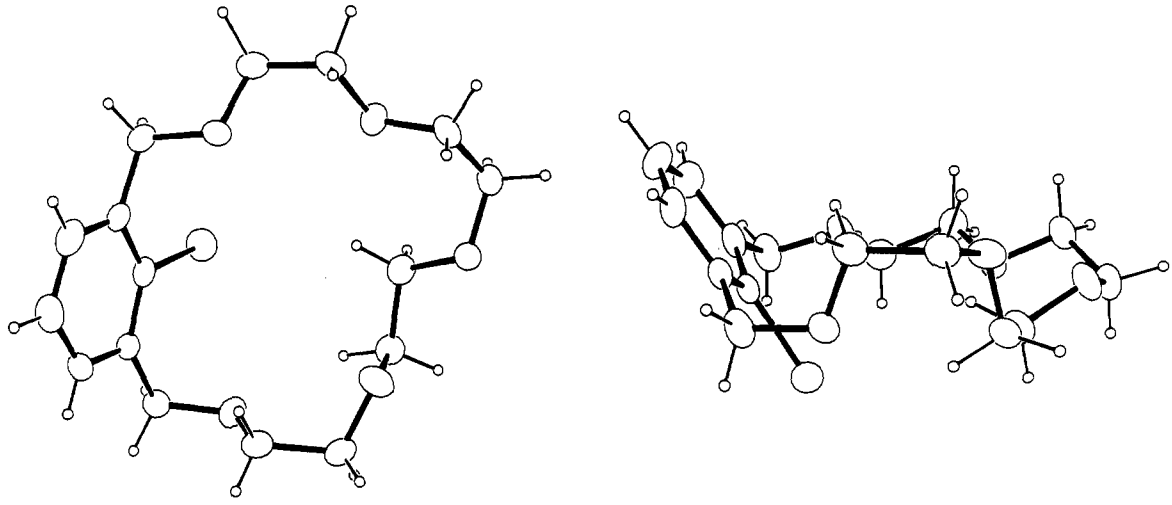

Figure 1. Crystal structure of **1b**; top and side view.

variation of the substituent at the 5-position. In the synthesis of the 2-hydroxy-1,3-xylyl-3*n*-crown-(n – 1) ethers (n = 5–7) described by McKervey, protection by a methyl group was used and the deprotection was accomplished by using anhydrous LiI in pyridine at 100 °C.[6c] Attempts to remove the methyl group in the larger macrocycles were unsuccessful, probably due to weaker complexation of lithium salts by the large crown ether rings.[6b] After the work described in this paper had been initiated, Bartsch et al. reported that $LiAlH_4$ could be used for demethylation of the intraannular aromatic methoxy group.[7] The method was successful for the demethylation of 18- and 21-membered 1,3-xylyl crown ethers.

We anticipated that both carboxyl and hydroxyl functions could be introduced in the aromatic ring of crown ethers starting from a common organolithium intermediate by reaction with CO_2 or oxidation, respectively.[8] Moreover, other acidic groups such as sulfino, sulfo, or mercapto might be introduced and the method could be extended to incorporate other reactive functionalities.

Although direct lithiation of aromatic compounds is the most effective, it cannot be applied to functionalization of simple 1,3-xylyl crown ethers, due to reactivity of benzylic groups toward lithium reagents.[9] Therefore we have prepared organolithium intermediates of 1,3-xylyl crown ethers via bromine-to-lithium exchange. In a preliminary communication, we have shown that 2-sulfino-1,3-xylyl crown ethers can be obtained in this way.[10] In this paper, our detailed studies of the synthesis of 1,3-xylyl crown ethers with different intraannular substituents via 2-lithio-1,3-xylyl crown intermediates are reported.

Results and Discussion

Synthesis of 2-Bromo-1,3-xylyl Crown Ethers. 2-Bromo-1,3-xylyl-18-crown-5 and 2-chloro-1,3-xylyl-18-crown-5 were previously obtained by Cram[5] by the addition of 2-bromo-1,3-bis(bromomethyl)benzene or 1,3-bis(bromomethyl)-2-chlorobenzene to 1 equiv of the disodium salt of tetraethylene glycol in THF with yields of 8% and 53%, respectively. Since attempts by Newcomb et al.[5] to convert 2-chloro-1,3-xylyl-18-crown-5 to 2-carboxy-1,3-xylyl-18-crown-5 had failed, we decided to prepare 2-bromo-1,3-xylyl-crown ethers **1** as the starting materials for halogen-to-lithium exchange.

The series of 2-bromo-1,3-xylyl crown ethers **1** were prepared by the simultaneous addition of equivalent amounts of 2-bromo-1,3-bis(bromomethyl)benzene and the appropriate polyethylene glycol in THF to a suspension of NaH in such a volume of THF that the concentration of the 2-bromo-1,3-xylyl crown ether **1** ultimately reached 0.01 M.[10] The yields of the larger crown ethers could not be enhanced by the use of cesium as the template cation, probably due to steric hindrance by the large bromine substituent in a cesium-templated ring closure reaction. This was also observed for the 2-(ethoxycarbonyl)-1,3-xylyl crown ethers.[11]

In order to separate the 2-bromo-1,3-xylyl-3*n*-crown-(n – 1) ethers **1** from a byproduct of the 2:2 ring closure reaction, purification by column chromatography was followed by vacuum distillation (10^{-4} mbar). The solid 15-, 18-, and 24-membered crowns can also be purified by crystallization from diethyl ether/ethanol/hexane. The ^1H NMR spectrum of the 18-membered macrocycle **1b** was in agreement with the spectrum of 2-bromo-1,3-xylyl-18-crown-5 obtained as an oil by Cram et al.[5] The structure of **1b** was determined by X-ray crystallography. Views of the structure are given in Figure 1. The covalent geometry is as found in other crown ethers (data are in the supplementary material); the C–Br distance of 1.90 Å is a normal value.[12] The macrocycle adopts a somewhat irregular conformation in order to fill part of its own cavity by the hydrogen atom of an inwardly oriented methylene

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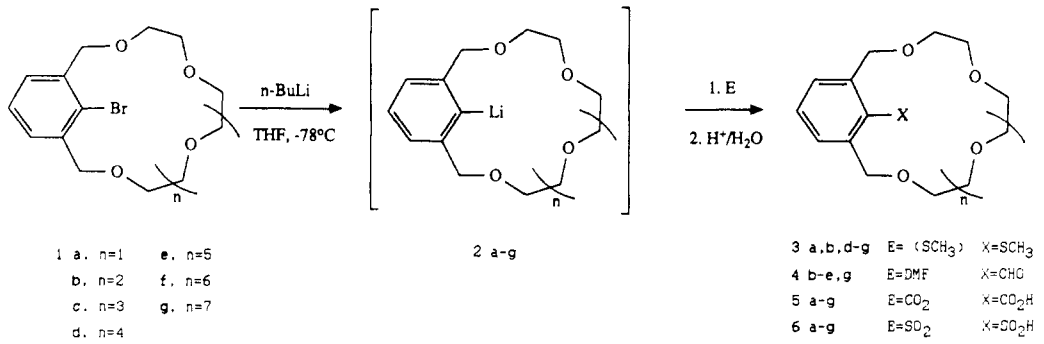
Scheme I



group.[13] The bromine is too large to fit in the macrocyclic cavity: the distances between bromine and adjacent ether oxygens, connected to the benzylic carbons, are 3.28 and 3.36 Å. This leads to an angle of 54° between the mean macrocyclic plane and the xylyl ring. The bromine is engaged in several short intermolecular contacts with hydrogen atoms, at 3.2–3.4 Å. For the new macrocycles **1a** and **1c–g**, the ^{1}H NMR data observed were in agreement with their structures. The 15-membered macrocycle showed an AB system for the benzylic protons, indicating that the ring inversion is slow on the NMR time scale. In the mass spectra of all macrocycles **1**, molecular ion peaks were observed. In the ^{13}C NMR spectra, absorptions were present for the OCH_2 units between δ 69 and 73, for the aryl carbon atoms C-1 and C-3 at δ 138, and for the aryl carbon atom C-5 at approximately δ 127. The absorptions of the aryl carbon atoms C-2, C-4, and C-6 depend on the ring size. In the 27-, 30-, and 33-membered macrocycles, C-4 and C-6 absorb at δ 128, while the C-2 carbon absorbs at δ 122.5. For smaller rings (15-24), downfield shifts of the C-4 and C-6 as well as the C-2 carbon absorptions are observed from δ 129 to 131 for the C-4 and C-6 carbon atoms and from δ 123 to 128 for the C-2 carbon atom with the decreasing ring size from **1d** to **1a**. These shift differences can be attributed to steric hindrance of the cavities of the smaller macrocycles, which are unable to encapsulate the bromine substituent.

Bromine-to-Lithium Exchange. Currently there is a growing interest in the interactions of organometallics with macrocycles, and complexes of crown ethers with organoaluminum[14] and organomagnesium compounds[15,16] have been isolated. This demonstrated the stability of the polyether ring toward organometallics of the II and III main groups. In the reactions of *n*-BuLi and *5-bromo*-1,3-xylyl crown ethers, high yields of *5-formyl*-1,3-xylyl crown ethers (74–90%) and *5-(ethoxycarbonyl)*-1,3-xylyl-18-crown-5 (70%) were obtained after being quenched with DMF[17] and ethyl chloroformate,[18] respectively. Obviously under these reaction conditions (–78 °C), the crown ether rings are stable and the well-known cleavage of ethers[19] with *n*-BuLi and the deprotonation of OCH_2CH_2O linkages in particular[20] do not take place. Recently

Table I. Yields (%) of 2-Functionalized (X) 1,3-Xylyl Crown Ethers

	yield, X =			
X	SCH_3 (3)	CO_2H (5)	SO_2H (6)	OH (8)
a	54	77	65	63
b	75	87	67	57
c	*a*	90	79	63
d	79	65	89	61
e	83	58	57	61
f	93	64	70	66
g	87	88	61	30

[a] Not prepared.

Bickelhaupt et al. have reported that the formation of *2-(bromomagnesio)*-1,3-xylyl-3*n*-crown-(n – 1) (n = 5, 6) was accompanied by crown ether ring cleavage, in which the crown ether coordinated Grignard compound formed is involved.[21]

2-Lithio-1,3-xylyl crown ethers **2a–g** were obtained by the addition of 1.1 equiv of *n*-butyllithium under nitrogen at –78 °C, to the solution of **1a–g**, dissolved in a minimal amount of freshly distilled THF (Scheme I). The yield of bromine-to-lithium exchange was monitored by the reaction of **2a–g** with dimethyl disulfide, which is extremely fast even at low temperature. The 2-(methylthio)-1,3-xylyl crown ethers **3** were obtained in satisfactory yields as shown in Table I. A reaction time of 2 h appeared to be sufficient for complete bromine-to-lithium exchange. As found in some reactions with other electrophiles, the 2-*n*-butyl-1,3-xylyl crown ether was formed as a minor product. The bromine-to-lithium exchange reactions were also carried out with *tert*-butyllithium. Although the incorporation of the *tert*-butyl group was no longer observed, a small amount of unsubstituted 1,3-xylyl crown ether was formed. This is probably due to *t*-BuLi degradation since no deuterium was incorporated when the reaction was carried out in deuteriotetrahydrofuran, followed by hydrolysis with D_2O.

These bromine-to-lithium exchange reactions form the basis for the modifications of 2-substituted-1,3-xylyl crown ethers.

Reaction of 2-Lithio-1,3-xylyl Crown Ethers with DMF. By quenching the 2-lithio-1,3-xylyl crown ethers **2** with *N,N*-dimethylformamide (Scheme I), 2-formyl-1,3-xylyl crown ethers **4b–e,g** could be obtained. However, satisfactory purification of these crown ethers **4** proved

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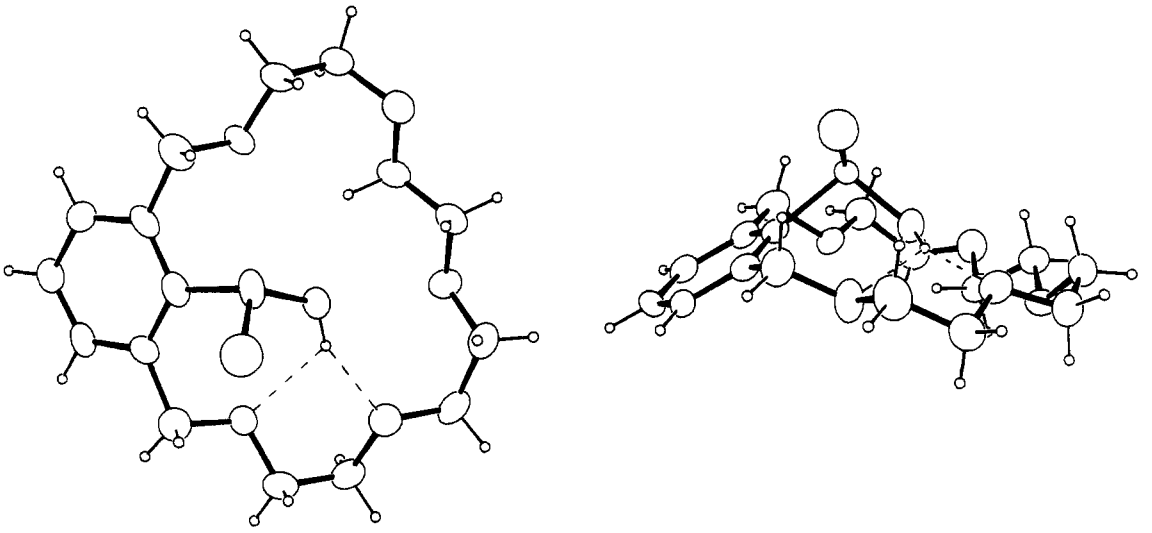


Figure 2. Structure of **6b**; top and side view. Hydrogen bonds indicated by dashed lines. Only majority positions are shown in the disordered sulfino group.

difficult and we were unable to separate them from other reaction products, such as unsubstituted and 2-*n*-butyl-1,3-xylyl crown ethers. Estimated yields of this reaction, based on spectral data of the crude products, varied between 60% and 90%. The carbonyl absorptions present in the IR spectra of these crown ethers at 1690 cm^{-1} proved that the aldehydes had been formed. Also in the ^1H NMR spectra, a peak of the aldehyde proton was observed at δ 10.6, and in the ^{13}C NMR spectra an absorption for the aldehyde carbon atom was present at approximately δ 194. In the mass spectra of crown ethers **4b–e,g** molecular ion peaks were observed.

Reaction of 2-Lithio-1,3-xylyl Crown Ethers with CO_2. When the 2-lithio-1,3-xylyl crown ethers **2a–g** were reacted with CO_2, 2-carboxy-1,3-xylyl crown ethers **5a–g** were obtained in good yields (Scheme I, Table I). The spectral data were in agreement with those reported previously when crown ethers **5** were prepared from 2-(methoxycarbonyl)-1,3-xylyl crown ethers. Our novel synthetic route with overall yields of 16–40% compares favorably with this method (overall yield 4–9%).[4,5] Purification was accomplished by acid–base extraction. Even the 18- and 21-membered rings could be purified in this way, when sodium hydroxide was used as a base. Complexes between the crown ethers and the sodium cation were obviously not formed under these conditions, thus preventing the extraction of the crown ether from the dichloromethane phase into the aqueous phase. This shows that the careful handling of these crown ethers during the purification process as used by Cram and coworkers[5] and our group[4] is superfluous.

Reaction of 2-Lithio-1,3-xylyl Crown Ethers with SO_2. Generally the reaction of organolithium compounds with SO_2 gives sulfinic acids.[19,20] Due to a strong tendency of the sulfinic acids to decompose, isolation and characterization is generally performed with the corresponding salts.

However, we were able to isolate 2-sulfino-1,3-xylyl crown ethers **6** upon reaction of the 2-lithio-1,3-xylyl crown ethers **2** with SO_2 at −78 °C. The 2-sulfino-1,3-xylyl crown ethers **6** could be purified by acid–base extraction and were obtained in good yields (Table I, Scheme I). It is possible that the macrocyclic ring has some stabilizing effect on the sulfino group. However, long-term storage of **6**, even in the dark and under argon, results in their decomposition.

In the ^{13}C NMR spectra of **6** absorptions were found for the OCH_2 carbon atoms between δ 69 and 71, for the aryl carbon atoms C-4, C-5, and C-6 at approximately δ 131, and for the aryl carbon atoms C-1 and C-3 at approximately δ 137. The peak of aryl carbon C-2 shifts in the ^{13}C NMR spectrum from δ 148 for the 15-membered ring to δ 146 for the 24-membered and larger macrocycles. In the ^1H NMR spectra of **6** the OCH_2 groups show absorptions between δ 3.6 and 3.7 and the aryl protons at approximately δ 7.35.

The ^1H NMR spectrum of **6b** shows a slightly broadened singlet for the benzylic protons, whereas the larger macrocycles **6c–g** show a sharp singlet at δ 5.0. This indicates that the sulfino group is too large to fit in the cavity of the 18-membered macrocycle ring, resulting in slow ring inversion on the NMR scale.

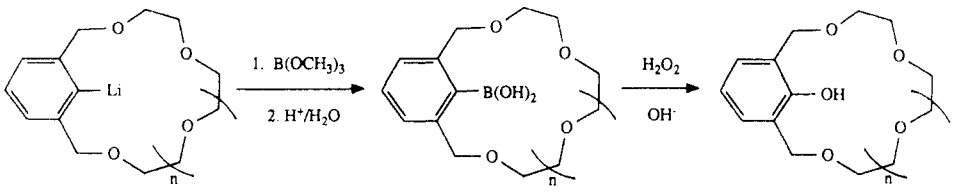
The structure of **6b** was determined by X-ray crystallography. Views of the structure are given in Figure 2. The macrocyclic cavity of **6b** is filled by the sulfino OH group, which is engaged in a bifurcated hydrogen bond with two ether oxygens. The O···O distances and the OH···O angles are 2.79 and 2.88 Å and 155° and 126°, respectively. This *self-complexation* phenomenon[13] has been observed before in macrocyclic polyethers. In the structure of **6a**[10] short contacts between the OH group and the ether oxygen also occur, with O···O distances of 2.81 and 2.89 Å (no hydrogen atom located). But due to the smaller ring size of **6a**, the SOH group is located further away from the cavity and the xylyl group is nearly perpendicular to the mean macrocyclic plane (with an angle of 71° vs 40° for **6b**).

In the ^1H NMR spectra of the 2-substituted 1,3-xylyl-15-crown-4 ethers, an AB system is usually observed as a result of slow ring inversion on the NMR scale.[5,6c,24] The AB system of 2-sulfino-1,3-xylyl-15-crown-4 (**6a**) is more complex, showing line broadening of the low-field part of the AB system. Temperature-dependent ^1H NMR spectra of **6a** show line broadening of both parts of the double doublet with decreasing of temperature, resulting in an AA′BB′ system at 218 K. It is possible that the intramolecular interaction between the S–O–H hydrogen and the oxygen atoms of the macrocyclic ring of **6a** is at least partly responsible for a further differentiation in magnetic nonequivalence of the AB system of **6a**.

In the mass spectra of the 2-sulfino-1,3-xylyl crown ethers **6**, molecular ion peaks were not observed. With the

(24) This paper, for 2-bromo-1,3-xylyl-15-crown-4 and 2-(methylthio)-1,3-xylyl-15-crown-4.

Scheme II



2 a-g 7 a-g 8 a-g

15-membered ring, a peak was observed for $M^+ - H_2O$ and with the 18-membered ring for $M^+ - H$. All other macrocycles did not reveal the presence of the sulfino group in the mass spectrum. This is consistent with the low stability of the sulfinic crown ethers in general but also indicates some stabilizing effect of the smaller macrocyclic rings.

Reaction of 2-Lithio-1,3-xylyl Crown Ethers with Trimethyl Borate and Oxidation. Direct oxidation of aryllithium compounds with oxygen leads to formation of phenols[25] and we observed sometimes the formation of 2-hydroxy-1,3-xylyl crown ethers **8** when the precautions of oxygen-free reaction conditions were not strictly obeyed. However, because the oxidation of organolithium compounds with air is difficult to control, and therefore not selective, we have carried out transmetalation of 2-lithio-1,3-xylyl crown ethers **2** to 2-(dimethoxyboryl)-1,3-xylyl crown ethers followed by hydrolysis and oxidation with hydrogen peroxide in the presence of base (Scheme II), which is quantitative and specific for the carbon–boron bond.[25]

For lithium-to-boron exchange, trimethyl borate was used. After hydrolysis, the 1,3-xylyl crown ether derivatives of boric acid **7** were separated from byproducts by base–acid extraction and without characterization were oxidized with hydrogen peroxide in the presence of $NaHCO_3$. After acidification and extraction, nearly pure 2-hydroxy-1,3-xylyl crown ethers **8** were obtained. Additional purification by column chromatography yielded spectrally pure products (Table I). Considerably lower yields of 2-hydroxy-1,3-xylyl crown ethers **8** were obtained when the oxidation was attempted without separation of the boric acid derivatives of the crown ethers. The smaller ring 2-hydroxy-1,3-xylyl crown ethers **8a,b** could be isolated by acid–base extraction. Larger macrocycles were not extractable into the basic aqueous phase probably due to the good solubility of the sodium salt in chloroform. Attempts to separate the product by column chromatography were also unsuccessful and the 2-hydroxy-1,3-xylyl crown ethers **8** obtained in this way were always contaminated with unsubstituted and 2-*n*-butyl-1,3-xylyl crown ethers.

The spectral data for 2-hydroxy-1,3-xylyl crown ethers **8a–c** are in agreement with these reported by McKervey.[6c] For the new macrocycles, the ^1H NMR spectra are in agreement with their structures, showing absorptions of OCH_2 groups between δ 3.6 and 3.8, a singlet for the benzylic protons at δ 4.7, and a characteristic multiplet for the aromatic protons between δ 6.7 and 7.35. In the mass spectra of all 2-hydroxy-1,3-xylyl crown ethers **8**, molecular ion peaks were observed.

The methodology described in this paper will be particularly useful for the synthesis of more complex macrocycles that contain intraannular functional groups. The bromo substituent is inert in most common transformations and the conversion by halogen-to-lithium exchange in the last step of the synthesis avoids the often cumbersome protection and deprotection steps.

(25) Zweifel, G.; Brown, H. C. *Org. React. (N.Y.)* **1964**, *13*, 1.

Experimental Section

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^1H NMR spectra (in $CDCl_3$ with Me_4Si as an internal standard) were recorded with a Bruker WP-80 spectrometer and ^{13}C NMR spectra were recorded with a Nicolet MT 200 spectrometer. Mass spectra were obtained with a Varian MAT 311A spectrometer and IR spectra with a Perkin-Elmer 257 spectrophotometer.

Materials. *n*-BuLi in *n*-hexane (Merck) was titrated with 2-butanol in the presence of 1,10-phenanthroline to determine its concentration.[26] Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl before use. Diethyl ether was distilled from CaH_2 and stored over 4-Å molecular sieves. 2-Bromo-1,3-bis(bromomethyl)benzene[5] and polyethylene glycols[27] were prepared according to literature procedures. Trimethyl borate (Janssen Chimica) was stored over anhydrous LiCl and was freshly distilled before use.[28] Most other compounds used were commercially available unless stated otherwise. All reactions were carried out under a nitrogen atmosphere.

2-Bromo-1,3-xylyl Crown Ethers 1. General Procedure. To a refluxing, stirred mixture of 1.1 g (45 mmol) of NaH and 2 L of dry THF was slowly added (2 mL/h) a solution of 5.0 g (14.6 mmol) of 2-bromo-1,3-bis(bromomethyl)benzene and 14.6 mmol of the appropriate polyethylene glycol in 50 mL of THF. The resulting mixture was stirred for 48 h at reflux temperature and hydrolyzed and the solvent was evaporated under vacuo. The residue was dissolved in $CHCl_3$ and washed with 4 M HCl and water. Subsequently, the chloroform layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was extracted with hot petroleum ether (60–80 °C) and chromatographed on silica gel with ethyl acetate–ethanol (90/10 v/v) or dichloromethane–methanol (95/5 v/v) as eluent.

2-Bromo-1,3-xylyl-15-crown-4 (1a):[29] yield 47%; mp 43–47 °C; mass spectrum, *m/e* 330.043 (M^+, calcd 330.047); ^1H NMR δ 3.35–3.7 (m, 12 H, OCH_2), 4.29 and 5.11 (AB q, J_{AB} = 16 Hz, 4 H, Ar CH_2), 7.26 (s, 3 H, Ar H); ^{13}C NMR δ 69.0–73.5 (t, OCH_2), 125.9 (d, Ar C-5), 131.3 (d, Ar C-4 and C-6), 128.2 (s, Ar C-2), 138.4 (s, Ar C-1 and C-3).

Anal. Calcd for $C_{14}H_{19}BrO_4$ (331.210): C, 50.77; H, 5.78. Found: C, 50.93; H, 5.80.

2-Bromo-1,3-xylyl-18-crown-5 (1b): yield 88%; mp 42–44 °C; mass spectrum, *m/e* 374.077 (M^+, calcd 374.073); ^1H NMR δ 3.50–3.70 (m, 16 H, OCH_2), 4.70 (s, 4 H, Ar CH_2), 7.31 (s, 3 H, Ar H); ^{13}C NMR δ 69.0–73.4 (t, OCH_2), 126.5 (d, Ar C-5), 126.7 (s, Ar C-2), 130.4 (d, Ar C-4 and C-6), 138.3 (s, Ar C-1 and C-3).

Anal. Calcd for $C_{16}H_{23}BrO_5$ (375.264): C, 51.21; H, 6.18. Found: C, 51.25; H, 6.16.

2-Bromo-1,3-xylyl-21-crown-6 (1c): yield 41% (oil); mass spectrum, *m/e* 418.097 (M^+, calcd for $C_{18}H_{27}BrO_6$ 418.099); ^1H

(26) Watson, S. C.; Eastman, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
(27) Kyba, E. P.; Helgeson, R. C.; Madan, K.; Gokel, G. W.; Tarnowski, T. L.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 2564.
(28) Schlesinger, H. I.; Brown, H. C.; Mayfield, D. L.; Gilbreath, J. R. *J. Am. Chem. Soc.* **1953**, *75*, 213.
(29) The official Chemical Abstracts names of these 1,3-xylyl crown ethers are based on the bicyclic structure, e.g.: **1**, 18-bromo-3,6,9,12-tetraoxabicyclo[12.3.1]octadeca-1(18),14,16-triene.

NMR δ 3.55–3.75 (m, 24 H, OCH_2), 4.70 (s, 4 H, Ar CH_2), 7.36 (m, 3 H, Ar H); ^{13}C NMR δ 69.4–73.3 (t, OCH_2), 125.2 (s, Ar C-2), 126.8 (d, Ar C-5), 129.5 (d, Ar C-4 and C-6), 138.2 (s, Ar C-1 and C-3).

2-Bromo-1,3-xylyl-24-crown-7 (1d): yield 73%; mp 55–58 °C; mass spectrum, *m/e* 462.124 (M^+, calcd 462.125); ^1H NMR δ 3.55–3.70 (m, 24 H, OCH_2), 4.70 (s, 4 H, Ar CH_2), 7.46 (s, 3 H, Ar H); ^{13}C NMR δ 69.9–72.8 (t, OCH_2), 123.3 (s, Ar C-2), 127.3 (d, Ar C-5), 128.5 (d, Ar C-4 and C-6), 138.0 (s, Ar C-1 and C-3).

Anal. Calcd for $C_{20}H_{31}BrO_7$ (463.372): C, 51.84; H, 6.74. Found: C, 51.78; H, 6.96.

2-Bromo-1,3-xylyl-27-crown-8 (1e): yield 61% (oil); mass spectrum, *m/e* 506.152 (M^+, calcd for $C_{22}H_{35}BrO_8$ 506.152): 506.152); ^1H δ 3.55–3.75 (m, 28 H, OCH_2), 4.68 (s, 4 H, Ar CH_2), 7.48 (m, 3 H, Ar H); ^{13}C NMR δ 68.8–72.6 (t, OCH_2), 122.5 (s, Ar C-2), 127.2 (d, Ar C-5), 128.0 (d, Ar C-4 and C-6), 138.0 (s, Ar C-1 and C-3).

2-Bromo-1,3-xylyl-30-crown-9 (1f): yield 61% (oil); mass spectrum, *m/e* 550.186 (M^+, calcd for $C_{24}H_{39}BrO_9$ 550.178); ^1H NMR δ 3.60–3.75 (m, 32 H, OCH_2), 4.67 (s, 4 H, Ar CH_2), 7.45 (m, 3 H, Ar H); ^{13}C NMR δ 70.1–72.7 (t, OCH_2), 122.6 (s, Ar C-2), 127.2 (d, Ar C-5), 128.0 (d, Ar C-4 and C-6), 138.0 (s, Ar C-1 and C-3).

2-Bromo-1,3-xylyl-33-crown-10 (1g): yield 60% (oil); mass spectrum, *m/e* 594.206 (M^+, calcd for $C_{26}H_{43}BrO_{10}$ 594.204); ^1H NMR δ 3.60–3.75 (m, 36 H, OCH_2), 4.66 (s, 4 H, Ar CH_2), 7.44 (m, 3 H, Ar H); ^{13}C NMR δ 70.0–72.7 (t, OCH_2), 122.3 (s, Ar C-2), 127.2 (d, Ar C-5), 128.0 (d, Ar C-4 and C-6), 138.0 (s, Ar C-1 and C-3).

2-Lithio-1,3-xylyl Crown Ethers 2. To a solution of 1.5 mmol of 2-bromo-1,3-xylyl crown ether **1** in 5 mL of THF was added 1.1 equiv of *n*-butyllithium (1.5 M in hexane) slowly at −78 °C. The bromine-to-lithium exchange was completed after 2 h and the 2-lithio-1,3-xylyl crown ether **2** was quenched with an electrophile.

2-(Methylthio)-1,3-xylyl Crown Ethers 3. General Procedure. An excess (3 equiv) of dimethyl disulfide was added at −78 °C to the solution of the 2-lithio-1,3-xylyl crown ether **2**. The reaction mixture was warmed to room temperature, acidified with 4 M HCl, and extracted with chloroform (3 × 20 mL). The combined chloroform layers were washed with water and dried over $MgSO_4$. After evaporation of the solvent the crude 2-(methylthio)-1,3-xylyl crown ether **3** was purified by column chromatography on silica gel with chloroform as eluent. The solid crown ethers were recrystallized from diethyl ether.

2-(Methylthio)-1,3-xylyl-15-crown-4 (3a): yield 54%; mp 49–51 °C; mass spectrum, *m/e* 298.124 (M^+, calcd for $C_{15}H_{22}O_4S$ 298.124); ^1H NMR δ 2.33 (s, 3 H, SCH_3), 3.0–3.7 (m, 12 H, OCH_2), 4.33 and 5.37 (AB q, J_{AB} = 12 Hz, 4 H, Ar CH_2), 7.32 (m, 3 H, Ar H); ^{13}C NMR δ 20.5 (q, SCH_3), 68.6–72.3 (t, OCH_2), 127.2 (d, Ar C-5), 130.4 (d, Ar C-4 and C-6), 138.1 (s, Ar C-2), 143.1 (s, Ar C-1 and C-3).

2-(Methylthio)-1,3-xylyl-18-crown-5 (3b): yield 75%; mp 52–53 °C; mass spectrum, *m/e* 342.154 (M^+, calcd 342.150); ^1H NMR δ 2.47 (s, 3 H, SCH_3), 3.46 (s, 8 H, OCH_2), 3.58 (s, 8 H, OCH_2), 4.87 (s, 4 H, Ar CH_2), 7.34 (m, 3 H, Ar H); ^{13}C NMR δ 20.9 (q, SCH_3), 68.6–72.6 (t, OCH_2), 127.6 (d, Ar C-5), 130.6 (d, Ar C-4 and C-6), 138.1 (s, Ar C-2), 143.1 (s, Ar C-1 and C-3).

Anal. Calcd for $C_{17}H_{26}O_5S$ (342.459): C, 59.62; H, 7.65. Found: C, 59.77; H, 7.73.

2-(Methylthio)-1,3-xylyl-24-crown-7 (3d): yield 79%; mp 47–48 °C; mass spectrum, *m/e* 430.196 (M^+, calcd for $C_{21}H_{34}O_7S$ 430.202); ^1H NMR δ 2.34 (s, 3 H, SCH_3), 3.55–3.75 (m, 24 H, OCH_2), 4.87 (s, 4 H, Ar CH_2), 7.3–7.6 (m, 3 H, Ar H); ^{13}C NMR δ 20.5 (q, SCH_3), 69.7–72.0 (t, OCH_2), 128.6 (d, Ar C-5), 128.9 (d, Ar C-4 and C-6), 135.2 (s, Ar C-2), 142.7 (s, Ar C-1 and C-3).

2-(Methylthio)-1,3-xylyl-27-crown-8 (3e): yield 83% (oil): mass spectrum, *m/e* 474.231 (M^+, calcd for $C_{23}H_{38}O_8S$ 474.229); ^1H NMR δ 2.30 (s, 3 H, SCH_3), 3.55–3.75 (m, 28 H, OCH_2), 4.88 (s, 4 H, Ar CH_2), 7.49 (m, 3 H, Ar H); ^{13}C NMR δ 20.2 (q, SCH_3), 69.5–72.0 (t, OCH_2), 128.3 (d, Ar C-4 and C-6), 128.7 (d, Ar C-5), 133.9 (s, Ar C-2), 142.7 (s, Ar C-1 and C-3).

2-(Methylthio)-1,3-xylyl-30-crown-9 (3f): yield 93% (oil); mass spectrum, *m/e* 518.248 (M^+, calcd for $C_{25}H_{42}O_9S$ 518.255); ^1H NMR δ 2.29 (s, 3 H, SCH_3), 3.60–3.75 (m, 32 H, OCH_2), 4.87 (s, 4 H, Ar CH_2), 7.47 (m, 3 H, Ar H); ^{13}C NMR δ 20.1 (q, SCH_3), 69.5–73.1 (t, OCH_2), 128.2 (d, Ar C-4 and C-6), 128.7 (d, Ar C-5), 138.5 (s, Ar C-2), 142.7 (s, Ar C-1 and C-3).

2-(Methylthio)-1,3-xylyl-33-crown-10 (3g): yield 87% (oil); mass spectrum, *m/e* 562.273 (M^+, calcd for $C_{27}H_{46}O_{10}S$ 562.281); ^1H NMR δ 2.29 (s, 3 H, SCH_3), 3.60–3.72 (m, 36 H, OCH_2), 4.87 (s, 4 H, Ar CH_2), 7.46 (m, 3 H, Ar H); ^{13}C NMR δ 20.1 (q, SCH_3), 69.9–71.7 (t, OCH_2), 128.2 (d, Ar C-4 and C-6), 128.7 (d, Ar C-5), 134.0 (s, Ar C-2), 142.6 (s, Ar C-1 and C-3).

2-Formyl-1,3-xylyl Crown Ethers 4. General Procedure. An excess (3 equiv) of *N,N*-dimethylformamide was added at −78 °C to the solution of a 2-lithio-1,3-xylyl crown ether. The reaction mixture was stirred for 2 h at −78 °C, slowly warmed to room temperature, next hydrolyzed with 4 M HCl, and extracted with chloroform (3 × 20 mL). The combined chloroform layers were washed with water (2 × 20 mL) and dried over $MgSO_4$ to obtain, after concentration, the crude 2-formyl-1,3-xylyl crown ethers **4**.

2-Formyl-1,3-xylyl-18-crown-5 (4b): mass spectrum, *m/e* 324.155 (M^+, calcd for $C_{17}H_{24}O_6$ 324.157); ^1H NMR δ 3.55–3.75 (m, 16 H, OCH_2), 4.78 (s, 4 H, Ar CH_2), 7.15–7.70 (m, 3 H, Ar H), 10.72 (s, 1 H, CHO); IR (KBr) 1690 (C=O) cm^{-1}.

2-Formyl-1,3-xylyl-21-crown-6 (4c): mass spectrum, *m/e* 368.184 (M^+, calcd for $C_{19}H_{28}O_7$ 368.184); ^1H NMR δ 3.55–3.70 (m, 20 H, OCH_2), 4.89 (s, 4 H, Ar CH_2), 7.25–7.55 (m, 3 H, Ar H), 10.65 (s, 1 H, CHO); ^{13}C NMR δ 69.3–72.6 (t, OCH_2), 128.8 (d, Ar C-4 and C-6), 132.9 (d, Ar C-5), 138.2 (s, Ar C-2), 140.6 (s, Ar C-1 and C-3), 194.6 (s, CHO); IR (KBr) 1690 (C=O) cm^{-1}.

2-Formyl-1,3-xylyl-24-crown-7 (4d): mass spectrum, *m/e* 412.210 (M^+, calcd for $C_{21}H_{32}O_8$ 412.210); ^1H NMR δ 3.60–3.75 (m, 24 H, OCH_2), 4.92 (s, 4 H, Ar CH_2), 7.20–7.60 (m, 3 H, Ar H), 10.58 (s, 1 H, CHO); ^{13}C NMR δ 69.3–72.5 (t, OCH_2), 128.3 (d, Ar C-4 and C-6), 132.6 (d, Ar C-5), 136.2 (s, Ar C-2), 141.1 (s, Ar C-1 and C-3), 193.8 (s, CHO); IR (KBr) 1690 (C=O) cm^{-1}.

2-Formyl-1,3-xylyl-27-crown-8 (4e): mass spectrum, *m/e* 456.228 (M^+, calcd for $C_{23}H_{36}O_9$ 456.236); ^1H NMR δ 3.55–3.75 (m, 28 H, OCH_2), 4.93 (s, 4 H, Ar CH_2), 7.20–7.60 (m, 3 H, Ar H), 10.57 (s, 1 H, CHO); ^{13}C NMR δ 69.2–72.5 (t, OCH_2), 128.1 (d, Ar C-4 and C-6), 132.8 (d, Ar C-5), 141.2 (s, Ar C-1 and C-3), 193.5 (s, CHO); IR (KBr) 1690 (C=O) cm^{-1}.

2-Formyl-1,3-xylyl-33-crown-10 (4g): mass spectrum, *m/e* 544.291 (M^+, calcd for $C_{27}H_{44}O_{11}$ 544.288); ^1H NMR δ 3.60–3.70 (m, 36 H, OCH_2), 4.91 (s, 4 H, Ar CH_2), 7.16–7.60 (m, 3 H, Ar H), 10.55 (s, 1 H, CHO); ^{13}C NMR δ 69.4–73.0 (t, OCH_2), 128.1 (d, Ar C-4 and C-6), 132.8 (d, Ar C-5), 138.3 (s, Ar C-2), 141.3 (s, Ar C-1 and C-3), 193.4 (s, CHO); IR (KBr) 1690 (C=O) cm^{-1}.

2-Carboxy-1,3-xylyl Crown Ethers 5. General Procedure. CO_2 was passed through a stirred solution of the 2-lithio-1,3-xylyl crown ether in THF during 30 min at −78 °C and the temperature of the mixture was allowed to rise to room temperature. Subsequently, the reaction mixture was acidified with 4 M HCl and extracted with chloroform (3 × 20 mL). The combined chloroform layers were extracted with a 4 M NaOH solution (3 × 20 mL). Subsequently the basic aqueous extracts were acidified and extracted with dichloromethane (3 × 20 mL). The combined dichloromethane layers were washed with water and dried over $MgSO_4$, to obtain, after concentration in vacuo, the pure 2-carboxy-1,3-xylyl crown ether (**5**) with spectral data in agreement with those previously reported.[4,5]

2-Sulfino-1,3-xylyl Crown Ethers 6. General Procedure. SO_2 was passed through a solution of the 2-lithio-1,3-xylyl crown ether in THF for 30 min at −78 °C. The reaction mixture was slowly warmed to room temperature and subsequently concentrated in vacuo. The residue was redissolved under argon in 15 mL of $CHCl_3$ and extracted with 10% NaOH (2 × 15 mL) and with water (2 × 20 mL). The combined aqueous phases were concentrated in vacuo, acidified with 4 M HCl, and subsequently extracted with chloroform (5 × 15 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated in vacuo to give the 2-sulfino-1,3-xylyl crown ether (**6**).

2-Sulfino-1,3-xylyl-15-crown-4 (6a): yield 65%; mp 102–104 °C (Et_2O); mass spectrum, *m/e* 298.085 ($M^+ - H_2O$, calcd for $C_{14}H_{18}O_5S$, 298.087); ^1H NMR δ 3.25–3.70 (m, 12 H, OCH_2), 4.16 and 5.88 (AB q, J_{AB} = 13 Hz, 4 H, Ar CH_2), 7.32 (s, 3 H, Ar H); ^{13}C NMR δ 68.6–70.3 (t, OCH_2), 130.0 (d, Ar C-4 and C-6), 131.8 (d, Ar C-5), 137.8 (s, Ar C-1 and C-3), 147.9 (s, Ar C-2).

Anal. Calcd for $C_{14}H_{20}O_6S$ (316.378): C, 53.15; H, 6.37. Found: C, 52.70; H, 6.35.

2-Sulfino-1,3-xylyl-18-crown-5 (6b): yield 67%; mp 101–104 °C (Et_2O); mass spectrum, *m/e* 359.119 (M^+ – H, calcd for $C_{16}H_{23}O_7S$, 359.121); ^1H NMR δ 3.5–3.65 (m, 16 H, OCH_2), 4.98 (br s, 4 H, Ar CH_2), 7.31 (s, 3 H, Ar H); ^{13}C NMR δ 68.7–70.7 (t, OCH_2), 130.4 (d, Ar C-4 and C-6), 131.4 (d, Ar C-5), 137.1 (s, Ar C-1 and C-3).

2-Sulfino-1,3-xylyl-21-crown-6 (6c): yield 79%; mp 66–67 °C (Et_2O); mass spectrum, *m/e* 340.193 (M^+ – SO_2, calcd for $C_{18}H_{28}O_6$ 340.189); ^1H NMR δ 3.59–3.70 (m, 20 H, OCH_2), 4.99 (s, 4 H, Ar CH_2), 7.37 (m, 3 H, Ar H); ^{13}C NMR δ 69.6–71.9 (t, OCH_2), 130.5 (d, Ar C-4 and C-6), 130.8 (d, Ar C-5), 136.7 (s, Ar C-1 and C-3), 146.6 (s, Ar C-2).

2-Sulfino-1,3-xylyl-24-crown-7 (6d): yield 89% (oil); mass spectrum, *m/e* 384.209 (M^+ – SO_2, calcd for $C_{20}H_{32}O_7$ 384.215); ^1H NMR δ 3.55–3.80 (m, 24 H, OCH_2), 5.00 (s, 4 H, Ar CH_2), 7.39 (s, 3 H, Ar H), 8.5 (br s, 1 H, SO_2H); ^{13}C NMR δ 69.8–70.8 (t, OCH_2), 130.1 (d, Ar C-4 and C-6), 130.8 (d, Ar C-5), 136.6 (s, Ar C-1 and C-3), 146.1 (s, Ar C-2).

2-Sulfino-1,3-xylyl-27-crown-8 (6e): yield 57% (oil); mass spectrum, *m/e* 428.234 (M^+ – SO_2, calcd for $C_{22}H_{36}O_8$ 428.241); ^1H NMR δ 3.55–3.75 (m, 28 H, OCH_2), 4.99 (s, 4 H, Ar CH_2), 7.40 (s, 3 H, Ar H), 8.0 (br s, 1 H, SO_2H); ^{13}C NMR δ 69.7–71.5 (t, OCH_2), 130.0 (d, Ar C-4 and C-6), 130.7 (d, Ar C-5), 136.6 (s, Ar C-1 and C-3), 145.9 (s, Ar C-2).

2-Sulfino-1,3-xylyl-30-crown-9 (6f): yield 70% (oil); mass spectrum, *m/e* 472.257 (M^+ – SO_2, calcd for $C_{24}H_{40}O_9$ 472.267); ^1H NMR δ 3.50–3.80 (m, 32 H, OCH_2), 4.99 (s, 4 H, Ar CH_2), 7.42 (s, 3 H, Ar H), 8.8 (br s, 1 H, SO_2H); ^{13}C NMR δ 69.7–70.7 (t, OCH_2), 130.1 (d, Ar C-4 and C-6), 130.8 (d, Ar C-5), 136.7 (s, Ar C-1 and C-3), 146.2 (s, Ar C-2).

2-Sulfino-1,3-xylyl-33-crown-10 (6g): yield 61% (oil); mass spectrum, *m/e* 516.283 (M^+ – SO_2, calcd for $C_{26}H_{44}O_{10}$ 516.293); ^1H NMR δ 3.45–3.70 (m, 36 H, OCH_2), 4.99 (s, 4 H, Ar CH_2), 7.41 (m, 3 H, Ar H), 7.5 (br s, 1 H, SO_2H); ^{13}C NMR δ 69.7–70.6 (t, OCH_2), 130.0 (d, Ar C-4 and C-6), 130.8 (d, Ar C-5), 136.6 (s, Ar C-1 and C-3), 145.9 (s, Ar C-2).

2-Hydroxy-1,3-xylyl Crown Ethers 8. General Procedure. An excess (3 equiv) of trimethyl borate was added at −78 °C to a solution of the 2-lithio-1,3-xylyl crown ether **2**. The reaction mixture was stirred at −78 °C for 2 h and slowly warmed to room temperature. Subsequently 5 mL of 4 N HCl was added and the reaction mixture was stirred for another 20 h. The THF was distilled off and the water phase was extracted with chloroform (3 × 30 mL). The combined chloroform layers were concentrated to ca. 20 mL and subsequently extracted with 3 N NaOH (3 × 15 mL) and water. The combined aqueous layers were washed with chloroform, acidified to pH 2, extracted with chloroform (4 × 25 mL), washed with water (20 mL), and dried over $MgSO_4$. After evaporation of the solvent, the residual colorless oil was dissolved in 20 mL of diethyl ether, and 10% hydrogen peroxide (480 μL) and 10% $NaHCO_3$ (160 μL) were added. The mixture was stirred at room temperature for 6 h. Subsequently 2 M HCl (5 mL) was added and the mixture was extracted with chloroform (3 × 25 mL). The chloroform layers were washed with water and dried over $MgSO_4$, to obtain, after concentration, the crude 2-hydroxy-1,3-xylyl crown ether **8**, which was purified by chromatography [SiO_2, ethanol–chloroform (3/97 v/v)].

2-Hydroxy-1,3-xylyl-15-crown-4 (8a): yield 63%; mp 65–66 °C (heptane) (lit.[6c] mp 66–66.5 °C); mass spectrum, *m/e* 268.132 (M^+, calcd for $C_{14}H_{20}O_5$ 268.131); ^1H NMR δ 3.5–3.7 (m, 12 H, OCH_2), 4.61 (s, 4 H, Ar CH_2), 6.6–7.2 (m, 3 H, Ar H), 7.66 (s, 1 H, OH); ^{13}C NMR δ 68.7, 69.4, and 70.2 (t, OCH_2), 119.4 (d, Ar C-5), 125.9 (s, Ar C-1 and C-3), 130.2 (d, Ar C-4 and C-6), 156.0 (s, Ar C-2); IR (KBr) 3360 (OH) cm^{-1}.

2-Hydroxy-1,3-xylyl-18-crown-5 (8b): yield 57%; mp 49–50 °C (heptane) (lit.[6c] mp 49–51 °C); mass spectrum, *m/e* 312.155 (M^+, calcd for $C_{16}H_{24}O_6$ 312.157); ^1H NMR δ 3.70 (s, 16 H, OCH_2), 4.67 (s, 4 H, Ar CH_2), 6.6–7.2 (m, 3 H, Ar H), 8.0 (br s, 1 H, OH); ^{13}C NMR δ 69.2–70.6 (t, OCH_2), 119.2 (d, Ar C-5), 124.7 (s, Ar C-1 and C-3), 129.7 (d, Ar C-4 and C-6), 155.7 (s, Ar C-2); IR (KBr) 3350 (OH) cm^{-1}.

2-Hydroxy-1,3-xylyl-21-crown-6 (8c): yield 63% (oil); mass spectrum, *m/e* 356.186 (M^+, calcd for $C_{18}H_{28}O_7$ 356.186); ^1H NMR δ 3.6–3.8 (m, 20 H, OCH_2), 4.90 (s, 4 H, Ar CH_2), 6.7–7.2 (m, 3 H, Ar H), 7.87 (s, 1 H, OH); ^{13}C NMR δ 69.6–71.0 (t, OCH_2), 119.2 (d, Ar C-5), 124.4 (s, Ar C-1 and C-3), 128.8 (d, Ar C-4 and C-6), 154.6 (s, Ar C-2); IR (KBr) 3360 (OH) cm^{-1}.

Table II. Crystal Data and Data Collection Parameters

	1b	6b
formula	$C_{16}H_{23}BrO_5$	$C_{16}H_{24}O_7S$
M_r	375.27	360.43
lattice type	monoclinic	orthorhombic
space group	$P2_1/n$	$P2_12_12_1$
T, K	173	166
cell dimensions		
a, Å	11.464 (2)	9.385 (1)
b, Å	8.082 (1)	12.686 (3)
c, Å	18.294 (4)	14.673 (4)
β, deg	97.95 (2)	
V, Å^3	1679 (1)	1747 (1)
Z	4	4
D_c, g cm^{-3}	1.48	1.37
$F(000)$	776	768
μ, cm^{-1}	24.4	2.1
θ range, deg	3–25	3–27.5
no. unique reflctns		
measd	2949	2275
obsd	1449	1250
no. variables	292	230
R, %	2.5	5.8
R_w, %	3.0	8.2
weighting factor p	0.04	0.08
extinctn g (×10^{-7})	0.7(3)	0.0

2-Hydroxy-1,3-xylyl-24-crown-7 (8d): yield 61% (oil); mass spectrum, *m/e* 400.206 (M^+, calcd for $C_{20}H_{32}O_8$ 400.210); ^1H NMR δ 3.6–3.8 (m, 24 H, OCH_2), 4.69 (s, 4 H, Ar CH_2), 6.7–7.3 (m, 3 H, Ar H), 7.9 (s, 1 H, OH); ^{13}C NMR δ 69.7–70.9 (t, OCH_2), 119.3 (d, Ar C-5), 124.2 (s, Ar C-1 and C-3), 128.8 (d, Ar C-4 and C-6), 154.5 (s, Ar C-2); IR (KBr) 3350 (OH) cm^{-1}.

2-Hydroxy-1,3-xylyl-27-crown-8 (8e): yield 61% (oil); mass spectrum, *m/e* 444.228 (M^+, calcd for $C_{22}H_{36}O_9$ 444.236); ^1H NMR δ 3.6–3.8 (m, 28 H, OCH_2), 4.68 (s, 4 H, Ar CH_2), 6.7–7.35 (m, 3 H, Ar H), 7.88 (s, 1 H, OH); ^{13}C NMR δ 69.6–70.7 (t, OCH_2), 119.3 (d, Ar C-5), 124.1 (s, Ar C-1 and C-3), 128.7 (d, Ar C-4 and C-6), 154.5 (s, Ar C-2); IR (KBr) 3360 (OH) cm^{-1}.

2-Hydroxy-1,3-xylyl-30-crown-9 (8f): yield 66% (oil); mass spectrum, *m/e* 488.259 (M^+, calcd for $C_{24}H_{40}O_{10}$ 488.262); ^1H NMR δ 3.6–3.8 (m, 32 H, OCH_2), 4.68 (s, 4 H, Ar CH_2), 6.7–7.35 (m, 3 H, Ar H), 7.84 (s, 1 H, OH); ^{13}C NMR δ 69.5–70.6 (t, OCH_2), 119.3 (d, Ar C-5), 124.1 (s, Ar C-1 and C-3), 128.5 (d, Ar C-4 and C-6), 154.3 (s, Ar C-2); IR (KBr) 3360 (OH) cm^{-1}.

2-Hydroxy-1,3-xylyl-33-crown-10 (8g): yield 30% (oil); mass spectrum, *m/e* 532.286 (M^+, calcd for $C_{26}H_{44}O_{11}$ 532.288); ^1H NMR δ 3.6–3.8 (m, 36 H, OCH_2), 4.68 (s, 4 H, Ar CH_2), 6.7–7.3 (m, 3 H, Ar H), 7.8 (br s, 1 H, OH); ^{13}C NMR δ 69.6–70.7 (t, OCH_2), 119.3 (d, Ar C-5), 124.1 (s, Ar C-1 and C-3), 128.6 (d, Ar C-4 and C-6), 154.3 (s, Ar C-2); IR (KBr) 3360 (OH) cm^{-1}.

X-ray Crystallography. X-ray diffraction measurements were performed on an Enraf-Nonius CAD4 diffractometer, using graphite-monochromated Mo Kα radiation. Crystal data and data collection parameters are given in Table II. Lattice parameters were determined by least-squares refinement from 25 centered reflections. Intensities were measured in the $\omega/2\theta$ scan mode and corrected for the decay of three control reflections, measured every hour, and for Lorentz polarization.

The structures were solved by direct methods.[30] Reflections with $F_o^2 > 3\sigma(F_o^2)$ were considered observed and included in the refinement (on F) by full-matrix least squares; weights were calculated as $w = 4F_o^2/\sigma^2(F_o^2)$, $\sigma^2(F_o^2) = \sigma^2(I) + (pF_o^2)^2$, $\sigma(I)$ based on counting statistics and p an instability factor obtained from plots of F_o vs weighted error. After completion of the isotropic refinement of the non-H atoms, an empirical absorption correction, using the DIFABS[31] routine, was performed for both structures. All H atoms were located on difference Fourier maps of the structures. For **1b**, all H atoms were included in the refinement. For **6b**, the sulfino H atom was included in the refinement; all other H atoms were put in calculated positions and treated as riding on their

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parent C atoms. Further details concerning the treatment of the H atoms are in the supplementary material. In the structure of **6b**, the sulfino group was found to be disordered; for the S and the (S=)O atom two partly occupied positions were found and refined to occupancies of 60% and 40%, respectively. The two partly occupied (S=)O positions could only be refined isotropically. Parameters refined were the overall scale factor, an isotropic extinction parameter g ($F_o = F_c/(1 + gI_c)$), positional and anisotropic thermal parameters for non-H atoms, and positional and isotropic thermal parameters for H atoms. Refinement converged with shift/error ratios less than unity. Final difference Fourier maps showed no significant features. All calculations were done with SDP.[32]

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Registry No. **1a**, 111982-21-9; **1b**, 55440-88-5; **1c**, 111982-22-0; **1d**, 111982-23-1; **1e**, 111982-24-2; **1f**, 111982-25-3; **1g**, 102096-98-0; **3a**, 116748-69-7; **3b**, 116748-70-0; **3d**, 116748-71-1; **3e**, 116748-72-2; **3f**, 116748-73-3; **3g**, 116748-74-4; **4b**, 116748-75-5; **4c**, 116748-76-6; **4d**, 116748-77-7; **4e**, 116748-78-8; **4g**, 116748-79-9; **5a**, 55440-82-9; **5b**, 55440-83-0; **5c**, 55440-84-1; **5d**, 103304-41-2; **5e**, 103304-43-4; **5f**, 55440-85-2; **5g**, 103304-45-6; **6a**, 111982-26-4; **6b**, 111970-24-2; **6c**, 111970-25-3; **6d**, 111970-26-4; **6e**, 111970-27-5; **6f**, 111970-28-6; **6g**, 111970-29-7; **8a**, 65112-35-8; **8b**, 65112-36-9; **8c**, 94707-40-1; **8d**, 116748-80-2; **8e**, 116748-81-3; **8f**, 116748-82-4; **8g**, 116748-83-5; $HO((CH_2)_2O)_3H$, 112-27-6; $HO((CH_2)_2O)_4H$, 112-60-7; $HO((CH_2)_2O)_5H$, 4792-15-8; $HO((CH_2)_2O)_6H$, 2615-15-8; $HO((CH_2)_2O)_7H$, 5617-32-3; $HO((CH_2)_2O)_8H$, 5117-19-1; $HO((CH_2)_2O)_9H$, 3386-18-3; 2-bromo-1,3-bis(bromomethyl)benzene, 25006-88-6; benzo-15-crown-5, 14098-44-3; benzo-18-crown-6, 14098-24-9; 3-(methylthio)benzo-15-crown-5, 116748-84-6; 3-(methylthio)benzo-18-crown-6, 116748-85-7.

Supplementary Material Available: Tables of positional and thermal parameters of all atoms, bond distances and angles, and torsion angles in the macrocycle, for the crystal structures of compounds **1b** and **6b** (10 pages). Ordering information is given on any current masthead page.

Stereoselective Intramolecular Haloamidation of N-Protected 3-Hydroxy-4-pentenylamines and 4-Hydroxy-5-hexenylamines

Yoshinao Tamaru,* Shin-ichi Kawamura, Takashi Bando, Kunitada Tanaka, Makoto Hojo, and Zen-ichi Yoshida*

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Kyoto 606, Japan

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Haloamidation of *N*-(*p*-tolylsulfonyl)-3-hydroxy-4-pentenylamines proceeds regio- and stereoselectively to provide *cis*-2-(halomethyl)-3-hydroxypyrrolidines in high yields. The tosylamides with phenyl and dimethyl substituents at C-5 cyclize to give six-membered piperidine products. *N*-(Methoxycarbonyl)-3-hydroxy-4-pentenylamines undergo a similar cyclization to furnish *cis*-*N*-(methoxycarbonyl)-2-(halomethyl)-3-hydroxypyrrolidines, which further undergo a cyclization to give bicyclic oxazolidones (1-aza-3-oxabicyclo[3.3.0]octan-2-ones). The above reactions proceed *in the dark*, while the haloamidation of *N*-(*p*-tolylsulfonyl)-4-hydroxy-5-hexenylamine only proceeds *upon exposure to ambient light* and provides 2-(halomethyl)-3-hydroxypiperidine.

Diastereoselective electrophilic addition to the double bond of allylic alcohols has attracted considerable interest in recent literature, and numerous experimental[1] and theoretical[2] approaches to this subject have appeared. The intramolecular version of the methodology, based on diastereoselective intramolecular addition of hetero nucleophiles, directed by an allylic hydroxyl group, has proved to be useful for the syntheses of heterocyclic compounds with stereochemically defined structures,[3] as exemplified by the syntheses of many natural products and their synthetic intermediates.

Most of these examples, however, are confined to the cyclization with oxygen nucleophiles. For example, 3-hydroxy-4-pentenoic acids[4] (and acid derivatives)[5] and 3-hydroxy-4-pentenols,[6] when treated with halogenating agents, stereoselectively provide *cis*-3-hydroxy-4-(halo-

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