Synthesis of novel chiral, cage-annulated macrocycles

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Dedicated to Professeor Kalevi Pihlaja on the occasion of his 60th birthday in recognition of his many significant contributions to organic and physical-organic chemistry

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Abstract

Methods used to prepare several new cage-annulated chiral macrocycles (i.e., **3a-3d**, **5**, **7**, and **12**) are reported. These novel host systems were synthesized either by incorporating an optically active monosaccharide derivative or a tartaric acid derivative into each crown ether to provide the source of chirality.

Keywords: Cyclic cage molecules, macrocyclic polyethers, host-guest chemistry

Introduction

Several chiral macrocylic crown ethers and related host systems have been synthesized, many of which are capable of forming complexes enantioselectively with chiral organic ammonium salts.[1] Despite some early successes, there is a clear need for the design and synthesis of additional chiral host molecules that will lead to an overall improvement in host-guest complexation efficiency, particularly with regard to enantioselectivity.

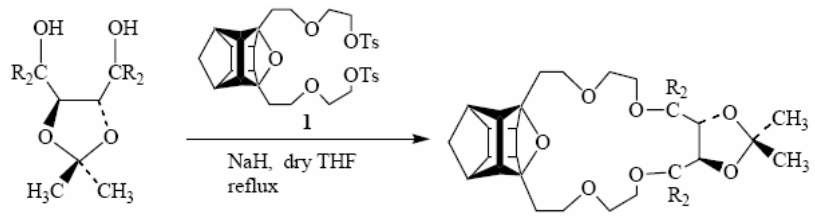
Incorporation of one or more chiral units into crown ethers was first reported by Cram[2] and subsequently by several other investigators.[3] The ability of optically active host systems of this type (i) to discriminate between the enantiomers of guest alkylammonium salts and (ii) to function as catalysts for a variety of organic reactions suggests their potential use as enzyme mimics.[4]

A particularly interesting group of chiral crown ethers contains carbohydrate units as the source of chirality. Compounds of this type have been reported by Stoddart,[3a,b] Penades,[5] and more recently by Seebach and coworkers.[6] Carbohydrates (monosaccharides) and simple derivatives of optically active tartaric acid are ideally suited for this purpose due to their ready availability and the ease with which they can be employed to prepare peripherally polyhydroxylated crown ethers by using routine synthetic protocols.

Pursuant to our ongoing interest in the synthesis of novel polycarbocyclic cage compounds,[7] we recently prepared several examples of cage functionalized molecular clefts[8] and crown

ethers.[9] Compounds of this type are of interest as members of new class of host systems for the study of host-guest interactions (i.e., molecular recognition and inclusion phenomena). In part, the incorporation of a cage moiety into chiral macrocycles affects their overall conformational mobility by introducing a measure of rigidity into the crown ether system. In addition, the cage moiety has been shown to influence the ability of cage-annulated crown ethers to serve as complexing ligands (relative to the corresponding noncage-containing crown ethers) by helping to define the size of the host cavity. Finally, the cage moiety serves as a lipophilic component, thereby improving the solubility of cage-containing crown ethers in nonpolar solvents relative to that of the corresponding noncage-containing systems.

As an extension of past investigations of host-guest interactions that involve cageannulated crown ethers as hosts, our attention has turned to the synthesis of chiral analogs, i.e., **3a-3d**, **5**, **7**, and **12** (Scheme 1). Compounds **2a-2d**, which were prepared from optically active (+)-diethyl **L**-tartrate),[10] provide the source of optical activity in crown ethers **3a-3d**. Simple monosaccharides provide the source of optical activity in the remaining host molecules, i.e., **5**, **7**, and **12**. The requisite syntheses and product characterizations are described below.



2a (R = H)
2b (R = CH_3)
2c (R = Ph)
2d (R = β-naphthyl)

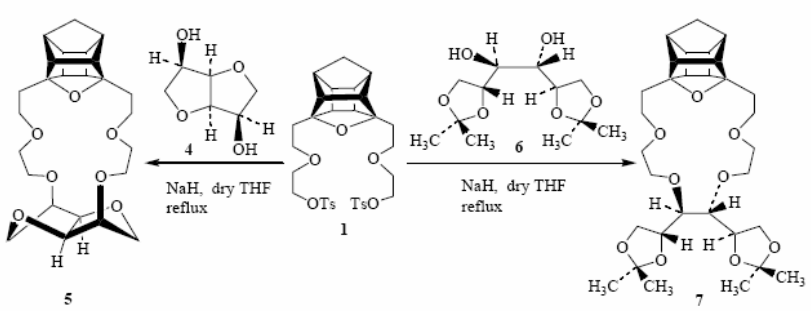
3a (R = H)
3b (R = CH_3)
3c (R = Ph)
3d (R = β-naphthyl)

Scheme 1

Results and Discussion

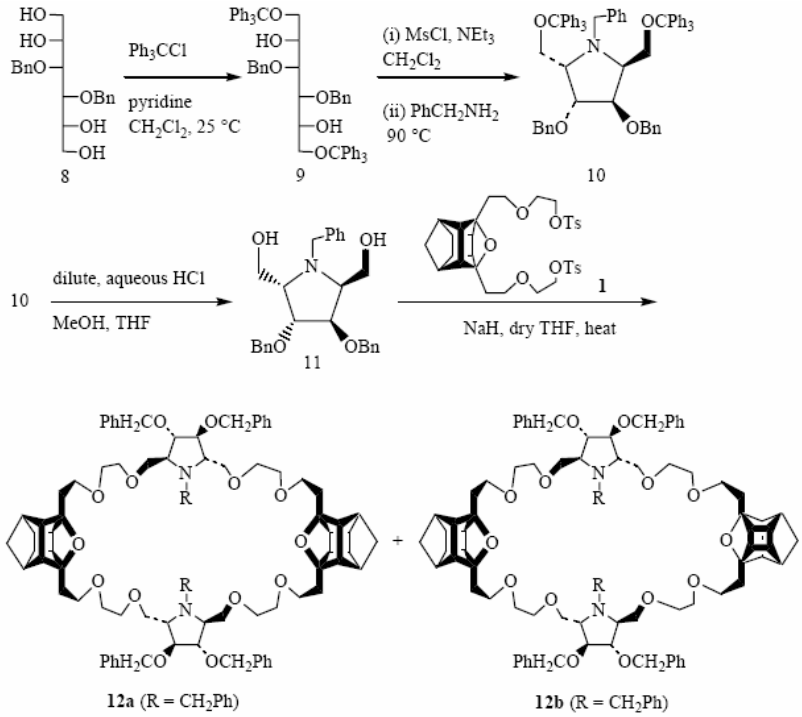
The approach employed to prepare four new chiral, cage-annulated crown ethers, i.e., **3a-3d**, is shown in Scheme 1. Thus, NaH promoted reaction of **1**[9c] with optically active[10] diol **2a** (which was prepared by starting with optically active (+)-diethyl **L**-tartrate)afforded the corresponding chiral, cage-annulated crown ether, **3a**, in 76% yield. Compounds **3b-3d** were prepared in analogous fashion by starting with optically active diols **2b**,[11] **2c**,[12] and **2d**,[12] respectively (Scheme 1).

A fifth chiral, cage annulated crown ether, i.e., **5**, was synthesized via NaH promoted reaction of **1**[9c] with optically active 1,4:3,6-dianhydro-**D**-(+)-mannitol (i.e., "isomannide", **4**, see Scheme 2). In addition, a sixth optically active crown ether, i.e., **7**, was prepared in similar fashion via NaH promoted reaction of **1**[9c] with optically active **6**[13] (derived from **D**-mannitol).



Scheme 2

Subsequently, **8** (Scheme 3) was prepared from **D**-mannitol in three steps by following a literature procedure.[14] The terminal CH2OH groups in **8** were protected via conversion of **8** to the corresponding bis(*O*-trityl) derivative, i.e., **9**. Sequential reaction of the remaining secondary OH groups in **9** with MsCl-pyridine followed by treatment of the resulting bis(mesylate ester) with benzylamine[15] afforded **10**. Subsequent acid promoted cleavage of the two *O*-trityl groups in **10** produced **11**[16] in 70% yield (Scheme 3).



Scheme 3

Interestingly, NaH promoted reaction of **11** with **1** resulted in the formation of a mixture of two diastereoisomeric, optically active crown ethers, i.e., **12a** and **12b** (Scheme 3). These diastereoisomeric macrocyclic crown ethers each resulted via 2 : 2 cyclization of **11** with **1**.

In summary, we have demonstrated herein that the chiral fragments **2a**-**2d**, **4**, **6**, and **11**, all of which can be prepared readily by starting with either **L**-tartaric acid or **D**-mannitol, can be coupled efficiently to a cage-containing moiety in a manner that results in the production of

seven novel, optically active crown ethers (i.e., **3a**-**3d**, **5**, **7**, and a diastereoisomeric mixture of **12a** and **12b**, respectively). We plan to report the results of our efforts to investigate the enantioselective complexation properties[17] of these unusual host systems in a future publication.

Experimental Section

General Procedures. Melting points are uncorrected. Elemental microanalytical data were obtained by personnel at M-H-W Laboratories, Phoenix, AZ. All ^{13}C NMR spectral integrations were performed on gated-decoupled NMR spectra. High-resolution mass spectral data reported herein were obtained at the Mass Spectrometry Facility at the Department of Chemistry and Biochemistry, University of Texas at Austin by using a ZAB-E double sector high-resolution mass spectrometer (Micromass, Manchester, England) that was operated in the chemical ionization mode.

Synthesis of crown ether (3a). A suspension of NaH (76 mg, 1.59 mmol, obtained as a 60% dispersion in mineral oil) in dry THF (5 mL) under argon was cooled to 0 °C via application of an external ice-water bath. To this cooled suspension was added dropwise with stirring under argon a solution of optically active diol (76 mg, 0.45 mmol) in dry THF (10 mL) during 15 minutes. After all of the diol had been added, the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 2 h. At that time, a solution of **1**[9c] (320 mg, 0.51 mmol) in dry THF (20 mL) was added dropwise with stirring to the reaction mixture during 1 h. After the addition of **1** had been completed, the reaction mixture was refluxed under argon during 4 days. The reaction mixture then was cooled 0 °C via application of an external ice-water bath, and the cooled reaction mixture subsequently was quenched via careful, dropwise addition of water (4 mL). The reaction mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc (40 mL). The resulting solution was washed sequentially with water (2 × 25 mL) and brine (1 × 30 mL). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue thereby obtained was purified via column chromatography on silica gel by eluting with 20% EtOAc in hexane to afford **3a** (172 mg, 76%), as a colorless viscous oil. $[\alpha]_D$ +9.4° (*c* 1.5, $CHCl_3$); IR (film) 2941 (s), 2858 (s), 1448 (w), 1371 (w), 1250 (m), 1116 cm^{-1} (s);^1H NMR ($CDCl_3$) δ 1.40 (s, 6 H), 1.48 (*A*B, *J*AB = 11.9 Hz, 1 H), 1.83 (A*B*, *J*AB = 11.9 Hz, 1 H), 1.96-2.06 (m, 4 H), 2.37 (br s, 2 H), 2.56-2.63 (m, 6 H), 3.56-3.71 (m, 16 H), 3.95-3.99 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 26.9 (q, 2 C), 32.4 (t, 2 C), 41.4 (d, 2 C), 43.4 (t), 43.9 (d, 2 C), 47.9 (d), 48.0 (d), 58.9 (d), 58.9 (d), 68.2 (t, 2 C), 70.1 (t, 2 C), 71.9 (t, 2 C), 72.0 (t, 2 C), 77.4 (d, 2 C), 94.3 (s, 2 C), 109.4 (s). Exact mass (CI HRMS) Calcd for $C_{26}H_{38}O_7$: $[Mr + H]^+$ *m/z* 463.2696. Found: $[Mr + H]^+$ *m/z* 463.2700.

Synthesis of crown ether (3b). Compound **3b** was prepared by starting with **2b** (56 mg, 0.26 mmol), **1** (181 mg, 0.28 mmol), and NaH (44 mg, 0.91 mmol) by following the procedure described previously for the synthesis of **3a** (*vide supra*). Crude **3b** thereby obtained was purified via column chromatography on silica gel by using 15% EtOAchexane as eluent. Workup of the chromatographic eluate afforded pure **3b** (103 mg, 72%) as a colorless microcrystalline solid: mp

136-138 °C, $[\alpha]_D$ = +11.2° (*c* 1.6, CHCl3); IR (KBr) 2933 (s), 2854 (m), 1479 (m), 1365 (s), 1238 (m), 1030 (m), 979 (w), 852 (s), 725 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.18 (s, 6 H), 1.21 (s, 3 H), 1.22 (s, 3 H), 1.45 (s, 6 H), 1.83 (*A*B, *J*AB = 8.0 Hz, 1 H), 1.95-2.02 (m, 5 H), 2.35-2.80 (m, 8 H), 3.40-3.89 (m, 12 H), 4.12 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.2 (q, 2 C), 22.8 (q, 2 C), 28.3 (q, 2 C), 32.6 (t, 2 C), 41.4 (d), 41.5 (d), 43.5 (t), 43.9 (d), 44.0 (d), 47.8 (d), 48.3 (d), 58.5 (d), 58.9 (d), 62.4 (t), 62.6 (t), 68.1 (t), 68.2 (t), 70.3 (t, 2 C), 75.9 (t, 2 C), 84.6 (d, 2 C), 94.5 (s, 2 C), 110.6 (s). Exact mass (CI HRMS) Calcd. for C30H46O7: $[Mr + H]^+$ *m/z* 519.33217. Found: $[Mr + H]^+$*m/z* 519.33290.

Synthesis of crown ether (3c). Compound **3c** was prepared by starting with **2c** (98 mg, 0.22 mmol), **1** (156 mg, 0.24 mmol), and NaH (36 mg, 0.76 mmol) and the ditosylate **1**(156 mg, 0.24 mmol) by following the procedure described previously for the synthesis of **3a** (*vide supra*). Crude **3c** thereby obtained was purified via column chromatography on silica gel by using 10% EtOAc-hexane as eluent. Workup of the chromatographic eluent afforded pure **3c** (150 mg, 66%) as a colorless, viscous oil. [α]D -21.1° (*c* 1.1, $CHCl_3$), IR (film) 2926 (s), 1580 (m), 1456 (s), 1366 (m), 1260 (m), 1070 (s), 736 (s),720 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.05 (s, 6 H), 1.55 (*A*B, *J*AB = 8.6 Hz, 1 H), 1.85-2.10 (m, 5 H), 2.38-2.81 (m, 8 H), 3.28-3.49 (m, 6 H), 3.50-3.68 (m, 2 H), 3.72 (t, *J* = 6.6 Hz,4 H), 4.75 (s, 2 H), 7.20-7.48 (m, 20 H); ^{13}C NMR (CDCl3) δ 27.4 (q, 2 C), 32.6 (t, 2 C),41.5 (d, 2 C), 43.6 (t), 44.0 (d, 2 C), 48.6 (d), 48.8 (d), 59.4 (d), 59.6 (d), 64.1 (t, 2 C), 68.6 (t, 2 C), 70.4 (t, 2 C), 79.4 (d, 2 C), 83.9 (s), 84.0 (s), 94.3 (s, 2 C), 107.2 (s), 126.6 (d, 4 C), 126.7 (d, 4 C), 126.9 (d, 2 C), 127.3 (d, 2 C), 129.2 (d, 2 C), 129.3 (d, 2 C), 129.6 (d, 4 C), 142.3 (s, 2 C), 143.5 (s), 143.6 (s). Exact mass (CI HRMS) Calcd for $C_{50}H_{54}O_7$: $[Mr + H]^+$ *m/z* 767.3948. Found: $[Mr + H]^+$ *m/z* 767.3942.

Synthesis of crown ether (3d). Compound **3d** was prepared by starting with **2d** (62 mg, 0.09 mmol), **1** (66 mg, 0.11 mmol), and NaH (15 mg, 0.28 mmol) by following the procedure described previously for the synthesis of **3a** (*vide supra*). Crude **3d** thereby obtained was purified via column chromatography on silica gel by using 10% EtOAc- hexane as eluent. Workup of the chromatographic eluate afforded pure **3d** (68 mg, 61%) as a colorless microcrystalline solid: mp 129-131 °C, $[\alpha]_D$ -47.2° (*c* 1.2, $CHCl_3$); IR(KBr) 3053 (s), 2955 (s), 2864 (s), 2362 (w), 1520 (s), 1376 (s), 1107 (s), 763 cm^{-1} (s);^1H NMR ($CDCl_3$) δ 1.38 (s, 6 H), 1.56 (*A*B, *J*AB = 10.9 Hz, 1 H), 1.88 (A*B*, *J*AB = 10.9 Hz, 1 H), 1.98-2.15 (m, 4 H), 2.40-2.51 (m, 2 H), 2.58-2.89 (m, 6 H), 3.25-3.98 (m, 12 H), 5.15 (s, 2 H), 7.20-8.12 (m, 28 H); ^{13}C NMR ($CDCl_3$) δ 27.4 (q, 2 C), 32.5 (t, 2 C), 41.4 (d, 2 C), 43.5 (t), 43.8 (d, 2 C), 48.4 (d, 2 C), 59.4 (d, 2 C), 64.6 (t, 2 C), 68.6 (t, 2 C), 70.2 (t, 2 C), 80.0 (d, 2 C), 84.1 (s, 2 C), 94.3 (s, 2 C), 107.3 (s), 125.6 (d, 2 C), 125.8 (d, 2 C), 125.9 (d, 2 C), 126.1 (d, 2 C), 126.2 (d, 2 C), 127.0 (d, 2 C), 127.2 (d, 2 C), 127.3 (d, 2 C), 127.8 (d, 2 C), 128.0 (d, 2 C), 128.1 (d, 2 C), 128.2 (d, 2 C), 128.4 (d, 2 C), 128.7 (d, 2 C), 132.4 (s, 2 C), 132.5 (s, 2 C), 139.8 (s, 2 C), 139.9 (s, 2 C), 140.8 (s, 2 C), 140.9 (s, 2 C). Exact mass (CI HRMS) Calcd for $C_{66}H_{62}O_7$: $[Mr + H]^+$ *m/z* 967.4574. Found: $[Mr + H]^+$ 967.4548.

Synthesis of crown ether (5). Compound **5** was prepared by starting with isomannide (**4**, 36 mg, 0.25 mmol), **1** (170 mg, 0.26 mmol), and NaH (40 mg, 0.84 mmol) by following the procedure described previously for the synthesis of **3a** (*vide supra*). Crude **5** thereby obtained was purified via column chromatography on silica gel by using 35% EtOAchexane as eluent. Workup of the chromato-graphic eluate afforded pure **5** (56 mg, 65%) as a colorless, viscous oil, $[\alpha]_D$ +74.1° (*c* 1.0, $CHCl_3$); IR (film) 2968 (w), 2872 (w), 1469 (s), 1357 (m), 1211 (s), 1114 (m), 752 cm^{-1} (s);

^{1}H NMR ($CDCl_3$) δ 1.49 (*A*B, *J*AB = 10.2 Hz, 1 H), 1.84 (A*B*, *J*AB = 10.2 Hz, 1 H), 1.95-2.20 (m, 4 H), 2.30-2.45 (m, 2 H), 2.50-2.74 (m, 6 H), 3.49-4.10 (m, 18 H), 4.55 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 32.6 (t, 2 C), 41.5 (d, 2 C), 43.5 (t), 44.0 (d, 2 C), 48.0 (d), 48.3 (d), 58.7 (d), 58.9 (d), 68.5 (t, 2 C), 70.2 (t, 2 C), 72.1 (t, 2 C), 72.3 (t, 2 C), 79.8 (d), 79.9 (d), 80.9 (d), 81.0 (d), 94.4 (s, 2 C). Exact mass (CI HRMS) Calcd for $C_{25}H_{34}O_7$: [*M*r + H]$^+$ *m/z* 447.2383. Found: [*M*r + H]$^+$ *m/z* 447.2380.

Synthesis of crown ether (7). Compound **7** was prepared by starting with **6** (41 mg, 0.15 mmol), **1** (110 mg, 0.17 mmol), and NaH (26 mg, 0.51 mmol) by following the procedure described previously for the synthesis of **3a** (*vide supra*). Crude **7** thereby obtained was purified via column chromatography on silica gel by using 20% EtOAc-hexane as eluent. Workup of the chromatographic eluate afforded pure **7** (59 mg, 42%) as a colorless, viscous oil, $[\alpha]_D$ = +0.65° (*c* 1.0, $CHCl_3$); IR (film) 2953 (s), 2870 (m), 1378 (m), 1215 (m), 1118 (s), 1070 (m), 846 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 6 H), 1.35 (s, 6 H), 1.80-2.10 (m, 6 H), 2.30-2.70 (m, 8 H), 3.45-4.30 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 25.4 (q, 2 C), 25.4 (q), 26.8 (q, 2 C), 32.2 (t, 2 C), 41.4 (d, 2 C), 43.5 (t), 43.8 (d, 2 C), 48.1 (d), 48.3 (d), 58.6 (d), 58.8 (d), 66.9 (t, 2 C), 68.9 (t, 2 C), 70.1 (t, 2 C), 73.5 (t, 2 C), 75.4 (d, 3 C), 80.2 (d), 94.3 (s, 2 C), 108.4 (s, 2 C). Anal. Calcd for C31H46O9: C, 66.17; H, 8.24. Found: C, 65.95; H, 7.99. Exact mass (CI HRMS) Calcd for $C_{31}H_{46}O_9$: [*M*r + H]$^+$ 563.32200. Found [*M*r + H]$^+$ 563.32226.

Base promoted reaction of 8 with trityl chloride. A solution of **8** (3.0 g, 8.3 mmol) in CH_2Cl_2 (60 mL) was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added sequentially with stirring NEt_3 (1.40 g, 18.2 mmol) and Ph_3CCl (5.08 g, 18.2 mmol). After all of the Ph_3CCl had been added, the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 24 h. At that time, water (50 mL) and CH_2Cl_2 (50 mL) were added. The organic layer was separated and was washed successively with water (50 mL) and brine (30 mL). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 25% EtOAc-hexane. Workup of the eluate afforded pure **9** (5.6 g, 80%) as a gummy semisolid, $[\alpha]_D$ = -4.64° (*c* 1.25, $CHCl_3$); IR (film) 3483 (br, s), 3065 (s), 3028 (s), 2928 (m), 2870 (m), 1492 (m), 1444 (s), 1072 (s), 1028 (m), 754 (s), 698 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 2.93 (d, *J* = 5.6 Hz, 2 H, peak disappears when sample is shaken with D_2O), 3.24 (dd, *J* = 5.8, 9.4 Hz, 2 H), 3.34 (dd, *J* = 4.0, 9.4 Hz, 2 H), 3.73 (d, *J* = 6.9 Hz, 2 H), 4.02-4.07 (m, 2 H), 4.36 (s, 4 H), 7.05-7.62 (m, 40 H); ^{13}C NMR ($CDCl_3$) δ 64 .7 (t), 70.1 (d), 73.0 (t), 77.0 (d), 86.6 (s), 127.0 (d), 127.6 (d), 127.7 (d), 128.1 (d), 128.2 (d), 128.6 (d), 137.6 (s), 143.6 (s). Exact mass (CI HRMS) Calcd for $C_{58}H_{52}O_6$: [*M*r + H]$^+$ *m/z* 845.38421. Found: [*M*r + H]$^+$ *m/z* 845.38430.

Preparation of 10. A solution of **9** (516 mg, 6.0 mmol) in CH_2Cl_2 (10 mL) under argon was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added NEt_3 (150 mg, 1.53 mmol). This was followed sequentially by dropwise addition with stirring of MsCl (150 mg, 1.345 mmol). After all of the MsCl had been added, the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring under argon during 24 h. The reaction was quenched via careful addition of water

(20 mL), and the resulting aqueous suspension was extracted with Et_2O (2 × 50 mL). The layers were separated, and the organic layer was washed successively with water (20 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The corresponding di-*O*-mesyl derivative of **9** (360 mg, 60%) was thereby obtained; this material was used as obtained in the next synthetic step, without further purification or characterization. A mixture of the di-*O*-mesyl derivative of **9** (360 mg, 0.36 mmol, *vide supra*) and $PhCH_2NH_2$ (4 mL, 37 mmol, excess) was heated with stirring at 90 °C during 24 h. The mixture was allowed to cool to ambient temperature, whereupon pentane (100 mL) and 2 N aqueous NaOH (50 mL) were added successively to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with pentane (3 × 30 mL). The combined organic layers were washed successively with water (2 × 30 mL) and brine (20 mL), dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue thereby obtained was purified via column chromatography on silica gel by eluting with 9% EtOAc-hexane. Workup of the chromatographic eluate afforded pure **10** (150 mg, 60%) as a colorless semisolid: $[\alpha]_D$ -7.8° (*c* 1.3, $CHCl_3$); IR (film) 3059 (s), 3028 (s), 2920 (m), 2876 (m), 1502 (m), 1452 (s), 1145 (w), 1064 (m), 746 (s), 698 cm^{-1} (s); ^1H NMR (CDCl3) δ 3.22-3.33 (m, 4 H), 3.43-3.49 (m, 2 H), 3.85 (d, *J* = 14.0 Hz, 2 H), 4.52 (d, *J* = 6.2 Hz, 2 H), 4.63 (s, 4 H), 6.75-6.79 (m, 2 H), 7.10 (m, 2 H), 7.24-7.39 (m, 35 H), 7.45-7.50 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 52.9 (t), 60.9 (d), 62.4 (d), 73.4 (t), 84.2 (d), 88.1 (s), 127.2 (d), 127.7 (d), 127.8 (d), 128.1 (d), 128.2 (d), 128.4 (d), 128.5 (d), 128.7 (d), 129.5 (d), 139.2 (s), 140.4 (s), 144.6 (s). Exact mass (CI HRMS) Calcd for $C_{65}H_{59}NO_4$: [*M*r + H]$^+$ *m/z* 918.45224. Found: [*M*r + H]$^+$ *m/z* 918.45272.

Preparation of (11). To a stirred solution of **10** (10.0 g, 10.9 mmol) in a mixture of MeOH (35 mL) and THF (15 mL) was added concentrated aqueous HCl (5 mL), and the resulting mixture was heated at 40 °C while stirring during 12 h. The reaction mixture was concentrated *in vacuo*; the residue was extracted with Et_2O (2 × 50 mL), and the organic layer was discarded. Water (10 mL) was added to the remaining aqueous residue, and 15% aqueous $NaHCO_3$ was added dropwise with stirring until the aqueous suspension became basic to litmus. The resulting aqueous suspension was extracted with CH_2Cl_2 (2 × 100 mL). The organic layer was washed successively with water (10 mL) and brine (10 mL), dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. Compound **11** (3.4 g, 70%) was thereby obtained as colorless semisolid: $[\alpha]_D$ -14.8° (*c* 0.4, $CHCl_3$); IR (film) 3420 (br, s), 3032 (s), 2916 (m), 2874 (s), 1452 (m), 1357 (m), 1145 (w), 1068 (m), 1036 (m), 732 (s), 698 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 2.42 (br, m, 2 H, peak disappears when sample is shaken with D2O), 3.38-3.48 (m, 2 H), 3.61-3.83 (m, 4 H), 3.92 (s, 2 H), 4.39 (dd, *J* = 5.5, 11.1 Hz, 2 H), 4.62 (dd, *J* =11.1, 13.8 Hz, 4 H), 7.25-7.42 (m, 15 H); ^{13}C NMR (CDCl3) δ 52.3 (t), 59.5 (t), 61.4 (d), 73.1 (t), 84.5 (d), 127.1 (d), 127.7 (d), 127.8 (d), 128.1 (d), 128.4 (d), 128.5 (d), 137.9 (s), 139.0 (s). Exact mass (CI HRMS) Calcd for $C_{27}H_{31}NO_4$: [*M*r + H]$^+$ *m/z* 434.23313. Found: [*M*r + H]$^+$ *m/z* 434.23321.

Synthesis of a mixture of diastereoisomeric crown ethers (12a) and (12b). A a suspension of NaH (0.57 mg, 1.43 mmol, obtained as a 60% dispersion in mineral oil) in THF (5 mL) under argon was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added dropwise with stirring under argon a solution of **11** (280 mg, 0.65 mmol) in THF

(3 mL). After the addition of reagents had been completed, the external ice-water bath was removed, and the reaction was allowed to warm slowly to ambient temperature while stirring during 1 h. The reaction mixture once again was cooled to 0 °C via application of an external ice-water bath, and a solution of 1 (282 mg, 0.71 mmol) in THF (3 mL) was added dropwise with stirring. After the addition of reagents had been completed, the external ice-water bath was removed, and the reaction was allowed to warm slowly to ambient temperature while stirring during 4 days. The reaction was quenched via addition of water (5 mL). The resulting aqueous suspension was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 10% EtOAc-hexane. Workup of the first chromatographic fraction afforded a material which subsequently was subjected to NMR spectral analysis. It was thereby determined that this material consisted of an inseparable mixture of **12a** and **12b** (23 mg, 5%); IR (film) 3030 (s), 2955 (s), 2860 (s), 1554 (m), 1508 (m), 1460 (m), 1107 (s), 1014 (w), 902 (w), 732 (m), 682 cm^{-1} (m), ^1H NMR ($CDCl_3$) δ 1.51 (*A*B, *J*AB = 10.6 Hz, 2 H), 1.75-2.20 (m, 12 H), 2.45-2.80 (m, 14 H), 2.78 (m, 2 H), 3.05-3.15 (m, 2 H), 3.27-3.45 (m, 4 H), 3.56-4.25 (m, 36 H), 4.56 (m, 4 H), 4.66 (*A*B, *J*AB = 12.1 Hz, 2 H), 4.80 (A*B*, *J*AB = 12.1 Hz, 2 H), 7.18-7.45 (m, 30 H); ^{13}C NMR ($CDCl_3$) δ32.3 (t, 8 C), 32.8 (t, 2 C), 32.9 (t, 2 C), 41.4 (d, 4 C), 41.5 (d, 2 C), 41.6 (d, 2 C), 43.4 (t, 2 C), 43.5 (t, 2 C), 43.9 (d, 2 C), 44.1 (d, 4 C), 47.0 (d, 2 C), 47.3 (d, 2 C), 48.5 (d, 2 C), 48.7 (d, 2 C), 52.8 (t, 2 C), 52.9 (t, 2 C), 57.2 (d, 4 C), 58.0 (d, 2 C), 58.3 (d, 2 C), 59.4 (d, 2 C), 59.7 (d, 2 C), 63.1 (d, 2 C), 63.2 (d, 2 C), 66.2 (d, 2 C), 66.3 (d, 2 C), 68.8 (t, 2 C), 68.9 (t, 2 C), 69.2 (t, 2 C), 69.4 (t, 6 C), 71.0 (t, 4 C), 72.3 (t, 8 C), 72.5 (t, 2 C), 72.6 (t, 2 C), 72.8 (t, 2 C), 72.9 (t, 2 C), 73.1 (t, 4 C), 83.1 (d, 4 C), 83.8 (d, 4 C), 94.2 (s, 2 C), 94.8 (s, 1 C), 94.9 (s, 1 C), 126.5 (d, 4 C), 127.1 (d, 6 C), 127.2 (d, 8 C), 127.3 (d, 10 C), 128.1 (d, 16 C), 128.2 (d, 16 C), 138.6 (s, 3 C), 139.3 (s, 3 C), 140.4 (s, 6 C). Exact mass (CI HRMS) Calcd for $C_{92}H_{110}NO_{14}$: [*M*r + H]$^+$ *m/z* 1465.7878. Found: [*M*r + H]$^+$ *m/z* 1465.7887. Continued elution of the chromatography fraction afforded a second fraction. Workup of this chromatography freaction afforded pure **11** (110 mg, 40%) as a colorless oil.

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References and Notes

1. (a) Cram, D. J. *Angew. Chem. Int. Ed.* **1988**, *27*, 1009. (b) Cram, D. J. *J.*

Incl. Phenom. Mol. Recongn. Chem. **1988**, *6*, 397 and references cited therein. (b) Naemura, K.; Tobe, Y.; Kaneda, T. *Coord. Chem. Rev*. **1996**, *148*, 199 and references cited therein. (c) Zhang, X. X.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev.* **1997**, *97*, 3313.

2. (a) Kyba, E. P.; Koga, K.; Sousa, L. R.; Siegel, M.G.; Cram, D. J. *J. Am. Chem.Soc*. **1973**, *95*, 2692. (b) Sogah, G. D. Y.; Cram, D. J. *J. Am. Chem. Soc* **1979**, *101*, 3035.
3. (a) Curtis, W. D.; Laidler, D. A.; Stoddart, J. F.; Wolstenholme, J. B.; Jones, G. H. *Carbohydr. Res*. **1977**, *57*, C17. (b) Curtis, W. D.; Laidler, D. A.; Stoddart, J. F.; Jones, G. H. *J. Chem. Soc., Perkin Trans 1* **1977**, 1756. (c) Stoddart J. F. *Chem. Soc. Rev*. **1979**, *8*, 85. (d) Lehn, J. M.; Sauvage, J. P. *J. Am. Chem. Soc*. **1975**, *97*, 6700. (e) Schurmann, G. Y.; Diederich, F. *Tetrahedron Lett*. **1986**, *27*, 4249. (f) Odashima, K.; Itai, A.; Iitaka, Y.; Koga, K. *J. Org. Chem*. **1985**, *50*, 4478.
4. Breslow, R.; Czarniecki, M. F.; Emert. J.; Hamaguchi, H. *J. Am. Chem. Soc*. **1980**, *102*, 762.
5. (a) Alonso-Lopez, M.; Bernabe, M.; Fernandez-Mayorolas, A.; Jimenez-Barbero, J.; Martin-Lomas, M.; Penades, S. *Tetrahedron* **1988**, *44*, 1535. (b) Alonso-Lopez, M.; Martin-Lomas, M.; Penades, S. *Tetrahedron* **1988**, *44*, 1535.
6. Seebach, D.; Pichota, A.; Beck, A.K.; Pinkerton, A.B.; Litz, T.; Karjalainen, J.; Gramich, V. *Organic Lett*. **1999**, *1*, 55.
7. Marchand, A. P., Ed.; In *Advances in Theoretically Interesting Molecules*, Thummel, R.P. JAI: Greenwich, CT, 1989; Vol. 1, pp 357-39. (b) Marchand, A. P. *Aldrichchimica Acta*. **1995**, *28*, 95.
8. (a) Haddadin, M. J.; Wang, Y.; Frenkel, S.; Bott, S. G.; Yang, L.; Braterman, P. S.; Carvallo, C.; Marchand, A. P.; Watson, W. H.; Kashyap, R. P.; Krawiec, M.; Bourne, S. A. *Heterocycles* **1994**, *37*, 869. (b) Marchand, A .P.; Reddy, G. M.; Zaragoza, F.; Bartsch, R. A.; Eley, M. D. *Tetrahedron Lett*. **1993**, *34*, 5377. (c) Bartsch, R. A.; Eley, M.; Marchand, A. P.; Shukla, R.; Kumar, K. A. *Tetrahedron* **1996**, *52*, 8979.
9. (a) Marchand, A. P.; Kumar, K. A.; McKim, A. S.; Mlinaric-Majerski, K.; Kragol, G. *Tetrahedron* **1997**, *53*, 3467. (b) Marchand, A. P.; Alihodzic, S.; McKim, A. S.; Kumar, K. A.; Mlinaric-Majerski, K.; Kragol, G. *Tetrahedron Lett*. **1998**, *39*, 1861. (c) Marchand, A. P.; Chong, H.-S.; Alihodzic, S.; Watson, W. H.; Bodige, S. G. *Tetrahedron* **1999**, *55*, 9687. (d) Marchand, A. P.; Chong. H.-S. *Tetrahedron* **1999**, *55*, 9697.
10. Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc*. **1972**, *94*, 6429.
11. Matteson, D. S.; Bedle, E. C.; Kandil, A. A. *J. Org. Chem*. **1987**, *52*, 5034.
12. Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kuhnle, F. N. M. *J. Org. Chem*. **1995**, *60*, 1788.
13. Elder, J. S; Man, J.; Walsh, E. B. *Tetrahedron* **1985**, *41*, 3117.
14. Jurczak, J.; Bauer, T.; Chemielewski, M. *Carbohydr. Res*. **1987**, *164*, 493.
15. Dureault, A.; Portal, M.; Depezay, J. C. *Synlett* **1991**, 225.
16. Poitout, L.; Merrer, Y. L.; Depezay, J. C. *Tetrahedron Lett*. **1996**, *37*, 1609.
17. See: Marchand, A. P; Chong, H.-S.; Ganguly, B. *Tetrahedron: Asymmetry* **1999**, *10* 4695 and references cited therein.