Pergamon

Tetrahedron 55 (1999) 5505–5514

TETRAHEDRON

Inherently Chiral α-Picolyloxy-*p-tert*-butylcalix[5]arene Crown Ethers: Synthesis, Structure Proof, and Enantioselective HPLC Resolution

Salvatore Caccamese,[a] Anna Notti,[b] Sebastiano Pappalardo,[a,*] Melchiorre F. Parisi,[b] and Grazia Principato[a]

[a] *Dipartimento di Scienze Chimiche, Università di Catania, Viale A. Doria 6, I-95125 Catania, Italy*

[b] *Dipartimento di Chimica Organica e Biologica, Università di Messina, Salita Sperone 31, I-98166 Vill. S. Agata, Messina, Italy*

Received 30 November 1998; revised 9 February 1999; accepted 25 February 1999

Abstract. Reaction of α-picolyloxy-*p-tert*-butylcalix[5]arene with tri- to pentaethylene glycol ditosylates and K_2CO_3 regioselectively affords racemic (1,2)-bridged crown ether derivatives in the cone conformation. Their structure is firmly established by NMR spectroscopy and by comparison with appropriate (1,3)-bridged crown-6 regioisomers, synthesized by unequivocal sequences. The enantiomeric resolution of racemates has been achieved by direct HPLC separation, using enantioselective stationary phases. The enantiomers of the (1,2)-bridged crown-5 derivative exhibit one of the largest separation factors (α) so far reported for inherently chiral calixarenes.

Keywords: Asymmetry; calixarenes; crown ethers; enantioselective resolution.

Introduction

Native calixarenes or suitable derivatives are commonly used in host-guest chemistry as three-dimensional building blocks for the construction of more sophisticated host molecules.[1] Synthetic strategies to chiral calixarenes are of particular interest, owing to the increasing demand for molecular receptors with chiral discriminating abilities.[2,3] Such molecules can be easily obtained by anchoring chiral residues either at the upper[4] or lower[5-8] rim of calixarenes. Besides, taking advantage of their non-planar structure, it is also possible to prepare 'inherently' chiral calixarenes by desymmetrization of appropriate precursors featuring a plane as the only symmetry element.[9]

A few years ago Reetz *et al.* devised a new carrier system for the transport of amino acids from neutral aqueous solution across organic media, which is based on the synergistic action of arylboronic acids/crown ethers, which bind to the carboxylate and ammonium moieties to form three-component supramolecular species.[10] This sparked our interest in the design and synthesis of inherently chiral α-picolyloxy-calix[*n*]arene crown ethers, which combine within the same molecule three potential converging binding sites (a crown ether moiety, one or more hydroxyl groups, and a pendant electron-poor heteroaromatic ring) in a well-defined stereochemical arrangement. Following our previous studies on the smallest members in this series ($n = 4$),[11] we report here the synthesis, structural characterization, and enantioselective HPLC separation of the higher homologues (1,2)-bridged α-picolyloxy-*p-tert*-butylcalix[5]arene crown ethers.[12]

Results and Discussion

Synthesis and NMR Characterization

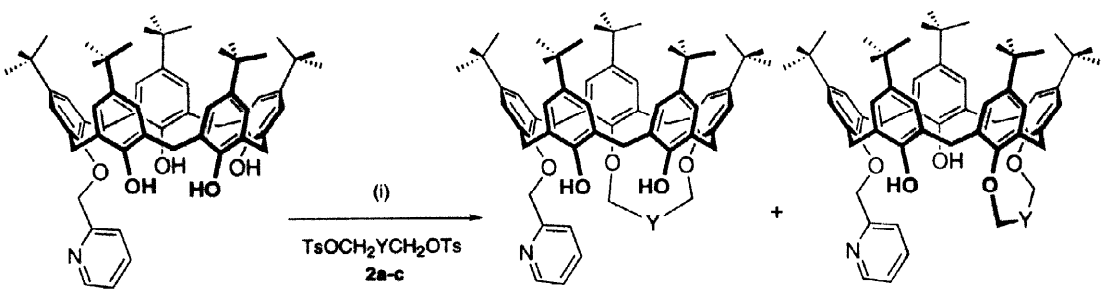
In this study we have used the readily available α-picolyloxy-*p-tert*-butylcalix[5]arene (**1**)[13] as an achiral

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00195-7

building block for the preparation of inherently chiral crown ether derivatives. The only symmetry element present in **1** is the mirror plane bisecting the alkylated aryl residue and the opposite methylene bridge. This can be lost by selective intrabridging of two OH groups with a polyether chain. Although four possible regioisomers in the *cone* conformation are theoretically possible for α-picolyloxy-*p*-*tert*-butylcalix[5]arene crown ethers,[14] alkylation of **1** with oligoethylene glycol ditosylates **2a–c** (1 equiv) and K_2CO_3 (excess) in dry DMF at 60 °C has invariably afforded a single isolated chiral crown ether derivative **3a–c** in 25–40% yield (Scheme 1). When triethylene glycol ditosylate **2a** was used, the achiral crown-4 regioisomer **4a** (18% yield) was also isolated.

Proton and carbon NMR spectra of **3a–c** are quite complex, and closely resemble those of the previously described mono-*O*-alkylated (1,2)-*p*-*tert*-butylcalix[4]arene crown ethers.[11] The asymmetric nature of **3a–c** is substantiated by their ^{1}H NMR spectra, which show five singlets for the *tert*-butyl groups, five pairs of partly overlapping doublets (J = 13.0–14.8 Hz) for $ArCH_2Ar$ groups, a complex pattern for the polyether chain in the range 3.5–4.3 ppm, a pseudo-singlet for the OCH_2Py group, five pairs of doublets for the aromatic protons of the calixarene skeleton, and a four-spin system for the 2-pyridyl group. Two low field resonances for the OH protons (singlets at 8.18 and 6.86 ppm in **3a**, at 7.91 and 6.87 ppm in **3b**, and a broad singlet integrating for two protons at 7.70 ppm in **3c**), are suggestive of the occurrence of two *proximal* OH groups involved in intramolecular hydrogen bonding. Using similar arguments, the structure of a number of (poly)hydroxylated calix[*n*]arenes has recently been assessed.[13,15–18] The absence of symmetry elements in **3a–c** is further corroborated by their ^{13}C NMR spectra, which at least in one case (compound **3c**) exhibit the expected thirty-line pattern for the aromatic carbons of the calix[5]arene skeleton, dispersed in the range 123–153 ppm.

Conversely, the ^{1}H and ^{13}C NMR spectra of **4a** are commensurate with a C_s symmetry of the molecule (see experimental). The *distal* relationship of the OH groups in **4a** was established as above on the basis of their upfield resonance (broad signal at 6.45 ppm), which rules out an alternate regioisomeric structure with two proximal OH groups.[14]

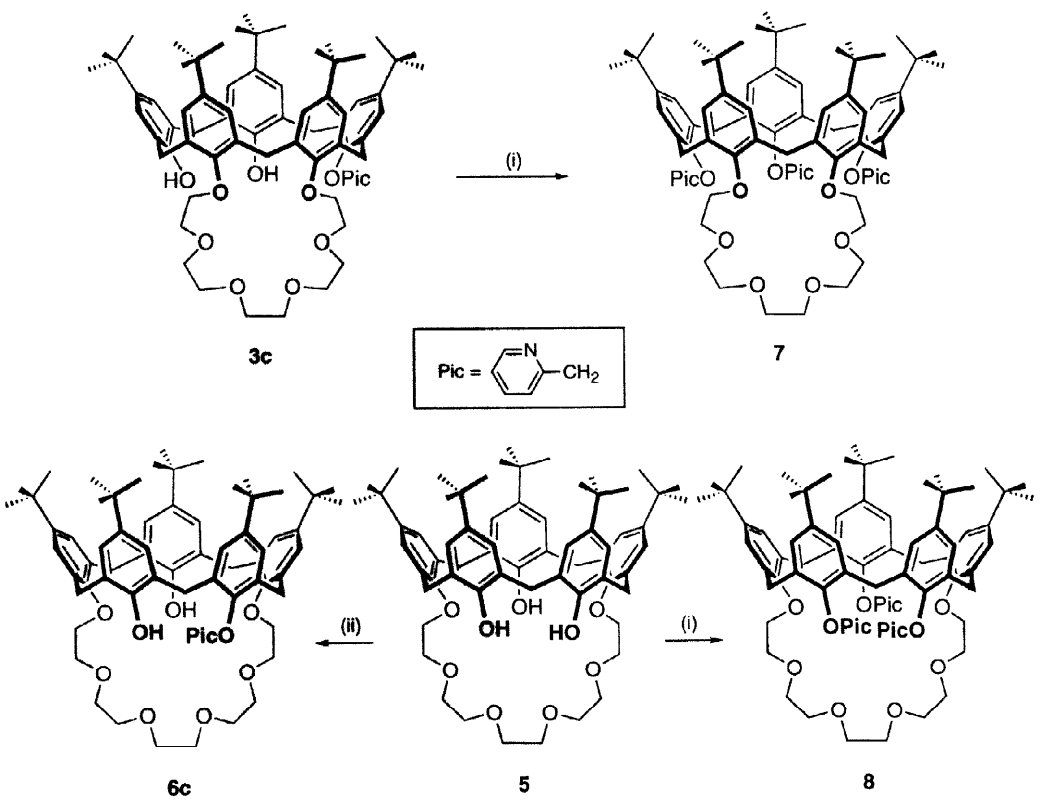


2,3	Y
a	$(CH_2OCH_2)_2$
b	$(CH_2OCH_2)_3$
c	$(CH_2OCH_2)_4$

Scheme 1. Reagents and conditions: (i) ditosylate (1 equiv), K_2CO_3 (10 equiv), DMF, 60 °C, 48 h.

Crown ethers **3a–c** and **4a** all adopt a *cone-in* conformation in solution, which is substantiated by (i) the chemical shift separation of geminal $ArCH_2Ar$ protons around 1 ppm, and resonances for the relevant carbons in the range 31.0±1.3 ppm,[19] and (ii) the upfield shift experienced by the protons of the *p-tert*-butylphenyl residue carrying the α-picolyl substituent (in particular, singlets for the *tert*-butyl group at 0.33 ppm in **3a**, 0.25 ppm in **3b**, 0.38 ppm in **3c**, and 0.50 ppm in **4a**), which shows the tendency to cant inward in the calix cavity.

A further confirmation of the occurrence of (1,2)-intrabridging in our chiral calix[5]crowns was provided by comparison of the NMR spectra of **3c** and its fully alkylated derivative **7** with those of the corresponding (1,3)-bridged regioisomers **6c** and **8**. Compound **7** was obtained in 53% yield by exhaustive alkylation of **3c** with 2-(chloromethyl)pyridine hydrochloride (PicCl·HCl) and K_2CO_3 in dry DMF, while **6c** (16%) and **8** (68%) were prepared unequivocally either by partial or exhaustive alkylation of the known[15] (1,3)-bridged *p-tert*-butylcalix[5]arene crown-6 triol (**5**) with PicCl·HCl and base, under the experimental conditions shown in Scheme 2. The physical and NMR spectral properties of the two pairs of chiral (**3c** and **6c**) and achiral (**7** and **8**) regioisomers resulted totally different, confirming the above structural assignments based on NMR spectroscopy. Sections of the ^1H NMR spectra of regioisomers **7** and **8** are reported in Fig. 1. As expected, the signals of the 'central' pyridine ring (Py') in **7** resonate at higher field than those of the corresponding 'isolated' pyridine ring in **8**, because of the diamagnetic shielding arising from the two flanking pyridine rings.



Scheme 2. Reagents and conditions: (i) PicCl·HCl (6 equiv), K_2CO_3 (12 equiv), DMF, 70 °C, 24 h; (ii) PicCl·HCl (1 equiv), NaH (6 equiv), THF, r.t., 24 h.

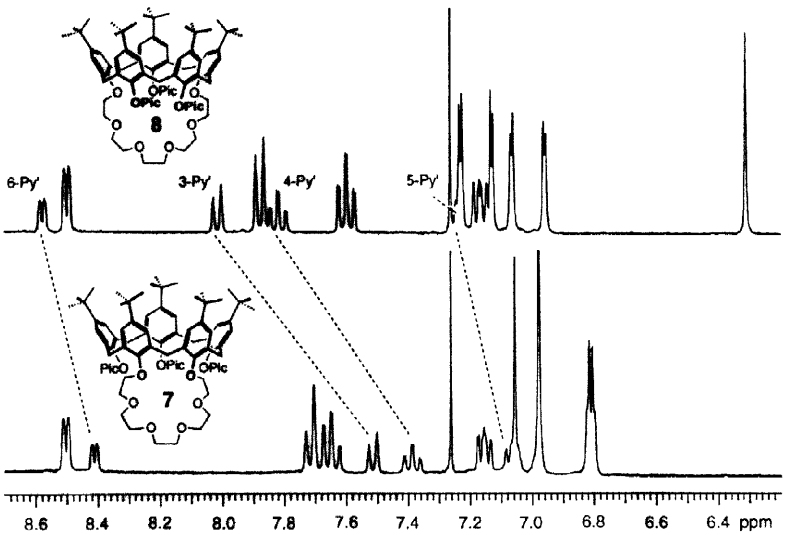


Fig. 1. The aromatic region in the ^{1}H NMR spectra ($CDCl_3$, 300 MHz) of regioisomers **7** and **8**.

The regio- and stereochemical arrangement of the *O*-alkyl residues has been unambiguously proved for **3b** by a single-crystal X-ray analysis, which has confirmed that two proximal oxygens are linked by the polyether chain, and adjacent to the *O*-picolyl residue. In the solid state, the calix[5]arene moiety of **3b** assumes a distorted cone conformation with an acetonitrile molecule of solvation enclathrated within the calix cup. Structural details have been reported in an earlier paper.[12]

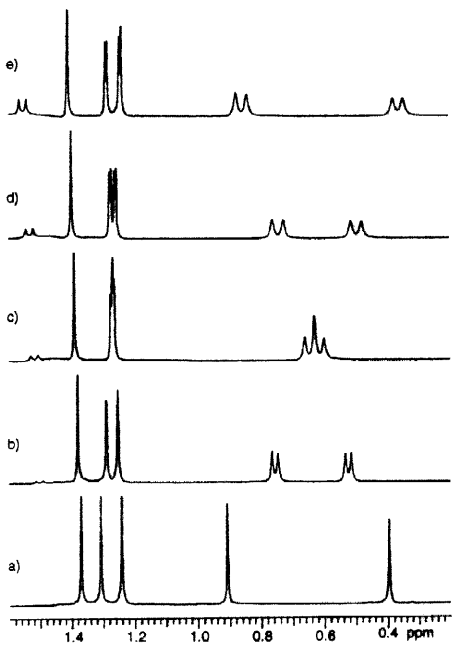


Fig. 2. The *tert*-butyl region of the ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **3c** (a) and spectral changes upon addition of (b) 0.25, (c) 0.5, (d) 0.75, and (e) 1 equiv of (*R*)-α-methylbenzylammonium picrate.

Further evidence of chirality for asymmetrical (1,2)-calix[5]arene crown ethers was provided by titration experiments of $CDCl_3$ solutions of **3** (containing one drop of CD_3OD) with both (*R*)- and (*S*)-α-methylbenzylammonium picrates. Whereas the ^{1}H NMR spectra of compounds **3a** and **3b** did not show any appreciable change upon titration with one equiv of the chiral salt, splitting and doubling of signals occurred in *every region* of the spectra of **3c** from the addition of the first aliquot (0.25 equiv) of each chiral salt. The *tert*-butyl region of the ^{1}H NMR spectra of the racemic receptor **3c** and the (*R*)-salt (traces b–e, Fig. 2) shows the formation of the two diastereomeric complexes in equal ratio. These results also confirm that a crown-6 moiety is likely to be a prerequisite for anchoring the NH_3^+ group of the primary ammonium cation into its crown ether-cavity via N-H···O hydrogen bonds.[11,20,21]

Chromatographic Enantioseparation

Racemic *p-tert*-butylcalix[5]arene crown ethers **3a–c** and **6c** were chromatographically resolved on enantioselective stationary phases, as shown in Table 1.

Table 1. Enantioselective HPLC Resolution of (1,2)- and (1,3)-Calix[5]arene Crown Ethers

Compd	column	A(%)[a]	FR[b]	k'_1[c]	α[d]	R_s[e]
3a	AD	10	0.5	0.253	3.78	5.2
	AD	5	0.5	0.279	3.98	6.5
	AD	5	1	0.254	2.69	3.4
	OD	10	0.5	0.182	2.68	1.8
3b	AD	10	0.5	0.046	18.62	7.3
	AD	5	0.5	0.046	19.14	7.5
	AD	5	1	0.049	19.31	6.3
	OD	10	0.5	0.135	2.13	1.0
3c	AD	10	0.5	0.107	3.75	3.3
	AD	5	0.5	0.111	4.02	3.7
	AD	5	1	0.148	3.36	2.9
	OD	10	0.5	0.292	1.64	0.9
6c	AD	5	0.5	0.840	1.86	0.7

[a] Percentage of 2-propanol in *n*-hexane. [b] Flow rate (mL/min); FR = 1, t_0 = 3.4 min; FR = 0.5, t_0 = 7.1 min (AD) and 7.0 min (OD). [c] Capacity factor of the first-eluted enantiomer. [d] Separation factor. [e] Resolution factor.

The Chiralpak AD [amylose tris-(3,5-dimethylphenylcarbamate)] column was much more effective than the Chiralcel OD [cellulose tris-(3,5-dimethylphenylcarbamate)] one in the enantiomeric separation of all compounds under the same experimental conditions (polarity of the mobile phase and flow rate). The difference in enantioselective recognition of cellulose and amylose derivatives may be due to the different chiral environment around the carbamate residue and to the wider and more compact helix of the amylose derivative.[22]

The separation factor (α) of the enantiomers of **3b** is exceptionally high, and to the best of our knowledge this is the largest enantioselectivity to date reported for inherently chiral calixarenes. The very low k'_1 and the high α values with such a large difference in binding affinities ($\Delta\Delta G = -1.7$ kcal/mol) suggest that the Chiralpak AD phase behaves as an effective 'molecular receptor' for one of the two enantiomers of **3b**. The separation factors for the enantiomers of **3a** and **3c** are also more than satisfactory and make feasible the separation of the enantiomers on a preparative scale. This trend was not observed in the enantiomeric separation of the corresponding calix[4]arene crown ethers.[11] In addition, a comparison of the α values of regioisomers **3c** and **6c** has shown that the enantioselectivity for the enantiomers of **6c** was remarkably lower than that observed for the regioisomer **3c**. This may be due to a higher affinity of the Chiralpak AD column for both enantiomers of **6c** (stronger interaction with the 1,3-positioned hydroxy groups), as shown by the higher k'_1 value. Thus, these results clearly indicate that small variations in the size of the crown moiety and of the calix, and in the number and/or position of residual hydroxy group(s) have a profound effect on the chances of enantiomeric separation. Similar behaviour has previously been observed for other chiral calix[4]arenes.[23] As expected, a decrease in the flow rate and particularly in the polarity of the mobile phase (Table 1, AD column) had a beneficial effect on separation (α) and resolution (R_s) factors. Fig. 3 shows typical chromatograms of the resolution of racemic crown ethers **3a–c** and comparison of the efficiencies of the columns used in this work. Furthermore, repeated 50 μL injections of the racemic **3c** (0.1–0.2 mg) and collection of the eluates of the two chromatographic peaks afforded two samples whose CD spectra are mirror images of each other (Fig. 4) indicating their enantiomeric nature.

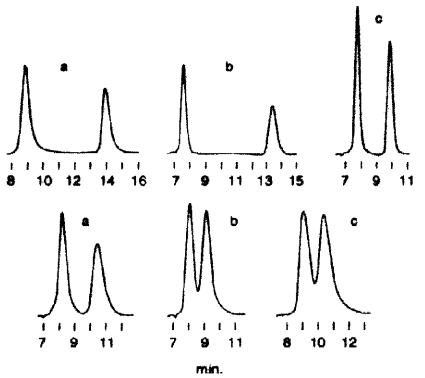


Fig. 3. HPLC separation (mobile phase *n*-hexane/2-propanol 9:1 at 0.5 mL/min) of the enantiomeric pairs of (a) **3a**, (b) **3b**, (c) **3c**. Upper traces: Chiralpak AD, lower traces: Chiralcel OD.

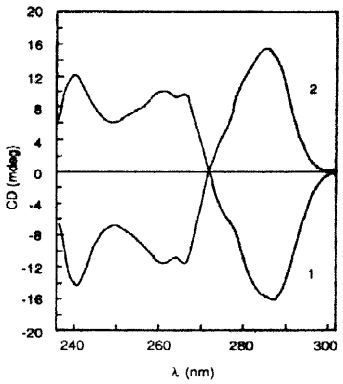


Fig. 4. CD spectra (ethanol, 22 °C) of the enantiomeric pair of **3c** obtained from the first- (1) and the second-eluted peak (2).

Conclusions

In summary, we have shown that the alkylation of α-picolyloxy-*p-tert*-butylcalix[5]arene (**1**) with oligoethylene glycol ditosylates and K_2CO_3 in dry DMF provides a simple route to the inherently chiral (1,2)-bridged crown ether derivatives **3** in the cone conformation. This strategy is complementary to the inverse one (formation of the 1,3-crown ether followed by its monoalkylation)[12] leading to the inherently chiral (1,3)-bridged crown ether regioisomers (*e.g.*, **6c**). All racemates have been separated into their enantiomers by enantioselective HPLC. Future work will be directed to the separation of the enantiomers on a preparative scale and to the study of their recognition properties.

Experimental

Melting points were determined on a Kofler or Electrothermal melting point apparatus and are uncorrected. NMR spectra were taken on a Varian Gemini 300 or Bruker AC-250 spectrometer. Chemical shifts (δ) refer to $CDCl_3$ solutions from internal Me_4Si. Multiplicities in ^{13}C NMR spectra were obtained by DEPT or APT experiments. FAB (+) mass spectra were obtained on a Kratos VG ZAB 2SE instrument, by using 3-nitrobenzyl alcohol as a matrix. R_f values were measured using silica gel TLC plates (absorbant thickness 0.25 mm) containing a fluorescence indicator. All chemicals were reagent grade and were used without further purification. *n*-Hexane and 2-propanol (HPLC grade), PicCl·HCl, and anhydrous solvents were purchased from Fluka. Compounds **1**,[13] **2a–c**,[24] and **5**[15] were prepared according to procedures described in the literature.

The HPLC system consisted of a Varian 5060 liquid chromatograph with Valco sample loops, a Jasco Uvidec III UV spectrophotometric detector operating at 265 nm, and a Varian CDS 401 Data System or a Omniscribe Houston recorder for fraction collecting. CD spectra were recorded on a Jasco 600 spectropolarimeter. The columns (25 cm × 4.6 mm) were packed with Chiralpak AD or Chiralcel OD coated on 10 μm silica gel, both from Daicel (Tokyo). Column void volume (t_0) was measured by injection of tri-*tert*-butylbenzene as a nonretained compound.[25] Retention time for each pair of enantiomers (t_1 and t_2) are mean values of two replicate determinations. The separation factor (α) was evaluated according to k'_2/k'_1, where k'_2 and k'_1 denote the capacity factors ($k' = (t - t_0)/t_0$) of the second and first peak, respectively. The resolution factor (R_s) was evaluated according to $R_s = 2(t_2 - t_1)/(w_1 + w_2)$, i.e. the peak separation divided by the mean value of the base line peak widths ($w_1 + w_2$).[26] All separations were carried out at 25 °C.

Chiral Calix[5]arene Crown Ethers 3a–c. General Procedure

A solution of **1** (0.45 g, 0.5 mmol) in dry DMF (20 mL) was slowly added to a stirred solution of oligoethylene glycol ditosylate (1 equiv) in dry DMF (30 mL) in the presence of anhydrous K_2CO_3 (10 equiv) under N_2. The mixture was kept at 60 °C under stirring for 2 days. The solvent was removed under reduced pressure, and the residue was partitioned between water and CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed (SiO_2) by eluting first with CH_2Cl_2 to remove the less polar unreacted starting material (ca. 20-25%), and then with a gradient of AcOEt in cyclohexane to afford the desired racemic crown ether **3a–c**. The reaction with **2a** produced also the achiral regioisomer **4a**. Further details are given for the individual compounds.

5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31,32-dihydroxy-33-[(2-pyridylmethyl)oxy]-34,35-crown-4-calix[5]arene (3a)

White solid (29% yield); mp 221–223 °C (MeOH–CH_2Cl_2); R_f = 0.38 (cyclohexane–AcOEt 3:1); ^{1}H NMR δ 0.33, 1.09, 1.23, 1.29, 1.39 [s, $C(CH_3)_3$, 9 H each], 3.21 and 4.05 (AX, J = 13.7 Hz, $ArCH_2Ar$, 2 H), 3.38 and 4.67 (AX, J = 13.7 Hz, $ArCH_2Ar$, 2 H), 3.40 and 4.38 (AX, J = 14.2 Hz, $ArCH_2Ar$, 2 H), 3.47 and 4.53 (AX, J = 15.6 Hz, $ArCH_2Ar$, 2 H), 3.48 and 4.56 (AX, J = 14.8 Hz, $ArCH_2Ar$, 2 H), 3.6–4.3 (m, OCH_2CH_2O, 12 H), 4.98 (pseudo-s, OCH_2Py, 2 H), 6.21 and 6.37 (ABq, J = 2.3 Hz, ArH, 2 H), 6.87 (bs, OH, 1 H), 7.01 (bs, ArH, 2 H), 7.05, 7.06, 7.16, 7.21, 7.25, 7.33 (d, J = 2.3–2.5 Hz, ArH, 1 H each), 7.26 (m, 5-PyH, 1 H), 7.79 (m, 3,4-PyH, 2 H), 8.18 (bs, OH, 1 H), and 8.62 (dt, J = 4.7, 1.3 Hz, 6-PyH, 1 H); ^{13}C NMR (75 MHz) δ 30.1, 31.1, 32.3 (t, $ArCH_2Ar$), 30.6, 31.2, 31.5, 31.6 [q, $C(CH_3)_3$], 33.5, 33.9, 34.1, 34.2 [s, $C(CH_3)_3$], 70.3, 70.4, 70.9, 71.0, 71.7, 74.3 (t, OCH_2), 75.8 (t, OCH_2Py), 121.4, 122.5 (d, 3,5-Py), 123.6 (×2), 124.7, 125.3, 125.48, 125.53, 125.9, 126.6, 126.7, 127.2 (d, Ar), 126.0, 126.5, 126.8, 127.7, 131.8, 132.6, 132.8, 133.1, 133.9, 135.2 (s, bridgehead-C), 136.9 (d, 4-Py), 142.2, 142.5, 145.3, 146.1, 146.7 [s, C_{sp2}–$C(CH_3)_3$], 149.0 (d, 6-Py), 148.4, 149.9, 150.2, 151.5, 152.9 (s, C_{sp2}–O), and 158.0 (s, 2-Py); FAB (+) MS, m/z 1016 (100, MH^+). Anal. Calcd for $C_{67}H_{85}NO_7 \cdot H_2O$: C, 78.48; H, 8.45; N, 1.37. Found: C, 78.32; H, 8.63; N, 1.50.

5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31,33-dihydroxy-32-[(2-pyridylmethyl)oxy]-34,35-crown-4-calix[5]arene (4a)

White solid (18% yield), mp 248–251 °C (MeOH–CH_2Cl_2); R_f = 0.15 (cyclohexane–AcOEt 3:1); ^{1}H NMR δ 0.50, 1.23, 1.34 [s, $C(CH_3)_3$, ratio 1:2:2, 45 H], 3.47 and 4.61 (AX, J = 14.7 Hz, $ArCH_2Ar$, 4 H), 3.48 and 4.25 (AX, J = 14.2 Hz, $ArCH_2Ar$, 4 H), 3.49 (d, J = 14.2 Hz, *exo*-$ArCH_2Ar$, 1 H), 3.6–4.0 (m, OCH_2CH_2O and *endo*-$ArCH_2Ar$, 13 H), 5.07 (pseudo-s, OCH_2Py, 2 H), 6.21 (s, ArH, 2 H), 6.45 (bs, OH, 2 H), 6.99, 7.07, 7.23, 7.25 (d, J = 2.3–2.5 Hz, ArH, 2 H each), 7.26 (ddd, J = 7.7, 4.9, 1.2 Hz, 5-PyH, 1 H), 7.83 (td, J = 7.7, 1.8 Hz, 4-PyH, 1 H), 7.99 (bd, J = 7.7 Hz, 3-PyH, 1 H), and 8.63 (ddd, J = 4.9, 1.8, 0.9 Hz, 6-PyH, 1 H); ^{13}C NMR (75 MHz) δ 30.3, 30.6, 32.3 (t, $ArCH_2Ar$), 30.7, 31.5 [q, $C(CH_3)_3$], 33.8, 34.3 [s, $C(CH_3)_3$], 70.6, 70.9, 74.3 (t, OCH_2), 76.0 (t, OCH_2Py), 121.9, 122.7 (d, 3,5-Py), 124.1, 125.1, 125.5, 126.0, 128.2 (d, Ar), 126.4, 127.9, 132.4, 133.3, 133.6 (s, bridgehead-C), 136.8 (d, 4-Py), 141.8, 146.0, 146.8 [s, C_{sp2}–$C(CH_3)_3$], 149.1 (d, 6-Py), 149.3, 151.0, 152.9 (s, C_{sp2}–O), and 158.0 (s, 2-Py); FAB (+) MS, m/z 1038 (98, MNa^+), 1016 (100, MH^+). Anal. Calcd for $C_{67}H_{85}NO_7$: C, 79.17; H, 8.43; N, 1.38. Found: C, 78.81; H, 8.57; N, 1.54.

5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31,32-dihydroxy-33-[(2-pyridylmethyl)oxy]-34,35-crown-5-calix[5]arene (3b)

White solid (25% yield); mp 265–268 °C (CH_2Cl_2–MeOH); R_f = 0.23 (cyclohexane–AcOEt 3:1); ^{1}H NMR δ 0.25, 1.06, 1.24, 1.33, 1.40 [s, $C(CH_3)_3$, 9 H each], 3.20–3.49 (partly overlapping d, *exo*-$ArCH_2Ar$, 5 H), 3.52–4.19 (m, OCH_2CH_2O, 16 H), 4.31–4.67 (m, *endo*-$ArCH_2Ar$, 5 H), 5.04 (pseudo-s, OCH_2Py, 2 H), 6.09 and 6.23 (ABq, J = 2.2 Hz, ArH, 2 H), 6.87 (s, OH, 1 H), 6.92 and 7.03 (ABq, J = 2.2 Hz, ArH, 2 H), 7.10 (t, J = 2.9 Hz, ArH, 2 H), 7.16 and 7.20 (ABq, J = 2.3 Hz, ArH, 2 H), 7.24 (m, 5-PyH, 1 H), 7.31 (t, J = 2.4 Hz, ArH, 2 H), 7.77 (td, J = 7.7, 1.7 Hz, 4-PyH, 1 H), 7.88 (bd, J = 7.7 Hz, 3-PyH, 1 H), 7.91 (s, OH, 1 H), and 8.59 (d, J = 4.8 Hz, 6-PyH, 1 H); ^{13}C NMR (62.5 MHz) δ 28.8 (t, $ArCH_2Ar$), 30.4, 31.2, 31.4, 31.7 [q, $C(CH_3)_3$], 33.4, 33.8, 33.9, 34.1, 34.2 [s, $C(CH_3)_3$], 67.8, 69.1 (×2), 70.0, 70.3, 71.3, 72.2, 74.7 (t, OCH_2), 75.4 (t, OCH_2Py), 120.9, 122.4 (d, 3,5-Py), 123.0, 123.1, 124.7, 125.1, 125.5, 126.9, 127.0 (d, Ar), 126.1, 127.5, 131.8, 132.3, 132.8, 133.3, 134.2, 135.3 (s, bridgehead-C), 136.8 (d, 4-Py), 142.3, 142.5, 145.7, 146.0, 146.6 [s, C_{sp2}–$C(CH_3)_3$], 149.0 (d, 6-Py), 148.2, 149.6, 150.3, 151.3, 152.9 (s, C_{sp2}–O), and 158.4 (s, 2-Py); FAB (+) MS, *m/z* 1082 (30, MNa^+), 1060 (100, MH^+). Anal. Calcd for $C_{69}H_{89}NO_8$: C, 78.15; H, 8.46; N, 1.32. Found: C, 78.23; H, 8.42; N, 1.42.

5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31,32-dihydroxy-33-[(2-pyridylmethyl)oxy]-34,35-crown-6-calix[5]arene (3c)

White solid (40% yield); mp 230–236 °C (MeOH); R_f = 0.04 (cyclohexane–AcOEt 3:1); ^{1}H NMR δ 0.38, 0.92, 1.26, 1.32, 1.38 [s, $C(CH_3)_3$, 9 H each], 3.23–3.50 (partly overlapping d, *exo*-$ArCH_2Ar$, 5 H), 3.55–4.20 (m, OCH_2CH_2O, 20 H), 4.27, 4.31, 4.42, 4.51, 4.57 (d, J = 13.0–14.2 Hz, *endo*-$ArCH_2Ar$, 1 H each), 5.02 (pseudo-s, OCH_2Py, 2 H), 6.26 and 6.38, 6.80 and 6.84, 7.09 and 7.10, 7.18 and 7.20 (ABq, J = 2.2–2.4 Hz, ArH, 2 H each), 7.25 (m, 5-PyH, 1 H), 7.28 (d, J = 2.2 Hz, ArH, 2 H), 7.70 (bs, OH, 2 H), 7.77 (td, J = 7.6, 1.7 Hz, 4-PyH, 1 H), 7.85 (bd, J = 7.6 Hz, 3-PyH, 1 H), and 8.61 (ddd, J = 4.8, 1.7, 0.9 Hz, 6-PyH); ^{13}C NMR (62.5 MHz) δ 29.3, 29.7, 30.3, 30.9 (t, $ArCH_2Ar$), 30.6, 31.1, 31.5, 31.6 [q, $C(CH_3)_3$], 33.5, 33.8, 33.89, 33.93, 34.2 [s, $C(CH_3)_3$], 69.4, 69.9, 70.0, 70.3, 70.7, 70.8, 71.0 (×2), 71.2, 74.3 (t, OCH_2), 75.7 (t, OCH_2Py), 121.3, 122.5 (d, 3,5-Py), 123.4, 123.6, 124.6, 125.1, 125.5, 125.6, 125.8, 126.6, 126.8, 126.9 (d, Ar), 125.9, 126.3, 126.5, 127.2, 131.8, 132.4, 132.9, 133.2, 134.3, 134.9 (s, bridgehead-C), 136.9 (d, 4-Py), 142.2, 142.5, 145.5, 146.1, 146.4 [s, C_{sp2}–$C(CH_3)_3$], 149.0 (d, 6-Py), 148.5, 149.9, 150.3, 151.2, 153.0 (s, C_{sp2}–O), and 158.0 (s, 2-Py); FAB (+) MS, *m/z* 1026 (15, MNa^+), 1104 (100, MH^+). Anal. Calcd for $C_{71}H_{93}NO_9$: C, 77.21; H, 8.49; N, 1.27. Found: C, 77.09; H, 8.67; N, 1.42.

5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31,33-dihydroxy-34-[(2-pyridylmethyl)oxy]32,35-crown-6-calix[5]arene (6c)

A mixture of **5** (346 mg, 0.34 mmol), PicCl·HCl (56 mg, 0.34 mmol) and NaH (49 mg, 2 mmol) in anhydrous THF (10 mL) was stirred at rt for 1 d. The reaction mixture was quenched with MeOH (1 mL), and the solvent was evaporated. The residue was treated with AcOH (2 mL), stirred for 12 h and concentrated to dryness. After partitioning between CH_2Cl_2 and water, the organic layer was washed with 1M Na_2CO_3, then with water and dried ($MgSO_4$). Evaporation of the solvent left a residue, which was purified by column chromatography (SiO_2, a gradient of AcOEt in cyclohexane as an eluent) to give asymmetric mono-picolyl

ether **6c** (56 mg, 16%); foamy solid, mp 113–117 °C; R_f = 0.31 (cyclohexane-AcOEt 1:2); ^{1}H NMR δ 0.92, 0.94, 0.96, 1.296, 1.300 [s, $C(CH_3)_3$, 9 H each], 3.28–3.86 (m, *exo*-$ArCH_2Ar$ and OCH_2CH_2O, 25 H), 4.37, 4.46, 4.48, 4.59 (d, J = 14.0–14.9 Hz, ratio 2:1:1:1, *endo*-$ArCH_2Ar$, 5 H), 5.04 and 5.18 (ABq, J = 13.4 Hz, OCH_2Py, 2 H), 6.83 (s, ArH, 2 H), 6.84 and 6.89, 6.91 and 6.93, 7.09 and 7.15, 7.16 and 7.21 (ABq, J = 2.4 Hz, ArH, 2 H each), 7.03 (s, OH, 1 H), 7.36 (ddd, J = 7.6, 4.8, 1.2 Hz, 5-PyH, 1 H), 7.82 (bd, J = 7.6 Hz, 3-PyH, 1 H), 8.20 (td, J = 7.6, 1.8 Hz, 4-PyH, 1 H), and 8.60 (ddd, J = 4.8, 1.8, 0.9 Hz, 6-PyH); ^{13}C NMR (75 MHz) δ 29.5, 29.8, 30.2, 30.5 (t, $ArCH_2Ar$), 31.1 (×2), 31.2, 31.6, 31.7 [q, $C(CH_3)_3$], 33.81, 33.86, 33.92, 33.95, 34.0 [s, $C(CH_3)_3$], 69.9, 70.1, 70.4, 70.89, 70.91, 71.3, 71.4, 71.7, 73.4, 74.2 (t, OCH_2), 75.8 (t, OCH_2Py), 122.1, 122.9 (3,5-Py), 124.7, 124.8, 125.0, 125.2, 125.3, 125.57, 125.63, 125.9, 126.0, 126.1 (d, Ar), 126.5, 126.6, 127.4, 128.2, 132.5, 132.8, 132.9, 133.40, 133.44, 133.5 (s, bridgehead-C), 138.6 (d, 4-Py), 141.2, 142.0, 146.2, 146.3, 146.8 [s, C_{sp2}–$C(CH_3)_3$], 148.3 (d, 6-Py), 149.9, 150.0, 150.4, 150.9, 151.3 (s, C_{sp2}–O), and 157.1 (s, 2-Py); FAB (+) MS, *m/z* 1104 (100, MH^+). Anal. Calcd for $C_{71}H_{93}NO_9$: C, 77.21; H, 8.49; N, 1.27. Found: C, 76.90; H, 8.77; N, 1.38.

5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31,32,33-tris[(2-pyridylmethyl)oxy]-34,35-crown-6-calix[5]arene (7)

A stirred mixture of diol **3c** (0.11 g, 0.1 mmol), PicCl·HCl (0.1 g, 0.6 mmol) and anhydrous K_2CO_3 (0.16 g, 1.2 mmol) in dry DMF (10 mL) was heated at 70 °C for 24 h under N_2. The solvent was removed under reduced pressure, and the residue was partitioned between water and CH_2Cl_2. The organic layer was dried ($MgSO_4$), concentrated to a small volume, and passed through a short alumina column, by eluting with a gradient of AcOEt in cyclohexane, to afford the desired tri-picolyl derivative **7** (68 mg, 53%); white powder, mp 182–185 °C (hexane–CH_2Cl_2); ^{1}H NMR δ 0.93, 1.09, 1.17 [s, $C(CH_3)_3$, ratio 2:2:1, 45 H], 3.15 and 4.41 (AX, J = 14.0 Hz, $ArCH_2Ar$, 4 H), 3.27 and 4.51 (AX, J = 13.9 Hz, $ArCH_2Ar$, 4 H), 3.30 and 4.68 (AX, J = 14.2 Hz, $ArCH_2Ar$, 2 H), 3.50–3.75 (m, OCH_2CH_2O, 20 H), 4.84, 4.87 (s, ratio 1:2, OCH_2Py' and OCH_2Py, 6 H), 6.80 and 6.82 (ABq, ArH, J = 2.5 Hz, ArH, 4 H), 6.98, 7.06 (s, ratio 2:1, ArH, 6 H), 7.07 (ddd, J = 7.6, 4.9, 1.2 Hz, 5-Py'H, 1 H), 7.15 (ddd, J = 7.6, 4.9, 1.2 Hz, 5-PyH, 2 H), 7.39 (td, J = 7.6, 1.8 Hz, 4-Py'H, 1 H), 7.51 (d, J = 7.6 Hz, 3-Py'H, 1 H), 7.65 (td, J = 7.6, 1.8 Hz, 4-PyH, 2 H), 7.72 (d, J = 7.6 Hz, 3-PyH, 2 H), 8.41 (ddd, J = 4.9, 1.8, 0.9 Hz, 6-Py'H, 1 H), and 8.50 (ddd, J = 4.9, 1.8, 0.9 Hz, 6-PyH, 2 H); ^{13}C NMR (75 MHz) δ 29.3, 29.5, 29.7 (t, $ArCH_2Ar$), 31.3, 31.4, 31.5 [q, $C(CH_3)_3$], 33.9, 34.00, 34.05 [s, $C(CH_3)_3$], 70.4, 70.7 (×2), 70.9, 72.4 (t, OCH_2), 76.5, 76.8 (t, OCH_2Py), 122.1, 122.3, 122.9, 123.1 (d, 3,5-Py), 125.2, 125.5, 125.69, 125.72, 126.2 (d, Ar), 133.3, 133.5 (×2), 133.7, 134.0 (s, bridgehead-C), 136.5 (d, 4-Py'), 136.7 (d, 4-Py), 145.0, 145.31, 145.33 [s, C_{sp2}–$C(CH_3)_3$], 148.3 (d, 6-Py'), 148.6 (d, 6-Py), 151.9, 152.3, 152.6 (s, C_{sp2}–O), 158.0 (s, 2-Py'), and 158.2 (s, 2-Py); FAB (+) MS, *m/z* 1286 (100, MH^+). Anal. Calcd for $C_{83}H_{103}N_3O_9$: C, 77.48; H, 8.07; N, 3.27. Found: C, 77.58; H, 8.23; N, 3.12.

5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31,32,34-tris[(2-pyridylmethyl)oxy]-33,35-crown-6-calix[5]arene (8)

The exhaustive alkylation of **5** with PicCl·HCl under conditions similar to those described for **7**, afforded triether **8** in 68% yield; colourless prisms, mp 285–287 °C (MeCN–CH_2Cl_2); ^{1}H NMR δ 0.49, 1.06, 1.30 [s, $C(CH_3)_3$, ratio 1:2:2, 45 H], 3.17 and 4.51 (AX, J = 13.8 Hz, $ArCH_2Ar$, 4 H), 3.26 and 4.48 (AX, J = 13.4 Hz,

$ArCH_2Ar$, 2 H), 3.30 and 4.61 (AX, J = 14.5 Hz, $ArCH_2Ar$, 4 H), 3.39–3.88 (m, OCH_2CH_2O, 20 H), 4.89 and 5.00 (ABq, J = 12.7 Hz, OCH_2Py, 4 H), 5.05 (s, OCH_2Py', 2 H), 6.31 (s, ArH, 2 H), 6.96 and 7.06 (ABq, J = 2.2 Hz, ArH, 4 H), 7.13 and 7.23 (ABq, J = 2.5 Hz, ArH, 4 H), 7.16 (ddd, J = 7.6, 4.9, 1.2 Hz, 5-PyH, 2 H), 7.25 (m, 5-Py'H, 1 H), 7.60 (td, J = 7.6, 1.8 Hz, 4-PyH, 2 H), 7.82 (td, J = 7.7, 1.8 Hz, 4-Py'H, 1 H), 7.88 (d, J = 7.6 Hz, 3-PyH, 2 H), 8.01 (d, J = 7.7 Hz, 3-Py'H, 1 H), 8.50 (ddd, J = 4.9, 1.8, 0.9 Hz, 6-PyH, 2 H), and 8.57 (ddd, J = 4.9, 1.8, 0.9 Hz, 6-Py'H, 1 H); ^{13}C NMR (75 MHz) δ 28.6, 28.8, 30.3 (t, $ArCH_2Ar$), 30.9, 31.4, 31.6 [q, $C(CH_3)_3$], 33.7, 34.0, 34.1 [s, $C(CH_3)_3$], 70.5, 70.6, 70.7, 71.0, 72.0 (t, OCH_2), 76.3, 77.3 (t, OCH_2Py), 122.38, 122.45 (d, 3,5-Py'), 122.48, 123.0 (d, 3,5-Py), 124.2, 125.1, 125.4, 126.6, 127.0 (d, Ar), 132.9, 133.3, 133.6, 134.0, 134.2 (s, bridgehead-C), 136.8 (4-Py'), 136.9 (d, 4-Py), 145.1, 145.3, 145.4 [s, C_{sp2}–$C(CH_3)_3$], 148.7 (d, 6-Py), 148.9 (d, 6-Py'), 151.3, 151.8, 152.8 (s, C_{sp2}–O), 157.8 and 158.1 (s, 2-Py); FAB (+) MS, m/z 1286 (100, MH^+). Anal. Calcd for $C_{83}H_{103}N_3O_9$: C, 77.48; H, 8.07; N, 3.27. Found: C, 77.18; H, 8.22; N, 3.21.

References and Notes

1. For a recent review on calixarenes see: Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713–745.
2. Kubo, Y.; Maeda, S.; Tokita, S.; Kubo, M. *Nature* **1996**, *382*, 522–524.
3. Araki, K.; Inada, K.; Shinkai, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 72–74.
4. Muthukrishnan, R.; Gutsche, C. D. *J. Org. Chem.* **1979**, *44*, 3962–3964.
5. Arimura, T.; Kawabata, H.; Matsuda, T.; Muramatsu, T.; Satoh, H.; Fujio, K.; Manabe, O.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 301–306.
6. Marra, A.; Schermann, M.-C.; Dondoni, A.; Casnati, A.; Minari, P.; Ungaro, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2479–2481.
7. Neri, P.; Bottino, A.; Geraci, C.; Piattelli, M. *Tetrahedron Asymm.* **1996**, *7*, 17–20.
8. Yashima, E.; Okamoto, Y. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3289–3307.
9. For a review on inherently chiral calixarenes see: Böhmer, V.; Kraft, D.; Tabatabai, M. *J. Incl. Phenom. Mol. Recogn.* **1994**, *19*, 17–39.
10. Reetz, M. T.; Huff, J.; Rudolph, J.; Töllner, K.; Deege, A.; Goddard, R. *J. Am. Chem. Soc.* **1994**, *116*, 11588–11589.
11. Arnaud-Neu, F.; Caccamese, S.; Fuangswasdi, S.; Pappalardo, S.; Parisi, M. F.; Petringa, A.; Principato, G. *J. Org. Chem.* **1997**, *62*, 8041–8048.
12. For a preliminary communication, see: Arnecke, R.; Böhmer, V.; Ferguson, G.; Pappalardo, S. *Tetrahedron Lett.* **1996**, *37*, 1497–1500.
13. Pappalardo, S.; Ferguson, G. *J. Org. Chem.* **1996**, *61*, 2407–2412.
14. Assuming the *O*-picolyl residue in the 1-position, two pairs of chiral [(2,3)- and (2,4)-bridged] and achiral [(2,5)- and (3,4)-bridged] *cone* regioisomers can exist, which are distinguishable by ^{1}H NMR spectroscopy on the basis of the number and/or position of the signal(s) of residual OH group(s).
15. Kraft, D.; Arnecke, R.; Böhmer, V.; Vogt, W. *Tetrahedron* **1993**, *49*, 6019–6024
16. Otsuka, H.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 1542–1547.
17. Neri, P.; Battocolo, E.; Cunsolo, F.; Geraci, C.; Piattelli, M. *J. Org. Chem.* **1994**, *59*, 3880–3889.
18. Arnaud-Neu, F.; Arnecke, R.; Böhmer, V.; Fanni, S.; Gordon, J. L. M.; Schwing-Weill, M.-J.; Vogt, W. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1855–1860.
19. Stewart, D. R.; Krawiec, M.; Kashyap, R. P.; Watson, W. H.; Gutsche, C. D. *J. Am. Chem. Soc.* **1995**, *117*, 586–601.
20. Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89–112.
21. Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009–1020.
22. Okamoto, Y.; Yashima, E. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1020–1043.
23. Caccamese, S.; Pappalardo, S. *Chirality* **1993**, *5*, 159–163.
24. Ouchi, M.; Inoue, Y.; Kanzaki; T., Hakushi, T. *J. Org. Chem.* **1984**, *49*, 1408–1412.
25. Pirkle, W. H.; Welch, C. J. *J. Liq. Chromatogr.* **1991**, *14*, 1–8.
26. Allenmark, S. *Chromatographic Enantioseparation. Methods and Applications*; Ellis Horwood: New York, 1991; Chapter 4.