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Chiral basket-shaped host compounds derived from diphenylglycoluril

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Abstract. The design and synthesis of two novel chiral receptors derived from diphenylglycoluril are described. The chirality in these molecules is due to the unsymmetrical positioning of amino functions in the crown ether rings with respect to the diphenylglycoluril subunit.

Introduction

The ability of enzymes to catalyze reactions in a stereoselective way depends to a large extent on a process of molecular recognition. The binding pocket of an enzyme has a chiral shape and, as a result of this, one particular substrate is bound and converted enantioselectively into the specified product[1]. Recently, we have described a synthetic supramolecular catalyst consisting of a basket-shaped receptor molecule provided with a catalytically active Rh(I) complex. This system was found to mimic certain features of enzymatic catalysis, *viz.* selective binding of a substrate in a cavity and conversion of the bound substrate at a catalytically active center[2]. In order to incorporate the aspect of enantioselective conversion into our supramolecular catalyst, it was felt necessary to modify the binding moiety of the receptor part in such a way that a chiral environment is obtained.
Chiral recognition requires a minimum of *three* simultaneous interactions between the binding site and the substrate[3]. Hydrogen bonding and electrostatic attractions are regarded to be *single-point* interactions, whereas *e.g.* dipole stacking and π-π interactions are *multi-point* in nature[3]. The chiral receptors described in this paper are based on the concave building block **1** (Figure 1)[4]. Earlier work in our group has shown that the binding of benzenediols in basket-shaped receptor molecules based on **1** is achieved by two hydrogen bonding interactions as well as by π-π stacking, as shown in Figure 2[5]. This implies that in principle no additional interaction is required to accomplish chiral recognition.
Several chiral host molecules have been described in the literature. In most cases the chirality is introduced by adding a chiral structural element to an existing host or by using a chiral building block to construct the host[6]. In this paper we describe a basket-shaped host molecule that is *intrinsically* chiral. Our ultimate objective is to use this molecule to achieve enantioselective catalysis by *shape recognition*, *i.e.* only one of the enantiomers of a racemic substrate should fit into the cavity of the metallohost to be constructed from this molecule.

Results and discussion

Strategy

As shown in Figure 1, compound **1** can be regarded as being composed of four subunits. To illustrate this, the molecule has been divided into four quadrants. Chirality can be easily built in by modifying one or two of these quadrants. As a result two chiral centers appear on the quaternary carbon atoms of the glycoluril unit, as indicated by asterisks in Figure 1. An obvious way to do this is by introducing dissymmetry in the handles of the basket compounds which can be synthesized from **1**. In compound **2**, only one of the handles is altered, leading to a completely asymmetric compound (C_1 symmetry). In **3**, two handles are modified which results in a chiral molecule with C_2 symmetry.
First, the synthesis of basket **2** is described and an attempt made to resolve this compound into enantiomers. After that the preparation of basket **3** is presented. This compound could be successfully resolved at the stage of a precursor molecule. This paper is concluded with some preliminary binding studies on **3**.

Basket with C_1 symmetry

The synthesis of compound **2** is summarized in Scheme 1. Benzene-1,4-diol was alkylated with 1-bromo-2-chloroethane in acetone using K_2CO_3 as a base to yield 4-(2-chloroethoxy)phenol (**4a**) (30%). Subsequently, **4a** was treated with 2-(2-chloroethoxy)ethyl *p*-toluenesulfonate and sodium hydride in DMF, resulting in 1-(2-chloroethoxy)-4-[2-(2-chloroethoxy)ethoxy]benzene (**4b**) (55%). Reaction of a 1:1 mixture of **4b** and 1,4-bis[2-(2-chloroethoxy)ethoxy]benzene (**4c**)[7] with the cyclic ether **5**[7,8] in acetic anhydride and trifluoroacetic acid gave a number of products, *viz.* the symmetric tetrachloride **6**, the *meso* compound **7**, a racemic mixture of the target molecule **8** and the racemate **9**. The molar ratio of these compounds amounted to approximately 2:1:4:1, which is close to the theoretically expected values. The compounds could be

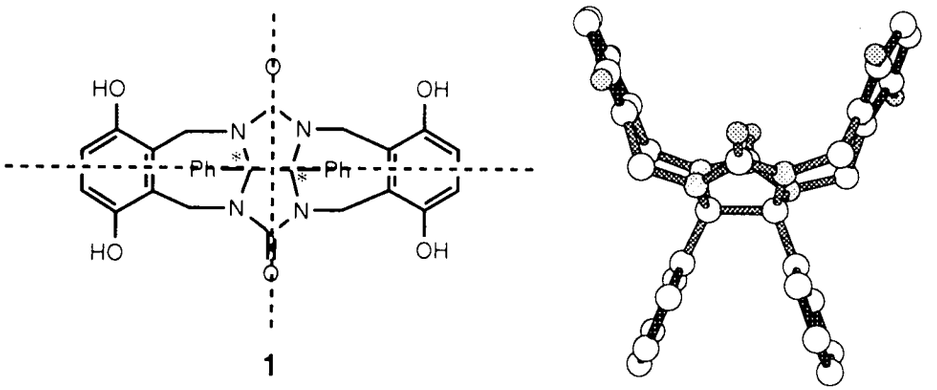


Figure 1. Division of compound 1 into four quadrants (left) and the X-ray structure of this compound (right).

separated by column chromatography and the racemate of **8** was obtained in 39% yield. The dissymmetry in the molecule is clearly visible in its ^{1}H-NMR spectrum. The aromatic xylylene protons on the symmetric side of the molecule are displayed as a singlet and those on the asymmetric side as an AB pattern. The methylene bridges, which link the xylylene walls to the glycoluril unit, give rise to three AX patterns, probably because two of them coincide.

Double ring closure of **8** with two equivalents of 4-(methoxymethoxy)benzylamine under dilute conditions in acetonitrile with Na_2CO_3 as the base gave the racemate of **2a** (76%). The protected phenolic hydroxyl groups in the latter compound provide functionalities for the coupling of a chiral auxiliary group or a catalytic center[2]. In the ^{1}H-NMR spectrum of **2a** the bridging methylene groups were visible as four AX patterns. The aromatic protons of the substituted benzyl groups gave rise to two different AB patterns and the xylylene wall protons displayed the same pattern as those in **8**. For the NCH_2 methylene protons in the ring, complicated signals were observed.

The methoxymethyl protecting groups were quantitatively removed by stirring a solution of **2a** in tetrahydrofuran/propan-2-ol with concentrated hydrochloric acid, resulting in **2b** · 2HCl.

We tried to separate the enantiomers of **2a**, **2b**, and also those of **8** on a chiral HPLC column. Unfortunately, we were not able to find a suitable stationary phase. Subsequently, we reacted **2b** with chiral reagents in order to obtain diastereomers, which can be separated chromatographically. However, the coupling of **2b** to (+)-10-camphorsulfonyl chloride, (R)-(+)-α-methoxy-α-(trifluoromethyl)benzeneacetyl chloride (Mosher's reagent), or (−)-menthyl chloroformate did not give separable diastereomers, as could be concluded from TLC and HPLC. Finally, we tried to achieve resolution by crystallization of the dibenzoyltartaric acid salt of compound **2a**. These attempts were also unsuccessful.

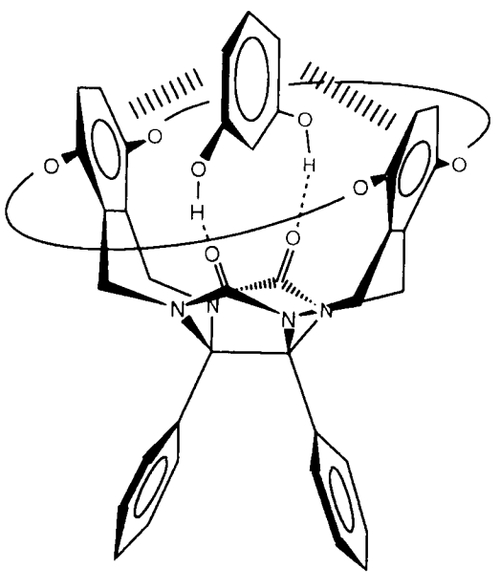
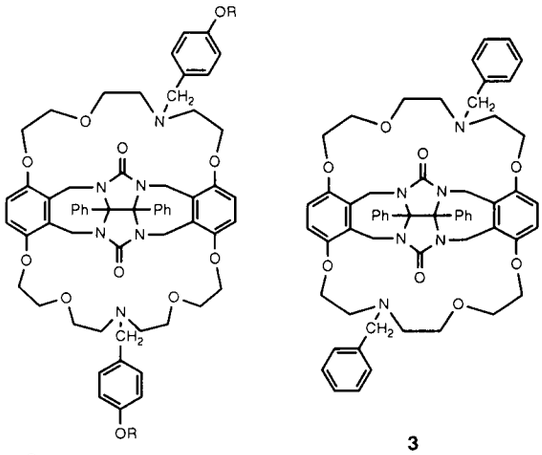


Figure 2. Schematic representation of the binding of benzene-1,3-diol in the basket-shaped receptor molecule based on 1.

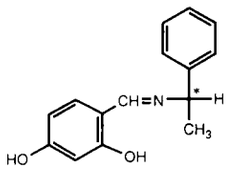
Basket with C_2 symmetry

The synthetic route to compound **3** is depicted in Scheme 2. The mono-alkylated benzene-1,4-diol derivative 4-[2-(2-chloroethoxy)ethoxy]phenol (**4d**) was coupled to the cyclic ether **5** in 1,2-dichloroethane in the presence of *p*-toluenesulfonic acid and molecular sieves. The racemate **10** and the *meso* compound **11** could be separated chromatographically. Their structures were assigned on the basis of the ^{13}C-NMR spectra (Figure 3): the *meso*



2 a: R = - CH_2-OCH_3
b: R = - H

3



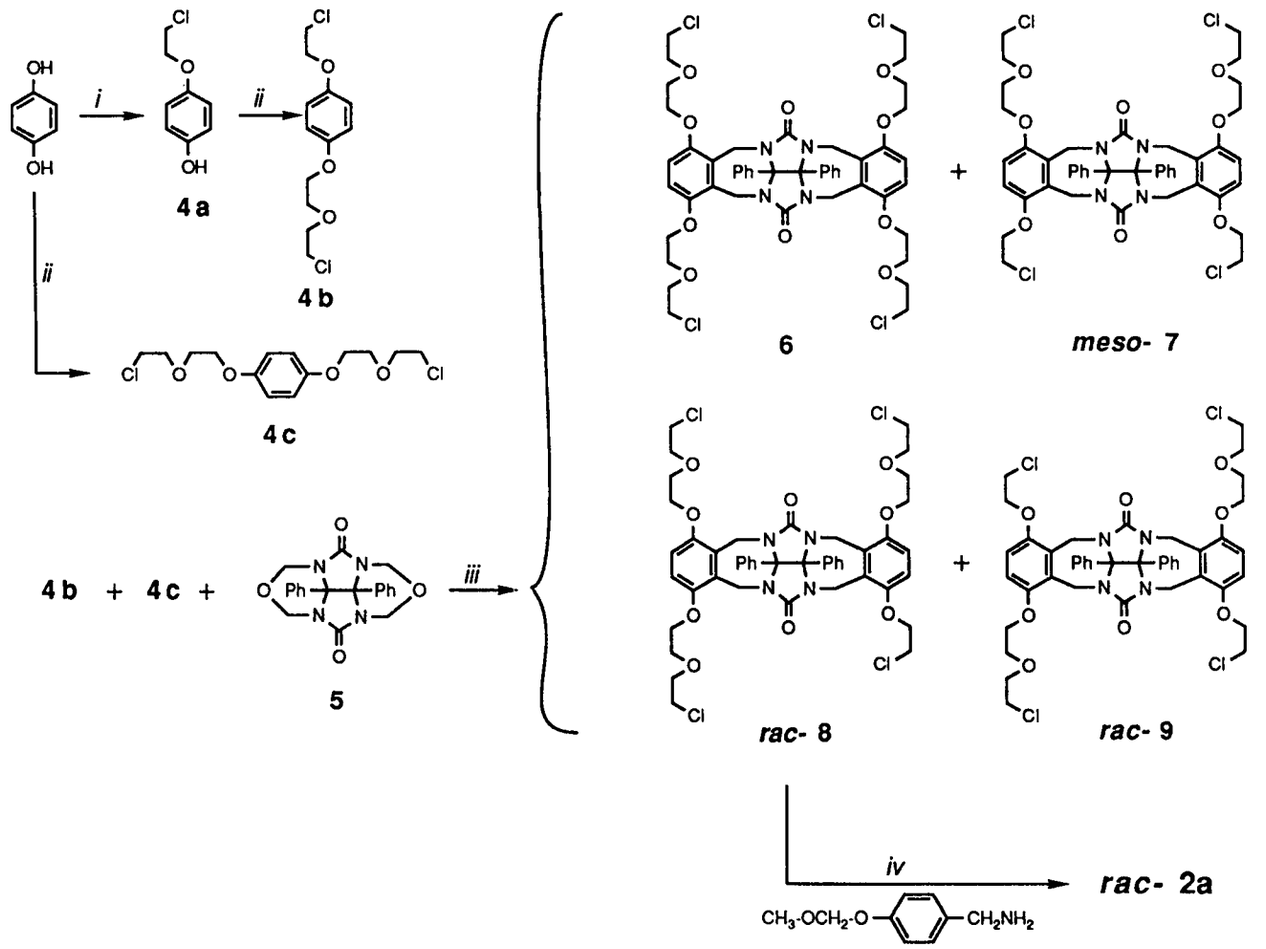
13

compound **11** displays two resonances for the carbonyl functionalities of the glycoluril unit, whereas the racemate gives only one signal due to the C_2 symmetry in the molecule. The bridging methylene groups in **10** form two sets which are non-equivalent and therefore give rise to two AX patterns in the ^{1}H-NMR spectrum. The signals of the xylylene wall protons appeared as an AB pattern and were shifted *ca.* 1 ppm to a higher field compared to the reference compounds **6–9**. This feature may be explained by assuming that the phenolic hydroxyl groups are hydrogen-bonded to the carbonyl groups of the glycoluril unit. The hydrogen bond will be optimized if the xylylene walls are moved towards the carbonyl groups, causing a twist in the molecule, as is shown in Figure 4. Such a twist is not unlikely and has been observed before in glycoluril derivatives[9]. An indication for such a twist is found in the ^{13}C-NMR spectrum of **10**. For the carbon atoms of the phenyl groups on the convex side of the glycoluril unit several well-separated signals are observed. Normally, these carbon atoms give rise to a narrow cluster of overlapping signals (*e.g.* see compound **11**, Figure 3). In **10**, the carbon atoms will be all magnetically different as a result of the ring current shifts, caused by the twisted benzene rings. The hydrogen bonds are broken by coordinating solvent molecules, as can be concluded from the fact that the ^{1}H-NMR signals of the xylylene walls of **10** are not shifted in DMSO-d_6. In the *meso* compound **11**, hydrogen bonds between the carbonyl groups of the glycoluril unit and the phenolic hydroxylgroups are possible but these hydrogen bonds cannot be stabilized by a twist in this molecule. In line with this, only small shifts of the xylylene wall protons were observed.

Rac-**10** was treated with two equivalents of (−)-menthyl chloroformate to give a mixture of diastereomers (**12a** and **12b**). The ^{1}H-NMR spectrum of this mixture displayed several distinct sets of resonances for each of the diastereomers. After chromatographical resolution (13% yield of each diastereomer), these sets were separately visible in the ^{1}H-NMR spectra of each of the diastereomers (see experimental section). The removal of the menthyl groups with sodium methoxide in methanol yielded each of the enantiomers of **10** in an optically pure form (74%). Reacting these enantiomers with a large excess of 1-bromo-2-chloroethane in DMSO with base, resulted in the quantitative formation of the enantiomers of **9** ($[\alpha]_{20}^{D}$ + and −13.4°). These compounds were also obtained as an inseparable racemate in the synthesis of **8** (see previous section). Double ring closure of **9** with two equivalents of benzylamine under dilute conditions in acetonitrile with Na_2CO_3 as a base yielded both enantiomers of the chiral basket compound **3** ($[\alpha]_{20}^{d}$ + and −16.4°, yields 77% and 90%, respectively).

Binding experiments

^{1}H-NMR spectroscopy was used to evaluate the binding properties of the two enantiomers of **3**[5,10]. First, the binding constant of benzene-1,3-diol was determined and found to be $K_a = 200 \pm 25\ M^{-1}$. This value is much lower than the values normally observed[5a] for this type of bas-



Scheme 1. i) $BrCH_2CH_2Cl / K_2CO_3$; ii) $TsO\frown O\frown Cl / NaH$, DMF; iii) Ac_2O / TFA; iv) Na_2CO_3 / NaI, MeCN.

ket-shaped compounds, *viz.* $K_a \approx 3000\ M^{-1}$. The lower binding affinity may be caused by the benzyl groups which probably partially cover the cavity of **3** as a result of the restricted flexibility of the handles. A similar situation is present in a related basket compound with small handles, of which we recently reported an X-ray structure[9b].

We carried out a titration with the guest compound **13** to investigate whether receptor **3** displays any enantioselectivity in the binding of a chiral substrate. Compound **13** was prepared by the condensation of 2,4-dihydroxybenzaldehyde and (−)-α-methylbenzylamine. Unfortunately, the affinity of **13** for both (+)-**3** and (−)-**3** was very low; the binding constants amounted to approximately $K_a \approx 60\ M^{-1}$. Probably, the cavity of the host is too shielded by the benzyl groups to accommodate a bulky substrate like **13**. Another complication is the fact that in **13** an intramolecular hydrogen bond can be formed between one of the phenolic hydroxyl groups and the N atom of the imine function. This feature is also unfavourable for binding.

Work is now in progress to connect ligands to the *para* positions of the benzyl groups in **3**. On complexation to a metal center, the benzyl groups will be lifted to a more upward position which opens the cavity of **3** and makes it more accessible for substrate molecules.

Experimental section

General

Unless otherwise indicated, commercial materials were used as received. Hexane, THF, diethyl ether, and toluene were distilled under nitrogen atmosphere from sodium ketyl. Dichloromethane was distilled from $CaCl_2$. All solvents were stored on molecular sieves under an inert atmosphere.

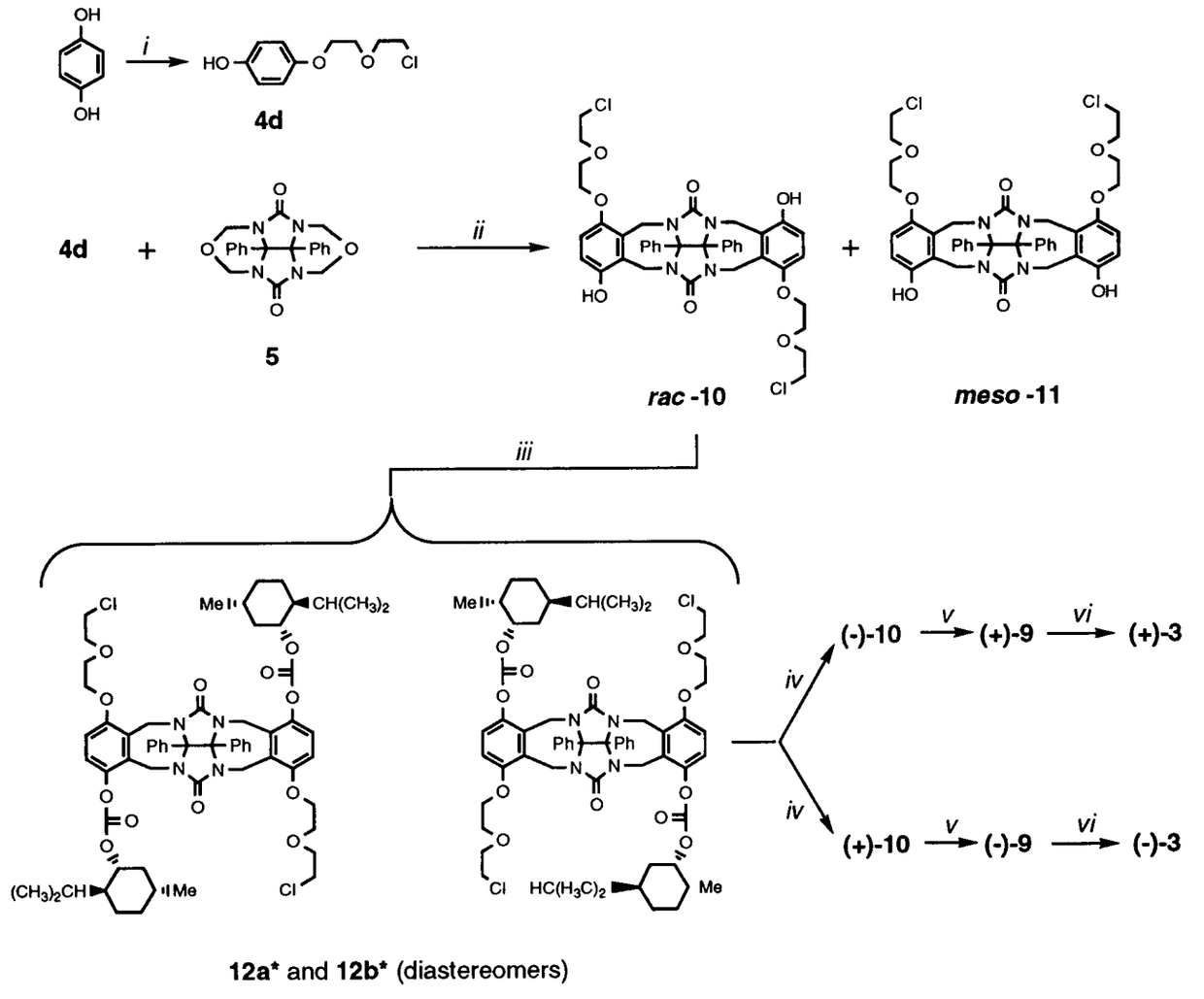
^{1}H-NMR spectra were recorded on Bruker WH-90, Bruker AC-100, and Bruker AM-400 instruments. Chemical shifts (δ) are reported in ppm downfield from internal Me_4Si. Abbreviations used are s = singlet, d = doublet, tr = triplet, q = quartet, m = multiplet, and br = broad. FAB mass spectra were recorded on a VG 7070E instrument, the matrix used was 3-nitrobenzyl alcohol. IR spectra were recorded on a Perkin-Elmer IRFT spectrometer 1720-X. The optical rotations were determined on a Perkin-Elmer 241 polarometer.

The HPLC columns used were a Machary Nagel Nucleosil Chiral-2, a LiChrosorb Si-100–10, and a LiChrosorb RP-18. For column chromatography Merck Silica Gel (60H) was used and for thin-layer chromatography Merck Silica Gel 60 F_{254} plates.

Elemental analyses were determined with a Carlo Erba Ea 1108 instrument.

4-(2-Chloroethoxy)phenol (**4a**)

A mixture of 3 g (27 mmol) of benzene-1,4-diol, 10 g (70 mmol) of 1-bromo-2-chloroethane, and 10 g (72 mmol) of K_2CO_3 in 50 ml of acetone was refluxed for 18 h. The mixture was filtered and the



Scheme 2.

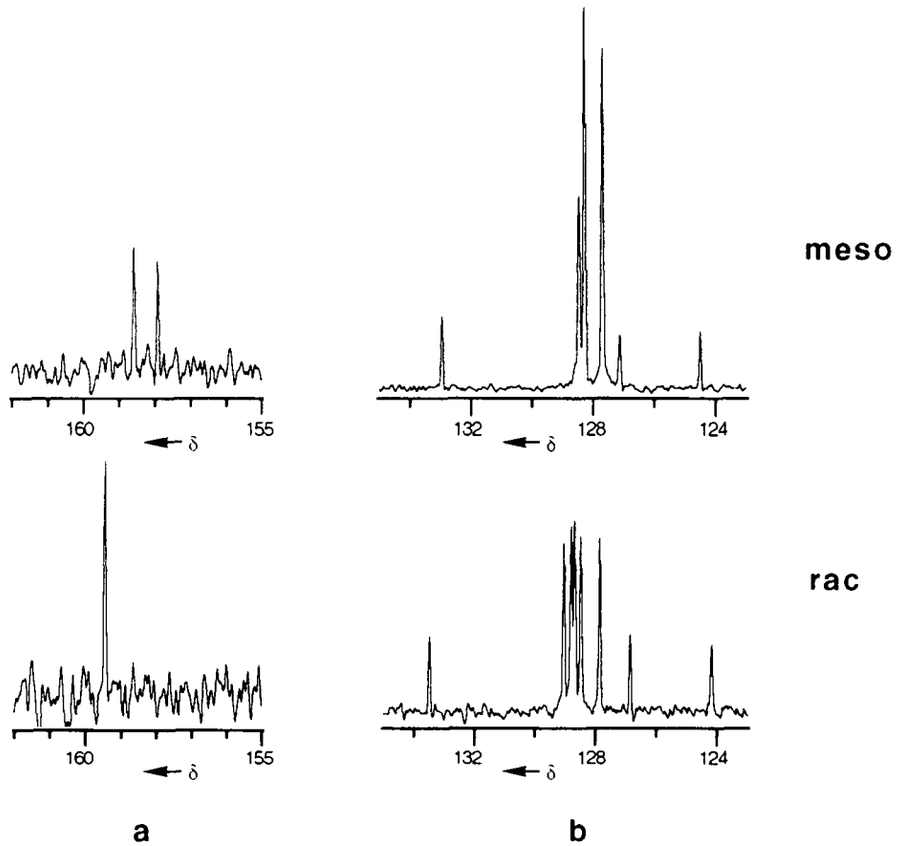


Figure 3. Low-field regions (a) and aromatic regions (b) of the ^{13}C-NMR spectra of meso-**11** *(above) and* rac-**10** *(below).*

solvent was removed under reduced pressure. The residue was taken up in 50 ml of CH_2Cl_2 and the solution was subsequently washed with 1N aqueous HCl, a saturated aqueous solution of $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and evaporated to dryness. The product was purified by column chromatography (silica, eluent: 0.5% MeOH in $CHCl_3$) to give 1.41 g (30%) of **4a** as a white crystalline solid. ^{1}H-NMR (100 MHz, $CDCl_3$) δ 6.79 (br s, 4H, ArH), 4.80 (s, 1H, OH), 4.17 (tr, 2H, CH_2O, *J* 6 Hz), 3.78 (tr, 2H, CH_2Cl, *J* 6 Hz).

1-(2-Chloroethoxy)-4-[2-(2-chloroethoxy)ethoxy]benzene (**4b**)

To a suspension of 0.4 g (10 mmol) of NaH (60% dispersion in oil) in 25 ml of DMF was added 1.73 g (10 mmol) of **4a**. After the evolution of gas had stopped, 2.79 g (10 mmol) of 2-(2-chloroethoxy)ethyl *p*-toluenesulfonate[11] was added and the mixture was stirred for 18 h under argon. The mixture was neutralized with aqueous HCl and the solvent was removed under vacuum. The residue was taken up in 50 ml of 1N aqueous HCl and the resulting emulsion was extracted three times with CH_2Cl_2. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated to dryness. After column chromatography (silica, eluent: 0.5% MeOH in $CHCl_3$) 1.53 g (55%) of **4b** was obtained as a yellowish oil. ^{1}H-NMR (100 MHz, $CDCl_3$) d 6.84 (br s, 4H, ArH), 4.22-4.03 (m, 4H, CH_2Cl), 3.88-3.57 (m, 8H, CH_2O).

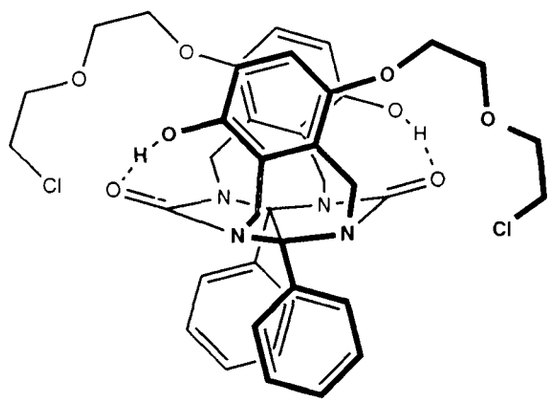


Figure 4. The optimization of the hydrogen bonds in **10** *by a twist in the molecule.*

1,4-Bis[2-(2-chloroethoxy)ethoxy]benzene (**4c**)

This compound was synthesized according to a literature procedure[8].

4-[2-(2-Chloroethoxy)ethoxy]phenol (**4d**)

This compound was synthesized from 0.44 g (4 mmol) of benzene-1,4-diol, 1.19 g (4.3 mmol) of 2-(2-chloroethoxy)ethyl *p*-toluenesulfonate and 0.18 g (4.5 mmol) of NaH (60% dispersion in oil) in 10 ml of DMF as described for **4b**. After column chromatography (silica, eluent: EtOAc:Hex, 1:2 v/v) 0.15 g (17%) of **4d** was obtained as a yellowish oil. ^{1}H-NMR (100 MHz, $CDCl_3$) δ 6.78 (s, 4H, ArH), 4.92 (s, 1H, OH), 4.18–3.98 (m, 2H, CH_2Cl), 3.95–3.53 (m, 6H, CH_2O).

*5,7,12,13b,13c,14-Hexahydro-1(and 11)-(2-chloroethoxy)-4,8,11 (and 1)-tris[2-(2-chloroethoxy)ethoxy]-13b,13c-diphenyl-6*H,*13*H*-5a,6a,12a, 13a-tetraazabenz[5,6]azuleno-[2,1,8-*ija*]benz*[f]*azulene-6,13-dione* (rac-**8**)

A solution of 2.34 g (6.2 mmol) of compound **5**[6] in a mixture of 6 ml of Ac_2O and 6 ml of trifluoroacetic acid was stirred at 95°C for 30 min. Subsequently, 1.73 g (6.2 mmol) of **4b** and 2.0 g (6.2 mmol) of **4c** were added and the solution was stirred for another 30 min at 95°C. After cooling to room temperature 25 ml of methanol was *carefully* and *slowly* added. The resulting precipitate was filtered off and washed three times with ice cold diethyl ether. The products were separated by column chromatography (silica, eluent: EtOAc:$CHCl_3$, 1:3 v/v), giving 2.25 g (39%) of *rac*-**8** as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.14-7.05 (m, 10H, Ar); 6.74 and 6.71 (2d, 2H, ArH, *J* 9 Hz), 6.73 (s, 2H, ArH); 5.57, 5.544 and 5.541 (3d, 4H, NC*H*HAr, *J* 16 Hz), 4.32-3.61 (m, 32H, NCH*H*Ar, CH_2CH_2); FAB MS *m/z* 944 ($[M+H]^+$); Anal. calcd. for $C_{46}H_{50}N_4O_9Cl_4$: C 58.48, H 5.33, N 5.93; found: C 58.52, H 5.35, N 5.87%.

Racemate of compound **2a**

Compound **2a** was prepared according to a previously published procedure[7] from 0.82 g (0.9 mmol) of **8**, 0.44 g (2.6 mmol) of

4-(methoxymethoxy)benzylamine[2a], 4 g of Na_2CO_3 (38 mmol) and 15 g of NaI in 400 ml of acetonitrile. The compound was purified by column chromatography (silica, eluent: $CHCl_3$ with 1% Et_3N and 0.5% methanol) to give 0.75 g (76%) of white **2a**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31 and 7.28 (2d, 4H, ArH, J 8.5 Hz); 7.17-7.04 (m, 10H, Ar); 7.00 and 6.99 (2d, 4H, ArH, J 8.5 Hz); 6.75 and 6.70 (2d, 2H, ArH, J 9 Hz), 6.74 (s, 2H, ArH); 5.68, 5.65, 5.64 and 5.58 (4d, 4H, NC*H*HAr, J 16 Hz), 5.18 (s, 4H, OCH_2O), 4.19-3.65 (m, 28H, NCH*H*Ar, CH_2CH_2); 3.50 (s, 6H, OCH_3), 3.15-2.82 (m, 8H, CH_2N). FAB MS m/z 1133 ($[M+H]^+$).

Racemate of compound **2b**·*2HCl*

To a solution of 0.5 g (0.44 mmol) of compound **2a** in a mixture of 10 ml of THF and 10 ml of propan-2-ol was added dropwise 2 ml of concd. aqueous HCl (30%). After stirring for 3 h, the solution was evaporated to dryness. The solid material was dried under high vacuum to give 0.49 g (100%) of white **2b**·2HCl. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.2-9.8 (br, 2H, N^+-H), 7.6-6.7 (m, 22H, ArH), 5.7-5.2 (m, 4H, ArCH*H*N), 4.6-3.2 (br m, 36H, $ArOCH_2$, ArC*H*HN, CH_2N). FAB MS m/z 1045 ($[\mathbf{2b}+H]^+$), 523 ($\frac{1}{2}\cdot[\mathbf{2b}+2H]^+$).

Coupling of chiral auxiliary groups

A solution of 0.33 g (0.3 mmol) of **2b**·2HCl, 1.2 ml of (−)-menthyl chloroformate and 0.2 ml of Et_3N in 5 ml of CH_2Cl_2 was stirred overnight at room temperature. The solution was washed three times with a $NaOH/NaHCO_3$ buffer (pH ≈ 10), dried ($MgSO_4$) and evaporated to dryness. The coupling of (+)-10-camphorsulfonyl chloride and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)benzeneacetyl chloride was achieved in a similar way. NMR indicated that the product was disubstituted with the chiral group. Attempts to separate the diastereomers on different chromatographic columns were unsuccessful.

*5,7,12,13b,13c,14-Hexahydro-1,8 (and 4,11)-bis[2-(2-chloroethoxy)-ethoxy]-4,11 (and 1,8)-dihydroxy-13b,13c-diphenyl-6*H,*13*H*-5a,6a,12a,13a-tetraazabenz[5,6]azuleno-[2,1,8-*ija*]benz[*f*]azulene-6,13-dione* (rac-**10**) *and 5,7,12,13b,13c,14-hexahydro-1,11-bis[2-(2-chloroethoxy)ethoxy]-4,8-dihydroxy-13b,13c-diphenyl-6*H,*13*H*-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-*ija*]benz[*f*]azulene-6,13-dione* (meso-**11**)

A solution of 12.7 g (67.0 mmol) of *p*-toluenesulfonic acid, 2.3 g (6.1 mmol) of **5** and 2.9 g (13.4 mmol) of **4d** in 150 ml of 1,2-dichloroethane was refluxed for 4 days, the condensed solvent running back over molecular sieves 4 Å. The mixture was concentrated to 20 ml. Subsequently, $CHCl_3$ was added and the mixture was washed with water, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated to dryness. After column chromatography (silica, eluent: 2% MeOH in $CHCl_3$) 1.75 g (37%) of *rac*-**10** and 1.62 g (34%) of *meso*-**11** were obtained as off-white solids.

Compound **10**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 2H, OH); 7.25-7.11 (m, 10H, ArH); 5.93 and 5.52 (2d, 4H, ArH, J 9 Hz); 5.58 and 5.17 (2d, 4H, NC*H*HAr, J 16 Hz), 3.95-3.67 (m, 20H, NCH*H*Ar, CH_2CH_2). ^{1}H-NMR (100 MHz, DMSO-d_6) δ 8.21 (s, 1H, OH); 7.32-6.90 (m, 10H, ArH); 6.67 and 6.62 (2d, 4H, ArH, J 9 Hz); 5.42 (br d, 4H, NC*H*HAr, J 16 Hz), 4.19-3.46 (m, 28H, NCH*H*Ar, CH_2CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.5 (C = O), 149.1, 148.8, 133.5, 129.0, 128.8, 128.7, 128.5, 127.9, 126.8, 124.2, 116.9 and 114.6 (xylylene and glycoluril), 86.2 (glycoluril), 71.5, 70.0, 69.4 (CO chain), 43.0 (CCl) 38.0 and 37.1 (NC glycoluril). FAB MS m/z 775 ($[M+H]^+$).

Compound **11**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 2H, OH); 7.18-7.11 (m, 10H, ArH); 6.40 and 6.38 (2d, 4H, ArH, J 9 Hz); 5.56 and 5.45 (2d, 4H, NC*H*HAr, J 16 Hz), 4.04-3.67 (m, 20H, NCH*H*Ar, CH_2CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 158.6 and 157.9 (C = O), 149.1, 148.1, 133.0, 128.5, 128.3, 127.7, 127.1, 124.5, 115.6, 114.2 (xylylene and glycoluril), 85.5 (glycoluril), 71.0, 69.7, 69.3 (CO chain), 42.5 (CCl) 36.9 and 36.7 (NC glycoluril). FAB MS m/z 775 ($[M+H]^+$).

*5,7,12,13b,13c,14-Hexahydro-1,11-bis[2-(2-chloroethoxy)ethoxy]-4,8-bis(menthylcarbonyloxy)-13b,13c-diphenyl-6*H,*13*H*-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-*ija*]benz[*f*]azulene-6,13-dione* (**12a**) *and 5,7,12,13b,13c,14-hexahydro-4,8-bis[2-(2-chloroethoxy)ethoxy]-1,11-bis(menthylcarbonyloxy)-13b,13c-diphenyl-6*H,*13*H*-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-*ija*]benz[*f*]azulene-6,13-dione* (**12b**)

To a cooled solution (0°C) of 2.63 g (3.4 mmol) of *rac*-**10** and 5 g (23 mmol) of (−)-menthyl chloroformate in 50 ml of CH_2Cl_2 was carefully added 5 ml of Et_3N. The mixture was allowed to warm to room temperature and stirred for 18 h. The solution was washed with water, 1N aqueous HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and evaporated to dryness. Purification by column chromatography (silica, eluent: 1% MeOH in $CHCl_3$) gave 0.5 g (13%) of **12a** and 0.5 g (13%) of **12b** as white solids. Compound **12a***[a] characterized by R_f 0.24. ^{1}H-NMR (100 MHz, $CDCl_3$) δ 7.23-6.95 (m, 10H, ArH); 6.93 and 6.76 (2d, 4H, ArH, J 9 Hz); 5.67 and 5.08 (2d, 4H, NC*H*HAr, J 16 Hz), 4.58 (d tr, 2H, -CHO-, J 12 Hz, J 3 Hz), 4.35-3.55 (m, 20H, NCH*H*Ar, CH_2CH_2), 2.30-0.70 (m, 32 H, CH menthyl). Compound **12b*** characterized by R_f 0.15. ^{1}H-NMR (100 MHz, $CDCl_3$) δ 7.23-6.95 (m, 10H, ArH); 6.99 and 6.73 (2d, 4H, ArH, J 9 Hz); 5.66 and 5.12 (2d, 4H, NC*H*HAr, J 16 Hz), 4.60 (d tr, 2H, -CHO-, J 12 Hz, J 3 Hz), 4.37-3.56 (m, 20H, NCH*H*Ar, CH_2CH_2), 2.30-0.70 (m, 32 H, CH menthyl).

*5,7,12,13b,13c,14-Hexahydro-1,8 (or 4,11)-bis[2-(2-chloroethoxy)-ethoxy]-4,11 (or 1,8)-dihydroxy-13b,13c-diphenyl-6*H,*13*H*-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-*ija*]benz[*f*]azulene-6,13-dione ((+)-***10*** *and (−)-***10***)

A solution of 0.5 g (0.45 mmol) of **12b** in a mixture of 50 ml of MeOH and 10 ml of CH_2Cl_2 was brought to pH 8 (wet pH paper) with NaOMe and stirred for 4 days. The solution was neutralized (HCl) and evaporated to dryness. After column chromatography (silica, eluent: 4% MeOH in $CHCl_3$), 0.25 g (74%) of white (+)-**10** was obtained: $[\alpha]_{20}^{D}$ +38°. Starting from **12a**, the same procedure was followed to give 0.25 g (74%) of (−)-**10**: $[\alpha]_{20}^{D}$ −30°. The spectral data of (+)-**10** and (−)-**10** were identical to those of *rac*-**10**.

*5,7,12,13b,13c,14-Hexahydro-1,8 (or 4,11)-bis(2-chloroethoxy)-4,11 (or 1,8)-bis[2-(2-chloroethoxy)ethoxy]-13b,13c-diphenyl-6H,13H-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-ija]benz[f]azulene-6,13-dione ((+)-***9*** *and (−)-***9***)

A mixture of 0.25 g (0.32 mmol) of (−)-**10**, 1 g of powdered KOH and 20 ml of 1-bromo-2-chloroethane in 5 ml of DMSO was stirred overnight. The solvent was removed under vacuum and 30 ml of water was added. The resulting emulsion was extracted three times with $CHCl_3$ and the organic layer was washed with 1N aqueous HCl and a saturated aqueous solution of $NaHCO_3$. Subsequently, this layer was concentrated to 5 ml and added dropwise to hexane with vigorous stirring. The resulting precipitate was filtered off and washed with ice-cold ether. Yield 0.27 g (93%) of white (+)-9: $[\alpha]_{20}^{D}$ +13.4°. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.21-6.97 (m, 10H, ArH); 6.65 (br s, 4H, ArH), 5.58 and 5.54 (2d, 4H, NC*H*HAr, J 16 Hz), 4.28-3.60 (m, 28H, NCH*H*Ar, CH_2CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 157.8 (C = O), 151.2, 150.4, 133.9, 128.8, 128.6, 128.3, 128.1, 115.1, 114.5 (xylylene and glycoluril), 85.3 (glycoluril), 71.6, 70.9, 70.2 (CO chain), 43.2 and 42.3 (CCl), 37.0 (NC glycoluril). FAB MS m/z 901 ($[M+H]^+$). Anal. calcd. for $C_{44}H_{46}N_4O_8Cl_4\cdot 1.5NaCl$: C 53.47, H 4.69, N 5.67; found: C 53.27, H 4.63, N 5.60%.
Starting from (+)-**10** the same procedure was followed to give 0.26 g (90%) of (−)-**9**: $[\alpha]_{20}^{D}$ −13.4°. The spectral data and physical properties of (−)-**9** were similar to those of (+)-**9**.

*Compound (+)-***3**

This compound was synthesized as described previously[7] from 0.24 g (0.27 mmol) of (+)-**9**, 89 mg (0.83 mmol) of freshly distilled benzylamine, 1 g of Na_2CO_3 and 2 g of NaI in 110 ml of acetonitrile. The compound was purified by column chromatography (silica, eluent: $CHCl_3$ with 1% Et_3N and 0.5% methanol) to give 0.20 g (77%) of white (+)-**3**: $[\alpha]_{20}^{D}$ +16.4°. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38-7.04 (m, 20H, Ar), 6.74 and 6.71 (2d, 2H, ArH, J 9 Hz), 5.65 and 5.55 (2d, 4H, NC*H*HAr, J 16 Hz), 4.17-3.64 (m, 24H, NCH*H*Ar, CH_2O, NCH_2Ar); 3.18-2.84 (m, 8H, CH_2N). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 157.3 (C = O), 151.5, 151.2, 139.8, 134.7, 129.8, 128.8, 128.5, 128.2, 126.9, 117.1, 114.5 (Ar), 85.0 (glycoluril), 71.5, 69.1, 69.0, 68.7 (CO crown), 61.0 (NCAr), 54.5 and 53.7 (CN crown), 37.1 and 36.8 (NC glycoluril). FAB MS m/z 969 ($[M+H]^+$). Anal. calcd. for $C_{58}H_{60}N_6O_8\cdot H_2O$: C 70.57, H 6.33, N 8.51; found: C 70.60, H 6.15, N 8.41%.

*Compound (−)-***3**

This compound was synthesized from (−)-**9** as described for (+)-**3**. Yield 0.22 g (85%) of white product: $[\alpha]_{20}^{D}$ −16.4°. The spectral data of (−)-**3** were identical to those of (+)-**3**. Anal. calcd. for

[a] An asterisk indicates that the absolute configuration of the compound is unknown.

$C_{58}H_{60}N_6O_8 \cdot H_2O$: C 70.57, H 6.33, N 8.51; found: C 69.43, H 5.94, N 8.37%.

(S)-N-(2,4-Dihydroxybenzylidene)-1-phenylethylamine (**13**)

A solution of 1 g (7.2 mmol) of 2,4-dihydroxybenzaldehyde and 1.4 g (11.6 mmol) of (*S*)-(−)-α-methylbenzylamine in 50 ml of 1,2-dichloroethane was refluxed for $1\frac{1}{2}$ h. The reaction volume was reduced to approx. 2 ml and added dropwise to 50 ml of hexane. The resulting yellow precipitate was filtered off. The precipitation procedure was repeated four times until the excess of amine had been removed. Yield 1.3 g (73%) of a yellow powder: $[\alpha]_{20}^{D}$ 320°. ^{1}H-NMR (100 MHz, $CDCl_3$) δ 8.00 (s, 1H, CH = N), 7.34 (m, 5 H, ArH), 7.00 (d, 1H, ArH, *J* 8.9 Hz), 6.28-6.21 (m, 2H, ArH), 4.62 (q, 1H, CH, *J* 6.8 Hz), 1.65 (d, 3H, CH_3, *J* 6.8 Hz).

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