Analytical Optical Resolution of Bromochlorofluoromethane by Enantioselective Inclusion into a Tailor-Made "Cryptophane" and Determination of Its Maximum Rotation

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Abstract: Analytical optical resolution of bromochlorofluoromethane (**1**) has been achieved by ^1H NMR spectroscopy by inclusion of the haloform within the cavity of a chiral host molecule (**5**) (cryptophane-C) designed to fit substrates of this size. The diastereomeric 1:1 complexes in which host (**5**) and guest (**1**) have like sign appear to be stabler than those formed from partners of unlike signs by about 1.1 kJ/mol. Under fast inclusion/exclusion exchange conditions (332 K, 200 MHz), and with the chiral host concentration ≥0.1 M, the NMR resonances of the (+) and (−) enantiomers of **1** are totally separated, allowing an easy determination of the guest enantiomeric composition. The enantiomeric excess of a partially enriched (+) sample of **1** having α_D +0.129° (neat) has been found by this method to be 4.3 ± 1%, and the maximum molar rotation $[\Phi]_D$ of this substrate has therefore been estimated to be in the range 1.2–2.2 deg·cm^2/dmol.

An experimental determination of the maximum rotation and absolute configuration of bromochlorofluoromethane (**1**) would be of considerable interest, especially in the context of the modern theories of optical activity.[1-4] For nearly a century, a number of attempts have been made to obtain this chiral haloform in optically active form,[5-9] and samples exhibiting weak rotations have already been isolated. In 1969, Hargreaves et al.[7] obtained (+)- and (−)-**1** with $[\alpha]_D$ +0.20° and −0.13° (in cyclohexane), on reaction of (+)- and (−)-BrClFC–$COCH_3$ of unknown enantiomeric excess (ee) with KOH, and a few years later Wilen et al.[8] were able to recover (+) and (−) fractions having α_D up to +0.128° (neat), upon complexation of (±)-**1** with solid brucine. However, no information could be drawn, at that time, on the ee of these optically active samples nor on the absolute configuration of **1**.

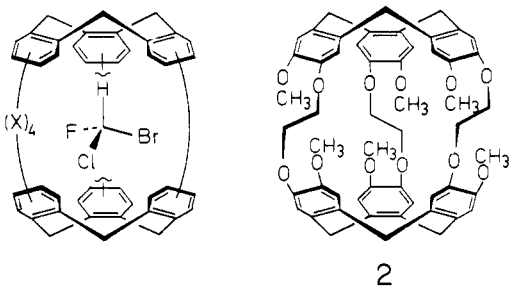
We report here the first NMR optical resolution of **1**, involving the inclusion of this haloform within the cavity of a chiral host molecule (*cryptophane-C*), specifically designed to fit substrates of this size. Application of this procedure to the determination of the ee of one of the partially resolved Wilen's samples leads us to conclude that the molar rotation $[\Phi]_D$ of CHFClBr should be in the range 1.2 to 2.2°.

Functionalized C_3-cyclotribenzylenes[10-12] offer a potential source of chiral subunits for the design of hollow molecules of the *speleand*[13] and *cavitand*[14] classes. Space-filling models (CPK) support the idea that cavitands consisting of two cyclotribenzylene caps, connected to one another by three bridges of four atoms (e.g., carbon and oxygen), could accommodate guests which do not exceed the size of a chloroform molecule; such hosts therefore seem appropriate for complexation of CHFClBr (Scheme I).

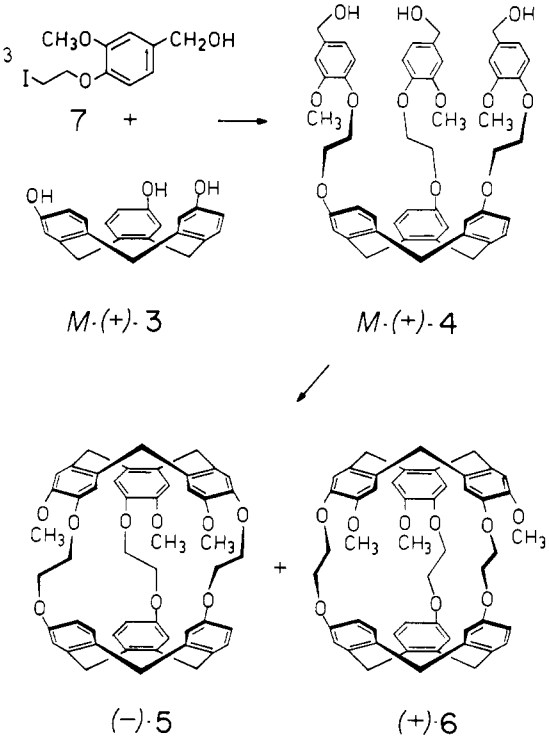
The first compound of this type that we synthesized for this purpose was **2** (cryptophane-A),[15] which has D_3 symmetry. Although **2** forms a crystalline complex with $CHCl_3$ (the structure of which is not known), thus far NMR experiments have not provided any conclusive evidence of an intramolecular inclusion of this guest. However, smaller molecules such as CH_2Cl_2 recently gave indication of a very weak, hardly detectable complexation.[22] Models suggest that the six OCH_3 groups of **2** obstruct the windows giving access to the host cavity, and we synthesized racemic cryptophane-C (**5**) from the cyclization precursor (±)-**4** (Scheme II); this reaction also yielded a small amount of isomer **6** (cryptophane-D).[17]

In **5**, the windows are more widely opened due to the replacement of three OCH_3 groups by three hydrogens on one of the caps; guests of the CH_2XY type can now easily enter the cavity, with a barrier of ~46 kJ/mol for inclusion, whereas $CHCl_3$ experiences a substantially higher barrier (~63 kJ/mol), probably on account of its larger cross section.[18] In fact, $CHCl_3$ appears to be only weakly complexed by **5**, with a stability constant K_s of the order of 0.1 M^{-1} at 310–330 K. Therefore $CDCl_3$ could

Scheme I. Cryptophane Design for CHFClBr Inclusion and Structure of (−)-Cryptophane-A (**2**)



Scheme II. Synthesis and Absolute Configurations of Cryptophane-C (**5**) and Cryptophane-D (**6**)



† C.N.R.S. Equipe de recherche 285.

(1) Applequist, J. *J. Chem. Phys.* **1973**, *58*, 4251–4259. Applequist, J. *Acc. Chem. Res.*, **1977**, *10*, 79–85.

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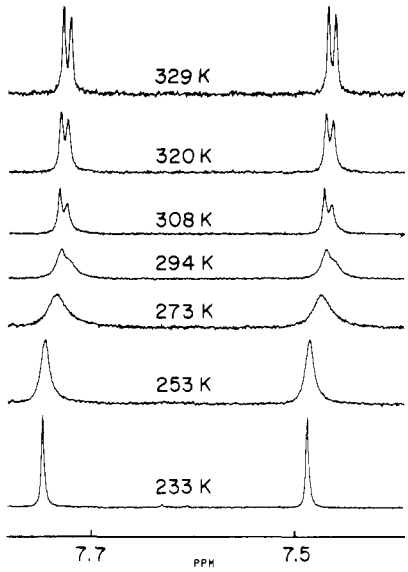

Figure 1. Variable-temperature 200-MHz ^1H NMR spectra of (±)-CHFClBr (**1**) (1.5×10^{-2} M) in the presence of (+)-**5** (1.5×10^{-2} M) in $CDCl_3$; the intensities are arbitrary, and the signal of residual $CHCl_3$ is used as the reference, δ_{CDCl_3} 7.26 (no Me_4Si was added).

be used as the solvent throughout the complexation studies, without too much inconvenience due to competition phenomena. In this solvent, the apparent stability constants K_s' of the 1:1 CH_2XY inclusion complexes of **5** ("cavitates") show a relatively sharp

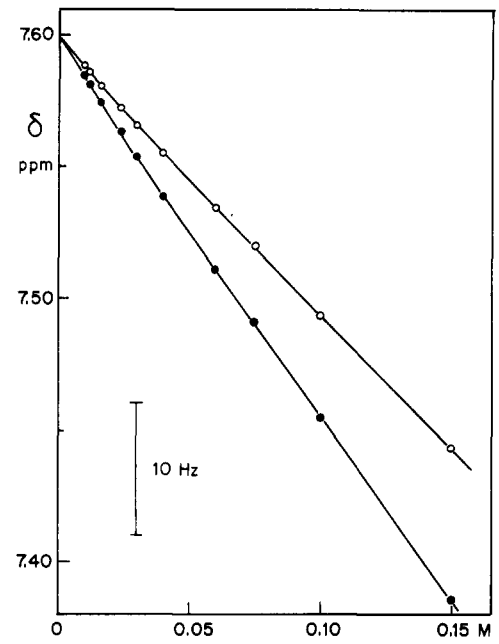

Figure 2. Variation of the chemical shifts of the enantiomers of **1** as a function of host and guest concentration in $CDCl_3$ (332 K, δ internal Me_4Si 0). The original solution which was 0.15 M in (+)-**5** and 0.30 M in (±)-**1** was progressively diluted by addition of $CDCl_3$; the lower curve (black circles) corresponds to (+)-**1** and the upper curve to (−)-**1**.

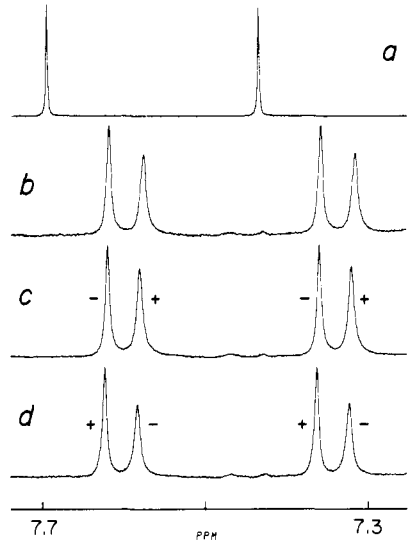

Figure 3. High-temperature (332 K) 200-MHz ^1H NMR spectra of **1** in $CDCl_3$, δ_{Me_4Si} 0: (a) (±)-**1** alone; (b) (±)-**1** (0.109 M) and (+)-**5** (0.095 M); (c) (+) sample of **1** having α^{25}_D +0.129° in the presence of (+)-**5**, same conditions as in part b; (d) (+) sample of **1** and (−)-**5**, same conditions as in part b.

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(4) Prasad, P. L.; Burow, D. F. *J. Am. Chem. Soc.* **1979**, *101*, 806–812. See also: Anderson, P. H.; Stephenson, B.; Mosher, H. S. *J. Am. Chem. Soc.* **1974**, *96*, 3171–3177. Julg, A. *Tetrahedron* **1961**, *12*, 146–162.
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(8) (a) Wilen, S. H.; Bunding, K. A.; Kasheres, C. M.; Wieder, M. J., unpublished results. Wilen, S. H. *Top. Stereochem.* **1971**, *6*, 122. Wilen, S. H. "Table of Resolving Agents and Optical Resolutions"; Eliel, E. L., Ed.; University of Notre Dame Press: Notre Dame, Indiana, 1972; p 299; (b) Wilen, S. H.; Bunding, K. A.; Kasheres, C. M.; Wieder, M. J. *J. Am. Chem. Soc.*, following paper in this issue.
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(15) The *Chemical Abstracts* name of **2** is the following: 3,22-(epoxyethanoxy)-6,9:25,28-dietheno-7,36:17,26-dimethano-14,18:33,37-dimetheno-18*H*,37*H*-dibenzo[*j*,a_1][1,4,18,21]tetraoxacyclotetratriacontin-5,11,12,19,21,30,31,38-octahydro-2,15,21,34,41,49-hexamethoxy. The term "cryptophane" that we have adopted for convenience should apply to hosts of the type depicted in Scheme I (left), i.e., to molecules consisting of two cyclotribenzylene units connected by bridges of various kinds (cyclotribenzylene is also named [1.1.1]orthocyclophane).
(16) Gabard, J.; Collet, A. *J. Chem. Soc., Chem. Commun.* **1981**, 1137–1139.
(17) Canceill, J.; Lacombe, L.; Collet, A. *C. R. Hebd. Seances Acad. Sci., Ser. II* **1984**, *298*, 39–42.
(18) In ref 17, owing to an erroneous assignment of the NMR resonance of complexed CH_2Cl_2 to a peak at 5.13 ppm (the correct location is in fact 0.74 ppm), the barrier for dichloromethane inclusion was slightly overestimated (revised value 45.1 kJ/mol instead of 52.3 kJ/mol). Also note that, at that time, chloroform was still considered *not* to be complexed by host **5**; the low-temperature stability constant of the CH_2Cl_2 cavitate, given in ref 17 (1.8 M^{-1}), is therefore an *apparent* stability constant (K_s'). The stability constant of the $CHCl_3$ cavitate at low temperature has not yet been established.
(19) The solvent ($CDCl_3$) being a competitor, the actual stability constants of the CH_2XY cavitates should be evaluated as $K_s = K_s'(1 + K_{CDCl_3}[CDCl_3])$, with $[CDCl_3] = 12.4$ M. If $K_{CDCl_3} \sim 0.1$ M^{-1} (a rough estimation), one should have $K_s \sim 2.1K_s'$ at high temperature (310–330 K).

decrease, from 2.6 to 0.7 M^{-1} at 310–330 K, on going from the smallest (CH_2Cl_2) to the bulkiest (CH_2Br_2) guest;[19] the X-ray crystal structure of the CH_2Cl_2 cavitate has been solved, confirming the intramolecular inclusion.[20]

Bromochlorofluoromethane is intermediate in size between CH_2Br_2 and $CHCl_3$, and on addition of (±)-**5** its ^1H NMR spectrum showed upfield shifts and peak broadening, indicating that complexation occurred and that the inclusion/exclusion process was slow, at room temperature, on the spectrometer time scale (200 MHz). Synthesis of the host enantiomers was therefore undertaken, starting from the (+) and (−) isomers of cyclotriphenolene **3**.[11] Alkylation of the phenolic groups of *M*-(+)-**3** by the vanillyl alcohol derivative **7** thus gave *M*-(+)-**4**, $[\alpha]_D$ +185° (in DMF), in 85% yield. A 6×10^{-4} M solution of (+)-**4** in HCO_2H (95 °C, 1 h) afforded a modest quantity of the diastereomeric cryptophanes **5** and **6**, which were easily separated by TLC; the minor isomer (+)-**6** (faster eluted) was isolated in 5% yield, $[\alpha]_D$ +145° (in $CHCl_3$), and the major isomer (−)-**5**, $[\alpha]_D$ −86°, in 20% yield. Both compounds are crystalline, high-melting solids showing TLC behavior and NMR spectra identical with those of the corresponding racemates.[17,20] Enantiomers (−)-**6** and (+)-**5** similarly obtained from (−)-**3** exhibited $[\alpha]_D$ −140° and +80°, respectively. Since the absolute configuration of **3** is known,[10,11] the sequence of transformations summarized in Scheme II also provides the absolute configurations of these two cryptophanes.

Variable-temperature ^1H NMR spectra of an equimolecular mixture (1.5×10^{-2} M) of (±)-**1** and (+)-**5** are shown in Figure 1 (only the guest signals are displayed). At low temperature (233 K), the inclusion/exclusion process is slow, and one only observes the doublet of free CHFClBr (δ_0 7.62 ppm, J_{HF} = 52 Hz); those of complexed (+)- and (−)-**1**, shifted upfield by ca 4.8 ppm (see below), are actually too weak to be observable under these conditions. On heating, the guest signals move upfield and broaden as the complexation rates increase. After a maximum broadening at ~273 K, *the signals sharpen and eventually split into two sets of doublets at high temperature* (323–333 K), representing the fast-exchange averaged resonances of the free and complexed enantiomers of **1**, involved in the equilibria leading to the diastereomeric "*p*" and "*n*" cavitates, [(+)-**1**·(+)-**5**] and [(−)-**1**·(+)-**5**].[21] As shown below, the most upfield doublet corresponds to the *p* equilibrium, hence to (+)-**1** in Figure 1.

The separation between the two sets (2 Hz in the above experiments) increases with the host concentration, reaching values as high as 8–10 Hz in the range 0.10 to 0.15 M of **5** at 332 K (Figure 2). The spectrum of (±)-**1** in the presence of 0.10 M concentration of (+)-**5** at this temperature effectively showed a nearly complete resolution into two doublets of equal area (Figure 3b). The peak half-width difference (1.31 vs. 1.75 Hz), responsible for the observed height difference of the doublets, is due to dynamic phenomena involved in the complexation equilibria, as will be discussed elsewhere.[22]

By using a 300-fold excess of guest **1** with respect to (+)-cryptophane-C and recording the spectrum at 215 K, the resonances of complexed (+)- and (−)-**1** could be observed as two partially merged doublets at δ_∞ 2.89 and 2.86 ppm (intensity ratio ~2:1).[23] The variation of the chemical shift of the fast exchange signal of the guest as a function of the overall host and guest concentration at 332 K (Figure 2) was analyzed according to the iterative procedure of Horman,[24] and the values of $K_s'(\delta_0-\delta_\infty)$ for the *p* and *n* cavitates were thus estimated to be 1.45 and 1.07 ppm·M^{-1}, respectively; since, $\delta_0 - \delta_\infty \sim 4.8$ ppm, the corresponding apparent stability constants in $CDCl_3$ should be about 0.30 and 0.22 M^{-1} at this temperature. These values are significantly smaller than that of CH_2Br_2, confirming the trend observed above as to the dependence of K_s' on the size of the guest. It is interesting that this NMR resolution of **1** proceeds from a difference between the *stability constants* for the diastereomeric cavitates, rather than from a purely spectroscopic effect on the induced chemical shifts ($\delta_0-\delta_\infty$). Consequently, a chromatographic resolution of **1**, using **5** as the chiral stationary phase, is theoretically feasible.

Table I. Optical Rotation of CHFClBr

λ (nm)	obsd rotation of Wilen's (+) sample[a,b] α^{25}_λ NY 1975	α^{25}_λ Paris 1985	calcd max rotation of CHFClBr[c] α^{25}_λ *a*	$[\alpha]^{25}_\lambda$ *a*
589	+0.128	+0.129	3.0	1.6
578	+0.136	+0.134	3.1	1.6
546	+0.154	+0.153	3.6	1.8
436	+0.224	+0.225	5.2	2.7
365	+0.263	+0.268	6.2	3.2

[a] All rotations refer to *neat* CHFClBr; α^{25}_λ in deg·dm^{-1}, $[\alpha]^{25}$ in deg·kg^{-1}·dm^2; the density of **1** is 1.91 kg·dm^{-3} at 25 °C. [b] Measurements carried out with Perkin-Elmer 141 (New York) and 241 (Paris) instruments in 1-dm quartz cells. [c] Assuming that the ee of Wilen's sample is 4.3%; the actual ee should be in the range 3.5–5.1%.

From the ratios of the stability constants at high and low temperatures (3:2 and 2:1, respectively), the *p* complex can be estimated to be favored over the *n* by $\Delta\Delta G \sim 1.1$ kJ/mol. The origin of this chiral discrimination energy is still difficult to explain, however, as the details of the host–guest interactions in the *p* and *n* cavitates are not known. Unfortunately, so far crystals of **5** grown from CHFClBr invariably consisted of empty cages.

The dextrorotatory sample of **1**, provided by S. H. Wilen, had a sharp mp at −119 °C (identical with that of the racemate) and a molar purity of 99.5% according to the DSC method.[25] Its rotation was strictly identical with that measured 10 years ago (Table I), indicating that CHFClBr is a stereochemically stable molecule.[29] The ^1H NMR spectra of this sample, in the presence of (+)- or (−)-cryptophane-C (Figure 3, c and d, respectively), displayed a weak, but significant, difference in the areas of the doublets and in their peak height ratios; hence, the (+) enantiomer of **1**, present in excess, could unambiguously be assigned to the upfield doublet when the (+) host was employed, and vice versa. The ee of this sample was estimated to be 4.3 ± 1%, by three methods: manual area measurements by planimetry, triangulation, and line-shape simulation, assuming that the spectrum is the sum of Lorentzian bands. In order to confirm the validity of this method and to determine its precision, the "ee" of a racemic sample of **1** was checked by the same procedures and found to be in the range −1 to +1%.

The calculated maximum rotations of CHFClBr, α_λ and $[\alpha]_\lambda$, are assembled in Table I. The corresponding molar rotation $[\Phi]_D = [\alpha]_D(M/100)(3/(n^2+2))$ should therefore be 1.7 ± 0.5 deg·cm^2/dmol.[26] This figure lies at the low limit of the range predicted by Applequist,[1] on the basis of an atom-dipole interaction model of optical activity (2–16 deg·cm^2/dmol). The theory also predicted the absolute configuration of **1** to be (*S*)-(+). However, our analytical resolution method cannot yet provide reliable information on this point; further work in this direction is in progress.

Finally, we would like to conclude with a general comment. In the last decade, a variety of synthetic hosts have been suc-

(20) Canceill, J.; Cesario, M.; Collet, A.; Guilhem, J.; Pascard, C. *J. Chem. Soc., Chem. Commun.* **1985**, 361–363.

(21) For the specification of diastereomers according to the "*p*" and "*n*" descriptors, see: Jacques, J.; Collet, A.; Wilen, S. H. In "Enantiomers, Racemates, and Resolutions"; J. Wiley and Sons: New York, 1981; pp 251–252.

(22) Canceill, J.; Lacombe, L.; Convert, O.; Collet, A., work to be published.

(23) The shift induced by cryptophane-C on molecules accommodated in the interior of its cavity seems to be relatively constant; the following values of $\delta_0-\delta_\infty$ have been observed in our experiments: CH_2Cl_2, 4.58 ppm; CH_2Br_2, 4.39 ppm; $CHCl_3$, 4.65 ppm. Thus, host **5** can be considered as an *organic NMR shift reagent*.

(24) Horman, I.; Dreux, B. *Anal. Chem.* **1983**, *55*, 1219–1221.

(25) DSC experiments suggest that, at least in the very narrow range of ee studied, the enantiomers of **1** cocrystallize, forming ideal solid solutions.

(26) The refractive index of **1** was taken as n_D = 1.414 from ref 7.

(27) About the specific complexation of neutral molecules, see references in ref 20.

(28) Hine, J.; Dowell, A. M., Jr.; Singles, J. E., Jr. *J. Am. Chem. Soc.* **1956**, *78*, 479–482.

(29) For comments on the optical stability of **1**, see ref 8b.

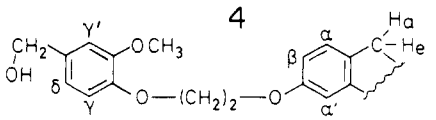
cessfully designed for specific recognition of mineral and organic ions in hydrophilic media, according to size, charge, shape, and even chirality criteria. The present work demonstrates that efficient selectivities among *neutral species* of very similar structures can also be achieved upon complexation of these substrates within the cavities of suitable synthetic host molecules, even in lipophilic solvents.[27]

Experimental Section

High-field ^1H nuclear magnetic resonance spectra were recorded at 200 MHz on a Brucker AM200SY instrument. Melting points were measured by differential scanning calorimetry by using a Perkin-Elmer DSC 2 microcalorimeter connected to a Hewlett-Packard HP86 calculator for data acquisition and processing (purity assessment). Rotations were measured as indicated in Table I. Mass spectra were obtained at 70 eV on a Thomson THN208 spectrometer. Analytical and preparative thin-layer chromatography were effected on Merck TLC plates silica gel F 254.

4-(2-Iodoethoxy)-3-methoxybenzenemethanol (7). In a first step, the corresponding *bromide* was prepared from vanillyl alcohol (12.3 g, 0.08 mol), 1,2-dibromoethane (14 mL, 0.16 mol), and aqueous (12 N) sodium hydroxide (6.8 mL, 0.08 mol) in 150 mL of ethanol. This mixture was refluxed for 5 h under N_2. The solvent was stripped, and the residue was taken up in a mixture of water and ether, which resulted in the crystallization of most of the dialkylated byproduct 1,2-bis(4-hydroxymethyl-2-methoxyphenoxy)ethane (mp 140 °C) which was separated by filtration. The ether layer afforded a brown oil which upon filtration over alumina (Merck, 0.063–0.200 mm, activity II–III, ether as the eluant) gave 5.55 g (26%) of 4-(2-bromoethoxy)-3-methoxybenzenemethanol, mp 77 °C.[30] The latter (0.021 mol) was then converted into **7** by reaction with sodium iodide (6.3 g, 0.042 mol) in 50 mL of acetone, with 8 h of refluxing: overall yield (from vanillyl alcohol) 5.85 g (23%); mp 88 °C (from methanol). Anal. Calcd for $C_{10}H_{13}O_3I$: C, 39.37; H, 4.25. Found: C, 39.3; H, 4.25. ^1H NMR spectrum (from internal Me_4Si in $CDCl_3$) δ 3.43 (m) and 4.29 (m, ICH_2CH_2O) 3.89 (s, OCH_3), 4.63 (s), and 1.65 (s, CH_2OH), 6.87, 6.88, and 6.95 (aromatic H's).

2,7,12-Tris[2-(4-hydroxymethyl-2-methoxyphenoxy)ethoxy]-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene ((±)-, *M*-(+)-, and *P*-(−)-4). *rac*-**4** was prepared from (±)-**3**[11] (1 g, 3.1 mmol) in 100 mL of DMF–HMPA 1:1 (v:v); 1.5 mL (9.3 mmol) of 25% aqueous NaOH was added and the mixture was stirred for 10 min, followed by addition of the iodide **7** (3 g, 9.7 mmol); after the mixture was stirred for 1 h under N_2 at room temperature further amounts of NaOH (0.75 mL) and of iodide **7** (1.5 g) were added; after 2 h the reaction mixture was poured into water, and the recovered precipitate of crude **4** was digested with methanol (yield 2.5 g, 90%, mp ~ 85 °C) and used without further purification for the cyclization step. Anal. Calcd for $C_{51}H_{54}O_{12}\cdot 2H_2O$: C, 68.45; H, 6.53. Found: C, 68.95; H, 6.6. ^1H NMR spectrum (from internal Me_4Si in CD_3SOCD_3) δ 3.60 (d, H_e) and 4.76 (d, H_a) (J = 13.1 Hz), 3.72 (s, OCH_3), 4.20 (s, OCH_2CH_2O), 4.40 (d, CH_2), and 5.08 (t, OH) (J = 5.2 Hz), 7.41 (d, H_α) (J = 8.5 Hz), 7.05 (d, $H_{\alpha'}$) (J = 2.4 Hz), 6.69 (dd, H_β) (J = 8.5 and 2.4 Hz), 6.91 (d, H_γ) (J = 8 Hz), 6.92 (d, $H_{\gamma'}$) (J = 1.5 Hz), 6.80 (dd, H_δ) (J = 8 and 1.5 Hz).

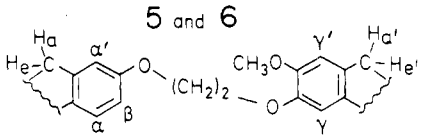


Similarly, 170 mg of *M*-(+)-**3**,[11] having $[\alpha]^{25}_D$ +196° (dioxane, *c* 0.25), gave on alkylation with **7** 399 mg (85%) of *M*-(+)-**4**, $[\alpha]^{25}_D$ +185° (DMF, *c* 0.3), and 148 mg of *P*-(−)-**3** with $[\alpha]^{25}_D$ −194° yielded 355 mg (89%) of *P*-(−)-**4**, $[\alpha]^{25}_D$ −171°.

Cryptophane-C (5) and -D (6). *rac*-**5** and -**6** were obtained from (±)-**4** as follows: In a 500-mL rotatory evaporator flask, 100 mg of (±)-4 was first dissolved in 1 mL of DMF, and 200 mL of formic acid was then added. The flask was fitted to the evaporator and heated in the water bath (95 °C) for 1 h, with slow rotation. The solvent was evaporated under vacuum; it was found convenient to add some $CHCl_3$ at the end, in order to facilitate formic acid removal through azeotrope formation.

(30) Alternatively, vanilly alcohol (1 eq) on reaction with 1,2-dibromoethane (2 eq) in acetone in the presence of anhydrous potassium carbonate (1 eq) (24 h, reflux) affords the same bromoethoxy derivative in 40–50% yield.

The two isomeric cryptophanes which represent about $^1/_3$ of the crude reaction product were freed from polymeric material and separated from one another by a first TLC on silica gel, with chloroform–ether 8:2 (v:v) as the eluant. The slower-running major isomer **5** was submitted to a second TLC with use of chloroform–acetone 9:1 (v:v) and was finally digested from acetone: yield 23 mg (25%) of a white, microcrystalline solid; mp ca. 325 °C dec. Anal. Calcd for $C_{51}H_{48}O_9$: C, 76.10; H, 6.01. Found: C, 76.0; H, 6.1. Mass spectrum m/z M^+ 804. On crystallization from CH_2Cl_2 it gave the *dichloromethane cavitate*.[20] ^1H NMR spectrum (from internal Me_4Si in $CDCl_3$) δ 3.38 (d, $H_{e'}$) and 4.60 (d, $H_{a'}$) (J = 13.6 Hz), 3.51 (d, H_e) and 4.59 (d, H_a) (J = 13.5 Hz), 3.80 (s, OCH_3), 3.97–4.42 (m, OCH_2CH_2O), 7.09 (d, H_α) (J = 8.5 Hz), 6.79 (d, $H_{\alpha'}$) (J = 2.5 Hz), 6.36 (dd, H_β) (J = 2.5 and 8.5 Hz), 6.62 (s) and 6.66 (s) (H_γ, $H_{\gamma'}$).



The faster-running minor isomer (**6**) was similarly submitted to a second TLC, using benzene acetone 85:15 (v:v) as the eluant, followed by a digestion from ether. Yield 6 mg (5%); mp 290 °C. Crystals grown from dichloromethane–acetone contain ca. two CH_2Cl_2 molecules per molecule of **6**, as suggested by C,H combustion analysis. Anal. Calcd for $C_{51}H_{48}O_9\cdot 2CH_2Cl_2$: C, 65.3; H, 5.38. Found: C, 65.6; H, 5.3. Mass spectrum m/z M^+ 804. ^1H NMR spectrum (from internal Me_4Si in $CDCl_3$) δ 3.45 (d, $H_{e'}$) and 4.64 (d, $H_{a'}$) (J = 13.5 Hz), 3.49 (d, H_e) and 4.63 (d, H_a) (J = 13.5 Hz), 3.65 (m) and 4.10–4.35 (m) (OCH_2CH_2O), 3.80 (s, OCH_3), 7.10 (d, H_α) (J = 8 Hz), 6.70 (s) and 6.83 (s) (H_γ, $H_{\gamma'}$), 6.63–6.73 (m, $H_{\alpha'}$, H_β).

Optically Active Cryptophanes 5 and 6. Since chiral cyclotribenzylenes undergo crown inversion, hence racemize, on heating,[11] the first cyclization experiments using either *M*-(+)- or *P*-(−)-**4** were carried out by allowing the formic acid solution to stand for 3 days at 20 °C, rather than 1 h at 95 °C as described above. In fact we later discovered that the cyclization of **4** into **5** + **6** could be effected at 95 °C without significant change in the rotation of the cryptophanes (the cyclization therefore seems to be a fast process, compared to crown inversion of the precursor). Thus, using the procedure described for the racemic series, 100 mg of (−)-**4** afforded 19 mg (20%) of (+)-**5** $[\alpha]^{25}_D$ +80° ($CHCl_3$, *c* 0.25), mp 273–279 °C, and 6 mg (5%) of (−)-**6**, $[\alpha]^{25}_D$ −140° ($CHCl_3$, *c* 0.25), mp ca. 320–330 °C dec.

In the same way, 100 mg of (+)-**4** gave 17 mg of (−)-**5**, $[\alpha]^{25}_D$ −85° ($CHCl_3$, *c* 0.27), mp 279–282 °C, and 5 mg of (+)-**6**, $[\alpha]^{25}_D$ +145° ($CHCl_3$, *c* 0.2), mp ca. 320 °C dec.

Bromochlorofluoromethane [(±)-1]. We employed a procedure essentially similar to that described by Hine.[28] Mercuric fluoride (25 g, 0.104 mol) and dibromochloromethane (48 g, 0.23 mol) were mixed in a 100-mL three-necked flask (magnetically stirred) equipped with a thermometer and a reflux condenser at 40–42 °C. On the top of the condenser was a short (10 cm) distilling column followed by a condenser at 20 °C, leading to a 25-mL receiver immersed in a dry ice–acetone bath. The flask was heated in an oil bath. The reaction started when the internal temperature reached 85 °C, and the haloform was allowed to distill gently while progressively raising the oil bath temperature to 150 °C (internal temperature 120 °C). In this way 23.6 g (70%) of crude **1** was collected; this product was stirred for ca. 15 min in the presence of anhydrous calcium chloride and powdered potassium carbonate and carefully distilled (bp 36 °C) to give 17.05 g (50%) of **1**, mp −119 °C (lit.[6] mp −115 °C); purity x = 0.995 by DSC and 99.5% by GLC (two 3 m length columns in series, 10% QF1 and 20% XE60, T 30 °C, carrier gas helium, 1.5 bar; retention time of **1** ca. 7 min).

Acknowledgment. We are particularly grateful to Prof. S. H. Wilen for providing us with an optically active sample of CHFClBr.

Registry No. (±)-**1**, 88987-26-2; (+)-**1**, 22611-58-1; (−)-**1**, 31747-37-2; (±)-**3**, 89209-34-7; *M*-(+)-**3**, 89255-54-9; *P*-(−)-**3**, 89255-53-8; (±)-**4**, 98688-20-1; *M*-(+)-**4**, 98757-24-5; *P*-(−)-**4**, 98757-25-6; (±)-**5**, 98757-87-0; (+)-**5**, 98757-26-7; (−)-**5**, 98757-30-3; (±)-**6**, 98757-27-8; (−)-**6**, 98757-28-9; (+)-**6**, 98757-29-0; **7**, 81329-97-7; $Br(CH_2)_2Br$, 106-93-4; HgF_2, 7783-39-3; Br_2ClCH, 124-48-1; vanillyl alcohol, 498-00-0; 1,2-bis[4-(hydroxymethyl)-2-methoxyphenoxy]ethane, 98688-18-7; 4-(2-bromoethoxy)-3-methoxybenzenemethanol, 98688-19-8.