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Synthesis and Chiroptical Properties of Cryptophanes Having C_1-Symmetry

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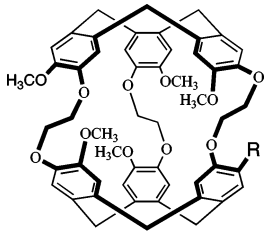

1: R = OCH_3
2: R = OH
3: R = OCH_2COOCH_3
4: R = OCH_2COOH
5: bis-cryptophane-A
6: R = OSO_2CF_3
7: R = H

New enantiopure cryptophanes **3**−**7** having C_1-symmetry have been synthesized. Electronic circular dichroism (ECD) and vibrational circular dichroism (VCD) have been used to investigate their chiroptical properties, and the results are compared to those obtained for cryptophane-A (**1**) having D_3-symmetry. The ECD spectra of compounds **3**−**7** show Cotton effects that differ from those of cryptophane-A. However, our results suggest that a confident determination of the absolute configuration of the monofunctionalized cryptophanes can be made using ECD spectroscopy. Interestingly, we have found that the ECD spectra of cryptophanes, especially the ^1L_b transition, are very sensitive to the nature of the solvent. These spectral modifications are essentially due to bulk solvent properties rather than the ability of a particular solvent to insert into the cavity of cryptophanes. On the other hand, VCD spectra of the monofunctionalized cryptophanes have not revealed significant spectral modifications with respect to the VCD spectrum of the $CHCl_3$@cryptophane-A complex, except for $CHCl_3$@**7** and to a smaller extent for $CHCl_3$@**6**. These spectral modifications, which essentially consist in lower intensities of VCD bands associated with the cryptophane backbone, were perfectly reproduced by ab initio calculations performed at DFT (B3PW91/6-31G*) level. These results clearly demonstrate that VCD measurements associated with DFT calculations allow an easy determination of the absolute configuration of cryptophane-A derivatives.

Introduction

Cryptophane molecules are fascinating supramolecular objects that may be isolated either in a chiral (anti-cryptophane) or in an achiral form (syn-cryptophane). Since their discovery, the chiral derivatives isolated as a racemic mixture or as enantiopure material have received much attention as they demonstrate remarkable binding properties toward small neutral molecules.[1] For instance, anti-cryptophane-A (**1**) isolated as a racemate shows interesting binding properties toward halogenomethanes and xenon, and the two partially resolved compounds anti-(+)-cryptophane-C and anti-(-)-cryptophane-C can discriminate the two enantiomers of the CHFClBr derivative as observed by ^1H

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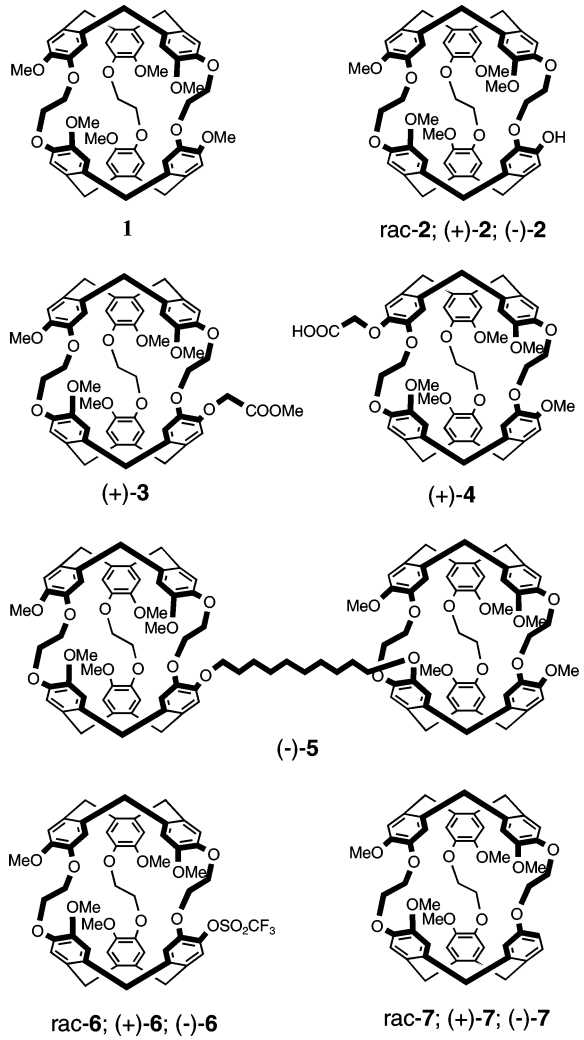
and ^{19}F NMR experiments.[2,3] In addition, the synthesis and the isolation of resolved cryptophanes have also allowed the investigation of their chiroptical properties by means of spectroscopic techniques. For instance, in the mid-1980s, Collet and co-workers investigated the UV−vis circular dichroism (ECD) spectra of several cryptophanes having D_3-symmetry.[4] On the basis of a semiempirical approach, they were able to interpret the Cotton effects observed in the ECD spectra of cryptophanes.

Recently, vibrational circular dichroism (VCD) has received much attention from chemists and has rapidly become a powerful technique for the conformational analysis of chiral molecules.[5] The growing interest in this technique arises from the ability of VCD spectroscopy to predict the absolute configuration of molecules when quantum mechanical calculations are done in parallel.[6] The determination of the absolute configuration of a molecule is thus made possible by comparison of the experimental spectrum with the predicted VCD spectrum calculated by using an arbitrarily chosen absolute configuration of a selected geometry of the molecule. With the computational power now available and the recent progress in computational methods, the determination of absolute configuration of chiral molecules by VCD spectroscopy is no longer restricted to the study of small chiral molecules. For instance, Urbanova et al. have determined the predominant conformation in the cyclic tetramer of (*S*)-2,2′-dimethylbiphenyl-6,6′-dicarboxylic acid and have shown that VCD spectroscopy can be used to determine the structure of supramolecular species.[7] More recently, Buffeteau et al. have clearly shown that the mixed approach (DFT calculations/VCD experiments) allows the unambiguous determination of the helical handedness of a quinoline-derived chiral tetramer ($C_{52}H_{41}O_{10}N_9$).[8] Finally, in a previous article, we have reported the synthesis and a complete study of both enantiomers of cryptophane-A ($C_{54}H_{54}O_{12}$) by VCD spectroscopy.[9]

So far, the synthesis of cryptophane derivatives has been mainly restricted to cryptophanes having D_3-symmetry, and very little is known about the chiroptical properties of cryptophanes having other symmetries. Interestingly, a recent synthetic route developed for the construction of the two enantiomers of the cryptophane-A derivative allows the preparation of new chiral cryptophanes of C_1-symmetry with very high enantiomeric excess (close to 100%).[10] This synthetic approach provides enough resolved material to study their chiroptical properties by means of several spectroscopic techniques. The lack of symmetry of the cryptophane backbone as well as the nature of the substituents attached on the phenyl rings should modify both the ECD and VCD spectra relative to those of the highly symmetric cryptophane-A derivative.

SCHEME 1. Chemical Structure of Compounds 1−7



In this article, the synthesis of new chiral cryptophanes **3**−**7** having C_1-symmetry (see Scheme 1) and studies of their chiroptical properties by ECD and VCD spectroscopies are presented. The effects of the symmetry of the cryptophane and of the nature of the substituent on the experimental ECD and VCD spectra are discussed. Solvent effects on the experimental ECD spectra are also studied.

Results and Discussion

Synthesis and Characterization of Chiral Cryptophanes 3−7. Chiral cryptophanes **3**−**7** have been synthesized from enantiopure cryptophanol-A derivatives (−)-**2** and (+)-**2**. Cryptophanol-A was first synthesized and isolated as a racemic

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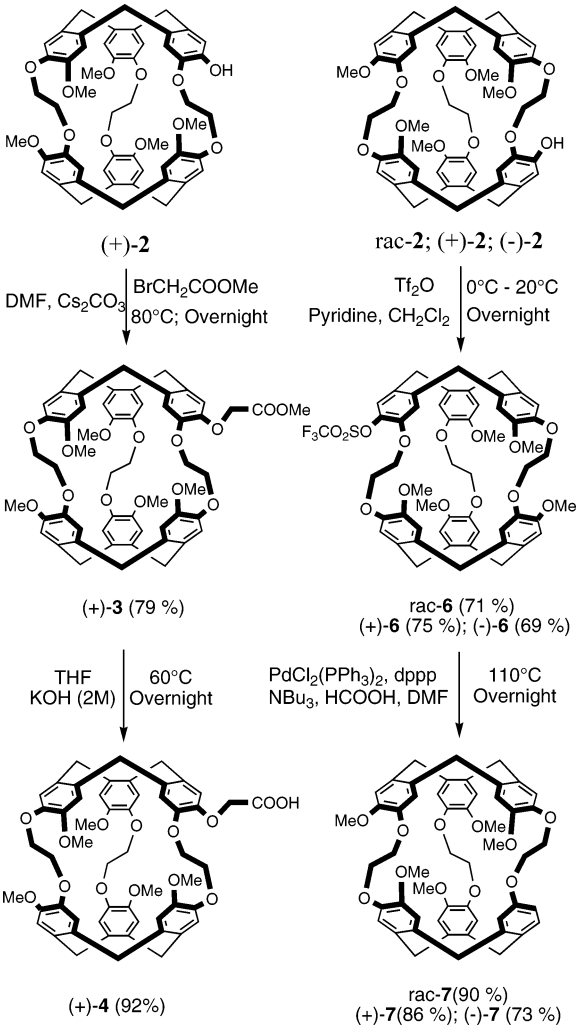
mixture using a multistep procedure described in the literature.[11] Chiral cryptophanol-A derivatives (−)-**2** and (+)-**2** were prepared from cryptophane diastereomers by reacting *rac*-**2** with (−)-camphanic acid chloride according to a known procedure.[10] The separation of the two diastereomers by crystallization in toluene, followed by hydrolysis under basic conditions, yielded the desired cryptophanol-A in their enantiopure form (99−100% ee; see Figure S1 in Supporting Information).[12] This approach gives the desired enantiopure (−)-**2** and (+)-**2** derivatives with a fair yield and provides a sizable amount of each enantiomer for subsequent reactions. For instance, the two cryptophanol-A enantiomers (−)-**2** and (+)-**2** were used as starting materials to provide the corresponding enantiopure cryptophane-A derivatives. Interestingly, the presence of the reactive hydroxyl function in **2** allows the synthesis of new cryptophanes having C_1-symmetry without any loss of optical purity. By using this approach, we have previously reported the synthesis of monofunctionalized cryptophane (−)-**3** by reacting (−)-**2** with methyl bromoacetate.[10] In this article, we report the synthesis of cryptophane (+)-**3** and biscryptophane (−)-**5** obtained in 40% yield by reacting (−)-**2** with 1,10-diiododecane. The cryptophane (−)-**5** exhibits ^{1}H NMR and ^{13}C NMR spectral characteristics identical to its congener which was previously obtained as a mixture of diastereomers. Treatment of compound (+)-**3** with a KOH (2 M) solution in THF, followed by acidification with concd HCl, yields derivative (+)-**4** in quantitative yield. Pines and co-workers have previously reported the synthesis of the racemate using a slightly different approach.[13]

Enantiopure cryptophanol-A (+)-**2** and (−)-**2** derivatives were used as starting materials to prepare new cryptophane derivatives **6** and **7**. In compounds **6** and **7**, a single electron-withdrawing triflic moiety or a hydrogen atom, respectively, replace a methoxy group in molecule **1**. The triflic moiety was introduced in a single step by reacting the racemate or an enantiomer of cryptophanol-A with an excess of anhydride triflic in a mixture of pyridine and CH_2Cl_2 at 0 °C. The compounds *rac*-**6**, (+)-**6**, and (−)-**6** have been obtained in fair yield after crystallization, and all three compounds show identical ^{1}H NMR and ^{13}C NMR spectra. Compounds *rac*-**7**, (+)-**7**, and (−)-**7** were prepared from *rac*-**6**, (+)-**6**, and (−)-**6**, respectively, by reduction of the triflic moiety with a palladium catalyst (see Scheme 2). Several synthetic routes have been reported for the reduction of the triflic moiety attached on a benzene ring.[14] However, the use of the procedure described by Saa et al.[14a] seems most appropriate in our case, as they reported several examples of hindered aromatic triflate derivatives. Thus, compounds *rac*-**6**, (+)-**6**, and (−)-**6** have been allowed to react in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$, 1,3-bis(diphenylphosphino)propane (dppp), tri-*n*-butylamine (NBu_3), and HCOOH in dimethylformamide (DMF) at 110 °C, giving rise to the new cryptophane derivatives *rac*-**7**, (+)-**7**, and (−)-**7**, respectively. Previous attempts to use a catalytic amount of palladium catalyst with *rac*-**6** yielded only a partial reduction of the triflate moiety as evidenced by TLC.[14a] This result has suggested a slow reaction rate probably due to the hindered position of the triflic moiety. However, a higher loading of palladium catalyst (15%, nonoptimized) has allowed complete conversion of the starting material overnight and the formation of the new cryptophanes *rac*-**7**, (+)-**7**, and (−)-**7** in good yields after purification. It is noteworthy that these new derivatives could not be obtained directly in their optically pure form or even as a racemic mixture by the classical procedures (*direct* or *template* methods) described by Collet and co-workers.[15]

All compounds except cryptophane **4**, which was isolated by precipitation, have been purified by column chromatography

SCHEME 2. Synthesis of Compound (+)-4 and Compounds *rac*-7, (−)-7, and (+)-7



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(12) The recrystallization procedure in toluene given in ref 10 is not easily reproducible as it is difficult to work under exactly the same experimental conditions. Thus, the recrystallization leads to the precipitation of the two diastereomers in various ratios. However, the less soluble diastereomer, identified as compound **1a** (ref 10), can be easily recovered by warming the resulting solid in hot toluene. Filtration followed by recrystallization in a mixture of $CHCl_3$/ethanol affords pure **1a** (25%). Evaporation of the filtrate, followed by hydrolysis under basic condition, gives rise to enantioenriched (+)-cryptophanol **2**, which can be used for subsequent reaction with (+)-camphanic acid chloride. A similar treatment performed with this diastereomer gives rise to optically pure diastereomer **1b** in similar yield.

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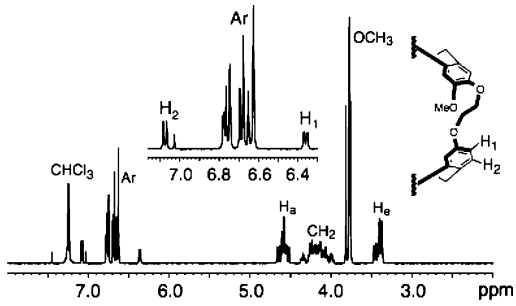

FIGURE 1. ^{1}H NMR spectrum of compound (−)-**7** recorded in $CHCl_3$ at 25 °C. Inset: Expansion of the aromatic region.

TABLE 1. Optical Rotations$[\alpha]_\lambda^{25}$ (10^{-1} deg cm^2 g^{-1}) of Cryptophanes 3−7 at 25 °C (Experimental Errors Are Estimated to ±5%)

compd	solvent	concn[a]	$[\alpha]_{589}^{25}$	$[\alpha]_{577}^{25}$	$[\alpha]_{546}^{25}$	$[\alpha]_{436}^{25}$	$[\alpha]_{365}^{25}$
(+)-**3**	$CHCl_3$	0.23	+245.0	+257.0	+295.5	+559.8	+1044.0
(+)-**4**	$CHCl_3$	0.18	+219.5	+232.0	+265.6	+502.4	+924.6
(-)-**5**	$CHCl_3$	0.21	−253.1	−266.7	−307.7	−581.7	−1075.8
(-)-**6**	$CHCl_3$	0.24	−206.3	−216.5	−249.3	−470.8	−874.9
(+)-**6**	$CHCl_3$	0.23	+205.9	+216.5	+249.3	+471.7	+878.7
(-)-**7**	$CHCl_3$	0.18	−254.9	−267.3	−310.0	−583.0	−1097.4
(+)-**7**	$CHCl_3$	0.15	+255.5	+270.6	+315.0	+600.5	+1126.6

[a] In g/100 mL.

on silica gel and then recrystallized as reported in the Experimental Section. Cryptophane (−)-**5** was purified by column chromatography and isolated as a glassy product. Derivatives **3**−**7** were isolated as crystalline compounds and were characterized by the usual spectroscopic method (^{1}H NMR, ^{13}C NMR, and HRMS). Molecules **3**−**7** display complex ^{1}H NMR spectra relative to that of **1** due to the lack of symmetry. As an example, the ^{1}H NMR spectrum of the enantiopure cryptophane (−)-**7** is presented in Figure 1. The aromatic region shows several signals, in good agreement with the proposed structure. The additional proton H_1 on the benzene ring is clearly visible and is high field shifted (6.35 ppm) with respect to the other aromatic protons. In contrast, the proton H_2 appears as a doublet at low field (7.09 ppm). The ^{1}H NMR spectrum also displays a complicated proton pattern in the region of the alkyl and the methylene protons due to the lack of a symmetry axis. All ^{13}C NMR spectra were recorded by the usual one-dimensional ^{13}C NMR sequence.

Optically pure derivatives **3**−**7** were also characterized by polarimetry in chloroform, and their optical rotation recorded at several wavelengths is reported in Table 1. The optical rotation values measured for compound (+)-**3** are in very good agreement with that previously reported for its enantiomer in the same experimental condition$[\alpha]_{589}^{25} = -249$ ($c = 0.18$, $CHCl_3$)).[10] Both enantiomers of compounds **6** and **7** show identical optical rotation values in the range of the experimental error as expected for enantiopure derivatives. Compound (−)-**5** shows similar, although slightly smaller, optical rotation values than cryptophane-A.[10]

UV−Vis and ECD Spectra of Chiral Cryptophanes 3−7 in Chloroform. The UV−vis spectra of cryptophanes **1** and **3**−**7** have been recorded in $CHCl_3$ solution, and the values of the absorption coefficients are reported in Table 2. All compounds show very similar UV−vis spectra in the 230−310 nm range that correspond to the absorption bands of the two ^1L_a and ^1L_b transitions of the benzene rings. The low energy ^1L_b transition (255−310 nm region) shows for all compounds a broad band whose intensity and shape is almost unchanged whatever the nature of the substituents attached to the cryptophane backbone. Similarly, the higher energy ^1L_a transition (230−250 nm) gives rise to a strong band whose shape and intensity also remain very similar through the series **1**, **3**−**7**. These results suggest that a decrease of the symmetry and the nature of the substituents have little effect on the absorption properties of the new cryptophanes with respect to **1**.

TABLE 2. Maximum Wavelength (nm) for the ^1L_a (B_{1u}) and the ^1L_b (B_{2u}) Transition of Compounds 1 and 3−7 Recorded in $CHCl_3$ at 22 °C (Extinction Coefficients (mol^{-1} L cm^{-1}) are Given in Parentheses)

compounds	**1**	**3**	**4**	**5**	**6**	**7**
^1L_b	290.0 (13600)	290.0 (13100)	289.0 (12400)	290.0 (28000)	290.0 (12600)	290.0 (12900)
^1L_a	239.0 (33800)	239.0 (32700)	239.0 (31100)	239.0 (71000)	242.0 (31300)	239.0 (33600)

The chiroptical properties of enantiopure cryptophanes **3**−**7** have been investigated by ECD in $CHCl_3$. Very few papers dealing with the study and the interpretation of the ECD spectra of cryptophanes have been reported in the past, probably due to the difficulties in preparing these molecules in their enantiopure form. Gottarelli and Collet pioneered this work in the mid-1980s and used a theoretical approach to interpret the experimental ECD spectra of cryptophanes having D_3-symmetry.[4] On the basis of the symmetry rules and the Kuhn−Kirkwood excitonic coupling model, they demonstrated that the Cotton bands of each ^1L_a and ^1L_b transition of a cryptophane could be interpreted as the sum of three components (one A_2 component and two degenerate E components parallel and perpendicular to the C_3 axis of the cyclotriveratrylene units, respectively). The relative intensities of these components with respect to each other determine the sign and the global shape of the Cotton bands observed in the ECD spectra of cryptophanes. The authors also reported the importance of the nature of the substituents attached to the six benzene rings for predicting the sign of the Cotton effect for the two transitions. They showed that the presence of two different substituents (OR and OR′) modifies the angle of polarization of the two ^1L_a and ^1L_b transitions. The magnitude of this effect depends mainly on the difference between spectroscopic moments (*sm*) of the two substituents OR and OR′.[16] The two substituents need not be very different to induce strong ECD signals; indeed, substituents such as methoxy and alkoxy groups induce large Cotton effects as observed in the ECD spectrum of cryptophane-A.

A more complex situation should be observed for cryptophanes **2**−**7** which have a C_1-symmetry. Indeed, the lack of symmetry leads to a situation where each Cotton band observed in the ECD spectrum should be the result of six nondegenerate components each having different intensities and polarization.

The Cotton effects observed in the ECD spectra of compound **3**−**7** are reported in Tables 3 and 4. Collet and co-workers previously recorded the ECD spectra of (−)-**1** in dioxane or in a mixture of dioxane and $CHCl_3$.[4] Since the ECD spectra are very sensitive to external factors such as the nature of the solvent, it was necessary to re-investigate the ECD spectrum of compound (−)-**1** in pure chloroform for comparison with the ECD spectra of cryptophanes **3**−**7**. As presented in Figure

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TABLE 3. ECD Values of Cryptophanes (−)-1, (+)-3, (+)-4, and (−)-5 Recorded in $CHCl_3$ at 25 °C

(−)-**1**		(+)-**3**		(+)-**4**		(−)-**5**	
λ (nm)	Δε	λ (nm)	Δε	λ (nm)	Δε	λ (nm)	Δε
238.0	73.5	238.5	−76.6	237.5	−75.1	238.0	155.6
253.5	−13.2	253.0	16.9	252.5	12.9	254.0	−19.5
278.0	−26.4	277.5	22.6	276.5	13.4	278.0	−48.0
291.5	2.13					291.5	1.50
302.0	−6.4	302.0	7.0	300.5	5.8	301.5	−12.9

TABLE 4. ECD Values of Cryptophanes (−)-6, (+)-6, (−)-7, and (+)-7 Recorded in $CHCl_3$ at 25 °C

(-)-**6**		(+)-**6**		(-)-**7**		(+)-**7**	
λ (nm)	Δε	λ (nm)	Δε	λ (nm)	Δε	λ (nm)	Δε
237.0	64.2	237.0	−64.0	238.5	77.5	238.5	−76.6
252.5	−16.3	252.5	17.3	252.0	−25.6	252.0	25.7
278.0	−10.0	279.0	10.3	278.0	−9.2	278.5	9.4
299.5	−5.8	300.0	6.4	298.5	−9.8	298.5	9.8

2, the ECD spectrum of (−)-**1** in the 230−310 nm region shows a quite different ECD spectrum than that previously recorded in pure dioxane. This spectrum exhibits three bands (two negative and one positive) with different intensities for the low energy ^1L_b transition and two bands with opposite signs for the higher energy ^1L_a transition. In contrast to what had been observed in dioxane solution, the presence of three Cotton bands for the ^1L_b transition in $CHCl_3$ is in good agreement with the semiempirical model proposed by Collet and co-workers.[4] The difference observed from measurements in dioxane (a solvent too large to enter into the cavity of **1**) and $CHCl_3$ could be the result of a difference in the mobility of the linkers. Indeed, accommodation of a $CHCl_3$ molecule by **1** leads to a more rigid molecular complex than the empty host dissolved in dioxane. As a consequence, the number of conformations adopted by the linkers in solution is significantly reduced. As shown in Figure 2, a quite similar ECD spectrum, but with twice the intensity of the (−)-**1** spectrum, is obtained for (−)-**5**, as expected since (−)-**5** possesses two cryptophane-A units connected by an alkyl chain (see also Supporting Information Figure S2). In contrast, the ECD spectra of the compounds (+)-**3** and (+)-**4** show small but clear differences compared to (−)-**1**. For instance, the component observed at 291.5 nm for the ^1L_b transition is no longer present.

A comparison between the ECD spectra of (−)-**1** and the new cryptophanes (−)-**6** and (−)-**7** is more interesting since strong modifications of the overall ECD spectra of these derivatives are expected due to substituent effects (each substituent replacing the methoxy group possesses a very different spectroscopic moment) and to the lack of a symmetry axis. The two enantiomers of **6** and **7** show perfect mirror image spectra in Figure 3, as expected for enantiopure derivatives. The ECD spectra of (−)-**6** and (−)-**7** exhibit Cotton bands different in shape and magnitude from those observed for compound (−)-**1**. In addition, clear differences of the band intensity can be observed between the ECD spectra of (−)-**6** and (−)-**7** (Table 4).

Solvent Effect on the ECD Spectra of (−)-1, (−)-6, and (−)-7. The effect of the nature of the solvent has been investigated for the highly symmetrical derivative (−)-**1** and the two cryptophanes (−)-**6** and (−)-**7** having C_1-symmetry. Experiments have been performed in $CHCl_3$ and CH_2Cl_2 (two solvents that enter into the cavity of cryptophanes) and in CH_3CN and THF (two solvents that do not enter into the cavity of cryptophane-A derivatives). These solvents have been chosen owing to their different physical (dielectric constant, dipole moment) and binding properties. The ECD spectra of compounds (−)-**1**, (−)-**6**, and (−)-**7** recorded in these four solvents reveal large modifications, especially for the low energy ^1L_b transition (see Figure 4). ECD spectra of (−)-**1** recorded in these solvents reveal a change in intensity of the band at 280 nm, the strongest intensity being observed in $CHCl_3$ and the weakest in CH_3CN (see Figure 4a). The opposite behavior is observed for the band at 300 nm (a small shift was also noticed for this band). In addition, similar solvent effects on the ^1L_b transition are observed in CH_2Cl_2 and THF, even though the latter does not enter the cavity of (−)-**1**.

Stronger solvent effects are observed in Figure 4b and 4c for the nonsymmetrical derivatives (−)-**6** and (−)-**7** where dramatic changes in shape and intensity are noted for the two bands of the ^1L_b transition. Compounds (−)-**6** and (−)-**7** respond similarly to the nature of the solvent, and their ECD spectra exhibit the same spectral modifications. For instance, in CH_3CN, the band at 280 nm almost completely disappears, while a significant enhancement of the band at 300 nm is observed, compared to the ECD spectra of (−)-**6** and (−)-**7** recorded in $CHCl_3$ solution.

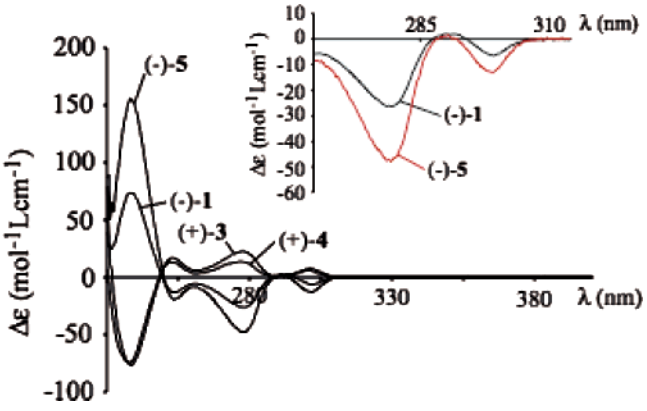

FIGURE 2. ECD spectra of compounds (−)-**1**, (+)-**3**, (+)-**4**, and (−)-**5** recorded in $CHCl_3$ at 25 °C. Inset: Expansion of the 260−320 nm region of the ECD spectra of (−)-**1** and (−)-**5**, showing the positive Cotton band at 291.5 nm.

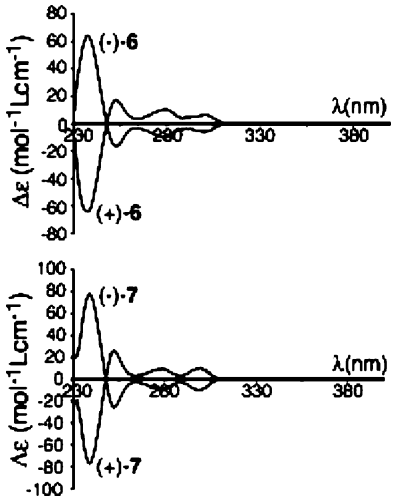

FIGURE 3. (a) ECD spectra of (−)-**6** and (+)-**6** recorded in $CHCl_3$ at 25 °C. (b) ECD spectra of (−)-**7** and (+)-**7** recorded in $CHCl_3$ at 25 °C.

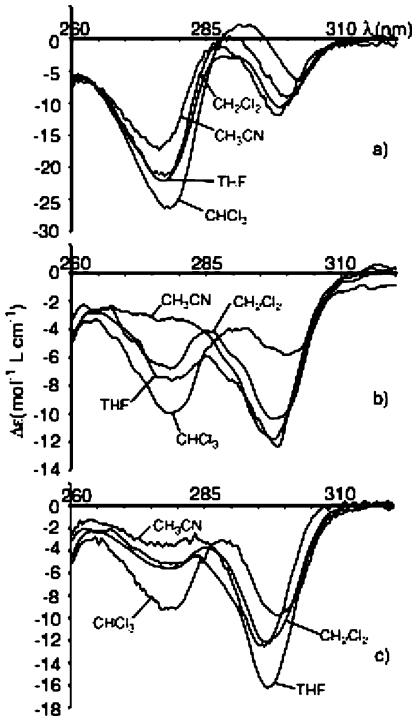

FIGURE 4. ECD spectra in the 260−310 nm region (^1L_b transition) in $CHCl_3$, CH_2Cl_2, THF, or CH_3CN recorded at 25 °C. (a) Compound (−)-**1**. (b) Compound (−)-**6**. (c) Compound (−)-**7**.

As previously noted for (−)-**1**, a similar behavior of the ^1L_b transition in the ECD spectra of (−)-**6** and (−)-**7** is observed in CH_2Cl_2 and THF solution.

The ECD spectra of compounds (−)-**1**, (−)-**6**, and (−)-**7** recorded in various solvents reveal that the solvent effect is more pronounced for the cryptophanes having C_1-symmetry. The modification observed in the ECD spectra cannot be explained by the ability of a solvent to enter into the cavity of cryptophanes since CH_2Cl_2 and THF give rise to very similar spectra having very different binding properties. On the other hand, a correlation between the dielectric constant of the four solvents studied (i.e., $\epsilon = 4.8$ for $CHCl_3$, $\epsilon = 7.52$ for THF, $\epsilon = 8.93$ for CH_2Cl_2, and $\epsilon = 36.64$ for CH_3CN) and the change in the ECD spectra of compounds (−)-**1**, (−)-**6**, and (−)-**7** can be noted. This suggests that the chiroptical properties of cryptophanes are more sensitive to the physical properties of the bulk solvent than to an encapsulated molecule or to a change in the conformation of the linkers. These results are in agreement with those obtained for (−)-**1** by VCD spectroscopy, which do not show any spectral modification for cryptophane-A with an empty (in $C_2D_2Cl_4$ solution) or filled (in $CDCl_3$ solution) cavity.

VCD Spectroscopy and DFT Calculations of Chiral Cryptophanes 1−7. The chiroptical properties of enantiopure cryptophanes having C_1-symmetry have been also investigated by VCD and compared to those of **1**. In a previous article, we have shown that VCD experiments coupled with DFT calculations allow the determination of the absolute configuration of **1**.[9] The spectral modifications induced by conformational changes in the aliphatic linkers were also investigated using DFT calculations. A good agreement between experimental and calculated VCD spectra has established the preferential anti conformation of the aliphatic linkers for the $CHCl_3$@cryptophane-A complex. Finally, similar VCD spectra were obtained for **1** whatever the nature of the solvent used and its ability to enter the cavity. In this study, the VCD spectra of chiral cryptophanes **2**−**7** have been analyzed to reveal the spectral modifications induced by the lack of symmetry of cryptophane-A and the nature of the substituent.

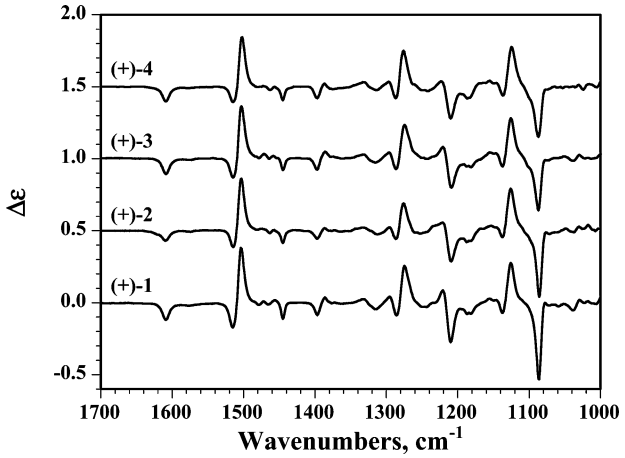

FIGURE 5. VCD spectra of compounds (+)-**1**, (+)-**2**, (+)-**3**, and (+)-**4** recorded in $CDCl_3$ at 25 °C in the 1700−1000 cm^{-1} region.

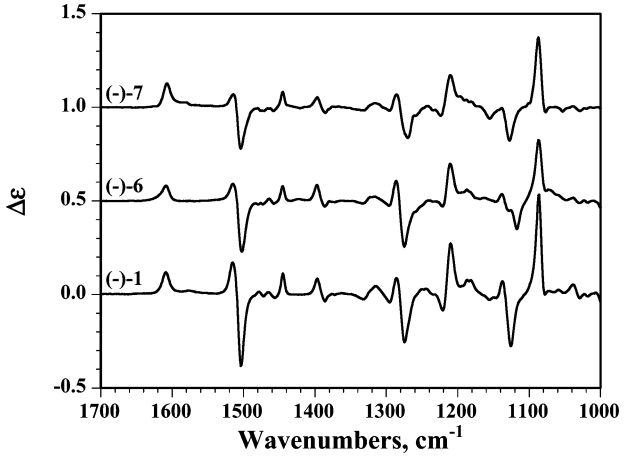

FIGURE 6. VCD spectra of compounds (−)-**1**, (−)-**6**, and (−)-**7** recorded in $CDCl_3$ at 25 °C in the 1700−1000 cm^{-1} region.

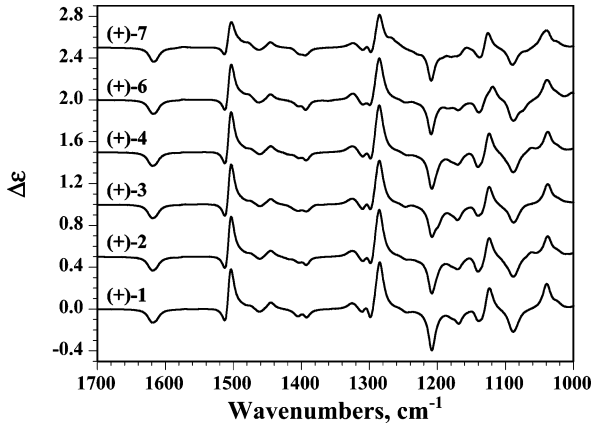

FIGURE 7. Calculated VCD spectra of compounds (+)-**1**, (+)-**2**, (+)-**3**, (+)-**4**, (+)-**6**, and (+)-**7** in the 1700−1000 cm^{-1} region.

The experimental VCD spectra of one enantiomer of **2**−**7** in $CDCl_3$ solvent are reported in Figures 5−7 in the 1700−1000 cm^{-1} regions and are compared to that previously published

for **1**. Only one enantiomer is presented since, for all compounds, the VCD spectra of the two enantiomers are nearly perfect mirror images, indicating identical optical purity. The overall shape of the VCD spectra is very similar for compounds **1**−**7**, and no new VCD bands are observed at the frequencies characteristic of the chemical groups of the substituents. The chiroptical properties observed by VCD arise essentially from the structural chirality of the cryptophane backbone.

The frequencies observed in the VCD spectra of **1** for the most important bands as well as their assignments have been previously reported. The bands due to the ν_{8a}C═C, ν_{8b}C═C, and ν_{19a}C═C stretching vibrations of the rings occur at 1607, 1577, and 1509 cm^{-1}, respectively. The bending vibrations of CH_2 and CH_3 groups give rise to the bands observed in the 1480−1420 cm^{-1} spectral range. The region between 1400 and 1250 cm^{-1} is more complex because the observed bands correspond to coupled modes involving wagging and twisting vibrations of the CH_2 groups (chains and bowls). The bands associated with the anti-symmetric (as) and symmetric (s) stretching vibrations of C_{ring}−O−C in C_{ring}−O−Me and C_{ring}−O−Et groups occur at 1212 and 1034 cm^{-1}, respectively. Finally, the bands at 1183, 1144, and 1086 cm^{-1} are assigned to the aromatic C_{ring}−H in-plane deformation vibration, to the rocking modes of CH_2 and CH_3 groups, and to the stretching vibration of C_{ring}−C, respectively. Even though the cryptophane-A molecule does not possess asymmetric carbons, the VCD spectrum exhibits strong bands (differential molar absorptivity up to ±0.4) across this spectral range. These large VCD intensities on most bands are due to large magnetic dipole contributions from charge circulation in the two cyclotriveratrylene (CTV) bowls. Thus, significant changes of the VCD intensities can be expected for cryptophanes monofunctionalized with substituents able to perturb this charge circulation in the CTV bowls. In addition, the lack of symmetry of monofunctionalized cryptophanes leads, for each vibration, to six nondegenerate modes, each having its own intensity and sign. As a consequence, a decrease in intensity of the overall VCD bands could by expected for cryptophanes having C_1-symmetry.

As observed in Figure 5, the replacement of the methoxy group by a OH, a OCH_2COOCH_3, or a OCH_2COOH moiety does not significantly change the VCD spectrum of **1**. For these three monofunctionalized cryptophanes, the electron-donating character of the substituents is expected to be very similar to the methoxy moiety. Thus, these substituents do not alter the electronic circulation in the CTV units and, consequently, do not significantly change the VCD band intensities. In addition, the breakdown of the symmetry resulting in the introduction of a single substituent does not appear to be sufficient to modify the VCD spectra of **2**−**4**. This last feature had been found for cryptophane-A studied with empty cavities (in $C_2D_2Cl_4$ solution) or with guest entities ($CDCl_3$ solution). Indeed, similar VCD spectra of cryptophane-A were observed for the two solvents, although empty and filled cavities give rise to D_3- and C_3-symmetry of the molecule, respectively. The overall shape of the VCD spectrum is also not modified when two cryptophane-A molecules are connected together by an alkyl chain (−)-**5** and results in twice the intensity of VCD bands of (−)-**1** (data not shown).

In contrast, as shown in Figure 6, larger spectral modifications are observed in the VCD spectra of compounds **6** and **7**. These spectral modifications, more pronounced for (−)-**7**, consist of an overall decrease of the band intensities. The lack of symmetry of (−)-**7** combined with the absence of an electron-donating methoxy group strongly affects the global electronic circulation in the CTV units. These two additive effects can explain the lower intensity of VCD bands observed for (−)-**7**. Even though a similar decrease in the VCD bands is noticed for (−)-**6**, the triflic moiety induces a weaker perturbation.

The VCD spectra calculated at the B3PW91/6-31G* level for the anti conformation of the aliphatic chains of (+)-cryptophanes **1**−**7** are reported in Figure 7 in the 1700−1000 cm^{-1} regions. Since it has been shown that chloroform complexes with the cryptophane-A molecules, VCD spectra were calculated with the presence of a chloroform molecule in the cryptophane cavity. For monofunctionalized cryptophane, the C−H bond of chloroform points toward to the nonfunctionalized CTV unit. As mentioned in a previous paper,[9] the predicted VCD spectrum of the $CHCl_3$@cryptophane-A complex is in good agreement with the experimental one. The sign of the experimental VCD spectrum for the νC═C stretching modes of the rings is well reproduced, in particular, the bisignate shape of the 1509 cm^{-1} band. This feature is due to the coupling of vibrations with E symmetry in the two CTV units of the cryptophane-A molecule. The calculated VCD intensities are also in good agreement with the experimental ones. On the other hand, the VCD spectra calculated at lower wavenumbers have been found to vary greatly with the conformation of the aliphatic linkers. Indeed, the rotational strengths calculated for wagging and twisting vibrations of CH_2 groups (bands occurring in the 1350−1250 cm^{-1} spectral range) and for anti-symmetric stretching vibration of C_{ring}−O−C (band at 1212 cm^{-1}) are very dependent on the conformation of the bridges. Nevertheless, the VCD spectrum calculated for the anti conformation of the aliphatic linkers reproduced fairly well the signs and the intensities of the major bands observed on the experimental spectrum, except for the bands at 1445 and 1050 cm^{-1}. The VCD calculated spectra of (+)-cryptophanes **1**−**4** are nearly identical, indicating that the nature of the substituent as well as the lack of symmetry have no effect on the chiroptical properties of cryptophanes monofunctionalized with electron-donating substituents. Indeed, similar VCD bands have been calculated for the νC═C stretching modes of the rings, even though each vibration (ν_{8a}C═C, ν_{8b}C═C, and ν_{19a}C═C) gives rise to six nondegenerate modes for monofunctionalized cryptophanes. On the other hand, the overall intensity of the VCD bands calculated for (+)-cryptophane **6** is slightly lower than that calculated for (+)-cryptophane **1**, and the intensity decrease is more pronounced for (+)-cryptophane **7**. All of the results obtained from DFT calculations are in excellent agreement with VCD experiments. This study clearly demonstrates that the DFT calculations are able to reproduce well the experimental VCD spectra of cryptophane-A and monofunctionalized cryptophanes. Consequently, the combined approach VCD experiments/DFT calculations allow the unambiguous determination of the absolute configuration of cryptophane derivatives, even for cryptophanes having C_1-symmetry. Finally, DFT calculations on a cryptophane−chloroform complex reveal that the VCD activity is transferred to the solvent molecules. However, this induced chirality predicted by the calculations is very small (for instance, $\Delta\epsilon = 0.0028$ for the νCH vibration of chloroform) and cannot be experimentally measured.

Conclusion

New enantiopure cryptophanes **3**−**7** have been synthesized by a multistep procedure, and the chiroptical properties of these

compounds have been examined by polarimetry, ECD, and VCD spectroscopies. The synthetic route used for the preparation of **3**−**7** demonstrates the ability of the synthetic method reported by Brotin and co-workers[10] to prepare, in a sizable amount, new optically pure derivatives having a very high enantiomeric excess (close to 100%). This approach also enables the preparation of new derivatives whose synthesis was not possible using the usual *direct* or *template* methods reported by Collet and co-workers[15] as illustrated by the preparation of compound **7**. The study of the chiroptical properties of the nonsymmetrical derivatives **3**−**7** by ECD spectroscopy reveals modifications in intensity and in shape for the Cotton bands of the two forbidden ^1L_a and ^1L_b transitions with respect to that observed for the D_3-symmetrical cryptophane-A derivative **1**. The lack of symmetry as well as the nature of the substituents attached to the benzene rings is, however, unable to reverse the sign of the Cotton bands of the ECD spectra of compounds **3**−**7**, suggesting that a confident determination of absolute configuration for monofunctionalized cryptophanes can be accomplished by ECD spectroscopy. In addition, strong solvent effects, especially for the ^1L_b transition, have been noticed for compounds **6** and **7** compared to those observed for compound **1**. The effects observed for the ECD spectra of **6** and **7** cannot be correlated with the ability of a particular solvent to enter the cavity of cryptophanes, whereas a correlation was observed between the spectroscopic change and the dielectric constant of the solvent used. On the other hand, VCD spectroscopy combined with ab initio calculations allows the unambiguous determination of the absolute configuration of cryptophanes **3**−**7**. Similar experimental VCD spectra have been observed in all cases, and only a decrease in the intensity of the signal was noted for compounds **6** and **7**. The decrease in intensity of the VCD bands was more pronounced for derivative **7** and was perfectly predicted by DFT calculations.

Dis-symmetrical derivatives, such as new cryptophane **7**, are particularly interesting compounds and require further investigation by VCD spectroscopy and DFT calculations. Indeed, the lack of symmetry and the presence of two different caps having different electronic densities can induce a preferred orientation of the guest molecule in the cavity. Other effects, which have been omitted in this article, such as the ability of the bridges to adopt the anti or gauche conformations, should be considered in the calculations since large differences in energy have been noticed for the $CHCl_3$@**1** complex and different VCD spectra have been predicted. Thus, these different aspects give a strong impulse for further investigation of the chiroptical properties of cryptophane derivatives by VCD spectroscopy. Such investigations are in progress, and their results will be published in due course.

Experimental Section

ECD Measurements. Electronic circular dichroism (ECD) spectra were recorded on a Chirascan equipped with a Peltier temperature controller and calibrated with 1*S*-(+)-10-camphorsulfonic acid. Measurements were carried out at room temperature using a 0.2 cm path length quartz cell. Spectra were recorded in the 230−450 nm wavelength range with a 0.5 nm increment and a 1s integration time. Spectra were processed with Chirascan software, baseline corrected, and slightly smoothed by using a third-order least-square polynomial fit. Spectral units were expressed in molar ellipticity.

VCD Measurements. The VCD spectra were recorded with 8 h of data collection time with 4 cm^{-1} resolution on a FTIR spectrometer equipped with a VCD optical bench.[17] Samples were held in a variable path length cell with BaF_2 windows. Spectra of **1**−**4**, **6**, and **7** were measured in $CDCl_3$ solvent at a concentration of 0.015 M and a path length of 250 μm, whereas the spectrum of **5** was measured in $C_2D_2Cl_4$ solvent at a concentration of 0.0045 M and a path length of 460 μm. Baseline corrections of the VCD spectra were performed by subtracting the raw VCD spectra of the solvents. The photoelastic modulator was adjusted for a maximum efficiency at 1400 cm^{-1}. Calculations were performed via the standard spectrometer software, using Happ and Genzel apodization, de-Haseth phase-correction, and a zero-filling factor of 1. Calibration spectra were recorded using a birefringent plate (CdSe) and a second BaF_2 wire grid polarizer, following the experimental procedure previously published.[18]

DFT Calculations. The geometry optimizations, vibrational frequencies, absorption, and VCD intensities were calculated by the Gaussian 03 program[19] on 16 processors at the M3PEC computing center of the University Bordeaux I. Calculations of the optimized geometry of (+)-**1**, (+)-**2**, (+)-**3**, (+)-**4**, (+)-**6**, and (+)-**7** were performed at the density functional theory level using the B3PW91 functional and 6-31G* basis set. The theoretical framework for geometry optimization of cryptophane molecules has been previously published.[9] All the calculations were performed with a chloroform molecule inside the cryptophane cavity and an anti conformation of the aliphatic linkers. Vibrational frequencies, IR, and VCD intensities were calculated at the same level of theory, utilizing the magnetic field perturbation method with gauge-invariant atomic orbitals.[20] For comparison to experiment, the calculated frequencies were scaled by 0.968 and the calculated intensities were converted to Lorentzian bands with a half-width of 7 cm^{-1}.

Synthesis of Cryptophanes. (+)-Cryptophane 3: Methyl bromoacetate (0.060 g, 0.39 mmol) was added in one portion to a solution of (+)-cryptophanol-A (0.14 g, 0.16 mmol) and cesium carbonate (0.05 g, 0.15 mmol) in DMF (4 mL). The solution was stirred overnight at 80 °C under argon atmosphere. The mixture was poured into water, and the product was extracted twice with CH_2Cl_2. The combined organic layer was then washed three times with brine and dried over sodium sulfate. Filtration and evaporation of the solvent under reduced pressure leaves a residue, which was then purified by column chromatography on silica gel (CH_2Cl_2/acetone 90:10). The glassy product was collected and recrystallized in a mixture of $CHCl_3$ and ethanol to give rise to (+)-**3** as white crystals (0.12 g, 79%): mp 224−225 °C; ^1H and ^{13}C NMR spectroscopy (see Figures S3−S6 in Supporting Information) are identical to those previously reported for the racemate.[10]

(+)-Cryptophane 4: A solution of KOH (2 M, 2 mL) was added in one portion to a solution of **3** (0.11 g, 0.12 mmol) in THF (3

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mL). The biphasic solution was stirred overnight at 60 °C under an argon atmosphere. THF was removed by rotary evaporation, and 5 mL of water was added. The solution was acidified at 0 °C with a solution of concd HCl to yield a white precipitate, which was collected on a frit and washed with water and with diethyl ether (0.1 g, 92%): ee ≥ 99%; mp 218−220 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) δ 6.845 (s, 1H; Ar), 6.84 (s, 1H; Ar), 6.82 (s, 1H; Ar), 6.74 (s, 1H; Ar), 6.725 (s, 1H; Ar), 6.71 (s, 1H; Ar), 6.67 (s, 1H; Ar), 6.66 (s, 1H; Ar), 6.64 (s, 2H; Ar), 6.63 (s, 1H; Ar), 6.61 (s, 1H; Ar), 4.71 (d, ^2J(H,H) = 16.5 Hz, *ABsyst.*, 1H; CH_2-COO), 4.62−4.54 (m, 6H; CH_a), 4.55 (d, ^2J(H,H) = 16.5 Hz, *ABsyst.*, 1H; CH_2COO), 4.31 (m, 1H; OCH_2), 4.28−4.10 (m, 9H; OCH_2), 4.00−3.80 (m, 2H; OCH_2), 3.89 (s, 3H; OCH_3), 3.79 (s, 3H; OCH_3), 3.785 (s, 3H; OCH_3), 3.78 (s, 3H; OCH_3), 3.76 (s, 3H; OCH_3), 3.42 (d, ^2J(H,H) = 13.5 Hz, 1H; H_e), 3.39 (d, ^2J(H,H) = 13.5 Hz, 3H; H_e), 3.38 (d, ^2J(H,H) = 13.5 Hz, 2H; H_e); ^{13}C NMR (126.7 MHz, $CDCl_3$, 20 °C) δ 170.9 (1C; *C*OO), 149.7, 149.65, 149.6, 149.5, 148.5, 147.9, 147.8, 146.9, 146.8, 146.7, 146.65, 146.1, 135.6, 134.7, 134.6, 134.0, 133.9, 133.7, 133.50, 132.9, 131.9, 131.6, 131.1, 131.0, 122.8, 122.3, 121.4, 120.9, 120.8, 120.6, 120.0, 114.4, 113.8, 113.7, 113.6, 113.4, 70.0, 69.7, 69.3, 69.1, 69.0, 68.9, 65.6, 60.2 (1C, O*C*H$_3$), 55.75 (1C, O*C*H$_3$), 55.7 (1C, O*C*H$_3$), 55.6 (1C, O*C*H$_3$), 55.5 (1C, O*C*H$_3$), 36.3 (1C, $C_{a,e}$), 36.25 (3C, $C_{a,e}$), 36.2 (1C, $C_{a,e}$), 35.8 (1C, $C_{a,e}$), (see Figures S7−S10 in Supporting Information); HRMS (LSIMS) calcd for $C_{55}H_{54}O_{14}$ [M^+] 938.3514, found 938.3512.

(−)-Biscryptophane 5: This compound was prepared according to a known procedure.[21] Compound (−)-biscryptophane **5** (40 mg, 25%) was obtained from (−)-**2** (0.148 g, 0.17 mmol), 1,10-diiododecane (0.033 g, 0.08 mmol), cesium carbonate (0.055 g, 0.17 mmol), and DMF (2.5 mL) as amorphous material: ee ≥ 98%; ^{1}H and ^{13}C NMR spectra (see Figures S11−S14 in Supporting Information) are identical to the NMR spectra previously reported for a mixture of diastereomers.[21]

(±)-Cryptophane 6: Anhydride triflic (0.21 μL, 0.36 g, 1.29 mmol) was added dropwise at 0 °C to a stirred solution of *rac*-**2** (0.378 g, 0.43 mmol) in a mixture of dichloromethane (6 mL) and pyridine (6 mL). After the addition was completed, the orange solution was stirred overnight at room temperature. Water was added, and the product was extracted twice with dichloromethane. The organic layers were then combined, washed twice with brine, and dried over sodium sulfate. Filtration followed by evaporation of the solvents under reduced pressure leaves a red residue. The desired compound **6** was then purified by chromatography on silica gel (CH_2Cl_2/acetone 90:10) to give cryptophane **6** as a white glassy product. Recrystallization in a mixture of dichloromethane and ethanol followed by filtration on a frit affords **6** as white crystals (0.310 g, 71%): ee ≥ 99%; mp >282−283 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) δ 6.97 (s, 1H; Ar), 6.86 (s, 1H; Ar), 6.85 (s, 1H; Ar), 6.75 (s, 1H; Ar), 6.73 (s, 2H; Ar), 6.67 (s, 3H; Ar), 6.66 (s, 1H; Ar), 6.65 (s, 1H; Ar), 6.64 (s, 1H; Ar), 4.64 (d, ^2J(H,H) = 13.5 Hz, 1H; H_a), 4.585 (d, ^2J(H,H) = 13.5 Hz, 3H; H_a), 4.535 (d, ^2J(H,H) = 13.5 Hz, 2H; H_a), 4.41−4.36 (m, 1H; OCH_2), 4.32−4.26 (m, 1H; OCH_2), 4.22−4.04 (m, 9H; OCH_2), 3.98−3.93 (m, 1H; OCH_2), 3.78 (s, 9H; OCH_3), 3.77 (s, 3H; OCH_3), 3.75 (s, 3H, OCH_3), 3.46 (d, ^2J(H,H) = 13.5 Hz, 1H; H_e), 3.425 (d, ^2J(H,H) = 13.5 Hz, 1H; H_e), 3.415 (d, ^2J(H,H) = 13.5 Hz, 1H; H_e), 3.41 (d, ^2J(H,H) = 13.5 Hz, 1H; H_e), 3.39 (d, ^2J(H,H) = 13.5 Hz, 2H; H_e); ^{13}C NMR (126.7 MHz, $CDCl_3$, 20 °C) δ 149.95, 149.8, 149.75 (2C), 149.5, 149.2, 147.1, 146.8, 146.6, 146.55, 146.5, 140.9, 138.7, 134.95, 134.3, 134.3, 134.0, 133.7, 132.5, 132.2, 131.9, 131.2, 131.0, 130.7, 123.3, 121.3, 121.1, 120.9, 120.7, 120.6, 120.2, 118.7 (q, $^1J_{CF}$ = 323 Hz, 1C, *C*F$_3$), 113.8, 113.75, 113.7, 113.6, 113.4, 69.6 (1C, O*C*H$_2$), 69.4 (1C, O*C*H$_2$), 69.35 (1C, O*C*H$_2$), 69.30 (1C, O*C*H$_2$), 69.25 (1C, O*C*H$_2$), 69.1 (1C, O*C*H$_2$), 55.8 (1C, O*C*H$_3$), 55.7 (2C, O*C*H$_3$), 56.65 (1C, O*C*H$_3$), 55.4 (1C, O*C*H$_3$), 36.50 (1C, *C*H$_{a,e}$), 36.3 (1C, *C*H$_{a,e}$), 36.2 (1C, *C*H$_{a,e}$), 36.1 (2C, *C*H$_{a,e}$), 35.7 (1C, *C*H$_{a,e}$) (see Figures S15, S16, S19, and S20 in Supporting Information); HRMS (LSIMS) calcd for $C_{54}H_{51}O_{14}F_3S$ [M^+] 1012.2952, found 1012.2953.

(+)-Cryptophane 6: This compound was prepared according to the procedure described for its racemate. Compound (+)-**6** (0.14 g, 75%) was obtained from (+)-**2** (0.16 g, 0.18 mmol), anhydride triflic (60 μL, 0.1 g, 0.36 mmol) in pyridine (3 mL), and dichloromethane (3.5 mL): ee ≥ 99%; mp 268−269 °C; ^{1}H and ^{13}C NMR spectra (see Figures S17 and S21 in Supporting Information) are identical to those reported for the racemic mixture.

(−)-Cryptophane 6: This compound was prepared according to the procedure described for the racemate. Compound (−)-**6** (0.15 g, 69%) was obtained from (−)-**2** (0.19 g, 0.21 mmol), anhydride triflic (107 μL, 0.182 g, 0.65 mmol) in pyridine (2 mL), and CH_2Cl_2: ee ≥ 99%; mp 268 °C; ^{1}H and ^{13}C NMR spectra (see Figures S18 and S22 in Supporting Information) are identical to those reported for the racemic mixture.

(±)-Cryptophane 7: A mixture of cryptophane *rac*-**6** (0.31 g, 0.31 mmol), $PdCl_2(PPh_3)_2$ (0.036 g, 0.05 mmol), 1,3-bis(diphenylphosphino)propane (0.042 g, 0.1 mmol), tributylamine (0.66 mL), and formic acid (60 μL) in DMF (2.5 mL) was stirred and heated overnight at 110 °C. Water was added, and the product was extracted three times with CH_2Cl_2. The organic layers were combined, washed three times with brine, and then dried over sodium sulfate. Filtration and evaporation of the solvent under reduced pressure leaves a red residue. Purification by chromatography on silica gel (CH_2Cl_2/acetone 90:10) affords *rac*-**7** as a white glassy solid. It was then recrystallized in a mixture of $CHCl_3$ and ethanol to give rise to *rac*-**7** as white crystals (0.24 g, 90%): ee ≥ 99%; mp 286 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) δ 7.07 (d, ^3J(H,H) = 8.5 Hz, 1H; Ar), 6.78 (d, ^4J(H,H) = 2.5 Hz, 1H; Ar), 6.76 (s, 1H; Ar), 6.745 (s, 1H; Ar), 6.74 (s, 1H; Ar), 6.695 (s, 1H; Ar), 6.68 (s, 2H; Ar), 6.65 (s, 1H; Ar), 6.63 (s, 3H; Ar), 6.36 (dd, ^3J(H,H) = 8.5 Hz, ^4J(H,H) = 2.5 Hz, 1H; Ar), 4.65 (d, ^2J(H,H) = 13.5 Hz, 1H; H_a), 4.59 (d, ^2J(H,H) = 13.5 Hz, 2H; H_a), 4.58 (d, ^2J(H,H) = 13.5 Hz, 1H; H_a), 4.565 (d, ^2J(H,H) = 13.5 Hz, 1H; H_a), 4.53 (d, ^2J(H,H) = 13.5 Hz, 1H; H_a), 4.38−3.94 (m, 12H; OCH_2), 3.81 (s, 3H; OCH_3), 3.77 (s, 6H; OCH_3), 3.76 (s, 3H; OCH_3), 3.75 (s, 3H; OCH_3), 3.45 (d, ^2J(H,H) = 13.5 Hz, 1H; H_e), 3.43 (d, ^2J(H,H) = 13.5 Hz, 1H; H_e), 3.39 (d, ^2J(H,H) = 13.5 Hz, 3H; H_e), 3.375 (d, ^2J(H,H) = 13.5 Hz, 1H; H_e); ^{13}C NMR (126.7 MHz, $CDCl_3$, 20 °C) δ 156.3, 149.9, 149.8, 149.6, 149.5, 148.5, 146.7 (2C), 146.6 (3C), 140.9, 134.3, 134.25, 134.0, 133.8, 132.8, 132.3, 131.95, 131.9, 131.8, 131.35, 130.9, 130.8, 121.5, 121.45, 120.9, 120.3, 118.9, 116.4, 114.5, 113.7, 113.6, 113.4, 113.4, 112.0, 69.7 (1C, O*C*H$_2$), 69.3 (1C, O*C*H$_2$), 69.2 (1C, O*C*H$_2$), 69.2 (1C, O*C*H$_2$), 66.4 (1C, O*C*H$_2$), 65.3 (1C, O*C*H$_2$), 56.1 (1C, O*C*H$_3$), 55.7 (1C, O*C*H$_3$), 55.65 (1C, O*C*H$_3$), 55.5 (2C, O*C*H$_3$), 36.7 (1C, $C_{a,e}$), 36.3 (1C, $C_{a,e}$), 36.2 (1C, $C_{a,e}$), 36.1 (2C, $C_{a,e}$), 35.5 (1C, $C_{a,e}$) (see Figures S23, S24, S27, and S28 in Supporting Information); HRMS (LSIMS) calcd for $C_{53}H_{52}O_{11}$ [M^+] 864.3510 found 864.3502.

(+)-Cryptophane 7: This compound was prepared as described for *rac*-**7**. Derivative (+)-**6** (0.15 g, 0.14 mmol), $PdCl_2(PPh_3)_2$ (0.018 g, 0.026 mmol), 1,3-bis(diphenylphosphino)propane (0.021 g, 0.051 mmol), NBu_3 (0.34 mL), formic acid (0.03 mL), and DMF (1.5 mL) give rise to derivative (−)-**7** (0.094 g, 73%) after recrystallization in a mixture of $CHCl_3$ and ethanol: ee ≥ 99%; mp 283 °C; ^{1}H NMR and ^{13}C NMR spectra (see Figures S26 and S30 in Supporting Information) are identical to that of *rac*-**7**.

(−)-Cryptophane 7: This compound was prepared and purified as described for the racemate derivative **7**. Derivative (−)-**6** (0.15 g, 0.14 mmol), $PdCl_2(PPh_3)_2$ (0.018 g, 0.026 mmol), 1,3-bis-(diphenylphosphino)propane (0.021 g, 0.051 mmol), NBu_3 (0.34 mL), formic acid (0.03 mL), and DMF (1.5 mL) give rise to derivative (−)-**7** (0.11 g, 86%) after recrystallization in a mixture of $CHCl_3$ and ethanol: ee ≥ 99%; mp 281 °C; ^{1}H NMR and ^{13}C NMR spectra (see Figures S25 and S29 in Supporting Information) are identical to that of *rac*-**7**.

(21) Darzac, M.; Brotin, T.; Rousset-Arzel, L.; Bouchu, D.; Dutasta, J.-P. *New J. Chem.* **2004**, *28*, 502−512.

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Supporting Information Available: General experimental methods. ^{1}H and ^{13}C NMR spectra of chiral cryptophanes **3**−**7** in chloroform-*d*. B3PW91/6-31G* optimized geometries and total energies for structures (+)-**1**, (+)-**2**, (+)-**3**, (+)-**4**, (+)-**6**, and (+)-**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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