Novel Synthetic Approach for Optical Resolution of Cryptophanol-A: A Direct Access to Chiral Cryptophanes and Their Chiroptical Properties

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Abstract: The separation by crystallization of the pair of cryptophane diastereomers **1a** and **1b**, obtained in 1:1 ratio by treating racemic *anti* cryptophanol-A (**2**) with (−)-camphanic acid chloride, provided a substantial amount of optically pure material (diastereomeric excess > 98 %). Subsequent hydrolysis afforded the optically pure cryptophanol-A enantiomers (+)-**2** and (−)-**2**, which were submitted to nucleophilic substitution reactions to provide cryptophane-A (+)-**3** and cryptophane monoester (−)-**4** in optically pure form. The chiroptical properties of the new cryptophanes **1**–**4** were investigated by using circular dichroism spectroscopy, and the absolute configuration of the molecules was clearly established. These new cryptophanes represent additional interesting examples for studying the Cotton effect of interacting multichromophoric systems. Moreover, this novel approach presents numerous advantages over the other methods developed so far to obtain optically pure cryptophanes, and compounds (−)-**2**, (+)-**2**, and (−)-**4** can give access to new enantiopure functionalized cryptophanes with host–guest properties similar to those of cryptophane-A.

Keywords: chiral resolution · circular dichroism · configuration determination · cryptophanes · supramolecular chemistry

Introduction

Cryptophanes constitute an important class of host molecules that possess a quasi-spherical lipophilic cavity suitable for complexing small neutral or cationic organic compounds.[1–8] Recently, the functionalization of cryptophanes with hydroxy or ester substituents was reported, and it was thus possible to develop a new family of functionalized hosts with a potential application as sensors or biosensors.[9] There exist several isomers of cryptophanes, and particular interest was devoted to the chiral *anti* isomers, which were able to achieve chiral recognition.[10–12] So far, the different routes used to prepare cryptophanes have given mostly the *anti* or the *syn* isomers, depending on the structure of the molecule and the synthetic procedure. Resolution of the chiral *anti* form is therefore an important aspect of cryptophane synthesis as it provides original optically active receptors with interesting physical and chemical properties. Two main approaches have been developed to resolve chiral cryptophanes, but both of them have some disadvantages. The first one is based on physical discrimination of the two enantiomers by HPLC on a chiral stationary phase (chiralpak OT$^+$). This method has been successfully used to discriminate the enantiomers of a large range of cyclotriveratrylene (CTV) and cryptophane derivatives.[13] However, its use on a semipreparative scale to obtain larger amounts of optically pure cryptophanes for synthetic purpose is not convenient. In particular, the high cost of semipreparative chiral columns, their sensitivity, and the large volume of mobile phase needed for these experiments make this approach inappropriate for scale-up. The second method, based on the synthesis and separation of optically pure CTV units by formation of diastereomers, represents a more interesting approach to obtain sizeable amounts of resolved cryptophanes.[10–15] This strategy has been successfully applied in our laboratory to study the chiroptical properties of several cryptophanes or to resolve *anti* cryptophane-C, which showed interesting binding properties toward chiral halogenomethanes.[10,12] However, the racemization of the CTV unit upon heating represents the main limitation of this method, and carefully controlled experimental conditions must be used during the subsequent synthetic steps to avoid any partial racemization of the CTV unit. This strongly limits the potential use of chiral CTV moieties to design optically pure cryptophanes, and the enantiomeric purity usually reported in the literature does not exceed 91–95 %. This would be even more crucial in the synthesis of optically pure functionalized cryptophanes, a synthesis that requires

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Abstract in French: *Les cryptophanes diastéréisomères **1a** et **1b** ont été obtenus dans le rapport 1:1 par réaction du cryptophanol-A anti (**2**, racémate) avec le (−)-chlorure de L'acide camphanique. Leur séparation par cristallisation a permis L'obtention des produits **1a** et **1b** optiquement purs (ee >98 %). Après hydrolyse, on obtient les cryptophanol-A (+)-**2** et (−)-**2** sans perte d'excès énantiomérique. Ceux-ci ont permis d'obtenir par substitution nucléophile le cryptophane-A (+)-**3** et le cryptophane monoester (−)-**4**. Les propriétés chiroptiques des nouveaux cryptophanes **1**–**4** ont été étudiées par dichroïsme circulaire (CD) et leur configuration absolue a été clairement établie. Ces nouvelles molécules sont des modèles intéressants pour L'étude de L'effet Cotton dans des systèmes où plusieurs chromophores interagissent. De plus, L'approche proposée pour L'obtention de cryptophanes énantiopurs présente de nombreux avantages par rapport aux méthodes développées antérieurement. Les nouveaux composés (−)-**2**, (+)-**2** et (−)-**4** permettent d'accéder à de nouveaux cryptophanes fonctionnalisés chiraux possédant des propriétés complexantes analogues à celles du cryptophane-A.*

numerous synthetic steps. Recently, Shinkai and co-workers reported the efficient synthesis of novel chiral cryptophanes by self-assembling CTV units through metal coordination.[16] Since the first synthesis of cryptophane-A in 1981,[17] several routes have been proposed for the preparation of this compound and other related cryptophanes. Whereas the *direct method* gave rapid access to cryptophane-A with a low yield,[18] the *template method*, which required the cyclization of the two CTV units at different stages of the synthesis, has been successfully applied to synthesize cryptophane-A with a good yield. Small amounts of resolved cryptophane-A have been obtained by this method.[19] The synthesis of cryptophanol-A **2** represents a new approach to the resolution of cryptophane-A. The multistep strategy used for the preparation of **2** appears more time consuming, but allows the design of new, interesting, functionalized hosts, whose complexing properties are close or similar to those of cryptophane-A.[20] Here, we report a novel approach for the resolution of cryptophane-A and related compounds based on the separation of cryptophane diastereomers by crystallization. The reaction of the free hydroxy group in **2** with a chiral substrate leads to diastereomers, whose separation is then conceivable by, for example, crystallization or chromatography on silica gel. Both techniques are interesting since they are able to furnish reasonable quantities of resolved material. The cryptophanol-A enantiomers (−)-**2** and (+)-**2** were thus obtained with high enantiomeric excess (*ee* = 98–100 %) by crystallization of diastereomers **1a** and **1b**, respectively, and subsequent removal of the chiral substituent. This method has many advantages over the two methods developed in the past, as will be discussed in detail in the next section. Cryptophane-A (+)-**3** was synthesized from (+)-**2** to ascertain the absolute configuration of new compounds **1**–**4**. Cryptophane monoester (−)-**4** was also prepared as its racemate has been used to build up original cryptophanes for biological applications.[9]

Results and Discussion

Synthesis of diastereomers 1a and 1b: Compound **1** was prepared by treating racemic cryptophanol-A **2** with camphanic acid chloride in the presence of triethylamine and DMAP (Scheme 1). The (−)-camphanic moiety was selected from a number of chiral substrates for several reasons. It is a readily available chiral molecule, which has been efficiently used to resolve CTV derivatives.[14,21] In addition, we expected that the close proximity of the camphanic group to the cryptophane backbone would favor the separation of the two diastereomers by crystallization or chromatographic techniques. Such requirements are important because bowl-shape molecules are known to be particularly difficult to resolve.[22] The reaction proceeded very slowly and was completed after 96 h under reflux conditions in CH_2Cl_2 with an excess of acid chloride. Under these conditions, thin-layer chromatography of the crude material showed one single

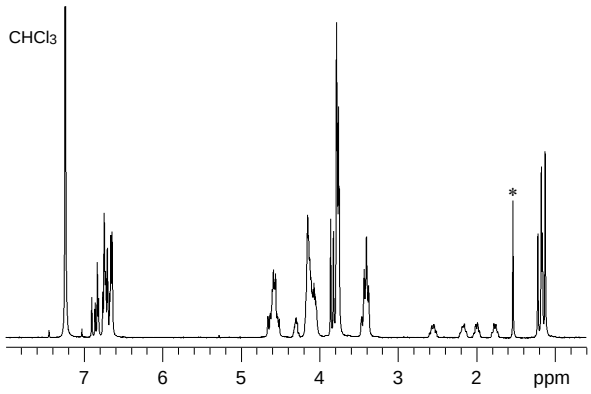
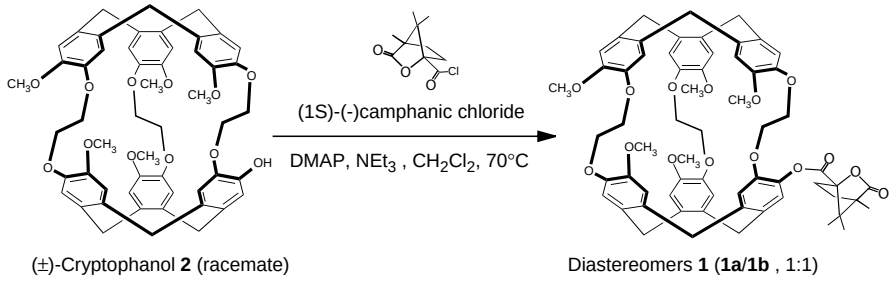


Figure 1. ^{1}H NMR spectrum of **1** as a mixture of diastereomers (−)-**1a** and (+)-**1b** (1:1) in $CDCl_3$ at 20 °C. The star denotes water from the solvent.



Scheme 1. Preparation of **1** from racemic cryptophanol-A **2**. DMAP = 4-dimethylaminopyridine.

spot, which was further identified as the two diastereomers **1a** and **1b**. A change in the experimental conditions (pyridine instead of triethylamine) led to no reaction and the starting material was recovered. These results suggest a strong steric hindrance around the hydroxy group in **2** and corroborate the difficulties encountered in attaching long alkyl chains onto cryptophanol-A in good yields.[20] Purification of compound **1** was critical and the procedure given in the Experimental Section is strongly recommended. Purification by silica gel chromatography gave a material that was washed with diethyl ether and recrystallized from EtOH/$CHCl_3$ to give pure cryptophane **1** in 87% yield as a 1:1 mixture of diastereomers **1a** and **1b**. The ^{1}H NMR spectrum in $CHCl_3$ appeared quite complicated due to the lack of symmetry in **1a** and **1b** (Figure 1). For instance, in the aromatic region we observed 17 peaks corresponding to overlapping singlets from both diastereomers (12 singlets each). Similarly, the 1.0–1.3 ppm region showed four distinct peaks, corresponding to the methyl groups of the camphanic moiety, whereas three singlets are expected for each diastereomer.

Attempts to separate the two diastereomers by column chromatography on silica gel or by HPLC on a C18 reversed stationary phase failed despite the use of different elution conditions. However, we observed that crystallization at low concentrations in toluene at room temperature afforded crystalline material whose ^{1}H NMR analysis corresponded to the single diastereomer (−)-**1a** (Figure 2). The choice of the solvent was limited for solubility reasons. Several experiments were run and showed that the efficient optical resolution of compound (−)-**1a** was only performed at very low concentrations (0.9 g of **1** in 220 mL of toluene; 15% overall yield). At higher concentrations, the collected crystalline compound was identified by ^{1}H NMR spectroscopy as the equimolar mixture of (−)-**1a** and (+)-**1b**. In the ^{1}H NMR spectrum of (−)-**1a**, the aromatic pattern (twelve singlets, some overlapped), the methoxy groups (five singlets), and the methyl signals of the camphanic group (three singlets) are clearly identifiable (Figure 2). These results ascertain the presence of one single diastereomer; the diastereomeric excess (*de*) was thus easily determined from the ^{1}H NMR spectra and estimated to be in the range of 98–100%.

After the crystals of (−)-**1a** had been collected, the mother liquor was heated under reflux conditions and filtered. This solution was then allowed to stand at room temperature for 48 h. During that time new crystals precipitated and were collected. Surprisingly, these new crystals, when characterized by ^{1}H NMR spectroscopy, did not correspond to diastereomer (−)-**1a** but to the second diasteromer (+)-**1b**. Compound (+)-**1b**, obtained in a somewhat lower yield (10%), was found to be diastereomerically pure by ^{1}H NMR spectroscopy (*de* = 98–100%). Identification of (+)-**1b** was easily achieved by ^{1}H and ^{13}C NMR spectroscopy. Figure 2 shows the three main regions of interest in the ^{1}H NMR spectrum, which prove the absence of (−)-**1a** in these new crystals. A similar conclusion can also be reached by studying the ^{13}C NMR spectra of both diastereomers. The expected signals are exhibited for both the ethylenedioxy linkers (δ = 68.5–70.0 ppm) and the methoxy groups (δ = 49.0–57.0 ppm). Well-resolved signals were observed for each set of carbon nuclei in the spectra of (−)-**1a** and (+)-**1b**, whose superposition corresponds to the spectrum of the mixture (Figure 3).

The sequential crystallization (and thus purification) of both diastereomers from the solution was unexpected and raises some questions: Was the thermodynamic equilibrium reached or are we dealing with a more complex phenomenon that occurred out of equilibrium? What was the role of the solvent? The first question is very important for the understanding of any crystallization process. As previously mentioned, the reproducible formation of crystals of (−)-**1a** at very low concentrations can be explained by assuming the presence of a single eutectic point in the ternary phase diagram [**1a**/**1b**/solvent]. This behavior, combined with a long delay of crystallization (48 h), agrees with a classical crystallization process where the thermodynamic equilibrium conditions are reached. The use of toluene as the solvent is also another important factor to consider because this solvent is too bulky to enter into the cavity of (−)-**1a** and (+)-**1b**. Therefore, in toluene the chiral substituent may adopt a peculiar orientation with respect to the portals of the host, thus favoring the discrimination of both diastereomers. The formation of crystals of (+)-**1b** in the solution is more intriguing and still unclear since their formation cannot be easily explained from the same ternary phase diagram. As noticed for (−)-**1a**,

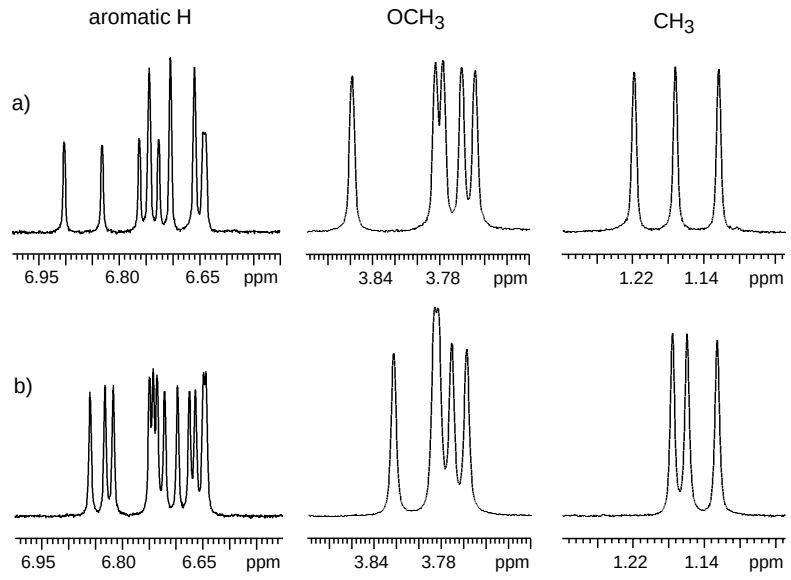


Figure 2. Part of the ^{1}H NMR spectra of diastereomers (−)-**1a** (a) and (+)-**1b** (b) in $CDCl_3$ at 20°C.

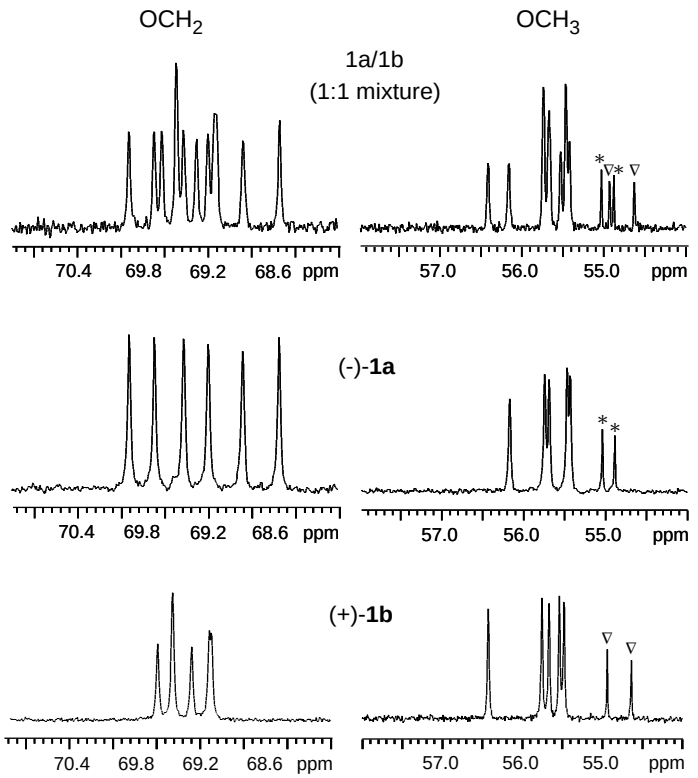
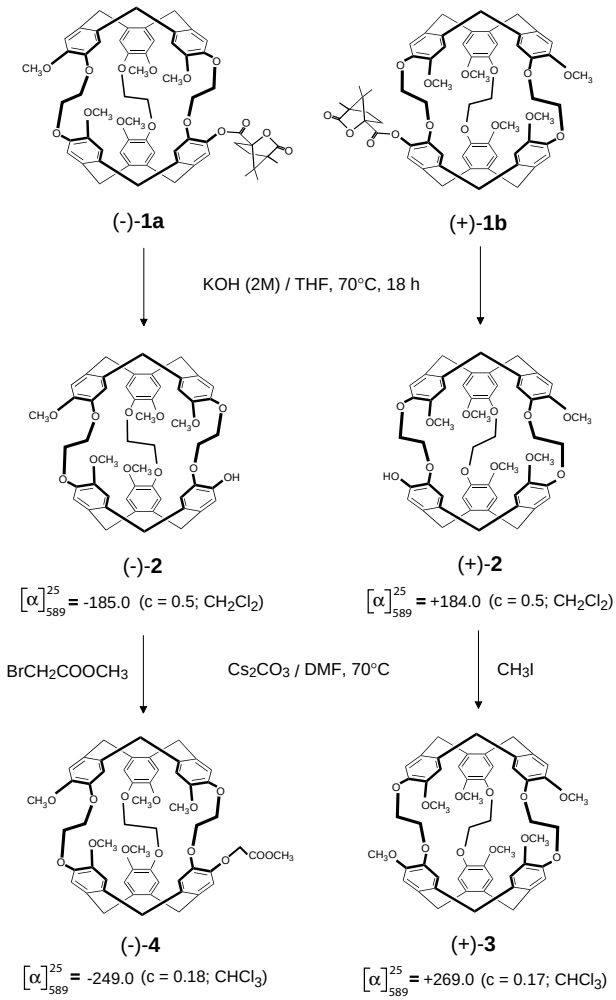


Figure 3. Part of the ^{13}C NMR spectra of (−)-**1a**, (+)-**1b**, and an equimolar mixture of **1a** and **1b** in $CDCl_3$ at 20°C. Stars and triangles are the quarternary carbons of the camphanic moiety.



Scheme 2. Preparation of enantiopure cryptophanes (−)-**2**, (+)-**2**, (+)-**3**, and (−)-**4** from (−)-**1a** and (+)-**1b**. THF = tetrahydrofuran, DMF = *N*,*N*-dimethylformamide.

the long delay of crystallization (48 h) would also favor a physical process where the thermodynamical conditions were reached. However, at this point we have not been able to rationalize the selective crystallization of (+)-**1b**, and additional experiments are needed to interpret properly its crystallization process.

Synthesis of resolved cryptophane-A and related compounds: In the first section we have described the synthesis and separation of cryptophane diastereomers (−)-**1a** and (+)-**1b**. They can now be utilized to prepare other novel cryptophanes after removal of the camphanic moiety *without any loss of optical activity*. This constitutes a significant advantage over the previous approach involving the synthesis of chiral cyclotriveratrilene units. Thus, enantiopure cryptophanol-A (−)-**2** and (+)-**2** were obtained by treatment of (−)-**1a** and (+)-**1b**, respectively, with KOH in THF solution (Scheme 2). The NMR spectra and R_f values were found to be identical with those of racemate **2**.[20] In addition, the optical rotations of the compounds recorded in $CHCl_3$ have the same magnitudes with opposite signs—within the range of the experimental error—as expected for a pair of enantiomers (Table 1). However, in the absence of X-ray crystal structure determinations for compounds (+)-**2**, (−)-**2**, and their precursors, their correct structures cannot be established unambiguously. Indeed, the introduction of a single hydroxy function lowers the symmetry of the cryptophane and complicates the attribution of the structure since both *syn* and *anti* cryptophanol-A are chiral compounds.

To clarify this point, cryptophanol-A (+)-**2** was allowed to react with methyl iodide in the presence of cesium carbonate in DMF to give cryptophane-A (+)-**3** in quantitative yield (Scheme 2). Its optical rotation, measured in $CHCl_3$, gave a positive rotation ($[\alpha]^{25}_{589} = +269$, $c = 0.17$) in good agreement with the previous values reported for the opposite enantiomer *anti* (−)-cryptophane-A.[23]

Table 1. Optical rotations $[\alpha]^{25}_{\lambda}$ (10^{-1} deg cm^2 g^{-1}) of cryptophanes **1**–**4** at 25 °C.[a]

Compd.	Solvent	Concn.[b]	$[\alpha]^{25}_{589}$	$[\alpha]^{25}_{577}$	$[\alpha]^{25}_{546}$	$[\alpha]^{25}_{436}$	$[\alpha]^{25}_{365}$
(−)-**1a**	$CHCl_3$	1.25	−161.0	−168.0	−194.0	−353.0	−658.0
(+)-**1b**	$CHCl_3$	1.00	+168.0	+177.0	+204.0	+392.0	+730.5
(−)-**2**	CH_2Cl_2	0.5	−185.0	−195.5	−226.5	−432.5	−772.0
(+)-**2**	CH_2Cl_2	0.5	+184.0	+194.0	+224.0	+433.0	+785.0
(+)-**3**	$CHCl_3$	0.17	+269.0	+284.0	+326.5	+626.5	+1152.0
(−)-**4**	$CHCl_3$	0.18	−249.0	−258.0	−296.5	−549.0	−1009.0

[a] Experimental errors are estimated to ±5%. [b] In grams per 100 mL.

This clearly demonstrates that cryptophanol-A **2** synthesized as described above, and therefore its precursors (the cryptophane bearing a single allyl moiety[20] and diastereomers (−)-**1a** and (+)-**1b**), were obtained as the *anti* isomers. The *syn* configuration would have led to the achiral *syn* isomer of **3** with no optical activity. Therefore, it becomes possible to assign unambiguously the absolute configuration of the (+)-cryptophane-A and other compounds studied herein (Scheme 2).

In an alternative procedure, cryptophane monoester (−)-**4** was prepared in 95% yield from cryptophanol-A (−)-**2** and methyl bromoacetate (Scheme 2). Recently, Spence et al. reported the synthesis of racemic **4** for the design of biosensors with xenon as the guest, and ^{129}Xe NMR was used to characterize the affinity of the parent hosts towards biological targets.[9] In such experiments, the use of optically pure cryptophanes would greatly simplify the NMR spectra and their interpretation by limiting the number of possible diastereomers. The reactivity of the hydroxy or ester group in optically pure (+)-**2**, (−)-**2**, and (−)-**4**, may be utilized to prepare further elaborated monofunctionalized cryptophanes. This method is an important step toward the design of novel chiral supramolecular systems containing cryptophanes (polymers, dendrimers) and their potential use as HPLC chiral stationary phases for the resolution of small neutral molecules such as halogenomethanes.

Circular dichroism spectroscopy of new cryptophanes 1–4: The chiroptical properties of new cryptophanes **1–4** were investigated by circular dichroism (CD) spectroscopy in various solvents. Collet, Gottarelli, and co-workers pioneered this work and reported the circular dichroism of C_3 cyclotriveratrylene derivatives and D_3 cryptophanes combined with a theoretical study based on the Kuhn–Kirkwood-coupled oscillator model.[19] They were able to interpret qualitatively the experimental CD spectra of a series of D_3 cryptophanes bearing different substituents or linkers for the two forbidden transitions that are easily accessible by UV spectroscopy and located in the ranges 230–260 and 275–300 nm, corresponding to the B_{1u} and B_{2u} regions of the benzene rings, respectively. In most cases, they could predict the sign of the observed Cotton effect as a function of the substituents and the conformation of the D_3 cryptophanes. They showed that the B_{1u} and B_{2u} transitions are the sum of three main polarized components (one A_2 and two nondegenerated E components) resulting from the interaction between chromophores (coupled oscillators). Additionally, they demonstrated that the observed Cotton effect is entirely governed by the polarization angles of the transition moments induced by the substituents.[24,25]

The CD spectrum of cryptophane-A (+)-**3** was recorded in 1,4-dioxane (a solvent too large to enter into the cavity). The spectrum showed two positive Cotton effects for the B_{2u} transition ($\Delta\varepsilon = 13.6$ at 299.0 nm and $\Delta\varepsilon = 22.1$ at 277.5 nm), whereas a positive Cotton effect ($\Delta\varepsilon = 40.9$ at 252.0 nm) and a negative one ($\Delta\varepsilon = -119$ at 238.5 nm) were observed for the B_{1u} transition. Another strong positive Cotton effect ($\Delta\varepsilon = 315$ at 217.5 nm) was observed at shorter wavelength for the allowed benzene transition ^1B according to Platt's notation (Table 2).[26] The CD spectrum of (+)-**3** is very similar (mirror image) to the spectrum of its enantiomer (−)-**3** previously reported. The values measured for the Cotton effect are somewhat higher than those reported for (−)-**3**, a fact suggesting a better enantiomeric excess of (+)-**3**. (A reported 95% *ee* was compared to 98–100% *ee* for (+)-**3** prepared as above.) The Kuhn–Kirkwood model predicts correctly the sign of the Cotton effect for the B_{1u} transition.[19] The interpretation of the sign of the Cotton effect for the B_{2u} transition is more difficult, since it was not possible to estimate accurately the splitting between the two E components, a splitting that was assumed to be very small.

Table 2. UV isotropic absorption spectra of **1–4** for the two forbidden transitions ^1L_a and ^1L_b (Platt's notation) in $CHCl_3$ and in 1,4-dioxane.[a]

Compd. no.	Solvent	B_{1u} (^1L_a)		B_{2u} (^1L_b)	
		λ [nm]	ε [M^{-1} cm^{-1}]	λ [nm]	ε [M^{-1} cm^{-1}]
(−)-**1a**	$CHCl_3$	242.5	26500	289.0	14000
(+)-**1b**	$CHCl_3$	242.0	25700	289.0	13600
(−)-**1a**[b]	1,4-dioxane	230.0 (s)	41500	289.0	12000
(−)-**2**	$CHCl_3$	242.5	24200	290.0	13600
(+)-**2**	$CHCl_3$	242.5	24200	290.0	13800
(+)-**3**[c]	1,4-dioxane	231.0 (s)	44100	290.0	13000
(−)-**4**	$CHCl_3$	243.0	25300	290.0	13500
(−)-**4**[d]	1,4-dioxane	230.0 (s)	44500	290.0	13000

[a] Experimental errors are estimated to be ± 5%. [b] $\lambda = 215.0$ nm; $\varepsilon = 66500$. [c] $\lambda = 215.0$ nm; $\varepsilon = 67500$. [d] $\lambda = 215.0$ nm; $\varepsilon = 67500$.

The CD spectrum of (−)-**4** recorded under the same conditions is an almost perfect mirror image of that of (+)-**3** (Figure 4, Table 3). We must notice that *anti* cryptophane-A (+)-**3** has D_3 symmetry and cryptophane monoester (−)-**4** has no symmetry axis due to the presence of the ester group. This suggests that the introduction of one methyl ester group in place of one methyl group causes a rather weak perturbation. The spectroscopic moment of the OCH_2COOCH_3 moiety is close enough in magnitude to that of the OCH_3 group ($OCH_3 > OCH_2COOCH_3$) to have only a little effect on the CD spectra.[14] The angles of polarization induced by these two substituents are very close in magnitude for both transitions, and the model describing the Cotton effect for compound (+)-**3** can thus be applied in a first approximation to compound (−)-**4**. In $CHCl_3$, a solvent which can enter into the cavity of (−)-**4**, the B_{1u} transition is more affected than the B_{2u} transition. Even though the sign of the Cotton effect is the same, the complexation of $CHCl_3$

Table 3. CD data for cryptophanes **2–4**.

(+)-**3** in 1,4-dioxane		(−)-**4** in 1,4-dioxane		(−)-**4** in $CHCl_3$		(−)-**2** in $CHCl_3$		(+)-**2** in $CHCl_3$	
λ [nm]	$\Delta\varepsilon$	λ [nm]	$\Delta\varepsilon$	λ [nm]	$\Delta\varepsilon$	λ [nm]	$\Delta\varepsilon$	λ [nm]	$\Delta\varepsilon$
217.5	315.0	217.5	−298.0	–	–	–	–	–	–
238.5	−119.0	238.5	128.0	238.5	87.3	238.5	67.1	238.5	−67.0
252.0	40.9	252.0	−34.8	253.0	−14.3	253.0	13.2	253.0	14.0
277.5	22.1	277.5	−11.2	278.0	−20.0	279.0	−32.0	279.0	30.7
288.5	–	288.5	2.97	292.0	3.5	293.5	1.4	293.5	−1.7
299.0	13.6	299.0	−6.21	302.5	−5.9	303.0	−8.6	303.0	8.2

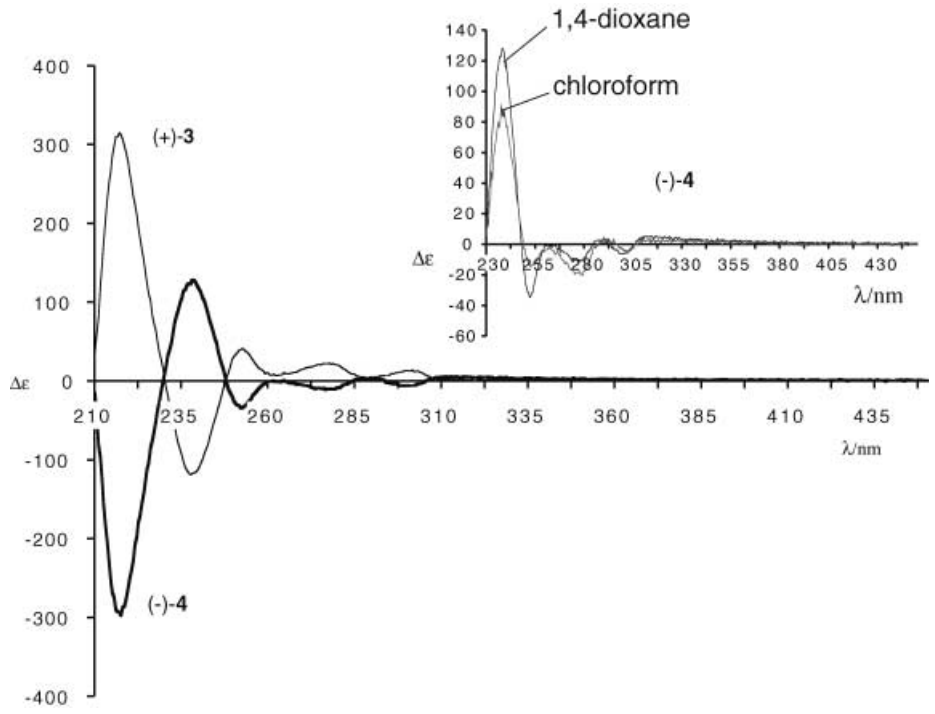


Figure 4. CD spectra of enantiopure cryptophanes (+)-**3** and (−)-**4** in 1,4-dioxane. The insert shows the CD spectra of (−)-**4** in 1,4-dioxane and $CHCl_3$.

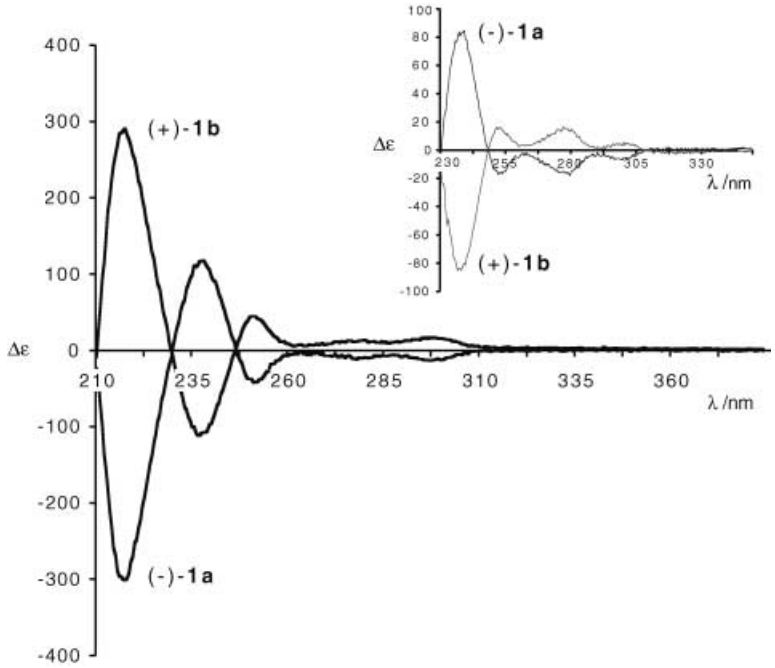


Figure 5. CD spectra of diastereomers (−)-**1a** and (+)-**1b** in 1,4-dioxane and in $CHCl_3$ (insert).

by (−)-**4** induces a decrease of the intensity of the B_{1u} transition. The effect of the complexation on the CD spectrum is still unclear but probably involves conformational changes of the ethylenedioxy linkers in the complex. It would be interesting to study the effects of the solvent on the CD spectra of cryptophanes, but the choice of solvent systems is very limited since only a few of them are able to dissolve cryptophanes or are sufficiently transparent to study the UV/Vis region of interest.

Similarly, CD spectra of cryptophanes (−)-**1a** and (+)-**1b** were recorded in chloroform and in 1,4-dioxane (Figure 5). The study of the chiroptical properties of these molecules is particularly interesting since the two substituents (OCH_3 and camphanic groups) induce opposite effects on the CD spectral bands. For instance, it was demonstrated that the OCH_3 group in (−)-**3** gives rise to a small positive angle and a small negative one for the two electric moments of the ^1L_b and ^1L_a transitions, respectively. On the other hand, the ester group is known to induce a positive angle with a larger magnitude for these two transitions.[19] It is therefore difficult to predict the sign of the B_{1u} (^1L_a) transition for compound (+)-**1b** with respect to (+)-**3**. The examination of the CD spectra of (−)-**1a** and (+)-**1b** recorded in 1,4-dioxane showed spectra which are mirror images—within experimental error—with similar Cotton effects to that observed for (+)-**3**. The sign for both transitions is unchanged; this indicates that the effect of the ester group is not strong enough to reverse the sign of the ^1L_a transition and that the structure of the CD bands is still largely dominated by the five OCH_3 substituents. In addition, we noticed that the transitions were more affected by changing the solvent from 1,4-dioxane to chloroform (Figure 5, Table 4).

The structure of the enantiomers of cryptophanol (−)-**2** and (+)-**2** is similar to that of (+)-**3** except that one OCH_3 group was replaced by an OH group. As expected, the CD spectrum of (−)-**2** recorded in chloroform is the mirror image of that of (+)-**2** (Figure 6, Table 3). In addition, the OH group is known to have a larger spectroscopic moment for the B_{2u} transition than OCH_3, and the induced polarization angles should be differ-

Table 4. CD data for diastereomers (−)-**1a** and (+)-**1b**.

(−)-**1a** in 1,4-dioxane		(+)-**1b** in 1,4-dioxane		(−)-**1a** in $CHCl_3$		(+)-**1b** in $CHCl_3$	
λ [nm]	$\Delta\varepsilon$	λ [nm]	$\Delta\varepsilon$	λ [nm]	$\Delta\varepsilon$	λ [nm]	$\Delta\varepsilon$
217.5	−302.0	217.5	290.0	–	–	–	–
238.5	117.0	238.5	−112.0	238.0	82.8	238.0	−85.1
252.0	−41.8	252.0	41.3	253.0	−15.7	252.5	16.2
278.0	−12.0	278.0	11.2	279.0	−16.8	278.0	15.3
298.0	−12.6	298.0	16.8	299.5	−6.9	301.0	4.9

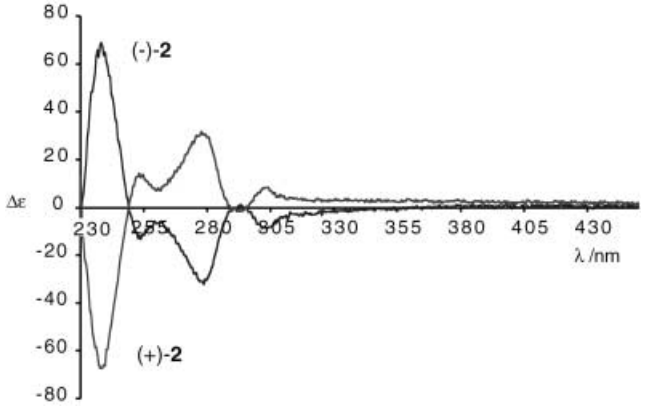


Figure 6. CD spectra of enantiopure cryptophanol-A compounds (−)-**2** and (+)-**2** in $CHCl_3$.

ent for this transition. Therefore, the CD spectra of (−)-**2** and (+)-**2** should be more sensitive to substitution than the ones observed for the related compound (−)-**4**. Experimentally we observed that the Cotton effect of the B_{1u} transitions is very similar in shape and intensity to that observed for compounds (−)-**1a**, (+)-**1b**, (+)-**3**, and (−)-**4** in the same solvent (Table 4). At longer wavelength the situation is somewhat different and the effect of substitution is more appreciable. Indeed, the sign of the Cotton effect remained the same for the B_{2u} transition, but a significant change in the shape and intensity of this transition was observed with respect to that of compounds (−)-**1a**, (+)-**1b**, and (−)-**4**. The intensity of the Cotton effect at 300 nm is strongly affected by the substitution and may result from the overlapping of the two E components with opposite signs.[19] Applying the theoretical model used for D_3 cryptophanes to these two enantiomers seems however questionable due to the changes observed in their CD spectra. Meanwhile, they provide interesting models for theoretical studies of the chiroptical properties of cryptophanes.

The CD spectra of the new optically active cryptophanes (−)-**1a**, (+)-**1b**, (−)-**2**, (+)-**2**, (+)-**3**, and (−)-**4** were compared to those of the previously published D_3 cryptophanes. For compounds **1**–**4** a change in the shape and intensity of the Cotton effect of the B_{2u} transitions was observed depending on the nature of the substituents attached onto the cryptophane hosts, whereas the B_{1u} transition was less affected. However, the Cotton effect of the two forbidden transitions in compounds (−)-**1a**, (+)-**1b**, and (−)-**4** is similar to that of compound (+)-**3**, a fact suggesting that the exciton model developed for D_3 cryptophanes can be applied in a first approximation.[19] The strong modifications observed in the CD spectra of enantiomers (−)-**2** and (+)-**2**, especially for the B_{2u} (^1L_b) transition, suggest a more complex interpretation, and the use of the former model is questionable.

Conclusion

We have described in this work a novel synthetic approach to obtain resolved cryptophanol-A based on the optical resolution of diastereomers (−)-**1a** and (+)-**1b** by crystallization. Optically pure (−)-**1a** and (+)-**1b** were obtained in moderate yield but the strategy used opens a new field of investigation to obtain chiral cryptophanes, which cannot be prepared easily with high enantiomeric excess by other methods. Enantiomers of cryptophanol-A (−)-**2** and (+)-**2** were easily recovered in high yields and with high enantiomeric excess ($ee = 98$–$100\,\%$) by hydrolysis of (−)-**1a** and (+)-**1b** under basic conditions. The advantages of the synthetic procedure reported here are obvious: 1) The resolved cryptophanols (−)-**2** and (+)-**2** bearing one free hydroxy function are starting compounds for the preparation of new enantiopure chiral cryptophanes. 2) More importantly, these new functionalized cryptophanes can now be prepared without any loss of optical activity whatever the experimental conditions used. For instance, cryptophane-A (+)-**3** was prepared as a model molecule to ascertain the absolute configuration of the cryptophanes described in this article. Cryptophane monoester (−)-**4**, of which the racemate has been used to build-up an elaborate host molecule for biological application,[9] was also synthesized and fully characterized. Even though the crystallization process is efficient, we believe that new derivatives allowing the separation of diastereomers by chromatographic techniques would be more suitable for the preparation of larger amounts of resolved cryptophanes. Finally, the chiroptical properties of enantiopure cryptophanes (−)-**1a**, (+)-**1b**, (−)-**2**, (+)-**2**, (+)-**3**, and (−)-**4** were investigated by CD spectroscopy. The effect of substitution on the B_{1u} and B_{2u} benzene transitions was experimentally established. These compounds provide interesting new models for explaining the CD spectra of molecules that have several different chromophores interacting with each other, and study of these compounds completes the fundamental work developed by Collet, Gotarelli, and co-workers for cryptophanes with D_3 symmetry.[19] The extension of this work towards larger cryptophanes like cryptophane-E is underway.

Experimental Section

General: Circular dichroism spectra were recorded at room temperature on a CD6 Jobin-Yvon dichrograph. Cells with a pathlength of 0.1 cm were used, and the instrument was routinely calibrated with an aqueous solution of (+)-10-camphorsulfonic acid. Inaccuracy on the mass sample

induces a 5% experimental error on the ε values, due to encapsulation of unknown guests into the cavity of cryptophane hosts. IR spectra were recorded on a Mattson 3000 FTIR spectrometer. UV spectra were recorded on a Jasco V-550 UV-Vis spectrophotometer with 10-mm cells. Optical rotations were measured on a Jasco P-1010 polarimeter with a 100-mm cell thermostated at 25°C. Mass spectra (HRMS, LSIMS) were performed by the Centre de Spectrométrie de Masse, University of Lyon, on a Thermo-Finnigan MAT 95XL spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity$^{\oplus}$ 500 spectrometer at 499.83 and 126.7 MHz, respectively. Chemical shift values (δ) were measured from Me_4Si (^{1}H, ^{13}C). Column chromatographic separations were carried out over Merck silica gel 60 (0.040–0.063 mm). Analytical thin-layer chromatography (TLC) was performed on Merck silica gel F-254 TLC plates. Melting points were measured on a Perkin-Elmer DSC7 calorimeter. The solvents were distilled prior to use: DMF from CaH_2, CH_2Cl_2 from $CaCl_2$, THF from Na/benzophenone, and NEt_3 from KOH. Camphanic acid chloride and Cs_2CO_3 were purchased from Acros; methyl bromoacetate was purchased from Prolabo and used without further purification.

Cryptophane 1 (mixture of diastereomers): Camphanic acid chloride (420 mg, 1.93 mmol) was added in one portion to a stirred solution of racemic cryptophanol **2** (850 mg, 0.97 mmol), DMAP (24 mg, 0.196 mmol), and triethylamine (6.8 mL), in CH_2Cl_2 (22 mL). The solution was stirred at 70°C for 48 h under argon. More camphanic acid chloride (420 mg, 1.93 mmol) was then added, and the solution was stirred for another 48 h until complete disappearance of the starting material as monitored by TLC (CH_2Cl_2/acetone (9:1)). The solvent was evaporated under vacuum, and the residue was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography on silica gel with CH_2Cl_2/acetone (9:1) as the eluent. The product was then washed with diethyl ether and recrystallized from $CHCl_3$/ethanol to yield pure **1** (895 mg, 87%) as a mixture of two diastereoisomers **1a** and **1b** in 1:1 ratio; ^{1}H and ^{13}C NMR spectra of **1** are the sum of the ^{1}H and ^{13}C NMR spectra of compounds **1a** and **1b**; HRMS (LSIMS): calcd for $C_{63}H_{64}O_{15}$ $[M]^+$: 1060.4245; found: 1060.4244; IR (KBr): $\tilde{\nu}$ = 2964–2935 (br.), 1785.8 (s), 1610, 1510 (s), 1477, 1460, 1450, 1398, 1313–1281 (s), 1269, 1213, 1188, 1144, 1086, 1049, 995, 933, 897, 742, 619 cm^{-1}.

Diastereoisomer 1a: Compound **1** (890 mg) was dissolved in hot toluene (220 mL) and the solution was filtered over filter paper and left at room temperature. After 48 h the crystalline material that formed was filtered off and recrystallized from chloroform/ethanol to give pure **1a** (130 mg, 15%); m.p. >300°C (decomp); ^{1}H NMR ($CDCl_3$, 20°C): δ = 6.90 (s, 1H; Ar), 6.83 (s, 1H; Ar), 6.76 (s, 1H; Ar), 6.74 (s, 2H; Ar), 6.73 (s, 1H; Ar), 6.71 (s, 2H; Ar), 6.66 (s, 2H; Ar), 6.64 (s, 1H; Ar), 6.639 (s, 1H; Ar), 4.645 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_a), 4.60 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_a), 4.59 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_a), 4.58 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_a), 4.57 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_a), 4.53 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_a), 4.27–4.34 (m, 1H; OCH_2), 4.19–4.00 (m, 11H; OCH_2), 3.86 (s, 3H; OCH_3), 3.785 (s, 3H; OCH_3), 3.780 (s, 3H; OCH_3), 3.76 (s, 3H; OCH_3), 3.75 (s, 3H; OCH_3), 3.445 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_e), 3.42 (d, ^2J(H,H) = 13.5 Hz, 2H; CH_e), 3.40 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_e), 3.39 (d, ^2J(H,H) = 13.5 Hz, 2H; CH_e), 2.54 (m, 1H; CH), 2.15 (m, 1H; CH), 1.99 (m, 1H; CH), 1.75 (m, 1H; CH), 1.22 (s, 3H; CH_3), 1.17 (s, 3H; CH_3), 1.12 (s, 3H; CH_3) ppm; ^{13}C NMR ($CDCl_3$, 20°C): δ = 178.14 (C=O), 165.99 (C=O), 150.11, 149.87, 149.62, 149.61, 149.28, 148.08, 147.00, 146.72, 146.54, 146.28, 146.25, 138.91, 138.73, 134.43, 134.27, 134.26, 134.19, 133.75, 133.06, 132.07, 131.71, 131.10 (2C), 130.92, 123.75, 121.87, 121.84, 121.14, 120.69, 120.32, 118.74, 113.90, 113.72, 113.52, 113.47, 113.43, 90.67, 69.91 (OCH_2), 69.68 (OCH_2), 69.41 (OCH_2), 69.19 (OCH_2), 68.87 (OCH_2), 68.53 (OCH_2), 56.17 (OCH_3), 55.74 (OCH_3), 55.69 (OCH_3), 55.47 (OCH_3), 55.42 (OCH_3), 55.04, 54.88, 36.66 ($C_{a,e}$), 36.30 ($C_{a,e}$), 36.09 (3C, $C_{a,e}$), 35.86 ($C_{a,e}$), 31.32, 28.83, 16.67 (CH_3), 16.53 (CH_3), 9.78 (CH_3) ppm; IR spectrum is identical to that of racemic **1**; elemental analysis: calcd for $C_{63}H_{64}O_{15}\cdot 0.2\,CHCl_3$: C 69.95, H 5.96; found: C 69.93, H 6.07.

Diastereoisomer 1b: After recovering **1a**, the remaining toluene solution was heated under reflux conditions, filtered over filter-paper, and left at room temperature. After the solution had stood for 48 h, new crystals were formed, which were recovered by filtration, washed with toluene (few mL) and diethyl ether (few mL), and recrystallized from chloroform/ethanol to give pure **1b** (90 mg, 10%); m.p. >300°C (decomp); ^{1}H NMR ($CDCl_3$, 20°C): δ = 6.86 (s, 1H; Ar), 6.83 (s, 1H; Ar), 6.82 (s, 1H; Ar), 6.75 (s, 1H; Ar), 6.74 (s, 1H; Ar), 6.735 (s, 1H; Ar), 6.72 (s, 1H; Ar), 6.695 (s, 1H; Ar), 6.675 (s, 1H; Ar), 6.665 (s, 1H; Ar), 6.65 (s, 1H; Ar), 6.645 (s, 1H; Ar), 4.64 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_a), 4.59 (d, ^2J(H,H) = 13.5 Hz, 2H; CH_a), 4.57 (d, ^2J(H,H) = 13.5 Hz, 2H; CH_a), 4.545 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_a), 4.33–4.25 (m, 1H; OCH_2), 4.21–4.00 (m, 11H; OCH_2), 3.82 (s, 3H; OCH_3), 3.79 (s, 3H; OCH_3), 3.78 (s, 3H; OCH_3), 3.77 (s, 3H; OCH_3), 3.76 (s, 3H; OCH_3), 3.46 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_e), 3.42 (d, ^2J(H,H) = 13.5 Hz, 2H; CH_e), 3.40 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_e), 3.39 (d, ^2J(H,H) = 13.5 Hz, 2H; CH_e), 2.57 (m, 1H; CH), 2.19 (m, 1H; CH), 2.01 (m, 1H; CH), 1.78 (m, 1H; CH), 1.18 (s, 3H; CH_3), 1.16 (s, 3H; CH_3), 1.125 (s, 3H; CH_3) ppm; ^{13}C NMR ($CDCl_3$, 20°C): δ = 177.90 (C=O), 165.98 (C=O), 150.00, 149.81, 149.61 (2C), 149.38, 148.38, 146.89, 146.59 (2C), 146.48, 146.36, 139.33, 138.83, 134.58, 134.43, 134.29, 134.25, 133.70, 133.02, 132.02, 131.79, 131.37, 131.12, 130.90, 123.52, 121.64, 121.50, 121.06, 120.91, 120.24, 119.97, 114.59, 113.67, 113.56 (2C), 113.48, 90.60, 69.61 (OCH_2), 69.47 (2C; OCH_2), 69.30 (OCH_2), 69.13 (2C; OCH_2), 56.42 (OCH_3), 55.75 (OCH_3), 55.66 (OCH_3), 55.53 (OCH_3), 55.48 (OCH_3), 54.94, 54.63, 36.57 ($C_{a,e}$), 36.29 ($C_{a,e}$), 36.11 (2C; $C_{a,e}$), 35.88 ($C_{a,e}$), 31.57, 29.02, 16.79 (CH_3), 16.64 (CH_3), 9.73 (CH_3) ppm; IR spectrum is identical to that of **1**; elemental analysis: calcd for $C_{63}H_{64}O_{15}$: C 71.34, H 6.08; found: C 71.26, H 6.23.

(−)-Cryptophanol (−)-2: A 2M solution of KOH (3 mL) was added to a solution of cryptophane **1a** (80 mg, 0.075 mmol) in THF (3 mL). The solution was stirred overnight at 70°C. THF was removed under vacuum. Water was then added and the resulting solution was acidified with concentrated HCl and extracted with CH_2Cl_2. The solution was washed once with water and the organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure to leave a residue that was purified by chromatography over silica gel (CH_2Cl_2/acetone (9:1)) to give **2** (60 mg, 90%), which was recrystallized from chloroform/ethanol; m.p. >300°C (decomp); ^{1}H NMR (CD_2Cl_2, 20°C): δ = 6.81 (s, 1H; Ar), 6.75 (s, 1H; Ar), 6.73 (s, 1H; Ar), 6.68 (s, 2H; Ar), 6.675 (s, 1H; Ar), 6.66 (s, 1H; Ar), 6.65 (s, 1H; Ar), 6.64 (s, 1H; Ar), 6.62 (s, 1H; Ar), 6.59 (s, 1H; Ar), 6.55 (s, 1H; Ar), 5.76 (s, 1H; OH), 4.625 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_a), 4.60 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_a), 4.55 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_a), 4.52 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_a), 4.49 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_a), 4.46 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_a), 4.42–4.08 (m, 10H; OCH_2), 3.95 (m, 2H; OCH_2), 3.92 (s, 3H; OCH_3), 3.79 (s, 6H; OCH_3), 3.75 (s, 3H; OCH_3), 3.74 (s, 3H; OCH_3), 3.38 (d, ^2J(H,H) = 13.5 Hz, 2H; CH_e), 3.37 (d, ^{2}J(H,H) = 13.5 Hz, 1H; CH_e), 3.36 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_e), 3.35 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_e), 3.33 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_e) ppm; ^{13}C NMR (CD_2Cl_2, 20°C): δ = 150.32, 150.18, 150.09, 150.02, 149.36, 147.22, 146.63 (2C), 146.36, 145.73, 145.12, 144.04, 135.28, 135.10, 134.84, 134.76, 133.28, 132.87, 132.83, 132.51, 132.38, 131.74, 131.54, 131.36, 122.47, 121.99, 121.81, 121.56, 118.87, 116.40, 116.16, 114.72, 114.56, 114.43, 114.18, 113.95, 69.78 (1C; OCH_2), 69.68 (1C; OCH_2), 69.54 (1C; OCH_2), 69.48 (1C; OCH_2), 69.00 (1C; OCH_2), 67.87 (1C; OCH_2), 57.74 (1C; OCH_3), 56.25 (2C; OCH_3), 56.04 (1C; OCH_3), 56.02 (1C; OCH_3), 36.65 (1C; $CH_{a,e}$), 36.51 (1C; $CH_{a,e}$), 36.37 (2C; $CH_{a,e}$), 36.28 (1C; $CH_{a,e}$), 36.04 (1C; $CH_{a,e}$) ppm; IR (KBr): $\tilde{\nu}$ = 3500 (br.), 2935 (br.), 1608, 1578, 1512 (s), 1475, 1460, 1446, 1398, 1280, 1211 (s), 1186, 1142, 1084 (s), 1047, 1032, 989, 895, 883, 854, 737, 617 cm^{-1}; elemental analysis: calcd for $C_{53}H_{52}O_{12}\cdot 0.9\,CHCl_3$: C 65.49, H 5.39; found: C 65.42, H 5.42.

(+)-Cryptophanol (+)-2: A solution of 2M KOH (3 mL) was added to a solution of cryptophane **1b** (40 mg, 0.038 mmol) in THF (2 mL). The solution was stirred overnight at 70°C. THF was removed under vacuum. Water was then added and the resulting solution was acidified with concentrated HCl and extracted with CH_2Cl_2. The solution was washed once with water and the organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure to leave a residue that was purified by chromatography over silica gel (CH_2Cl_2/acetone (9:1)) to give **2** (30 mg, 90%), which was recrystallized from chloroform/ethanol; m.p. >300°C (decomp); ^{1}H NMR, ^{13}C NMR, and IR spectra are identical to those of compound (−)-**2**; elemental analysis: calcd for $C_{53}H_{52}O_{12}\cdot 0.9\,CHCl_3$: C 65.49, H 5.39; found: C 65.67, H 5.49.

(+)-Cryptophane-A (+)-3:[19] An excess of methyl iodide (50 mg, 0.35 mmol) was added to (+)-cryptophanol-A (+)-**2** (30 mg, 0.034 mmol) and $CsCO_3$ (26 mg, 0.079 mmol) in dry DMF (2 mL). The solution was heated overnight at 70°C under argon and then poured into water. The crude

product was extracted twice with dichloromethane. The combined organic layers were washed with water and dried over Na_2SO_4. The solvent was removed under vacuum and the crude product was purified by chromatography over silica gel (CH_2Cl_2/acetone (9:1)) to give (+)-cryptophane-A (+)-**3** as a white glassy solid (30 mg, 100%), which was recrystallized from chloroform/ethanol; m.p. >300°C (decomp); ^{1}H NMR ($CDCl_3$, 20°C): δ = 6.74 (s, 6H; Ar), 6.66 (s, 6H; Ar), 4.58 (d, ^2J(H,H) = 14.0 Hz, 6H; CH_a), 4.5 (m, 12H; OCH_2), 3.78 (s, 18H; OCH_3), 3.39 (d, ^2J(H,H) = 14.0 Hz, 6H; CH_e) ppm; ^{13}C NMR ($CDCl_3$, 20°C): δ = 149.50, 146.47, 134.02, 131.46, 120.68, 113.55, 69.20 (OCH_2), 55.56 (OCH_3), 36.10 ($C_{a,e}$) ppm; IR (KBr): $\tilde{\nu}$ 2956–2862 (br.), 1608, 1576, 1512 (s), 1475, 1460, 1446, 1396, 1317, 1281, 1265 (s), 1211 (s), 1184, 1142 (s), 1084 (s), 1047, 1032, 989, 941, 885, 852, 746 (s), 619, 530 cm^{-1}; elemental analysis: calcd for $C_{54}H_{54}O_{12}\cdot 1.1\,CHCl_3$: C 64.68, H 5.41; found: C 64.64, H 5.51.

(−)-Cryptophane (−)-4: An excess of methyl bromoacetate (50 mg, 0.32 mmol) was added to (−)-cryptophanol-A (−)-**2** (50 mg, 0.057 mmol) and $CsCO_3$ (40 mg, 0.011 mmol) in dry DMF (2 mL). The solution was heated overnight to 70°C under argon and then poured in water. The crude product was extracted twice with water. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to leave a residue, which was purified by chromatograhy over silica gel (CH_2Cl_2/acetone (9:1)). The solvent was removed under vacuum to give (−)-**4** as a white glassy solid (53 mg, 98%), which was recrystallized from chloroform/ethanol; ^{1}H NMR (CD_2Cl_2, 20°C): δ = 6.71 (s, 1H; Ar), 6.705 (s, 1H; Ar), 6.70 (s, 1H; Ar), 6.69 (s, 1H; Ar), 6.672 (s, 3H; Ar), 6.669 (s, 1H; Ar), 6.66 (s, 2H; Ar), 6.655 (s, 1H; Ar), 6.65 (s, 1H; Ar), 4.61 (d, ^2J(H,H) = 15.5 Hz, AB, 1H; CH_2COO), 4.58 (d, ^2J(H,H) = 15.5 Hz, AB, 1H; CH_2COO), 4.56 (d, ^2J(H,H) = 13.5 Hz, 2H, CH_a), 4.545 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_a), 4.535 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_a), 4.525 (d, ^2J(H,H) = 13.5 Hz,1H; CH_a), 4.52 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_a), 4.33–3.99 (m, 12H; OCH_2), 3.84 (s, 3H; OCH_3), 3.80 (s, 3H; OCH_3), 3.795 (s, 3H; OCH_3), 3.79 (s, 3H; OCH_3), 3.785 (s, 3H; OCH_3), 3.76 (s, 3H; OCH_3), 3.38 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_e), 3.37 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_e), 3.365 (d, ^2J(H,H) = 13.5 Hz, 3H; CH_e), 3.34 (d, ^2J(H,H) = 13.5 Hz, 1H; CH_e) ppm; ^{13}C NMR ($CDCl_3$, 20°C): δ = 169.20 (1C; *C*OO), 149.82, 149.67, 149.63, 149.58, 149.40, 147.77, 147.60, 146.77, 146.70, 146.57, 146.52 (2C), 134.24, 134.13, 134.10, 134.08, 133.98, 133.95, 133.76, 131.76, 131.62, 131.51, 131.44, 131.22, 121.49, 121.21, 121.15, 120.74, 120.69, 120.10, 118.24, 114.62, 113.61, 113.58, 113.56, 113.53, 69.49 (1C; OCH_2), 69.42 (1C; OCH_2), 69.36 (1C; OCH_2), 69.31 (1C; OCH_2), 69.27 (1C; OCH_2), 69.00 (1C; OCH_2), 67.08 (1C; OCH_2COO), 56.12 (1C; OCH_3), 55.66 (2C; OCH_3), 55.58 (1C; OCH_3), 55.54 (1C; OCH_3), 52.10 (1C; $COOCH_3$), 36.17 (5C; $CH_{a,e}$), 36.00 (1C; $CH_{a,e}$) ppm; IR (KBr): $\tilde{\nu}$ = 2954–2862 (br.), 1759 (w), 1608 (w), 1576, 1510 (s), 1477, 1446, 1398, 1281 (s), 1211, 1186, 1144, 1086, 1049, 1032, 991, 895, 883, 852, 744, 619 cm^{-1}; HRMS (LSIMS): calcd for $C_{56}H_{56}O_{14}$ $[M]^+$: 952.3670; found: 952.3672; elemental analysis: calcd for $C_{56}H_{56}O_{14}\cdot 0.75\,CHCl_3$: C 65.38, H 5.44; found: C 65.48, H 5.53.

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