Synthesis of *C*-Alkylcalix[4]arenes. 4. Design, Synthesis, and Computational Studies of Novel Chiral Amido[4]resorcinarenes

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In extending our studies involving BF_3·Et_2O-catalyzed reaction of cinnamic acid analogues, we have shown that amido derivatives also can afford [4]resorcinarene octamethyl ethers. Subsequently, chiral monomeric amides, derived from the mixed anhydride of cinnamic acid and L- or D-valine, upon treatment with BF_3·Et_2O, yielded for the first time chiral amido [4]resorcinarenes in enantiomerically pure forms. Four stereoisomers were isolated, and three of them were attributed the flattened-cone, chair, and 1,2-alternate conformations. The major product was assigned a *novel* chairlike structure, namely flattened partial cone 1. The flattened-cone stereoisomer, which was indicated by molecular modeling studies to be the most stable, became the major product under more drastic experimental conditions. Chromatographic studies on chiral phases revealed that the above tetramers could be used for the enantiodiscrimination of racemic molecules.

Introduction

Molecular recognition by artificial enzymes is an important goal in current bioorganic chemistry. The selectivity of recognition is determined by a number of features—such as electrostatic or hydrophobic interactions, hydrogen bonds, *etc.*—that are incorporated by the molecular receptor to fit, in a multiple-points binding, the chemical characteristics of the substrate.[1,2]

Chiral recognition, one of the most sophisticated functions of enzymes, has been achieved in cyclodextrin-based artificial enzymes[3−6] but remains difficult to realize with other enzyme mimics.

Calixarenes[7] are synthetic macrocycles, endowed with a cavity-shaped architecture similar to that of cyclodextrins. Due to the fact that the basic 1_4-metacyclophane skeleton cannot be planar, there are several possibilities to construct intrinsically chiral calix[4]arenes.[8] Molecular asymmetry can be generated not only by different substituents but also by conformational isomerism. All possible chiral isomers, which can be derived from calix[4]arenes by modification of the phenolic groups, were systematically classified by Shinkai *et al.*[9] Chiral substituents can be also introduced directly into the calix[*n*]arene framework[9−11] either on the phenolic OH group or at the *p*-position of the phenolic ring.

Chiral calix[4]resorcinarenes have been recently prepared by a Mannich reaction of [4]resorcinarene in the cone conformation with formaldehyde and amino acids such as L-proline.[12]

Chiral calix[4]resorcinarene octamethyl ethers are not known, nor has the synthesis of a chiral [4]resorcinarene starting from a chiral monomer been reported.

In previous studies, we have shown that ethereal BF_3 catalyzes the conversion of (*E*)-2,4-dimethoxycinnamic acid esters to the corresponding mixture of [4]resorcinarene octamethyl ethers.[13] For instance, ethyl ester **1** gave the 1,2-alternate (**2a**), the flattened cone (**2b**), and the 1,3-alternate (**2c**) stereoisomers in the ratio **2a**:**2b**:**2c** of 2:3:1. The relationship between the nature of the ester and the stereoisomer distribution in the reaction mixture has been discussed in a previous publication.[14] It was of interest to establish whether a starting mono-

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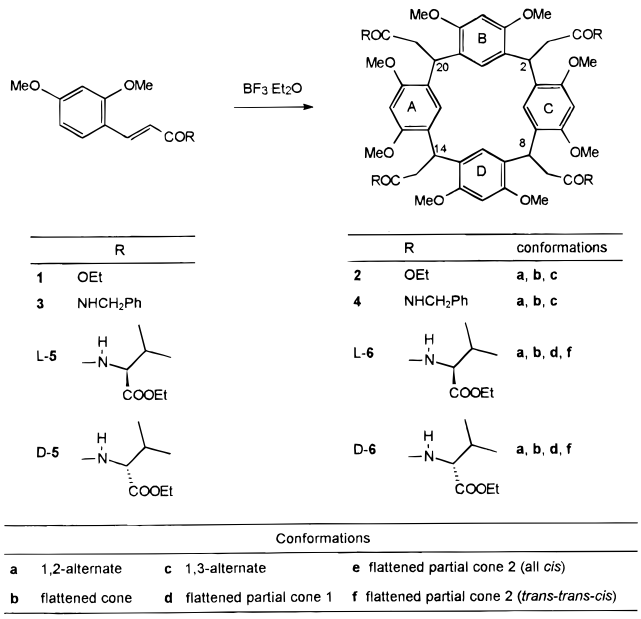


Figure 1. Tetramerization reaction of 2,4-dimethoxycinnamic acid amido derivatives.

mer incorporating an amide group could similarly afford the calixarene system nucleus. Successful results would then allow extension of this route to chiral end products since amides derived from chiral amino acids could be utilized.

With these objectives in mind, we investigated the $BF_3{\cdot}Et_2O$-catalyzed cyclization of amide **3** and found that the corresponding calixarenes bearing the 1,2-alternate, flattened-cone, and 1,3-alternate conformations were indeed obtained. It was therefore appropriate to extend our studies into the chiral series with amides derived from D- and L-valine. The present discussion describes our results directed to the first synthesis of chiral *C*-alkyl-[4]resorcinarenes, starting from a chiral unit.

Results and Discussion

Synthesis and Characterization. The monomer **3** was synthesized by treatment of (*E*)-2,4-dimethoxycinnamic acid in anydrous THF with diethyl chlorophosphate and benzylamine in the presence of K_2CO_3 under reflux for 2 h. Treatment of **3** with $BF_3{\cdot}Et_2O$ (1:6 molar ratio) under reflux for 2 h gave a mixture of tetramers in 60% overall yield. Three products (**4a**, **4b**, **4c** in the ratio 2:3:1) were purified by crystallization and column chromatography. On the basis of the similarity of their ^1H and ^{13}C NMR spectra with those of esters **2a**, **2b**, and **2c**, the three stereoisomers (Figure 1) were attributed the structures **4a (**1,2-alternate conformation with a *cis-trans-cis*—relative to C(2)—arrangement of the pseudoaxial side chains), **4b** (flattened cone conformation with an *all-cis* relative configuration of the pseudoaxial side chains), and **4c** (1,3-alternate conformation with the pseudoequatorial side chains in an *all-cis* position). The relative orientation of the side chains was confirmed by additional DIF NOE experiments.[14]

As expected from *C*-alkyl[4]resorcinarenes,[14] FAB MS spectra of **4a**−**c** showed a base peak corresponding to the loss of one side chain, whereas EIMS spectra were characterized by further losses of neutral benzylamine.

The above findings prompted us to synthesize chiral amido[4]resorcinarenes starting from the chiral unit L-**5**, obtained by coupling of the mixed anhydride of 2,4-dimethoxycinnamic acid with L-valine, the latter protected as the ethyl ester. The enantiomeric monomers D-**5** and the racemic (D,L-**5**) were also prepared by the same procedure starting from D-valine and D,L-valine, respectively. Both D- and L-**5** showed an ee >98% [^1H NMR after addition of Eu(fod)$_3$] or >99% by HPLC on CSP1 (*vide infra*).

The monomer L-**5** was converted into the expected mixture of macrocycles in a 75% overall yield by treatment with $BF_3{\cdot}Et_2O$ (see Experimental). Extensive chromatography of the reaction mixture afforded three optically active stereoisomeric tetramers $(MH]^+$ at *m*/*z* 1341 and $M - chain]^+$ at *m*/*z* 1154 in the FAB MS spectra) with a gross [1_4] metacyclophane structure **6** (Figure 1).

Compound L-**6b** showed the simplest ^1H NMR spectra (only one signal for each type of proton) and was attributed a flattened cone conformation. Notably, the methoxyl groups and the quaternary nonoxygenated aromatic carbons gave two signals in the ^{13}C NMR spectrum, thus showing the nonequivalence, *e.g.*, of C-1 and C-3 carbons due to the presence of a chiral center in the C-2 substituent. The influence of the chiral center on the C-25/C-28 or C-4/C-24 pair was not observable as two distinct lines.

The substituents in L-**6b** were *all cis* and pseudoaxial since DIF NOE experiments revealed the proximity of the methine and the methoxyl groups as well as that of the methylene group and the aromatic H_i protons.[14]

In the ^1H- and ^{13}C-NMR spectra of compound L-**6a** every carbon and every proton gave its own signal, thus not revealing any diagnostic symmetry.

On consideration of the presence in the ^1H NMR spectrum of two high-field signals (δ 2.24 and 2.02) attributable to the protons of the C-14 methylene group,[14] a 1,2-alternate structure can be proposed for L-**6a**. As confirmation of this, irradiation of the signal at 2.24 ppm in a DIF NOE experiment showed the proximity of the methylene with aromatic (H_i) protons at 6.80 and 6.43 (H-26/H-27), that is, *cis-trans-cis* configuration relative to C-2.

The most abundant isomer (45%) **6d** was assigned a novel conformation on the basis of the spectral data (Table 1). The compound revealed in the ^1H NMR spectrum three signals with an integrated intensity of 1:2:1 for the external (H_e) and internal (H_i) aromatic protons and two signals (2H:2H distribution) for the bridged methine protons. Accordingly, the distribution pattern of signals in the ^{13}C NMR spectrum suggested the presence of a plane of symmetry passing through two opposite nonequivalent aromatic rings (*e.g.*, A and C in Figure 1).

This statement is only a rationale since with the chiral side chains an "actual" plane of symmetry is not possible. The splitting patterns of the NMR signals of the aromatic framework are not significantly influenced by the distant chiral centers of the side chains and thus approximate the result that would be expected if a plane of symmetry were present.

The symmetry consistent with the distribution pattern of protonated carbon signals in **6d** can be associated with a flattened partial cone 1 geometry (C_s type), obtained by our previous molecular-modeling studies of *C*-alkyl-[4]resorcinarene.[14] Irradiation of the 2H signal at 6.92 ppm in a DIF NOE experiment showed the proximity of the equivalent H-25 and H-27 protons with both the C-2/

Table 1. ^{1}H- and ^{13}C-NMR Spectral Data of Compounds L-6d/D-6d in the Flattened-Partial Cone 1 Conformation[a]

position	δ_C	δ_H
1,21; 3,19	124.27, 124.07	
7,15; 9,13	122.74, 122.48	
2,20	33.19	5.04 (2H, dd, 9, 6)
8,14	33.16	4.99 (2H, t, 7)
4,18; 6,16	156.34, 156.31	
10,12; 22,24	156.14, 156.02	
5,17	96.17 (×2)	6.38 (2H, s)
11	95.69	6.44 (2H, s)
23	95.57	
25	127.62	6.45 (1H, brs)
26,27	126.95 (×2)	6.92 (2H, brs)
28	127.21	6.40 (1H, brs)
OMe	55.89	3.76 (3H, s)
	55.83 (×2)	3.90 (6H, s)
	55.77	3.74 (3H, s)
CH_2	41.69	2.75 (2H, dd, 15, 7)
		2.66 (2H, dd, 15, 9)
	41.63	2.77 (4H, d, 7)
CO	172.03	
	172.01	
NH		6.31 (2H, d, 8.5)
		6.11 (2H, d, 8.5)
CHN	57.04	4.35 (2H, dd, 8.5, 6)
	56.97	4.37 (2H, dd, 8.5, 6)
CH	31.32	1.84 (2H, dh, 7 × 6, 6)
	31.02	1.94 (2H, dh, 7 × 6, 5)
Me	18.59, 18.55	0.70 (9H, d, 7)
	17.76, 17.71	0.59 (3H, d, 7)
CO	171.82, 171.75	
OCH_2	60.77	4.09 (8H, m)
Me	14.19	1.23 (6H, t, 7)
	14.12	1.19 (6H, t, 7)

[a] Proton and carbon signals were correlated by a HETCOR experiment.

Table 2. Physical Data of Chiral *C*-Alkyl[4]resorcinarenes and Starting Monomers

compd	amino acid	conformation of the tetramers	mp (°C)	$[\alpha]_D$ ($CHCl_3$)	*c*
6a	D-valine	1,2-alternate	*a*	+77.4	0.16
6a	L-valine	1,2-alternate	*a*	−77.4	0.23
6b	D-valine	flattened cone	192−193	+41.0	0.12
6b	L-valine	flattened cone	194−195	−41.6	0.12
6d	D-valine	flattened partial cone 1	218−219	+23.0	0.30
6d	L-valine	flattened partial cone 1	219−220	−22.9	0.20
6f	L-valine	chair	*a*	−22.0	0.18
5	D-valine		112−113	−59.6	0.4
5	L-valine		112−113	+59.7	1.2

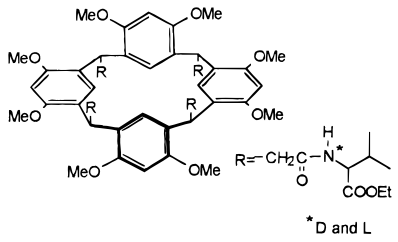
[a] Vitreous solid.

C-20 and C-8/C-14 methylene pairs, thus requiring the side chains to be *all-cis* and axial.

When the tetramerization reaction was repeated with the D-valine derivative **5** as the starting monomer, compounds D-**6a,b,d** were obtained and showed ^{1}H and ^{13}C NMR spectra identical with those of L-**6a,b,d**. Furthermore, the same absolute values, but of course opposite sign (Table 2), were observed in optical rotations for each couple of enantiomers.

Finally, treatment of the racemic monomer (D,L-**5**) with $BF_3{\cdot}Et_2O$ gave a very complex mixture of products that resisted chromatographic separation. Studies with these racemic products were discontinued.

Chromatographic Behavior of Chiral Calixarenes on HPLC Chiral Phases. Optical resolutions of inherently chiral calixarenes have been recently obtained by HPLC using both polymeric[15] and brush-type[16] chiral stationary phases. Here, we report the separation of the enantiomeric pairs of compounds **6a,b,d** on three different brush-type CSPs. CSPs 1−3 are known to afford facile resolutions of many racemates having different types and combinations of stereogenic elements and functionalities, the highest levels of enantioselective separations usually being observed for compounds that can simultaneously establish H-bond (or dipole−dipole) and aromatic−aromatic interactions with the stationary phase. Our chiral calixarenes, featuring the electron-rich aromatic nucleus and a series of H-bond donor/acceptor sites surrounding the macrocycle core, possess the required complementary functionalities and are thus expected to have high and different affinities for the above phases. For instance, when the product mixture from the reaction of L-**5** with $BF_3{\cdot}Et_2O$ was submitted to separation on chiral columns CSP 1, CSP 2, and CSP 3, it was possible to separate the chiral calixarenes L-**6a,b,d**. The analysis revealed the presence of another minor product (L-**6f**), which was in turn obtained by preparative TLC of column fractions selected on the basis of CSP chromatograms.



6f flattened partial cone 2

Figure 2. Amido[4]resorcinarene with flattened-partial cone 2 (chair) conformation.

An interesting feature in the ^{1}H NMR spectra of the new compound was the "absence" of signals for the methylene protons at room temperature. Heating to 60 °C led to the appearance of a broad signal centered at *ca.* 2.56 ppm, which by irradiation of the unique methine signal (t at 5.15 ppm) gave two broadened doublets at 2.61 and 2.51 ppm with a geminal coupling of *ca.* 15 Hz. These findings suggest a very rigid structure and a hindered rotation of the substituents.

Moreover, the distribution pattern of the signals for the methoxyl groups (2 signals) and aromatic protons and carbons (two signals for both CH_e and CH_i) in ^{1}H- and ^{13}C-NMR spectra is compatible with either a C_{2h} (flattened partial cone 2)[14] or D_{2d} (1,3-alternate) symmetry.

Irradiation of the signal at 2.56 ppm (at 60 °C) in a DIF NOE experiment revealed the proximity of the methylene group with both H_i protons. Conversely, the irradiation of the methine signal showed no effect on the aromatic protons.

On the basis of these results, a flattened-partial cone 2 structure, with all axial substituents having a *trans-trans-cis* configuration relative C-2, was attributed to compound L-**6f** (Figure 2). A similar structure, named chair, was attributed to the minor [4]resorcinarenes obtained from the reaction of resorcinol with heptanal and dodecanal.[17]

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The mixtures comprising the D-series (D-**6a,b,d,f**) were also separated on chiral columns CSP 1, CSP 2, and CSP 3. The best results in both the cases were obtained with CSP 3.

In order to fully establish the utility of this HPLC method in future studies relating to the separation of racemate calixarene mixtures, the D- and L-derived calixarenes were mixed to provide authentic samples of D,L-**6a,b,d,f**. The three phases shown in Scheme 2s (Supporting Information) were tested for their ability to separate the above racemic mixtures into the pure enantiomers. Pertinent chromatographic data are provided in the Supporting Information. All of the examined chiral phases show some degree of selectivity for the enantiomers; retention and enantioselectivity are largely dependent (although at present in unpredictable manner) on both the stationary-phase structure and analyte conformation, a finding that was expected considering the large differences in the spatial arrangement of the interaction sites among the four calixarenes derivatives. Thus, racemic compound D,L-**6a** is the only stereoisomer separated on the three phases, with the highest separation factor ($\alpha = 3.31$, corresponding to a $\Delta\Delta G \sim 0.7$ kcal/mol) found on CSP 3. Interestingly, while CSP 2 and 3 always select for the same amino acid configuration of the monomer and of the cyclic tetramers, CSP 1 preferentially retains the D enantiomer of the former and the L enantiomer of the latter.

Although the chiral tetramers are obtained in enantiomerically pure form, and therefore chromatography on chiral phases is of little interest from the analytical point of view in the present study,[18] examination of our chromatographic data in a reciprocal sense[19] suggests that the roles played by hosts and guests could be conveniently exchanged. For example, by covalent attachment of a homochiral calixarene to silica particles it should be possible to generate new, easily accessible enantioselective stationary phases with recognition ability toward aromatic substrates. Such HPLC phases should facilitate the screening of larger sets of racemic candidates for enantioselective binding. Work in this area is underway in our laboratories.

Molecular Modeling Studies

The conformational study of the [4]resorcinarene with general formula **6** (Figure 1) bearing four valine moieties, one for each side chain, has been performed.

The presence of amide groups in the side chains of compound **6** allows intramolecular H-bond formation, thereby distinguishing this compound from the [4]resorcinarenes with ester side chains previously studied by us.[13,14] For this reason, a complete conformational study of compound **6** becomes necessary, since the sequence of the steric energies of the different geometries of the calixarene nucleus can be substantially modified by the presence of nonbonded intramolecular interactions among the amide side chains. Nevertheless, it is necessary to point out that the presence in **6** of amide, instead of ester, functionalities makes in principle the conformational steric energies of this compound, calculated by molecular mechanics, less reliable due to the difficulty of accurate energetical evaluation of the H-bond contribution to the total conformational energy.

The conformational searching of compound **6** was performed by adding the amino acidic side chains at the methylene bridges of every minimum energy conformation of the [4]resorcinarene nucleus[13] and executing five separate random studies of the preferred spatial orientations of these moieties. The reliability of such a procedure of conformational analysis of resorcinarenes has been discussed previously.[13,14] According to that protocol the program BKM (generalized MM2 force field)[20−22] was chosen in a first attempt to carry out statistical searches on the side chains of **6a**−**e**. In order to reduce the number of rotatable bonds of the side chains, the four carbethoxy residues of the valine moieties were replaced with four carbomethoxyl groups. We were confident that the computational results were not dependent on these minor structural modifications.

A further Monte Carlo conformational search was performed on the side chains of **6a**−**e** with the program MacroModel[22] with the aim to take into account the contribution of intramolecular H-bond formation to the total steric energy in a more appropriate manner. The AMBER*[23] force field, as implemented in the version 4.0 of this program, was selected for this purpose for two main reasons: first, the possibility to compare the results obtained in the search carried out with the generalized MM2 force field implemented in BKM with those obtained using AMBER*, a force field expecially suited to model molecular systems possessing H-bond donor and acceptor groups, and second, the finding that, among the different force fields implemented in MacroModel, only AMBER* allowed reliable parameters to be applied in this study. It is well known that conformational energy differences and even more geometries may not be accurate if low-quality generalized parameters are in use.

Although the solvent can play a crucial role when, as in calixarenes, there is a cavity in the molecular structure, two observations convinced us to neglect the study of the solvent effects on the conformational preferences of **6**: first, the lack of high-quality reliable parameters in the MacroModel force field OPLS*,[24] usually used to calculate the steric energy of molecules in a continuum solution model,[25] when it was applied to **6**, and second, the molecular dimensions of **6** (20 rotatable bonds) that prevented us from applying an explicit solvatation model, because very time-consuming searches were required even without explicit solvent molecules added to the system.

The results of the conformational study of compound **6** are summarized in Tables 3 and 4. In Table 3 are reported the global steric energies (kcal/mol) of the lowest energy conformations found in the searches performed

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(18) However, we do use HPLC on CSP 3 to rapidly determine stereoisomer ratios in crude mixtures, taking advantage of the large diastereoselectivity often displayed by brush-type phases.

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(20) The BKM Program is available from Prof. Kosta Steliou, Boston University, MA.

(21) In this conformational study the BAKMDL Program has been substituted by the BKM Program. The latter one is the Unix version of BAKMDL and maintains the force field and the capabilities of that program.

(22) MacroModel V4.0: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

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Table 3. Steric Energies of MM2-Minimized and AMBER*-Minimized (All-Atoms and United-Atoms Charge Sets in MacroModel) Conformations of *C*-Alkyl[4]resorcinarenes

	steric energy (kcal/mol)		
conformation	MacroModel AMBER* all-atoms	MacroModel AMBER* united-atoms	BKM
6b (flattened cone)	−4.8	−11.2	62.2
6a (1,2-alternate)	−0.4	−8.4	68.5
6d (flattened partial cone 1)	not found[a]	−4.2	77.4
6e (flattened partial cone 2)	2.8	not found[b]	75.1
6c (1,3-alternate)	7.0	0.9	76.7

[a] The exhaustive reminimization of the geometries collected in the SPMC AMBER* all-atoms searches on **6d** gave the flattened partial cone 2 (**6e**) minimum energy conformation. [b] The exhaustive reminimization of the geometries collected in the SPMC AMBER* united-atoms searches on **6e** gave the flattened partial cone 1 (**6d**) minimum energy conformation.

on **6a**−**e** with both BKM and MacroModel (all-atoms and united-atoms AMBER*). Table 4 shows the contributions of bonded and nonbonded intramolecular interactions to the steric energies found in the AMBER* all-atoms search.

The BKM analysis yielded energy values of **6a**−**e** distributed in a large range but did not find a substantial energy difference between the flattened partial-cones and the 1,3-alternate conformations. The MacroModel analyses, on the contrary, clearly indicate that the 1,3-alternate geometry of the calixarene nucleus corresponds to the less stable conformation of compound **6**.

Regardless of which of the two input geometries (**6d** or **6e**) the search was initiated with, the Monte Carlo conformational analysis always found both of the flattened partial-cone geometries among the output structures collected within 25 kJ/mol energy window. The following exhaustive reminimization of these structures with AMBER* all-atoms and AMBER* united-atoms force fields gave **6d** and **6e**, respectively, as the minimum energy conformation of the flattened partial-cone geometry (Table 3). This result is due to different evaluations of the relative steric energies performed by the two force fields.

As shown in Table 4, the steric energy differences among the studied geometries of **6** can be ascribed to a balance between bonded and nonbonded interactions. The disposition in 3D space of the side chains in the flattened cone and 1,2-alternate geometries of the calixarene nucleus appears to be favorable for the optimization of the intramolecular H-bonds (see Figure 3). By contrast, in the flattened partial cone and in the 1,3-alternate geometries the optimization of the H-bonds causes a distortion of the calixarene nucleus, as indicated by the bonded terms of the steric energy (Table 4), which disfavors these conformations with respect to the previous ones. This effect is even stronger for the 1,3-alternate geometry.

Due to the new experimental findings about the stereochemistry of the side chains of compound **6f** (*trans-trans-cis* instead of *all-cis* as in the flattened partial-cone 2 structure **6e**), a further MacroModel-AMBER* conformational analysis was performed on this compound.

The steric energies of the lowest-energy conformation found in this search are comparable to the values reported in Table 4 (−0.1 and −9.1 kcal/mol, respectively). The contributions of the bonded and nonbonded intramolecular interactions to the steric energy are listed in Table 5. Both AMBER* all-atoms and AMBER* united-atoms calculations found a very low steric energy for **6f** justifying its obtainment as one of the products of the synthesis.

Conformational Studies

According to the relative orientation of the substituents at the methylene bridges of the [4]resorcinarene skeleton **6** (Figure 3), the isomers **6b** and **6d** (cone and flattened partial cone 1 conformations), possessing an *all-cis* orientation of the side chains, are conformationally isomeric, whereas the isomer **6a** (1,2-alternate conformation with *cis-trans-cis* relative configuration of the side chains) and the isomer **6f** (chair conformation with *trans-trans-cis* relative configuration of the side chains) have a diastereomeric relationship with **6b** and **6d**.

The sequence of stabilities (in terms of steric energy) derived from the molecular modeling studies, that is, **6b** > **6a** ∼ **6f** > **6d**, was largely different from the order of decreasing yields, that is, **6d** > **6a** > **6b** > **6f**. The discrepancy could be explained if we assume that **6d** was the kinetic product, whereas **6b** was the thermodynamic one. It could thus be expected that **6d** may be converted in the more stable conformational isomer **6b** by heating. However, when L-**6d** was heated in refluxing $CHCl_3$ for 8 h, no conversion was detected and L-**6d** remained stable. Analogous results were obtained with all the other stereoisomers. On the other hand, inspection of CPK molecular models revealed that in each stereoisomers all the side chains are located in a crowded region of the [4]resorcinarene and would suffer in any conformational change a severe unfavorable steric interaction with the methoxyl groups of two adiacent aromatic rings. Conversely, an interconversion could take place when at least two covalent bonds are broken.[14,26] In order to provide additional information, we performed a series of experiments, in which each stereoisomer was treated with an excess of $BF_3{\cdot}Et_2O$. The reaction mixtures were maintained under reflux for 6 h and, after workup, were partially purified by silica gel column chromatography. The ^1H NMR spectra of the total mixture of tetramers were analyzed in comparison with those of the single starting calix[4]resorcinarenes to establish in a semiquantitative way (by integration of selected signals) which ones were present. The results, summarized in Table 5, showed that stereoisomers L-**6d** and L-**6f** gave the thermodynamic isomer (L-**6b**) as the major product (experiments 3 and 4). Under similar conditions, the isomer L-**6a** reacted only partially to give a mixture of L-**6d** and L-**6b** in a 2:1 ratio (experiment 1). Finally, L-**6b** was recovered almost unchanged (experiment 2).

In summary, these findings indicate the flattened-cone conformation to be the thermodynamically most stable product in agreement with the results of molecular modeling calculations. As a confirmation, treatment of monomer L-**5** with a large excess of $BF_3{\cdot}Et_2O$ for 12 h (Table 5, experiment 5) gave a mixture in which L-**6b** was predominant. Notably, the pure product L-**6b** showed no racemization ($[\alpha]_D = +40.5$, see Table 2).

Our experiments also revealed that [4]resorcinarenes L-**6a** and L-**6d** are in equilibrium, since they are converted into each other, but by more drastic conditions afford finally L-**6b**. Also, the minor stereoisomer L-**6f** was

(26) Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663.

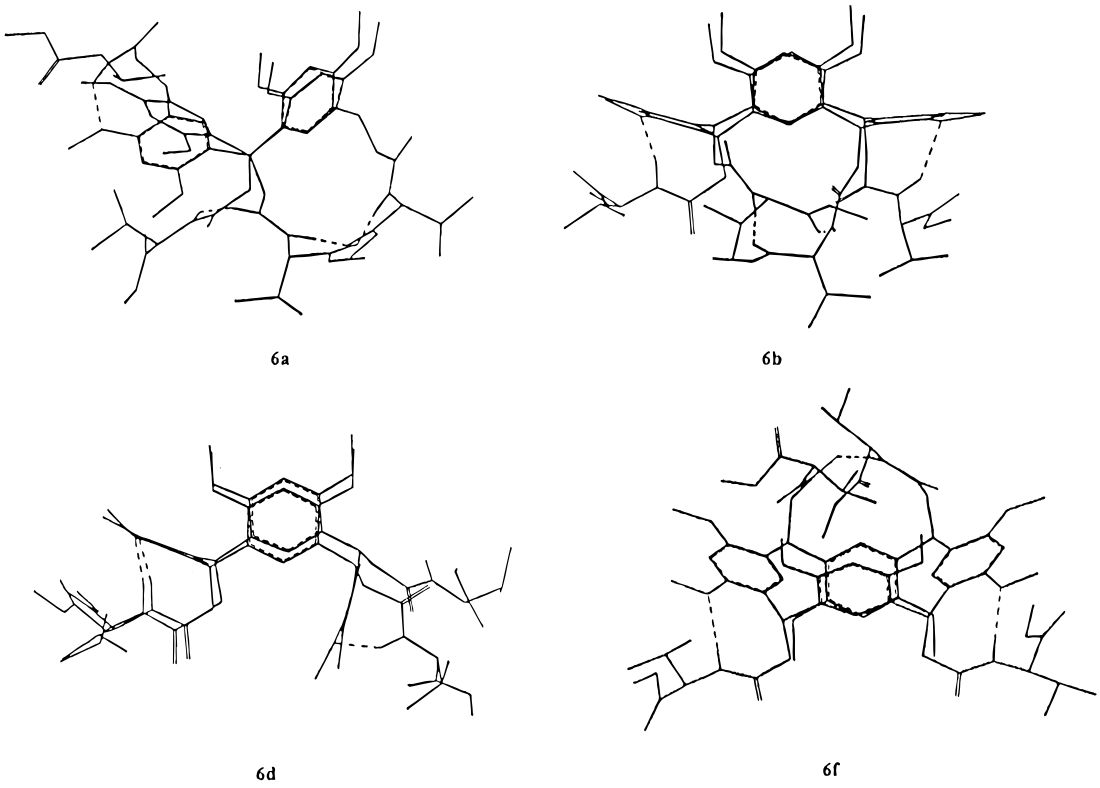

Figure 3. Minimized conformation of **6** *via* MacroModel AMBER* all-atoms calculations (dotted lines represent hydrogen bonds).

Table 4. Contributions of Bonding and Nonbonding Intramolecular Interactions to the Steric Energies of the AMBER*-Minimized (All-Atoms Charge Sets in MacroModel) Conformations of the C-Alkyl[4]resorcinarenes 6a−d (Table 3) and 6f

	steric energy (kcal/mol)					
conformation	stretching	bending	torsion	impr tors	electrost	van der Waals
6b (flattened cone)	4.4	20.1	25.4	0.3	−53.9	−1.1
6a (1,2-alternate)	4.9	22.1	20.6	0.2	−48.2	0.0
6d (flattened partial cone 1)	4.4	22.7	29.7	0.5	−56.7	2.2
6c (1,3-alternate)	4.4	26.9	32.8	0.3	−52.8	−4.6
6f (chair)	4.6	21.8	20.0	0.1	−49.5	2.9

Table 5. Summary of Reactions with an Excess of $BF_3{\cdot}Et_2O$ (1:400 Molar Ratio) of L-Valinamido [4]Resorcinarenes

exp	substrate	time (h)	major product(s)	minor product(s)
1	L-**6a**	6	**6b**, **6d**[a]	
2	L-**6b**	6	**6b**	**6d**
3	L-**6d**	6	**6b**	**6a**
4	L-**6f**	6	**6b**	**6d**
5	L-**5**	12	**6b**	**6a**, **6d**

[a] 40−45% of **6a** unreacted.

shown to be in equilibrium with L-**6d** and to give L-**6b** as final product. These equilibria require that at least two C−C bonds are cleaved before recombination can give the other isomer.

Conclusions

The experimental results obtained in the Lewis acid-catalyzed cyclization of chiral cinnamic acid amide analogues afford a novel and direct synthetic route to chiral [4]resorcinarenes octamethyl ethers.

A [4]resorcinarene with the novel flattened-partial-cone 1 conformation was isolated for the first time from the reaction mixture together with three other stereoisomers (1,2-alternate, flattened cone, and chair[17]).

The molecular modeling studies suggest that hydrogen bond formation could be the driving force of the reaction and indicate that the flattened-cone stereoisomer **6b** is the thermodynamic sink. Compound **6b**, which is formed as minor product in kinetic condiction, becomes the main component of the reaction mixture under more drastic conditions (higher amount of $BF_3{\cdot}Et_2O$).

These results, in agreement with those previously obtained by us[13,14] and by other authors,[17,26] suggest that the length and the steric hindrance of the side chains play an important role in the stereoselectivity of the reaction, when it is carried out under kinetic conditions. Moreover, the above tetramerization reaction also revealed a high reproducibility since each pair of enantiomers showed the same absolute value of optical rotation.

Although the chiral [4]resorcinarenes were obtained in enantiomerically pure form, chromatographic studies on chiral phases revealed that the above tetramers could be used, in future studies, for the enantiodiscrimination of racemic molecules bearing 3,5-dinitrobenzoylamido substituents.

Experimental Section

Melting points are uncorrected. NMR spectra, in $CDCl_3$, are referred to TMS (0.00 ppm). FAB-MS were obtained using a thioglycerol matrix.

(*E*)-*N*-Benzyl-2,4-dimethoxycinnamamide (3). To a solution of (*E*)-2,4-dimethoxycinnamic acid (2.0 g, 9.6 mmol) and

distilled Et_3N (3.0 mL, 21.4 mmol) in anhydrous THF (60 mL) was added a solution of diethyl chlorophosphate (2.0 g, 11.7 mmol) in anhydrous THF (15 mL) slowly under N_2 atmosphere. The mixture was stirred for 2 h at room temperature, filtered, and added dropwise to a solution of benzylamine (1.4 g, 13.3 mmol) and Et_3N (3.0 mL, 21.4 mmol) in anhydrous CH_2Cl_2 (107 mL) under N_2. The reaction mixture was stirred for 2 h at room temperature, concentrated, and extracted with an aqueous solution of 10% Na_2CO_3. The organic phase was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue gave by crystallization from *n*-hexane/ EtOAc, 3:2, compound **3** (1.7 g, yield 60%), as white needles, mp 139−40 °C. ^{1}H- and ^{13}C-NMR spectra are provided in Supporting Information.

2,8,14,20-Tetrakis(benzylamido)[4]resorcinarenes (4a−c). To a solution of the (*E*)-*N*-benzyl-2,4-dimethoxycinnamamide (0.3 g, 1 mmol) in $CHCl_3$ (6 mL) was added $BF_3{\cdot}Et_2O$ (0.7 mL, 5 mmol), and the mixture was left under reflux and stirring for 2.5 h. The reaction mixture was poured into ice−water and left under stirring overnight at room temperature. Column chromatography (on silica gel eluting with CH_2Cl_2−EtOAc−MeOH, 90:7:3) and crystallization (from acetone) gave [4]resorcinarenes **4a** (64 mg, 21%), **4b** (97 mg, 32%), and **4c** (30 mg, yield 10%).

Compound **4a** (1,2-alternate conformation): vitreous solid; ^{1}H- and ^{13}C-NMR spectra are provided in the Supporting Information; EIMS *m*/*z* (rel int) 1188 $[M]^+$ (100), 1040 $[M - CH_2CONHCH_2Ph]^+$ (73), 933 $[1040 - H_2NCH_2Ph]^+$ (21), 824 $[933\text{-}H_2NCH_2Ph]^+$ (38). Anal. Calcd for $C_{72}H_{76}N_4O_{12}$: C, 72.69; H, 6.44; N, 4.71. Found: C, 72.67; H, 6.45; N, 4.70.

Compound **4b** (cone conformation): mp 241−2 °C; ^{1}H- and ^{13}C-NMR spectra are provided in the Supporting Information; EIMS *m*/*z* (rel int) 1188 $[M]^+$ (48), 1040 $[M - CH_2CONHCH_2Ph]^+$ (41), 933 $[1040 - H_2NCH_2Ph]^+$ (16), 824 $[933 - H_2NHCH_2Ph]^+$ (100). Anal. Calcd for $C_{72}H_{76}N_4O_{12}$: C, 72.69; H, 6.44; N, 4.71. Found: C, 72.58; H, 6.51; N, 4.65.

Compound **4c** (1,3-alternate conformation): mp 286−7°C; ^{1}H- and ^{13}C-NMR spectra are provided in the Supporting Information; EIMS *m*/*z* (rel int) 1188 $[M]^+$ (96), 1040 $[M - CH_2CONHCH_2Ph]^+$ (100), 933 $[1040 - H_2NCH_2Ph]^+$ (17), 824 $[933\text{-}H_2NCH_2Ph]^+$ (33). Anal. Calcd for $C_{72}H_{76}N_4O_{12}$: C, 72.69; H, 6.44; N, 4.71. Found: C, 72.64; H, 6.50; N, 4.62.

D-Valine Ethyl Ester Hydrochloride. To absolute EtOH (20 mL), cooled to −5 °C, was added $SOCl_2$ (1.0 mL, 1.62 g, 13.6 mmol) over 5 min. This mixture was then cooled to −5 °C, and D-valine hydrochloride 1.90 g (12.4 mmol) was added. The solution was stirred for 2 h at room temperature, heated under reflux for 2 h, and then cooled to rt. Removal of the solvent *in vacuo* afforded the title compound (yield 80%): $[\alpha]_D = -6.7$ ($c = 2$, H_2O); mp 102−105 °C.

***(E)-N*-[1-(Carboxyethyl)-2-methylpropyl]-2,4-dimethoxycinnamamide (L-5, D-5).** To a solution of (*E*)-2,4-dimethoxycinnamic acid (1 g, 4.8 mmol) in dry THF (40 mL) under N_2 were added distilled Et_3N (1.5 mL, 10.7 mmol) and diethyl chlorophosphate (0.85 mL) in dry THF (1 mL). The resultant solution was maintained at 30 °C for 2 h, after which time was added, dropwise, a solution of the appropriate valine ethyl ester hydrochloride (1.6 g, 4.8 mmol) in dry THF (5 mL), and the mixture was stirred at 30 °C for a further 3 h. The reaction mixture was concentrated *in vacuo* and diluted with aquous $NaHCO_3$ solution. The aqueous layer was extracted with $CHCl_3$ and then acidified with concentrated HCl and reextracted with $CHCl_3$. The pooled organic layers were dried over Na_2SO_4 and evaporated. Silica gel chromatography (CH_2Cl_2:EtOAc, 95:5) of the residue yielded 1.2 g (75%) of the amide **5**. ^{1}H and ^{13}C-NMR and MS spectral data are provided in the Supporting Information.

2,8,14,20-Tetrakis(valinamido)[4]resorcinarenes. To a solution of L-**5** (1 mmol, 335 mg) in $CHCl_3$ (5 mL) was added $BF_3{\cdot}Et_2O$ (6 mmol, 0.72 mL). The mixture was stirred at reflux for 1.50 h. The reaction mixture was quenched with ice and water and stirred at room temperature overnight. The solution was extracted with CH_2Cl_2, and the combined organic layers were washed with H_2O and dried with Na_2SO_4. Evaporation of the solvent and purification by column chromatography eluting with CH_2Cl_2/EtOAc/MeOH mixtures afforded L-**6a** (100 mg, yield 30%. Anal. Calcd for $C_{72}H_{100}N_4O_{20}$: C, 64.44; H, 7.52; N, 4.18. Found: C, 64.38; H, 7.58; N, 4.20); L-**6b** (27 mg, 8%. Anal. Calcd for $C_{72}H_{100}N_4O_{20}$: C, 64.44; H, 7.52; N, 4.18. Found: C, 64.26; H, 7.65; N, 4.12); L-**6f** (10 mg, 3%. Anal. Calcd for $C_{72}H_{100}N_4O_{20}$: C, 64.44; H, 7.52; N, 4.18. Found: C, 64.28; H, 7.55; N, 4.21); and L-**6d** (114 mg, 34%. Anal. Calcd for $C_{72}H_{100}N_4O_{20}$: C, 64.44; H, 7.52; N, 4.18. Found: C, 64.30; H, 7.64; N, 4.16). The minor product **6f** was obtained by preparative TLC (CH_2Cl_2:EtOAc:MeOH, 90:7:3) of enriched fractions selected on the basis of CSPs chromatograms. The reaction of D-**5** with $BF_3{\cdot}Et_2O$ gave comparable results, but compound D-**6f** was not isolated

Compounds **6a,b,d,f** gave very similar FAB MS spectra. A typical fragmentation (**6d**) is reported: 1341 $[MH]^+$ (78), 1340 $[M]^+$ (100), 1454 $[M - chain]^+$ (96), 981 (19), 808 (9).

Reaction of L-Valine [4]resorcinarene with an Excess of $BF_3{\cdot}Et_2O$. In a typical experiment, to a solution of L-valine [4]resorcinarene (27 mg, 2×10^{-2} mmol) in $CHCl_3$ (5 mL) was added $BF_3{\cdot}Et_2O$ (0.96 mL, 8 mmol). Standard workup gave a residue that was partially purified by silica gel column chromatography (CH_2Cl_2:EtOAc:MeOH, 90:7:3) to give the mixture of tetramers.

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Supporting Information Available: Tetramerization reactions of 2,4-dimethoxycinnamic acid amido derivatives (Scheme 1s); ^{1}H- and ^{13}C-NMR and MS spectral data of monomers **3** and D-**5**/L-**5**; ^{1}H- and ^{13}C-NMR spectra of *C*-alkyl-[4]resorcinarenes **2a**, **4a**, D-**6a**/L-**6a** (1,2-alternate, Tables 1s and 2s), **2b**, **4b**, D-**6b**/L-**6b** (flattened-cone, Table 3s), and **2c**, **4c**, D-**6f**/L-**6f** (1,3-alternate and chair, Table 4s). Chiral phases used for enantiodiscrimination studies (Scheme 2s) and separation of the racemic mixture of valinamido calix [4]resorcinarenes (Table 5s). Details on molecular modeling studies (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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