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En route to inherently chiral tetraoxacalix[2]arene[2]triazines

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Abstract—This paper describes our attempts to synthesize inherently chiral heteroatom-bridged calixaromatics. Based on a stepwise fragment-coupling approach using a chiral 3,5-dihydroxybenzamide or benzoate, 2,4-dihydroxyacetophenone, and cyanuric chloride as reactants, chiral tetraoxacalix[2]arene[2]triazine derivatives **16** and **17** were synthesized in good yields. Subsequent macrocyclic condensation with a diamine **6** furnished efficiently the pairs of diastereomers of inherently chiral tetraoxacalix[2]arene[2]triazine azacrowns **18** and **19**.

1. Introduction

Owing to their easy availability, interesting conformational and cavity structures, and versatile recognition properties and functions, calix[*n*]arenes constitute an important and indispensable tool of supramolecular chemistry.[1] While development of the synthesis of diverse calix[*n*]arene derivatives[2] and other calixaromatics[3] continues, there is also a fast growing interest in the construction of heteroatom-bridged calixaromatics.[4] Compared to conventional calixaromatics in which all aromatic units are linked by methylene units, introduction of heteroatoms into the bridge positions has led to a wide variety of novel macrocyclic molecules.[5–9] For example, as reported by Miyano et al. in 1997, heating a mixture of *p-tert*-butylphenol and elemental sulfur at 230 °C in the presence of NaOH yielded tetrathiacalix[4]arene in 54% yield.[5] This practical preparation has paved the way to the extensive study of sulfur-bridged calixarenes.[6] A few years ago, we started our program in supramolecular chemistry, and found that the stepwise fragment-coupling strategy provided an efficient method for the synthesis of azacalix[*m*]arene[*n*]pyridines (*n*=2, 4)[8d] and azacalix[*n*]pyridines (*n*=4, 8).[8e] Later, we established a very convenient, cost-effective, and high-yielding synthetic route to diverse nitrogen and/or oxygen-bridged calix[2]arene[2]triazines.[7a] Recently, Katz et al. have reported a useful one-pot reaction for the preparation of symmetric tetraoxacalixarene derivatives.[7]

Being different from the conventional calixarenes,[1–3] heteroatom-bridged calixaromatics exhibit unique conformational structures and a fine-tunable cavity. Heteroatoms, particularly nitrogen, can have either sp^2 or sp^3 electronic configurations, and can have different degrees of conjugation with adjacent aromatic rings. These features can give rise to slight variations in both the bond lengths and the bond angles, yielding a range of macrocycles of varied conformational structures and of different size. This has been well demonstrated[7a,k] by aza- and/or oxacalix[2]arene[2]triazines, which give a series of differently sized macrocyclic molecules. Furthermore, heteroatom-bridged calixaromatics are fluxional in solution and interconversion of conformers is rapid. This flexibility allows the host molecules to self-regulate their conformation and cavity structure in order to achieve strongest interaction with the guest species in presence.[8d–f] For example, when treated with different acids,[8e] mono- and diols,[10] azacalix[4]pyridine was found to adjust its conformational structure to form stable inclusion complexes.

Heteroatom-bridged calixaromatics also provide a unique and versatile platform for further elaboration and functionalization. As with calixarenes, a range of functional groups can be introduced onto the aromatic rings of the heteroatom-bridged calixaromatics.[11] In addition, the bridging atoms of the macrocyclic rings can be derivatized and functionalized.[7k] The reactions of both the aromatic segments and the bridging units should render heteroatom-bridged calixaromatics useful in the fabrication of sophisticated synthetic receptors.

Inherently chiral molecules are important and intriguing chemical entities in terms of creation of chiral spaces for enzyme mimics and chiral recognition.[12] A challenging task, synthesis of inherently chiral forms of macrocyclic molecules such as calixarenes, remains largely unexplored.[13] Very recently, inherently chiral calixarene crown derivatives have been synthesized and isolated in enantiomerically pure forms through the formation of diastereomers using a chiral

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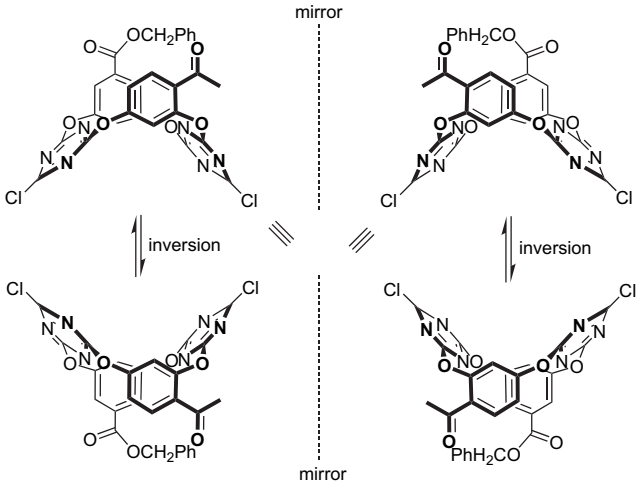
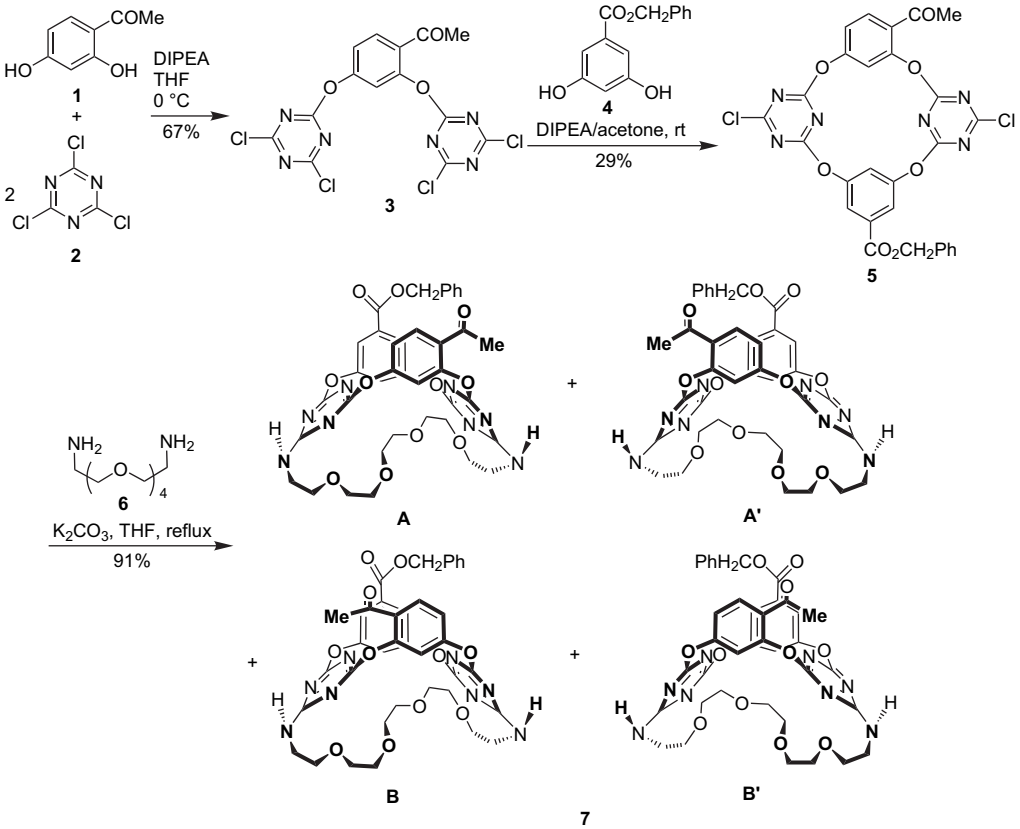
auxiliary.[14] Success in the efficient preparation of heteroatom-bridged calix[2]arene[2]triazines from the stepwise fragment-coupling approach[7a,k] prompted us to attempt the synthesis of inherently chiral heteroatom-bridged calixaromatics. We envisaged that the fragment-coupling strategy employing unsymmetrically substituted aromatic compounds would allow us to readily construct the desired inherently chiral macrocycles.

2. Results and discussion

We started our investigation with the preparation of racemic inherently chiral tetraoxacalix[2]arene[2]triazine azacrown **7** using 2,4-dihydroxyacetophenone **1** as an unsymmetrical fragment. As depicted in Scheme 1, 2,4-dihydroxyacetophenone **1** reacted with 2 equiv of cyanuric chloride **2** at 0 °C in the presence of diisopropyl(ethyl)amine as an acid scavenger to give intermediate **3** in 67% yield. A (macro)-cyclocondensation reaction of **3** with benzyl 3,5-dihydroxybenzoate **4** took place at room temperature to afford the desired target molecule **5**, albeit in 29% yield. It should be noted that the unsymmetrically substituted tetraoxacalix[2]-arene[2]triazine **5** is not an inherently chiral molecule. It is known that sterically less hindered heteroatom-bridged calixaromatics are fluxional in solution and that they undergo very rapid conformation interconversions.[7] As illustrated in Scheme 2, the 'enantiomers' of tetraoxacalix[2]arene[2]-triazine **5** are actually interconvertible due to the rapid conformational inversion. To obtain the inherently chiral tetraoxacalix[2]arene[2]triazine derivatives, it is therefore essential to freeze the conformation of macrocyclic molecule. We then decided to take advantage of the two reactive chlorotriazine moieties in the molecule by transforming compound **5** into the crown derivative **7**, in order to restrict the rotation of two triazine rings around the *meta–meta* axes or through the annulus. Very recently, we have demonstrated that dichlorinated tetraoxacalix[2]arene[2]triazines derived from 1,3-benzenediols bearing a large substituent at 5-position were able to react with diamines to give symmetric calixazacrown compounds. However, because of the conjugation of the amino groups with the triazine rings, most



Scheme 2. Inversion of 1,3-alternate conformers.



Scheme 1. Synthesis of tetraoxacalix[2]arene[2]triazine **5** and its *anti*-azacrown-7 derivative.

tetraoxacalix[2]arene[2]triazine azacrowns were found to exist as a mixture of *syn*- and *anti*-isomer. Only with the incorporation of a diamine **6** derived from 3,6,9,12-tetraoxatetradecane-1,14-diol did the calixazacrown products adopt an exclusively *anti*-isomeric structure.[15] To avoid the complexity of forming both *syn*- and *anti*-isomer in our inherently chiral molecules, diamine **6** was employed. In the presence of K_2CO_3, dichlorinated tetraoxacalix[2]arene[2]triazine **5** reacted with diamine **6** in refluxing tetrahydrofuran (THF) to furnish tetraoxacalix[2]arene[2]triazine azacrown **7** in 91% yield (Scheme 1). The structure of **7** is worth addressing. Since two benzene rings in the macrocycle **5** are differently substituted, the *anti*-configured azacrown product **7** might in theory give rise to two isomeric forms **A** and **B** and their enantiomers **A′** and **B′** (Scheme 1). Very interestingly, in its ^{1}H (Fig. 1) and ^{13}C NMR spectra, tetraoxacalix[2]arene[2]triazine azacrown **7** gave only one set of proton and carbon resonance signals, respectively. This indicated that product **7** existed as a single *anti*-isomer, or more probably that isomers **A** and **B** equilibrate rapidly on the NMR time scale (Scheme 1). We attempted the resolution of racemic tetraoxacalix[2]arene[2]triazine azacrown **7** by means of HPLC, using commercially available chiral columns such as Diacel AD, OD, and OJ and Cyclobond. Unfortunately, no resolution was achieved.

An alternative strategy was then applied utilizing a chiral auxiliary. It was hoped that the introduction of a chiral auxiliary into the inherently chiral heteroatom-bridged calixaromatics would result in the formation of a pair of diastereomers, which would therefore facilitate the separation. To test this approach, enantiomerically pure *R*-(+)-α-phenylethylamine and (1*R*,2*S*,5*R*)-(−)-menthol were employed because of their easy availability. The preparations of chiral building blocks **11** and **13** were rather straightforward. Starting with 3,5-dihydroxybenzoic acid, protection of two hydroxyl groups by THP, followed by amidation or esterification and deprotection yielded chiral amide **11** or ester **13** in high yields (Scheme 3). Under similar reaction conditions as for the preparation of **3**, reaction of **11** and **13** with 2 equiv of cyanuric chloride **2** produced the corresponding intermediates **14** and **15** in yields of 70% and 42%, respectively. Chiral tetraoxacalix[2]arene[2]triazine products **16** and **17** were successfully obtained in fairly good yields from macrocyclic coupling reactions between 2,4-dihydroxyacetophenone **1** and intermediates **14** and **15**. Further reaction of **16** and **17** with the diamine **6**, following the reaction conditions for the synthesis of **5**, led efficiently to chiral tetraoxacalix[2]arene[2]triazine azacrowns **18** and **19** (Scheme 4).

The structures of all chiral products were established on the basis of spectroscopic data and microanalyses. To establish the chiral tetraoxacalix[2]arene[2]triazine structure beyond doubt, the X-ray single crystal structure of **17**[16] was determined (Fig. 2). Like most of the heteroatom-bridged calixaromatics,[7a] compound **17** adopted a 1,3-alternate conformation. The introduction of a chiral auxiliary and an unsymmetrically substituted benzene ring did not change the 1,3-alternate conformation of macrocyclic ring. The two differently substituted benzene rings are face-to-face and almost parallel, whereas the two triazines are nearly edge-to-edge oriented, giving the distances between C(11) and C(31), and C(16) and C(30) around 4.946 and 8.841 Å, respectively. The bond lengths and bond angles (see the caption of Fig. 2) of bridging oxygen atoms indicate

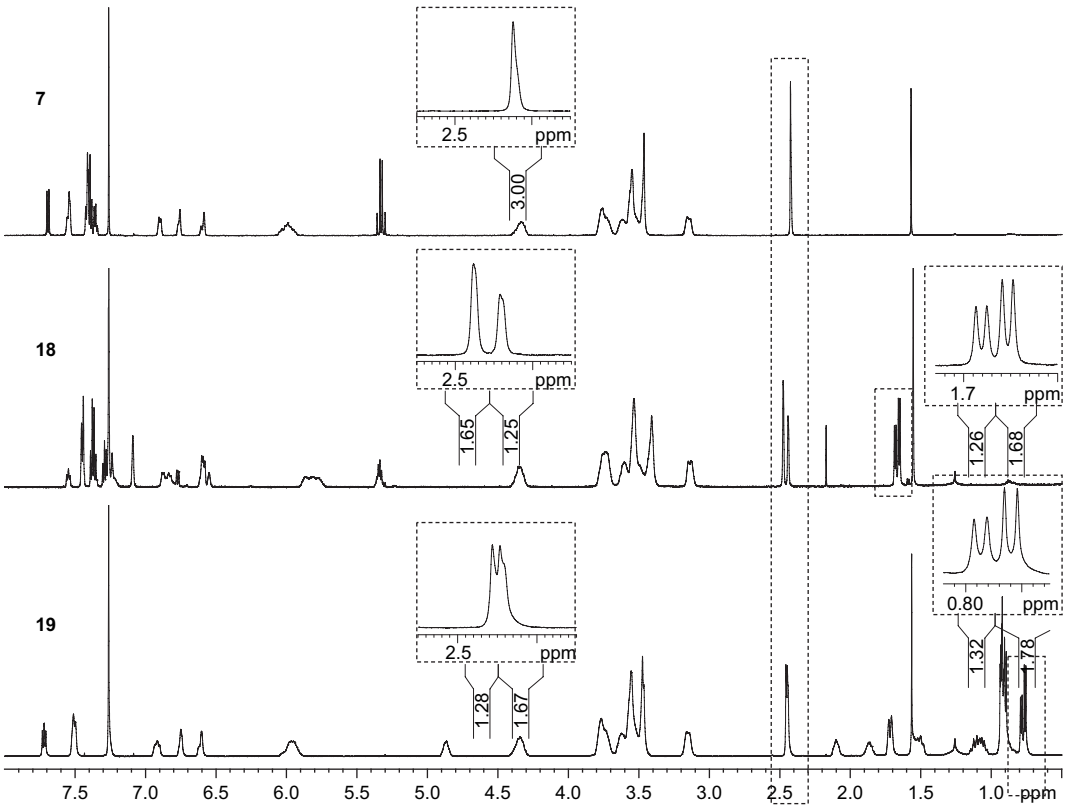
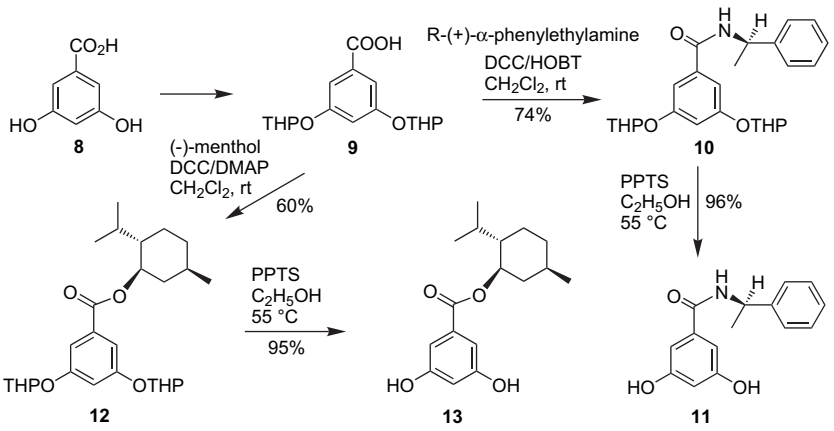


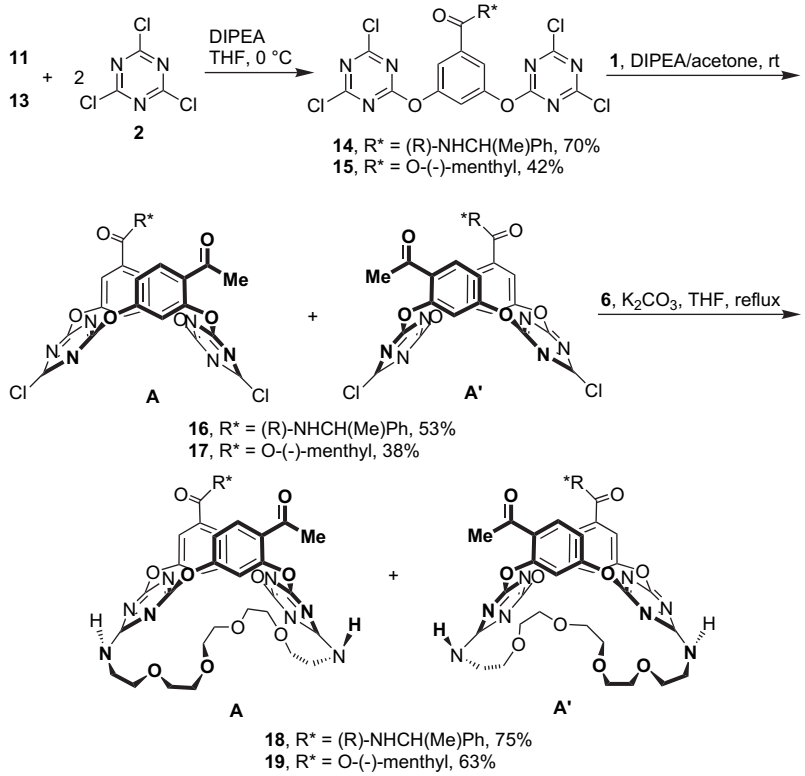
Figure 1. Partial ^{1}H NMR spectra of compounds **7**, **18**, and **19**.



Scheme 3. Preparation of chiral building blocks **11** and **13**.

conjugation of the linking oxygen atoms with triazine rings rather than benzene rings. It is very interesting to note that chiral product **17** existed actually as a single diastereomerically pure isomer in this crystal (Fig. 2). It should be noted, however, that diastereomers were not detected for products **16** and **17** in solution, as both their ^{1}H and ^{13}C NMR spectra showed only one set each of proton and carbon signals. Such spectroscopic characteristics are most likely attributable to the rapid conformation inversion in solution (Scheme 2) as we discussed previously. Therefore, the presence of only a single diastereomer in the crystal is most probably an effect of lattice forces.

As shown by the ^{1}H (Fig. 1) and ^{13}C NMR spectra of products **18** and **19**, which displayed, respectively, two sets of proton and carbon resonance signals, chiral *anti*-tetraoxacalix[2]arene[2]triazine azacrowns **18** and **19** existed as a pair of diastereomers. For example, in contrast to the spectrum of compound **7**, there are two singlet peaks (2.44–2.48 ppm) corresponding to the acetyl methyl protons in the ^{1}H NMR spectrum of **18** and **19** (Fig. 1). In addition, two sets of doublet signals at 1.65–1.68 ppm and two sets of doublet signals at 0.76–0.79 ppm were observed for chiral amido- and ester-bearing azacrown products **18** and **19**, respectively. The diastereomer ratio in both cases was around 1:1, as determined roughly by the integration of the intensity of two peaks (Fig. 1). It is quite clear that by the introduction of unsymmetrically substituted aromatic rings and inhibition of the conformational inversion, stable, inherently chiral heteroatom-bridged calixaromatics may be obtained. We have



Scheme 4. Synthesis of inherently chiral tetraoxacalix[2]arene[2]triazines and their azacrown derivatives.

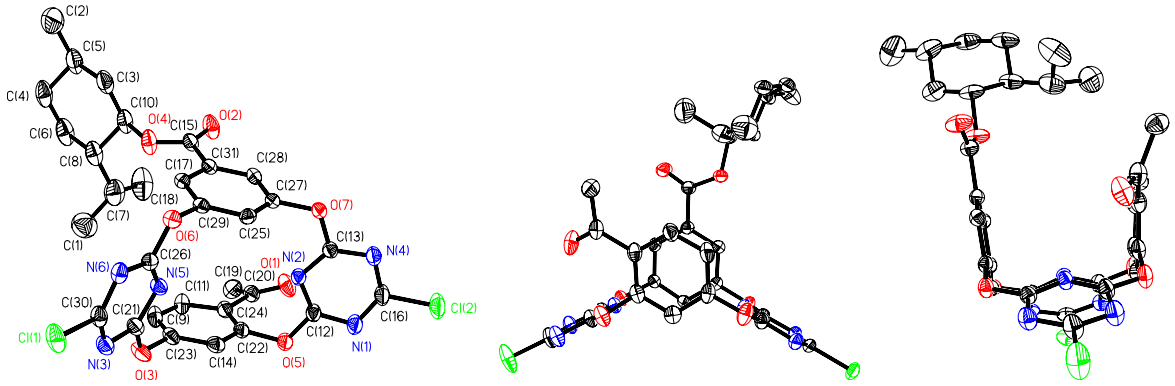


Figure 2. X-ray molecular structure of **17**: top (left) and side (middle and right) views. Selected interatomic distances [Å]: N(2)···N(5) 4.601, C(16)···C(30) 9.209, Cl(1)···Cl(2) 12.246, C(14)···C(25) 4.453, C(11)···C(31) 4.946, N(2)···C(25), 3.244, C(25)···N(5) 3.137, N(5)···C(14) 3.267, C(14)···N(2) 3.158. Selected bond lengths [Å]: C(13) ···O(7) 1.340, O(7)···C(27) 1.408, C(29)···O(6) 1.395, O(6) ···C(26) 1.335, C(21) ···O(3) 1.344, O(3) ···C(23) 1.402, C(22) ···O(5) 1.420, O(5) ···C(12) 1.339. Selected bond angles: C(13)–O(7)–C(27) 117.5°, C(29)–O(6)–C(26) 117.7°, C(21)–O(3)–C(23) 118.2°, C(22)–O(5)–C(12) 117.1°.

attempted separation of diastereomers of **18** and **19** using various chromatographic methods but have as yet been unsuccessful.

3. Conclusions

In summary, we have developed a rather efficient and straightforward strategy for the construction of inherently chiral heteroatom-bridged calixaromatics. Two pairs of diastereomers of inherently chiral tetraoxacalix[2]arene[2]-triazine azacrowns have been synthesized conveniently using *R*-(+)-α-phenylethylamine and (1*R*,2*S*,5*R*)-(−)-menthol as chiral auxiliaries. Although the separation of the diastereomers, which are the precursors to enantiomerically pure inherently chiral tetraoxacalix[2]arene[2]triazine azacrowns, is yet to be achieved, we are confident that the strategy is correct and worth pursuing. Searching for separable diastereomers of inherently chiral heteroatom-bridged calixaromatics using other effective chiral auxiliaries is being actively investigated in this laboratory.

4. Experimental

4.1. General information

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300 and 600 spectrometers. Chemical shifts are reported in parts per million with either tetramethylsilane or the residual solvent resonance peak as an internal standard. Melting points are uncorrected. Elemental analyses were performed at the Analytical Laboratory of the Institute. All chemicals were dried or purified according to standard procedures prior to use.

4.2. Synthesis of 3

To an ice-cooled solution of cyanuric chloride **2** (9.23 g, 50 mmol) in THF (100 mL) was added dropwise a mixture of **1** (3.80 g, 25 mmol) and diisopropyl(ethyl)amine (8.06 g, 62.5 mmol) in THF (80 mL) over 1 h. The resulting mixture was stirred for another 1 h. After removal of diisopropyl(ethyl)amine hydrochloride by filtration, the filtrate was concentrated and chromatographed on a silica gel column (100–200 mesh) with a mixture of petroleum ether and acetone as the mobile phase to give pure **3** (7.50 g, 67%) as pale yellow solid: mp 113–114 °C; IR (KBr) ν 1687, 1536 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (1H, d, J=8.6 Hz), 7.35 (1H, dd, J=2.3, 8.6 Hz), 7.16 (1H, d, J=2.3 Hz), 2.58 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5, 173.4, 173.1, 170.9, 170.3, 154.0, 150.2, 132.4, 128.4, 120.0, 117.0, 29.0; MS (ESI) *m/z* (%) 447.1 ($M+H^+$, 100), 445.1 (94), 443.1 (74), 449.1 (67), 469.0 ($M+Na^+$, 82), 467.0 (80), 465.0 (81), 471.0 (38), 485.0 ($M+K^+$, 31), 482.0 (25), 479.0 (27). HRMS (ESI) *m/z* 446.9340. $C_{14}H_6O_3N_6Cl_4$ requires 446.9328.

4.3. Synthesis of 5

At room temperature, solutions of benzyl 3,5-dihydroxybenzoate (4.0 mmol) in acetone (200 mL) and **3** (4.0 mmol) in acetone (200 mL) were added dropwise simultaneously and at the same rate to a solution of diisopropyl(ethyl)amine (1.24 g, 9.6 mmol) in acetone (1400 mL). After addition of the two reactants, which took about 12 h, the resulting mixture was stirred at room temperature for another 24 h. The solvent was then removed under vacuum, and the residue was chromatographed on a silica gel column (200–300 mesh) with a mixture of petroleum ether and acetone as the mobile phase to give pure **5** (0.72 g, 29%) as white solid: mp 230–231 °C; IR (KBr) ν 1729, 1695, 1551 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (1H, d, J=8.4 Hz), 7.58 (2H, t, J=1.8 Hz), 7.44–7.40 (5H, m), 6.96 (1H, dd, J=1.8, 8.4 Hz), 6.91 (1H, t, J=1.8 Hz), 6.77 (1H, d, J=2.4 Hz), 5.34 (2H, s), 2.42 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 175.0, 174.9, 172.5, 172.3, 172.1, 163.8, 154.1, 151.7, 151.4, 150.4, 135.2, 133.5, 132.0, 128.8, 128.6, 121.0, 120.9, 120.5, 119.9, 117.8, 67.6, 29.3; MS (MALDI-TOF) *m/z* (%) 618.8 ($M+H^+$, 100), 619.8 (32), 620.8 (71), 621.8 (21), 622.8 (13), 623.8 (6), 640.7 ($M+Na^+$, 24), 641.7 (8), 642.7 (15), 643.7 (6), 644.7 (4), 656.8 ($M+K^+$, 6), 657.8 (5), 658.8 (4). Anal. Calcd for $C_{28}H_{16}O_7N_6Cl_2$: C, 54.30; H, 2.60; N, 13.57. Found: C, 54.25; H, 2.65; N, 13.35.

4.4. Synthesis of 7

Solutions of a diamine **6** (1.0 mmol) in THF (200 mL) and a dichlorinated tetraoxacalix[2]arene[2]triazine **5** (1.0 mmol) in THF (200 mL) were added dropwise simultaneously and at the same rate to a refluxing suspension of K_2CO_3 (2.76 g, 20 mmol) in THF (480 mL). After addition of the reactants, which took about 10 h, the resulting mixture was refluxed for another 12 h. Filtration removed the solids and the filtrate was concentrated under vacuum. The residue was then chromatographed on a silica gel column (200–300 mesh) with a mixture of petroleum ether and acetone as the mobile phase to give pure product **7** (0.71 g, 91%) as white solid: mp 204–205 °C; IR (KBr) ν 3280, 3150, 1717, 1692, 1590 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.69 (1H, d, J=8.6 Hz), 7.56–7.54 (2H, m), 7.42–7.38 (4H, m), 7.36–7.34 (1H, m), 6.90 (1H, d, J=7.9 Hz), 6.76 (1H, br s), 6.61–6.58 (1H, m), 6.05–5.95 (2H, m), 5.34 (1H, d, J=12.3 Hz), 5.31 (2H, d, J=12.3 Hz), 4.35–4.34 (2H, m), 3.76–3.73 (4H, m), 3.62–3.46 (12H, m), 3.16–3.14 (2H, m), 2.42 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.8, 171.9, 171.5, 170.0, 164.6, 155.3, 152.4, 151.7, 135.6, 132.6, 131.5, 128.7, 128.5, 128.3, 120.6, 120.1, 120.0, 119.3, 117.3, 71.2, 70.8, 70.5, 70.1, 67.3, 40.8, 30.3; MS (MALDI-TOF) m/z 783.0 ($M+H^+$), 805.0 ($M+Na^+$), 821.0 ($M+K^+$). Anal. Calcd for $C_{38}H_{38}O_{11}N_8$: C, 58.31; H, 4.89; N, 14.32. Found: C, 58.06; H, 5.13; N, 14.13.

4.5. Synthesis of 10 and 12

At room temperature, to a solution of **9** (4.83 g, 15 mmol) and *R*-(+)-α-phenylethylamine (1.82 g, 15 mmol) or (−)-menthol (2.34 g, 15 mmol) in dry CH_2Cl_2 (200 mL) were added DCC (3.09 g, 15 mmol) and HOBT (2.03 g, 15 mmol) or DMAP (0.18 g, 1.5 mmol). The resulting mixture was stirred for 24 h. After removal of solid through filtration, the filtrate was concentrated and chromatographed on a silica gel column (200–300 mesh) with a mixture of petroleum ether and ethyl acetate as the mobile phase to give pure **10** (4.72 g, 74%) as a colorless oil or **12** (4.14 g, 60%) as a yellow oil.

4.6. Synthesis of 11 and 13[17]

At room temperature, to a solution of **10** (8.50 g, 20 mmol) or **12** (9.2 g) in EtOH (200 mL) was added PPTS (1.00 g, 4 mmol). The resulting mixture was stirred at 55 °C for 4 h. After removal of EtOH under vacuum, the residue was chromatographed on a silica gel column (200–300 mesh) with a mixture of petroleum ether and acetone as the mobile phase to give pure **11** (4.93 g, 96%) or **13** (5.55 g, 95%) both as pale yellow foam. Compound **11**: mp 75–76 °C; IR (KBr) ν 3415, 3251, 1644, 1595 cm^{-1}; ^1H NMR (300 MHz, MeOD-d_3) δ 7.43–7.23 (5H, m), 6.74 (2H, d, J=2.2 Hz), 6.43 (1H, t, J=2.2 Hz), 5.21 (1H, q, J=7.0 Hz), 3.38 (2H, s), 1.56 (3H, d, J=7.1 Hz); ^{13}C NMR (75 MHz, d_3-MeOD) δ 170.0, 159.8, 145.4, 138.2, 129.5, 128.0, 127.1, 106.9, 106.6, 50.6, 22.3; MS (EI) m/z (%) 257 (M^+, 23), 56 (84), 43 (100). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.47; H, 6.10; N, 5.57. Compound **13**: mp 70–71 °C; IR (KBr) ν 3395, 1686, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (2H, d, J=2.2 Hz), 6.59 (1H, t, J=2.1 Hz), 5.57 (2H, s), 4.90 (1H, dt, J=4.4, 10.8 Hz), 2.11–2.06 (1H, m), 1.96–1.89 (1H, m), 1.74–1.70 (2H, m), 1.57–1.48 (2H, m), 1.14–1.02 (2H, m), 0.97–0.86 (7H, m), 0.78 (3H, d, J=6.9 Hz); ^{13}C NMR (75 MHz, MeOD-d_3) δ 167.8, 159.8, 133.6, 108.8, 108.2, 76.0, 42.1, 35.5, 32.7, 27.8, 24.8, 22.4, 21.0, 16.9; MS (EI) m/z (%) 292 (M^+, 7), 154 (40), 138 (94), 137 (100), 95 (67), 81 (42). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.48; H, 8.45.

4.7. Synthesis of 14

Following the same procedure for preparation of **3**, pure **14** (70%) was obtained as white solid: mp 92–93 °C; IR (KBr) ν 3311, 1645, 1527 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (2H, d, J=2.2 Hz), 7.39–7.28 (5H, m), 7.22 (1H, t, J=2.2 Hz), 6.28 (1H, d, J=7.4 Hz), 5.31 (1H, quin, J=7.1 Hz), 1.63 (3H, d, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 170.6, 163.8, 151.5, 142.4, 138.1, 128.9, 127.8, 126.3, 118.6, 118.0, 49.8, 21.5; MS (EI) m/z (%) 551 (M^+, 60), 552 (21), 553 (82), 554 (22), 555 (39), 556 (8), 557 (10), 558 (2), 435 (50), 433 (100), 431 (75), 104 (93). Anal. Calcd for $C_{21}H_{13}N_7O_3Cl_4$: C, 45.59; H, 2.37; N, 17.72. Found: C, 45.99; H, 2.58; N, 17.43.

4.8. Synthesis of 15

Following the same procedure for preparation of **3**, **15** (42%) was obtained as white solid: mp 46–47 °C; IR (KBr) ν 1719, 1529 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (2H, d, J=2.2 Hz), 7.29 (2H, t, J=2.2 Hz), 4.96–4.95 (1H, m), 2.14–2.11 (1H, m), 1.95–1.94 (1H, m), 1.76–1.72 (2H, m), 1.58–1.52 (3H, m), 1.15–1.08 (2H, m), 0.95–0.91 (6H, m), 0.82–0.79 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 170.6, 163.5, 151.3, 134.3, 121.9, 119.2, 76.3, 47.2, 40.8, 34.2, 31.4, 26.5, 23.6, 22.0, 20.8, 16.5; MS (EI) m/z (%) 588 (M^++2, 5), 590 (2), 437 (5), 436 (5), 435 (27), 434 (10), 433(61), 432 (8), 431(51), 138 (100), 95 (53). Anal. Calcd for $C_{23}H_{22}N_6O_4Cl_4$: C, 46.96; H, 3.77; N, 14.29. Found: C, 47.03; H, 4.12; N, 14.22.

4.9. Synthesis of 16

Following the same reaction procedure for preparation of **5**, pure **16** (53%) was obtained as white solid: mp 154–155 °C; $[\alpha]_D^{25}$ 5.4 (c 1.0, $CHCl_3$); IR (KBr) ν 3351, 1690, 1662, 1552 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.41–7.36 (5H, m), 7.32–7.30 (2H, m), 7.15 (1H, s), 6.91 (1H, d, J=8.4 Hz), 6.78 (1H, s), 6.74 (1H, s), 6.60 (1H, d, J=7.8 Hz), 5.29 (1H, quin, J=7.2 Hz), 2.45 (3H, s), 1.63 (3H, d, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 174.9, 172.4, 172.3, 172.2, 164.0, 154.2, 151.8, 151.79, 150.1, 142.7, 138.4, 131.5, 130.0, 128.8, 127.7, 126.3, 120.3, 119.1, 118.5, 118.2, 117.4, 49.6, 29.6, 21.4; MS (EI) m/z (%) 631 (M^+, 37), 632 (13), 633 (26), 634 (8), 635 (6), 636 (2), 511 (71), 512 (20), 513 (49), 514 (13), 515 (10), 516 (3), 120 (93), 104 (100), 103 (50). Anal. Calcd for $C_{29}H_{19}N_7O_6Cl_2$: C, 55.08; H, 3.03; N, 15.50. Found: C, 54.94; H, 3.09; N, 15.18.

4.10. Synthesis of 17

Following the same reaction procedure for preparation of **5**, pure **17** (38%) was obtained as white solid: mp 290–291 °C;

$[\alpha]_D^{25}$ −23.4 (*c* 1.0, $CHCl_3$); IR (KBr) *ν* 1713, 1691, 1553 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) *δ* 7.72 (1H, d, *J*=8.4 Hz), 7.53 (2H, d, *J*=1.8 Hz), 6.99 (1H, dd, *J*=2.4 Hz, 8.4 Hz), 6.89 (1H, t, *J*=2.4 Hz), 6.78 (1H, d, *J*=2.4 Hz), 4.91–4.87 (1H, m), 2.47 (3H, s), 2.07–2.05 (1H, m), 1.84–1.81 (1H, m), 1.74–1.72 (2H, m), 1.55–1.49 (2H, m), 1.12–1.04 (2H, m), 0.94–0.88 (7H, m), 0.77 (3H, d, *J*=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 195.1, 174.9, 172.5, 172.3, 172.2, 163.5, 154.1, 151.7, 151.4, 150.4, 134.2, 131.8, 128.8, 120.8, 120.7, 120.1, 119.9, 117.9, 76.1, 47.1, 40.8, 34.1, 31.4, 29.3, 26.6, 23.6, 22.0, 20.7, 16.6; MS (MALDI-TOF) *m/z* (%) 667.6 ($M+H^+$, 100), 668.6 (37), 669.6 (71), 670.6 (25), 671.6 (16), 672.6 (5), 673.6 (1). Anal. Calcd for $C_{31}H_{28}O_7N_6Cl_2$: C, 55.78; H, 4.23; N, 12.59. Found: C, 55.82; H, 4.36; N, 12.27. X-ray quality single crystals were obtained by slow evaporation of the solvent from **17** solvent in a mixture of ethyl acetate and *n*-hexane.

4.11. Synthesis of 18

Following the same procedure for the synthesis of **7**, pure **18** (75%) was obtained as white solid: mp 179–180 °C; $[\alpha]_D^{25}$ −1.6 (*c* 1.0, $CHCl_3$); IR (KBr) *ν* 3388, 3282, 3154, 1590 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) *δ* 7.55 (1H, t, *J*=7.6 Hz), 7.45 (2H, d, *J*=7.6 Hz), 7.39–7.35 (2H, m), 7.30–7.28 (1H, m), 7.24 (1H, br s), 7.09 (1H, br s), 6.88–6.76 (2H, m), 6.60–6.55 (2H, m), 5.87–5.78 (2H, m), 5.36–5.32 (1H, m), 4.36–4.34 (2H, m), 3.73 (4H, br s), 3.60–3.41 (12H, m), 3.15–3.13 (2H, m), 2.48 (1.67H, s), 2.44 (1.27H, s), 1.68 (1.27H, d, *J*=7.0 Hz), 1.65 (1.70H, d, *J*=6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 7.9, 197.7, 172.2, 172.0, 171.9, 171.7, 171.4, 172.0, 170.1, 165.3, 165.1, 155.5, 152.6, 152.5, 151.5, 151.3, 143.2, 143.1, 137.8, 137.6, 130.6, 128.7, 128.6, 127.5, 127.4, 126.5, 126.3, 120.1, 118.6, 118.5, 118.4, 118.3, 117.5, 117.4, 117.2, 117.1, 71.1, 70.8, 70.5, 70.1, 69.9, 49.6, 49.3, 40.7, 30.3, 21.8, 21.1; MS (MALDI-TOF) *m/z* 796.6 ($M+H^+$), 818.6 ($M+Na^+$), 834.6 ($M+K^+$). Anal. Calcd for $C_{39}H_{41}N_9O_{10}$: C, 58.86; H, 5.19; N, 15.84. Found: C, 58.52; H, 5.24; N, 15.77.

4.12. Synthesis of 19

Following the same procedure for the synthesis of **7**, pure **19** (63%) was obtained as white solid: mp 213–214 °C; $[\alpha]_D^{25}$ −20.9 (*c* 1.0, $CHCl_3$); IR (KBr) *ν* 3280, 3150, 1717, 1692, 1590 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) *δ* 7.72 (1H, dd, *J*=1.7, 8.4 Hz), 7.51–7.50 (2H, m), 6.92–6.90 (1H, m), 6.75 (1H, br s), 6.60 (1H, br s), 5.96–5.95 (2H, m), 4.86 (1H, br s), 4.34 (2H, br s), 3.76–3.74 (4H, m), 3.62–3.46 (12H, m), 3.16–3.14 (2H, m), 2.46 (1.28H, s), 2.45 (1.67H, s), 2.10 (1H, br s), 1.87–1.85 (1H, m), 1.73–1.71 (2H, m), 1.54–1.48 (2H, m), 1.14–1.03 (2H, m), 0.94–0.89 (7H, m), 0.79 (1.32H, d, *J*=6.9 Hz), 0.76 (1.78H, d, *J*=6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 195.84, 195.8, 172.0, 171.9, 171.8, 171.4, 171.3, 169.9, 164.2, 155.2, 152.3, 152.1, 152.0, 151.7, 151.5, 133.3, 133.2, 131.4, 128.6, 128.5, 120.4, 120.1, 119.9, 119.8, 119.7, 119.3, 119.1, 117.6, 117.4, 117.3, 75.7, 75.67, 71.1, 70.8, 70.5, 70.1, 70.0, 69.8, 69.6, 47.1, 40.8, 40.7, 34.2, 31.4, 30.4, 30.3, 26.6, 23.6, 22.0, 20.7, 20.67, 16.6, 16.5; MS (MALDI-TOF) *m/z* 831.4 ($M+H^+$), 853.4 ($M+Na^+$), 869.4 ($M+K^+$). Anal. Calcd for $C_{41}H_{50}N_8O_{11}$: C, 59.27; H, 6.07; N, 13.49. Found: C, 59.17; H, 6.11; N, 13.46.

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Supplementary data

Preparations of starting materials, copies of ^1H and ^{13}C NMR spectra of all products. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.05.129.

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