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Synthesis of an Inherently Chiral Calix[4]arene Amino Acid and Its Derivatives: Their Application to Asymmetric Reactions as Organocatalysts

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The synthesis of an inherently chiral calix[4]arene amino acid as a chiral building block has been achieved in order for subsequent transformation to various types of inherently chiral calix[4]arenes. The optically pure, inherently chiral calix[4]arene amino acids were prepared by the separation of a diastereomeric mixture of calix[4]arene amino acid derivatives bearing a (*R*)-BINOL moiety. The separated optically pure calix[4]arene amino acid derivatives with a (*R*)-BINOL moiety were easily transformed to novel inherently chiral calix[4]arenes containing an amino alcohol structure or a quaternary ammonium moiety. These optically pure chiral calix[4]arenes were applied to asymmetric reactions as organocatalysts.

Introduction

Optically active amino acids are a biologically significant class of compounds since they are the basic building blocks for peptides and proteins and are the biopolymers responsible for both the structure and function of most living things.[1] Furthermore, optically active amino acids are used extensively as chiral building blocks for chiral catalysts and auxiliaries in modern organic synthesis.[2]

Interest in the chemistry of chiral calixarenes has increased in recent years due to their importance in the development of new chiral receptors for asymmetric recognition. This provides a potent tool for understanding the stereochemistry of biochemical systems.[3] Hence, many chiral calixarenes containing chiral residues at either the wide or the narrow rim have been prepared for use as chiral receptors[4] and catalysts.[5] A more challenging and attractive approach to the introduction of chirality is to make the calixarene "inherently" chiral by creating an asymmetrical array of achiral substituents on the calixarene skeleton.[6] For the past two decades, many inherently chiral calixarenes have been prepared and some of them have been resolved into individual enantiomers.[7] In spite of these efforts, only a few examples of enantiomeric recognition[8] and asymmetric catalysis[9–11] with inherently chiral calixarenes have been reported. These limited results might arise from difficulties associated with both the design of a synthetic route to functionalised inherently chiral calixarenes and separation of the synthesised chiral calixarenes into optically pure enantiomers.

We recently developed a novel and efficient method for the synthesis and optical resolution of inherently chiral calix[4]arenes, the latter then being applied to asymmetric reactions as organocatalysts.[10,11] Chiral calix[4]arenes have traditionally been synthesised as racemates and each of the calixarenes was then resolved into optically pure enantiomers. In the course of these studies we became interested in the design and synthesis of an inherently chiral calix[4]arene amino acid[12,13] as a chiral building block for subsequent transformation to various types of inherently chiral calix[4]-arenes. We herein report the synthesis and optical resolution of a novel inherently chiral calix[4]arene amino acid **1**

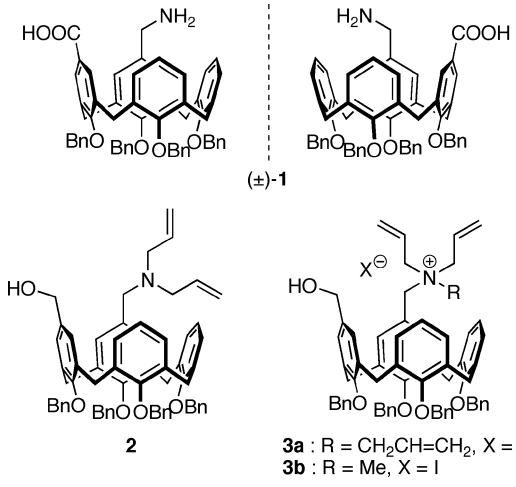

Figure 1. Inherently chiral calix[4]arene amino acid and its derivatives.

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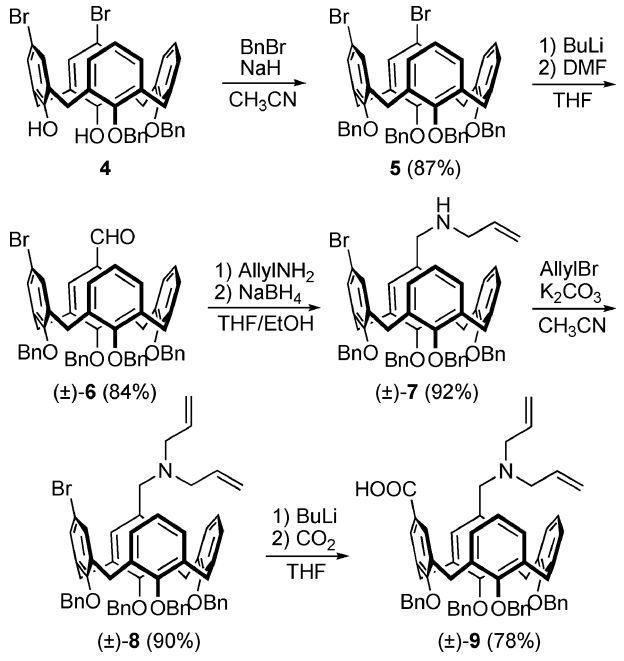
(Figure 1). The optically pure synthetic intermediate of **1** was easily transformed to different types of inherently chiral calix[4]arenes **2** and **3** in optically pure form (Figure 1). Furthermore, the inherently chiral calix[4]arenes were applied to asymmetric reactions as organocatalysts.[14]

Results and Discussion

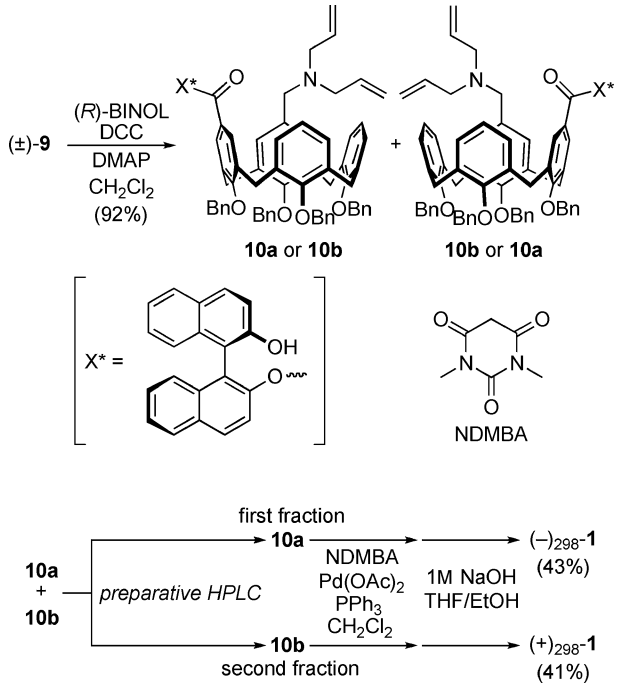
Synthesis and Optical Resolution of an Inherently Chiral Calix[4]arene Amino Acid 1

The *N*-protected calix[4]arene amino acid **9** can be prepared from the already reported proximally *p*-dibrominated calix[4]arene dibenzyl ether **4**.[15] The process is outlined in Scheme 1. Treatment of **4** with benzyl bromide in the presence of NaH gave the proximally *p*-dibrominated calix[4]arene tetrabenzyl ether **5** in the cone conformation as a key intermediate. The *p*-dibromocalix[4]arene **5** was transformed into the mono-formylated compound **6** by treatment with 1.1 equiv. of *n*BuLi and the subsequent addition of dimethylformamide (DMF). The reductive amination of the formyl group of **6** with allylamine gave the secondary amine **7** in 92% yield. Compound **7** was transformed with allyl bromide to the tertiary amine **8** in 90% yield. Lithiation of the bromine substituent on **8** and trapping of the resultant anion with CO_2 gave the target *N*-protected calix[4]arene amino acid **9** as a racemate in 78% yield.



Scheme 1. Synthesis of *N*-protected calix[4]arene amino acid **9**.

The efficient resolution of an inherently chiral calix[4]arene amino acid was achieved by preparative high performance liquid chromatography (HPLC) after conversion into diastereomeric (*R*)-BINOL esters **10a** and **10b** (Scheme 2). Thus, treatment of racemic *N*-protected calix[4]arene amino acid **7** with (*R*)-BINOL in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) gave the ≈ 1:1 mixture of diastereomers **10a** and **10b**. The diastereomeric mixture (0.30 g) of **10a** and **10b** was loaded onto the preparative HPLC column and diastereomerically pure **10a** (≈ 0.10 g) and **10b** (≈ 0.10 g) were obtained.



Scheme 2. Resolution of an inherently chiral calix[4]arene amino acid.

The ^{1}H NMR spectra of diastereomers **10a** and **10b**, and the mixture of **10a** and **10b** are shown in Figure 2. Diastereomers **10a** and **10b** exhibited differences in their ^{1}H NMR spectra and a comparison of the spectra with the diastereomerically pure **10a** (Figure 2, a) and **10b** (Figure 2, b), and the mixture (Figure 2, c) clearly indicated that a perfect separation of diastereomers **10a** and **10b** was achieved by preparative HPLC. The diastereomeric purity of **10a** and **10b** also was confirmed by means of HPLC analysis (Figure 3).

The NMR spectra of **10a** and **10b** provide structural information. The ^{1}H NMR spectrum of **10a** shows four doublets at 4.17, 4.16, 4.00 and 3.98 ppm, corresponding to the axial protons of the methylene bridges and the ^{13}C NMR spectrum shows peaks at 31.25, 31.18, 31.05 and 31.02 ppm for the four pertinent carbons. The values of the ^{13}C NMR chemical shifts and the ^{1}H and ^{13}C NMR spectroscopic patterns indicate that **10a** is present in the cone conformation[16] and possesses inherent chirality. The NMR spectra of **10b** showed a similar situation.

Finally, the palladium-catalysed de-*N*-allylation[17] of **10a** and **10b**, followed by hydrolysis with NaOH to remove the BINOL moiety afforded the optically pure calix[4]arene

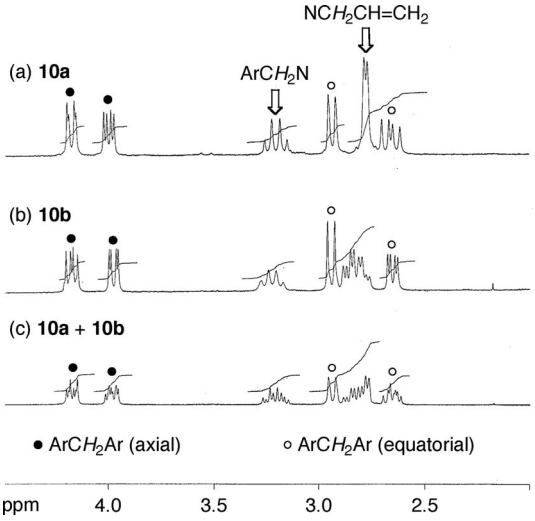


Figure 2. A section of the ^{1}H NMR spectra of calix[4]arenes **10a** (a) and **10b** (b), and mixture of **10a** and **10b** (c) in $CDCl_3$ at 27 °C.

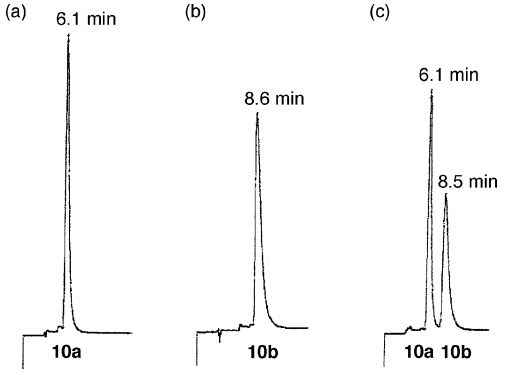


Figure 3. HPLC chromatographs of **10a** (a) and **10b** (b), and a mixture of **10a** and **10b** (c) [column: SUMICHIRAL OA-4800 (0.46 × 25 cm), eluent: $CHCl_3$/hexane (80:20), flow rate: 1.0 mL min^{-1}].

amino acids $(-)_{298}$-**1** and $(+)_{298}$-**1**,[18,19] respectively (Scheme 2). The circular dichroism (CD) spectra of the enantiomers of **1** showed perfect mirror images (Figure 4).

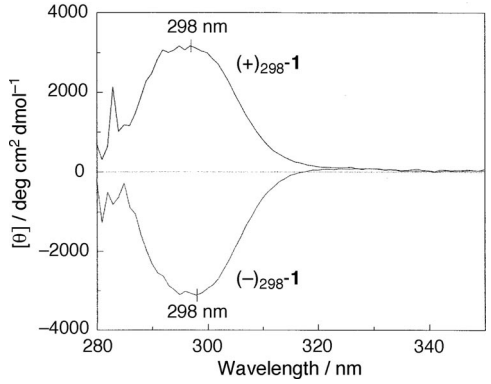
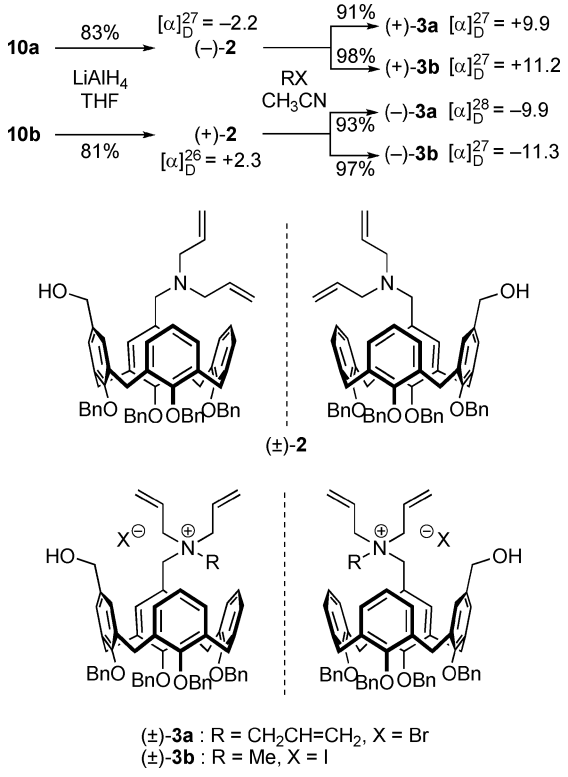


Figure 4. CD spectra of the enantiomers of calix[4]arene amino acid **1** in $CHCl_3$.

Amino acids (especially L-proline) have been utilised as organocatalysts in various asymmetric reactions including direct aldol reactions.[20] Therefore, an inherently chiral calix[4]arene amino acid **1** was applied to the asymmetric direct aldol reaction of acetone. Unfortunately, no catalytic activity of chiral calix[4]arene **1** was observed presumably due to low nucleophilicity of the nitrogen on the calix[4]arene **1**. The improvements in the structure of an inherently chiral calix[4]arene amino acid that will promote the reaction are now in progress in our laboratory.

Synthesis of Inherently Chiral Calix[4]arenes 2 and 3

Using an efficient synthetic scheme for the inherently chiral calix[4]arene amino acid, the derivatisation of separated diasteromers **10a** and **10b** to different types of inherently chiral calix[4]arenes was examined. The chiral calix[4]arene **2** containing an amino alcohol structure was synthesised by the reduction of **10a** or **10b** with $LiAlH_4$ and optically pure chiral calix[4]arenes (–)-**2** and (+)-**2** were obtained, respectively, in yields of 81–83% (Scheme 3). These amino alcohol structures are often present in useful chiral molecules such as cinchonidine, ephedrine and prolinol. Furthermore, chiral calix[4]arenes containing a quaternary ammonium moiety **3a** and **3b** were prepared by the *N*-alkylation of chiral calix[4]arene **2**. The optical rotations of (+)-**2** and (–)-**2**, and (+)-**3** and (–)-**3** showed similar values with opposite signs (Scheme 3) and the circular dichroism (CD) spectra of the enantiomers of **2** and **3** showed mirror images (Figure 5) which definitively proved they were a pair of enantiomers.



Scheme 3. Synthesis of inherently chiral calix[4]arenes **2** and **3**.

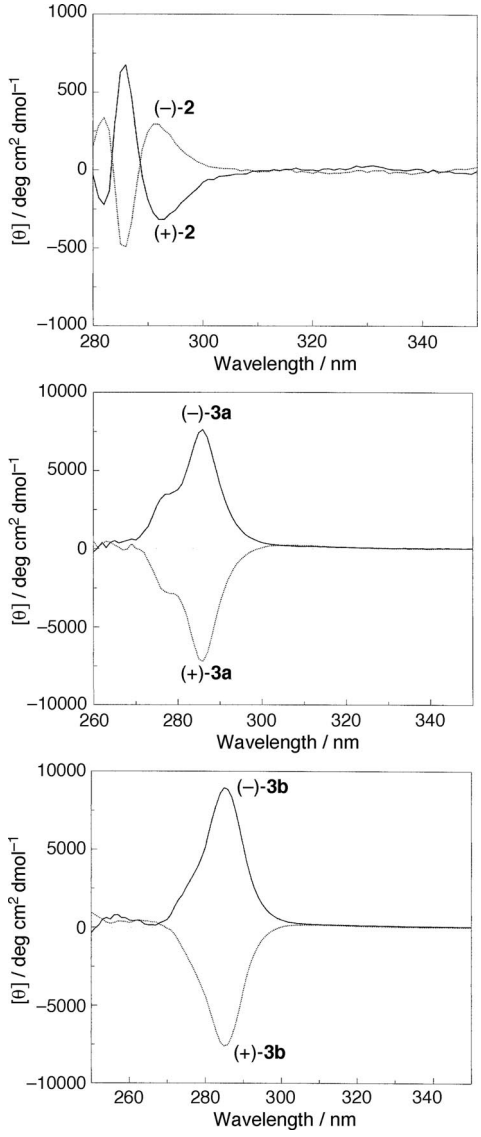
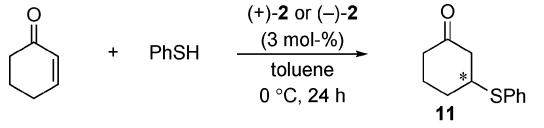


Figure 5. CD spectra of enantiomers of calix[4]arenes **2**, **3a** and **3b** in $CHCl_3$.

Asymmetric Michael Addition Reactions Catalysed by Inherently Chiral Calix[4]arenes 2 and 3

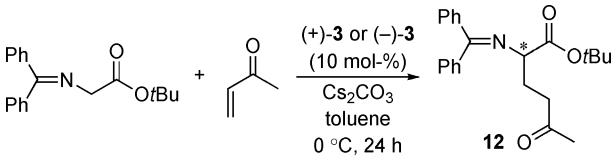
The application of inherently chiral calixarenes as chiral catalysts is a worthy challenge in organic syntheses. However, quite a limited number of examples of asymmetric catalysis with inherently chiral calixarenes have been reported.[9–11] As an additional example of an inherently chiral calixarene catalyst, chiral calix[4]arene **2** was applied to the asymmetric Michael addition reaction of thiophenol which is known to be catalysed by chiral amino alcohols (Scheme 4).[21] Both enantiomers (+)-**2** and (–)-**2** promoted the reaction efficiently and gave a Michael addition product **11** in good yields. The chiral induction of the product was observed as 15% *ee* and the configuration of the major enantiomer was *S* with (+)-**2** and *R* with (–)-**2**. The observed enantioselectivities were comparable with our previous results using an inherently chiral calix[4]arene with an aminophenol structure.[10]



(+)-**2**: 73% yield, 15% *ee* (*S*)
(–)-**2**: 71% yield, 15% *ee* (*R*)

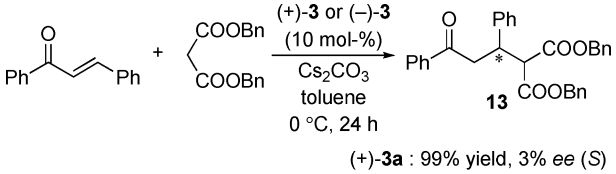
Scheme 4. Asymmetric Michael addition reaction of thiophenol catalysed by **2**.

Over the past decade, asymmetric phase-transfer catalysis based on the use of chiral quaternary ammonium salts as catalysts has become a topic of great scientific interest.[22] The inherently chiral calix[4]arenes **3a** and **3b**, containing a quaternary ammonium moiety, were applied to asymmetric reactions as chiral phase-transfer catalysts. In a preliminary trial, they were applied to an asymmetric Michael addition reaction of a glycine derivative (Scheme 5).[23] Thus, the asymmetric Michael addition of a glycine derivative with methyl vinyl ketone in toluene with solid Cs_2CO_3 under the influence of either (+)-**3a** or (–)-**3a** gave the corresponding α-amino acid derivative **12** in excellent yields with low enantioselectivities (5% *ee*). The reaction under the influence of **3b** gave the product **12** in excellent yield with slightly low selectivity compared with the reaction using **3a**. Asymmetric Michael addition reactions of malonate catalysed by **3a** and **3b** were also examined under similar reaction conditions (Scheme 6).[24] In the case of Michel additions of malonate, catalyst **3b** was better than **3a** in terms of enantioselectivity. These results may indicate that the tuning of the catalyst structure in each reaction is important



(+)-**3a** : 99% yield, 5% *ee* (*S*)
(–)-**3a** : 99% yield, 5% *ee* (*R*)
(+)-**3b** : 97% yield, 4% *ee* (*S*)
(–)-**3b** : 98% yield, 4% *ee* (*R*)

Scheme 5. Asymmetric Michael addition reaction of a glycine derivative catalysed by **3** under phase-transfer conditions.



(+)-**3a** : 99% yield, 3% *ee* (*S*)
(–)-**3a** : 99% yield, 3% *ee* (*R*)
(+)-**3b** : 99% yield, 6% *ee* (*R*)
(–)-**3b** : 99% yield, 6% *ee* (*S*)

Scheme 6. Asymmetric Michael addition reaction of malonate catalysed by **3** under phase-transfer conditions.

for the improvement of enantioselectivity. Although the observed enantioselectivities in the reactions were poor, these are the first examples of an inherently chiral calixarene being applied to asymmetric phase-transfer catalysis.[25]

Conclusions

In this study, we have described the synthesis of an inherently chiral calix[4]arene amino acid as a chiral building block. The optically pure, inherently chiral calix[4]arene amino acid **1** was prepared by the separation of a diastereomeric mixture of the calix[4]arene amino acid derivatives **10a** and **10b** bearing a (*R*)-BINOL moiety. The separated **10a** and **10b** were easily transformed to different types of inherently chiral calix[4]arenes **2** and **3** in optically pure forms. The calix[4]arenes **2** and **3** were applied to asymmetric reactions as chiral base catalysts and as chiral phase-transfer catalysts. Further improvements in the structure of chiral calix[4]arenes that will allow more efficient asymmetric catalysis are now in progress in our laboratory.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$. Tetramethylsilane (TMS) served as the internal standard (δ = 0 ppm) for ^{1}H NMR and $CDCl_3$ served as the internal standard (δ = 77.0 ppm) for ^{13}C NMR spectroscopy. IR spectra were measured with a Jasco FTIR-700 spectrometer using KBr discs. Circular dichroism (CD) spectra were measured with a Jasco J-820 spectrometer. Optical rotations were measured on a Jasco DIP-1000 digital polarimeter. High performance liquid chromatography (HPLC) was performed on a Hitachi 655 Liquid Chromatograph. Preparative gel-permeation chromatography (GPC) and preparative HPLC were performed using a JAI model 908 liquid chromatograph with JAIGEL-1H and -2H columns with a SUMICHIRAL OA-4800 column (2.0 × 25 cm), respectively. SUMICHIRAL OA-4800 columns were preactivated by $CHCl_3$ containing 0.2% TFA. Analytical thin-layer chromatography (TLC) and column chromatography were carried out on precoated silica gel 60 F_{254} glass plates (E. Merck) and with silica gel 60 (spherical 0.040–0.100 mm, Kanto), respectively. Tetrahydrofuran (THF) was freshly distilled from Na/benzophenone.

5,11-Dibromo-25,26,27,28-tetrabenzyloxycalix[4]arene (5): To a solution of 5,11-dibromo-25,26-dibenzyloxy-27,28-dihydroxycalix[4]arene **4**[15] (13.0 mmol) and NaH (130 mmol, 60% dispersion in paraffin liquid) in CH_3CN (300 mL) was added benzyl bromide (130 mmol) at room temperature. The reaction mixture was stirred for 2 h at room temperature and then quenched with 1 N aqueous HCl (150 mL). After the removal of CH_3CN by evaporation, organic materials were extracted with $CHCl_3$ (3× 70 mL) and the organic extracts were dried with $MgSO_4$. Evaporation of solvents and purification of the residue by column chromatography on silica gel ($CHCl_3$/hexane = 1:3 to 1:1 as eluent) afforded **5** in 87% yield (10.7 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.30 (m, 20 H), 6.52–6.74 (m, 10 H), 4.83–4.96 (m, 8 H), 4.26 (d, *J* = 13.7 Hz, 1 H), 4.12 (d, *J* = 13.7 Hz, 2 H), 3.98 (d, *J* = 13.8 Hz, 1 H), 3.02 (d, *J* = 13.7 Hz, 1 H), 2.87 (d, *J* = 13.8 Hz, 2 H), 2.70 (d, *J* = 13.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.24, 154.33, 137.77, 137.43, 136.87, 135.29, 134.40, 131.09, 130.44, 129.62, 129.41, 128.56, 128.05, 128.03, 127.99, 127.86, 122.60, 115.02, 76.48, 76.28, 31.21, 31.09, 30.91 ppm. IR: $\tilde{\nu}$ = 3061, 3029, 2916, 2866, 1457, 1210, 1190, 977, 750, 697 cm^{-1}. $C_{56}H_{46}Br_2O_4$ (942.77): calcd. C 71.34, H 4.92; found C 71.05, H 4.82.

5-Bromo-11-formyl-25,26,27,28-tetrabenzyloxycalix[4]arene [(±)-6]: To a solution of 5,11-dibromo-25,26,27,28-tetrabenzyloxycalix[4]arene **5** (5.0 mmol) in THF (80 mL), was added *n*BuLi (5.5 mmol, 1.5 M in hexane) at –78 °C under an argon atmosphere and the mixture was stirred for 15 min at this temperature. Dry dimethylformamide (7.5 mmol) was then added and the mixture was stirred for 15 min at –78 °C. The reaction mixture was then quenched with 0.1 N aqueous HCl (60 mL). After the removal of THF by evaporation, organic materials were extracted with $CHCl_3$ (3× 30 mL). The organic extracts were washed with water and dried with $MgSO_4$. Evaporation of solvents and purification of the residue by column chromatography on silica gel ($CHCl_3$/hexane = 1:2 to 2:1 as eluent) afforded **6** in 84% yield (3.75 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1 H), 7.09–7.34 (m, 22 H), 6.42–6.70 (m, 8 H), 4.79–5.06 (m, 8 H), 4.27 (d, *J* = 13.7 Hz, 1 H), 4.21 (d, *J* = 13.8 Hz, 1 H), 4.12 (d, *J* = 13.7 Hz, 1 H), 4.05 (d, *J* = 13.9 Hz, 1 H), 3.04 (d, *J* = 13.7 Hz, 1 H), 3.02 (d, *J* = 13.9 Hz, 1 H), 2.88 (d, *J* = 13.8 Hz, 1 H), 2.83 (d, *J* = 14.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.67, 160.95, 155.38, 155.07, 154.18, 137.44, 137.35, 137.28, 137.03, 136.78, 136.54, 136.48, 136.24, 135.70, 134.96, 134.82, 133.96, 131.09 130.96, 130.51, 130.40, 129.86, 129.57, 129.53, 129.30, 128.73, 128.54, 128.15, 128.07, 128.00, 127.97, 127.91, 127.88, 122.75, 122.43, 115.18, 76.70, 76.53, 76.47, 76.11, 31.24, 31.14, 31.04, 31.01 ppm. IR: $\tilde{\nu}$ = 3061, 3029, 2917, 2865, 2725, 1688, 1456, 1191, 977, 748, 698 cm^{-1}. $C_{57}H_{47}BrO_5 \cdot 0.1CHCl_3$ (891.88·0.1$CHCl_3$): calcd. C 75.89, H 5.24; found C 75.81, H 5.10.

5-[(Allylamino)methyl]-11-bromo-25,26,27,28-tetrabenzyloxycalix[4]arene [(±)-7]: To a solution of **6** (4.0 mmol) in a THF (20 mL) and (15 mL) mixture was added allylamine (20 mmol) at room temperature and the mixture was stirred for 24 h. $NaBH_4$ (4.0 mmol) was then added and the mixture was stirred for 30 min. The reaction mixture was quenched with sat. aqueous NH_4Cl. After the removal of THF and EtOH by evaporation, organic materials were extracted with $CHCl_3$ (3× 30 mL). The organic extracts were washed with water and dried with $MgSO_4$. Evaporation of solvents and purification of the residue by column chromatography on silica gel ($CHCl_3$/AcOEt = 1:0 to 0:1 as eluent) afforded **7** in 92% yield (3.43 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12–7.52 (m, 20 H), 6.61–6.74 (m, 6 H), 6.39–6.46 (m, 4 H), 5.89–5.99 (m, 1 H), 5.17–5.22 (m, 2 H), 4.78–5.00 (m, 8 H), 4.23 (d, *J* = 13.5 Hz, 1 H), 4.21 (d, *J* = 13.5 Hz, 1 H), 4.08 (d, *J* = 13.5 Hz, 1 H), 4.05 (d, *J* = 13.5 Hz, 1 H), 3.66 (s, 2 H), 3.19 (d, *J* = 6.2 Hz, 2 H), 2.99 (d, *J* = 13.7 Hz, 1 H), 2.97 (d, *J* = 13.7 Hz, 1 H), 2.82 (d, *J* = 13.6 Hz, 1 H), 2.80 (d, *J* = 13.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.44, 155.03, 154.16, 137.61, 137.38, 137.32, 137.08, 137.02, 136.89, 136.29, 136.06, 135.40, 135.17, 134.52, 134.35, 134.12, 130.54, 130.51, 129.80, 129.78, 129.43, 129.19, 129.15, 128.77, 128.54, 128.15, 128.02, 127.98, 127.94, 127.87, 127.83, 122.55, 122.15, 118.38, 115.02, 76.67, 76.54, 76.14, 76.00, 51.54, 50.15, 31.22, 31.08 ppm. IR: $\tilde{\nu}$ = 3423, 3061, 3029, 2975, 2916, 2865, 1456, 1211, 1190, 981, 753, 697 cm^{-1}. $C_{60}H_{54}BrNO_4 \cdot 0.5CHCl_3$ (932.98·0.5$CHCl_3$): calcd. C 73.24, H 5.49, N 1.41; found C 73.47, H 5.45, N 1.45.

5-Bromo-11-[(diallylamino)methyl]-25,26,27,28-tetrabenzyloxycalix[4]arene [(±)-8]: To a mixture of **7** (3.0 mmol), K_2CO_3 (6.0 mmol) and CH_3CN (60 mL) was added allyl bromide (3.3 mmol) and the mixture was heated at 50 °C for 15 h. The reaction mixture was cooled to room temperature and the mixture quenched with water.

After the removal of CH_3CN by evaporation, organic materials were extracted with $CHCl_3$ (3× 30 mL) and the organic extracts were dried with $MgSO_4$. Evaporation of solvents and purification of the residue by column chromatography on silica gel ($CHCl_3$/AcOEt = 30:1 to 15:1 as eluent) afforded **8** in 90% yield (2.63 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10–7.38 (m, 20 H), 6.59–6.77 (m, 6 H), 6.34–6.41 (m, 4 H), 5.81–5.90 (m, 2 H), 5.13–5.18 (m, 4 H), 4.80–5.15 (m, 8 H), 4.23 (d, J = 13.6 Hz, 1 H), 4.21 (d, J = 13.5 Hz, 1 H), 4.07 (d, J = 13.5 Hz, 1 H), 4.05 (d, J = 13.5 Hz, 1 H), 3.39 (s, 2 H), 2.94–3.00 (m, 6 H), 2.81 (d, J = 13.7 Hz, 1 H), 2.78 (d, J = 13.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.39, 154.96, 154.51, 154.09, 137.68, 137.40, 137.09, 136.96, 136.11, 135.81, 135.23, 134.98, 134.41, 130.53, 130.41, 129.88, 129.70, 129.39, 129.16, 129.05, 128.78, 128.16, 128.15, 128.00, 127.83, 127.80, 122.54, 122.28, 117.70, 115.04, 76.65, 76.56, 76.03, 56.82, 56.15, 31.26, 31.21, 31.11, 31.08 ppm. IR: $\tilde{\nu}$ = 3062, 3029, 2975, 2917, 2867, 2807, 1458, 1211, 1190, 979, 916, 697 cm^{-1}. $C_{63}H_{58}BrNO_4 \cdot 0.1CHCl_3$ (973.04·0.1$CHCl_3$): calcd. C 76.95, H 5.94, N 1.42; found C 76.75, H 5.89, N 1.23.

5-Carboxy-11-[(diallylamino)methyl]-25,26,27,28-tetrabenzyloxycalix[4]arene [(±)-9]: To a solution of **8** (2.0 mmol) in THF (50 mL) was added *n*BuLi (3.0 mmol, 1.5 M in hexane) at –78 °C under an argon atmosphere and the mixture was stirred for 15 min at this temperature. CO_2 gas was then bubbled through a needle into the solution for 15 min at –78 °C. The reaction mixture was quenched with 0.1 N aqueous HCl (40 mL). After removal of THF by evaporation, organic materials were extracted with $CHCl_3$ (3× 20 mL). The organic extracts were washed with water and dried with $MgSO_4$. Evaporation of solvents and purification of the residue by column chromatography on silica gel ($CHCl_3$/MeOH = 40:1 to 10:1 as eluent) afforded **9** in 78% yield (1.46 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.03 (br. s, 1 H), 7.19–7.44 (m, 22 H), 6.41–6.73 (m, 8 H), 6.03–6.13 (m, 2 H), 5.39–5.42 (m, 2 H), 5.01–5.15 (m, 6 H), 4.78–4.88 (m, 4 H), 4.23 (d, J = 13.4 Hz, 1 H), 4.18 (d, J = 13.4 Hz, 1 H), 4.16 (d, J = 13.4 Hz, 1 H), 4.10 (d, J = 13.6 Hz, 1 H), 3.83 (d, J = 13.6 Hz, 1 H), 3.76 (d, J = 13.5 Hz, 1 H), 3.01–3.18 (br. m, 2 H), 2.98 (d, J = 13.5 Hz, 1 H), 2.96 (d, J = 14.1 Hz, 1 H), 2.93 (d, J = 14.4 Hz, 1 H), 2.89 (d, J = 14.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.85, 159.82, 156.13, 155.11, 155.07, 137.25, 136.99, 136.64, 136.56, 136.40, 136.03, 135.84, 135.32, 135.22, 134.75, 134.04, 131.48, 130.98, 130.73, 130.16, 129.79, 129.75, 129.47, 129.44, 128.72, 128.28, 128.16, 128.14, 128.09, 128.03, 127.92, 127.71, 127.28, 124.61, 124.09, 122.65, 122.23, 121.20, 77.03, 76.82, 76.11, 76.01, 53.86, 53.68, 31.17 ppm. IR: $\tilde{\nu}$ = 3422, 3060, 3029, 2920, 2868, 2526, 1703, 1455, 1212, 1189, 979, 763, 698 cm^{-1}. $C_{64}H_{59}NO_6 \cdot 0.7CHCl_3$ (938.16·0.7$CHCl_3$): calcd. C 76.11, H 5.82, N 1.37; found C 76.14, H 5.89, N 1.38.

Diastereomers 10a and 10b: To a solution of **9** (2.0 mmol), DCC (3.0 mmol) and DMAP (1.0 mmol) in CH_2Cl_2 (30 mL) was added (*R*)-BINOL (2.2 mmol) at room temperature and the mixture was stirred for 6 h. The reaction mixture was filtered through celite and the filtrate was dried with $MgSO_4$. Evaporation of CH_2Cl_2 and purification of the residue by column chromatography on silica gel ($CHCl_3$/AcOEt = 30:1 to 5:1 as eluent) afforded a ca. 1:1 mixture of diastereomers **10a** and **10b** in 92% yield (2.22 g).

Resolution of Calix[4]arenes 10a and 10b by Preparative HPLC: Resolution of diastereomers **10a** and **10b** was carried out by preparative HPLC using a SUMICHIRAL OA-4800 column (2.0 × 25 cm) with $CHCl_3$ as the eluent. The diastereomeric mixture of **10a** and **10b** (≈ 1:1) (300 mg) was then loaded onto the preparative column. The $CHCl_3$ solutions of separated diastereomers were washed with sat. aqueous $NaHCO_3$ and pure calix[4]arenes **10a** (first fraction) (≈ 100 mg) and **10b** (second fraction) (≈ 100 mg) were obtained. The diastereomeric purity of **10a** and **10b** was determined by HPLC analysis.

10a: $[a]_D^{25}$ = +49.3 (c = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 8.9 Hz, 1 H), 7.98 (d, J = 8.2 Hz, 1 H), 7.78 (d, J = 8.8 Hz, 2 H), 7.61 (d, J = 8.9 Hz, 1 H), 7.50 (dt, J = 1.5, 7.3 Hz, 1 H), 7.09–7.36 (m, 26 H), 6.90–6.94 (m, 2 H), 6.37–6.59 (m, 6 H), 6.23–6.25 (m, 2 H), 6.12 (br. s, 1 H), 5.66–5.76 (m, 2 H), 4.98–5.06 (m, 8 H), 4.76–4.86 (m, 4 H), 4.17 (d, J = 13.5 Hz, 1 H), 4.16 (d, J = 13.5 Hz, 1 H), 4.00 (d, J = 13.4 Hz, 1 H), 3.98 (d, J = 13.5 Hz, 1 H), 3.24 (d, J = 13.7 Hz, 1 H), 3.16 (d, J = 13.8 Hz, 1 H), 2.93 (d, J = 13.5 Hz, 1 H + 1 H), 2.77 (d, J = 6.1 Hz, 4 H), 2.68 (d, J = 13.6 Hz, 1 H), 2.63 (d, J = 13.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.57, 160.04, 155.20, 154.89, 153.95, 151.90, 148.22, 137.59, 137.36, 136.94, 135.93, 135.91, 135.64, 135.60, 135.42, 135.33, 134.52, 134.30, 133.78, 133.75, 133.53, 133.45, 131.84, 130.56, 130.26, 130.00, 129.86, 129.68, 129.60, 129.44, 128.87, 128.69, 128.43, 128.35, 128.24, 128.19, 128.16, 128.04, 128.01, 127.97, 127.95, 127.87, 127.82, 127.75, 127.00, 126.47, 125.81, 124.79, 123.12, 122.61, 122.31, 122.23, 121.95, 118.23, 117.70, 114.28, 76.73, 76.62, 76.04, 75.89, 56.77, 56.20, 31.25, 31.18, 31.05, 31.02 ppm. IR: $\tilde{\nu}$ = 3525, 3446, 3060, 3030, 2976, 2918, 2867, 2816, 1730, 1457, 1303, 1211, 1171, 980, 747, 698 cm^{-1}. $C_{84}H_{71}NO_7 \cdot 0.1CHCl_3$ (1206.47·0.1$CHCl_3$): calcd. C 82.91, H 5.87, N 1.15; found C 82.60, H 5.74, N 0.93.

10b: $[a]_D^{23}$ = +77.3 (c = 0.88, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 8.9 Hz, 1 H), 7.99 (d, J = 8.2 Hz, 1 H), 7.76–7.80 (m, 2 H), 7.51 (dt, J = 1.1, 7.4 Hz, 1 H), 7.47 (d, J = 8.9 Hz, 1 H), 7.12–7.36 (m, 26 H), 6.89–6.95 (m, 2 H), 6.37–6.61 (m, 6 H), 6.12–6.19 (m, 2 H), 5.70–5.80 (m, 2 H), 5.48 (br. s, 1 H), 4.91–5.12 (m, 8 H), 4.75–4.87 (m, 4 H), 4.18 (d, J = 13.4 Hz, 1 H), 4.16 (d, J = 13.3 Hz, 1 H), 3.98 (d, J = 13.5 Hz, 1 H), 3.97 (d, J = 13.5 Hz, 1 H), 3.26 (d, J = 13.4 Hz, 1 H), 3.19 (d, J = 13.4 Hz, 1 H), 2.94 (d, J = 13.6 Hz, 1 H + 1 H), 2.86 (dd, J = 6.3, 13.9 Hz, 2 H), 2.78 (dd, J = 7.1, 13.8 Hz, 2 H), 2.66 (d, J = 13.7 Hz, 1 H), 2.64 (d, J = 13.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.84, 160.12, 155.23, 154.90, 154.02, 151.79, 148.43, 137.58, 137.35, 136.88, 135.93, 135.58, 135.48, 135.21, 135.16, 134.57, 134.44, 133.75, 133.58, 133.51, 133.34, 131.98, 130.48, 130.36, 130.32, 130.00, 129.61, 129.59, 129.46, 129.40, 129.07, 128.82, 128.68, 128.33, 128.26, 128.19, 128.02, 127.98, 127.95, 127.90, 127.86, 127.76, 127.71, 127.24, 126.54, 125.99, 125.61, 124.62, 123.27, 123.13, 122.27, 122.17, 121.85, 118.30, 117.66, 114.25, 76.69, 76.55, 76.17, 75.80, 56.33, 55.87, 31.21, 31.14, 31.05 ppm. IR: $\tilde{\nu}$ = 3522, 3446, 3060, 3030, 3006, 2976, 2917, 2867, 2814, 1728, 1457, 1303, 1210, 1171, 979, 763, 747, 698 cm^{-1}. $C_{84}H_{71}NO_7$ (1206.47): calcd. C 83.62, H 5.93, N 1.16; found C 83.69, H 5.83, N 1.28.

5-(Aminomethyl)-11-carboxy-25,26,27,28-tetrabenzyloxycalix[4]arene (1): The mixtures of **10a** and **10b** (0.50 mmol), each with *N*,*N*′-dimethylbarbituric acid [NDMBA (2.5 mmol)], $Pd(OAc)_2$ (0.10 mmol) and PPh_3 (0.40 mmol) in CH_2Cl_2 (20 mL) were stirred for 8 h at 35 °C. After the removal of CH_2Cl_2 by evaporation, the solvent was replaced with benzene (20 mL). The benzene solution was washed with sat. aqueous $NaHCO_3$ (3× 10 mL) and dried with $MgSO_4$. Evaporation of solvents and purification of the residue by column chromatography on silica gel ($CHCl_3$/MeOH = 30:1 to 5:1 as eluent) afforded the de-*N*-allylated product. The de-*N*-allylated product in a THF (5.0 mL) ethanol (3.0 mL) solvent mixture was treated with 1 M aqueous NaOH (1.5 mL) and the mixture was heated at 60 °C for 6 h. The reaction mixtures were then cooled to 0 °C and neutralised with 1 N aqueous HCl (1.6 mL). After removal of THF and ethanol by evaporation, organic materials were ex-

tracted with $CHCl_3$ (3× 10 mL). The organic extracts were washed with water and dried with $MgSO_4$. Evaporation of solvents and purification of the residue by column chromatography on silica gel ($CHCl_3$/MeOH = 15:1 to 3:1 as eluent) afforded $(-)_{298}$-**1** and $(+)_{298}$-**1** in yields of 43% (0.184 g) and 41% (0.176 g), respectively. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (br. s, 3 H), 6.20–7.28 (m, 30 H), 4.69–4.97 (m, 8 H), 3.91–4.17 (m, 6 H), 2.79–2.94 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.16, 159.80, 156.05, 155.33, 154.84, 137.55, 137.40, 137.26, 136.98, 136.61, 136.12, 135.28, 134.98, 134.78, 134.14, 133.83, 130.67, 130.18, 129.69, 129.60, 129.04, 128.84, 128.48, 128.25, 128.09, 127.97, 127.82, 127.76, 127.74, 126.41, 123.79, 122.52, 122.17, 76.59, 76.49, 75.96, 43.11, 31.15, 31.04, 30.87 ppm. IR: $\tilde{\nu}$ = 3398, 3060, 3030, 2974, 2916, 2868, 2610, 1685, 1602, 1455, 1376, 1281, 1213, 1191, 983, 762, 734, 698 cm^{-1}. $C_{58}H_{51}NO_6$·0.5$CHCl_3$ (858.03·0.5$CHCl_3$): calcd. C 76.60, H 5.60, N 1.53; found C 76.54, H 5.81, N 1.50.

5-[(Diallylamino)methyl]-11-hydroxymethyl-25,26,27,28-tetrabenzyloxycalix[4]arene (2): To solutions of **10a** and **10b** (0.50 mmol), each in THF (15 mL) was $LiAlH_4$ (1.5 mmol) at 0 °C. The mixtures were warmed to room temperature and stirred for 1 h. The reaction mixtures were quenched with 0.2 N aqueous HCl (30 mL). After the removal of THF by evaporation, organic materials were extracted with $CHCl_3$ (3× 10 mL). The organic extracts were washed with sat. aqueous $NaHCO_3$ and dried with $MgSO_4$. Evaporation of solvents and purification of the residue by column chromatography on silica gel ($CHCl_3$/AcOEt = 10:1 to 1:1 as eluent) afforded (–)-**2** ($[\alpha]_D^{27}$ = –2.2 [c = 1.1, $CHCl_3$]) and (+)-**2** ($[\alpha]_D^{26}$ = +2.3 [c = 1.1, $CHCl_3$]) in yields of 83% (0.384 g) and 81% (0.374 g), respectively. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.34 (m, 16 H), 7.11–7.16 (m, 4 H), 6.61–6.72 (m, 5 H), 6.35–6.46 (m, 5 H), 5.78–5.88 (m, 2 H), 5.10–5.15 (m, 4 H), 4.94–5.02 (m, 4 H), 4.82–4.88 (m, 4 H), 4.14–4.21 (m, 6 H), 3.39 (d, J = 13.3 Hz, 1 H), 3.35 (d, J = 13.3 Hz, 1 H), 2.87–2.99 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.32, 155.21, 154.76, 154.38, 137.61, 137.57, 137.54, 135.79, 135.76, 135.50, 135.42, 134.76, 134.55, 129.88, 129.35, 129.27, 129.22, 128.39, 128.11, 128.07, 127.86, 127.81, 127.80, 127.72, 127.13, 126.98, 122.18, 121.69, 117.63, 76.59, 75.99, 65.10, 56.99, 56.08, 31.27 ppm. IR: $\tilde{\nu}$ = 3423, 3062, 3030, 2918, 2865, 1456, 1211, 1190, 1133, 985, 916, 763, 698 cm^{-1}. $C_{64}H_{61}NO_5$ (924.17): calcd. C 83.18, H 6.65, N 1.52; found C 82.95, H 6.59, N 1.47.

5-Hydroxymethyl-11-[(triallylammonio)methyl]-25,26,27,28-tetrabenzyloxycalix[4]arene Bromide (3a): The mixtures of (–)-**2** and (+)-**2** (0.20 mmol) each with allyl bromide (1.0 mmol) in CH_3CN (5.0 mL) were heated at 80 °C for 8 h. Evaporation of CH_3CN and purification of the residue by column chromatography on silica gel ($CHCl_3$/MeOH = 20:1 to 5:1 as eluent) afforded (+)-**3a** ($[\alpha]_D^{27}$ = +9.9 (c = 1.1, $CHCl_3$)) and (–)-**3a** ($[\alpha]_D^{28}$ = –9.9 [c = 1.1, $CHCl_3$]) yields of 91% (0.190 g) and 93% (0.194 g), respectively. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.32 (m, 20 H), 7.11 (d, J = 1.7 Hz, 1 H), 6.86–6.90 (m, 2 H), 6.82 (dd, J = 1.5, 7.5 Hz, 1 H), 6.78 (d, J = 1.5 Hz, 1 H), 6.74 (t, J = 7.4 Hz, 1 H), 6.48 (dd, J = 1.6, 7.3 Hz, 1 H), 6.37 (t, J = 7.4 Hz, 1 H), 6.30–6.34 (m, 2 H), 5.82–5.93 (m, 3 H), 5.57 (d, J = 10.4 Hz, 3 H), 5.51 (d, J = 16.8 Hz, 3 H), 5.02–5.18 (m, 4 H), 4.68–4.77 (m, 4 H), 4.54 (s, 2 H), 4.20 (d, J = 13.0 Hz, 1 H), 4.19 (d, J = 13.2 Hz, 1 H), 4.15 (s, 2 H), 4.06 (d, J = 13.1 Hz, 1 H), 4.03 (d, J = 13.3 Hz, 1 H), 3.60 (dd, J = 7.0, 13.8 Hz, 3 H), 3.35 (dd, J = 6.9, 13.8 Hz, 3 H), 2.87–2.94 (m, 3 H), 2.74 (d, J = 13.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.34, 155.01, 154.93, 154.24, 137.53, 137.27, 137.07, 136.75, 136.51, 136.48, 136.37, 135.72, 135.67, 135.64, 135.20, 134.16, 133.88, 133.29, 131.29, 130.23, 130.08, 129.35, 129.28, 128.87, 128.31, 128.17, 128.01, 127.86, 127.83, 127.82, 127.71, 127.51, 127.47, 127.21, 124.65, 122.48, 122.02, 120.03, 77.43, 77.10, 76.06, 75.32, 63.85, 62.75, 61.00, 31.26, 31.13, 31.04 ppm. IR: $\tilde{\nu}$ = 3377, 3060, 3029, 2920, 2866, 1456, 1214, 1190, 1135, 982, 748, 698 cm^{-1}. $C_{67}H_{66}BrNO_5$·H_2O (1045.15·H_2O): calcd. C 75.69, H 6.45, N 1.32; found C 75.75, H 6.32, N 1.29.

5-[(Diallyl-methylammonio)methyl]-11-hydroxymethyl-25,26,27,28-tetrabenzyloxycalix[4]arene Iodide (3b): Mixtures of (–)-**2** and (+)-**2** (0.20 mmol) each with methyl iodide (2.0 mmol) in CH_3CN (5.0 mL) were heated at 80 °C for 8 h. Evaporation of CH_3CN and purification of the residue by column chromatography on silica gel ($CHCl_3$/MeOH = 20:1 to 5:1 as eluent) afforded (+)-**3b** ($[\alpha]_D^{27}$ = +11.2 [c = 0.93, $CHCl_3$]) and (–)-**3b** ($[\alpha]_D^{27}$ = –11.3 [c = 1.1, $CHCl_3$]) yields of 98% (0.209 g) and 97% (0.207 g), respectively. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.33 (m, 21 H), 6.96 (d, J = 1.9 Hz, 1 H), 6.92 (dd, J = 1.4, 7.4 Hz, 1 H), 6.86–6.89 (m, 2 H), 6.76 (t, J = 7.4 Hz, 1 H), 6.51 (d, J = 7.2 Hz, 1 H), 6.36 (t, J = 7.4 Hz, 1 H), 6.32 (dd, J = 1.5, 7.4 Hz, 1 H), 6.20 (d, J = 1.5 Hz, 1 H), 5.57–5.86 (m, 5 H), 5.36 (d, J = 16.7 Hz, 1 H), 5.15–5.22 (m, 3 H), 5.05 (d, J = 11.8 Hz, 1 H), 4.61–4.76 (m, 5 H), 4.52 (dd, J = 7.0, 12.7 Hz, 1 H), 4.33 (d, J = 12.7 Hz, 1 H), 4.22 (d, J = 12.9 Hz, 1 H), 4.17 (d, J = 13.1 Hz, 1 H), 4.06 (d, J = 13.0 Hz, 1 H), 4.00 (d, J = 13.0 Hz, 1 H), 3.97 (d, J = 10.1 Hz, 1 H), 3.90 (dd, J = 7.1, 13.2 Hz, 1 H), 3.80 (t, J = 6.8 Hz, 1 H), 3.70 (dd, J = 6.8, 13.3 Hz, 1 H), 3.18 (dd, J = 6.6, 13.8 Hz, 1 H), 2.95 (d, J = 12.9 Hz, 1 H), 2.92 (d, J = 13.7 Hz, 1 H), 2.89 (d, J = 13.6 Hz, 1 H), 2.75 (dd, J = 7.4, 13.5 Hz, 1 H), 2.68 (d, J = 13.5 Hz, 1 H), 2.18 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.14, 154.83, 154.77, 154.27, 137.51, 137.24, 136.92, 136.78, 136.64, 136.40, 136.03, 135.83, 135.04, 134.88, 133.96, 133.86, 131.17, 130.31, 130.10, 129.51, 129.30, 128.85, 128.54, 128.26, 128.16, 128.03, 127.88, 127.84, 127.76, 127.72, 127.62, 127.07, 124.12, 124.00, 122.61, 122.29, 119.71, 77.59, 77.29, 76.10, 75.09, 63.70, 63.37, 62.33, 61.20, 46.41, 31.26, 31.16, 31.02, 30.86 ppm. IR: $\tilde{\nu}$ = 3376, 3060, 3029, 2920, 2866, 1458, 1215, 1191, 1136, 982, 766, 748, 699 cm^{-1}. $C_{65}H_{64}INO_5$·H_2O (1066.11·H_2O): calcd. C 72.01, H 6.14, N 1.29; found C 72.09, H 5.73, N 1.25.

Asymmetric Michael Addition Reaction of Thiophenol Catalysed by Either (+)- or (–)-2 (Scheme 4): To a solution of either (+)- or (–)-**2** (0.015 mmol) and 2-cyclohexen-1-one (0.50 mmol) in toluene (1.0 mL) was added thiophenol (0.60 mmol) at 0 °C under an argon atmosphere and the mixture was stirred for 24 h at this temperature. The reaction was quenched with 0.2 N aqueous HCl (2.0 mL) and the organic materials were extracted with $CHCl_3$ (2× 3.0 mL). The organic solution was washed with water (5.0 mL) and dried with $MgSO_4$. Evaporation of solvents and purification of the residue using flash chromatography on silica gel afforded the Michael addition product **11**. The enantioselectivity of the product was determined using chiral HPLC analysis and the absolute configuration was determined by comparison of the observed optical rotation with the reported value.[21]

3-(Phenylthio)cyclohexanone (11):[21] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.43 (m, 2 H), 7.25–7.33 (m, 3 H), 3.39–3.45 (m, 1 H), 2.65–2.70 (m, 1 H), 2.28–2.40 (m, 3 H), 2.10–2.16 (m, 2 H), 1.66–1.78 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.71, 133.15, 132.96, 129.03, 127.74, 47.69, 46.04, 40.83, 31.15, 23.97 ppm. IR: $\tilde{\nu}$ = 2946, 1715, 1222, 745, 694 cm^{-1}. MS (EI) m/z 206 $[M]^+$, 110, 97.

Asymmetric Michael Addition Reaction of a Glycine Derivative Catalysed by Either (+)- or (–)-3 (Scheme 5): To a mixture of either (+)- or (–)-**3** (0.010 mmol), *tert*-butyl glycinate benzophenone Schiff base (0.10 mmol) and Cs_2CO_3 (0.30 mmol) in toluene (0.50 mL) was added methyl vinyl ketone (0.50 mmol) at 0 °C under an argon atmosphere and the mixture was stirred for 24 h at

this temperature. The reaction was quenched with water (3.0 mL) and the organic materials were extracted with $CHCl_3$ (2× 3.0 mL). The organic solution was washed with water (5.0 mL) and dried with $MgSO_4$. Evaporation of solvents and purification of the residue using flash chromatography on silica gel afforded a Michael addition product **12**. The enantioselectivity of the product was determined using chiral HPLC analysis, and the absolute configuration was determined by comparison of the HPLC retention time with the reported time.[23]

***tert*-Butyl 2-(Diphenylmethyleneamino)-5-oxohexanoate (12):**[23] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.65 (m, 2 H), 7.30–7.47 (m, 6 H), 7.15–7.18 (m, 2 H), 3.96 (t, J = 6.1 Hz, 1 H), 2.44–2.58 (m, 2 H), 2.13 (s, 3 H), 2.08–2.20 (m, 2 H), 1.44 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.29, 170.92, 170.46, 139.38, 136.38, 130.27, 128.70, 128.57, 128.43, 127.97, 127.64, 81.10, 64.62, 39.80, 29.88, 27.98, 27.64 ppm. IR: $\tilde{\nu}$ = 3060, 2977, 2932, 1719, 1151, 699 cm^{-1}.

Asymmetric Michael Addition Reaction of Malonate Catalysed by Either (+)- or (–)-3 (Scheme 6): To a mixture of either (+)- or (–)-**3** (0.010 mmol), chalcone (0.10 mmol) and Cs_2CO_3 (0.30 mmol) in toluene (0.50 mL) was added dibenzyl malonate (0.50 mmol) at 0 °C under an argon atmosphere and the mixture was stirred for 24 h at this temperature. The reaction was quenched with water (3.0 mL) and the organic materials were extracted with $CHCl_3$ (2× 3.0 mL). The organic solution was washed with water (5.0 mL) and dried with $MgSO_4$. Evaporation of solvents and purification of the residue using flash chromatography on silica gel afforded the Michael addition product **13**. The enantioselectivity of the product was determined using chiral HPLC analysis, and the absolute configuration was determined by comparison of the observed optical rotation with the reported value.[26]

Dibenzyl 2-(3-Oxo-1,3-diphenylpropyl)malonate (13):[26] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, J = 7.8 Hz, 2 H), 7.50 (t, J = 7.4 Hz, 1 H), 7.38 (t, J = 7.7 Hz, 2 H), 7.13–7.30 (m, 13 H), 7.04–7.07 (m, 2 H), 5.16 (d, J = 12.2 Hz, 1 H), 5.11 (d, J = 12.2 Hz, 1 H), 4.90 (s, 2 H), 4.22 (dt, J = 9.5, 6.8 Hz, 1 H), 3.95 (d, J = 9.5 Hz, 1 H), 3.44 (d, J = 6.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.28, 167.94, 167.42, 140.23, 136.63, 135.07, 134.97, 132.96, 128.51, 128.44, 128.38, 128.35, 128.25, 128.17, 128.10, 127.99, 127.13, 67.28, 67.07, 57.46, 42.20, 40.68 ppm. IR: $\tilde{\nu}$ = 3060, 3033, 2954, 1744, 1688, 1262, 1165, 1135, 747, 698 cm^{-1}.

Supporting Information (see also the footnote on the first page of this article): ^{1}H NMR and ^{13}C NMR spectra of all new compounds, as well as HPLC chromatographs for Michael addition products.

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