Synthesis and optical resolution of an inherently chiral calix[4]arene amino acid†

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The first synthesis and optical resolution of an inherently chiral calix[4]arene amino acid has been achieved.

Optically active natural 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, natural amino acids are used extensively as chiral starting materials, auxiliaries and catalysts in modern organic synthesis.[2] Also, artificial non-natural amino acids are of increasing interest for their special role in the design of biologically active compounds,[3] and more recently in the design of asymmetric organocatalysts.[2,4]

Calixarenes are versatile molecular scaffolds for the design of efficient and selective receptors.[5] Recently, interest has focused on the use of calixarenes in biological systems,[6] and some chiral calixarenes containing chiral residues at the wide or narrow rim have been applied to biological systems as biologically active compounds.[7]

In the course of our recent studies[8] on the design of "inherently" chiral calix[4]arenes,[9,10] which offer unique chiral building blocks, we became interested in the design and synthesis of an inherently chiral calix[4]arene amino acid.[11] Herein, we report the first synthesis of an inherently chiral calix[4]arene amino acid in an optically pure form.

The design of an inherently chiral calix[4]arene amino acid is shown in Fig. 1. The conformation of the chiral calix[4]arene amino acid, **1**, is fixed in the cone conformation, and the amino and carboxy groups are located in proximal positions on the wide rim. The near position of the amino and carboxy groups of **1**, which cooperate for chiral molecular recognition, provides a unique chiral environment at the cavity of the calixarene.

The *N*-protected calix[4]arene amino acid, **7**, can be prepared from the already reported proximally *para*-dibrominated calix[4]arene dibenzyl ether, **2**,[12] as outlined in Scheme 1. The dihydroxy groups of **2** were *O*-alkylated with benzyl bromide in the presence of NaH, and gave the proximally *para*-dibrominated calix[4]arene tetrabenzyl ether, **3**, in the cone conformation as a key intermediate. The *para*-dibromocalix[4]arene, **3**, was transformed into the mono-formylated compound, **4**, by treatment with 1.1 equivalents of *n*-BuLi and the subsequent addition of *N*,*N*-dimethylformamide (DMF). The reductive amination of the formyl group of **4** with allylamine gave the secondary amine, **5**, in 92% yield. Compound **5** was transformed with allyl bromide into tertiary amine **6** in 90% yield. Lithiation of the bromine substituent on **6**, and the trapping of the resulting anion with CO_2, gave the target *N*-protected calix[4]arene amino acid, **7**, as a racemate in 78% yield.

The efficient resolution of the inherently chiral calix[4]arene amino acid could be achieved by preparative HPLC after its conversion into the diastereomeric (*R*)-BINOL esters **8a** and **8b** (Scheme 2).[13] 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-(*N*,*N*-dimethylamino)pyridine (DMAP) gave a ~1 : 1 mixture of the diastereomers **8a** and **8b**. The diastereomeric mixture (0.30 g) of **8a** and **8b** was loaded onto a preparative HPLC column, and diastereomerically pure **8a** (~0.10 g) and **8b** (~0.10 g) were then obtained.[14] Although it was possible to separate the diastereomers by silica gel column chromatography, the method was, unfortunately, not efficient.

The ^{1}H NMR spectra of diastereomers **8a**, **8b**, and the mixture of **8a** and **8b**, are shown in Fig. 2. The diastereomers demonstrated differences in their ^{1}H NMR spectra, and a comparison of the spectra of diastereomerically pure **8a** (Fig. 2(a)), **8b** (Fig. 2(b)), and a mixture of the two (Fig. 2(c)), clearly indicates that a perfect separation of them was achieved by preparative HPLC. The diastereomeric purity of **8a** and **8b** was also confirmed by means of HPLC analyses.[15]

The NMR spectra of **8a** and **8b** provide evidence of their structure. The ^{1}H NMR spectrum of **8a** 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, corresponding to the four pertinent carbons. The values of the ^{13}C NMR chemical shifts, and the ^{1}H and ^{13}C NMR spectral patterns,

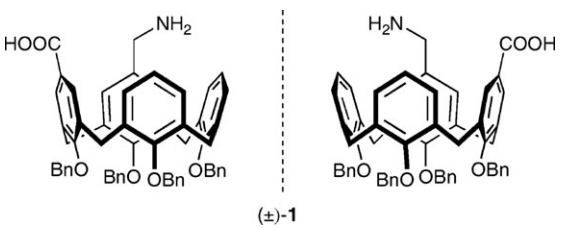

Fig. 1 An inherently chiral calix[4]arene amino acid, **1**.

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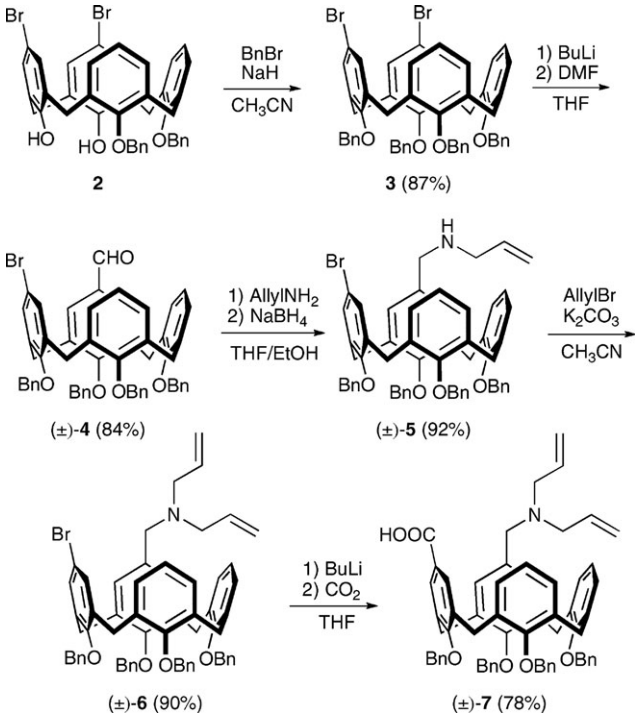
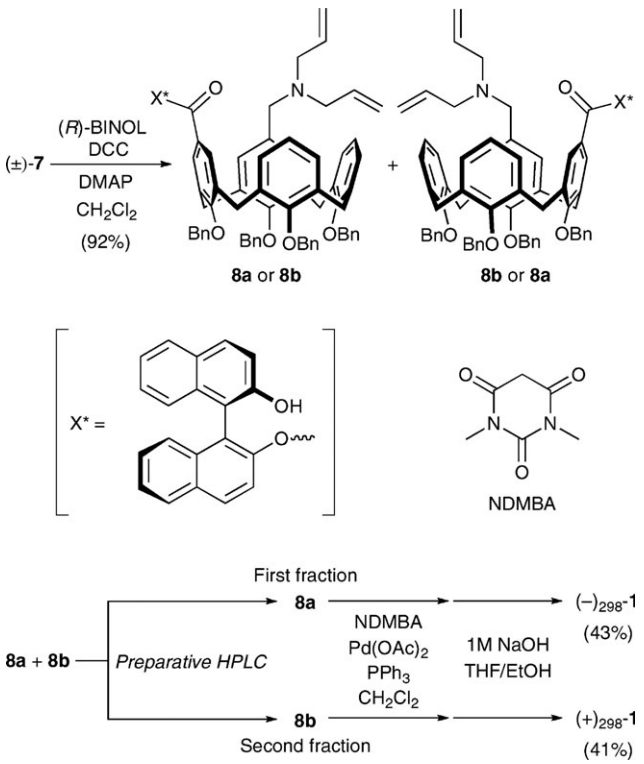


Scheme 1 The synthesis of *N*-protected calix[4]arene amino acid **7**.



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

indicate that **8a** is present in the cone conformation[16] and possesses inherent chirality. The NMR spectra of **8b** show a similar tendency.

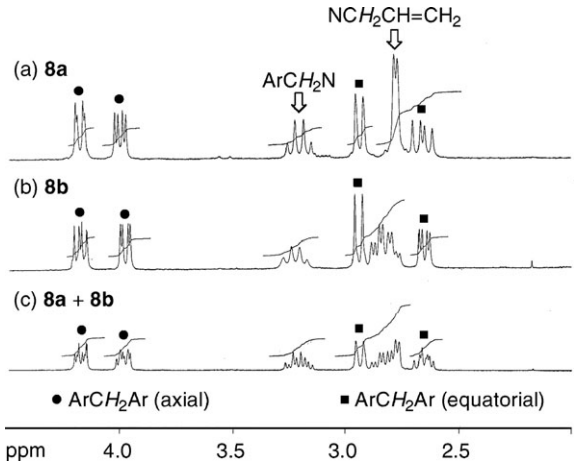


Fig. 2 A section of the ^{1}H NMR spectra of calix[4]arene (a) **8a**, (b) **8b**, and (c) a mixture of **8a** and **8b**, in $CDCl_3$ at 27 °C.

Finally, the palladium-catalyzed de-*N*-allylation[17] of **8a** and **8b**, and the subsequent hydrolysis with NaOH to remove the BINOL moiety, afforded the optically pure calix[4]arene amino acids $(-)_{298}$-**1** and $(+)_{298}$-**1**,[18] respectively (Scheme 2). The circular dichroism (CD) spectra of the enantiomers of **1** are perfect mirror images (Fig. 3).

In summary, we have presented the first synthesis of an inherently chiral calix[4]arene amino acid. 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 **8a** and **8b**, bearing a (*R*)-BINOL moiety. To advance the understanding of these biological systems, the application of **1** to chiral receptors and as an organocatalyst in asymmetric reactions is now in progress in our laboratory.

Experimental

Diastereomers 8a and 8b

To a solution of **7** (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 over Celite and the filtrate dried over $MgSO_4$. Evaporation of CH_2Cl_2 and

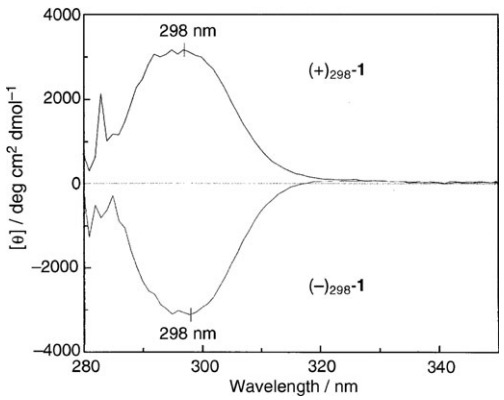


Fig. 3 The CD spectra of the enantiomers of calix[4]arene amino acid **1** in $CHCl_3$.

purification of the residue by column chromatography on silica gel ($CHCl_3$/AcOEt = 30 : 1 to 5 : 1 as eluent) afforded a ~1 : 1 mixture of diastereomers **8a** and **8b** in 92% yield.

Resolution of calix[4]arenes 8a and 8b by preparative HPLC

The resolution of diastereomers **8a** and **8b** 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 **8a** and **8b** (~1 : 1) (300 mg) was loaded onto a preparative column. $CHCl_3$ solutions of the separated diastereomers were washed with saturated aqueous $NaHCO_3$, and the pure calix[4]arenes **8a** (first fraction) (~100 mg) and **8b** (second fraction) (~100 mg) were then obtained. The diastereomeric purity of the calix[4]arenes **8a** and **8b** were determined by HPLC analysis.

8a. $[\alpha]_D^{25}$ +49.3 (*c* 1.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.9 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.9 Hz, 1H), 7.50 (dt, *J* = 1.5 and 7.3 Hz, 1H), 7.09–7.36 (m, 26H), 6.90–6.94 (m, 2H), 6.37–6.59 (m, 6H), 6.23–6.25 (m, 2H), 6.12 (br s, 1H), 5.66–5.76 (m, 2H), 4.98–5.06 (m, 8H), 4.76–4.86 (m, 4H), 4.17 (d, *J* = 13.5 Hz, 1H), 4.16 (d, *J* = 13.5 Hz, 1H), 4.00 (d, *J* = 13.4 Hz, 1H), 3.98 (d, *J* = 13.5 Hz, 1H), 3.24 (d, *J* = 13.7 Hz, 1H), 3.16 (d, *J* = 13.8 Hz, 1H), 2.93 (d, *J* = 13.5 Hz, 1H + 1H), 2.77 (d, *J* = 6.1 Hz, 4H), 2.68 (d, *J* = 13.6 Hz, 1H) and 2.63 (d, *J* = 13.7 Hz, 1H); ^{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 and 31.02; IR/cm^{-1}: 3525, 3446, 3060, 3030, 2976, 2918, 2867, 2816, 1730, 1457, 1303, 1211, 1171, 980, 747 and 698. Anal. calc. for $C_{84}H_{71}NO_7 \cdot 0.1CHCl_3$: C, 82.91; H, 5.87; N, 1.15. Found: C, 82.60; H, 5.74; N, 0.93%.

8b. $[\alpha]_D^{23}$ +77.3 (*c* 0.88 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.9 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.76–7.80 (m, 2H), 7.51 (dt, *J* = 1.1 and 7.4 Hz, 1H), 7.47 (d, *J* = 8.9 Hz, 1H), 7.12–7.36 (m, 26H), 6.89–6.95 (m, 2H), 6.37–6.61 (m, 6H), 6.12–6.19 (m, 2H), 5.70–5.80 (m, 2H), 5.48 (br s, 1H), 4.91–5.12 (m, 8H), 4.75–4.87 (m, 4H), 4.18 (d, *J* = 13.4 Hz, 1H), 4.16 (d, *J* = 13.3 Hz, 1H), 3.98 (d, *J* = 13.5 Hz, 1H), 3.97 (d, *J* = 13.5 Hz, 1H), 3.26 (d, *J* = 13.4 Hz, 1H), 3.19 (d, *J* = 13.4 Hz, 1H), 2.94 (d, *J* = 13.6 Hz, 1H + 1H), 2.86 (dd, *J* = 6.3 and 13.9 Hz, 2H), 2.78 (dd, *J* = 7.1 and 13.8 Hz, 2H), 2.66 (d, *J* = 13.7 Hz, 1H) and 2.64 (d, *J* = 13.7 Hz, 1H); ^{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 and 31.05; IR/cm^{-1}: 3522, 3446, 3060, 3030, 3006, 2976, 2917, 2867, 2814, 1728, 1457, 1303, 1210, 1171, 979, 763, 747 and 698. Anal. calc. for $C_{84}H_{71}NO_7$: 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 or (−)-1]

A mixture of **8a** or **8b** (0.50 mmol), *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) was stirred for 8 h at 35 °C. After the removal of CH_2Cl_2 by evaporation, the solvent was replaced by benzene (20 ml). The benzene solution was washed with saturated aqueous $NaHCO_3$ (3 × 10 ml) and dried over $MgSO_4$. Evaporation of the solvent 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 ml)–ethanol (3 ml) mixed solvent was treated with 1 M aqueous NaOH (1.5 ml), and the mixture was heated at 60 °C for 6 h. Then, the reaction mixture was cooled to 0 °C and neutralized with 1 M aqueous HCl (1.6 ml). After the removal of THF and ethanol by evaporation, the organic materials were extracted with $CHCl_3$ (3 × 10 ml). The organic extracts were washed with water and dried over $MgSO_4$. Evaporation of the solvent and purification of the residue by column chromatography on silica gel ($CHCl_3$/MeOH = 15 : 1 to 3 : 1 as eluent) afforded $(-)_{298}$-**1** or $(+)_{298}$-**1** in 43 and 41% yields, respectively: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (br s, 3H), 6.20–7.28 (m, 30H), 4.69–4.97 (m, 8H), 3.91–4.17 (m, 6H) and 2.79–2.94 (m, 4H); ^{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 and 30.87; IR/cm^{-1}: 3398, 3060, 3030, 2974, 2916, 2868, 2610, 1685, 1602, 1455, 1376, 1281, 1213, 1191, 983, 762, 734 and 698. Anal. calc. for $C_{58}H_{51}NO_6 \cdot 0.5CHCl_3$: C, 76.60; H, 5.60; N, 1.53. Found: C, 76.54; H, 5.81; N, 1.50%.[19]

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