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ORIGINAL ARTICLE

An inherently chiral calix[4]crown carboxylic acid in the 1,2-alternate conformation

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Abstract For better understanding of the structure/property relationship of inherently chiral calixarenes in the 1,2-alternate conformation, we designed and synthesized an inherently chiral calix[4]crown-4 carboxylic acid 1,2-alternate conformer. Resolution of the racemates was effected by condensation with (*S*)-BINOL as a chiral auxiliary and separation of the resultant diastereomers via preparative TLC plates, followed by hydrolysis of the isolated diastereomers to afford enantiopure antipodes of the title compound. Preliminary property study revealed that the title compound has the ability to enantioselectively discriminate 2-phenylglycinol by ^{1}H NMR spectroscopy.

Keywords Inherently chiral · Calix[4]arene · 1,2-Alternate · Resolution · Chiral recognition

Introduction

The study of functionalized chiral calixarenes is attractive to researchers because of its theoretical significance and prospect of application. The two major structural features of calixarenes, namely, the readiness of modification and the richness of stereochemistry provide an excellent opportunity of generating calixarene-based chiral species. At molecular level, a calixarene could be chiral by virtue of incorporating chiral subunit(s) into its skeleton, in which case the chirality is owing to local chiral element(s) such as a chiral center [1–7] and a chiral axis [8, 9]. Alternatively, a calixarene could be endowed with "inherent chirality", which is based on the asymmetric arrangement of achiral subunit(s) on its skeleton [10–18]. It is this stereochemical appeal that stimulates chemists to study the structures and functions of inherently chiral calixarenes.

The past decade has witnessed concrete advances in inherently chiral calixarenes. As regards synthesis, efficient resolution of racemates has become most widely used to obtain enantiopure enantiomers [19–29]. A few efforts have also been made on the asymmetric synthesis of inherently chiral calixarenes [30–37], with an impressive example recently reported by Arnott et al. [38, 39] demonstrating high enantiomeric excesses of no less than 92%. Accompanied with the development of synthetic methodologies, increasing attempts have been made on the applications of enantiopure inherently chiral calixarenes. Encouraging (but not satisfactory) results have been obtained, which to some extent reflected the crucial role that could be played by inherent chirality in chiral recognition [19–21, 30], and asymmetric catalysis [21–24, 31, 32, 40, 41].

Attainment of structural/functional diversity as well as establishment of structure/function relationship is one of the central topics of calixarene chemistry. So far, though inherently chiral calix[4]arenes with diverse substitution patterns (wide and/or narrow rim, *meta*-position) have emerged, most of them are based on cone, partial cone and 1,3-alternate conformers. The scarcity of synthesis of

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inherently chiral calix[4]arene 1,2-alternate conformers [28, 42, 43] and the vacancy of resolution and property study have aroused our attention. To gain deeper insight into inherently chiral calix[4]arene 1,2-alternate conformers, we designed the target molecule **4** (Fig. 1) on the basis of the following considerations: (i) the use of two triethylene glycolic bridges may lead to a rigid 1,2-alternate conformation in acceptable yield [44, 45]; (ii) the carboxyl attached on the calixarene is an advantageous site for optical resolution; (iii) the crown ether moiety, the carboxyl and the inverted aromatic rings, as potential recognition sites, are convergent and may form a chiral environment suitable for enantioselective recognition.

Results and discussion

The synthetic pathway is depicted in Scheme 1. Selective modification of one of the two phenol units of 1,2-calix[4]monocrown-4 **1** [25] via the Gross formylation afforded the monoformylated product **2** as a cone conformer in 32% yield. In this step, inherent chirality was generated in the calix[4]monocrown-4 skeleton. To lock the conformation into a 1,2-alternate one, **2** was further reacted with triethylene glycol ditosylate in the presence of *t*-BuOK in toluene to furnish the inherently chiral calix[4]biscrown aldehyde 1,2-alternate conformer **3** as racemates in 41% yield. Subsequent oxidation converted (±)-**3** into the title compound (±)-**4** in 44% yield. In an attempt to optically resolve racemates **4** using the attached carboxyl as a resolution site, (*S*)-BINOL proved to be a most efficient chiral auxiliary compared with (*S*)-α-phenylethylamine and (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle's reagent). By condensation of (±)-**4** with (*S*)-BINOL in the presence of DCC and DMAP, a pair of diastereomers were formed in ca. 1:1 ratio (based on the integral intensity of the phenoxy hydrogens of the BINOL moiety in the ^{1}H NMR spectrum of the crude diastereomeric mixture), which were separated by preparative TLC in yield of 10% for **5-1** (the less polar component) and 14% for **5-2**, respectively. Hydrolysis of **5-1** and **5-2** afforded

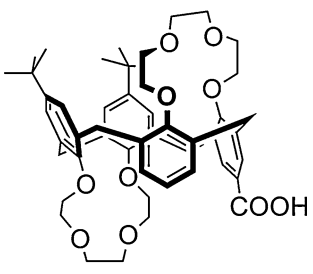

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Fig. 1 The structure of the inherently chiral calix[4]arene 1,2-alternate conformer **4**

both antipodes of inherently chiral calix[4]arene 1,2-alternate conformers (−)-**4** and (+)-**4**, respectively.

Spectroscopic data are consistent with the given structures of all new compounds and herein only representative data were detailed. In the ^{1}H NMR spectrum of (±)-**3**, the proton signals attributable to the methylene bridges connecting two *syn* aromatic rings appear at 4.51/3.36 ppm (a pair of doublets, $J = 12.4$ Hz) and 4.26/3.15 ppm (a pair of doublets, $J = 12.4$ Hz), while the proton signals attributable to the methylene bridges connecting two *anti* aromatic rings appear at 3.97/3.86 ppm (a pair of doublets, $J = 16.0$ Hz) and 3.90 ppm (a singlet). Several multiplets (3.1–2.4 ppm) assignable to the protons of the crown ether moiety undergo dramatic down-field shift, indicating the existence of a strong shield effect imposed by the opposite aromatic rings. The conformation information was also supported by the ^{13}C NMR spectrum, where the two signals appearing at 38.7/38.4 ppm and that appearing at 28.8/28.4 ppm correspond to the methylene bridge carbons connecting two *anti* and two *syn* aromatic rings, respectively. The NMR spectra of (±)-**4** revealed similar structure features with that of (±)-**3** (see Supplementary material).

Slow crystallization of (±)-**3** (from CH_2Cl_2/C_2H_5OH) and (±)-**4** (from CH_2Cl_2/CH_3CN) resulted in single crystals suitable for X-ray diffraction studies, which unambiguously confirmed their 1,2-alternate conformations [46] (Fig. 2). The four methylene bridge carbons in each structure form a plane which could serve as a reference plane (E) to define the detailed structures of 1,2-alternate conformers (Table 1). Thus, in the solid states, **3** and **4** share such common structural features that the crown ether moiety connecting rings A and B orients almost face to face with the inverted aromatic benzene ring D, while the inverted ring **C** tilts away from the chiral cavity formed by the crown ether moiety and rings A and B.

The ^{1}H NMR spectra of the separated diastereomers **5-1** and **5-2** are shown in Fig. 3. The signals of the BINOL protons and aromatic protons of the calix[4]arene (8.15–6.75 ppm), as well as the signals of the methylene protons of the crown ether moiety (3.25–2.35 ppm) which are shielded by the facing aromatic rings show distinct differences in splitting patterns and chemical shifts, reflecting the structural differences of the diastereomeric pair. The signal of hydroxyl proton of **5-1** appears at 6.38 ppm, while that of **5-2** appears at 6.64 ppm. This could be advantageously used to assess the diastereomeric purity of each diastereomer. Base on the above observations, it is reasonable to assume that the introduction of the bulky axially chiral BINOL unit in close proximity to the inherently chiral calix[4]arene units via covalent bonds favors the structural differentiation of the resultant diastereomers.

To investigate the recognition ability of the calix[4]-crown acid 1,2-alternate conformer **4**, which contains a

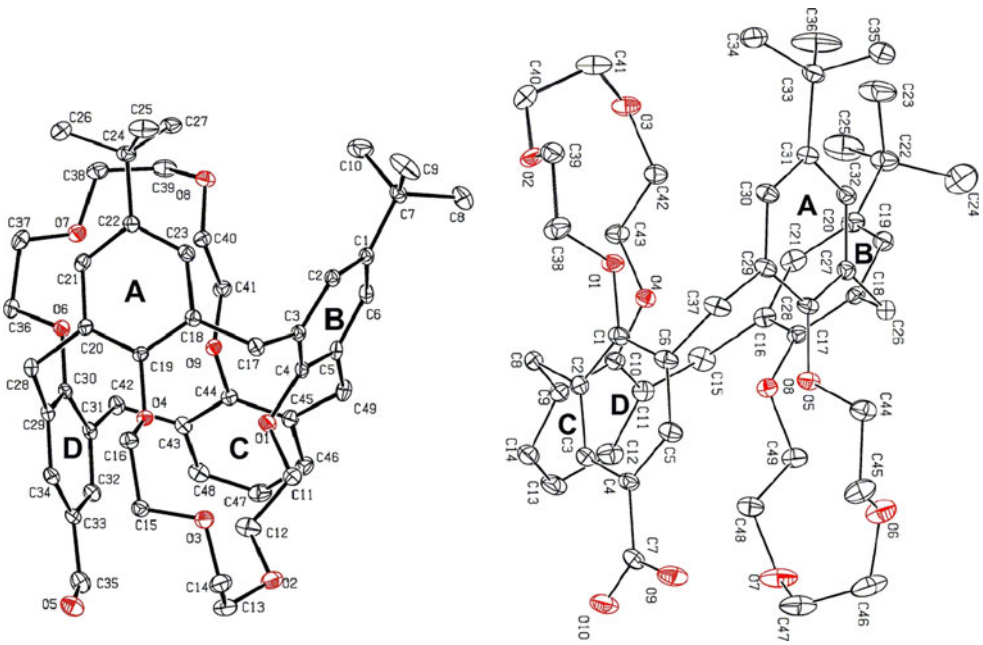
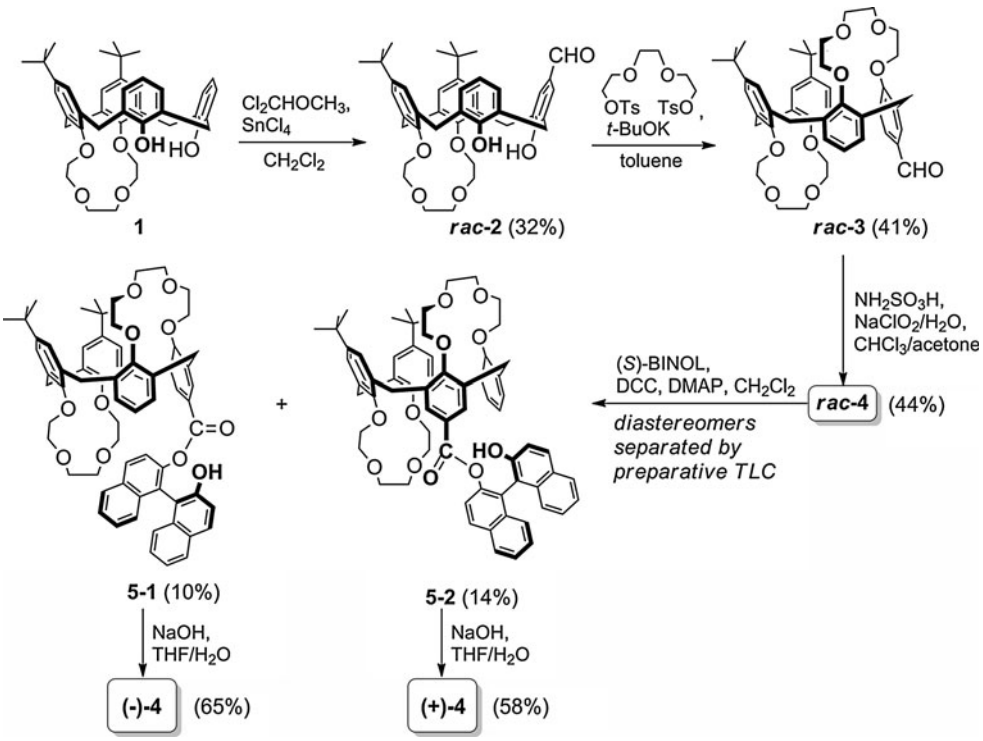


Fig. 2 Crystal structures of compounds **3** (*left*) and **4** (*right*). Hydrogen atoms are omitted for clarity



Scheme 1 Synthesis and optical resolution of **4**

Table 1 The interplanar angles of the phenolic rings (A, B, C, and D) with the reference plane (E) containing the four methylene bridge carbons

Compound	Interplanar angle							
	A/E	B/E	C/E	D/E	A/B	B/C	C/D	D/A
3	98.8	123.8	141.7	88.5	84.6	65.1	89.7	85.5
4	101.8	130.9	133.2	96.7	78.2	61.3	79.8	79.1

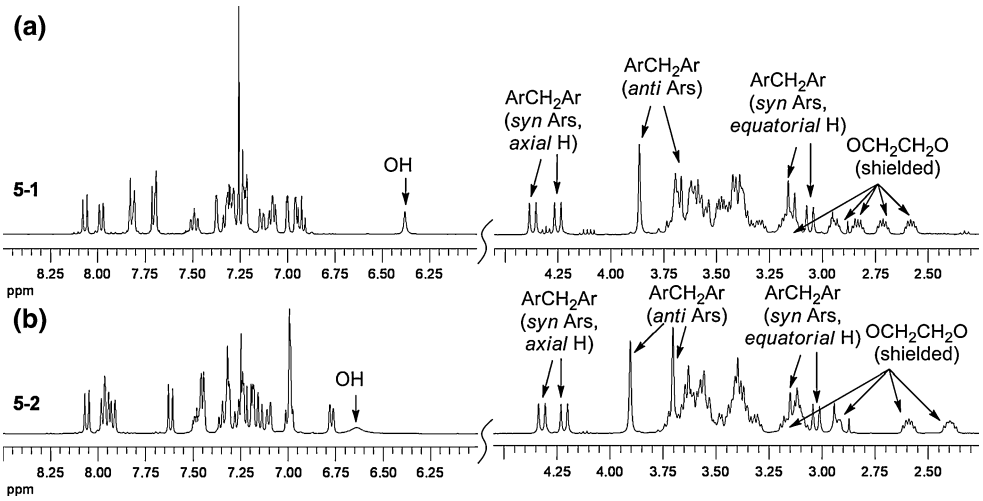


Fig. 3 A comparison of partial ^{1}H NMR spectra of **5-1** and **5-2** ($CDCl_3$, 25 °C)

carboxyl group and a crown ether unit, we chose chiral amines and aminoalcohols as guests because acid–base interaction and crown ether-primary ammonium cation interaction are popular in molecular recognition. We first measured the ^{1}H NMR spectra of (±)-**4** in the presence of ten equivalents of enantiopure amine or aminoalcohols. The complexation is a fast process on the NMR time-scale, because a single set of time-averaged signals were observed for both free and complexed species of the host and guest. In the presence of (*R*)-1-phenylethylamine, L-2-amino-1-propanol, L-leucinol and L-phenylalaninol as guests, the signals of the host generally demonstrated discernible changes. Particularly, the signals of the aromatic protons *ortho* to the carboxyl and the axial methylene bridge protons undergo slight up-field shifts. However, nearly no clear splitting was observed (see Supplementary material). This phenomenon suggested that in these cases there is a non-selective interaction between the host and guest, which is believed to be the acid–base interaction.

In contrast, in the presence of ten equivalents of (*S*)-2-phenylglycinol, the signals of the host exhibit obvious splitting in regions of 8.0–7.8 ppm (aromatic protons *ortho* to the carboxyl), 4.5–4.1 ppm (axial methylene bridge protons) and 1.37–1.32 ppm (*tert*-butyl) (Fig. 4), indicating the diastereomeric properties of the complexed species. This prompted us to measure the ^{1}H NMR spectra of (−)-**4** and (+)-**4** (5 mM) in the presence of (*S*)-2-phenylglycinol (10 equiv), respectively. The results showed that the chemical shift differences between the diastereomeric host–guest complexes are large enough ($\Delta\delta$ = 0.02–0.06 ppm for ArH and axial $ArCH_2Ar$) (Table 2). Accordingly, enantiopure calix[4]crown acid 1,2-alternate conformer **4** could be used as a chiral solvating agent for enantioselectively discriminating (*S*)-phenylglycinol by ^{1}H NMR spectroscopy.

By analysis of the structures of the host and guests, as well as the host–guest complexation behavior, we could deduce that the acid–base interaction between the host and guest is the major cause of the recognition event. The recognition is most likely to occur at the rim where the crown ether moiety and the carboxyl are convergent because it has been known that the neighboring crown ether moiety may help stabilize the ammonium cation (which is positioned around the carboxylate) through additional hydrogen bond between the $-NH^{3+}$ group of the guest and the oxygen atom of the crown ether moiety [47]. The coexistence of the hydroxyl and benzene ring in 2-phenylglycinol as a discriminately recognizable guest implies that maybe hydrogen bonding and π-concerned interaction are key to the enantioselectivity of the recognition event.

Conclusion

We have synthesized an inherently chiral calix[4]crown carboxylic acid in the 1,2-alternate conformation. NMR spectra and crystallographic data provided the structural details of the 1,2-alternate conformer. The success of resolution by use of (*S*)-BINOL was attributed to the differential interactions existing between the BINOL unit and the inherently chiral calix[4]arene units with different configurations in the diastereomers. NMR experiments showed that the title compound could interact enantioselectively with 2-phenylglycinol. The enantioselectivity of the recognition event was thought to be associated with hydrogen bonding and π-concerned interaction. We wish this work may attract more attention to the study of inherently chiral calix[4]arenes in the 1,2-alternate conformation.

Experimental

Melting points were measured on a Beijing Taike X-5 apparatus and uncorrected. NMR spectra were recorded on

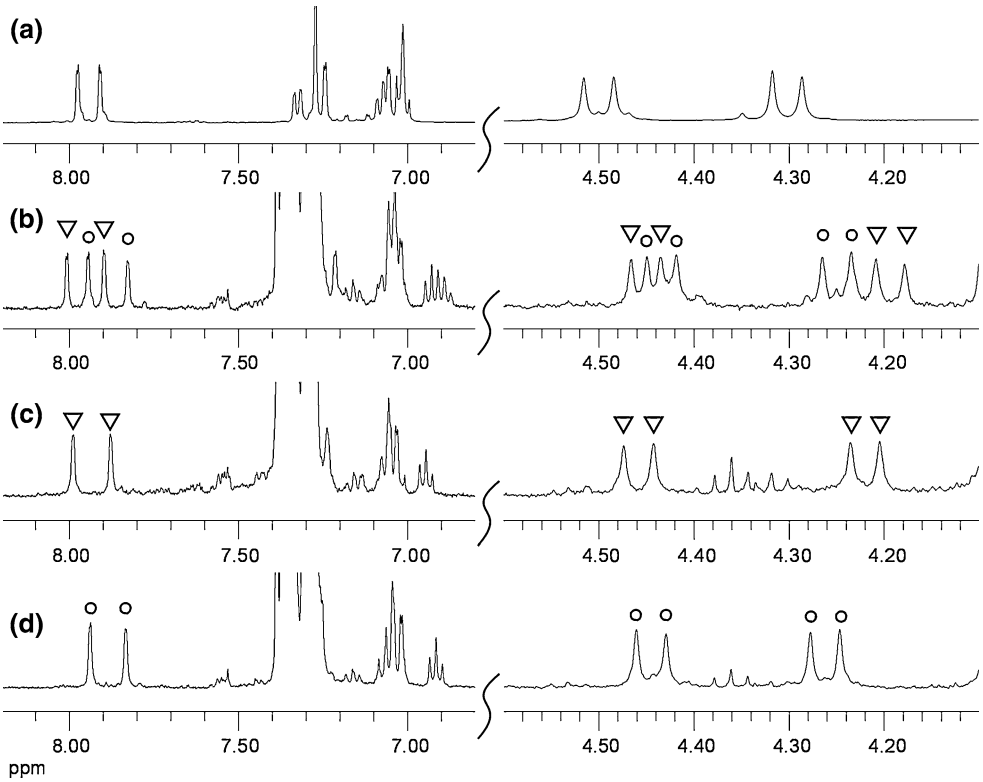


Fig. 4 A comparison of the partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 25 °C) of (a) (±)-**4**, (b) (±)-**4** in the presence of (*S*)-2-phenylglycinol (10 equiv), (c) (−)-**4** (5 mM) in the presence of (*S*)-2-phenylglycinol (10 equiv), and (d) (+)-**4** (5 mM) in the presence of (*S*)-2-phenylglycinol (10 equiv)

Table 2 Selected chemical shifts in the ^{1}H NMR spectra (400 MHz, $CDCl_3$, 25 °C) of (−)-**4** and (+)-**4** (5 mM) in the presence of (*S*)-2-phenylglycinol (10 equiv)

^{1}H NMR signals	δ[(−)-4]	δ[(+)-4]	Δδ[c]
ArH[a]	7.98 (d)	7.92 (d)	0.06
	7.87 (d)	7.82 (d)	0.05
$ArCH_2Ar$[b]	4.45 (d)	4.43 (d)	0.02
	4.21 (d)	4.25 (d)	-0.04

[a] The aromatic hydrogens *ortho* to the carboxyl

[b] The axial hydrogens of the methylene bridges connecting two *syn* aromatic rings

[c] $\Delta\delta = \delta[(-)\text{-}\mathbf{4}] - \delta[(+)\text{-}\mathbf{4}]$

a Bruker Av-400 spectrometer with $CDCl_3$ as a solvent and TMS as an internal standard. ESI–MS spectra were recorded on an LCD Deca XP mass spectrometer. Optical rotation was measured on a Perkin Elmer-341LC polarimeter. Preparative TLC was self-made in our laboratory. Toluene was freshly distilled from Na-benzophenone prior to use. Compound **1** was synthesized according to the literature [25].

Compound (±)-**2**

To a solution of **1** (1.2 g, 1.84 mmol) and Cl_2CHOCH_3 (445 μL, 4.60 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added $SnCl_4$ (1.97 mL, 18.4 mmol). The reaction mixture was stirred at 0 °C for 2.5 h. Water (50 mL) was added and the reaction mixture was stirred for another 1 h. The organic layer was separated and washed with water (25 mL) and dried over $MgSO_4$. Column chromatography (SiO_2, petroleum ether/ethyl acetate = 9/2) gave (±)-**2** as a white solid in 32% yield (0.41 g). Mp 192–194 °C (CH_2Cl_2/CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 9.72 (s, 1H), 9.37 (s, 1H), 7.59 (d, 1H, J = 2.0 Hz), 7.56 (d, 1H, J = 2.0 Hz), 7.24 (d, 1H, J = 2.4 Hz), 7.09–7.01 (m, 3H), 7.00 (d, 1H, J = 2.4 Hz), 6.93 (d, 1H, J = 2.4 Hz), 6.69 (t, 1H, J = 7.6 Hz), 4.63 (d, 1H, J = 12.0 Hz), 4.50–4.43 (m, 1H), 4.45 (d, 1H, J = 13.6 Hz), 4.36 (d, 1H, J = 12.8 Hz), 4.34–4.30 (m, 1H), 4.25–4.10 (m, 7H), 4.14 (d, 1H, J = 13.6 Hz), 4.00–3.85 (m, 3H), 3.48 (d, 1H, J = 14.0 Hz), 3.46 (d, 1H, J = 13.6 Hz), 3.44 (d, 1H, J = 13.6 Hzr), 3.40 (d, 1H, J = 12.4 Hz), 1.21 (s, 9H), 1.12 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.20, 159.20, 151.64, 150.74, 150.51, 148.13, 146.96, 135.10, 133.73, 132.31, 131.67, 131.09, 130.73, 130.52, 129.45, 129.28, 128.98, 128.91, 128.70, 126.93, 126.33, 126.14, 125.82, 121.30, 76.10, 75.83, 72.85, 70.97, 70.52, 69.77, 34.37, 34.25, 32.95, 32.30, 31.76, 31.51, 31.42, 29.97. ESI–MS m/z 701.4 [M + Na^+].

Compound (±)-**3**

To a solution of (±)-**2** (0.74 mmol, 500 mg) in dry toluene (100 mL) was added *t*-BuOK (0.21 g, 1.87 mmol) and the reaction mixture was stirred at 70 °C under N_2 for 1 h.

Triethylene glycol ditosylate (0.41 g, 0.99 mmol) was added and the reaction mixture was stirred at 70 °C under N_2 for 2 days. After removal of the solvent under reduced pressure, the residue was partitioned between water (50 mL) and CH_2Cl_2 (50 mL). The water layer was extracted with CH_2Cl_2 (20 mL). The combined organic layer was dried over anhydrous $MgSO_4$. Column chromatography (SiO_2, petroleum ether/ethyl acetate = 4/1) afforded (±)-**3** as a white solid in 41% yield (0.24 g). Mp 208–211 °C (CH_2Cl_2/C_2H_5OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.71 (d, 1H, J = 2.0 Hz), 7.69 (d, 1H, J = 2.0 Hz), 7.28–7.23 (m, 3H), 7.08–6.96 (m, 4H), 4.51 (d, 1H, J = 12.4 Hz), 4.26 (d, 1H, J = 12.4 Hz), 3.97 (d, 1H, J = 16.0 Hz), 3.90 (s, 2H, $ArCH_2Ar$), 3.86 (d, 1H, J = 16.0 Hz), 3.76–3.56 (m, 10H), 3.48–3.28 (m, 8H), 3.26 (d, 1H, J = 12.8 Hz), 3.21–3.15 (m, 2H), 3.15 (d, 1H, J = 12.4 Hz), 3.09–3.05 (m, 1H), 2.92–2.86 (m, 1H), 2.63–2.58 (m, 1H), 2.47–2.41 (m, 1H), 1.34 (s, 9H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.38, 161.45, 156.29, 153.36, 153.00, 145.21, 145.03, 135.95, 135.01, 134.80, 134.54, 134.34, 133.02, 132.52, 131.61, 131.50, 131.38, 130.25, 129.46, 128.90, 126.47, 125.91, 125.43, 125.37, 122.99, 71.68, 71.35, 71.07, 70.94, 69.59, 69.57, 68.98, 68.81, 68.75, 68.41, 68.30, 67.91, 38.65, 38.45, 34.26, 34.24, 31.87, 31.86, 28.79, 28.40. ESI–MS m/z 815.4 [M + Na^+].

Compound (±)-**4**

To a solution of (±)-**3** (0.2 g, 0.25 mmol) in CH_2Cl_2 (50 mL) and acetone (50 mL) was added a solution of NH_2SO_3H (73 mg, 0.75 mmol) and $NaClO_2$ (79 mg, 0.88 mmol) in water (2.25 mL). The reaction mixture was stirred at room temperature for 1 h. Another batch of NH_2SO_3H (37 mg, 0.38 mmol) and $NaClO_2$ (40 mg, 0.44 mmol) in water (1.2 mL) was added and the reaction mixture was stirred at room temperature for another 1 h. After the complete consumption of (±)-**3** (TLC monitor), the solvent was removed under reduced pressure. The residue was partitioned between 10% aqueous HCl (50 mL) and CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layer was dried over $MgSO_4$. Recrystallization (CH_2Cl_2/CH_3CN) furnished (±)-**4** as a white solid in 44% yield (89 mg). Mp 203–206 °C (CH_2Cl_2/CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, 1H, J = 2.0 Hz), 7.89 (d, 1H, J = 2.0 Hz), 7.32–6.98 (m, 7H), 4.49 (d, 1H, J = 12.4 Hz), 4.29 (d, 1H, J = 12.4 Hz), 3.97–3.35 (m, 22H), 3.25 (d, 1H, J = 12.8 Hz), 3.21–3.17 (m, 2H), 3.16 (d, 1H, J = 12.8 Hz), 3.14–3.08 (m, 1H), 2.97–2.91 (m, 1H), 2.69–2.60 (m, 1H), 2.53–2.47 (m, 1H), 1.34 (s, 9H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.84, 160.50, 156.13, 153.26, 152.89, 145.01, 144.81, 135.21, 134.71, 134.40, 134.36, 134.07, 132.78, 131.78, 131.72, 131.44, 131.40, 129.21, 128.91, 126.24, 125.76, 125.30, 125.22, 123.21, 122.89, 71.39, 71.30, 70.93, 70.78, 69.63, 69.41, 68.76, 68.65, 68.63, 68.33, 68.30, 67.83, 38.55, 38.32, 34.11, 31.75, 31.73, 28.70, 28.28. ESI–MS m/z 831.5 [M + Na^+].

Chemical resolution of (±)-4

To a solution of (±)-**4** (200 mg, 0.24 mmol) was added DCC (76 mg, 0.37 mmol), DMAP (6 mg, 0.049 mmol) and (*S*)-BINOL (82 mg, 0.287 mmol). The reaction mixture was stirred at room temperature for 1 day. After filtration, the solvent was removed under reduced pressure. To the residue was added ethyl acetate (3 mL) and the precipitate was removed by filtration. After removal of the solvent of the filtrate under reduced pressure, the residue was subjected to column chromatography (SiO_2, petroleum ether/ethyl acetate = 4/1) to afford the diastereomeric mixture **5-1** and **5-2** as a white solid. The diastereomeric mixture was subjected to preparative TLC (SiO_2, $CHCl_3$/acetone = 40/1) to give the isolated **5-1** (the less polar diastereomer) and **5-2** as white solids in yield of 10% (26 mg) and 14% (36 mg), respectively. **5-1**: Mp 179–184 °C. $[\alpha]_D^{25} = -24.2$ (c = 4.68 mg/mL, THF). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, 1H, J = 8.8 Hz), 7.98 (d, 1H, J = 8.0 Hz), 7.82–7.81 (m, 2H), 7.71–7.69 (m, 2H), 7.51–7.41 (m, 1H), 7.37 (d, 1H, J = 2.0 Hz), 7.34–7.28 (m, 4H), 7.24–7.21 (m, 3H), 7.15–7.06 (m, 3H), 7.00 (d, 1H, J = 2.4 Hz), 6.96 (d, 1H, J = 2.0 Hz), 6.93 (t, 1H, J = 7.6 Hz), 6.38 (s, 1H), 4.37 (d, 1H, J = 12.4 Hz), 4.25 (d, 1H, J = 12.4 Hz), 3.87 (s, 2H), 3.74–3.27 (m, 20H), 3.21–3.10 (m, 2H), 3.15 (d, 1H, J = 12.4 Hz), 3.06 (d, 1H, J = 12.8 Hz), 2.96–2.92 (m, 1H), 2.86–2.81 (m, 1H), 2.74–2.69 (m, 1H), 2.61–2.56 (m, 1H), 1.32 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.15, 160.73, 155.87, 152.92, 152.80, 152.20, 148.17, 145.03, 144.94, 135.22, 134.60, 134.43, 134.21, 134.03, 133.63, 133.40, 133.23, 132.42, 131.92, 131.43, 131.28, 131.20, 129.99, 129.88, 129.30, 128.91, 128.89, 128.22, 127.99, 127.01, 126.57, 126.03, 125.89, 125.81, 125.25, 125.23, 125.05, 123.47, 123.29, 122.92, 122.63, 122.38, 118.27, 114.47, 70.54, 70.43, 70.14, 70.01, 69.78, 69.54, 69.27, 68.51, 68.27, 68.17, 68.02, 38.51, 38.14, 34.11, 34.09, 31.71, 28.70, 27.92. ESI–MS m/z 1099.6 [M + Na^+]. **5-2**: Mp 177–179 °C. $[\alpha]_D^{25} = +29.4$ (c = 9.40 mg/mL, THF). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, 1H, J = 9.2 Hz), 7.97 (d, 1H, J = 7.2 Hz), 7.95 (d, 1H, J = 8.4 Hz), 7.62 (d, 1H, J = 9.2 Hz), 7.92 (d, 1H, J = 8.0 Hz), 7.51–7.44 (m, 3H), 7.36–7.26 (m, 4H), 7.24–7.18 (m, 3H), 7.15 (d, 1H, J = 8.4 Hz), 7.10 (d, 1H, J = 7.2 Hz), 7.01–6.98 (m, 2H), 6.77 (d, 1H, J = 6.8 Hz), 6.64 (s, 1H), 4.32 (d, 1H, J = 12.8 Hz), 4.22 (d, 1H,

$J = 12.4$ Hz), 3.90 (s, 2H), 3.74–3.28 (m, 20H), 3.20–3.07 (m, 3H), 3.13 (d, 1H, $J = 12.8$ Hz), 3.03 (d, 1H, $J = 12.4$ Hz), 2.97–2.89 (m, 1H), 2.62–2.56 (m, 1H), 2.43–2.37 (m, 1H), 1.33 (s, 9H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.18, 160.13, 156.07, 153.11, 152.68, 152.39, 147.92, 145.13, 144.80, 135.05, 134.76, 134.26, 134.20, 134.03, 133.93, 133.66, 132.60, 131.96, 131.83, 131.61, 131.43, 130.27, 130.08, 129.08, 128.81, 128.24, 128.01, 126.90, 126.42, 126.26, 126.17, 125.80, 125.74, 125.23, 125.20, 125.14, 123.48, 123.25, 123.15, 123.11, 122.37, 118.39, 114.00, 71.22, 71.18, 70.99, 70.73, 69.28, 68.76, 68.66, 68.48, 68.41, 68.24, 67.75, 67.11, 38.48, 38.07, 34.09, 31.72, 31.71, 28.66, 28.19. ESI–MS m/z 1099.6 [M + Na^+]. Compounds (-)-**4** and (+)-**4** were produced by hydrolysis of **5**-**1** and **5**-**2**, respectively under basic condition: To a solution of **5**-**1** or **5**-**2** (36 mg, 0.033 mmol) in THF (2 mL) was added a solution of NaOH (13 mg, 10 equiv) in water (2 mL) and the reaction mixture was stirred under reflux overnight. After removal of the solvent, the residue was partitioned between aqueous HCl (10%, 10 mL) and CH_2Cl_2 (2 × 10 mL). The combined organic layer was dried over $MgSO_4$. Column chromatography (SiO_2, petroleum ether/ethyl acetate = 8/1 to 1/1) afforded (−)-**4** or (+)-**4** as a white solid in ca. 60% yield. The NMR spectra and ESI–MS spectra of (−)-**4** and (+)-**4** are identical with that of (±)-4. Enantiopure (−)-**4** and (+)-**4** have identical melting points of 178-180 °C. The specific rotation of (−)-**4** and (+)-**4** are $[\alpha]_D^{25} = -41.3$ ($c = 4.34$ mg/mL, THF) and $[\alpha]_D^{25} = +47.6$ ($c = 3.93$ mg/mL, THF), respectively.

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