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Synthesis of an inherently chiral *O*,*O*′-bridged thiacalix[4]crowncarboxylic acid and its application to a chiral solvating agent

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Abstract—Treatment of readily available *O*,*O*′-1,1,3,3-tetraisopropyldisiloxane-1,3-diyl-bridged *p-tert*-butylthiacalix[4]arene (**1**) with tri(ethylene glycol) di-*p*-tosylate and subsequent desilylation gave *O*,*O*′-bridged thiacalix[4]crown **3** in an excellent yield. Mono-*O*-alkylation of **3** with ethyl bromoacetate, followed by optical resolution by chiral HPLC, and subsequent hydrolysis of the ester moiety gave inherently chiral *O*,*O*′-bridged thiacalix[4]crowncarboxylic acid (+)-**6**, which clearly discriminated enantiomeric primary amines, as well as amino esters, by ^{1}H NMR spectroscopy.

1. Introduction

Calix[*n*]crowns which are composed of two kinds of receptor elements, a calix[*n*]arene[1] and a crown ether,[2] have attracted much interest as host compounds in the hope for improving the binding ability as well as selectivity to a particular guest species such as an organic molecule[3] or alkali metal ion[4] by the synergic effects of the two receptor elements arranged in a defined three-dimensional alignment. In these endeavors, *O*,*O*″-bridged calix[4]crowns, in which a calix[4]arene is linked at the distal phenolic oxygens with a poly(oxyethylene) chain, have been employed as a molecular scaffold, while only little attention has been paid toward the proximally *O*,*O*′-bridged analogs.[5] This is partly due to the difficulty in preparing the latter type of compounds in substantial quantities. In previous papers, we reported an efficient method for a net proximal dialkylation of calix[4]arenes at the lower rim via the dialkylation of readily available *O*,*O*′-disiloxane-diyl-bridged calix[4]arenes (e.g., **1**) and subsequent desilylation,[6] which could be advantageously utilized for the synthesis of *O*,*O*′-bridged thiacalix[4]crowns.[7] It is readily conceivable that *O*,*O*′-bridged calix[4]crowns having only one symmetry plane are desymmetrized to inherently chiral derivatives by introducing an achiral substituent at one of the two remaining hydroxy groups.[8] In this respect, it should be noted that in spite of the considerable efforts which had been paid to the preparation of inherently chiral calixarenes,[8,9] their chiral recognition abilities have yet to be improved except a recent report by Matt et al. dealing with an application to chiral ligands for asymmetric catalysis.[10] This is in sharp contrast to the fact that another type of chiral calixarenes prepared by introducing chiral substituents at the lower rim through the phenolic oxygens have enjoyed many successful applications to chromogenic receptors,[11] additives in capillary electrophoresis,[12] chiral stationary phases for GC and HPLC,[13] chiral solvating agents for NMR,[14] and so on.[15] Herein, we report facile synthesis of inherently chiral *O*,*O*′-bridged thiacalix[4]-crowncarboxylic acid **6** and its chiral recognition ability as a chiral solvating agent in discriminating enantiomeric amines, as well as amino esters, by ^{1}H NMR spectroscopy. Also reported is the absolute stereochemistry of acid **6** determined by an X-ray crystallographic analysis.

2. Results and discussion

2.1. Synthesis of inherently chiral *O*,*O*′-bridged thiacalix[4]crowncarboxylic acid (+)-6

O,*O*′-Bridged thiacalix[4]crown **3** was prepared according

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to our previously reported procedure (Scheme 1). Thus, treatment of *O*,*O*′-disiloxane-1,3-diyl-bridged thiacalix[4]-arene **1**[6] with tri(ethylene glycol) di-*p*-tosylate in the presence of Cs_2CO_3 in THF gave *O*″,*O*‴-bridged thiacalix[4]crown **2** in high yield, which was desilylated with tetrabutylammonium fluoride to liberate diol **3**. Subsequent monoalkylation of **3** with ethyl bromoacetate in the presence of Na_2CO_3 in THF gave two stereoisomers **4** and **5**, originated from the *syn* and *anti* conformations of the ethoxycarbonylmethyl and crown moieties with respect to the mean plane defined by the calix ring. The ^{1}H NMR spectrum of the major isomer **4** showed two doublets (each 1H) for the methylene protons of the $OCH_2C{=}O$ moiety at 4.71 and 4.87 ppm, while one of the corresponding signals (4.05 and 4.87 ppm) of the minor isomer **5** resonated at a higher field owing to the shielding effects by the facing benzene rings. This indicates that compound **5** adopts a partial cone or 1,2-alternate conformation with the *anti* arrangement of the ethoxycarbonylmethyl and crown moieties and that the relative configuration of the two substituents in compound **4** can consequently be assigned to *syn*. This assignment was unambiguously confirmed by an X-ray crystallographic analysis of acid **6** prepared from compound **4** (vide infra). Although the unsymmetrical ^{1}H NMR resonance pattern of compound **4** gave no information about the conformation of the free *p*-*tert*-butylphenol residue, it is conceivable that this compound adopted a cone conformation in the solution by virtue of possible intramolecular hydrogen bond of the hydroxyl proton to the nearby oxygen atoms at the lower rim. Compound **4** could be optically resolved by chiral HPLC on a preparative scale to give several 100-mg yields of both the enantiomers (>99% ee) (Fig. 1). Subsequent alkaline hydrolysis of one enantiomer (+)-**4** gave enantiomerically pure acid (+)-**6** (Scheme 2).

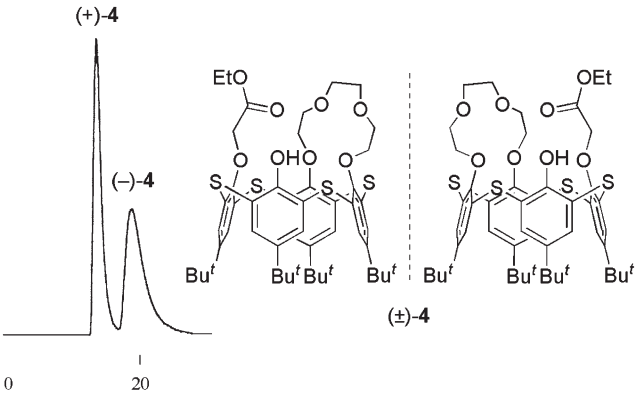
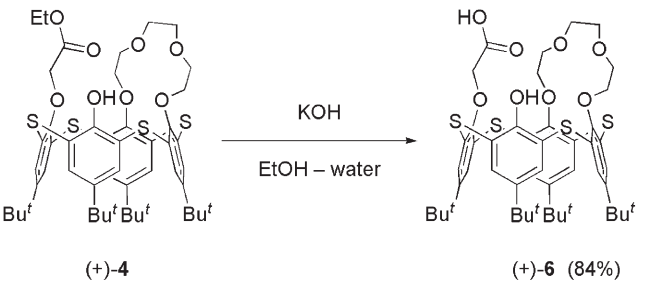
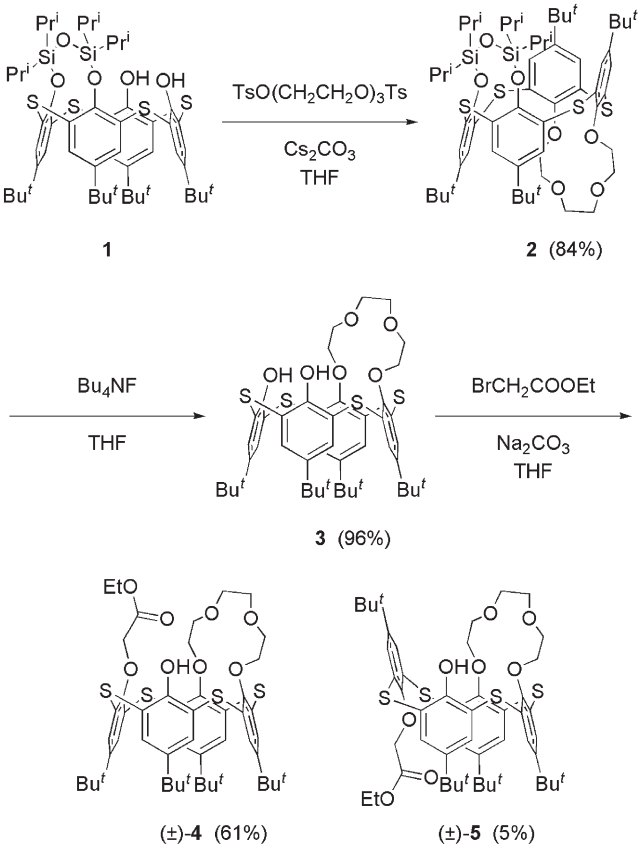


Figure 1. HPLC chromatogram of compound (±)-**4**. Column: Daicel Chiralpak AD (4.6 mm i.d.×250 mm); mobile phase: hexane–2-propanol (98:2); flow rate: 0.5 ml min^{-1}.



Scheme 2.



Scheme 1.

2.2. Chiral recognition ability of acid (+)-6

Measurement of the enantiomeric composition of a chiral compound with the aid of a chiral solvating agent in NMR spectroscopy is a classical but convenient and reliable way based on the transient diastereomeric interactions between the chiral compound and the agent.[16,17] With the desired acid in hand, we next examined its chiral recognition ability as a chiral solvating agent in discriminating enantiomeric amines as well as amino esters. Figure 2 shows the ^{1}H NMR spectra of 1-phenylethylamine in the presence or absence of acid (+)-**6**. The methyl signal of the racemic amine resonating at 1.39 ppm as a doublet (a) shifted to downfield with splitting into two doublets (b) upon addition of 1.0 mol equiv. of acid (+)-**6**, while the broad NH_2 signal centered at 1.52 ppm (a) shifted to 8.0–9.0 ppm (not shown), indicating the formation of diastereomeric ammonium salts. One diastereomer, which showed the methyl signal at the lower field, was assigned to the (*S*)-ammonium salt by comparison of the chemical shift value with that of the sample prepared from the (*S*)-amine and acid (+)-**6** (c). The results of enantiodiscrimination of amines, as well as amino esters are listed in Table 1. The

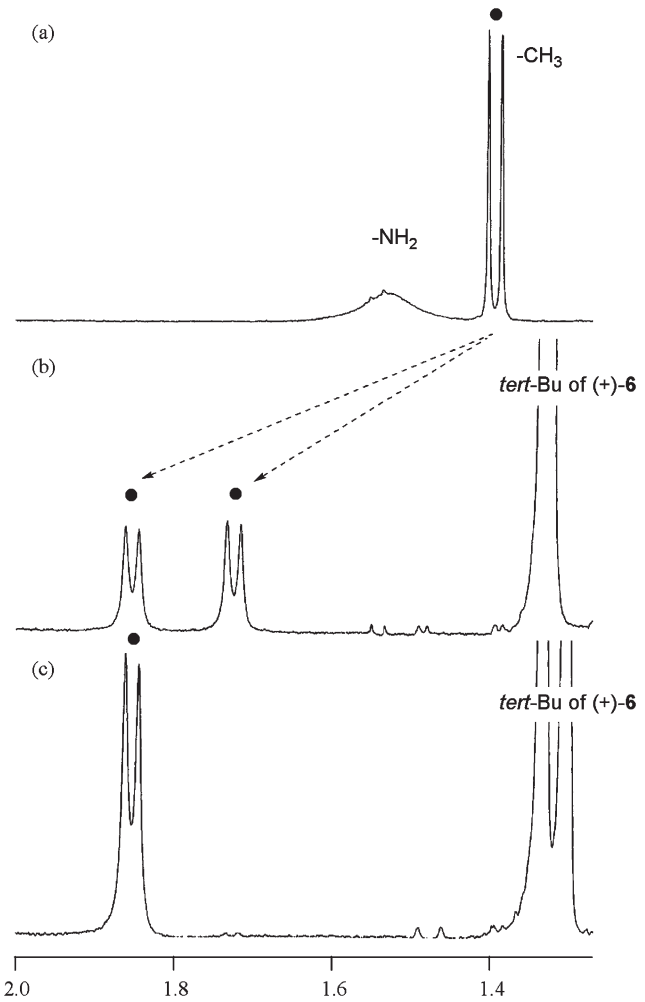
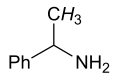
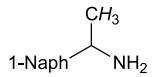
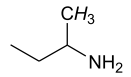
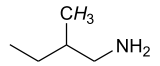
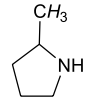
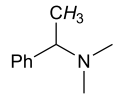
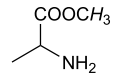
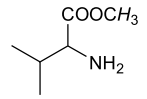
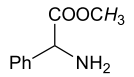
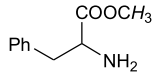
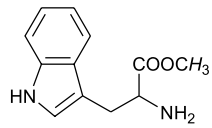


Figure 2. 500 MHz ^{1}H NMR spectra of 10 mM 1-phenylethylamine in $CDCl_3$ in the presence or absence of 1.0 mol equiv. of acid (+)-**6**. (a) (±)-1-Phenylethylamine; (b) (±)-1-phenylethylamine in the presence of acid (+)-**6**; (c) (*S*)-1-phenylethylamine in the presence of acid (+)-**6**.

methyl signals of an enantiomeric pair of primary amines were clearly differentiated from each other (entries 1–4), including the cases of *sec*-butylamine and 2-methylbutylamine (entries 3 and 4) where the difference in the steric bulk of the two alkyl substituents attached to the asymmetric carbon center is rather subtle; in both cases it required differentiation between methyl and ethyl group and furthermore, in the latter case the chiral carbon was separated from the amino nitrogen by a methylene group. It is noteworthy that the methyl signal of an (*S*)-ammonium salt shifted to a lower field than that of the (*R*)-counterpart in every case (entries 1–3). Although secondary and tertiary amines could also be discriminated by acid (+)-**6** (entries 5 and 6), the chemical shift difference between the diastereomeric salts $\Delta\delta_H(S-R)$ was insufficient for quantitative analysis. In the case of amino acid methyl esters, chiral discrimination could be advantageously carried out by using the intense singlet signal of the ester methyl moiety (entries 7–11). Consequently, baseline separation of the methyl signals were achieved for each amino ester except the case of the phenylalanine derivative (entry 10) although the $\Delta\delta_H(S-R)$ values are relatively small as compared to those for primary amines.

Table 1. Chiral recognition ability of acid (+)-**6** in discriminating enantiomeric amines and amino esters by ^{1}H NMR spectroscopy in $CDCl_3$ at 22 °C

Entry	Analyte	δ_H(Free)[a]	$\delta_H(S)$[a]	$\delta_H(R)$[a]	$\Delta\delta_H(S-R)$[b]
1		1.393	1.856	1.733	0.123
2		1.560	2.006	1.863	0.143
3		1.052	1.493	1.415	0.078
4		0.886	1.070, 1.031[c]		(0.039)
5		1.154	1.403, 1.401[c]		(0.002)
6		1.373	1.606	1.619	−0.013
7		3.727	3.676	3.752	−0.076
8		3.724	3.700	3.673	0.027
9		3.706	3.721	3.697	0.024
10		3.722	3.686	3.682	0.004
11		3.717	3.645	3.665	−0.020

[a] Chemical shift values of the methyl protons specified in italics in the presence [$\delta_H(S)$ and $\delta_H(R)$] or absence [δ_H(Free)] of 1.0 mol equiv. of acid (+)-**6**.
[b] $\Delta\delta_H(S-R)=\delta_H(S)-\delta_H(R)$.
[c] The signals are not assigned to the (*S*)- and (*R*)-isomers.

2.3. Determination of the absolute stereochemistry of acid (+)-6 by X-ray crystallographic analysis and consideration of the chiral discrimination mechanism

The ammonium salt prepared from acid (+)-**6** and (*S*)-1-phenylethylamine was crystallized from methanol–water to give colorless plates, one of which was subjected to X-ray crystallographic analysis (Fig. 3). The absolute stereochemistry of acid (+)-**6** could be determined to be *S* by using the (*S*)-1-phenylethyl moiety as an internal reference.[18] It can be seen that the 1-phenylethylammonium cation is associated with the deprotonated (+)-**6** by three

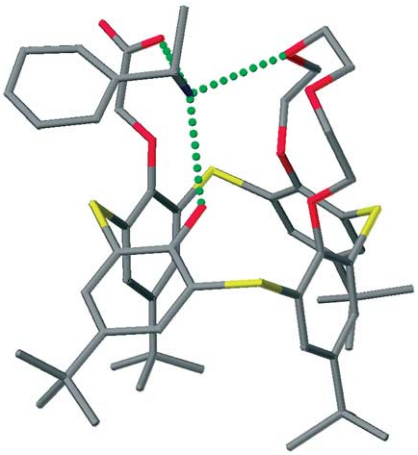


Figure 3. X-ray structure of the ammonium salt between acid (+)-**6** and (*S*)-1-phenylethylamine. Dotted lines indicate hydrogen bonds.

hydrogen bonds between the ammonio group and three oxygen atoms, that is, the carboxylato oxygen, the phenolic hydroxy oxygen and one of the four oxygens of the crown moiety, the distance from the nitrogen to these oxygens being 2.703, 2.901, and 2.886 Å, respectively. It should be noted that the phenyl group of the ammonium ion is arranged to turn away from the crown and carboxylato moieties to avoid steric repulsion.

A Job plot between (*S*)-1-phenylethylamine and acid (+)-**6** revealed that the stoichiometry of the ammonium salt in $CDCl_3$ was the same as that in the crystals (amine:acid=1:1) (Fig. 4).[20] In the ^{13}C NMR spectrum of a diastereomeric mixture of 1-phenylethylammonium salts, the asymmetric carbon centers of the (*S*)- and (*R*)-1-phenylethyl moieties resonated in the close vicinity [$\Delta\delta_C(S-R)$=0.098 ppm], while the methyl signals appeared considerably apart from each other [$\Delta\delta_C(S-R)$=0.441 ppm]. This suggests that the asymmetric carbons are located at a nearly same position in both the diastereomeric salts, because the electrostatic interaction between the carboxylate anion and ammonium cation assisted with three intramolecular hydrogen bonds as were found in the X-ray structure (Fig. 3) should play a

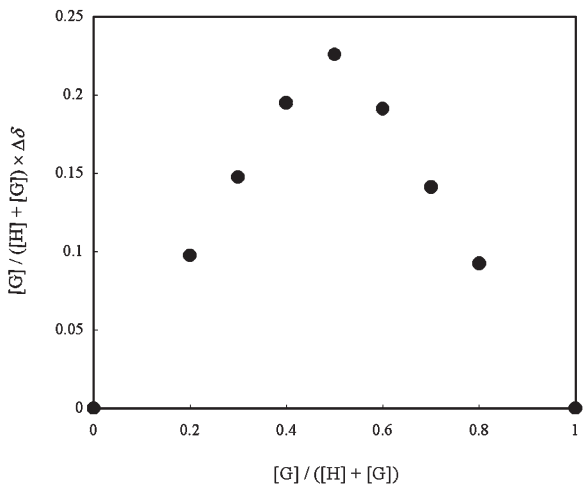


Figure 4. Job plot for the titration of (*S*)-1-phenylethylamine with acid (+)-**6** in $CDCl_3$.

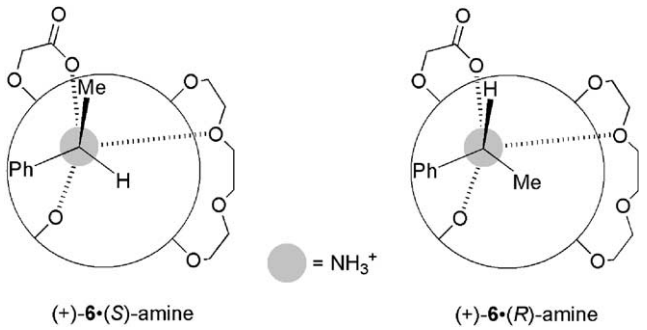


Figure 5. A steric model for the chiral discrimination of (*S*)- and (*R*)-1-phenylethylamine by acid (+)-**6**.

critical role for the salt formation. On the other hand, the difference in the chemical shifts of the methyl protons between the diastereomeric salts is ascribed to the dispositions of three substituents bonded to the asymmetric carbon center (Fig. 5). Molecular model inspections suggest that the bulkiest substituent should orient as far apart as possible from the crown and carboxylato moieties to minimize steric repulsion. This forces the methyl group of the (*R*)-ammonium salt to face against the crown ring to be the more strongly affected by its electronic effects, showing the ^1H NMR signal at a higher field than that of the (*S*)-counterpart.[21] In the case of the secondary and tertiary amines, the bulkiness of the ammonium center seemingly makes it difficult to form such a well-arranged ammonium salt, resulting in the insufficient separation of the methyl signals. If the chiral discrimination model depicted in Figure 5 were applicable to amino esters where the bulkiest substituent directs apart from the crown and carboxylato moieties, an (*S*)-amino ester having a substituent bulkier than the ester moiety at the asymmetric carbon center should show the methyl signal at a higher field than the (*R*)-counterpart because the relevant methoxycarbonyl group will locate near to the polyoxyethylene chain. However, inspection of the results shown in Table 1 indicates that the simple steric model based on apparent bulk of the substituents cannot be applied to the methyl esters (entries 7–11), indicating participation of stereoelectronic effect of the polar ester function.

3. Conclusion

We have shown here an efficient method for the synthesis of optically active *O*,*O*′-bridged thiacalix[4]crowncarboxylic acid (+)-**6**. The absolute stereochemistry was determined by an X-ray crystallographic analysis. The compound could discriminate enantiomeric amines as well as amino acid methyl esters by ^1H NMR spectroscopy.

4. Experimental

4.1. General

Melting points (mps) were taken using a Mitamura Riken MP-P apparatus. Samples for the mp measurement were routinely recrystallized from chloroform–methanol, unless

otherwise noted. Optical rotations were measured on a JASCO DIP-1000 polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Microanalyses were carried out in the Microanalytical Laboratory of the Institute of Multidisciplinary Research for Advanced Materials, Tohoku University. IR spectra were recorded on a JEOL JIR-3510 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 or DRX-500 spectrometer using tetramethylsilane (^{1}H NMR) or chloroform (^{13}C NMR) as an internal standard and $CDCl_3$ as a solvent. Mass spectra were measured on a JEOL JMS-DX602 spectrometer. Silica gel columns were prepared by use of Merck silica gel 60 (63–200 μm). THF was distilled from sodium diphenylketyl just before use. Compound **1** was prepared as reported previously.[6] Other materials were used as purchased.

4.2. Synthesis of acid (+)-6

4.2.1. 5,11,17,23-Tetra-*tert*-butyl-25,26-(2,2,4,4-tetraisopropyl-1,3,5-trioxa-2,4-disilapentane-1,5-diyl)-27,28-(1,4,7,10-tetraoxadecane-1,10-diyl)thiacalix[4]arene (2). To a solution of *O*,*O*′-disiloxane-bridged thiacalix[4]arene **1** (482 mg, 500 μmol) in THF (50 ml) were added Cs_2CO_3 (489 mg, 1.50 mmol) and tri(ethylene glycol) di-*p*-tosylate (275 mg, 600 μmol). After heating at reflux with stirring for 30 h, the mixture was cooled to 0 °C and quenched with 2 M HCl. The mixture was extracted with chloroform and the extract was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel with hexane–ethyl acetate (10:1) as an eluent to give disiloxane-bridged thiacalix[4]crown **2** (451 mg, 84%) as a colorless powder, mp 319–321 °C (Found: C, 64.5; H, 7.85; S, 11.6. Calcd for $C_{58}H_{84}O_7S_4Si_2$: C, 64.6; H, 7.9; S, 11.9%); δ_H (400 MHz) 0.43 (6H, d, *J*=7.4 Hz, CHC*H*$_3$×2), 0.76 (6H, d, *J*=7.5 Hz, CHC*H*$_3$×2), 0.80–0.92 [2H, m, C*H*(CH$_3$)$_2$×2], 1.02 (6H, d, *J*=7.5 Hz, CHC*H*$_3$×2), 1.06 (6H, d, *J*=7.4 Hz, CHC*H*$_3$×2), 1.15–1.24 [2H, m, C*H*(CH$_3$)$_2$×2], 1.28 [18H, s, C(CH$_3$)$_3$×2], 1.35 [18H, s, C(CH$_3$)$_3$×2], 2.64–2.73 (2H, m, OCH$_2$), 3.28–3.60 (6H, m, OCH$_2$×3), 3.73–3.82 (4H, m, OCH$_2$×2), 7.32 (2H, d, *J*=2.4 Hz, ArH×2), 7.55 (2H, d, *J*=2.4 Hz, ArH×2), 7.57 (2H, d, *J*=2.5 Hz, ArH×2) and 7.78 (2H, d, *J*=2.5 Hz, ArH×2); FAB-MS *m*/*z* 1076 (M^+).

4.2.2. 5,11,17,23-Tetra-*tert*-butyl-25,26-dihydroxy-27,28-(1,4,7,10-tetraoxadecane-1,10-diyl)thiacalix[4]arene (3). To a solution of disiloxane-bridged thiacalix[4]crown **2** (323 mg, 300 μmol) in THF (15 ml) was added a 1.0 M solution of tetrabutylammonium fluoride in THF (300 μl, 300 μmol). The mixture was stirred at room temperature for 1 h and quenched with 2 M HCl. The mixture was extracted with chloroform and the extract was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel with hexane–ethyl acetate (3:1) as an eluent to give calix[4]crown **3** (240 mg, 96%) as a colorless powder, mp 132–134 °C (Found: C, 65.9; H, 7.05; S, 15.6. Calcd for $C_{46}H_{58}O_6S_4$: C, 66.15; H, 7.00; S, 15.4%); δ_H (400 MHz) 1.04 [18H, s, C(CH$_3$)$_3$×2], 1.23 [18H, s, C(CH$_3$)$_3$×2], 3.28–4.65 (12H, m, OCH$_2$CH$_2$O×3), 7.36 (4H, br, ArH×4), 7.55 (2H, d, *J*=2.5 Hz, ArH×2), 7.58 (2H, d, *J*=2.5 Hz, ArH×2) and 8.87 (2H, s, OH×2); FAB-MS *m*/*z* 835 [(M+1)$^+$].

4.2.3. *syn*- and *anti*-5,11,17,23-Tetra-*tert*-butyl-25-ethoxycarbonylmethoxy-26-hydroxy-27,28-(1,4,7,10-tetraoxadecane-1,10-diyl)thiacalix[4]arene (4 and 5). To a solution of calix[4]crown **3** (835 mg, 1.00 mmol) in THF (20 ml) were added Na_2CO_3 (106 mg, 1.10 mmol) and ethyl bromoacetate (1.67 g, 9.96 mmol) and the mixture was heated at reflux with stirring for 48 h. After cooling, the mixture was quenched with 2 M HCl and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel with hexane–ethyl acetate (4:1) as an eluent to give ester **4** (562 mg, 61%) and **5** (42.3 mg, 5%) as colorless powders. Ester **4**: mp 104–106 °C (Found: C, 65.2; H, 7.0; S, 14.0. Calcd for $C_{50}H_{64}O_8S_4$: C, 65.2; H, 7.0; S, 13.9%); ν_{max} (KBr)/cm^{-1} 1765 (CO); δ_H (400 MHz) 0.62 [9H, s, C(CH$_3$)$_3$], 1.04 [9H, s, C(CH$_3$)$_3$], 1.31 (3H, t, *J*=7.1 Hz, OCH$_2$C*H*$_3$), 1.32 [18H, s, C(CH$_3$)$_3$×2], 3.80–4.51 (12H, m, OCH$_2$CH$_2$O×3), 4.26 (2H, q, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 4.71 (1H, d, *J*=16.3 Hz, OCH$_2$CO), 4.87 (1H, d, *J*=16.3 Hz, OCH$_2$CO), 6.57 (1H, d, *J*=2.4 Hz, ArH), 6.63 (1H, d, *J*=2.4 Hz, ArH), 7.29 (1H, d, *J*=1.9 Hz, ArH), 7.31 (1H, d, *J*=2.5 Hz, ArH), 7.59 (1H, d, *J*=2.5 Hz, ArH), 7.65 (1H, d, *J*=2.5 Hz, ArH), 7.68 (1H, d, *J*=2.5 Hz, ArH), 7.71 (1H, d, *J*=2.5 Hz, ArH) and 8.02 (1H, s, OH); FAB-MS *m*/*z* 921 [(M+1)$^+$]. Ester **5**: δ_H (400 MHz) 1.00 (3H, t, *J*=7.2 Hz, OCH$_2$C*H*$_3$), 1.23 [9H, s, C(CH$_3$)$_3$], 1.31 [9H, s, C(CH$_3$)$_3$], 1.32 [9H, s, C(CH$_3$)$_3$], 1.36 [9H, s, C(CH$_3$)$_3$], 2.67–4.09 (12H, m, OCH$_2$CH$_2$O), 3.98 (2H, q, *J*=6.8 Hz, OC*H*$_2$CH$_3$), 4.05 (1H, d, *J*=15.1 Hz, OCH$_2$CO), 4.87 (1H, d, *J*=15.1 Hz, OCH$_2$CO), 7.42 (1H, d, *J*=2.4 Hz, ArH), 7.43 (1H, d, *J*=2.4 Hz, ArH), 7.46 (1H, d, *J*=2.4 Hz, ArH), 7.54 (1H, d, *J*=2.5 Hz, ArH), 7.59 (1H, d, *J*=2.5 Hz, ArH), 7.64 (1H, d, *J*=2.5 Hz, ArH), 7.65 (1H, d, *J*=2.5 Hz, ArH), 7.77 (1H, d, *J*=2.5 Hz, ArH) and 7.91 (1H, s, OH).

4.2.4. Optical resolution of compound 4. Racemic ester **4** was subjected to optical resolution by chiral HPLC [column: Daicel CHIRALPAK AD, 20 mm i.d.×25 cm; mobile phase:hexane-2-propanol (98:2); flow rate: 6.0 ml min^{-1}]. A solution of racemic **4** (20 mg) in hexane (500 μl) was injected into the column per one operation and three fractions were collected. Enantiomerically pure (+)- and (−)-**4** (>99% ee) were recovered in 37 and 24% yields from the first and third fractions, respectively. Ester (+)-**4**: $[\alpha]_D^{26}$=+9.0 (*c* 0.50, ethanol). Ester (−)-**4**: $[\alpha]_D^{26}$=−9.0 (*c* 0.50, ethanol).

4.2.5. *syn*-5,11,17,23-Tetra-*tert*-butyl-25-hydroxy-26-hydroxycarbonylmethoxy-27,28-(1,4,7,10-tetraoxadecane-1,10-diyl)thiacalix[4]arene (+)-6. A mixture of ester (+)-**4** (340 mg, 369 μmol), 5.5 M KOH (2.0 ml) and ethanol (15 ml) was heated at reflux with stirring for 48 h. After cooling, the mixture was quenched with 2 M HCl and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by recrystallization from methanol to give acid (+)-**6** as a colorless powder (326 mg, 99%); mp 145–147 °C (Found: C, 64.3; H, 6.8; S, 14.5. Calcd for $C_{48}H_{60}O_8S_4$: C, 64.5; H, 6.8; S, 14.4%); $[\alpha]_D^{27}$=+14.5 (*c* 1.05, chloroform); ν_{max} (KBr)/cm^{-1} 1722 (CO); δ_H (400 MHz) 1.03 [9H, s, C(CH$_3$)$_3$], 1.04 [9H, s, C(CH$_3$)$_3$], 1.18 [9H, s, C(CH$_3$)$_3$], 1.22 [9H, s, C(CH$_3$)$_3$], 3.81–4.59 (12H, m, OCH$_2$CH$_2$O×3), 4.55 (1H, d, *J*=16.2 Hz, OCH$_2$CO), 5.53 (1H, d, *J*=16.2 Hz,

OCH_2CO), 7.30 (1H, d, J=2.5 Hz, ArH), 7.31 (2H, br, ArH), 7.34 (1H, d, J=2.5 Hz, ArH), 7.50 (1H, d, J=3.3 Hz, ArH), 7.51 (1H, d, J=2.5 Hz, ArH), 7.57 (1H, d, J=2.5 Hz, ArH), 7.60 (1H, d, J=2.5 Hz, ArH) and 8.35 (1H, s, OH); FAB-MS m/z 893 [$(M+1)^+$].

4.3. General procedure for the ^{1}H NMR shift experiments

The sample containing an amine was prepared by mixing a 20.0 mM solution of acid (+)-**6** (0.25 ml) in $CDCl_3$ with a 20.0 mM solution of an appropriate amine (0.25 ml) in $CDCl_3$. The sample containing an amino ester was similarly prepared from two 40.0 mM solutions of acid (+)-**6** and an amino ester (0.25 ml each). These samples, together with the solutions of the amine (10.0 mM) and amino ester (20.0 mM) in $CDCl_3$, were analyzed by ^{1}H NMR spectroscopy (500 MHz) at 22 °C.

4.4. Determination of the stoichiometry of the salt between acid (+)-6 and (*S*)-1-phenylethylamine

Two 10.0 mM solutions of acid (+)-**6** and (*S*)-1-phenylethylamine in $CDCl_3$ were mixed in the following volume ratios; 10:0, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 0:10. These samples were analyzed by ^{1}H NMR spectroscopy (500 MHz) at 22 °C. The chemical shift value of the methyl protons of the amine (δ_{obs}) was converted to the chemical shift change ($\Delta\delta$) as follows: $\Delta\delta=\delta_{obs}-\delta_{amine}$, where δ_{amine} is the chemical shift value in the absence of acid (+)-**6**. Finally $[G]/([H]+[G])\times\Delta\delta$ was plotted against $[G]/([H]+[G])$, where [G] is the total concentration of the amine and [H] is that of acid (+)-**6**.

4.5. X-ray analysis of the salt between acid (+)-6 and (*S*)-1-phenylethylamine

Data were collected on a Rigaku/MSC Mercury CCD diffractometer using Mo K_α radiation (λ=0.71069 Å). The calculation was performed using the software package TeXsan (v. 1.11).[22] The structure was solved by the direct methods with SIR92[23] and refined by full-matrix least squares methods with SHELXL-97.[24] All non-hydrogen atoms were refined anisotropically. Crystal data and refinement statistics are as follows: $C_{57}H_{81}NO_{14}S_4$, M=1132.51, monoclinic, a=15.459(4), b=14.821(3), c=15.978(4) Å, β=113.416(3)°, V=3359(1) Å^3, T=223(2) K, space group $P2_1$, Z=2, μ (Mo K_α)=0.197 mm^{-1}, 42641 reflections measured, 12887 unique (R_{int}=0.058). Final R_1=0.077 for 9856 data [$I>2\sigma(I)$] and wR_2=0.214 for all data, GOF=1.047. The absolute stereochemistry of acid (+)-**6** was assigned to be *S* by using the (*S*)-1-phenylethyl moiety as an internal reference. The details of the crystal data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 238754.

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