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Azacalix[4]arene tetramethyl ether with inherent chirality generated by substitution on the nitrogen bridges

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This paper is dedicated to Professor Yoshiteru Sakata on the occasion of his 70th birthday

ABSTRACT

The first inherently chiral azacalix[4]arene has been prepared by introducing three benzyl groups onto the nitrogen bridges. The highly enantioenriched compound was easily obtained via a moderately enantioselective cyclization followed by a simple crystallization procedure. NMR and X-ray crystallographic studies revealed that easy access to the enantiomer was permitted by the non-racemizable 1,3-alternate conformation in solution, up to 110 °C, as well as by the preferential crystallization of a racemic compound.

1. Introduction

The term 'inherent chirality' is employed for three-dimensional molecular frameworks that lack a mirror plane, an inversion center, or an alternating axis in the molecules.[1–4] Certain fullerenes,[2] molecular clips,[3] and calixarenes with a specific substitution pattern[1,4] can show inherent chirality. Of them, inherently chiral calixarenes have attracted much interest in both fundamental research and application, including enantioselective molecular recognition and asymmetric catalysis.[4] A variety of inherently chiral calixarenes were prepared in a sophisticated manner by introducing achiral substituents to the upper- and/or lower-rim in an asymmetric or dissymmetric fashion.[1,4] In contrast, the bridging units[5] are less exploited for generating inherent chirality; to the best of our knowledge, the use of achiral substituents has only been reported for thiacalix[4]arene, of which the inherent chirality was generated via the partial oxidation of the sulfur bridges.[6] In these foregoing studies, the inherently chiral calixarenes and thiacalix[4]arenes anchoring the achiral substituents on the periphery were initially prepared as racemates, which were then resolved into each enantiomer by a direct HPLC separation or through the derivatizations to the corresponding diastereomer.[1,4,6] The direct enantioselective synthesis has been limited, though highly favorable from a synthetic point of view, to three examples in which inherently chiral calix[4]arenes and resorcinarene are prepared by lipase-catalyzed transesterification,[7] kinetic resolution,[8] or stereoselective synthesis exploiting chiral auxiliaries.[9]

We anticipate that the nitrogen-bridged calixarene analogs[10,11] would provide an easier access to inherent chirality via direct enantioselective synthesis because azacalixarenes have been generally prepared using Buchwald–Hartwig aryl amination reaction catalyzed by Pd(0) complex.[10,12] Another advantage is the presence of the easily functionalizable nitrogen bridges, of which the appropriate N-substitution can generate inherent chirality in the molecule, as shown in Figure 1 where all possible conformations and N-substitution patterns for creating inherently chiral azacalix[4]arenes are schematically summarized. Herein, in order to verify this fundamental and widely applicable approach, we have prepared azacalix[4]arene **1** by introducing three benzyl groups onto the nitrogen bridges in an AAAB substitution pattern. As a result, it was found that the direct enantioselective synthesis of inherently chiral azacalix[4]arene **1** in a 1,3-alternate conformation was feasible in high yields with moderate enantioselectivities. More interestingly, simple crystallizations of the resulting enantiomerically enriched **1** allowed us to isolate the enantiomer. Herein, we report the synthesis, molecular structure, and enantiomeric enrichment of azacalix[4]arene **1**, which furnishes the first example of an inherently chiral nitrogen-bridged calixarene analog.

2. Results and discussion

Inherently chiral azacalix[4]arene **1** was prepared by modifying our previously reported procedure for the synthesis of achiral **2**.[13] As shown in Scheme 1, the synthesis started from additional Boc protection of the terminal amino group of linear tetramer **3**[13] using Boc_2O in the presence of DMAP. The product **4** was subjected to *N*-benzylation of the bridging nitrogen atoms, and the subsequent deprotection of Boc groups afforded *N*′,*N*″-tribenzylated acyclic tetramer **5** in 64% yield in two steps. Finally, racemic azacalix[4]arene (±)-**1** was obtained in 65% yield (Table 1, entry 1) by intramolecular cyclization reaction of precursor **5** using a Pd(0)-catalyzed Buchwald–Hartwig aryl amination reaction.[12] The reaction yield was improved by switching the ligand from *t*-Bu_3P to (±)-BINAP to afford (±)-**1** in 81% yield (entry 2). The observed high yield is notable because the nitrogen-bridged calixarene analogs reported thus

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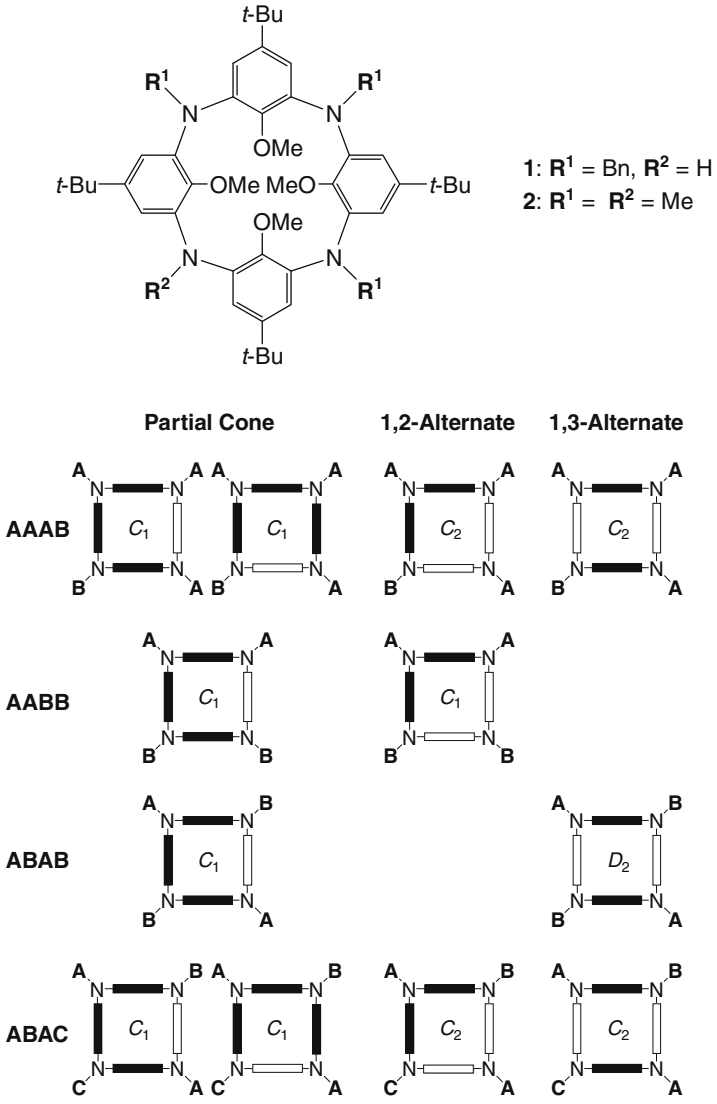
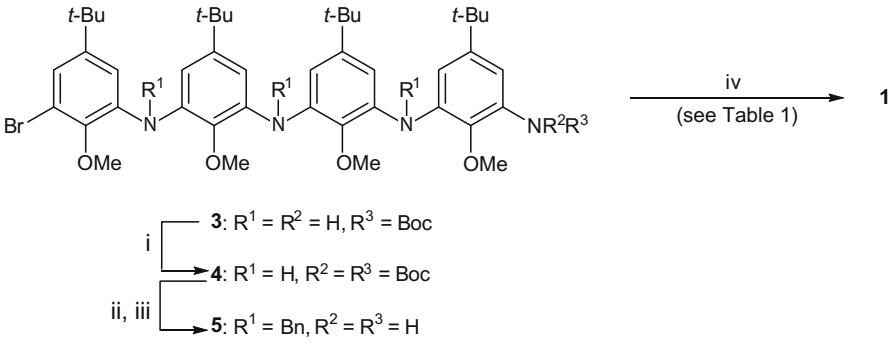


Figure 1. Possible conformations and substitution patterns on the nitrogen bridges of inherently chiral azacalix[4]arenes (only one enantiomer shown). **A**, **B**, **C**, and **D** denotes N-substituent groups, and black/white rectangles represent the aromatic units pointing upward/downward, respectively. Possible highest point groups are indicated in the center of each molecule. Substitution patterns **AABC** and **ABCD** always generate inherent chirality, irrespective of the conformation, including a cone conformation.



Scheme 1. Synthesis of inherently chiral azacalix[4]arene **1**. Conditions: (i) Boc_2O, DMAP (cat.), THF, reflux, 83%. (ii) BnBr, NaH, DMF, −20 °C to 0 °C. (iii) TFA/CH_2Cl_2 (1:1), room temperature, 64% in two steps. (iv) $Pd(dba)_2$, Ligand, *t*-BuONa, PhMe, reflux.

far have been generally synthesized in low yields;[10] for example, fully methylated azacalix[4]arene **2** was prepared in 37% yield.[13] The lack of an alkyl group on the reacting terminal nitrogen atom in **5** precludes the undesirable β-elimination side reaction,[12,14] thereby improving the reaction yield of the intramolecular cyclization.

A single crystal suitable for X-ray crystallography was obtained from the hexane solution of (±)-**1**. As shown in Figure 2a, azaca-

Table 1
Effect of ligands on the Pd(0)-catalyzed intramolecular cyclization reaction of **5**[a]

Entry	Ligand	Product	Yield[b] (%)	ee[c] (%)
1[d]	*t*-Bu_3P	(±)-**1**	65	0
2	(±)-BINAP	(±)-**1**	81	0
3	(*R*)-BINAP	(+)-**1**	81	21
4	(*R*)-SEGPHOS	(+)-**1**	78	35
5	(*R*)-DTBM-SEGPHOS	—	0	—

[a] Conditions: acyclic tetramer **5** (0.10 mmol), 5 mol % $Pd(dba)_2$, 7.5 mol % ligand, *t*-BuONa (0.20 mmol), and toluene (20 mL, 5 mM).
[b] Isolated yield.
[c] Determined by HPLC analysis using a Daicel Chiralpak AD column.
[d] 20 mol % $Pd(dba)_2$ and 16 mol % *t*-Bu_3P were used.

lix[4]arene **1** adopts a slightly distorted 1,3-alternate conformation similar to that of **2**.[13] Two enantiomers of **1** are alternatively packed in the crystal (Fig. 2b and c), indicating that the crystal of (±)-**1** is classified as a racemic compound.

The 1,3-alternate conformation of **1** is also retained in solution. The ^{1}H NMR spectrum (Fig. 3a) comprised two sharp singlet signals (1:1 intensity ratio) for the methoxy protons, four doublet signals (1:1:1:1) for the skeletal aromatic protons, and two sets of double doublet signals (1:2) for the diastereotopic N-benzylic protons, indicating that azacalix[4]arene **1** had a time-averaged C_2-symmetry in solution.[†] The methoxy hydrogens experienced an upfield-shift characteristic of a 1,3-alternate conformation, as in the case of **2**.[13] The conformation was further supported by ROESY measurement, where the close proximity of the methoxy and aromatic hydrogens was observed (Fig. 3b), implying that azacalix[4]arene **1** adopted a 1,3-alternate conformation in solution.

More important is the conformational stability of **1** in solution because inherently chiral calix[4]arenes may be racemized by the macrocyclic ring inversion via the 'lower rim through the annulus' pathway.[16] To elucidate the molecular flexibility of **1**, the ^{1}H NMR relaxation time (T_1) was determined. In our previous report,[17] this technique was successfully applied to **2** to conclude the inflexible 1,3-alternate conformation of **2**, on the basis of the small T_1 value (1.03 s) of the aromatic protons as compared to that of conformationally flexible thiacalix[4]arene (2.51 s).[18] The T_1 values for each aromatic proton ***a***, ***b***, ***c***, and ***d*** of **1** were determined to be 0.98, 0.74, 0.77, and 0.77 s, respectively. The observed T_1 values are comparable to those of **2**, eventually demonstrating that the 1,3-alternate conformation of **1** is also rigid in solution. The conformational stability of **1** was clearly reflected in the perfect separation of the two enantiomers by using HPLC analysis (Fig. 4).

Our efforts were next directed to the preparation of enantiomerically enriched azacalix[4]arene **1** through a Pd(0)-catalyzed aryl amination reaction using a chiral ligand. Under the optimized reaction conditions (Table 1), the enantioselective intramolecular cyclization of **5** was examined. The cyclization reaction, catalyzed by 5 mol % $Pd(dba)_2$/(*R*)-BINAP,[19] proceeded smoothly to afford (+)-enriched **1** in 81% yield, although the enantioselectivity (21% ee) was unsatisfactory (Table 1, entry 3). The low ee observed seems to be caused by racemization resulting from the macrocyclic ring inversion of **1** at a high temperature. However, this was not the case for **1** because no racemization of **1** took place at 110 °C for at least 6 h. The enantioselectivity was further improved to 35% ee by using (*R*)-SEGPHOS[20] (entry 4), whereas no cyclization reaction occurred when using (*R*)-DTBM-SEGPHOS[20] (entry 5), which was reported to be the most effective ligand in the similar asymmetric N-arylation reactions.[21] It is likely that 3,5-di-*tert*-butyl-4-methoxyphenyl groups on the phosphorus atoms of DTBM-SEGPHOS are too bulky to bring about the cyclization reaction of **5**. Although high enantioselectivity was not achieved in the present study, it is worth noting that the inherently chiral **1** can be prepared with a moderate enantioselectivity by using a chiral Pd catalyst.

By using (*S*)-BINAP as the ligand, (−)-enriched **1** was also obtained with an analogous enantioselectivity (18% ee). Crystallization of (−)-**1** of 18% ee from MeCN with a few drops of MeOH gave crystals of nearly racemic **1** (3% ee), leading to the enantiomeric enrichment of (−)-**1** to 45% ee in the mother liquor. After the crystallization was repeated five times, (−)-**1** in 99% ee was obtained. The enantiomeric antipode was also obtained by applying this process to (+)-enriched **1**. As shown in Figure 5, (+)- and (−)-

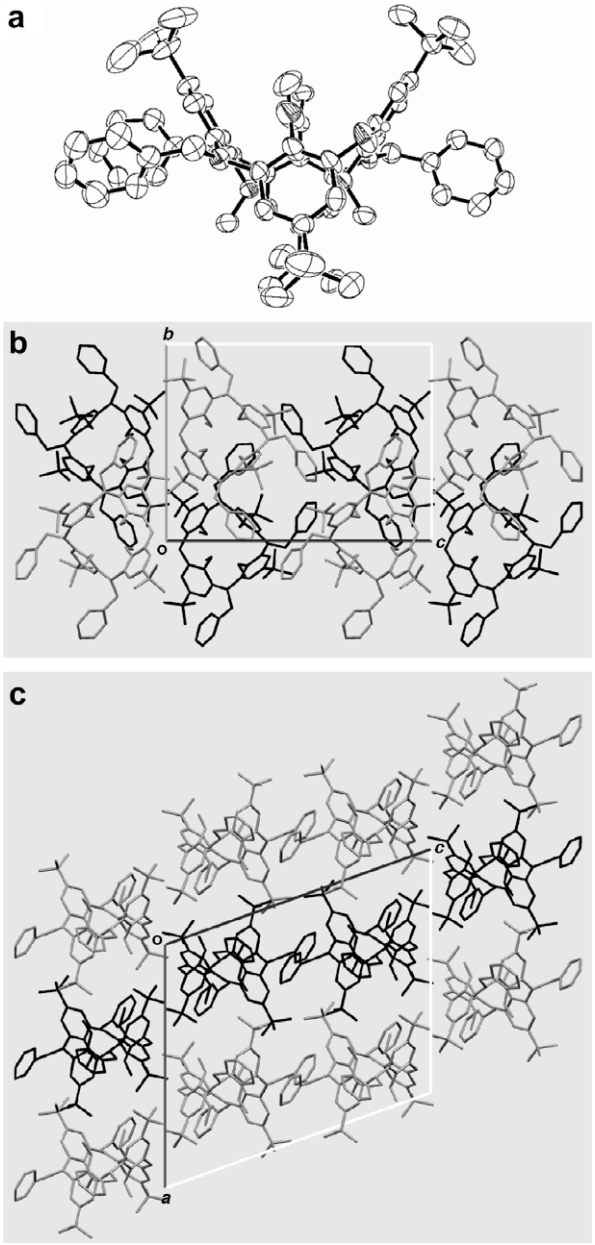


Figure 2. (a) ORTEP drawing[15] of racemic azacalix[4]arene (±)-**1** (one enantiomer shown), and (b) and (c) its crystal packing. In panel (a), the displacement ellipsoids are drawn at the 50% probability level. All the hydrogen atoms except for the bridging NH hydrogen atom are omitted for clarity. In panels (b) and (c), each of the enantiomers is indicated using black or gray color.

[†] X-ray crystallographic analysis revealed that the three bridging nitrogen atoms with benzyl groups adopted an almost planar geometry as evidenced by the 351.4°, 356.4°, and 356.2° summations of the three CNC bond angles. Nitrogen inversion is generally rapid in solution, and the local site chirality generated by the slightly pyramidal nitrogens is thus negligible.

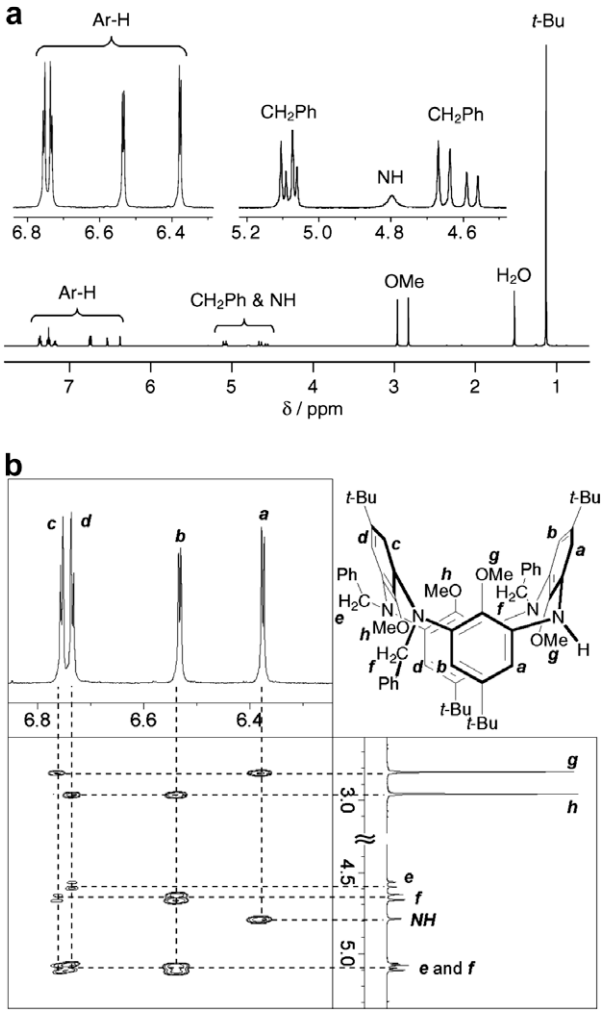


Figure 3. (a) ^{1}H NMR and (b) ROESY spectra of inherently chiral azacalix[4]arene **1** in $CDCl_3$ at room temperature.

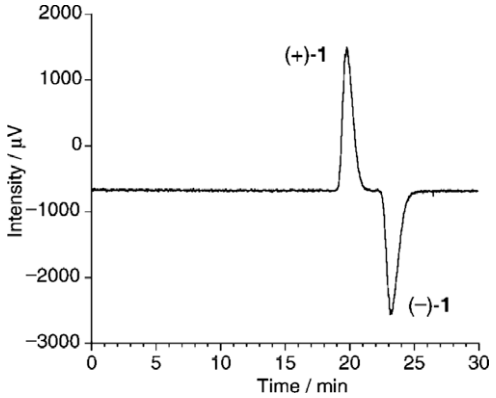


Figure 4. HPLC analysis of racemic azacalix[4]arene (±)-**1** using a CD detector. Separation conditions: Daicel Chiralpak AD; mobile phase, 5% 2-PrOH/hexane; flow rate, 0.2 mL min^{-1}; detection at 254 nm; temperature, 25 °C.

1 display mirror image CD spectra, demonstrating conclusively that azacalix[4]arene **1** is inherently chiral. The present enantiomeric resolution based on simple crystallization is favorable because neither HPLC separation nor derivatization to the corresponding diastereomers is required, both of which were typically used in the enantiomeric resolution of the inherently chiral

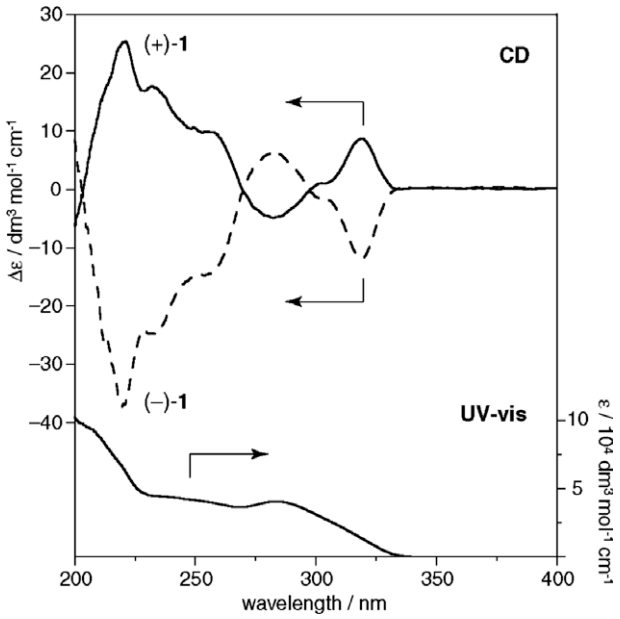


Figure 5. CD and UV–vis spectra of inherently chiral azacalix[4]arene **1** in hexane. Enantiomeric excesses of the samples were 87% ee for (+)-**1** and 99% ee for (−)-**1**.

calixarenes.[3] As a result, the easy access to both enantiomers of **1** was accomplished by its inflexible and thereby non-racemizable structure, as well as the preferential deposition of the racemic compound crystal (Fig. 2b and c), the stability of which is supported by the experimental result that the melting point of (±)-**1** is ca. 90 °C higher than that of (−)-**1** of 99% ee.

3. Conclusion

In conclusion, we have clearly demonstrated that the first inherently chiral azacalix[4]arene **1** can be prepared in high yields by the direct enantioselective synthesis using a chiral Pd(0) catalyst. Although the enantioselectivity was unsatisfactory, the enantiomer of **1** was easily obtained by a simple crystallization procedure owing to the non-racemizable 1,3-alternate conformation in solution as well as the preferential crystallization of the racemic compound. Our efforts are now being directed toward preparing a single crystal of the isolated enantiomers of **1** in order to determine the absolute configuration.

4. Experimental

4.1. General

Melting points were determined on a Yanaco MP-J3 apparatus and are uncorrected. NMR spectra were recorded on a JEOL JNM-A500 instrument using tetramethylsilane (^{1}H NMR) and solvent resonance (^{13}C NMR) as internal standards. ^{1}H NMR relaxation time measurements were performed on a JEOL JNM-EX270 instrument. Infrared spectra were obtained on a Shimadzu IRPrestige-21 spectrometer. UV–vis spectra were recorded on a Shimadzu UV-3101PC spectrometer. CD spectra were measured in a 1 mm path-length cell on a JASCO J-805 spectropolarimeter. Specific rotations were measured in a 1 dm path-length cell on a JASCO P-1030 polarimeter. HPLC analyses (mobile phase, 5% 2-PrOH/hexane; flow rate, 0.2 mL min^{-1}; detection at 254 nm; temperature, 25 °C) were carried out using the following two instruments A and B. Instrument A is a JASCO HPLC system equipped with a CD-2095 Plus detector, a PU-2080 Plus pump, a CO-2060 Plus col-

umn oven, and a ChromNAV recorder. Instrument B is constituted with a JASCO 870-UV detector, a JASCO 880-PU pump, a Shimadzu CTO-10AS column oven, and a Shimadzu C-R6A recorder. Daicel Chiralpak AD (ϕ 0.46 cm × 25 cm) was used as a chiral stationary-phase column. Mass spectra were recorded at the GC–MS and NMR Laboratory, Faculty of Agriculture, Hokkaido University, Japan. Elemental analyses were conducted at the Microanalytical Center, Kyoto University, Japan. Flash column chromatography was performed with Kanto Chemical Silica gel 60N. DMF and THF were refluxed over, and then distilled from CaH_2 and benzophenone ketyl, respectively, under Ar before use. Other chemicals were purchased from commercial suppliers and were used as received.

4.2. Synthesis

4.2.1. *N*-{3-[3-(3-Bromo-5-*tert*-butyl-2-methoxyanilino)-5-*tert*-butyl-2-methoxyanilino]-5-*tert*-butyl-2-methoxyphenyl}-*N*′,*N*′-di(*tert*-buthoxycarbonyl)-5-*tert*-butyl-2-methoxy-1,3-phenylenediamine 4

A suspension of **3**[12] (5.34 g, 6.00 mmol), Boc_2O (2.62 g, 12.0 mmol), and DMAP (73 mg, 0.60 mmol) in anhydrous THF (60 mL) was refluxed for 13 h. After cooling to room temperature, the reaction mixture was concentrated, extracted with EtOAc, and washed with brine three times. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was washed with MeOH to afford **4** (4.96 g, 83%) as a colorless solid, mp 192−194 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 2.2 Hz, 1H, ArH), 7.47 (d, J = 2.2 Hz, 1H, ArH), 7.17 (d, J = 2.2 Hz, 1H, ArH), 7.13 (d, J = 2.2 Hz, 1H, ArH), 7.07 (d, J = 2.2 Hz, 1H, ArH), 7.03 (d, J = 2.2 Hz, 1H, ArH), 7.02 (d, J = 2.2 Hz, 1H, ArH), 6.70 (d, J = 2.2 Hz, 1H, ArH), 6.56 (s, 1H, NH), 6.50 (s, 1H, NH), 6.42 (s, 1H, NH), 3.87 (s, 3H, OMe), 3.80 (s, 6H, OMe), 3.77 (s, 3H, OMe), 1.47 (s, 18H, *t*-Bu), 1.32 (s, 9H, *t*-Bu), 1.31 (s, 18H, *t*-Bu), 1.30 (s, 9H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 148.8, 147.43, 147.37, 146.7, 143.8, 143.1, 137.1, 136.5, 136.2, 136.04, 135.95, 135.6, 135.5, 135.1, 132.5, 120.8, 117.9, 116.6, 114.2, 112.6, 106.4, 106.1, 106.0, 105.6, 82.4, 60.24, 60.23, 59.9, 59.8, 34.88, 34.86, 34.75, 34.6, 31.5, 31.4, 31.3, 27.9; IR (KBr) 3426, 3393 (ν_{N-H}) cm^{-1}; Anal. Calcd for $C_{54}H_{77}BrN_4O_8$: C, 65.51; H, 7.84; N, 5.66. Found: C, 65.24; H, 7.90; N 5.42.

4.2.2. *N*-Benzyl-*N*-{3-[*N*-benzyl-3-(*N*-benzyl-3-bromo-5-*tert*-butyl-2-methoxyanilino)-5-*tert*-butyl-2-methoxyanilino]-5-*tert*-butyl-2-methoxyphenyl}-5-*tert*-butyl-2-methoxy-1,3-phenylenediamine 5

To a solution of **4** (4.95 g, 5.00 mmol) in anhydrous DMF (100 mL) was added 60% NaH (800 mg, 20.0 mmol) at −20 °C under Ar. After stirring for 15 min, BnBr (1.85 mL, 15.5 mmol) was added. Stirring was continued at 0 °C for 8 h, and then Et_2O and H_2O were added to the reaction mixture. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. Next, TFA (10 mL) and CH_2Cl_2 (10 mL) were added to the residue, and the mixture was stirred for 3 h at room temperature. After cooling to 0 °C, the mixture was made basic to pH 11 with 5% NaOH, then extracted with CH_2Cl_2, and washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and evaporated. Flash column chromatography on silica gel (hexane/EtOAc = 9:1, v/v) gave **5** (3.38 g, 64%) as a colorless solid, mp 72−74 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.10 (m, 15H, ArH), 7.06 (d, J = 2.3 Hz, 1H, ArH), 6.87 (d, J = 2.3 Hz, 1H, ArH), 6.71 (d, J = 2.3 Hz, 1H, ArH), 6.67 (d, J = 2.3 Hz, 1H, ArH), 6.65 (d, J = 2.3 Hz, 1H, ArH), 6.59 (d, J = 2.3 Hz, 1H, ArH), 6.40 (s, 2H, ArH), 4.84 (s, 2H, CH_2Ph), 4.82 (s, 2H, CH_2Ph), 4.80 (s, 2H, CH_2Ph), 3.62 (s, 6H, NH_2), 3.50 (s, 3H, OMe), 3.483 (s, 3H, OMe), 3.479 (s, 3H, OMe), 3.41 (s, 3H, OMe), 1.12 (s, 18H, *t*-Bu), 1.04 (s, 9H, *t*-Bu), 1.03 (s, 9H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 147.4, 146.6, 145.9, 145.7, 145.2, 145.0, 143.3, 142.7, 142.62, 142.59, 142.3, 140.1, 139.9, 139.8, 139.4, 138.5, 128.04, 128.00, 127.88, 126.5, 126.3, 126.2, 123.2, 119.9, 117.5, 117.4, 117.1, 117.0, 116.7, 111.5, 107.5, 59.9, 59.2, 58.7, 56.9, 56.84, 56.80, 34.4, 34.29, 34.27, 34.24, 31.2, 31.13, 31.09; IR (KBr) 3447, 3368 (ν_{N-H}) cm^{-1}; Anal. Calcd for $C_{65}H_{79}BrN_4O_4$: C, 73.63; H, 7.51; N, 5.28. Found: C, 73.78; H, 7.75; N, 5.00.

4.2.3. General procedure for the synthesis of 2,8,14-tribenzyl-5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetramethoxy-2,8,14,20-tetraazacalix[4]arene 1 (Table 1, entry 3)

After a mixture of **5** (106.4 mg, 0.100 mmol), $Pd(dba)_2$ (2.9 mg, 5.0 μmol), and (*R*)-BINAP (4.7 mg, 7.5 μmol) in anhydrous toluene (20 mL) was refluxed for 5 min, *t*-BuONa (19.2 mg, 0.200 mmol) was added, and the mixture refluxed for 6 h. The mixture was then cooled to room temperature, filtered through Celite, and evaporated. Flash column chromatography on silica gel (hexane/CH_2Cl_2 = 3:2, v/v) gave (+)-**1** (79.2 mg, 81% yield, 21% ee) as a colorless solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.16 (m, 15H, ArH), 6.75 (d, J = 2.3 Hz, 2H, ArH), 6.73 (d, J = 2.3 Hz, 2H, ArH), 6.53 (d, J = 2.3 Hz, 2H, ArH), 6.37 (d, J = 2.3 Hz, 2H, ArH), 5.09 (d, J = 16.0 Hz, 2H, CH_2), 5.08 (d, J = 15.3 Hz, 1H, CH_2), 4.79 (s, 1H, NH), 4.66 (d, J = 16.0 Hz, 2H, CH_2), 4.58 (d, J = 15.3 Hz, 1H, CH_2), 2.96 (s, 6H, OMe), 2.82 (s, 6H, OMe), 1.13 ppm (s, 36H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.7, 144.6, 144.4, 143.3, 142.8, 142.5, 141.4, 140.28, 140.24, 137.6, 128.2, 128.11, 128.09, 127.6, 126.6, 126.5, 114.31, 114.29, 111.1, 110.7, 59.6, 59.5, 59.3, 58.02, 34.2, 34.1, 31.34, 31.33; IR (KBr) 3408 (ν_{N-H}) cm^{-1}; MS (FD) m/z 978 [M$^+$]; Anal. Calcd for $C_{65}H_{78}N_4O_4$: C, 79.72; H, 8.03; N 5.72. Found: C, 79.88; H, 7.84; N 5.55. mp (of (±)-**1**) 171−173 °C.

In entries 1, 2, 4, and 5 of Table 1, the experiments were conducted according to the above protocol. Entry 1: (±)-**1** (64.1 mg, 65% yield) was obtained from **5** (105.9 mg, 0.100 mmol), $Pd(dba)_2$ (11.5 mg, 20.0 μmol), and *t*-Bu_3P (10 wt % hexane solution, 50 μL, 16 μmol), *t*-BuONa (19.3 mg, 0.201 mmol), and anhydrous toluene (20 mL). Entry 2: (±)-**1** (79.0 mg, 81% yield) was obtained from **5** (106.1 mg, 0.100 mmol), $Pd(dba)_2$ (2.9 mg, 5.0 μmol), and (±)-BINAP (4.7 mg, 7.5 μmol), *t*-BuONa (19.2 mg, 0.200 mmol), and anhydrous toluene (20 mL). Entry 4: (+)-**1** (76.4 mg, 78% yield, 35% ee) was obtained from **5** (106.4 mg, 0.100 mmol), $Pd(dba)_2$ (2.9 mg, 5.0 μmol), and (*R*)-SEGPHOS (4.6 mg, 7.5 μmol), *t*-BuONa (19.1 mg, 0.199 mmol), and anhydrous toluene (20 mL). Entry 5: Compound **1** was not obtained from **5** (105.8 mg, 0.100 mmol), $Pd(dba)_2$ (2.9 mg, 5.0 μmol), and (*R*)-DTBM-SEGPHOS (8.8 mg, 7.5 μmol), *t*-BuONa (19.2 mg, 0.200 mmol), and anhydrous toluene (20 mL).

4.3. General procedure for the enantiomeric enrichment of (+)- and (−)-1

A solution of (−)-**1** of 18% ee (582 mg, 0.594 mmol) in MeCN (ca. 20 mL) with a few drops of MeOH was sonicated at ambient temperature for 10 min. The resulting suspension was filtered to afford a colorless powder of (−)-**1** of 3% ee (381 mg). The mother liquor was evaporated to yield (−)-**1** of 45% ee (199 mg) as colorless solid. After similar crystallization procedures were repeated four times, (−)-**1** in 82% ee (100 mg) was obtained. Recrystallization from MeCN with a few drops of water at −15 °C deposited (−)-**1** of 10% ee (20 mg) as colorless solid and left (−)-**1** of 99% ee in the mother liquor, from which colorless solid of (−)-**1** (70 mg) was obtained. An analogous procedure was applied for (+)-**1**. (+)-**1** (87% ee): mp 79–83 °C, $[\alpha]_D^{27}$ = +106.5 (*c* 0.1, $CHCl_3$); (−)-**1** (99% ee): mp 77–82 °C, $[\alpha]_D^{27}$ = −122.5 (*c* 0.1, $CHCl_3$).

4.4. ^{1}H NMR relaxation time (T_1) measurements

The relaxation time (T_1) values of (±)-**1** were determined in degassed $CDCl_3$ at 270 MHz and 23 °C by using the inversion recovery method. Since the aromatic protons ***c*** and ***d*** were not resolved so well in the ^{1}H NMR spectra (270 MHz), those signals were assumed as a single one in the T_1 calculation.

4.5. Racemization experiment of (+)-1

A solution of (+)-**1** of 93% ee (2.2 mg) in toluene (5 mL) was heated at 110 °C in a thermostat-controlled bath. The changes in the enantiomeric excess were followed at appropriate intervals by using a chiral HPLC. No change of the ee value (93% ee) of (+)-**1** was observed at this temperature for 6 h.

4.6. X-ray crystallographic analysis

Measurement was made by using graphite-monochromated Mo Kα radiation (λ = 0.71075 Å). All the crystallographic calculations were performed by using a crystallographic software package, CrystalStructure version 3.8.2.[22] The crystal structure was solved by direct methods and refined by full-matrix least-squares. All non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were refined using the riding model. Crystal data for (±)-**1**: M_r = 979.36, monoclinic, space group $P2_1/a$ (No. 14), a = 18.721(1), b = 15.116(1), c = 21.688(1) Å, β = 109.796(1)°, V = 5775(1) Å^3, Z = 4, ρ_{calcd} = 1.126 g cm^{-3}, μ = 0.695 cm^{-1}, T = 113(1) K, 13,102 independent reflections, 664 refined parameters. R_1 = 0.1234 ($I > 2\sigma(I)$), wR_2 = 0.4116 (all reflections), S = 0.975. Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC-706406. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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