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Preparation and separation of all possible rotamers of a stereochemical analog of *meso*-tartaric acid: optically inactive and optically active isomers of (*R*,*S*)-2,2′-bis(methoxycarbonyl)-6,6′-dimethyl-9,9′-bitriptycyl

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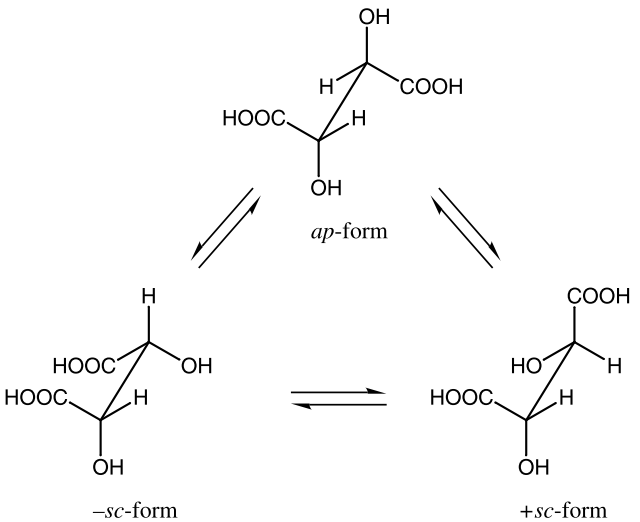
Abstract—All the three possible rotamers of the title compound were separated by chromatography, and unambiguously identified by NMR and X-ray analysis. One of the isomers was optically inactive C_i conformation. The other optical active forms were resolved to give a pair of enantiomers, which were characterized by optical rotation and CD spectra. Thus the optical inactivity of a compound such as *meso*-tartaric acid that can take C_i conformation in solution, is now ascribed to that the molecule has an optically inactive C_i conformer and equal amounts of optically active conformers, that are enantiomers, in solution.

1. Introduction

meso-Tartaric acid is known to have a structure which is made by connecting a group –CH(OH)(COOH) whose stereochemistry is *R* to another same group of which stereochemistry is *S*. Though classically it is said that this compound is optically inactive because its Fischer projection has a plane of symmetry, or because a mirror image of a Fischer projection of *meso*-tartaric acid is identical with the original one, it can also be written in several conformations. The rotational circuit of *meso*-tartaric acid is shown in Scheme 1.

The feature of the structure of the *ap*-form is that it is a C_i molecule, namely there is a center of symmetry in the molecule, whereas in $+sc$ and $-sc$ forms, there is no symmetry element, thus these conformations are C_1 and optically active when isolated. It is predicted that *meso*-tartaric acid is optically inactive because its conformers include optically inactive *ap* form and $+sc$ and $-sc$ forms, which are enantiomers, thus existing in the same amounts and canceling the optical activity of another. This point was first mentioned by Noller [1] but has not been experimentally proved. Noller mentioned that there were optically active rotamers in solution, but they racemize quickly because



Scheme 1. Rotational circuit of *meso*-tartaric acid.

internal rotation is rapid. We can rephrase this point in the following way: because the optically active rotamers are enantiomers, they exist in the same amount in solution due to the same free energy, even though the internal rotation is slow. The optical activity of one isomer is cancelled because of the presence of its enantiomers. We thought it would be interesting, if we could provide compounds of this sort, because we have various stable rotamers in hand.[2] It will be another basic contribution to stereochemistry of organic

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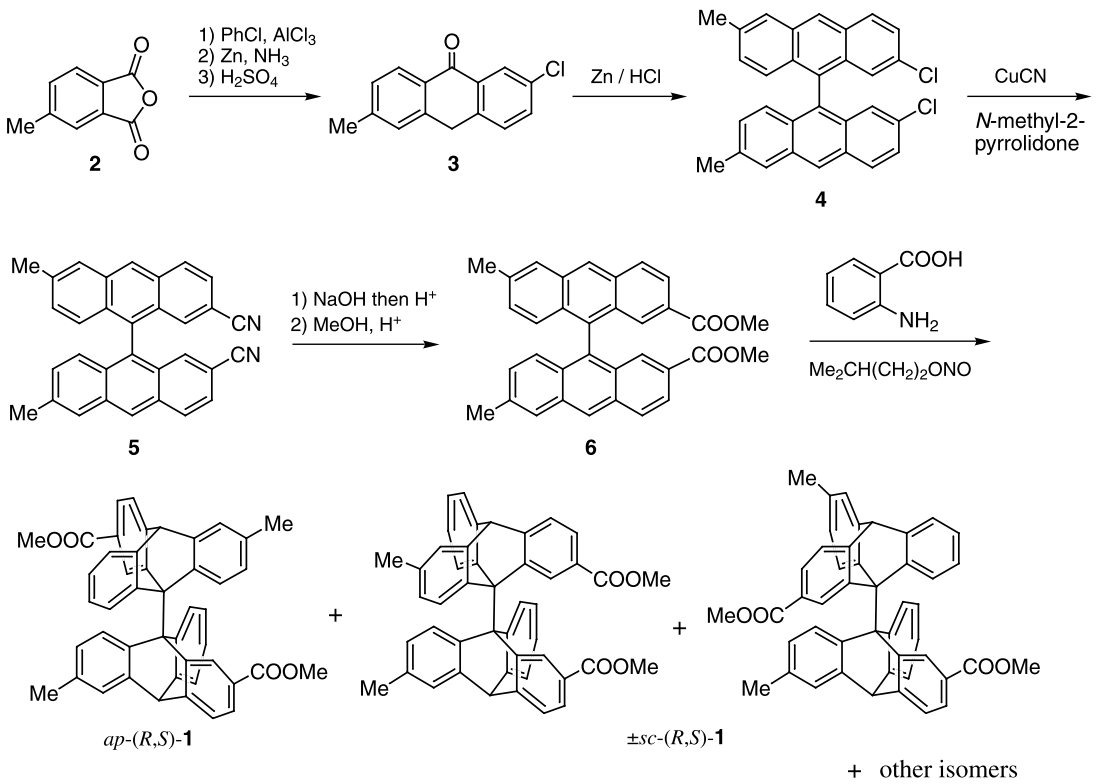


Scheme 2. Synthetic sequence of compound **1**.

compounds, following an example of optically active rotamers of a C_{2h} molecule.[3] We selected the title compounds because of the convenience of syntheses.

2. Results and discussion

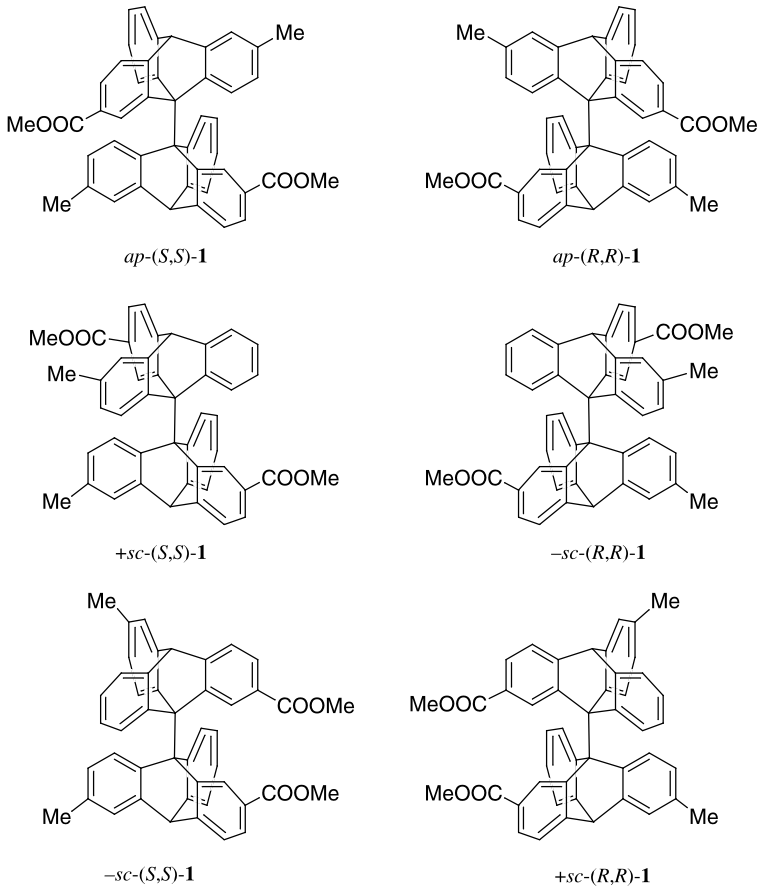
The target molecule was decided to be 2,2′-bis(methoxycarbonyl)-6,6′-dimethyl-9,9′-bitriptycyl (**1**), because this compound carries three different substituents in the top half of the molecule and the same substituents in the bottom half: In addition, the barrier to rotation is expected to be higher than 55 kcal/mol[4] which is high enough for isolation of isomers at room temperature. The sequence of syntheses of **1** is shown in Scheme 2. 2-Chloro-6-methyl-9-anthrone **3** was prepared from 4-methylphthalic anhydride **2** by the Friedel–Crafts acylation of chlorobenzene followed by zinc–ammonia reduction and cyclization under acidic conditions with a small amount of the positional isomer.[5] The mixture was separated by chromatography and **3** was further reduced with zinc to produce 2,2′-dichloro-6,6′-dimethyl-9,9′-bianthryl (**4**). This compound was transformed into the methoxycarbonyl compound **6** via **5** according to the literature method.[4] **6** was treated with benzyne generated from anthranilic acid and isopentyl nitrite. This will provide the desired bitriptycyl, which carries three different benzeno bridges and yet the benzeno bridges in the top half are all present in the bottom half. Thus providing a C_i molecule when the substituted bridge is suitably located.

However, another problem arises. That is, this method of preparation affords not only the stereochemical analogues of *meso*-tartaric acid but also those of (±)-tartaric acid which are shown in Scheme 3. Hereafter, we wish to use a name (*R*,*S*)-tartaric acid for *meso*-tartaric acid and (*R**,*R**)-tartaric acid for (±)-tartaric acid for clarity as well as brevity of the discussion.

There should be five diastereomers in the product. They must be separated and identified. It seemed a difficult problem at the outset. However, the separation of the diastereomers was proved to be rather easy. Gel permeation chromatography afforded four fractions, which were further purified by HPLC on silica gel to obtain fractions at retention times of 23, 93, 101, and 113 min.

Identification of the diastereomers could be made by considering the structural features of the diastereomers. The important point can be seen in Newman projections of these molecules (Scheme 4), in which methylbenzeno, methoxycarbonylbenzeno, and benzeno groups are shown by abbreviated forms X Y, and Z, respectively: the priority in the Cahn–Ingold–Prelog rules is –CXYZ>X>Y>Z. When we discuss the priority of ligands attached to C(9), the sequence is C(9′)>X>Y>Z.

In Scheme 4, (A) represents an (*R*,*S*) molecule and (B) an (*R**,*R**) molecule. The *ap* conformer in (A) is a C_i molecule, whereas +*sc* and −*sc* are C_1 molecules. The relationship between +*sc* and −*sc* isomers in (A) is not directly apparent but one notices that the −*sc* form is a mirror image of the +*sc* form, when one looks at the −*sc* form from the rear. In addition we notice that two X's are not equivalent in the C_1 molecules, because one X is flanked by X and Y, whereas another X is flanked by X and Z. Two X's, two Y's, as well as two Z's are equivalent in *ap*-(*R*,*S*)-**1**. We also notice that all the conformations given in (B) are C_2

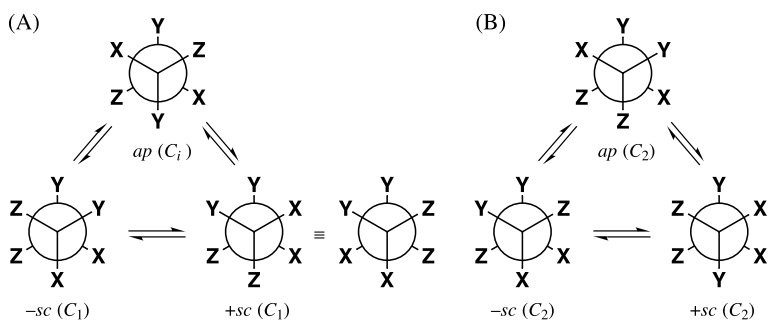


Scheme 3. Possible rotamers of (R^*,R^*)-**1** (Each row is a pair of enantiomers).

molecules and the benzeno bridges with a same substituent are all equivalent in these molecules. It can be summarized that, if there is a molecule which exhibits nonequivalency of the bridge with a same substituent, it should be the *sc* form of (*R*,*S*)-**1** and others show all equivalent bridges when the substituent is the same. This means also, if we can find a molecule that shows the ^{1}H NMR signal of a substituent in the benzeno bridges as two peaks, that must be ±*sc*-(*R*,*S*)-**1**. If the molecule cannot be resolved, it is possible that the molecule is *ap*-(*R*,*S*)-**1**. *ap*-(*R*,*S*)-**1** is also expected to be eluted early in chromatography because it is centrosymmetric and nonpolar.

There was indeed a fraction which was eluted very early (23 min retention time) in HPLC: in addition, it was not resolved into optical isomers under the conditions which provided the optical isomers of (R^*,R^*)-**1** and ±*sc*-(*R*,*S*)-**1** as described later. Trials to get suitable crystals for X-ray crystallography afforded tiny but large enough crystals for modern X-ray crystallography. The result of structural analysis is shown as an ORTEP diagram in Fig. 1. It was indeed the *ap* form of (*R*,*S*)-**1**.

We could also find a fraction, retention time of 101 min, which exhibited two methyl signals and two methoxycarbonyl-methyl signals. In addition, this compound showed 33 aromatic carbon signals in ^{13}C NMR spectrum: theoretically, there should be 36 aromatic carbon signals if all the six benzeno bridges are nonequivalent, whereas the signals should be 18, if two benzeno bridges with a same substituent are equivalent. These pieces of evidence clearly show that this compound is the C_1 molecule and should



Scheme 4. Newman projections of (*R*,*S*)-**1** (A) and (R^*,R^*)-**1** (B): the substituted benzeno bridges are abbreviated to X, Y, and Z for brevity.

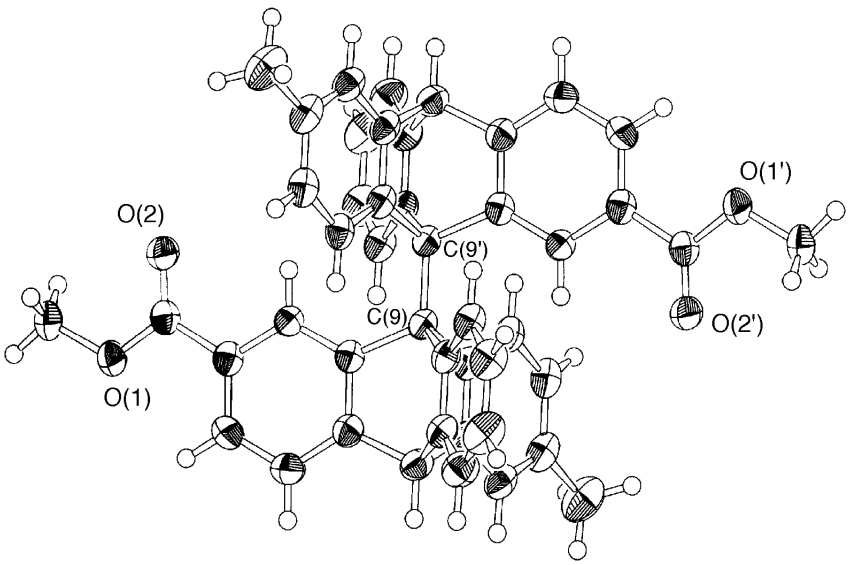


Figure 1. ORTEP diagram of optically inactive *ap*-(*R*,*S*)-**1** (C_i symmetry).

correspond to ±*sc*-(*R*,*S*)-**1**. The other two isomers (retention times 93 and 113 min) are inevitably rotamers of (*R**,*R**)-**1**, their ^{13}C NMR pattern being consistent with the symmetry.[6]

The ±*sc*-(*R*,*S*)-**1** fraction was submitted to a chiral chromatography with the use of a Daicel CHIRALCEL OD column and 20:1 hexane/2-propanol eluent. It gave two fractions of which retention times were 15.4 and 18.0 min, showing baseline separation. The more easily eluted isomer was found to be levorotatory, $[\alpha]_D^{22}=-56$, and the less easily eluted isomer, dextrorotatory, $[\alpha]_D^{22}=+54$. The CD spectra of these compounds are shown in Fig. 2. The CD spectra are very close to a body and its mirror image. A relatively intense Cotton effect was observed at 233 nm, the (−)- and (+)-isomers giving a peak and a trough, respectively. The specific rotations of these compounds and the CD spectra also indicate that these are enantiomers.

Thus we claim that we succeeded in isolating an optically inactive and optically active rotamers of a stereochemical analog of *meso*-tartaric acid or (*R*,*S*)-tartaric acid. Although these are not isomerized by heating because of a very high barrier to rotation, these are conceptually rotamers.

Though a term 'internal compensation' was coined by Landolt more than a century ago to account for the optical inactivity of (*R*,*S*)-tartaric acid because the chiral centers in this compound are *R* and *S*,[7] the experimental results presented in this paper clearly show that optical inactivity of (*R*,*S*)-tartaric acid is due to the presence of a pair of enantiomers and an optically inactive C_i molecule. Thus the

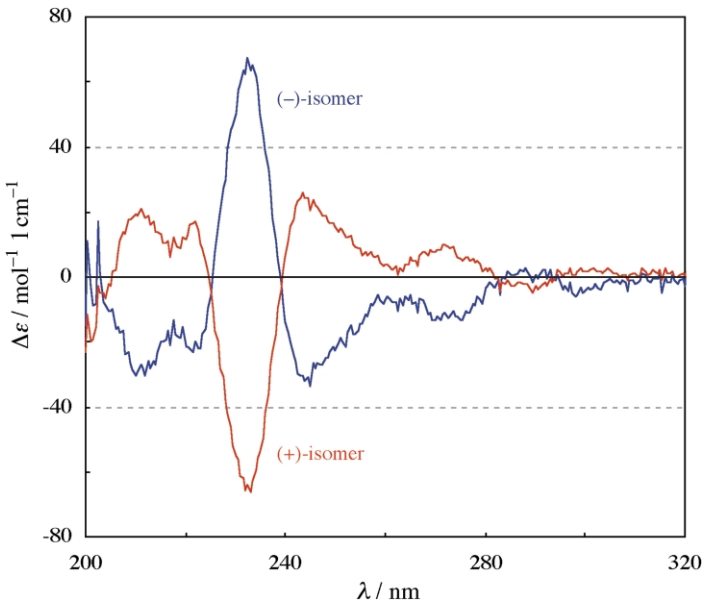


Figure 2. CD spectra of (−)- and (+)-isomers of ±*sc*-(*R*,*S*)-**1** in MeOH.

concept of internal compensation is incorrect and unnecessary.

3. Experimental

3.1. General

^{1}H NMR spectra were measured on a Varian Gemini-300 spectrometer at 300 MHz. ^{13}C NMR spectra were measured on a JEOL Lambda-500 spectrometer at 125 MHz. Melting points are not corrected. High-resolution mass spectra were measured on a JEOL JMS-700 MStation spectrometer. GPC was carried out with a Japan Analytical Industry Co. LC-908 Recycling HPLC system using JAIGEL-1H and 2H columns (eluent: chloroform). Preparative HPLC was carried out with a HITACHI L-6250 pump using a Develosil 60-7 column (20 mmϕ×250 mm). Optical rotation was measured on a JASCO DIP-370 polarimeter with the use of a 10 mmϕ×100 mm cell. CD spectra were measured on a JASCO J-820 spectropolarimeter with the use of a 1 mm cell.

3.1.1. 2-Chloro-6-methyl-9-anthrone (3). To a solution of 10.0 g (63 mmol) of 4-methylphthalic anhydride **2** in 50 ml of chlorobenzene was added 20.0 g (150 mmol) of aluminium chloride slowly in an ice bath. The whole was stirred for 30 min, and heated at 90°C for 1 h. After cooling, the reaction mixture was carefully quenched by the addition of ca. 70 g of ice and then 75 ml of 10% hydrochloric acid. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic solution was dried over $MgSO_4$, and concentrated to ca. 30 ml by evaporation. The formed solid was collected by filtration to give 10.7 g (62%) of a mixture of 2-(4-chlorobenzoyl)-4-methylbenzoic acid and 2-(4-chlorobenzoyl)-5-methylbenzoic acid in ca. 5:1 ratio. 2-(4-Chlorobenzoyl)-4-methylbenzoic acid: ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 7.15 (s, 1H), 7.36–7.40 (m, 3H), 7.65 (d, J=8.5 Hz, 2H), 7.98 (d, J=7.9 Hz, 1H). A signal due to the carboxylic proton was missing. The minor isomer gave a singlet at δ 2.47 (s, 3H). This mixture was used for the next reaction without separation. To 170 ml of 25% aqueous ammonia were added 3.00 g (10.9 mmol) of the benzoic acid, 8.30 g (127 mmol) of zinc powder, and 0.10 g (0.40 mmol) of $CuSO_4{\cdot}5H_2O$. While the whole was vigorously stirred under reflux for 3 days, 10 ml of 25% aqueous ammonia was added every 12 h. The reaction mixture was diluted by 200 ml of water and filtrated. The solid was washed with hot aqueous ammonia for several times. The combined filtrate was acidified by conc. hydrochloric acid. The formed solid was collected by filtration to afford 2.30 g (81%) of a mixture of the corresponding chlorobenzyl compounds. 2-(4-Chlorobenzyl)-4-methylbenzoic acid: ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 4.38 (s, 2H), 7.02 (s, 1H), 7.08 (d, J=8.6 Hz, 2H), 7.13 (d, J=8.1 Hz, 1H), 7.22 (d, J=8.6 Hz, 2H), 7.98 (d, J=8.0 Hz, 1H). The cyclization with sulfuric acid was carried out according to the literature method.[8] The crude material was purified by chromatography on silica gel with hexane/dichloromethane 10:1 eluent. The less easily eluted isomer was collected and recrystallized from hexane/dichloromethane to give the desired compound in 64% yield as colorless crystals. mp 181.5–183.5°C (lit. 182–185°C).[8] ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H), 4.29 (s, 2H), 7.25–7.30 (m, 2H), 7.41 (d, J=8.2 Hz, 1H), 7.54 (dd, J=8.2, 2.3 Hz, 1H), 8.25 (d, J=8.3 Hz, 1H), 8.32 (d, J=2.3 Hz, 1H). Anal. Found: C, 74.01; H, 4.52%. Calcd for $C_{15}H_{11}ClO$: C, 74.23; H, 4.57%. The easily eluted isomer was 2-chloro-7-methyl-9-anthrone: ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H), 4.29 (s, 2H), 7.33–7.47 (m, 3H), 7.55 (dd, J=8.0, 2.3 Hz, 1H), 8.16 (s, 1H), 8.33 (d, J=2.3 Hz, 1H).

3.1.2. 2,2′-Dichloro-6,6′-dimethyl-9,9′-bianthryl (4). To a suspension of 3.08 g (12.7 mmol) of 2-chloro-6-methyl-9-anthrone (**3**) and 2.49 g (38.1 mmol) of zinc powder in 30 ml of acetic acid was added 27 ml of conc. hydrochloric acid under reflux in 1 h. After the reflux for 2 h, the mixture was diluted with 100 ml of water. The insoluble materials were collected by filtration, and extracted with dichloromethane. Chromatography on silica gel (eluent hexane/ethyl acetate=50:1) and the subsequent recrystallization from hexane/dichloromethane afforded 1.40 g (48%) of the desired compound as pale yellow crystals. mp 271–273°C. ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 6H), 6.90 (d, J=8.8 Hz, 2H), 6.97–7.04 (m, 4H), 7.35 (dd, J=2.1, 8.9 Hz, 2H), 7.88 (s, 2H), 8.06 (d, J=8.9 Hz, 2H), 8.55 (s, 2H). Anal. Found: C, 79.51; H, 4.40%. Calcd for $C_{30}H_{20}Cl_2$: C, 79.83; H, 4.47%.

3.1.3. 2,2′-Dicyano-6,6′-dimethyl-9,9′-bianthryl (5). A suspension of 1.40 g (3.10 mmol) of **4** and 3.33 g (37.2 mmol) of CuCN in 50 ml of *N*-methyl-2-pyrrolidone was heated at 200°C for 96 h under a nitrogen atmosphere. The reaction mixture was treated with 17.5 g (64.7 mmol) of $FeCl_3{\cdot}6H_2O$ and 30 ml of conc. hydrochloric acid at ca. 70°C for 2 h. The mixture was diluted with 50 ml of water, and the solids were collected by filtration. The solid was treated with dichloromethane for several times, and the soluble materials were chromatographed on silica gel with hexane/ethyl acetate=5:1 eluent. Recrystallization from dichloromethane gave the desired compound as yellow crystals (72%). mp 270–278°C (decomp). ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 6H), 6.94 (d, J=8.9 Hz, 2H), 7.10 (dd, J=1.7, 8.9 Hz, 2H), 7.36 (s, 2H), 7.51 (dd, J=1.6, 8.8 Hz, 2H), 7.96 (s, 2H), 8.22 (d, J=8.9 Hz, 2H), 8.65 (s, 2H). Anal. Found: C, 88.70; H, 4.74; N, 6.44%. Calcd for $C_{32}H_{20}N_2$: C, 88.86; H, 4.66; N, 6.48%.

3.1.4. 2,2′-Bis(methoxycarbonyl)-6,6′-dimethyl-9,9′-bianthryl (6). To a solution of 20 g of NaOH in 85 ml of methanol and 25 ml of H_2O was added 807 mg (1.87 mmol) of **5**. The solution was refluxed for 48 h. After dilution with 100 ml of H_2O, the solution was filtered to remove insoluble materials. The filtrate was acidified by conc. hydrochloric acid, and the resulting yellow solid was collected by filtration. This acid was used for the next reaction without purification. The dried solid was dissolved in 30 ml of methanol and heated in the presence of 0.4 ml of conc. sulfuric acid for 48 h. The reaction mixture was pored into 50 ml of ice water, and the solid was collected by filtration. This material was purified by recrystallization from dichloromethane/hexane to give 897 mg of the desired compound. The overall yield was 96%. mp 305–316°C (decomp). ^{1}H NMR ($CDCl_3$): δ 2.51 (s, 6H), 3.67 (s, 6H), 6.87 (d, J=8.9 Hz, 2H), 6.99 (dd, J=1.7, 8.9 Hz, 2H), 7.82

(d, J=1.2 Hz, 2H), 7.92 (s, 2H), 7.98 (dd, J=1.3, 8.9 Hz, 2H), 8.18 (d, J=8.9 Hz, 2H), 8.61 (s, 2H). Anal. Found: C, 81.62; H, 5.22%. Calcd for $C_{34}H_{26}O_4$: C, 81.91; H, 5.26%.

3.1.5. 2,2′-Bis(methoxycarbonyl)-6,6′-dimethyl-9,9′-bitriptycyl (1). To a refluxing solution of 190 mg (0.381 mmol) of **6** in 20 ml of 1,4-dioxane were added a solution of 346 mg (3.81 mmol) of anthranilic acid in 10 ml of 1,4-dioxane and a solution of 0.77 ml (5.7 mmol) of isopentyl nitrite in 10 ml of 1,4-dioxane from respective dropping funnels in 2 h. After the addition was completed, the reaction mixture was refluxed for 3 h. The volatile materials were removed by evaporation, and the residue was passed through a plug column of silica gel with dichloromethane eluent. The crude material was recycled for several times by GPC with chloroform eluent to afford four bands. The second fraction was a mixture of the isomers of the desired compound and some amounts of by-products (ca. 50 mg). These were separated by HPLC (1:2 hexane/dichloromethane eluent), and the four rotamers were eluted at the retention times of 23, 93, 101, and 113 min. The yields of these isomers were 8, 2, 6, and 3 mg, respectively, the combined yield being 8% with the recovery of 20% of the starting bianthryl.

The first fraction was *ap*-(*R*,*S*)-**1**. mp>340°C (sublimation). ^{1}H NMR ($CDCl_3$): δ 2.25 (s, 6H), 3.54 (s, 6H), 5.61 (s, 2H), 6.40 (d, J=8.0 Hz, 2H), 6.59–6.69 (m, 4H), 6.80 (dd, J=2.5, 7.7 Hz, 2H), 7.02 (t, J=7.4 Hz, 2H), 7.37 (s, 2H), 7.46 (s, 2H), 7.53 (d, J=7.5 Hz, 2H), 7.56 (d, J=7.7 Hz, 2H), 7.71 (dd, J=1.5, 7.7 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 20.91, 51.68, 55.69, 57.99, 122.67, 122.93, 123.26, 123.30, 124.15, 124.59, 125.27, 126.76, 130.77, 130.84, 131.93, 134.93, 138.84, 141.98, 143.54, 145.58, 145.67, 151.63, 166.69. HRMS (FAB) calcd for $C_{46}H_{34}O_4$ (MH^+) 651.2535, found 651.2554.

The third fraction was ±*sc*-(*R*,*S*)-**1**. mp>300°C (decomp). ^{1}H NMR ($CDCl_3$): δ 2.25 (s, 3H), 2.26 (s, 3H), 3.50 (s, 3H), 3.51 (s, 3H), 5.61 (s, 2H), 6.42 (dt, J=1.3, 8.2 Hz, 2H), 6.57–6.68 (m, 3H), 6.74 (d, J=8.0 Hz, 1H), 6.79 (d, J=7.7 Hz, 1H), 6.87 (d, J=7.8 Hz, 1H), 7.01 (dt, J=1.1, 7.7 Hz, 2H), 7.39 (d, J=8.8 Hz, 4H), 7.53 (d, J=7.4 Hz, 2H), 7.57 (d, J=7.7 Hz, 2H), 7.71 (dt, J=7.7, 1.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 20.89, 20.93, 51.66, 55.70, 58.00, 122.56, 122.71, 123.11, 123.15, 123.21, 123.30, 123.34, 123.96, 124.18, 124.62, 124.64, 125.19, 125.34, 126.95, 126.97, 130.78, 130.89, 131.31, 131.39, 131.57, 134.97, 135.00, 138.84, 139.32, 142.00, 142.46, 143.09, 143.13, 145.63, 145.68, 145.89, 145.91, 151.46, 166.68. HRMS (FAB) calcd for $C_{46}H_{34}O_4$ (MH^+) 651.2535, found 651.2562.

Spectroscopic and other relevant data of the other two fractions follow. Second fraction (one of the rotamers of (R^*,R^*)-**1**): Colorless powder. mp>300°C. ^{1}H NMR ($CDCl_3$): δ 2.25 (s, 6H), 3.51 (s, 6H), 5.61 (s, 2H), 6.40 (dd, J=8.4, 1.5 Hz, 2H), 6.62 (dt, J=1.5, 7.6 Hz, 2H), 6.66 (d, J=8.4 Hz, 2H), 6.86 (d, J=7.7 Hz, 2H), 7.01 (dt, J=7.1, 1.1 Hz, 2H), 7.37 (d, J=1.5 Hz, 2H), 7.41 (s, 2H), 7.51 (dd, J=7.2, 1.3 Hz, 2H), 7.57 (d, J=7.7 Hz, 2H), 7.71 (dd, J=1.6, 7.7 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 20.93, 51.65, 55.70, 58.00, 122.55, 123.10, 123.33, 124.18, 124.64, 125.17, 126.92, 130.76, 131.41, 131.48, 134.96, 138.83, 142.34, 143.11, 145.66, 145.87, 151.45, 166.68. HRMS (FAB) calcd for $C_{46}H_{34}O_4$ (MH^+) 651.2535, found 651.2538. Fourth fraction (one of the rotamers of (R^*,R^*)-**1**): Colorless powder. mp>300°C. ^{1}H NMR ($CDCl_3$): δ 2.26 (s, 6H), 3.49 (s, 6H), 5.61 (s, 2H), 6.43 (d, J=8.3 Hz, 2H), 6.60 (dt, J=1.2, 7.6 Hz, 2H), 6.75 (d, J=8.0 Hz, 2H), 6.80 (d, J=7.7 Hz, 2H), 7.01 (dt, J=1.2, 7.2 Hz, 2H), 7.37 (d, J=1.5 Hz, 2H), 7.39 (s, 2H), 7.53 (dd, J=1.2, 7.4 Hz, 2H), 7.57 (d, J=7.7 Hz, 2H), 7.71 (dd, J=1.5, 7.7 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 20.87, 51.64, 55.68, 57.98, 122.70, 123.12, 123.20, 123.28, 123.95, 124.60, 125.32, 126.97, 130.89, 131.27, 131.51, 139.31, 141.98, 143.08, 145.62, 145.91, 151.44, 166.65. HRMS (FAB) calcd for $C_{46}H_{34}O_4$ (MH^+) 651.2535, found 651.2549.

3.1.6. Enantiomer separation by HPLC. Chiral HPLC was carried out with a HITACHI L-6250 pump using a Daicel CHIRALCEL OD column (10 mmϕ×250 mm) and 20:1 hexane/2-propanol eluent. About 1 mg of a sample of racemic ±*sc*-(*R*,*S*)-**1** was injected for each separation. The retention times of the enantiomers were 15.4 and 18.0 min. The data of optical rotation and CD are as follows. The easily eluted enantiomer: $[\alpha]_D^{22}$=−56 (c 0.02, $CHCl_3$), CD (MeOH): λ ($\Delta\varepsilon$) 221.5 (−23.2), 232.5 (+67.5), 245.0 (−33.7), 265.0 (−5.3), 269.5 (−13.3), 269.5 (−13.3), 288.0 (+2.8) nm. The less easily eluted enantiomer: $[\alpha]_D^{22}$=−54 (c 0.02, $CHCl_3$), CD (MeOH): λ ($\Delta\varepsilon$) 222.0 (+16.9), 233.0 (−67.4), 243.5 (−25.8), 262.5 (+0.8), 272.0 (+10.0), 289.5 (−5.1) nm. The other rotamers were also submitted to the chiral HPLC under the same condition. Although no sign of separation was observed for *ap*-(*R*,*S*)-**1**, the two rotamers of (R^*,R^*)-**1** showed two peaks due to the enantiomers. The second fraction was partially resolved with 15.0 and 16.2 min retention times, whereas the fourth fraction was completely resolved with retention times of 15.2 and 19.0 min. The samples of these enantiomers were obtained in so small quantities that their chiroptical data were not collected.

3.2. X-Ray analysis of *ap*-(*R*,*S*)-1

A crystal used for the measurement was grown form a hexane/dichloromethane solution. The crystal size was 0.15×0.15×0.10 mm^3. X-Ray data were collected by a Rigaku-AXIS RAPID diffractometer with Mo Kα radiation (λ=0.71070 Å) at 173 K. The scan mode was the ω-method. The reflections were collected in the range of $2.5<\theta<27.5°$. The reflection data were corrected for the Lorentz-polarization effects and secondary extinction (coefficient=0.0019). The structure was solved by the direct method (SHELXS97), and refined by the full-matrix least-squares method by using a teXsan program. The non-hydrogen atoms were refined anisotropically. Some hydrogen atoms were refined isotropically, and the rest were included in fixed positions. Among 5481 observed reflections, 3900 reflections ($I>2.0\sigma(I)$) were used for the refinement of 227 variables. The function minimized was $\sum[w(|F_o|-|F_c|)^2]$, where $w=[\sigma_c^2|F_o|^2+(0.0919P)^2+14.0796P]^{-1}$ and $P=(|F_o|^2+2|F_c|^2)/3$. Formula $C_{46}H_{34}O_4$. FW=650.73, trigonal, space group $R\bar{3}$ (# 148), a=38.696(3), c=8.3500(7) Å, V=10828.0(14) Å^3, Z=9,

D_c=0.898 g/cm^3, R=0.0782, R_w=0.1958, GOF=1.090. The crystal contained disordered solvent molecules in the cavities made by the bitriptycyl molecules in random positions and orientations. The formula weight and density were calculated with ignoring the presence of solvent molecules. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 194389. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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