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Folding of dihelicenetriamines in water

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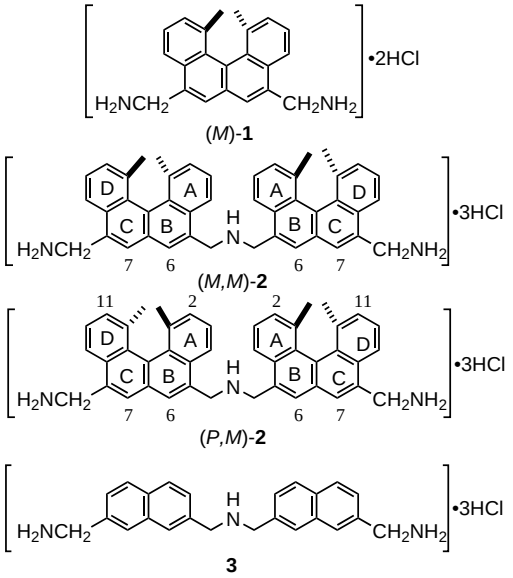
Abstract—Diastereomeric triamines containing two helicene moieties, 1,12-dimethylbenzo[*c*]phenanthrene, were synthesized and found to form folded structures in the water. Such folding was not observed for an achiral compound possessing a naphthalene moiety. The (*M*,*M*)-dihelicenetriamine with matching configuration at the helicene moieties formed a more stable folded structure than the (*P*,*M*)-isomer containing two enantiomeric helicene groups. The most stable folded conformation was predicted by the Monte Carlo method with Amber force field of the dihelicenetriamine.

1. Introduction

Non-bonding interactions and chiral recognition between the helical π-electron systems play important roles in the chemistry of helicenes, 1,12-dimethylbenzo[*c*]phenanthrene derivatives. Electron-rich and electron-deficient helicenes formed a charge-transfer (CT) complex in solution, and the (*M*)-helicene acceptor exhibited higher affinity with the (*M*)-donor than the (*P*)-donor.[1] A CT-complex of the racemic electron-deficient helicene and pyrene crystallized in the columnar structure, each of which contained a single enantiomer of the helicene.[2] Macrocyclic alkynes containing three helicene moieties aggregated in organic solvents by π-π interactions, and the homo-aggregation of the (*M*,*M*,*M*)-isomer turned out to be stronger than the hetero-aggregation between the (*M*,*M*,*M*)-isomer and the (*P*,*P*,*P*)-isomer.[3] As an extension of helicene chemistry,[4,5] the basic derivatives, 5,8-bis(aminomethyl)-1,12-dimethylbenzo[*c*]phenanthrene **1** and its dimers **2**, were synthesized.[6] The isomers **2** were found to form folded structures in water, and the behavior of (*M*,*M*)-**2** was compared with that of (*P*,*M*)-**2**.

2. Results and discussion

The diamine **1**, prepared by hydrogenation of the dinitrile **4**[1] in 71% yield, was used for the synthesis of **2** (Scheme 1). In order to discriminate two amino groups, (*M*)-**1** was treated with 1 equiv. of Boc_2O followed by CbzCl giving (*M*)-**5**. A half aldehyde (*M*)-**6** was obtained by DIBAL reduction of (*M*)-**4**. Compound (*M*)-**5** was then converted to the monoamine by selective removal of the benzyloxycarbonyl group and coupled with (*M*)-**6** in refluxing toluene followed by $NaBH_4$ reduction giving (*M*,*M*)-**7** in 70% yield. The nitrile (*M*,*M*)-**7** was reduced by a two-step procedure using $NaBH_4$ and DIBAL, and *t*-butoxycarbonylation of the crude product gave (*M*,*M*)-**8**. The protecting groups of (*M*,*M*)-**8** were removed with trifluoroacetic acid, and treatment with hydrochloric acid gave (*M*,*M*)-**2**. The antipode (*P*,*P*)-**2**



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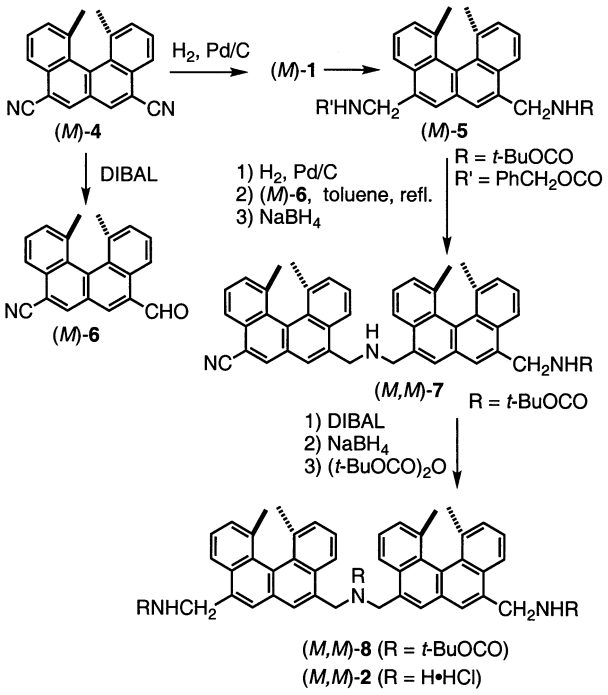
was synthesized by the same procedure starting from (*P*)-**4**. The diastereoisomer (*P*,*M*)-**2**, a *meso*-compound, was obtained from (*P*)-**5** and (*M*)-**6**. An achiral dimer **3** was also synthesized from 2,7-naphthalenedicarboxylic acid[7] in order to compare its properties with those of **2**.

The dimers **2** exhibited different ^{1}H NMR spectra in water and organic solvents. While the aromatic protons of (*M*,*M*)-**2** in CD_3OD appeared at $>\delta$ 7.4, they were all shifted to higher field in D_2O (Fig. 1). In particular, in the spectra of (*M*,*M*)-**2**, the two singlet signals for 6-*H* and 7-*H* were shifted by more than 1 ppm; from δ 8.3 (CD_3OD) to δ 7.0 (D_2O) for 6-*H*, and from δ 8.0 (CD_3OD) to δ 6.7 (D_2O) for 7-*H*. The peaks were assigned unambiguously using 2D-NMR of (*M*,*M*)-**2** as well as ^{1}H NMR of (*M*,*M*)-**2**-*d* obtained by $NaBD_4$ reduction of (*M*,*M*)-**7**. The ^{1}H NMR spectra of (*M*,*M*)-**2** in DMSO-d_6, DMF-d_7, and CD_3CO_2D were similar to that recorded in CD_3OD. The ^{1}H NMR spectra in D_2O were concentration independent between 0.1 and 5 mM indicating the intramolecular nature of the phenomenon. In accordance, ^{1}H NMR of the monomeric (*M*)-**1** did not show such solvent effects. UV, CD, and fluorescence spectra of (*M*,*M*)-**2** exhibited hypochromism on changing the solvent from methanol to water (Figs. 2 and 3), which suggests the formation of π-stacked structures in water. These observations are consistent with the formation of folded, most likely



Scheme 1.

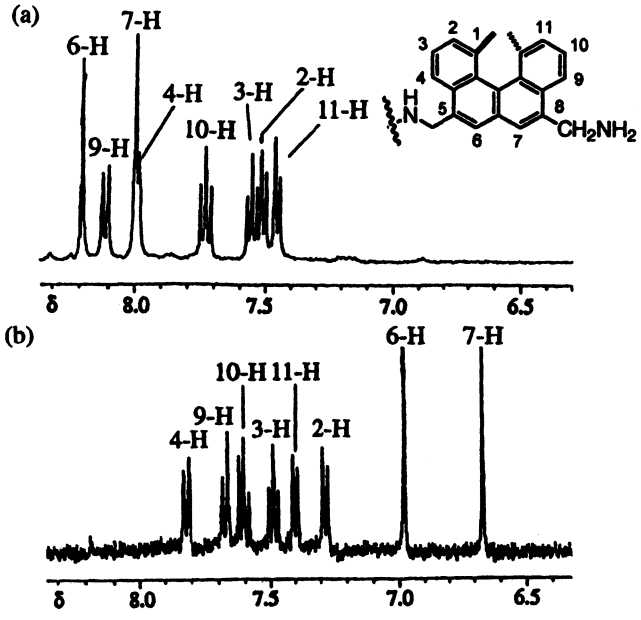


Figure 1. ^{1}H NMR (23°C, 1.0 mM) spectra of (*M*,*M*)-**2** in CD_3OD (a) or D_2O (b).

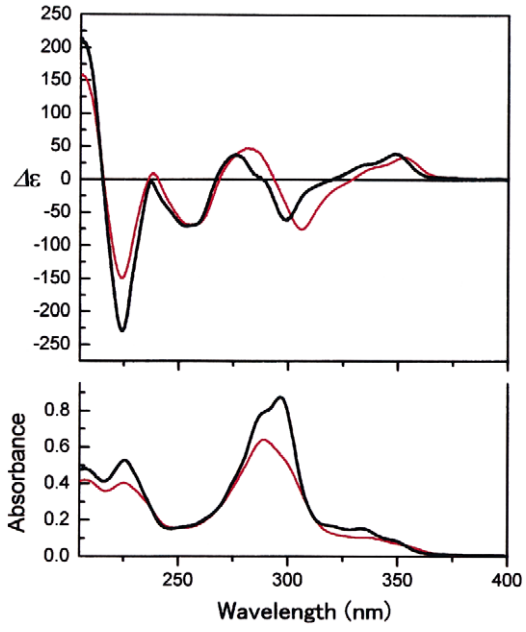


Figure 2. UV and CD spectra of (*M*,*M*)-**2** (1.0×10^{-5} M, 25°C) in CH_3OH (black lines) and in H_2O (red lines).

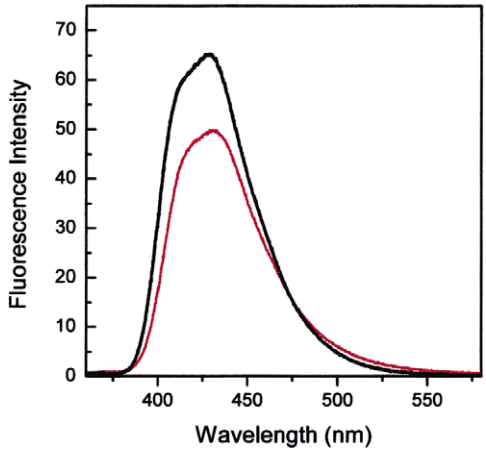


Figure 3. Fluorescence spectra of (*M*,*M*)-**2** (1.0×10^{-5} M, 25°C) in CH_3OH (black line) and in H_2O (red line) with excitation at 350 nm.

layered structures[8,9] of (*M*,*M*)-**2** in water, while the compound is not folded in organic solvents. Such solvent effects were also observed in the ^{1}H NMR, UV, and fluorescence spectra of the diastereomer (*P*,*M*)-**2** (Figs. 4–6). The ^{1}H NMR spectra of this compound exhibited high field shift of not only 6-*H* and 7-*H* but also 2-*H* and 11-*H*, when the solvent was changed from CD_3OD to D_2O (Fig. 4).

In contrast to the chiral compounds **2**, the ^{1}H NMR and UV spectra of the achiral **3** were similar in organic solvents and in water. The folding of **2** in water is therefore due to stronger intramolecular interactions, not only hydrophobic effects but also π-π interactions. The difference

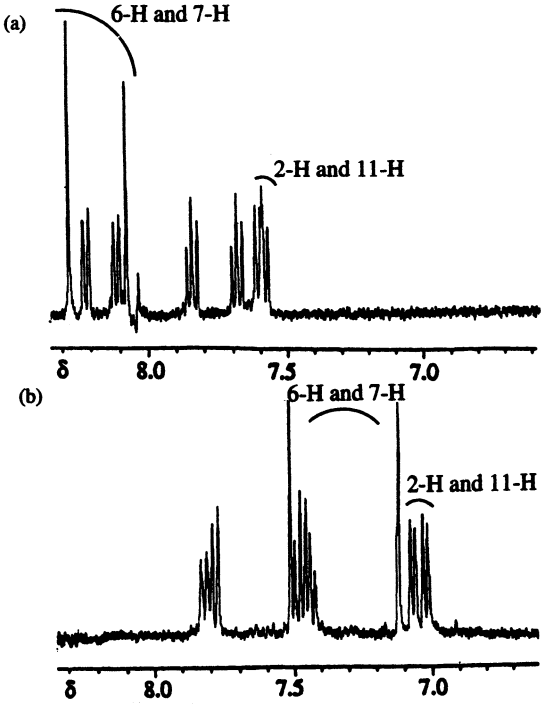


Figure 4. ^{1}H NMR (23°C, 1.0 mM) spectra of (*P*,*M*)-**2** in CD_3OD (a) or D_2O (b).

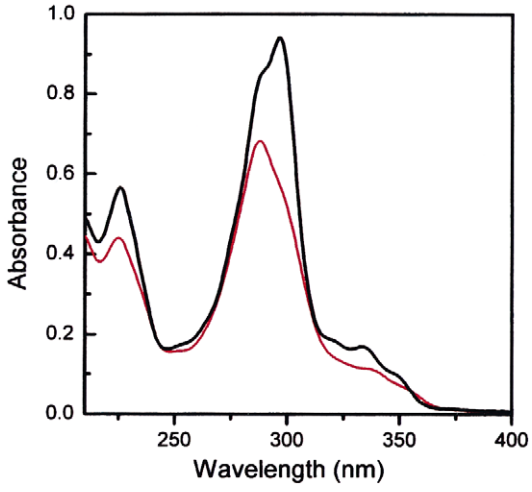


Figure 5. UV spectra of (*P*,*M*)-**2** (1.0×10^{-5} M, 25°C) in CH_3OH (black line) and in H_2O (red line).

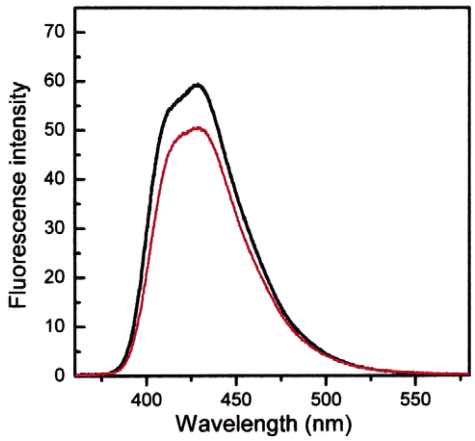


Figure 6. Fluorescence spectra of (*P*,*M*)-**2** (1.0×10^{-5} M, 25°C) in CH_3OH (black line) and in H_2O (red line) with excitation at 350 nm.

in the number of benzene rings at the aromatic moiety, four for compound **2** and two for compound **3**, or the chirality of the π-electron system is playing an important role. At present, we prefer the latter interpretation, since some indications were obtained for the strong affinity of the helical π-electron system with the same absolute configuration.[3] In addition, different folding behaviors observed between the isomeric (*M*,*M*)-**2** and (*P*,*M*)-**2** support the interpretation. When the UV absorption coefficients ε at 290 nm of the isomeric **2** were plotted against the solvent composition of methanol and water, sigmoidal curves were obtained (Fig. 7). The ratio of the folded and unfolded structures in solution were obtained at each solvent composition, and the free energy differences ΔG between the two states could be calculated (Fig. 8). Linear extrapolation of these data to 100% water gave the values $\Delta G_{M,M}(H_2O) = -1.8$ kcal/mol and $\Delta G_{P,M}(H_2O) = -1.5$ kcal/mol, which are the free energy differences in water between the folded and unfolded structures for each isomer.[10] The results indicate that (*M*,*M*)-**2**, with matching configuration of helicenes, forms more stable folded structure(s) than (*P*,*M*)-**2** with enantiomeric helicene moieties.

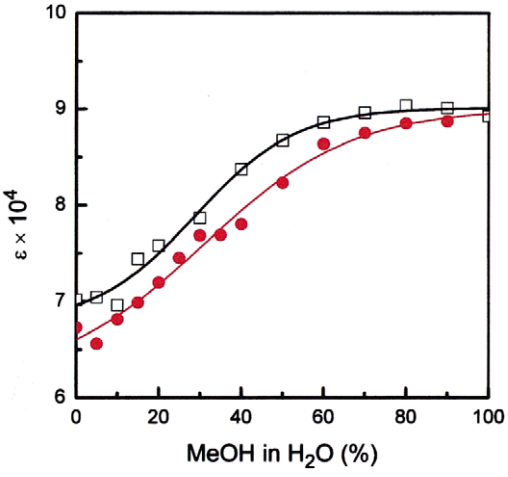


Figure 7. Plots of the UV absorption coefficient ε at 290 nm versus the volume percent of H_2O in CH_3OH for (*M*,*M*)-**2** (□) and (*P*,*M*)-**2** (●) (25°C, 1.1×10^{-5} to 1.5×10^{-5} M).

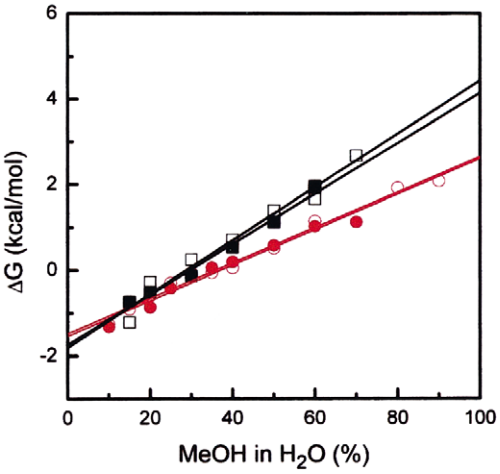


Figure 8. Plots of ΔG versus the volume percent of CH_3OH in H_2O for (*M*,*M*)-**2** (□,■) and (*P*,*M*)-**2** (○,●) (25°C, 1.0×10^{-5} to 1.5×10^{-5} M). Linear extrapolation of these data to 100% H_2O gives the values: $\Delta G_{M,M}(H_2O)=-1.8\pm0.6$ (□) and -1.7 ± 0.4 (■) kcal/mol; $\Delta G_{P,M}(H_2O)=-1.5\pm0.3$ (○) and -1.5 ± 0.3 (●) kcal/mol. The same experiments were conducted twice.

The most stable conformations of (*M*,*M*)-**2** and (*P*,*M*)-**2** in water were obtained by the Monte Carlo method with Amber force field (Fig. 9). Both isomers of **2** stack at the B ring of the helicene moiety, and the structures are consistent with the high field shifts of **2** at 6-*H* and 7-*H* on folding. Reflecting the helicity, however, the distances between the two D-rings of (*M*,*M*)-**2** (7.1 Å) is substantially longer than that of (*P*,*M*)-**2** (5.8 Å), which reasonably explains the high field shifts at 2-*H* and 11-*H* for the latter compound (Fig. 9b). The calculations also indicated the higher stability of the folded structure of (*M*,*M*)-**2** over (*P*,*M*)-**2** by 1.7 kcal/mol, which is in fair agreement with 0.3 kcal/mol obtained by the above experiments (Fig. 8).

X-Ray crystallographic analyses of (*M*)-**1** and (±)-**1** provided additional information on the folded structure of **2** (Fig. 10a and b).[11] Both crystals contained columnar structures of the helicene, in which the B-rings stack with each other. The calculated structures of **2** (Fig. 9) are therefore probable. It may also be interesting to note that, in the crystal of (±)-**1**, (*M*)-**1** and (*P*)-**1** formed different columns (Fig. 10c). Thus, the helicene favors the same configuration of the compound via π-π stacking in the crystallization process.

3. Conclusion

To summarize, dihelicenetriamines form folded structures in the water and unfolded structures in organic solvents, and the folding behaviors of these structures were affected by the chirality at the helicene moiety. Studies on the synthesis and folding behavior of higher oligoamines are now underway.

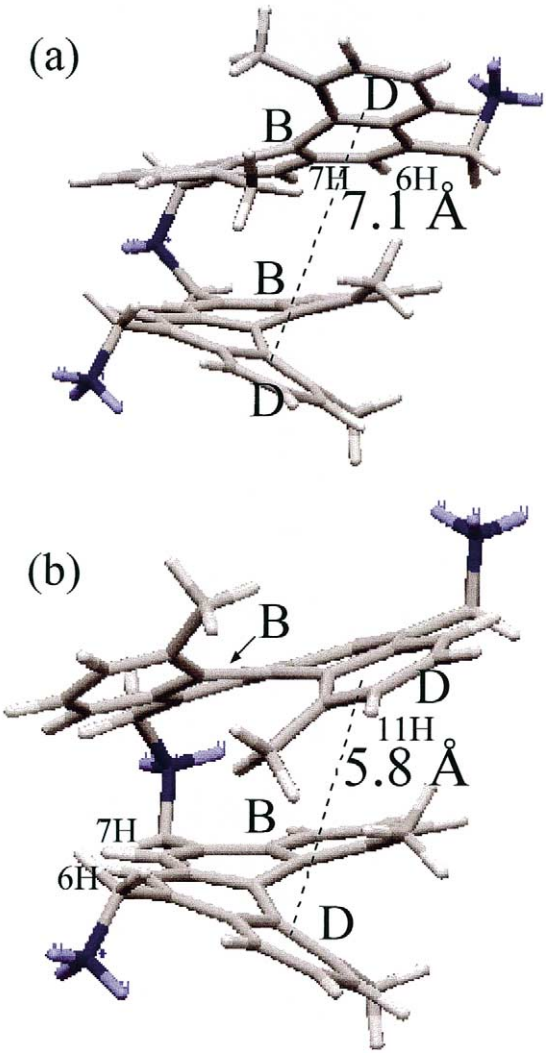


Figure 9. The calculated structures of (*M*,*M*)-**2** (a) and (*P*,*M*)-**2** (b) in water obtained by the Monte Carlo method with Amber force field using Macromodel.

4. Experimental

4.1. (*M*)-1,12-Dimethyl-5,8-bis(aminomethyl)benzo[*c*]-phenanthrene dihydrochloride, (*M*)-1

Under a hydrogen atmosphere, a mixture of (*M*)-**4**[1] (200 mg, 0.65 mmol), palladium on carbon (5%, 200 mg), ethyl acetate (20 mL), methanol (20 mL) and 2 M hydrochloric acid (2 mL) was vigorously stirred at 40°C for 36 h. The insoluble materials were removed by filtration and the solution was concentrated in vacuo. Recrystallization from ethanol gave (*M*)-**1** (180 mg, 71%). Mp 240°C dec. (ethanol). $[\alpha]_D^{31}$ +102 (*c* 0.49, methanol). Anal calcd for $C_{22}H_{22}N_2Cl_2\cdot H_2O$: C, 65.19; H, 6.46; N, 6.91; Cl, 17.49. Found: C, 64.59; H, 6.61; N, 7.06; Cl, 17.73%. LRMS (EI, 70 eV) *m*/*z* 314 (M^+-2HCl, 100%), 282 (M^+-2NH_3Cl, 49%). HRMS (EI, 70 eV) calcd for $C_{22}H_{22}N_2$: 314.1783. Found: 314.1768. IR (KBr) 3700–3300 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.85 (6H, s), 4.67 (2H, d, $J=15$ Hz), 4.73 (2H, d, $J=15$ Hz), 7.55 (2H, d, $J=7$ Hz), 7.73 (2H, dd, $J=7$, 8 Hz), 8.02 (2H, s), 8.18 (2H, d, $J=8$ Hz). ^{13}C

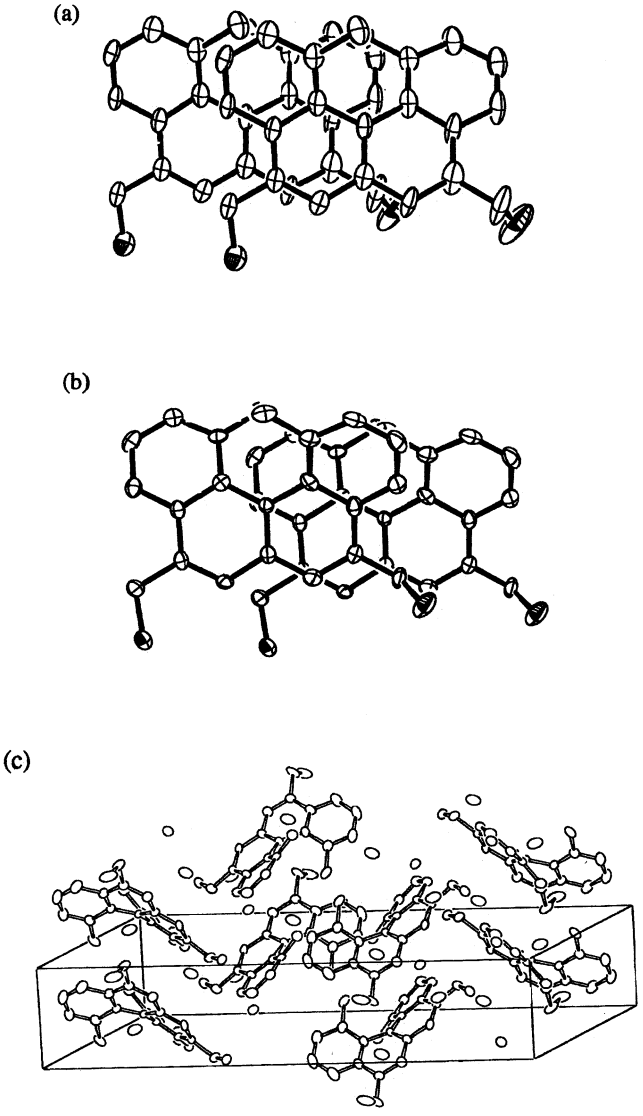


Figure 10. X-Ray structures of (*M*)-**1** (a) and (±)-**1** (b,c). Protons are omitted for clarity.

NMR (DMSO-d_6) δ 23.2, 48.8, 121.0, 125.3, 125.9, 126.8, 128.8, 129.7, 129.8, 130.3, 130.6, 136.2. (*P*)-**1**: $[\alpha]_D^{31}$ −97 (*c* 0.23, methanol).

4.2. (*M*)-1,12-Dimethyl-5-formyl-benzo[*c*]phenanthrene-8-carbonitrile, (*M*)-6

Under an argon atmosphere, to a solution of (*M*)-**4** (770 mg, 2.50 mmol) in dichloromethane (20 mL) was added diisobutylaluminum hydride in hexane (1.0 M, 3.0 mL, 3.0 mmol) at −90°C. After stirring the mixture for 10 min at the temperature, 1 M hydrochloric acid (20 mL) was added, and the mixture was warmed to room temperature. The organic materials were extracted with chloroform three times. The combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Purification by silica gel chromatography gave (*M*)-**6** (330 mg, 42%). An analytical sample was obtained by recrystallization from toluene/hexane. Mp 240°C sublimation. $[\alpha]_D^{29}$ −182 (*c* 0.38, $CHCl_3$). Anal. calcd for $C_{22}H_{15}NO$: C, 85.41; H, 4.89; N, 4.53. Found: C, 84.85; H, 5.20; N, 4.63%. LRMS (EI, 70 eV) *m*/*z* 309 (M^+, 100%), 294 (M^+–Me, 20%), 281 (M^+–CHO, 7%). HRMS (EI, 70 eV) calcd for $C_{22}H_{15}NO$: 309.1154. Found: 309.1172. IR (KBr) 2730, 2221, 1685 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.90 (3H, s), 1.92 (3H, s), 7.53 (1H, d, *J*=7 Hz), 7.57 (1H, d, *J*=7 Hz), 7.79 (1H, dd, *J*=7, 8 Hz), 7.81 (1H, dd, *J*=7, 8 Hz), 8.29 (1H, s), 8.33 (1H, d, *J*=8 Hz), 8.38 (1H, d, *J*=8 Hz), 9.25 (1H, d, *J*=8 Hz), 10.51 (1H, s). ^{13}C NMR ($CDCl_3$) δ 23.2, 23.5, 110.1, 117.5, 122.4, 122.9, 129.0, 129.0, 129.3, 129.8, 129.9, 130.3, 130.5, 131.1, 131.3, 131.5, 132.6, 132.6, 136.1, 136.9, 137.9, 192.1. (*P*)-**6**: $[\alpha]_D^{22}$ +195 (*c* 0.53, $CHCl_3$).

4.3. (*M*)-8-Benzyloxycarbonylaminomethyl-5-(*t*-butoxycarbonylaminomethyl)-1,12-dimethylbenzo[*c*]phenanthrene, (*M*)-5

To a mixture of (*M*)-**1** (390 mg, 1.0 mmol), dichloromethane (10 mL), water (5 mL) and 10% aqueous sodium hydroxide (5 mL) was added di(*t*-butyl) dicarbonate (220 mg, 1 mmol) at 0°C. After being stirred for 30 min at the temperature, benzyloxycarbonyl chloride (0.28 mL, 2 mmol) was added, and the mixture was stirred for another 30 min. The reaction was quenched by adding saturated aqueous ammonium chloride, and the organic materials were extracted with ethyl acetate three times. The combined organic layers were washed with water and brine, dried over magnesium sulfate and concentrated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane=1/2) gave (*M*)-**5** (180 mg, 35%). Mp 124–125°C (toluene). $[\alpha]_D^{27}$ +70 (*c* 0.9, $CHCl_3$). Anal. calcd for $C_{35}H_{36}N_2O_4$: C, 76.62; H, 6.61; N, 5.11. Found: C, 76.38; H, 6.90; N, 4.86%. LRMS (EI, 70 eV) *m*/*z* 548 (M^+, 9%), 448 (M^+–Boc, 100%). HRMS (EI, 70 eV) calcd for $C_{35}H_{36}N_2O_4$: 548.2675. Found: 548.2699. IR (KBr) 3500–3300, 1698 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.50 (9H, s), 1.91 (3H, s), 1.92 (3H, s), 4.80–5.10 (2H, m), 5.18 (2H, s), 5.21 (2H, br), 7.28–7.40 (5H, m), 7.40 (2H, d, *J*=7 Hz), 7.60 (1H, t, *J*=8 Hz), 7.60 (1H, t, *J*=8 Hz), 7.68 (1H, s), 7.69 (1H, s), 8.02 (1H, d, *J*=7 Hz), 8.04 (1H, d, *J*=8 Hz). ^{13}C NMR ($CDCl_3$) δ 23.4, 23.4, 28.4, 42.7, 43.1, 66.7, 79.4, 120.3, 120.4, 124.6, 124.7, 125.1, 125.8, 127.8, 127.8, 128.0, 128.2, 130.0, 130.2, 131.0, 131.4, 132.5, 133.0, 136.2, 136.5, 136.5, 155.5, 156.0. (*P*)-**5**:$[\alpha]_D^{26}$ −70 (*c* 0.6, $CHCl_3$).

4.4. (*M*)-5-Aminomethyl-8-(*t*-butoxycarbonylaminomethyl)-1,12-dimethylbenzo[*c*]phenanthrene

Under a hydrogen atmosphere, a mixture of (*M*)-**5** (250 mg, 0.5 mmol), 5% palladium on carbon (350 mg), ethyl acetate (5 mL) and methanol (5 mL) was vigorously stirred for 1 h at room temperature. Insoluble materials were removed by filtration, and the solution was concentrated in vacuo. Purification by silica gel chromatography (ethyl acetate/methanol=1/1) gave the title compound (150 mg, 72%). $[\alpha]_D^{27}$ +88 (*c* 1.1, $CHCl_3$). Anal. calcd for $C_{27}H_{30}N_2O_2$: C, 78.23; H, 7.29; N, 6.76. Found: C, 77.96; H, 7.25; N, 6.74%. LRMS (EI, 70 eV) *m*/*z* 415 (M^++1, 30%), 414 (M^+, 90%), 357 (M^+–*t*Bu, 100%). HRMS (EI, 70 eV) calcd for $C_{27}H_{30}N_2O_2$:

414.2307. Found: 414.2307. IR (KBr) 3500–3200, 1702 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.50 (9H, s), 1.93 (6H, s), 4.42 (1H, d, $J=15$ Hz), 4.50 (1H, d, $J=14$ Hz), 4.85 (1H, dd, $J=5$,14 Hz), 4.97 (1H, dd, $J=6$,14 Hz), 5.03 (1H, br), 7.39 (2H, d, $J=7$ Hz), 7.59 (1H, t, $J=8$ Hz), 7.59 (1H, t, $J=8$ Hz), 7.71 (1H, s), 7.74 (1H, s), 8.04 (1H, d, $J=8$ Hz), 8.06 (1H, d, $J=8$ Hz). ^{13}C NMR ($CDCl_3$) δ 23.6, 23.6, 28.6, 43.0, 44.1, 79.5, 120.2, 120.5, 123.1, 124.8, 125.0, 125.8, 128.0, 128.1, 130.2, 130.3, 131.5, 131.6, 131.7, 133.0, 136.7, 136.8, 137.8, 155.6. (*P*)-isomer: $[\alpha]_D^{26}$ −90 (*c* 1.0, $CHCl_3$).

4.5. (*M*,*M*)-5-{8-(*t*-Butoxycarbonylaminomethyl)-1,12-dimethylbenzo[*c*]phenanthrene-5-yl}methylaminomethyl-8-cyano-1,12-dimethylbenzo[*c*]phenanthrene, (*M*,*M*)-7

A solution of (*M*)-monoamine obtained as above (150 mg, 0.36 mmol) and (*M*)-6 (120 mg, 0.4 mmol) in toluene (10 mL) was heated under reflux for 24 h. The mixture was added to a suspension of sodium borohydride (300 mg, 8 mmol) in methanol (20 mL) and tetrahydrofuran (10 mL) at 0°C. The mixture was stirred at the temperature for 10 min, and the reaction was quenched by adding saturated aqueous ammonium chloride. The organic materials were extracted with ethyl acetate three times. The combined organic layers were washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane = 1/2) gave (*M*,*M*)-**7** (180 mg, 70%). Mp 150°C dec. (ethyl acetate/hexane). $[\alpha]_D^{27}$ −14 (*c* 1.2, $CHCl_3$). Anal. calcd for $C_{49}H_{45}N_3O_2$: C, 83.14; H, 6.41; N, 5.94. Found: C, 82.98; H, 6.09; N, 5.57%. LRMS (EI, 70 eV) *m*/*z* 707 (M^+, 1%), 607 (M^+−Boc, 5%), 299 (MeAr*CH_2NH_2, 100%). IR (KBr) 3500–3300, 2222, 1704 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.50 (9H, s), 1.89 (3H, s), 1.92 (3H, s), 1.93 (6H, s), 4.49 (1H, d, $J=14$ Hz), 4.49 (1H, d, $J=14$ Hz), 4.59 (1H, d, $J=15$ Hz), 4.63 (1H, d, $J=13$ Hz), 4.81–5.00 (3H, m), 7.39 (1H, d, $J=7$ Hz), 7.41 (1H, d, $J=7$ Hz), 7.42 (1H, d, $J=8$ Hz), 7.49 (1H, d, $J=7$ Hz), 7.53 (1H, dd, $J=7$, 8 Hz), 7.59 (1H, dd, $J=7$, 8 Hz), 7.60 (1H, dd, $J=7$, 8 Hz), 7.70 (1H, t, $J=8$ Hz), 7.71 (1H, s), 7.83 (1H, s), 7.86 (1H, s), 8.04 (1H, d, $J=8$ Hz), 8.14 (2H, d, $J=8$ Hz), 8.23 (1H, s), 8.28 (1H, d, $J=8$ Hz). ^{13}C NMR ($CDCl_3$) δ 23.3, 23.5, 23.6, 23.6, 28.6, 43.0, 51.4, 51.8, 79.6, 109.0, 118.1, 120.6, 120.9, 121.2, 122.6, 124.3, 124.9, 125.2, 125.3, 125.7, 125.9, 127.2, 127.3, 128.0, 128.1, 128.2, 128.6, 129.7, 129.8, 130.1, 130.3, 130.6, 130.9, 131.1, 131.2, 131.7, 132.3, 132.7, 133.0, 134.6, 136.2, 136.7, 136.9, 137.3, 155.5. (*P*,*P*)-**7**: $[\alpha]_D^{26}$ +13 (*c* 1.0, $CHCl_3$). (*P*,*M*)-**7** was obtained from (*P*)-**5** and (*M*)-**6** in 82% yield. Mp 150°C dec. (ethyl acetate/hexane). $[\alpha]_D^{26}$ −52 (*c* 0.6, $CHCl_3$). Anal. calcd for $C_{49}H_{45}N_3O_2$: C, 83.14; H, 6.41; N, 5.94. Found: C, 83.41; H, 5.89; N, 6.07%. LRMS (EI, 70 eV) *m*/*z* 707 (M^+, 3%), 607 (M^+−Boc, 19%), 310 (NC-Ar*CH_2NH_2, 100%). IR (KBr) 3500–3300, 2222, 1705 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.50 (9H, s), 1.90 (3H, s), 1.91 (3H, s), 1.93 (6H, s), 4.48 (1H, d, $J=14$ Hz), 4.49 (1H, d, $J=14$ Hz), 4.61 (1H, d, $J=15$ Hz), 4.65 (1H, d, $J=14$ Hz), 4.80–5.00 (3H, m), 7.39 (1H, d, $J=7$ Hz), 7.41 (1H, d, $J=7$ Hz), 7.43 (1H, d, $J=8$ Hz), 7.49 (1H, d, $J=7$ Hz), 7.54 (1H, t, $J=8$ Hz), 7.60 (2H, t, $J=8$ Hz), 7.70 (1H, t, $J=8$ Hz), 7.72 (1H, s), 7.84 (1H, s), 7.87 (1H, s), 8.04 (1H, d, $J=8$ Hz), 8.15 (2H, d, $J=8$ Hz), 8.24 (1H, s), 8.28 (1H, d, $J=8$ Hz). ^{13}C NMR ($CDCl_3$) δ 23.3, 23.5, 23.6, 23.6, 28.6, 43.0, 51.4, 51.8, 79.6, 108.9, 118.1, 120.5, 120.9, 121.2, 122.6, 124.3, 124.9, 125.1, 125.2, 125.7, 125.9, 127.2, 127.3, 128.0, 128.1, 128.2, 128.6, 129.7, 129.8, 130.1, 130.2, 130.6, 130.9, 131.1, 131.2, 131.7, 132.3, 132.7, 133.0, 134.5, 136.1, 136.7, 136.9, 137.3, 155.5.

4.6. (*M*,*M*)-5-{8-(*t*-Butoxycarbonylaminomethyl)-1,12-dimethylbenzo[*c*]phenanthrene-5-yl}methylaminomethyl-8-(*t*-butoxycarbonylaminomethyl)-1,12-dimethylbenzo[*c*]-phenanthrene, (*M*,*M*)-8

Under an argon atmosphere, to a solution of (*M*,*M*)-**7** (90 mg, 0.13 mmol) in dichloromethane (20 mL) was added 1.0 M diisobutylaluminum hydride in hexane (1.0 mL, 1.0 mmol) at 0°C and the mixture was stirred for 30 min at the temperature. Then the mixture was added to a suspension of sodium borohydride (200 mg, 5.4 mmol) in tetrahydrofuran (10 mL) and methanol (20 mL) at 0°C. The ice bath was removed and stirring was continued at room temperature for 30 min, when saturated aqueous ammonium chloride was added. After being stirred for 30 min at room temperature, aqueous 10% sodium hydroxide was added. The organic materials were extracted with dichloromethane three times. The combined organic layers were washed with water and brine, dried over potassium carbonate, and concentrated in vacuo. The resulted amorphous solid was diluted with dichloromethane (10 mL), to which di(*t*-butyl) dicarbonate (2 g, 10 mmol), water (5 mL), and aqueous 10% sodium hydroxide (5 mL) were added successively. The mixture was stirred for 30 min at room temperature, and the reaction was quenched by adding saturated aqueous ammonium chloride. The organic materials were extracted with ethyl acetate three times. The combined organic layers were washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane = 1/2) gave (*M*,*M*)-**8** (80 mg, 70%). Mp 180°C dec. (ethyl acetate/hexane). $[\alpha]_D^{27}$ −8.2 (*c* 2.0, $CHCl_3$). Anal. calcd for $C_{59}H_{65}N_3O_6$: C, 77.69; H, 7.18; N, 4.61. Found: C, 78.06; H, 7.12; N, 4.25%. MS (FAB, NBA) *m*/*z* 911 (M^+). IR (KBr) 3500–3300, 1696 cm^{-1}. ^1H NMR ($CDCl_3$ at 50°C) δ 1.48 (18H, s), 1.60 (9H, s), 1.87 (6H, s), 1.91 (6H, s), 4.57 (2H, d, $J=14$ Hz), 4.65 (2H, brs), 4.79 (2H, dd, $J=5$, 14 Hz), 4.85 (2H, d, $J=14$ Hz), 5.33 (2H, brs), 7.09 (2H, s), 7.14 (2H, s), 7.35 (2H, d, $J=7$ Hz), 7.40 (2H, d, $J=7$ Hz), 7.49 (2H, t, $J=7$ Hz), 7.59 (2H, t, $J=8$ Hz), 7.98 (2H, d, $J=8$ Hz), 8.00 (2H, brs). ^{13}C NMR ($CDCl_3$ at 50°C) δ 23.5, 23.5, 28.6, 28.7, 42.8, 48.1, 79.5, 80.5, 120.4, 124.0, 124.9, 125.8, 127.4, 127.7, 127.9, 128.0, 128.1, 130.3, 130.5, 131.1, 131.6, 131.7, 132.1, 132.9, 136.6, 136.7, 155.5, 155.8. (*P*,*P*)-**8**: $[\alpha]_D^{28}$ +8.3 (*c* 1.6, $CHCl_3$). (*P*,*M*)-**8**: Mp 180°C dec. (ethyl acetate/hexane). Anal. calcd for $C_{59}H_{65}N_3O_6 \cdot H_2O$: C, 76.18; H, 7.26; N, 4.52. Found: C, 76.41; H, 7.02; N, 4.18%. MS (FAB, NBA) *m*/*z* 911 (M^+). IR (KBr) 3500–3300, 1697 cm^{-1}. ^1H NMR

($CDCl_3$ at 45°C) δ 1.51 (18H, s), 1.55 (9H, s), 1.79 (6H, s), 1.81 (6H, s), 4.81 (2H, dd, $J=6$, 16 Hz), 4.89 (2H, dd, $J=6$, 16 Hz), 5.13 (2H, brs), 5.16 (2H, brs), 7.31 (2H, d, $J=7$ Hz), 7.33 (2H, d, $J=7$ Hz), 7.48 (2H, brs), 7.49 (2H, brs), 7.55 (4H, t, $J=8$ Hz), 8.01 (4H, d, $J=8$ Hz). ^{13}C NMR ($CDCl_3$) δ 23.4, 23.4, 28.4, 28.6, 43.0, 48.0, 79.6, 80.5, 120.4, 124.8, 125.2, 125.7, 125.8, 128.0, 128.1, 128.9, 130.3, 131.1, 131.5, 131.7, 132.1, 133.0, 136.6, 136.7, 155.6, 155.9. When the imine derived from (*M*,*M*)-**7** was reduced with $NaBD_4$, (*M*,*M*)-**8**-*d* was obtained. ^1H NMR ($CDCl_3$ at 45°C) δ 1.50 (18H, s), 1.57 (9H, s), 1.87 (6H, s), 1.92 (6H, s), 4.55 (2H, d, $J=14$ Hz), 4.60 (1H, brs), 4.79 (2H, dd, $J=5$, 14 Hz), 4.84 (2H, d, $J=14$ Hz), 5.34 (2H, brs), 7.09 (2H, s), 7.15 (2H, s), 7.33 (2H, d, $J=7$ Hz), 7.40 (2H, d, $J=7$ Hz), 7.49 (2H, t, $J=7$ Hz), 7.60 (2H, t, $J=8$ Hz), 7.99 (2H, d, $J=8$ Hz), 8.01 (2H, brs).

4.7. (*M*,*M*)-5-{8-(Aminomethyl)-1,12-dimethylbenzo[*c*]-phenanthrene-5-yl}methylaminomethyl-8-aminomethyl-1,12-dimethylbenzo[*c*]phenanthrene trihydrochloride, (*M*,*M*)-2

To a solution of (*M*,*M*)-**8** (64 mg, 0.07 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.5 mL) at 0°C, and the mixture was stirred for 1 h at the temperature. Then, 2 M hydrochloric acid (3 mL) was added and the solvents were removed in vacuo. Recrystallization from toluene/methanol gave (*M*,*M*)-**2** (45 mg, 89%). Mp 275°C dec. (toluene/methanol). $[\alpha]_D^{25}$ +11 (*c* 0.12, methanol). Anal. calcd for $C_{44}H_{44}N_3Cl_3{\cdot}3H_2O$: C, 68.17; H, 6.50; N, 5.42. Found: C, 68.03; H, 6.32; N, 4.96%. LRMS (EI, 70 eV) *m*/*z* 611 (M^+, 7%), 579 ($M^+-CH_2NH_2$, 66%), 298 ($CH_2ArCH_2NH_2$, 100%). HRMS (EI, 70 eV) calcd for $C_{44}H_{41}N_3$: 611.3300. Found: 611.3289. IR (KBr) 3500–2500 (br) cm^{-1}. ^1H NMR (CD_3OD) δ 1.87 (6H, s), 1.89 (6H, s), 4.70 (2H, d, $J=14$ Hz), 4.87 (2H, d, $J=14$ Hz), 5.02 (2H, d, $J=14$ Hz), 5.23 (2H, d, $J=14$ Hz), 7.49 (2H, d, $J=8$ Hz), 7.55 (2H, d, $J=8$ Hz), 7.60 (2H, t, $J=8$ Hz), 7.78 (2H, t, $J=8$ Hz), 8.03 (2H, d, $J=8$ Hz), 8.04 (2H, s), 8.17 (2H, d, $J=8$ Hz), 8.24 (2H, s). ^{13}C NMR (CD_3OD) δ 23.6, 23.7, 41.6, 49.3, 121.2, 121.2, 127.7, 128.2, 128.4, 128.4, 129.9, 130.0, 130.2, 130.2, 131.4, 131.5, 131.7, 132.4, 132.4, 138.3, 138.3. (*P*,*P*)-**2**: $[\alpha]_D^{25}$ –12 (*c* 0.44, methanol). (*P*,*M*)-**2**: Mp 270°C dec. (toluene/methanol). Anal. calcd for $C_{44}H_{44}N_3Cl_3{\cdot}4H_2O$: C, 66.62; H, 6.61; N, 5.30; Cl, 13.41. Found: C, 66.53; H, 6.43; N, 5.10; Cl, 12.80%. LRMS (EI, 70 eV) *m*/*z* 611 (M^+, 2%), 579 ($M^+-CH_2NH_2$, 15%), 299 ($MeArCH_2NH_2$, 100%). IR (KBr) 3500–2600 cm^{-1}. ^1H NMR (CD_3OD) δ 1.81 (6H, s), 1.85 (6H, s), 4.68 (2H, d, $J=14$ Hz), 4.85 (2H, d, $J=14$ Hz), 5.02 (2H, d, $J=14$ Hz), 5.23 (2H, d, $J=14$ Hz), 7.49 (2H, d, $J=8$ Hz), 7.52 (2H, d, $J=8$ Hz), 7.61 (2H, t, $J=8$ Hz), 7.77 (2H, t, $J=8$ Hz), 8.02 (2H, s), 8.06 (2H, d, $J=8$ Hz), 8.17 (2H, d, $J=8$ Hz), 8.22 (2H, s). ^{13}C NMR (CD_3OD) δ 23.6, 23.6, 41.6, 49.5, 121.2, 121.2, 127.7, 128.2, 128.4, 128.5, 129.9, 130.1, 130.2, 130.2, 131.4, 131.6, 131.6, 132.4, 132.4, 138.3, 138.3. **Triperchlorate derivative of (*M*,*M*)-2**. To a solution of (*M*,*M*)-**8** (110 mg, 0.12 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (3 mL) at 0°C, and the mixture was stirred for 1 h at the temperature. Then, 2 M hydrochloric acid (3 mL) was added, and the solvents were removed in vacuo. The resulted solid was diluted with a small amount of methanol, to which was added 10% lithium perchlorate in methanol (2 mL). The solid was collected, and recrystallization from water/methanol gave the title compound (80 mg, 73%). Mp 200°C dec. (H_2O/methanol). $[\alpha]_D^{28}$ +19 (*c* 0.3, methanol). Anal. calcd for $C_{44}H_{44}N_3Cl_3O_{12}$: C, 57.87; H, 4.86; N, 4.60; Cl, 11.65. Found: C, 57.90; H, 5.06; N, 4.31; Cl, 11.38%. LRMS (EI, 70 eV) *m*/*z* 611 (M^+, 7%), 579 ($M^+-CH_2NH_2$, 66%), 298 ($CH_2ArCH_2NH_2$, 100%). HRMS (EI, 70 eV) calcd for $C_{44}H_{41}N_3$: 611.3300. Found: 611.3322. IR (KBr) 3500–2500 cm^{-1}. ^1H NMR (D_2O at 50°C) δ 1.78 (12H, s), 4.06 (2H, d, $J=14$ Hz), 4.53 (2H, d, $J=14$ Hz), 4.99 (2H, d, $J=14$ Hz), 5.49 (2H, d, $J=14$ Hz), 7.10 (2H, s), 7.40 (2H, s), 7.60 (2H, d, $J=6$ Hz), 7.69 (2H, d, $J=7$ Hz), 7.82 (2H, t, $J=8$ Hz), 7.93 (2H, t, $J=8$ Hz), 8.02 (2H, d, $J=8$ Hz), 8.17 (2H, d, $J=8$ Hz). ^{13}C NMR ($CDCl_3$) δ 23.4, 24.0, 41.3, 48.9, 120.5, 120.9, 127.0, 127.5, 127.5, 128.2, 128.3, 128.4, 128.9, 130.0, 130.3, 130.4, 130.4, 130.5, 131.6, 131.7, 138.1, 138.4. Triperchlorate derivative of (*P*,*P*)-**2**:$[\alpha]_D^{26}$ –20 (*c* 0.2, methanol). Triperchlorate derivative of (*P*,*M*)-**2**: Mp 200°C dec. (H_2O/methanol). Anal. calcd for $C_{44}H_{44}N_3Cl_3O_{12}{\cdot}H_2O$: C, 56.75; H, 4.98; N, 4.51; Cl, 11.42. Found: C, 56.37; H, 5.38; N, 4.32; Cl, 11.70%. LRMS (EI, 70 eV) *m*/*z* 611 (M^+, 2%), 579 ($M^+-CH_2NH_2$, 15%), 299 ($MeArCH_2NH_2$, 100%). HRMS (EI, 70 eV) calcd for $C_{44}H_{41}N_3$: 611.3300. Found: 611.3301. IR (KBr) 3500–2600 (br) cm^{-1}. ^1H NMR (CD_3OD) δ 1.81 (6H, s), 1.85 (6H, s), 4.69 (2H, d, $J=14$ Hz), 4.86 (2H, d, $J=14$ Hz), 5.03 (2H, d, $J=14$ Hz), 5.24 (2H, d, $J=14$ Hz), 7.49 (2H, d, $J=7$ Hz), 7.51 (2H, d, $J=7$ Hz), 7.61 (2H, t, $J=8$ Hz), 7.77 (2H, t, $J=8$ Hz), 8.01 (2H, s), 8.07 (2H, d, $J=8$ Hz), 8.16 (2H, d, $J=8$ Hz), 8.23 (2H, s). ^{13}C NMR (CD_3OD) δ 23.6, 23.6, 41.6, 121.2, 127.7, 127.7, 128.2, 128.3, 128.4, 129.9, 130.1, 130.1, 130.2, 131.3, 131.6, 131.6, 132.4, 132.4, 138.3.

4.8. 2,7-Dicyanonaphthalene

A mixture of 2,7-naphthalenedicarboxylic acid[7] (130 mg, 0.62 mmol) and thionyl chloride (5 mL) was heated at reflux for 3 h. After removing the excess thionyl chloride under reduced pressure, the resulted solid was dissolved in dichloromethane (10 mL) and the solution was added to excess ammonia at −78°C. The cooling bath was removed, and the reaction mixture was warmed to room temperature. After being stirred for 1 h water was added. The resulted crude diamide was collected by filtration, washed with water, and dried in vacuo. The residue was dissolved in thionyl chloride (6 mL) and the mixture was heated at reflux for 18 h under an argon atmosphere. Then excess thionyl chloride was removed under reduced pressure, and purification by silica gel chromatography (ethyl acetate/hexane = 1/2) gave the title compound (50 mg, 45%). An analytical sample was obtained by sublimation at 1 mmHg. Mp 180°C sublimation. Anal calcd for $C_{12}H_6N_2$: C, 80.89; H, 3.39; N, 15.72. Found: C, 80.94;

H, 3.48; N, 15.42%. LRMS (EI, 70 eV) m/z 179 (M^++1, 16%), 178 (M^+, 100%), 151 (M^+–HCN, 19%). HRMS (EI, 70 eV) calcd for $C_{12}H_6N_2$: 178.0531. Found: 178.0544. IR (KBr) 2227 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.79 (2H, dd, $J=2$, 8 Hz), 8.01 (2H, d, $J=8$ Hz), 8.31 (2H, t, $J=2$ Hz). ^{13}C NMR ($CDCl_3$) δ 111.6, 118.0, 129.3, 129.3, 131.1, 134.1, 135.5.

4.9. 2-Cyano-7-naphthalenecarbaldehyde

Under an argon atmosphere to a solution of 2,7-dicyanonaphthalene (15 mg, 0.084 mmol) in dichloromethane (15 mL) was added 1.0 M diisobutylaluminum hydride in hexane (0.090 mL, 0.090 mmol) at –78°C. After stirring the mixture for 15 min at the temperature, 2 M hydrochloric acid (10 mL) was added, and the mixture was warmed to room temperature. The organic materials were extracted with chloroform three times. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. Purification by silica gel chromatography (toluene/ethyl acetate = 20/1) gave the title compound (5.2 mg, 34%). Mp 140–141°C (toluene/hexane). Anal calcd for $C_{12}H_7NO$: C, 79.55; H, 3.89; N, 7.73. Found: C, 79.58; H, 4.17; N, 7.56%. LRMS (EI, 70 eV) m/z 181 (M^+, 98%), 180 (M^+–H, 100%), 152 (M^+–HCN, 76%). HRMS (EI, 70 eV) calcd for $C_{12}H_7NO$: 181.0528. Found: 181.0513. IR (KBr) 2226, 1695 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.77 (1H, dd, $J=2$, 8 Hz), 8.01 (2H, d, $J=8$ Hz), 8.12 (1H, dd, $J=2$, 8 Hz), 8.40 (2H, s), 10.21 (1H, s). ^{13}C NMR ($CDCl_3$) δ 110.8, 118.3, 125.8, 129.1, 129.2, 129.3, 131.5, 133.9, 135.1, 135.2, 137.3, 190.9.

4.10. 2,7-Bis(aminomethyl)naphthalene

Under an argon atmosphere, to a solution of 2,7-dicyanonaphthalene (50 mg, 0.28 mmol) in dichloromethane (7 mL) was added 1.0 M diisobutylaluminum hydride in hexane (1.0 mL, 1.0 mmol) at 0°C, and the mixture was stirred for 30 min at the temperature. Then the mixture was added to a suspension of sodium borohydride (200 mg, 5.4 mmol) in tetrahydrofuran (7 mL) and methanol (14 mL) at 0°C. Ice bath was removed, and stirring was continued at room temperature for 30 min, when the reaction was quenched by adding 2 M hydrochloric acid. After being stirring for 30 min, aqueous 10% sodium hydroxide was added, and the organic materials were extracted with dichloromethane three times. The combined organic layers were washed with water and brine, dried over potassium carbonate, and concentrated in vacuo. The resulted solid was recrystallized from toluene/hexane giving the title compound (12 mg, 23%). Mp 158–160°C (toluene/hexane). LRMS (EI, 70 eV) m/z 186 (M^+, 100%), 169 (M^+–NH_3, 90%). HRMS (EI, 70 eV) calcd for $C_{12}H_{14}N_2$: 186.1157. Found: 186.1139. IR (KBr) 3500–3200 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.03 (4H, s), 7.41 (2H, dd, $J=2$, 8 Hz), 7.72 (2H, s), 7.80 (2H, d, $J=8$ Hz). ^{13}C NMR ($CDCl_3$) δ 46.7, 124.8, 125.4, 127.9, 128.1, 128.9, 140.9.

4.11. 2-(Benzyloxycarbonyl)aminomethyl-7-(*t*-butoxycarbonylaminomethyl)naphthalene

To a mixture of 2,7-bis(aminomethyl)naphthalene (83 mg, 0.44 mmol), dichloromethane (20 mL) and 1 M sodium hydroxide (20 mL) was added di(*t*-butyl) dicarbonate (89 mg, 0.41 mmol) in dichloromethane (1 mL) at room temperature. After being stirred for 30 min, benzyloxycarbonyl chloride (0.076 mL, 0.53 mmol) was added, and the mixture was stirred for 30 min. The reaction was quenched by adding saturated aqueous ammonium chloride, and the organic materials were extracted three times with ethyl acetate. The combined organic layers were washed with water and brine, dried over magnesium sulfate and concentrated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane = 1/5) gave the title compound (54 mg, 29%). Mp 154–156°C (ethanol). LRMS (EI, 70 eV) m/z 420 (M^+, 6%), 363 (M^+–*t*-Bu, 18%), 319 (M^+–Boc, 27%), 273 (M^+–C_4H_8–$PhCH_2$, 33%), 156 (CH_3-Np-CH_3, 87%), 91($PhCH_2^+$, 100%). HRMS (EI, 70 eV) calcd for $C_{25}H_{28}N_2O_4$: 420.2049. Found: 420.2403. IR (KBr) 3500–3300, 1687 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.48 (9H, s), 4.46 (2H, d, $J=5.2$ Hz), 4.53 (2H, d, $J=6.0$ Hz), 4.93 (1H, brs), 5.16 (2H, s), 5.17 (1H, brs), 7.20–7.42 (7H, m), 7.65 (1H, brs), 7.66 (1H, brs), 7.78 (2H, d, $J=8.4$ Hz). ^{13}C NMR ($CDCl_3$) δ 28.4, 44.7, 45.2, 66.8, 79.4, 125.3, 125.5, 125.6, 127.9, 128.0, 128.2, 131.8, 133.0, 135.9, 136.1, 136.6, 155.5, 156.1

4.12. 7-{7-(*t*-Butoxycarbonyl)aminomethyl-2-naphthylmethylaminomethyl}naphthalene-2-carbonitrile

Under a hydrogen atmosphere, a mixture of the above compound (25 mg, 0.060 mmol), 10% palladium on carbon (10 mg), ethyl acetate (2 mL), and methanol (2 mL) was vigorously stirred for 1 h at room temperature. The insoluble materials were removed by filtration and the filtrate was concentrated in vacuo. The residue was dissolved in toluene (2 mL), to which was added 2-cyano-7-naphthalenecarbaldehyde (9 mg, 0.05 mmol). The mixture was heated under reflux for 4 h. After being cooled to room temperature the mixture was added to a suspension of sodium borohydride (21 mg, 0.57 mmol) in methanol (1.5 mL) and tetrahydrofuran (1.5 mL) at 0°C. The mixture was stirred at the temperature for 10 min, and water was added. The mixture was extracted three times with ethyl acetate. The combined organic layers were washed with water and brine, dried over sodium sulfate and concentrated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane = 1/1) gave the title compound (11 mg, 47%). LRMS (EI, 70 eV) m/z 451 (M^+, 4%), 395 (M^+–C_4H_8, 22%), 350 (M^+–Boc, 74%), 215 (100%). HRMS (EI, 70 eV) calcd for $C_{29}H_{29}N_3O_4$: 451.2260. Found: 451.2251. IR (KBr) 3500–3300, 2226, 1709 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.48 (9H, s), 4.01 (2H, s), 4.03 (2H, s), 4.48 (2H, d, $J=5.2$ Hz), 4.92 (1H, brs), 7.39 (1H, d, $J=8.4$ Hz), 7.48 (1H, dd, $J=1.4$, 8.4 Hz), 7.58 (1H, dd, $J=1.6$, 8.4 Hz), 7.67 (1H, m), 7.69 (1H, s), 7.75 (1H, s), 7.80 (1H, d, $J=8.4$ Hz), 7.81 (1H, d, $J=8.4$ Hz), 7.86 (1H, s), 7.86 (1H, d), 7.90 (1H, d, $J=8.4$ Hz), 8.20 (1H, s). ^{13}C NMR ($CDCl_3$) δ 28.4, 44.8, 52.7, 53.2, 79.5,

109.3, 119.0, 125.3, 125.8, 126.1, 126.2, 126.5, 127.7, 127.9, 128.6, 129.5, 131.7, 132.0, 133.6, 133.6, 136.4, 137.5, 139.7, 155.6.

4.13. 1,1-Bis(7-aminomethyl-2-naphthylmethyl)amine trihydrochloride, 3

Under an argon atmosphere, to a solution of the above compound (3 mg, 0.006 mmol) in dichloromethane (0.5 mL) was added diisobutylaluminum hydride in hexane (1.0 M, 0.064 mL, 0.064 mmol) at 0°C. The mixture was stirred for 10 min at the temperature and then added to a suspension of sodium borohydride (2.5 mg, 0.066 mmol) in tetrahydrofuran (0.5 mL) and methanol (0.5 mL) at 0°C. Stirring was continued at 0°C for 1 h, when the reaction was quenched by adding water. The organic materials were extracted three times with dichloromethane. The combined organic layers were washed with water and brine, dried over potassium carbonate and concentrated in vacuo. The residue was dissolved in dichloromethane (0.7 mL), to which 1 M sodium hydroxide (0.5 mL) was added. Then, di(*t*-butyl) dicarbonate (9 mg, 0.041 mmol) was added, and the mixture was stirred at room temperature overnight. The organic layer was separated, and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with water and brine, dried over sodium sulfate and concentrated in vacuo. Silica gel chromatography (ethyl acetate/hexane = 3/2) gave tri(*t*-butoxycarbonyl) derivative of **3** (3 mg, 71%). LRMS (FAB, NBA) *m*/*z* 656 (M^++H), 598 (M^++H–*t*-Bu), 554 (M^+–Boc), 500 (M^+–$2C_4H_8$–CO_2), 498 (M^+–Boc–*t*-Bu). IR (neat) 3500–3000, 1693 cm^{-1}. ^1H NMR (DMSO-d_6 at 90°C) δ 1.11 (18H, s), 1.13 (9H, s), 3.99 (4H, d, J = 6.4 Hz), 4.27 (4H, s), 6.74 (2H, brs), 7.05 (2H, dd, J = 1.6, 8.4 Hz), 7.09 (2H, dd, J = 1.6, 8.4 Hz), 7.34 (4H, s), 7.51 (2H, d, J = 8.4 Hz), 7.52 (2H, d, J = 8.4 Hz). ^{13}C NMR (DMSO-d_6 at 90°C) δ 27.9, 28.0, 43.8, 49.7, 77.6, 79.0, 124.5, 124.9, 125.1, 125.2, 127.0, 127.3, 130.9, 132.4, 135.5, 137.6, 154.8, 155.2.

Under an argon atmosphere, to a solution of the above compound (3 mg, 0.004 mmol) in dichloromethane (0.5 mL) was added trifluoroacetic acid (0.3 mL) in dichloromethane (0.5 mL) at 0°C, and the mixture was stirred for 1 h at the temperature. The solvents were removed under reduced pressure, to which was added 1 M hydrochloric acid (1 mL) and methanol (5 mL). After being stirred at room temperature for 10 min, the solvents were removed under reduced pressure to give **3** (2 mg, quant.). Mp 265°C dec. (methanol/ethanol). Anal. calcd for $C_{24}H_{28}N_3Cl_3 \cdot H_2O$: C, 59.70; H, 6.26; N, 8.70; Cl, 22.03. Found: C, 60.31; H, 6.07; N, 8.65; Cl, 21.96%. IR (KBr) 2924, 2853, 1613 cm^{-1}. LRMS (EI, 70 eV) *m*/*z* 355 (free base, M^+, 19%), 338 (free base, M^+–NH_2–H, 15%), 185 (H_2NCH_2-Np-CH_2NH, 57%), 183 (HN=CH-Np-CH_2NH, 56%), 170 (H_2NCH_2-Np-CH_3, 100%). HRMS (EI, 70 eV) calcd for $C_{24}H_{25}N_3$: 355.2048. Found: 355.2033. ^1H NMR (CD_3OD) δ 4.31 (4H, s), 4.52 (4H, s), 7.63 (2H, dd, J = 1.6, 8.5 Hz), 7.69 (2H, dd, J = 1.6, 8.7 Hz), 8.02 (2H, d, J = 8.5 Hz), 8.03 (2H, d, J = 8.7 Hz), 8.07 (2H, s), 8.16 (2H, s). ^{13}C NMR (CD_3OD) δ 44.4, 52.3, 128.1, 128.7, 129.7, 129.9, 129.9, 130.6, 131.2, 132.7, 134.3, 134.7.

4.14. Free energy differences between the folded and unfolded conformers of 2[10]

UV absorption coefficients ε of **2** at 290 nm were measured at various ratios of CH_3OH and H_2O. At each solvent ratio, the folded and unfolded conformers are considered to be in equilibrium. At higher compositions of CH_3OH in solution, **2** should have an unfolded conformer, and at lower compositions of CH_3OH a folded conformer. At each solvent composition, the mole fraction x of **2** in the unfolded state can be expressed as follows:

$$x = (\varepsilon_{fold} - \varepsilon)/(\varepsilon_{fold} - \varepsilon_{unfold})$$

where ε_{fold} corresponds to a UV absorption coefficient at lower composition of CH_3OH, ε_{unfold} an UV absorption coefficient at higher composition of CH_3OH, and ε an UV absorption coefficient at a given composition of CH_3OH. The values ε_{fold} and ε_{unfold} can be determined from the plateau of titration curves at a higher and lower CH_3OH compositions in the plots of ε verses solvent compositions. Equilibrium constants K_{eq} and corresponding free energy changes ΔG for the conformational transition at any point along the titration curve were obtained by the standard relationships $K_{eq} = x/(1-x)$ and $\Delta G = -RT \ln K_{eq}$. The free energy change between these conformational states was assumed to depend linearly on solvent composition.

$$\Delta G = \Delta G(H_2O) - m[CH_3OH]$$

$\Delta G(H_2O)$ represents the free energy difference between the folded and unfolded conformations in water, and the value of m describes how rapidly the free energy of the transition changes with solvent composition, and $[CH_3OH]$ means the percent concentration of CH_3OH in water. The intercept of a plot of ΔG verses composition thus provides $\Delta G(H_2O)$.

4.15. X-Ray crystallography

Details of crystal data, data collection, and refinement for (*M*)-**1** and (±)-**1** are summarized in Table 1. The cell and intensity data were collected using Rigaku/MSC Mercury CCD diffractometer with graphite monochromated Mo-Kα radiation. The data for (*M*)-**1** were measured at a temperature of −50°C, and those for (±)-**1** at −100°C. All the calculations were carried out using the teXsan software package (Crystal Structure Analysis Package, Molecular Structure Corporation).

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Table 1. Summary of crystal data, data collection, and refinement details

Compound	(*M*)-**1**	(±)-**1**
Formula	$C_{22}H_{24}N_2Cl_2{\cdot}CH_3OH$	$C_{22}H_{24}N_2Cl_2{\cdot}CH_3OH$
Mr	418.16	418.16
Crystal size (mm)	$0.07\times0.1\times0.35$	$0.07\times0.1\times0.3$
Space group	$P2_12_12_1$ (#19)	$P2_1/c$ (#14)
Crystal system	Orthorhombic	Monoclinic
Temp. (K)	223	173
a (Å)	5.147 (2)	15.572 (5)
b (Å)	13.329 (4)	5.320 (2)
c (Å)	29.895 (10)	25.693 (8)
β (°)		100.010 (7)
V (Å^3)	2050 (1)	2096 (1)
Z	4	4
D_{calcd} (g/cm^3)	1.358	1.329
μ (cm^{-1})	3.33	3.26
Radiation	Mo-Kα	Mo-Kα
λ (Å)	0.71070	0.71070
Measured data	53295	9190
Unique	8676	4355
R_{int}	0.049	0.033
Observed data	2631	1990
	[$Io>3\sigma(Io)$]	[$Io>3\sigma(Io)$]
No. of variables	254	251
R	0.069	0.068
Rw	0.075	0.075
$(\Delta\rho)_{max}$ (e Å^{-3})	0.40	0.52
Flack parameter	0.01(2)	

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11. Crystallographic data (excluding structure factors) for (*M*)-**1** and (±)-**1** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 184943 and CCDC 184944, respectively. 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].