Synthesis of a novel tweezers-type host aiming at chiral discrimination by circular dichroism spectroscopy †

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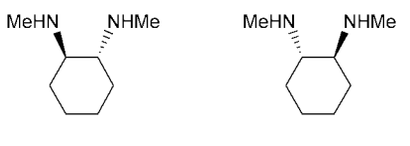
Received (in Cambridge, UK) 30th November 1999, Accepted 3rd February 2000

In order to develop a methodology for chiral discrimination by utilizing complexation-induced circular dichroism (ICD) in host–guest systems, the novel tweezers-type host **1** was synthesized. From UV-VIS and fluorescence emission studies, it was confirmed that the host **1** formed a 1 : 1 complex with optically active *N*,*N*′-dimethyl-*trans*-1,2-diaminocyclohexane **16**, and the CD spectrum was induced as the concentration of the complex increased. The sign of the Cotton effect induced by (*S*,*S*)-**16** was opposite to that induced by (*R*,*R*)-**16**, indicating that enantioselective formation of the atropisomer of **1** upon complexation leads to determination of the chirality of the guest by CD. On the other hand, the ICD of **1** upon complexation with the chiral monoamine **17** implied that the axial chirality of **1** was not induced until the host complexed two molecules of **17**.

Introduction

The read-out of chemical information by synthetic host molecules is one of the final goals in molecular recognition chemistry.[1] In particular, discrimination of chirality is very important for the analytical application to pharmacology and chemical industries,[2–8] because almost all the biologically important molecules possess one or more stereogenic centers in their skeletons, for example amino acids and carbohydrates, and because so many chiral ligands have been used in asymmetric syntheses of drugs and natural products.[9] In analyses of chirality of molecules with their absorption in the near-UV and/or visible regions, circular dichroism (CD) spectroscopy is often a powerful tool to obtain structural information such as absolute configurations of optically active compounds as demonstrated by Nakanishi and Harada.[10] Even when guest molecules do not possess a chromophore, utilization of complexation-induced CD (ICD) in chromogenic hosts makes detection of chirality of guests possible.[4–8]

In this regard, we designed the novel tweezers-type diarylbutadiyne host **1**.[11] As shown in Fig. 1, the host **1** exists in the racemic state of two atropisomers, (*R*)-**1** and (*S*)-**1**. These isomers interconvert in the absence of guest molecules due to the free rotation along the diyne axis. The axial chirality is expected to be induced by complexation with chiral guests through diastereomeric host–guest interactions. In particular difunctionalized molecules, which bind complementarily to the cleft formed by the recognition sites ($-CONH_2$) in **1** through hydrogen bonds, are good candidates for the guest. Here we report the synthesis of host **1** and chiral discrimination by the CD spectroscopic technique. We selected optically active *N*,*N*′-dimethyl-*trans*-1,2-diaminocyclohexane **16**



(*R*,*R*)-**16** (*S*,*S*)-**16**

as a target guest, because it is a simple, C_2 symmetric molecule suitable for preliminary investigation of the chiral discrimination property of the host **1**. In addition, 1,2-diaminocyclohexane derivatives are widely used as chiral auxiliaries in asymmetric synthesis[12] and as building blocks of the chiral host[13] for enantioselective molecular recognition.

Results and discussion

The synthesis of host **1** is described in Scheme 1. The synthetic strategy is as follows: first, the butadiyne unit and pyreno side arms are independently prepared, and then, these are united to afford the precursor of the host, **14**, which is converted into **1** by hydrolysis followed by amidation. The pyreno side arms are necessary to effectively induce the axial chirality of the host through the steric interaction between two pyrene rings. In addition, they should serve as fluorescent indicators to detect the host–guest complexation behavior and to monitor the complexation-induced conformational change of the host by the excimer formation.[14] Thus, the combination of UV-VIS, fluorescence emission and CD spectroscopies should make analysis of the chiral discrimination mechanism in the **1**–guest system more precise. The octyl groups in the pyrene moieties were introduced to increase solubility in the solvent employed here.

Construction of the diyne unit began with 2-amino-5-methylbenzoic acid, which was esterified with butan-1-ol (to give compound **3**), followed by bromination to afford the compound **4**. Diazotization followed by iodination by the Sandmeyer reaction with KI yielded the benzoate **5**.[15] A masked acetylene was introduced by the Pd-catalyzed cross-coupling reaction[16] with 3-methylbut-1-yn-3-ol to afford compound **6** which was converted into the ethynylbenzoate **7** by demasking with NaH.[17] The Glaser-type oxidative coupling of the compound **7** afforded the diyne unit **8**.[18] The total yield from 2-amino-5-methylbenzoic acid to the diyne **8** was 32%.

The precursor of the side arm units **13** was prepared in 5 steps from 1,6-dibromopyrene. Introduction of an octynyl group by the Pd-catalyzed cross-coupling reaction followed by hydrogenation afforded 1-bromo-6-(1-octyl)pyrene **10**, which was converted to the ethynylpyrene **12** by a similar conversion

† ^{1}H NMR spectra for compounds **3**, **4**, **5**, **7** and **13** are available as supplementary data from BLDSC (SUPPL. NO. 57693, pp. 6) or the RSC Library. See Instructions for Authors available *via* the RSC web page (http://www.rsc.org/authors).

DOI: 10.1039/a909468g

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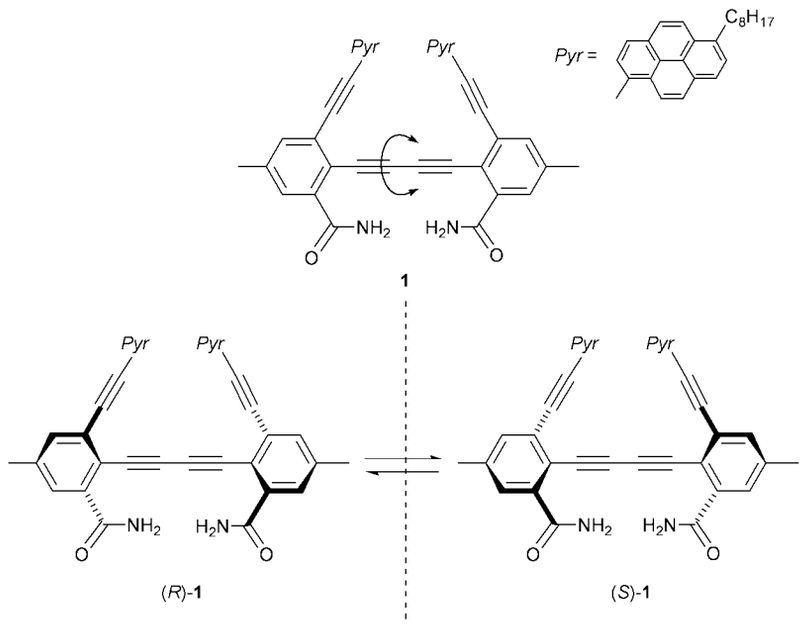
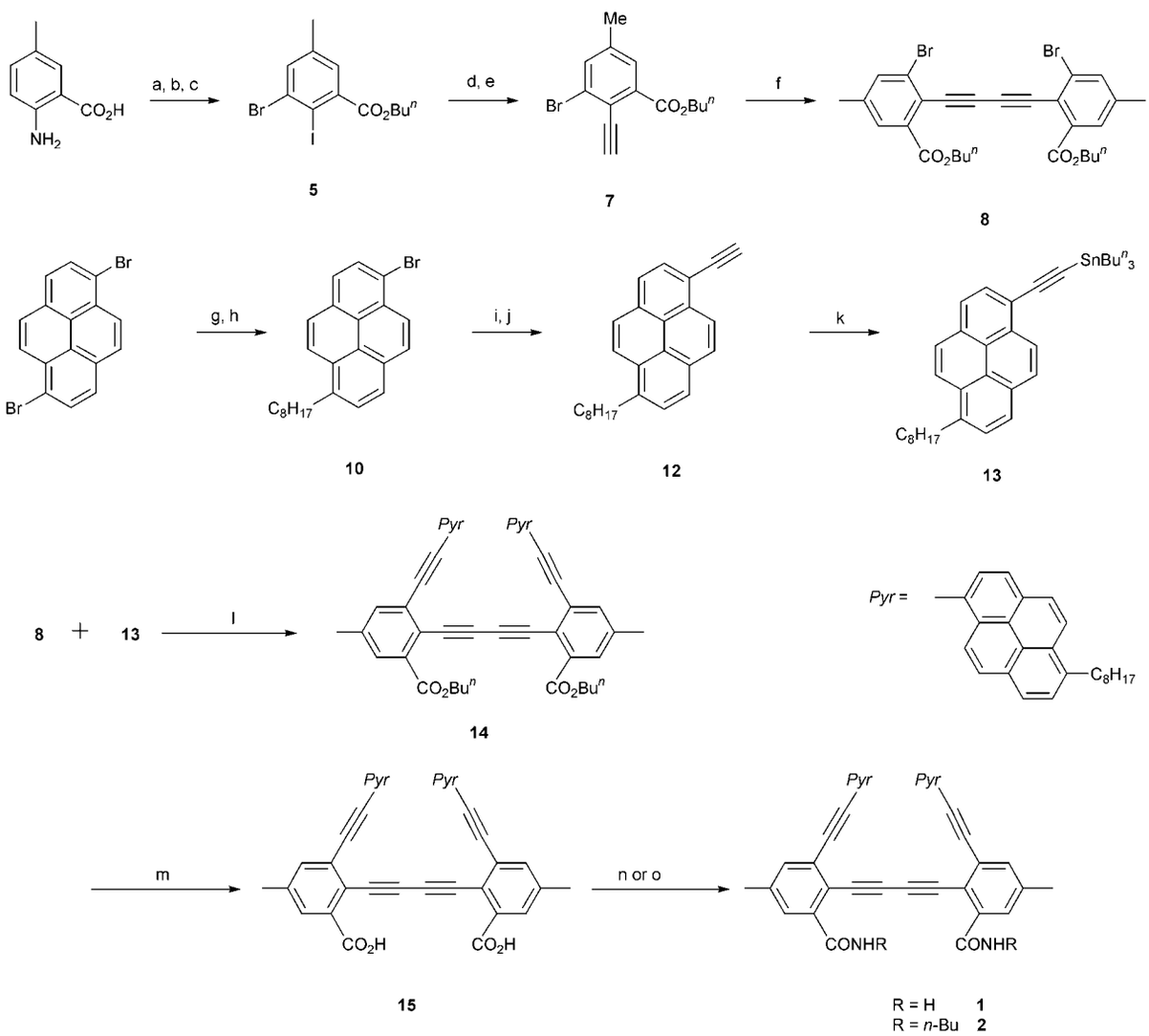


Fig. 1 The structure of host **1** and its atropisomers. The absolute configuration, (*R*) or (*S*), is described based on chirality of the diyne skeleton.



Scheme 1 *Reagents and conditions*: (a) butan-1-ol, cat. H_2SO_4, reflux, 13 h, **3** (87%); (b) Br_2, CCl_4, rt, 3 h, **4** (97%); (c) $NaNO_2$, HCl, H_2O below 5 °C, 1 h, then KI, rt, 30 min, **5** (71%); (d) 3-methylbut-1-yn-3-ol, $PdCl_2(PPh_3)_2$, CuI, NEt_3, reflux, 15 h, **6** (79%); (e) NaH, toluene, reflux, 40 min, **7** (80%); (f) $Cu(OAc)_2$, CH_3CN, 60 °C, 2 h, **8** (84%); (g) oct-1-yne, $PdCl_2(PPh_3)_2$, CuI, morpholine, 100 °C, 10 h, **9** (58%); (h) H_2, Pd–C, AcOEt, rt, 21 h, **10** (94%); (i) 3-methylbut-1-yn-3-ol, $PdCl_2(PPh_3)_2$, CuI, morpholine, 100 °C, 14 h, **11** (75%); (j) NaH, toluene, reflux, 40 min **12** (95%); (k) *n*-BuLi in hexane, dry THF, 0 °C, and then, *n*-Bu_3SnCl, rt, 12 h, **13**, not purified; (l) $PdCl_2(PPh_3)_2$, toluene, **14** (55%); (m) NaOH, THF–EtOH–H_2O, rt, 10 h, **15** (98%); (n) NH_{3aq}, EDC·HCl, THF–H_2O, rt, 15 h, **1** (63%); (o) 1-butylamine, 2-chloro-1-methylpyridinium iodide, NEt_3, CH_2Cl_2, reflux, 24 h, **2** (27%).

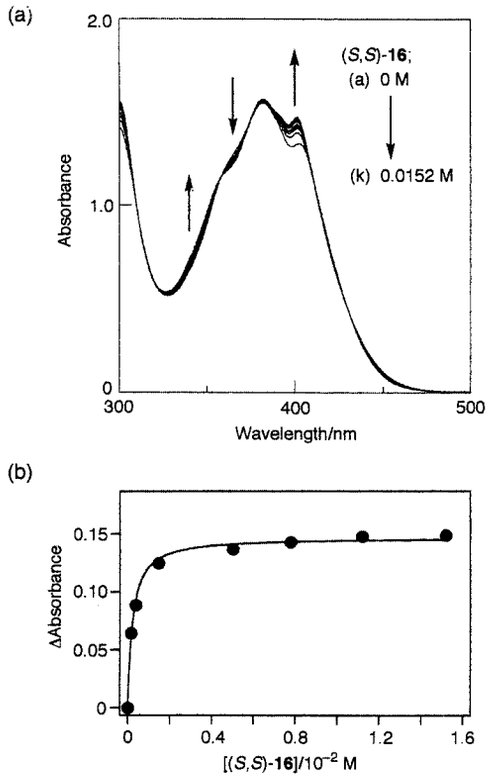


Fig. 2 (a) UV-VIS spectra of host **1** in the presence of varying concentrations of (*S*,*S*)-**16** in $CHCl_3$ at 298 K. [**1**] = 3.01×10^{-5} M. [(*S*,*S*)-**16**] = 0, 1.51×10^{-4}, 3.75×10^{-4}, 6.69×10^{-4}, 1.03×10^{-3}, 1.48×10^{-3}, 2.88×10^{-3}, 5.01×10^{-3}, 7.79×10^{-3}, 1.12×10^{-2}, 1.52×10^{-2} M. (b) The plot of UV-VIS titration for complexation of **1** and (*S*,*S*)-**16** monitored at 400 nm. The solid line is a theoretical curve generated by the least-squares calculation.

used for compound **5** into **7**. Reaction of the acetylide of **12** with *n*-Bu_3SnCl afforded compound **13**.‡

The diyne **8** and the pyreno side arms **13**, were connected by the Stille-type coupling reaction employing $PdCl_2(PPh_3)_2$ as a catalyst[19] to yield the precursor of the host, **14**, in 55% yield. Subsequent hydrolysis afforded the dicarboxylic acid **15** in 98% yield, and the amidation employing NH_3 and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) finally afforded host **1** in 63% yield from **15**. The host **2**, which possesses butyl groups on the amide nitrogens, was also prepared in 27% yield by condensation of **15** with 1-butylamine, where 2-chloro-1-methylpyridinium iodide was employed as a carboxy group activating reagent. The structures of **1** and **2** were confirmed by ^{1}H NMR, IR and FAB mass spectra and elemental analysis.

The preliminary Corey–Pauling–Koltun (CPK) modeling study for complexation of the host **1** with the diaminocyclohexane **16** indicated that the cleft formed by two amide groups of **1** was complementary towards the two amino groups of **16** through hydrogen bonds between the amide protons of **1** and the amino nitrogens of **16**. Unfortunately, monitoring the complexation behavior of the host **1** with the guest by ^{1}H NMR was not successful: the amide protons were not observed probably due to rapid proton exchanges, and complexation-induced chemical shift changes for the other protons of **1** on complexation with **16** were less than 0.1 ppm. Therefore, the complexation was monitored using UV-VIS and fluorescence emission spectroscopies. In Fig. 2 are shown UV-VIS spectral changes of the host **1** upon addition of the guest (*S*,*S*)-**16** in $CHCl_3$ at

‡ Compound **13** could not be purified due to low stability. Production of **13** was confirmed by ^{1}H NMR of the crude sample, where the signal of the acetylenic proton of **12** disappeared and generation of new resonance peaks assigned to the butyl groups of the *n*-Bu_3Sn group was observed.

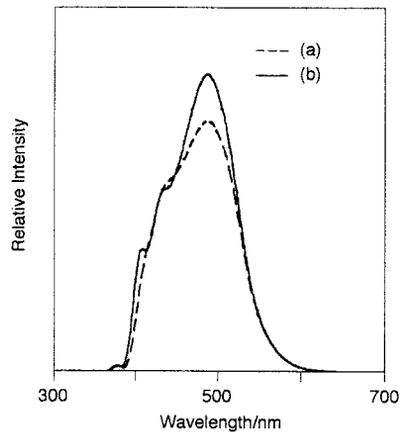


Fig. 3 Fluorescence emission spectra of **1** (broken line, a) and **1**·(*S*,*S*)-**16** (solid line, b) in $CHCl_3$ at 298 K. [**1**] = 6.0×10^{-6} M. [(*S*,*S*)-**16**] = 3.0×10^{-2} M. The excitation wavelength is 381 nm.

298 K. The absorption from 330 to 470 nm, which is due to the π–π* transition of the π conjugation system from the pyrene to the benzamide moiety, successively changed as the concentration of the guest increased, showing isosbestic points at 357, 375, and 432 nm. The spectral changes exhibited a saturation behavior as shown in Fig. 2b, and the Job's plot for the **1**·(*S*,*S*)-**16** system indicated that the stoichiometry of the complexation is 1 : 1. The binding constant of **1**·(*S*,*S*)-**16** complex was obtained as $K_{abs} = 4750$ M^{-1} (sd 470) by computer-assisted least-squares analysis of the absorbance changes as a function of guest concentrations. On the other hand, no spectral change was observed when (*S*,*S*)-**16** was added to a solution of the host **2**, indicating that the bulkiness of the butyl groups in **2** significantly hinders the complexation with the guest.

The complexation behavior was also monitored by fluorescence emission spectroscopy. The emission spectra of the host **1** and **1**·(*S*,*S*)-**16** complex are shown in Fig. 3. The fluorescence excitation spectrum at 492 nm corresponded well with the absorption spectrum, indicating that the fluorescence emission originates from the chromophoric system containing the pyrene moiety. The original spectrum of the host **1** (a) successively changed to the spectrum (b) upon addition of the guest. The analysis of the increases of the emission intensity upon addition of the guest afforded the binding constant $K_{em} = 5860$ M^{-1} (sd 840), which is similar to the value of K_{abs} although the standard deviation is somewhat large. This result indicates that the changes of the emission spectra also originate from the host–guest complexation. The fluorescence spectroscopic study affords more information about the conformational change of the host **1**. The decay of the fluorescence emission of **1** at 492 nm exhibited a biphasic profile. The lifetimes of the emission are 3.9 ns (±0.1 ns, 34.6%) and 12.0 ns (±0.1 ns, 65.4%), each of which should originate from either the pyrene monomer emission or the excimer emission. As the excimer emission is usually observed at the longer wavelength than the monomer emission, the fluorescence emission of **1** at 492 nm is assigned to the excimer. Thus, the increase of the emission intensity at 492 nm as seen in Fig. 3 indicates the complexation-induced conformational change of the host **1**, where the two pyrene moieties come in contact so as to form the excimer.

The chiral discrimination property of the host **1** for the chiral guest **16** was investigated by CD spectra. In Fig. 4 are shown CD spectra of **1**·(*S*,*S*)-**16** and **1**·(*R*,*R*)-**16** complexes in $CHCl_3$ at 298 K. The alternative signs of the Cotton effect were observed for each complex in the host's absorption band, although the CD spectrum of the host **1** was silent. The spectra of the two complexes are symmetrical along the horizontal axis. In a CD titration experiment, the intensity successively increased as the concentration of the guest increased: the CD emergence paralleled the increase of the concentration of the

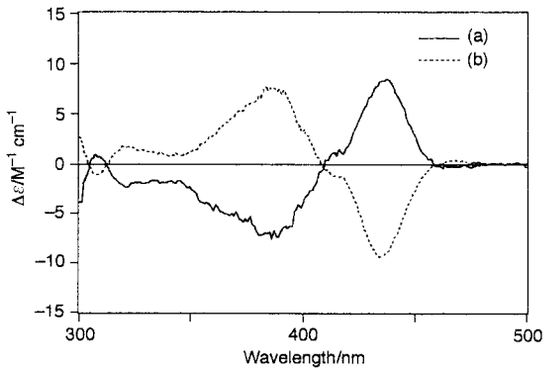


Fig. 4 Circular dichroism spectra of host **1** (4.0×10^{-5} M) in the presence of (*S*,*S*)-**16** (solid line, a) and (*R*,*R*)-**16** (broken line, b) in $CHCl_3$ at 298 K. [**16**] = 4.0×10^{-2} M.

complex. Taking into consideration that the stoichiometry of the complexation is 1 : 1 as confirmed in the UV-VIS study, these results strongly indicate that the ICD was induced by the enantioselective formation of the atropisomer of the host **1** complementary to the chirality of the guest.

Determination of the absolute configuration of **1** upon complexation with **16** was examined by the CD exciton chirality method.[10] In the case of the **1**·(*S*,*S*)-**16** complex, the positive first Cotton effect and the negative second one were observed in the low energy absorption of **1** (see Fig. 2), indicating the emergence of positive chirality. Supposing that the electric transition moment of the low energy absorption of **1** is in a similar direction to that of the pyrene's transverse axis transition, the manner of the exciton coupling can be illustrated as shown in Fig. 5. Thus, the (*S*)-form of **1** affords positive chirality and the (*R*)-form affords negative chirality. Therefore, the absolute configuration of **1** in the **1**·(*S*,*S*)-**16** complex can be assigned to the (*S*)-form. In a similar way, it can be determined that (*R*)-**1** is induced by complexation with (*R*,*R*)-**16**.

As a referential study, chiral discrimination of the monoamine **17** by the host **1** was also examined. The ICD profile upon complexation with guest **17** was quite different from that

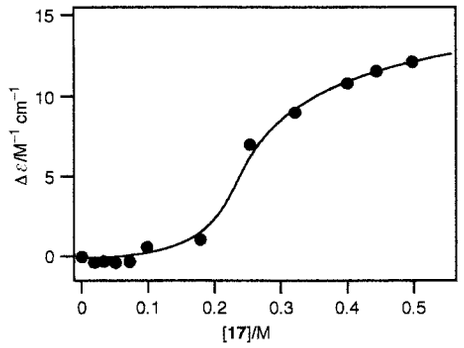
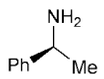


Fig. 6 CD spectral changes at 440 nm in the presence of varying concentrations of **17** in $CHCl_3$ at 298 K. [**1**] = 3.0×10^{-5} M.



17

observed in the **1**·**16** system. As shown in Fig. 6, the ICD was silent over the wide range of the guest concentration (up to *ca.* 0.1 M), whereas it was induced in the higher concentration of the guest (>0.2 M). Taking into consideration that the increases of the fluorescence emission intensity of the host **1** were observed in the presence of the lower concentrations of **17** (<0.1 M, data not shown),§ one can see that the host **1** forms a complex with one molecule of **17** and then with another molecule of **17** to give a 1 : 2 complex. The CD titration profile implies that cooperative chiral induction of the host by stepwise binding of the guests occurs. A possible mechanism is proposed in Fig. 7a. In this mechanism, the guest binds to one recognition site, where the aryl group with the other recognition site could freely rotate along the diyne axis, leading to interconver-

§ The fluorescence emission spectral changes of **1** on complexation with **17** exhibited a complicated behavior, so that binding constants for both of 1 : 1 and 1 : 2 complexation could not be obtained.

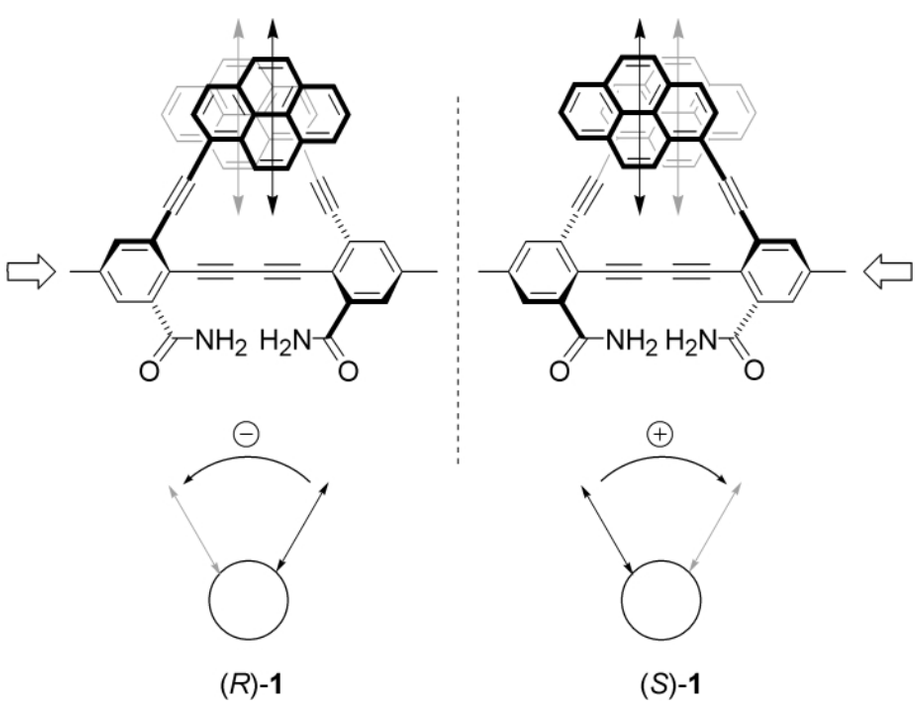


Fig. 5 The directions of the low energy transitions of the pyrene moieties in **1**. The octyl groups in the pyrene rings are omitted for clarity. The exciton coupling manner in each atropisomer is also shown at the bottom as a projection from the wide arrow in the upper figure. The signs of plus and minus mean positive and negative chirality, respectively.

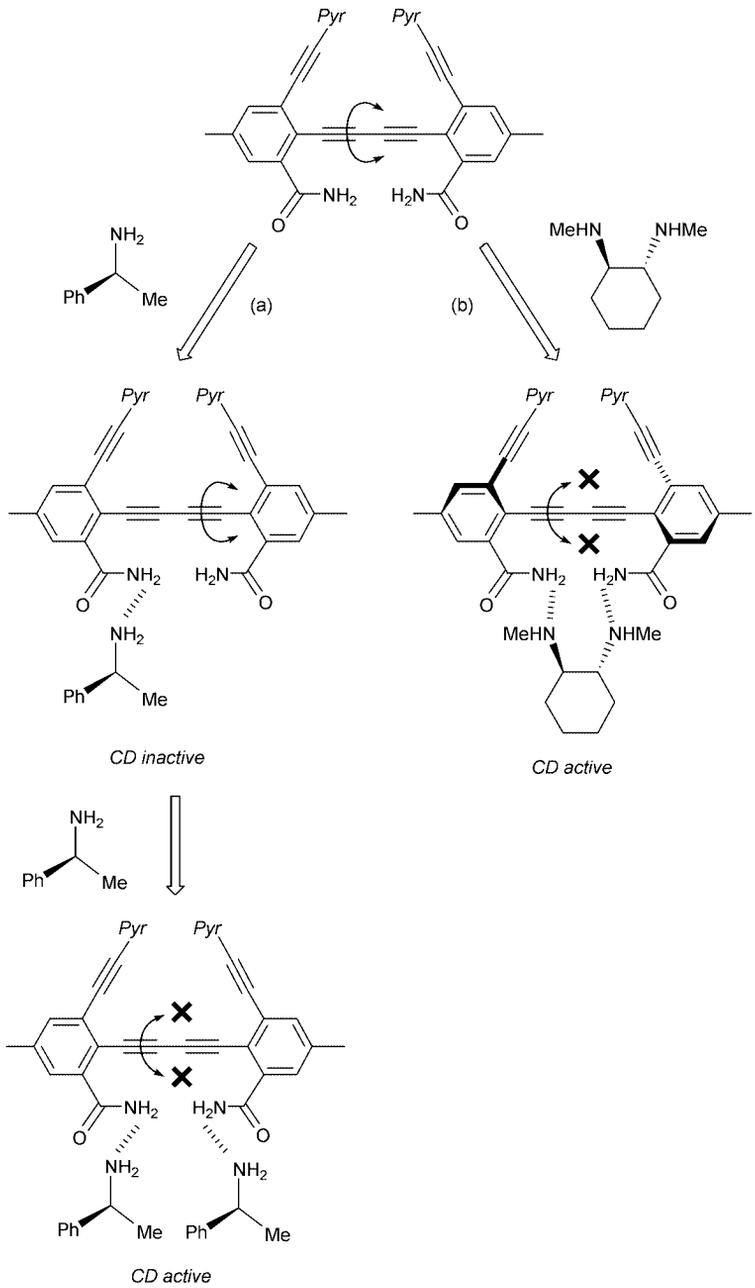


Fig. 7 Proposed mechanisms for complexation of **1** (a) with monoamine **17** and (b) with 1,2-diamine **16**.

sion between two atropisomers of **1**. When the second guest binds to the 1 : 1 complex to form the 1 : 2 complex, the two guests behave as extrinsic chiral auxiliaries to induce axial chirality of **1**. On the other hand, the two amino groups in **16** would tightly fix the recognition sites of the host, *i.e.* prevent the rotation of the diyne, leading to effective chiral induction of the diyne skeleton of **1** (Fig. 7b).

Conclusion

In conclusion, we achieved the synthesis of the novel tweezers-type host molecule **1**. It was confirmed by UV-VIS, fluorescence emission, and CD spectroscopies that the host **1** is able to effectively bind the optically active 1,2-diamine such as the guest **16** in its cleft and discriminate the absolute configuration of the guest through the complexation-induced enantioselective formation of the atropisomer. The result obtained here implies that wider utilization of the host–guest chemistry towards chemosensory systems would develop a novel analytical methodology.

Experimental

^{1}H and ^{13}C NMR spectra were obtained at 270 and 67.8 MHz, respectively, on a JEOL JNM–GX spectrometer. In ^{1}H NMR measurements, TMS (0 ppm) was used as an internal standard, and in ^{13}C NMR the signal of $^{13}CDCl_3$ (77.0 ppm) was employed as an internal standard. IR spectra were taken for KBr disks of solid samples and a CCl_4 solution of liquid samples, and recorded on a Horiba FT-200 spectrometer. Mass spectra were obtained by EI and FAB techniques on Shimadzu RF-5000 and Finnigan mat TSQ-70 spectrometers, respectively. For FAB-mass spectra, 3-nitrobenzyl alcohol was used as a matrix. Elemental analyses were carried out using a Yanaco CHN-CORDER MT3 recorder. UV-VIS absorption and fluorescence emission spectra were recorded on a Jasco V-550 spectrometer and Shimadzu RF-5000 spectrometer, respectively. Fluorescent lifetimes of the emission of **1** were obtained by time-correlated, single-photon counting methodology using a Horiba NAES-550 nanosecond fluorophotometer. The sample concentration was 6×10^{-6} M and the excitation wavelength

was 381 nm. CD spectra were obtained on a Jasco J-720W spectropolarimeter.

2-Amino-5-methylbenzoic acid and (*S*)-1-phenylethylamine **17** were purchased from Nacalai Tesque, Inc. 1,6-Dibromopyrene[20] and optically active **16**[21] were prepared according to the reported procedures. Chloroform used in spectroscopic measurements was of spectroscopic grade and purchased from Aldrich, and contained amylene as a stabilizer. ^{1}H NMR spectra for compounds **3**, **4**, **5**, **7** and **13** are available as supplementary data.†

Butyl 2-amino-5-methylbenzoate, 3

To a stirred mixture of 2-amino-5-methyl benzoic acid (7.47 g, 49.4 mmol) and butan-1-ol (120 mL) was added dropwise sulfuric acid (4 mL) at 0 °C, and the mixture was heated at reflux for 13 h with removal of water. After cooling, the solvent was removed by distillation, and the residue was dissolved in CH_2Cl_2. The organic was washed with saturated aqueous $NaHCO_3$, water (×3), and saturated brine, and dried over anhydrous $MgSO_4$. The solvent was removed on a rotary evaporator, and purification of the residue by silica gel column chromatography (CH_2Cl_2–hexane, 1 : 2, v/v, as eluent) afforded **3** as a colorless oil (8.95 g, 43.2 mmol, 87%): ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J = 7.3 Hz, 3H), 1.47 (sext, J = 7.3 Hz, 2H), 1.75 (quint, J = 7.3 Hz, 2H), 2.23 (s, 3H), 4.27 (t, J = 7.3 Hz, 2H), 5.55 (br s, 2H), 6.58 (d, J = 7.9 Hz, 1H), 7.08 (dd, J = 1.8 and 7.9 Hz, 1H), 7.65 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.78, 19.34, 20.29, 30.86, 64.15, 111.05, 116.85, 125.36, 130.80, 135.09, 148.29, 168.26; IR (CCl_4) 3510, 3381, 2962, 1693, 1289, 1251, 1203 cm^{-1}; EI MS *m*/*z* 133 ([M − $C_4H_{10}O$]$^+$, 100%), 207 (M^+, 21).

Butyl 2-amino-3-bromo-5-methylbenzoate, 4

To a stirred solution of **3** (6.90 g, 33.3 mmol) in CCl_4 (120 mL) was added dropwise a solution of Br_2 (5.32 g, 33.3 mmol) in CCl_4 (30 mL) over 2 h at −5 °C on an ice–salt bath. The mixture was stirred at rt for 3 h, and then, the solvent was removed on a rotary evaporator. The residue was dissolved in CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, water (×3), and saturated brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, purification of the residue by silica gel column chromatography (CH_2Cl_2–hexane, 1 : 3, v/v, as eluent) afforded **4** as a colorless oil (9.20 g, 32.2 mmol, 97%): ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J = 7.3 Hz, 3H), 1.48 (sext, J = 7.3 Hz, 2H), 1.75 (quint, J = 7.3 Hz, 2H), 2.23 (s, 3H), 4.28 (t, J = 7.3 Hz, 2H), 5.51 (br s, 2H), 7.42 (d, J = 1.2 Hz, 1H), 7.65 (d, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.78, 19.32, 20.04, 30.80, 64.64, 110.65, 112.08, 125.77, 130.64, 137.94, 145.35, 167.67; IR (CCl_4) 3500, 2961, 2929, 1717, 1361, 1219 cm^{-1}; EI MS *m*/*z* 211 ([M − $C_4H_{10}O$]$^+$, 100%), 215 ([M − $C_4H_{10}O$]$^+$ + 2, 100), 285 (M^+, 27), 287 (M^+ + 2, 24).

Butyl 3-bromo-2-iodo-5-methylbenzoate, 5

To a stirred mixture of **4** (10.5 g, 36.7 mmol), concentrated HCl (70 mL) and water (70 mL) was added dropwise a solution of $NaNO_2$ (2.76 g, 40.0 mmol) in water (40 mL) over 1 h below 5 °C in an ice–salt bath. Then a solution of KI (60.9 g, 367 mmol) in water (50 mL) was added, and the mixture was stirred at rt for an additional 30 min. After neutralization with saturated aqueous $NaHCO_3$, the organic mixture was extracted with CH_2Cl_2 (×3), and the organic phases were combined and dried over anhydrous $MgSO_4$. After removal of the solvent on a rotary evaporator, purification by silica gel column chromatography (hexane as eluent) afforded **5** as a colorless oil (10.3 g, 25.9 mmol, 71%): ^{1}H NMR ($CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.48 (sext, J = 7.3 Hz, 2H), 1.76 (quint, J = 7.3 Hz, 2H), 2.30 (s, 3H), 4.34 (t, J = 7.3 Hz, 2H), 7.25 (d, J = 3.2 Hz, 1H), 7.57 (d, J = 3.2 Hz, 1H); ^{13}C NMR (CCl_4) δ 13.72, 19.26, 20.53, 30.54, 65.99, 96.31, 128.64, 132.13, 135.17, 139.78, 140.89, 167.69; IR (KBr) 2961, 2929, 1717, 1361, 1219 cm^{-1}; EI MS *m*/*z* 340 ([M − C_4H_8]$^+$, 100%), 342 ([M − C_4H_8]$^+$ + 2, 99), 396 (M^+, 25), 398 (M^+ + 2, 23).

Butyl 3-bromo-2-(3-hydroxy-3-methylbut-1-ynyl)-5-methylbenzoate, 6

A mixture of **5** (8.21 g, 20.7 mmol), $PdCl_2(PPh_3)_2$ (295 mg, 0.420 mmol) and CuI (40.0 mg, 0.210 mmol) in NEt_3 (70 mL) was stirred for 10 min at 0 °C under an Ar atmosphere, and to the mixture was added 3-methylbut-1-yn-3-ol (1.77 g, 21.0 mmol). The reaction mixture was stirred at reflux for 15 h. After cooling, the solvent was removed on a rotary evaporator. The residue was purified by silica gel column chromatography (CH_2Cl_2–hexane, 2 : 1,v/v, as eluent) to afford **6** as a colorless syrup (5.80 g, 16.4 mmol, 79%): ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3H), 1.45 (sext, J = 7.3 Hz, 2H), 1.65 (s, 6H), 1.73 (quint, J = 7.3 Hz, 2H), 2.34 (s, 3H), 3.13 (br s), 4.31 (t, J = 7.3 Hz, 2H), 7.57 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.68, 19.19, 20.91, 30.62, 31.10, 65.47, 65.57, 79.39, 103.59, 121.58, 127.81, 129.45, 134.26, 136.02, 138.97, 165.79; IR (CCl_4) 3500, 2978, 2962, 1718, 1362, 1218 cm^{-1}; FAB MS *m*/*z* 335 ([M − OH]$^+$), 337 ([M − OH]$^+$ + 2). Anal. Calcd for $C_{17}H_{21}O_3Br$: C, 57.79; H, 5.99. Found: C, 57.63; H, 5.92%.

Butyl 3-bromo-2-ethynyl-5-methylbenzoate, 7

A mixture of **6** (5.57 g, 15.8 mmol) and NaH (63.0 mg, 60 wt% oil dispersion, 1.58 mmol) in dry toluene (50 mL) was heated at reflux with stirring for 40 min under an Ar atmosphere. After cooling, the solvent was removed on a rotary evaporator. The residue was dissolved in CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, water (×3), and saturated brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, purification of the residue by silica gel column chromatography ($CHCl_3$–hexane, 1 : 1, v/v, as eluent) afforded **7** as a colorless oil (3.73 g, 12.6 mmol, 80%): ^{1}H NMR ($CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.47 (sext, J = 7.3 Hz, 2H), 1.75 (quint, J = 7.3 Hz, 2H), 2.36 (s, 3H), 3.63 (s, 1H), 4.34 (t, J = 7.3 Hz, 2H), 7.60 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.64, 19.20, 20.93, 30.52, 65.49, 80.06, 86.63, 120.71, 127.91, 129.47, 135.37, 136.06, 139.78, 165.69; IR (CCl_4) 2953, 1717, 1507, 1437, 1361, 1219 cm^{-1}; EI MS *m*/*z* 238 ([M − C_4H_8]$^+$, 100%), 240 ([M − C_4H_8]$^+$ + 2, 98), 294 (M^+, 5), 296 (M^+ + 2, 5).

1,4-Bis(1-bromo-3-*n*-butoxycarbonyl-5-methyl-2-phenyl)-butadiyne 8

A mixture of **6** (3.68 g, 12.5 mmol) and $Cu(OAc)_2 \cdot H_2O$ (9.68 g, 48.5 mmol) in acetonitrile (80 mL) was stirred for 2 h at 60 °C. After cooling, the solvent was removed on a rotary evaporator. The residue was dispersed in CH_2Cl_2 (100 mL), and the insoluble matter was removed by filtration. The filtrate was washed with water (×2) and dried over anhydrous $MgSO_4$. The solvent was removed by evaporation, and purification of the residue by silica gel column chromatography (CH_2Cl_2–hexane, 1 : 1, v/v, as eluent) afforded **8** as a white solid (3.08 g, 5.24 mmol, 84%): mp 135–137 °C; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 6H), 1.51 (sext, J = 7.3 Hz, 4H), 1.81 (quint, J = 7.3 Hz, 4H), 2.39 (s, 6H), 4.36 (t, J = 7.3 Hz, 4H), 7.61 (d, J = 1.8 Hz, 2H), 7.70 (d, J = 1.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.80, 19.36, 21.14, 30.60, 65.85, 80.87, 82.85, 120.79, 128.60, 130.19, 135.59, 136.40, 140.26, 165.63; IR (KBr) 2955, 2930, 2870, 1727, 1594, 1449, 1288, 1268, 1200, 1103 cm^{-1}; FAB MS *m*/*z* 587 ([M + H]$^+$), 589 ([M + H]$^+$ + 2), 591 ([M + H]$^+$ + 4). Anal. Calcd for $C_{28}H_{28}O_4Br_2$: C, 57.15; H, 4.80. Found: C, 57.52; H, 4.86%.

1-Bromo-6-(oct-1-ynyl)pyrene, 9

A mixture of 1,6-dibromopyrene (5.16 g, 14.3 mmol), $PdCl_2(PPh_3)_2$ (134 mg, 0.191 mmol) and CuI (18.2 mg, 0.0956 mmol) in morpholine (130 mL) was stirred for 10 min at 0 °C, and then oct-1-yne (1.05 g, 9.55 mmol) was added. The mixture was stirred for 10 h at 100 °C. After cooling, the solvent was removed on a rotary evaporator, and the residue was purified by silica gel column chromatography (hexane as eluent) to afford **9** as a yellow viscous syrup (2.16 g, 8.29 mmol, 58%): ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3H), 1.39 (m, 4H), 1.60 (quint, J = 7.3 Hz, 2H), 1.77 (quint, J = 7.3 Hz, 2H), 2.65 (t, J = 7.3 Hz, 2H), 7.90–8.05 (m, 5H), 8.17 (d, J = 7.9 Hz, 1H), 8.33 (d, J = 9.2 Hz, 1H), 8.51 (d, J = 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.14, 20.00, 22.67, 28.82, 28.96, 31.47, 79.48, 97.06, 119.80, 120.21, 123.83, 124.94, 125.71, 125.97, 126.17, 127.55, 128.74, 129.73, 130.17, 130.25, 130.34, 130.52, 130.62, 131.79; IR (KBr) 2929, 2313, 1361, 1218 cm^{-1}; EI MS m/z 237 ([M − $C_5H_{12}Br$]$^+$, 100%), 388 (M^+, 16), 390 (M^+ + 2, 16). Anal. Calcd for $C_{24}H_{21}Br$: C, 74.02; H, 5.44. Found: C, 73.78; H, 5.52%.

1-Bromo-6-octylpyrene, 10

Compound **9** (1.53 g, 3.93 mmol) was hydrogenated on Pd–carbon (153 mg, 5% Pd) in ethyl acetate (80 mL) over 21 h at rt. The catalyst was removed by filtration, and the filtrate was evaporated. The residue was purified by silica gel column chromatography (hexane as eluent) to afford **10** as a pale yellow solid (1.45 g, 3.69 mmol, 94%): mp 71–74 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.3 Hz, 3H), 1.28 (m, 8H), 1.48 (quint, J = 7.3 Hz, 2H), 1.82 (quint, J = 7.3 Hz, 2H), 3.33 (t, J = 7.3 Hz, 2H), 7.90 (d, J = 7.9 Hz, 2H), 7.99 (d, J = 7.9 Hz, 2H), 8.04 (d, J = 9.2 Hz, 2H), 8.12 (d, J = 9.2 Hz, 2H), 8.14 (d, J = 7.9 Hz, 1H), 8.20 (d, J = 7.9 Hz, 2H), 8.29 (d, J = 9.2 Hz, 1H), 8.37 (d, J = 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.13, 22.71, 29.34, 29.57, 29.87, 31.93, 32.03, 33.77, 97.79, 99.25, 100.74, 102.82, 110.10, 123.87, 125.06, 125.16, 125.40, 126.82, 127.95, 129.20, 130.00, 131.73, 135.81, 138.32; IR (KBr) 2954, 2921, 2860, 1468, 1082 cm^{-1}; EI MS m/z 293 ([M − C_7H_{15}]$^+$, 100%), 295 ([M − C_7H_{15}]$^+$ + 2, 100), 392 (M^+, 36), 394 (M^+ + 2, 38). Anal. Calcd for $C_{24}H_{25}Br$: C, 73.27; H, 6.40. Found: C, 73.21; H, 6.30%.

1-(3-Hydroxy-3-methylbut-1-ynyl)-6-octylpyrene, 11

A mixture of **10** (1.44 g, 3.66 mmol), $PdCl_2(PPh_3)_2$ (77.1 mg, 0.110 mmol) and CuI (10.5 mg, 0.0551 mmol) in morpholine (90 mL) was stirred for 10 min at 0 °C, and then 3-methylbut-1-yn-3-ol (0.920 g, 11.0 mmol) was added. The mixture was stirred at 100 °C for 14 h. After cooling, the solvent was removed by evaporation, and the residue was purified by silica gel column chromatography (CH_2Cl_2–hexane, 1 : 1, v/v, as eluent). Further purification by recrystallization from hexane afforded **11** as a yellow crystal (1.10 g, 2.75 mmol, 75%): mp 106–107 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.3 Hz, 3H), 1.27 (m, 8H), 1.46 (quint, J = 7.3 Hz, 2H), 1.79 (s, 6H), 1.82 (quint, J = 7.3 Hz, 2H), 2.33 (br s, 1H), 3.28 (t, J = 7.3 Hz, 2H), 7.83 (d, J = 7.9 Hz, 1H), 7.97–8.10 (m, 5H), 8.24 (d, J = 9.2 Hz, 1H), 8.41 (d, J = 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.14, 22.71, 29.34, 29.57, 29.89, 31.81, 31.93, 32.05, 33.69, 33.81, 66.09, 81.50, 99.33, 116.87, 124.03, 124.25, 124.39, 124.70, 124.80, 125.46, 126.88, 127.59, 128.50, 128.70, 129.57, 131.08, 132.26, 138.10; IR (KBr) 3389, 2935, 2923, 2853, 1558, 1467, 1260, 1150 cm^{-1}; FAB MS m/z 397 ([M + H]$^+$). Anal. Calcd for $C_{29}H_{32}O$: C, 87.83; H, 8.13. Found: C, 87.77; H, 8.18%.

1-Ethynyl-6-octylpyrene, 12

A mixture of **11** (409 mg, 1.03 mmol) and NaH (8.12 mg, 60 wt% oil dispersion, 0.203 mmol) in dry toluene (40 mL) was heated at reflux with stirring for 40 min under an Ar atmosphere. After cooling, the solvent was removed by evaporation, and the residue was dissolved in ether, and the organic was washed with saturated aqueous $NaHCO_3$, water (×3), and saturated brine, and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed on a rotary evaporator. Purification of the residue by silica gel column chromatography (hexane, as eluent) afforded **12** as a pale yellow solid (332 mg, 0.981 mmol, 95%): mp 85–87 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 1.28 (m, 8H), 1.48 (quint, J = 7.3 Hz, 2H), 1.85 (quint, J = 7.3 Hz, 2H), 3.28 (t, J = 7.3 Hz, 2H), 3.61 (s, 1H), 7.89 (d, J = 7.9 Hz, 1H), 8.04–8.16 (m, 5H), 8.31 (d, J = 9.2 Hz, 1H), 8.53 (d, J = 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.14, 22.71, 29.34, 29.59, 29.87, 31.93, 32.11, 33.71, 82.45, 116.21, 124.03, 124.39, 124.59, 124.68, 125.61, 126.88, 127.73, 128.72, 128.76, 129.55, 130.11, 131.47, 132.88, 138.32; IR (KBr) 2956, 2924, 2850, 1468, 1133 cm^{-1}; FAB MS m/z 338 (M^+). Anal. Calcd for $C_{26}H_{26}$: C, 92.26; H, 7.74. Found: C, 92.40; H, 7.81%.

1-(2-Tributylstannylethyn-1-yl)-6-octylpyrene, 13 and 1,4-bis[1-butoxycarbonyl-5-methyl-3-(6-octylpyren-1-ylethynyl)-2-phenyl]butadiyne, 14

To a stirred solution of **12** (873 mg, 2.58 mmol) in dry THF (15 mL) was added dropwise a hexane solution of *n*-BuLi (1.57 M, 1.97 mL, 3.09 mmol) at 0 °C under an Ar atmosphere. Then, tributyltin chloride (924 mg, 2.84 mmol) was added, and the mixture was stirred at rt for 12 h. The solvent was removed on a rotary evaporator, and the residue was dissolved in ether. The organic was washed with saturated KF_{aq} (×3), water and saturated brine, and then dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator to afford a crude product of **13** as a pale yellow solid (1.62 g, containing small amounts of unreacted *n*-BuSnCl), which was used in the next step without purification. A solution of the crude product of **13** (1.62 g) in dry toluene (40 mL) was added into a mixture of **8** (450 mg, 0.765 mmol) and $PdCl_2(PPh_3)_2$ (11.1 mg, 0.0158 mmol), and the mixture was stirred at 50 °C for 24 h under an Ar atmosphere. After cooling, the solvent was removed on a rotary evaporator and the residue was dissolved in CH_2Cl_2. The organic was washed with saturated KF_{aq} (×3), water and saturated brine, and then dried over anhydrous $MgSO_4$. After evaporation, purification by silica gel column chromatography (CH_2Cl_2–hexane, 1 : 1, v/v, as eluent) followed by recrystallization from benzene–hexane afforded **14** as a yellow crystal (467 mg, 0.423 mmol, 55% based on **8**): mp 144–148 °C; ^{1}H NMR ($CDCl_3$) δ 0.87–0.99 (m, 12H), 1.31–1.57 (m, 24H), 1.78–1.90 (m, 8H), 2.52 (s, 6H), 3.25 (t, J = 7.3 Hz, 4H), 4.37 (t, J = 7.3 Hz, 4H), 7.35 (d, J = 7.9 Hz, 2H), 7.51–7.56 (m, 4H), 8.69–7.94 (m, 12H), 8.42 (d, J = 9.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.82, 14.16, 19.44, 21.40, 22.75, 29.44, 29.67, 29.99, 30.70, 31.99, 32.15, 33.67, 65.73, 82.12, 83.38, 92.90, 94.96, 97.06, 116.25, 121.22, 123.22, 123.64, 124.09, 124.61, 125.28, 126.45, 127.10, 128.31, 128.90, 129.14, 129.47, 129.79, 130.52, 130.86, 131.87, 134.50, 135.63, 137.35, 138.77, 166.16; IR (KBr) 2925, 2852, 2202, 1716, 1593, 1196 cm^{-1}; FAB MS m/z 1103 ([M + H]$^+$). Anal. Calcd for $C_{80}H_{78}O_4$: C, 87.08; H, 7.12. Found: C, 87.07; H, 7.04%.

1,4-Bis[1-carboxy-5-methyl-3-(6-octylpyren-1-ylethynyl)-2-phenyl]butadiyne, 15

To a stirred solution of **14** (84.0 mg, 0.0761 mmol) in THF (3.6 mL) was added NaOH (91.0 mg, 2.28 mmol) dissolved in EtOH–H_2O (2 : 1,v/v, 1.5 mL). The mixture was stirred at rt for 10 h. The solvent was removed by evaporation and the residue was dissolved in water. The aqueous solution was acidified with 1 M HCl to pH 4 to afford a precipitate, which was collected by filtration. The solid was dried *in vacuo*, washed with a small amount of hexane and dried again *in vacuo* over silica gel to afford **15** as a yellow solid (74.0 mg, 0.0746 mmol, 98%). Compound **15** exhibited low solubility in any solvents, and the structural confirmation was carried out by IR and FAB mass spectra and elemental analysis: mp 190–193 °C; IR (KBr) 3103,

3039, 2923, 2852, 2170, 1697, 1593, 1464, 1439, 1257, 1200 cm^{-1}; FAB MS *m/z* 990 (M^+). Anal. Calcd for $C_{72}H_{62}O_4$: C, 87.24; H, 6.30. Found: C, 87.30; H, 6.54%.

1,4-Bis[1-aminocarbonyl-5-methyl-3-(6-octylpyren-1-ylethynyl)-2-phenyl]butadiyne, 1

A mixture of **15** (100 mg, 0.101 mmol), EDC·HCl (143 mg, 1.01 mmol) and NH_{3aq} (30 wt%, 15 mL) in THF–H_2O (2:1, v/v, 45 mL) was stirred at rt for 15 h. The solvent was removed by evaporation and the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 5:4, v/v as eluent). The product was dissolved in $CHCl_3$ (5 mL) and the insoluble residue was removed by filtration. The filtrate was evaporated, and the residue was dissolved in a small amount of $CHCl_3$. The solution was poured into MeOH (20 mL) to afford a precipitate, which was washed with hexane and dried *in vacuo* to yield **1** as a yellow solid (63.4 mg, 0.0641 mmol, 63%): mp 209–213 °C; ^{1}H NMR (270 MHz, $CDCl_3$–CD_3OD, 5:1, v/v) δ 0.93 (t, J = 7.3 Hz, 6H), 1.23–1.58 (m, 20H), 1.89 (m, 4H), 2.50 (s, 6H), 3.14 (t, J = 7.3 Hz, 4H), 6.92 (d, J = 7.9 Hz, 2H), 7.08 (d, J = 7.9 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 7.41–7.90 (m, 12H), 8.38 (m, 2H); IR (KBr) 3466, 2924, 2850, 2170, 1626, 1603, 1568, 1385 cm^{-1}; FAB MS *m/z* 989 ($[M + H]^+$). Anal. Calcd for $C_{72}H_{64}N_2O_2$: C, 87.41; H, 6.52; N, 2.83. Found: C, 87.53; H, 6.61; N, 2.68%.

1,4-Bis[1-(butylaminocarbonyl)-5-methyl-3-(6-octylpyren-1-ylethynyl)2-phenyl]butadiyne, 2

A mixture of **15** (71.0 mg, 0.0716 mmol), *n*-butylamine (52.3 mg, 0.716 mmol), 2-chloro-1-methylpyridinium iodide (40.4 mg, 0.169 mmol) and NEt_3 (0.02 mL) in dry CH_2Cl_2 (8 mL) was stirred at reflux for 24 h. After cooling, the solvent was removed by evaporation and the residue was dissolved in CH_2Cl_2. The organic was washed with saturated $NaHCO_3$, water and saturated brine and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was purified by preparative thin-layer chromatography (silica gel, CH_2Cl_2–hexane, 5:3, v/v as eluent) to afford **2** as a yellow solid (21.0 mg, 0.0191 mmol, 27%): mp 155–157 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 6H), 0.98 (t, J = 7.3 Hz, 6H), 1.28–1.53 (m, 24H), 1.73 (m, 4H), 1.87 (m, 4H), 2.56 (s, 6H), 3.35 (t, J = 7.3 Hz, 4H), 3.76 (t, J = 7.3 Hz, 4H), 7.63 (s, 2H), 7.76 (s, 2H), 7.92 (d, J = 7.9 Hz, 2H), 8.09 (d, J = 9.2 Hz, 2H), 8.14 (d, J = 9.2 Hz, 2H), 8.19 (d, J = 7.9 Hz, 2H), 8.26–8.32 (m, 4H), 8.36 (d, J = 9.2 Hz, 2H), 8.98 (d, J = 9.2 Hz, 2H); IR (KBr) 3423, 2962, 2925, 2852, 2214, 1765, 1701, 1404, 1261, 1095, 1024 cm^{-1}; FAB MS *m/z* 1101 ($[M + H]^+$). Anal. Calcd for $C_{80}H_{80}N_2O_2$: C, 87.23; H, 7.32; N, 2.54. Found: C, 87.30; H, 7.32; N, 2.34%.

Acknowledgements

This work was financially supported by the Shorai Foundation for Science and Technology.

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Paper a909468g