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Inherently Chiral Molecular Clips: Synthesis, Chiroptical Properties, and Application to Chiral Discrimination

Gaku Fukuhara,[a] Süreyya Madenci,[b] Jolanta Polkowska,[b] Frank Bastkowski,[b] Frank-Gerrit Klärner,*[b] Yumi Origane,[a] Masayuki Kaneda,[a] Tadashi Mori,[a] Takehiko Wada,[a] and Yoshihisa Inoue*[a]

Abstract: Inherently chiral molecular clips (MCs), pseudoenantiomeric *anti*-**1** and *anti*-**2**, as well as *mesoid syn*-**3**, were synthesized by diastereodifferentiating repetitive Diels–Alder reactions of the achiral bisdienophile **6** with chiral diene **5** generated in situ from (−)-menthyl 3,4-bis(dibromomethyl)-benzoate **4**. These MCs were successfully separated by chiral HPLC to give optically active *anti*-**1** and *anti*-**2** and almost optically inactive *syn*-**3**. The structures of *anti*-**1**, *anti*-**2**, and *syn*-**3** were assigned by high-resolution NMR and the absolute configurations of *anti*-**1** and *anti*-**2** were determined by the exciton-chirality method. Optically active *anti*-**2** can serve as a chiral host. It binds the HCl adduct of D-tryptophan methyl ester (D-TrpOMe·HCl) 3.5 times stronger than the L-enantiomer ($K_D/K_L = 3.5$).

Keywords: chirality · circular dichroism · exciton coupling · host–guest systems · molecular clips

Introduction

A large variety of synthetic hosts reported so far[1–3] may be classified on the basis of skeletal flexibility into two categories: rigid (in the meaning of preorganization) and flexible. The binding behavior of the former is generally easier to rationally design, predict, and discuss than that of the latter. One of the most successful, well-preorganized synthetic hosts is a molecular clip (MC)[4–13] that is composed of two parallel aromatic subunits connected by a rigid spacer.

Our previous studies on MCs demonstrated that multiple noncovalent interactions of arene subunits in the host with neutral or ionic aromatic guests, such as the π–π, CH–π, charge-transfer (CT), cation–π, and hydrophobic interactions, play important roles in the control of guest binding in nonpolar[14] and polar solvents,[15] and also in the solid state.[16] One of the unique features of a MC is its hemicyclic, and thus size-flexible, "pseudocavity", which clearly differentiates it from other preorganized macrocyclic hosts[1] such as cyclodextrins, some cyclophanes, carcerands, cryptophanes, cucurbiturils, and supramolecular capsules. This pseudocavity can readily gain facial chirality by simply introducing two (achiral) substituents at *anti* positions of the MC's tips. Nonetheless, the synthesis, optical resolution, chiroptical properties,[17d] and enantiodifferentiation behavior of chiral MC[17–19] have attracted little attention since Wilcox reported Tröger's base analogues as the first example of a chiral molecular cleft in 1985.[20]

Here, we report the novel synthesis of facially chiral MCs, that is, pseudoenantiomeric *anti*-**1** and *anti*-**2**, and *mesoid syn*-**3** (Scheme 1), their chiroptical properties, and application to chiral recognition of an amino acid ester. The MC reported here possesses a chiral skeleton created by introducing a substituent at each tip of the aromatic moieties, whereas the central spacer unit itself is achiral, as is also the case in the previous MCs.[17–19] We also compare the chiroptical properties of MCs to inherent and peripheral chirality.

[a] G. Fukuhara, Y. Origane, Dr. M. Kaneda, Prof. Dr. T. Mori, Prof. Dr. T. Wada, Prof. Dr. Y. Inoue
ICORP Entropy Control Project (JST) and
Department of Applied Chemistry
Osaka University, 2–1 Yamada-oka, Suita 565–0871 (Japan)
Fax: (+81) 668-797-921
E-mail: inoue@chem.eng.osaka-u.ac.jp

[b] Dr. S. Madenci, Dr. J. Polkowska, Dipl.-Chem. F. Bastkowski, Prof. Dr. F.-G. Klärner
Institute für Organische Chemie der Universität Duisburg-Essen
45117 Essen (Germany)
Fax: (+49) 201-183-4252
E-mail: frank.klaerner@uni-duisburg-essen.de

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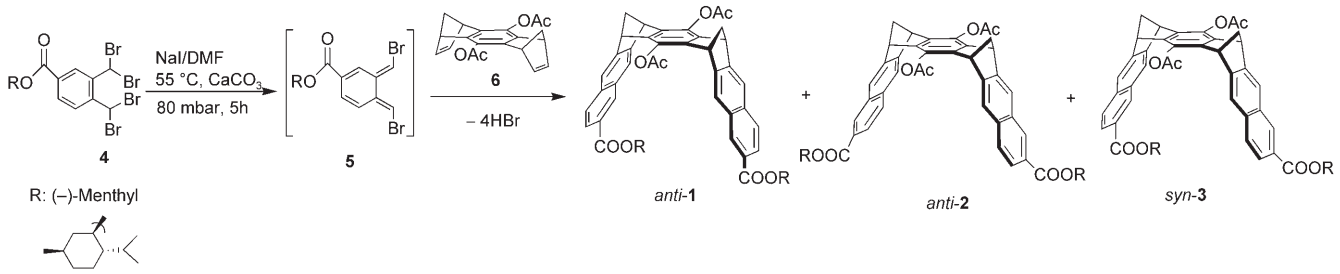


Scheme 1. Synthesis of MCs **1**–**3**.

Results and Discussion

MCs **1**–**3** were obtained in a ratio of approximately 1:1:3 in 52% combined yield by performing a one-pot reaction of bisdienophile **6**[16c] with diene **5** derived from **4** (Scheme 1), which was prepared by the conventional esterification of 3,4-bis(dibromomethyl)benzoyl chloride[16d] with (−)-menthol. The key step in the synthesis of the dimethylene-bridged MCs is the successive Diels–Alder reaction of one mole of **6** with two moles of **5** via the tetrabromo-substituted primary bisadducts that finally undergo fourfold HBr eliminations to afford the MC's naphthalene moieties. It should be noted that, due to the presence of the (−)-menthyl auxiliary, *anti*-**1** and *anti*-**2** are pseudoenantiomeric to each other in the MC skeleton, but actually diastereomeric in a strict sense. Similarly, *syn*-**3** is not a pure *meso*, but only a "*mesoid*" isomer with chiral substituents at the tips.

These diastereomers were resolved by chiral HPLC. Analytical HPLC was performed at room temperature (ca. 20 °C) on a chiral column (Sumichiral OA 3300, 250 × 4.6 mm, 5 μm) by using a JASCO LC-2000 plus instrument; the mobile phase was an 85:15 (v/v) mixture of *n*-hexane/ethanol eluted under isocratic conditions and the run time was 40 min at a flow rate of 0.5 mL min^{-1}. UV and circular dichroism (CD) detectors were set at 254 nm. As illustrated in Figure 1, fractions P_1 and P_2 give oppositely signed CD signals, whereas P_3 is almost CD silent, despite the strong UV absorption. This indicates that the chiral auxiliary, (−)-menthyl, introduced at the periphery cannot induce appreciable CD signals in the naphthalene and/or diacetoxybenzene chromophores. From this observation, we tentatively assigned fractions P_1 and P_2 to facially chiral *anti*-**1** and *anti*-**2**, and P_3 to *mesoid syn*-**3**.

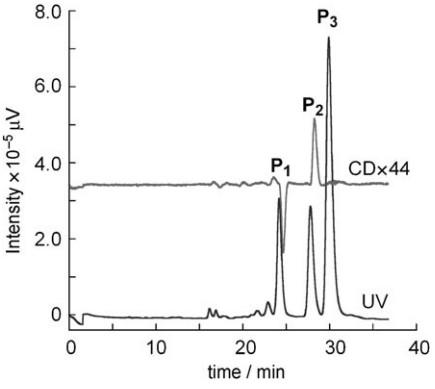


Figure 1. HPLC charts for a mixture of **1**–**3** detected by UV (bottom) and CD (top) spectroscopy at 254 nm.

The mixture of MCs was separated by preparative HPLC using a JASCO LC-908 instrument fitted with a UV detector (254 nm), by using a Sumichiral OA 3300 column (250 × 20 mm, 5 μm) eluted with an 80:15 (v/v) *n*-hexane/ethanol mixture at a flow rate of 8.0 mL min^{-1} under isocratic conditions; the run time was approximately 2 h, due to recycling two times. The injection volume was 1 mL, which contained approximately 50 mg of sample dissolved in the mobile phase. Detection was performed at 254 nm and room temperature.

The isolated samples, P_1–P_3, were subjected to high-resolution NMR spectroscopy by using the 1D and 2D NMR techniques (COSY and HMQC)[21] to confirm the structural assignment shown in Figure 2. As a consequence of the molecular symmetry, the NMR spectrum of *syn*-**3** is clearly different from those of *anti*-**1** and *anti*-**2**. In the aliphatic region, the two acetoxy methyl groups of *syn*-**3** are not equivalent to each other, giving two independent signals at $\delta = 2.495$ and 2.503 ppm, whereas the same protons of each *anti* isomer (*anti*-**1** or *anti*-**2**) show only one singlet. Similarly, the pseudoequivalent naphthyl protons of *syn*-**3**, that is, H_1/H_{13}, H_3/H_{11}, H_4/H_{10}, and H_{14}/H_{18} pairs, appear at distinctly different positions due to the diastereotopic relationship to the peripheral (−)-menthyl group. In sharp contrast, no such difference in chemical shifts was observed for the H_1/H_{10}, H_3/H_{12}, H_4/H_{13}, H_5/H_{14}, and H_9/H_{18} pairs of the pseudo-C_2 symmetric *anti*-**1** and *anti*-**2**, although each pair shows slightly different chemical shifts due to the diastereomeric nature of **1** and **2**.

For further structural elucidation, the UV-visible and CD spectra were recorded and the anisotropy factors ($g = \Delta\varepsilon/\varepsilon$) were calculated therefrom (Figure 3). As was the case with the chiral HPLC analysis, the fractions P_1 and P_2 exhibited essentially the same UV-visible and mirror-imaged CD spectra, but fraction P_3 showed slightly stronger UV absorption and extremely weak CD intensities, confirming the pseudoenantiomeric nature of *anti*-**1** and *anti*-**2** and the *mesoid* nature of *syn*-**3**. Interestingly, the maximum *g* factor of *anti*-**1** or *anti*-**2** reaches 0.015 at 335 nm, which is much higher than the typical *g* value of 10^{-3}–10^{-5} reported for the allowed transition of aromatic chromophores,[22] and most

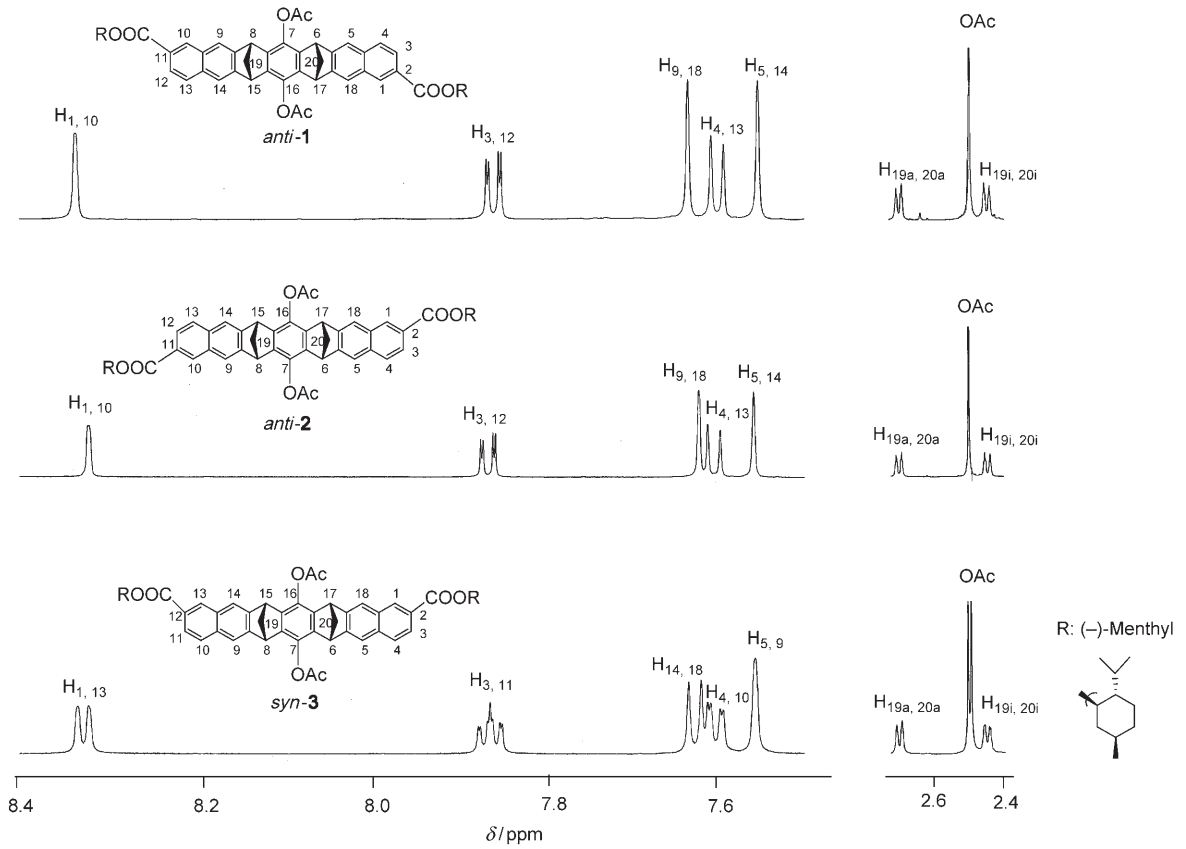


Figure 2. ^{1}H NMR spectra of *anti*-**1**, *anti*-**2**, and *syn*-**3** in $CDCl_3$ at room temperature measured at 600 MHz, and notations of MCs **1**–**3**.

probably ascribable to the rigid skeleton of the MC. In the CD spectra and *g*-factor profiles, there is a clear crossover at around 250 nm in the major transition region, which is most reasonably assigned as the exciton-coupling interaction of the ^1B_b transitions of the two naphthalene chromophores placed face-to-face in the rigid MC skeleton. If this coupling involves a transition of the 1,4-diacetoxybenzene chromophore, similar behavior should be observed with *syn*-**3**. By applying the exciton-chirality theory,[23] the negative CD couplet signal observed for *anti*-**1** is related to the counterclockwise rotation of the two transition moments. Therefore, the absolute configuration of the skeleton of *anti*-**1** is assigned as 6*S*,8*R*,15*S*,17*R*.[24] On the other hand, the positive couplet observed for *anti*-**2** indicates the clockwise rotation of the transition moments, corresponding to the antipodal 6*R*,8*S*,15*R*,17*S* configuration. In fact, we originally intended to determine the absolute configurations of the chiral MCs by means of X-ray crystallography and, therefore, introduced the (−)-menthyl moiety as an internal chirality reference. However, we could not obtain a suitable single crystal of **1** or **2** after repeated recrystallization under a variety of conditions. In this context, we are fortunate to be able to determine the absolute configurations of *anti*-**1** and *anti*-**2** by using the exciton-chirality method, owing to the strong exciton couplets.

To briefly examine the chiral recognition ability of this pseudoenantiomeric MC, we investigated the binding behavior of *anti*-**2** with an amino acid derivative, L- and D-tryptophan methyl esters (Trp-OMe•HCl). The choice of the guest is based on the similarity in size and shape of the guest's indole ring with the MC's cavity. CD spectral titrations of *anti*-**2** with L- and D-Trp-OMe•HCl were performed in a somewhat special solvent, that is, a 4:1:5 mixture of tetrahydrofuran, methanol, and water, which dissolves the host and guest. As shown in Figure 4, the CD intensity was gradually reduced upon stepwise addition of the guest, but the changing profile is significantly different between the antipodal L- and D-Trp-OMe•HCl guests. The resulting titration curves were analyzed by the nonlinear least-squares fitting to the 1:1 binding model to afford the binding constants (K) of 3900 ± 390 and $13600\pm1500\,M^{-1}$ for L- and D-Trp-OMe•HCl, respectively. Therefore, this chiral MC displays a high enantioselectivity of $K_D/K_L=3.5$ relative to native and modified cyclodextrins (enantioselectivity = 1.3–3.6),[25] whereas Cram's sophisticated chiral binaphthyl-crown ethers were shown to exhibit much higher enantioselectivities of up to 52 for D- and L-Phe and 36 for D- and L-Trp upon solvent extraction.[26]

To obtain further insights into this chiral discrimination, we performed a Monte-Carlo conformer search of structures of the host–guest complexes of *anti*-**2** with L- and with D-

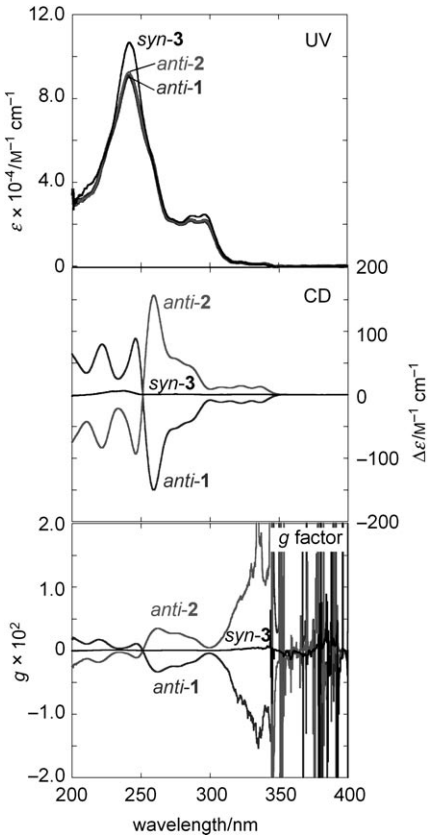


Figure 3. UV/Vis and CD spectra, and *g*-factor profiles of 0.1-mM MCs (**1**–**3**) in methanol at 25 °C, measured in a 1-mm cell.

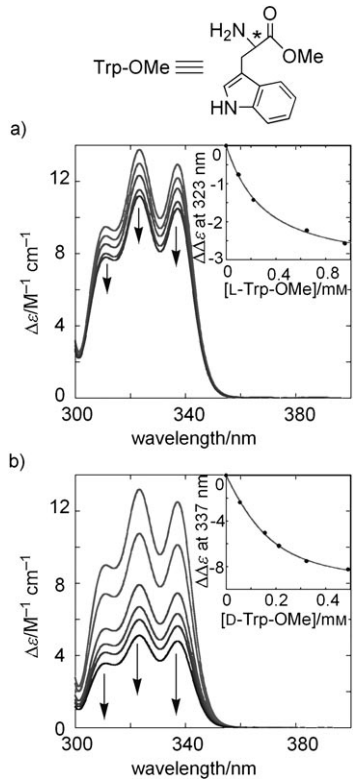


Figure 4. CD spectra of a) *anti*-**2** (0.07 mM) upon gradual addition of L-Trp-OMe (0–0.954 mM) and b) *anti*-**2** (0.15 mM) upon addition of D-Trp-OMe (0–0.491 mM) in a 4:1:5 (v/v) mixture of THF/MeOH/H_2O at 25 °C, measured in a 1-cm cell; the insets show the least-squares fit assuming the 1:1 stoichiometry.

Trp-OMe•H^+ by using the Amber*/H_2O force field.[27,28] This technique has been already successfully employed to elucidate the structures of host–guest complexes between molecular clips or tweezers as host molecules and, for example, pyridinium salts (such as NAD^+) as guest molecules.[15] The complex structures obtained by these calculations, shown in Figure 5, indicate that D-Trp-OMe•H^+ forms a more stable complex than the antipodal L-Trp-OMe•H^+ with *anti*-**2**, which is better fitted to the MC's cavity and is more efficiently covered by the menthoxycarbonyl substituent. In fact, the calculated energies reveal that the complex of *anti*-**2** with D-Trp-OMe•H^+ is more stable by 3.1 kJ mol^{-1} than that with L-Trp-OMe•H^+. This finding is consistent, at least qualitatively, with the enantioselectivity ($K_D/K_L = 3.5$) obtained in the CD titration experiments mentioned above. Despite the moderate chiral recognition in the ground state, these MCs are promising as chiral sensitizing hosts for supramolecular photochirogenesis,[29] as we can expect the chiral supramolecular interactions both in the ground and the excited states.

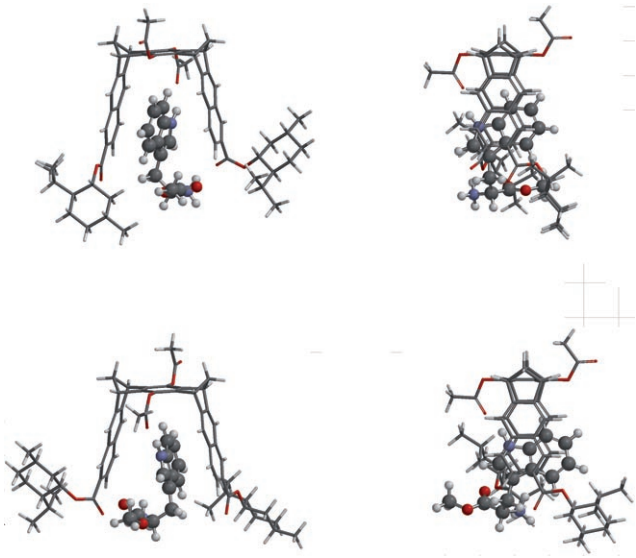


Figure 5. Results of Monte-Carlo conformer search of complex structures of optically active *anti*-**2** and D-Trp-OMe•H^+ (top left: front view, top right: side view) and L-Trp-OMe•H^+ (bottom left: front view, bottom right: side view) (Macromodel 9.0, Amber*/H_2O, 5000 steps).

Conclusion

We synthesized and separated novel inherently chiral MCs, *anti*-**1** and *anti*-**2**, as well as *syn*-**3**, and further elucidated their chiroptical properties for the first time. The *anti*-isomers displayed oppositely signed, strong exciton couplets in

the CD spectra, which enabled us to determine their absolute configurations, according to the exciton-chirality theory. We also demonstrated that the inherently chiral MC can be used as an enantioselective host for the amino acid derivative Trp-OMe·HCl.

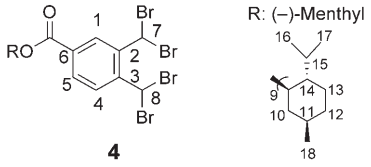
The synthetic methodology developed here can be extended to a wide variety of facially chiral, structurally rigid MCs by simply changing the substituents in the arene units. Studies on the chiral recognition of other enantiomeric guests, as well as the supramolecular photochirogenic reactions, are currently in progress.

Experimental Section

Instruments: FAB-MS spectra were obtained by using a JEOL JMS-DX303 instrument. NMR spectra were measured by using a Varian INOVA-600 at 600 MHz for ^{1}H and 150 MHz for ^{13}C. Electronic absorption and CD spectra were measured in a quartz cell (with light path of 1 or 10 mm) by using JASCO V-560 and J-820 spectrometers equipped with a PTC-423L temperature controller.

Synthesis and characterization of compounds 1–4

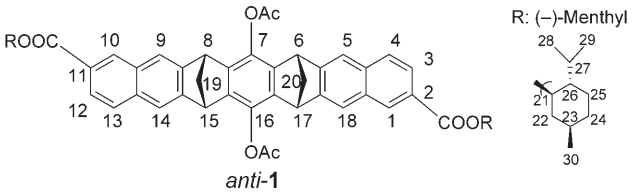
4: 3,4-Bis(dibromomethyl)benzoyl chloride (30.2 g, 62.4 mmol)[16d] and (−)-menthol (9.96 g, 63.7 mmol) were dissolved in pyridine (100 mL) in a 300-mL round-bottomed flask, which was cooled to below 0 °C and then stirred for 20 min. Water (10 mL) was added to the flask to quench the reaction. After removing pyridine and (−)-menthol under high vacuum, the resulting crude mixture was dissolved in diethyl ether (400 mL), washed successively with water (200 mL), 1 M HCl (200 mL), saturated aqueous sodium hydrogen carbonate (200 mL), and saturated aqueous sodium chloride (200 mL). The organic residue was dried over magnesium sulfate and concentrated. Flash chromatography (SiO_2, 2:3 dichloromethane/cyclohexane) gave the desired product (9.24 g, 25 % yield) as white oily solid.



4

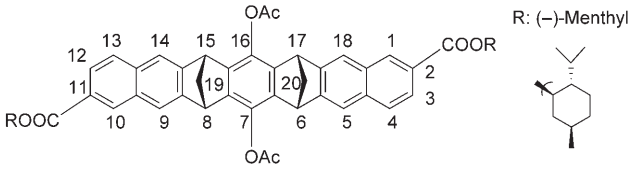
^{1}H NMR ($CDCl_3$, 22 °C): δ_H = 8.23 (s, 1H; H1), 8.04 (d, J = 8.40 Hz, 1H; H5), 7.90 (d, J = 7.80 Hz, 1H; H5), 7.27 (s, 1H; H8), 7.06 (s, 1H; H7), 4.96 (dt, 1H; H9), 2.12–2.10 (m, 1H; H10), 1.94–1.91 (m, 1H; H14), 1.76–1.72 (m, 2H; H12, H13), 1.60–1.56 (m, 2H; H11, H14), 1.15–1.09 (m, 2H; H10, H13), 0.94–0.92 (m, 7H; H12, H16, H18), 0.80 ppm (d, J = 6.60 Hz, 3H; H17); ^{13}C NMR ($CDCl_3$, 22 °C): δ_C = 164.1 (C=O), 144.3 (C3), 138.8 (C2), 132.3, 132.1, 131.3–130.9 (overlapped; C1, C4, C5, C6), 75.7 (C9), 47.2 (C11, C14), 40.8 (C10), 35.7 (C12), 26.5 (C15), 23.6 (C13), 22.0 (C16), 20.7 (C18), 20.6 ppm (C17); HR-MS (FAB): m/z calcd for $C_{19}H_{24}Br_4O_2Na$ $[M+Na]^+$: 622.8408; found: 622.8402.

Molecular clips 1–3: A mixture of **4** (9.30 g, 15.4 mmol), **6** (630 mg, 1.95 mmol), sodium iodide (15.0 g, 100 mmol), and calcium carbonate (3.10 g, 31.0 mmol) dissolved in anhydrous DMF (100 mL) was stirred at 55 °C under a reduced pressure (80 mbar) for 5 h. After cooling, the solution was poured into ice, and the resultant mixture was extracted with dichloromethane. The organic layer was washed with aqueous sodium hydrogen carbonate and water, dried over magnesium sulfate, and concentrated. Flash chromatography (SiO_2, 1:3 ethyl acetate/cyclohexane) gave a mixture of MCs **1**–**3** (900 mg, 52 % yield) as brown solid (*anti*-**1**, *anti*-**2**, and *syn*-**3**). The product ratio was determined by HPLC and ^{1}H NMR to be approximately 1:1:3 (*anti*-**1**:*anti*-**2**:*syn*-**3**).



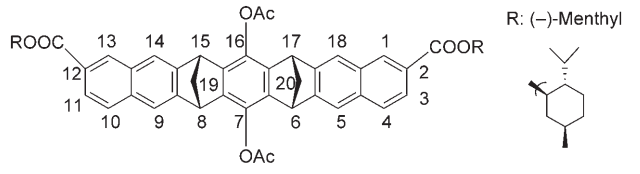
anti-**1**

anti-**1**: ^{1}H NMR ($CDCl_3$, 22 °C): δ_H = 8.34 (s, 2H; H1, H10), 7.86 (dd, 2H; H3, H12), 7.63 (s, 2H; H9, H18), 7.56 (d, J = 9.00 Hz, 2H; H4, H13), 7.55 (s, 2H; H5, H14), 4.89 (dt, 2H; H21), 4.32 (d, J = 1.80 Hz, 4H; H6, H8, H15, H17), 2.67 (d, J = 7.80 Hz, 2H; H19a, H20a), 2.49 (s, 6H; −OAc), 2.45 (d, J = 7.80 Hz, 2H; H19i, H20i), 2.09–2.07 (m, 2H; H22), 1.91–1.89 (m, 2H; H27), 1.70 (d, J = 11.4 Hz, 4H; H24, H25), 1.54–1.50 (m, 4H; H23, H26), 1.11–1.02 (m, 4H; H22, H25), 0.93–0.86 (m, 14H; H24, H28, H30), 0.73 ppm (d, J = 6.60 Hz, 6H; H29); ^{13}C NMR ($CDCl_3$, 22 °C): δ_C = 168.5 (CH_3−C=O), 166.4 (C=O−OR), 148.5 (C7, C16), 140.7 (C5a, C14a), 140.5 (C8a, C17a), 137.3 (C6a, C7a, C15a, C16a), 134.6 (C4a, C13a), 131.3 (C9a, C18a), 130.5 (C1, C10), 127.7 (C4, C13), 127.4 (C2, C11), 125.1 (C3, C12), 121.3 (C9, C18), 120.0 (C5, C14), 74.7 (C21), 64.8 (C19, C20), 48.17, 48.00, 47.30 (C6, C8, C15, C17, C23, C26), 41.0 (C22), 34.4 (C24), 26.5 (C27), 23.7 (C25), 22.0 (C28), 20.7 (C30), 16.6 ppm (C29); FAB-MS: m/z: 887 $[M]^+$; HR-MS (FAB): m/z calcd for $C_{58}H_{62}O_8Na$ $[M+Na]^+$: 909.4342; found: 909.4355.



anti-**2**

anti-**2**: ^{1}H NMR ($CDCl_3$, 22 °C): δ_H = 8.32 (s, 2H; H1, H10), 7.86 (dd, 2H; H3, H12), 7.62 (s, 2H; H9, H18), 7.60 (d, J = 8.40 Hz, 2H; H4, H13), 7.56 (s, 2H; H5, H14), 4.90 (dt, 2H; H21), 4.32 (d, J = 1.80 Hz, 4H; H6, H8, H15, H17), 2.68 (d, J = 8.40 Hz, 2H; H19a, H20a), 2.50 (s, 6H; −OAc), 2.45 (d, J = 7.80 Hz, 2H; H19i, H20i), 2.10–2.08 (m, 2H; H22), 1.91–1.88 (m, 2H; H27), 1.70 (d, J = 13.8 Hz, 4H; H24, H25), 1.56–1.49 (m, 4H; H23, H26), 1.11–1.04 (m, 4H; H22, H25), 0.94–0.86 (m, 14H; H24, H28, H30), 0.73 ppm (d, J = 7.20 Hz, 6H; H29); ^{13}C NMR ($CDCl_3$, 22 °C): δ_C = 168.6 (CH_3−C=O), 166.4 (C=O−OR), 148.5 (C7, C16), 140.7 (C5a, C14a), 140.5 (C8a, C17a), 137.3 (C6a, C7a, C15a, C16a), 134.6 (C4a, C13a), 131.3 (C9a, C18a), 130.4 (C1, C10), 127.7 (C4, C13), 127.4 (C2, C11), 125.1 (C3, C12), 121.3 (C9, C18), 120.0 (C5, C14), 74.7 (C21), 64.9 (C19, C20), 48.20, 48.01, 47.31 (C6, C8, C15, C17, C23, C26), 41.0 (C22), 34.4 (C24), 26.4 (C27), 23.6 (C25), 22.0 (C28), 20.8 (C30), 16.4 ppm (C29); HR-MS (FAB): m/z calcd for $C_{58}H_{62}O_8$ $[M]^+$: 886.4445; found: 886.4441.



syn-**3**

syn-**3**: ^{1}H NMR ($CDCl_3$, 22 °C): δ_H = 8.33 (d, J = 7.80 Hz, 2H; H1, H13), 7.87–7.85 (m, 2H; H3, H11), 7.63–7.59 (m, 4H; H14, H18, H4, H10), 7.56 (s, 2H; H5, H9), 4.91–4.89 (m, 2H; H21), 4.33–4.32 (m, 4H; H6, H8, H15, H17), 2.68 (d, J = 8.40 Hz, 2H; H19a, H20a), 2.50 (s, 3H; −OAc), 2.50 (s, 3H; −OAc), 2.45 (d, J = 6.60 Hz, 2H; H19i, H20i), 2.09–2.08 (m, 2H; H22), 1.89–1.88 (m, 2H; H27), 1.70 (d, J = 10.8 Hz, 4H; H24, H25), 1.56–1.50 (m, 4H; H23, H26), 1.11–1.04 (m, 4H; H22, H25), 0.91–0.86 (m, 14H; H24, H28, H30), 0.72 ppm (t, J = 7.80 Hz, 6H; H29); ^{13}C NMR ($CDCl_3$, 22 °C): δ_C = 168.6 (CH_3–C=O), 166.3 (C=O–OR), 148.5 (C16), 146.6 (C7), 140.7 (C8a, C5a), 140.5 (C14a, C17a), 137.32, 137.27 (C6a, C7a, C15a, C16a), 134.6 (C4a, C9a), 131.33, 131.31 (C13a, C18a), 130.5, 130.4 (C1, C13), 127.7, 127.5 (C4, C10), 127.4 (C2, C12), 125.12, 125.08 (C3, C11), 121.31, 121.28 (C14, C18), 120.01 (C5, C9), 74.68, 74.65 (C21), 64.82, 64.75 (C19, C20), 48.20, 47.99, 47.97, 47.31 (C6, C8, C15, C17, C23, C26), 41.00, 40.97 (C22), 34.4 (C24), 26.53, 26.35 (C27), 23.9, 23.6 (C25), 22.04, 22.03 (C28), 20.9, 20.7 (C30), 16.6, 16.4 ppm (C29); HR-MS (FAB): m/z calcd for $C_{58}H_{62}O_8$ $[M]^+$: 886.4445; found: 886.4450.

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