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Synthesis of Chiral [60]Fullerene–Steroid Bisadducts using Steroid Templates

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Abstract: The double [4+2] cycloadditions between [60]fullerene and steroid–appended dibenzoates **7** and **8**, the reaction sites of which were controlled by diols in chiral template molecules, afforded [60]fullerene–steroid bisadducts **11** and **12** regio- and chiroselectively. CD spectroscopic studies of **11** and **12** indicated that the magnitude of the *Cotton* effects changes reflecting the chiral structure of the steroid moiety in **11** and **12**.

INTRODUCTION

Recently, regio- and chiroselective introduction of two functional groups into [60]fullerene has been of much concern, which are very useful for design of novel redox systems,[1] amphiphiles,[2] and hybride molecules of [60[fullerene.[3] The principle idea common to these studies is to use a template effect, which regularly arranges two functional groups so that they can selectively react with two carbon–carbon bonds on the [60]fullerene surface.[4–10] Recently we reported the regio- and chiroselective double [4+2] cycloaddition between [60]fullerene and 1:2 saccharide–boronic acid complex utilizing a saccharide as a template molecule.[11–13] In these studies, the saccharide template had several specific advantages which other template molecules did not have, *i.e.* i) naturally abundant saccharides can be used as a potential template family to cover various spacer lengthes and angles between the two carbon–carbon bonds on the [60]fullerene surface,[11,12] ii) both chiroselectivity and regioselectivity are controllable by the inherent chirality of the saccharide templates,[11,12] and iii) removal and re-binding of the saccharide templates occurs reversibly to provide a novel molecular recognition system, in which [60]fullerene–diboronic acids can selectively recognize the original saccharides used as template molecules.[13] Here, we have newly selected diols as a chiral template family instead of saccharides, because we can utilize naturally abundant steroidal diols such as cholic acid derivatives and commercially available vicinal diols. In practice, the regio- and chiroselectivities have successfully been achieved in the intramolecular double [4+2] cycloaddition between [60]fullerene and diol–bis[3,4-bis(bromomethyl)benzoate], which can generate active *o*-quinodimethane species to react with the two [6,6]junction bonds in [60]fullerene.[14] In this paper, we report a new idea to achieve the regio- and chiroselectivities by the double addition: that is to use steroids as a chiral template family. The structure of the bisadduct products were determined and their chiroptical properties were studied by CD spectroscopy.

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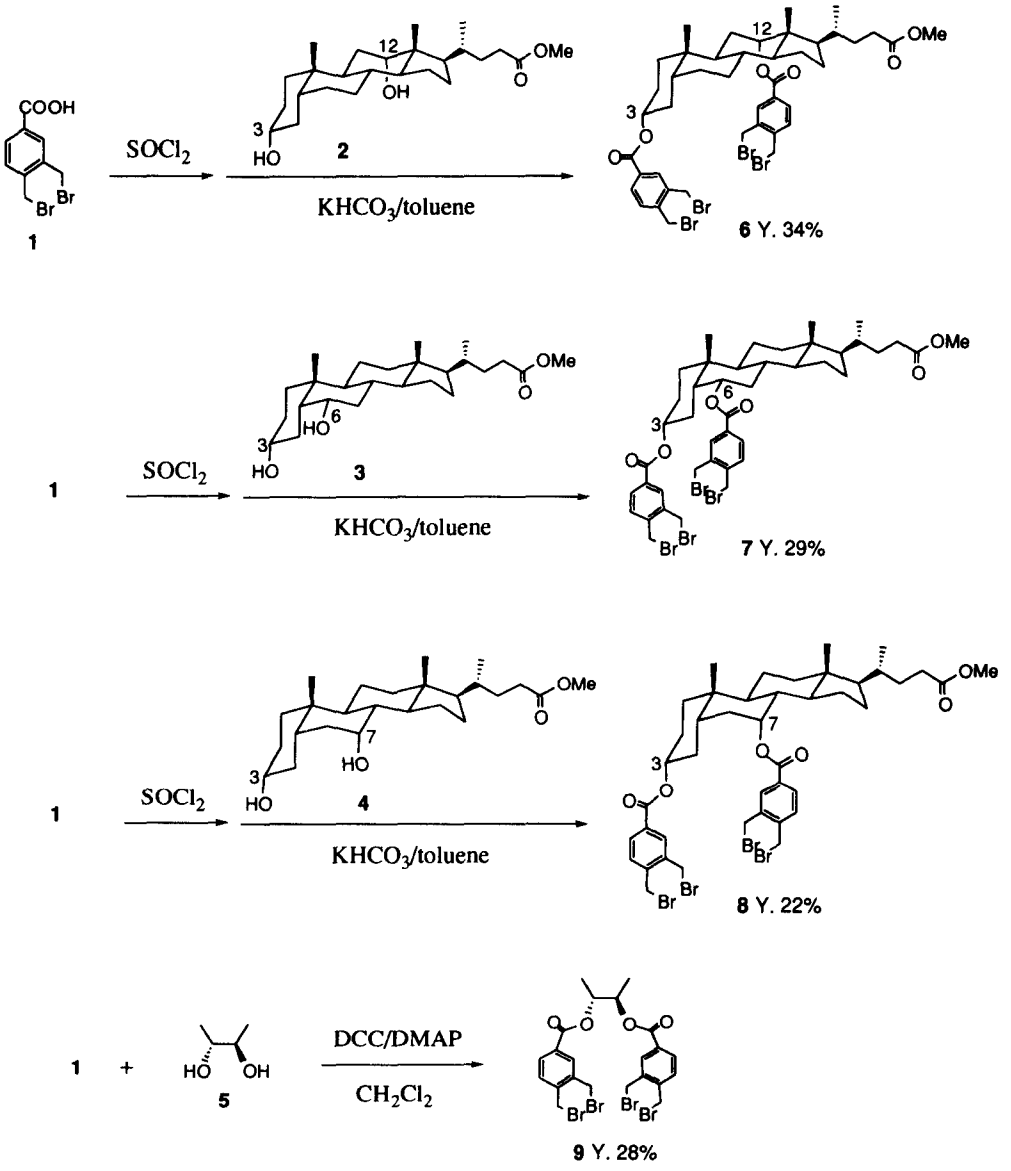
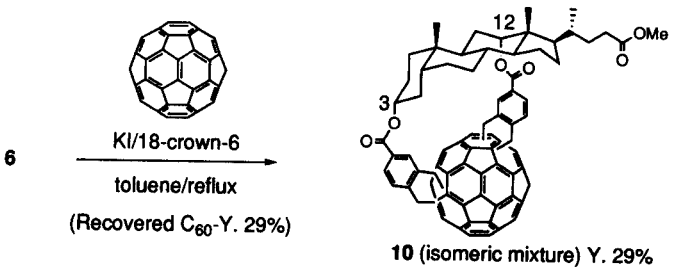
RESULTS AND DISCUSSION

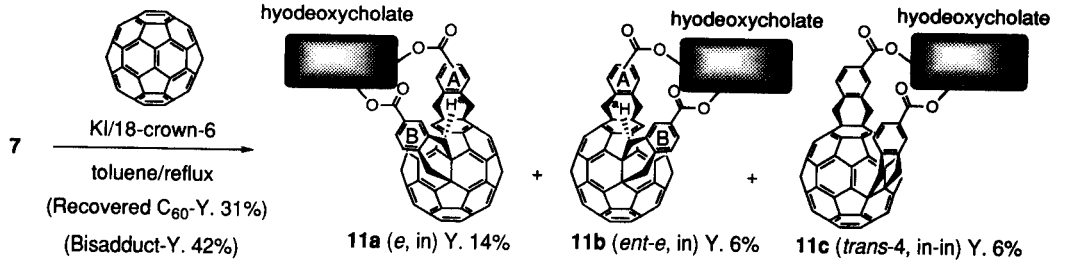
Double Additions between [60]Fullerene and Diol–Dibenzoates.

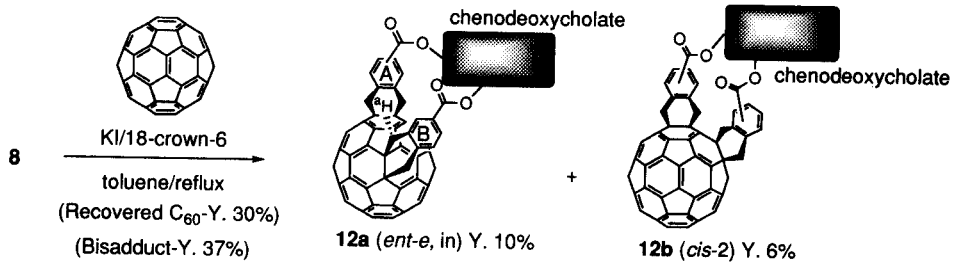
Steroid–dibenzoates **6**, **7**, and **8** were prepared from methyl deoxycholate (**2**), methyl hyodeoxycholate (**3**), and methyl chenodeoxycholate (**4**) by acylation with aroyl chloride of **1**, respectively. A dibenzoate derivative of (2*R*,3*R*)-butanediol **9** was obtained by DCC condensation between **1** and **5** (Scheme 1).

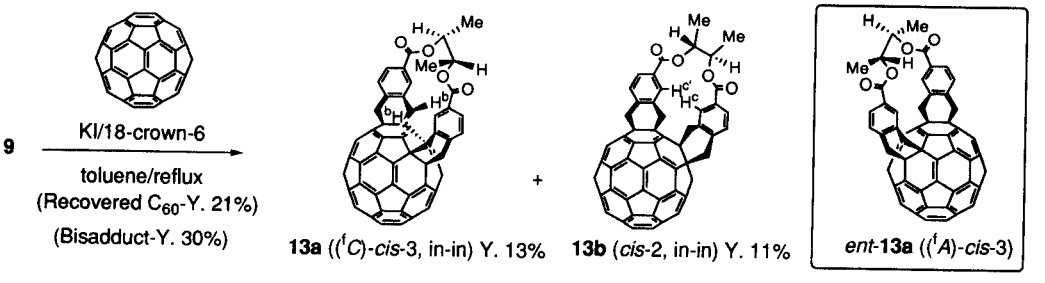


Scheme 1


6
KI/18-crown-6
toluene/reflux
(Recovered C_{60}-Y. 29%)
12
OMe
3
10 (isomeric mixture) Y. 29%


7
KI/18-crown-6
toluene/reflux
(Recovered C_{60}-Y. 31%)
(Bisadduct-Y. 42%)
hyodeoxycholate
hyodeoxycholate
hyodeoxycholate
11a (e, in) Y. 14%
11b (ent-e, in) Y. 6%
11c (trans-4, in-in) Y. 6%


8
KI/18-crown-6
toluene/reflux
(Recovered C_{60}-Y. 30%)
(Bisadduct-Y. 37%)
chenodeoxycholate
chenodeoxycholate
12a (ent-e, in) Y. 10%
12b (cis-2) Y. 6%


9
KI/18-crown-6
toluene/reflux
(Recovered C_{60}-Y. 21%)
(Bisadduct-Y. 30%)
13a ((^{t}C)-cis-3, in-in) Y. 13%
13b (cis-2, in-in) Y. 11%
ent-13a ((^{t}A)-cis-3)

Scheme 2

Double [4+2] cycloadditions between [60]fullerene and **6–9** were carried out in refluxing toluene in the presence of KI and 18-crown-6, from which the desired bisadducts **10–13** were obtained as isomeric mixtures in 29–42% yields (Scheme 2).[15] In order to check the isomer distribution, the isomeric mixtures of **10–13** were subjected to HPLC analysis. The results are summarized in Table 1.

Table 1. Results of HPLC Analysis[a] of Bisadducts **10**, **11**, **12**, and **13**

Bisadducts	Peak number	Retention time/min	Peak area/%	Isolated bisadducts[b] [Isolated yield/%]
10	1	79.0	4	
	2	84.8	25	
	3	89.7	25	
	4	101.0	25	
	5	107.6	6	
	6	112.4	11	
	7	127.0	4	
11	1	86.0	54	**11a** (*e*) [14%]
	2	100.5	4	
	3	105.8	22	**11c** (*trans*-4) [6%]
	4	124.8	14	**11b** (*ent*-*e*) [6%]
	5	148.5	6	
12	1	87.7	10	
	2	100.5	4	
	3	104.6	35	**12b** (*cis*-2) [6%]
	4	107.0	39	**12a** (*ent*-*e*) [10%]
	5	110.0	9	
	6	118.7	3	
13	1	84.7	57	**13a** ((†*C*)-*cis*-3) [13%]
	2	98.0	6	
	3	103.8	34	**13b** (*cis*-2) [11%]
	4	109.8	3	

[a] Conditions: stationary phase, COSMOSIL 5PBB (10 × 250 mm); eluent, *n*-hexane/toluene (3:7 (v/v)); flow rate, 1.0 mL/min; detection wavelength, 350 nm.
[b] Isolated by silica gel column chromatography.

In the HPLC analysis of **11**, **12**, and **13** bearing methyl hyodeoxycholate, methyl chenodeoxycholate, and (2*R*,3*R*)-butanediol, respectively, used as templates, 1 or 2 major peaks were observable indicating that 1 or 2 major bisadducts are formed selectively in **11–13**. The major bisadducts were easily isolated by silica gel column chromatography: Peak 1 (54%)/**11a** for **11**; Peak 3 (35%)/**12b** and Peak 4 (39%)/**12a** for **12**; Peak 1 (57%)/**13a** and Peak 3 (34%)/**13b** for **13**. In **11**, the second major isomers, Peak 3 (22%)/**11c** and Peak 4 (14%)/**11b** could be separated. On the other hand, **10** bearing methyl deoxycholate as a template consisted of several peaks, featuring nonselective product formation. The three medium peaks Peaks 2–4 in **10** could not be isolated, because more than 3 peaks overlapped with each other in the region of Peaks 2–4.[16] The results of HPLC analysis indicate that the diol templates in **7–9** can regularly arrange the two *o*-xylenyl groups in specific positions suitable to regio- and chiroselective reactions with the [6,6]junction bonds on the [60]fullerene surface.

Identification of Bisadducts.

The isolated bisadducts **11a–c**, **12a,b**, and **13a,b** were identified on the basis of the ^{1}H and ^{13}C NMR, UV/Vis, and CD spectroscopy (Table 1 and Scheme 2).

The absorption spectra of **11a–c**, **12a,b**, and **13a,b** in 400–800 nm gave the similar absorption patterns comparable with those reported in the preceding references (Fig. 1).[10,12,17,18] The characteristic absorption maxima at 665 and 738 nm for *cis*-3 isomer **13a**, at 423 nm for *e* isomers **11a**, **11b**, and **12a**, and at 644 and 708 nm for *trans*-4 isomer **11c** strongly indicate the proposed addition patterns for *cis*-3, *e*, and *trans*-4, respectively. *Cis*-2 isomers **12b** and **13b** did not show the characteristic absorption maxima in 400–800 nm, indicating the similar trend with those reported previously.[10,12,17,18]

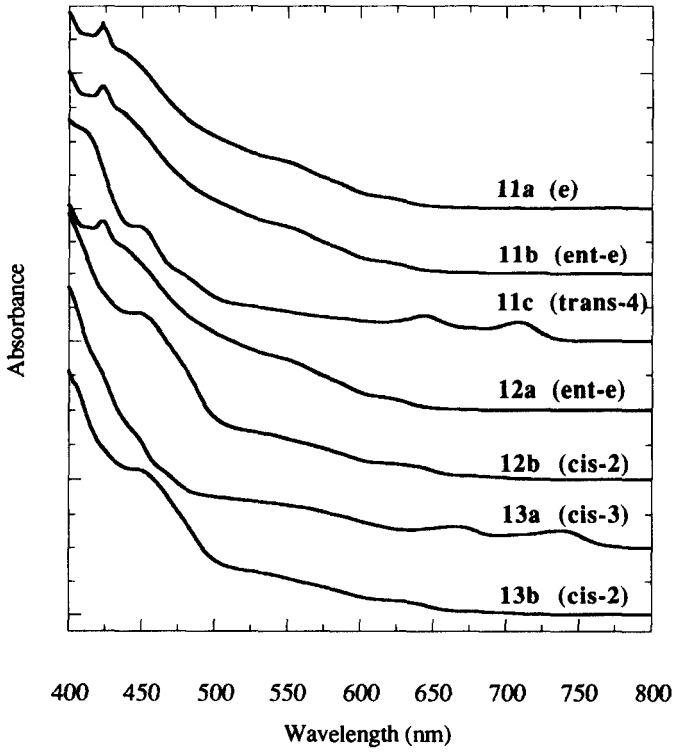


Fig. 1 Absorption spectra of **11a–c**, **12a,b**, and **13a,b** in dichloromethane.

The molecular symmetry deduced from ^{1}H and ^{13}C NMR spectra has been used for identification of fullerene–bisadducts.[17,18] As expected, the ^{1}H and ^{13}C NMR spectra of **13a,b** bearing a C_2 symmetrical template gave the C_2 symmetrical splitting pattern for **13a** and the C_1 symmetrical splitting pattern for **13b**. In contrast, the molecular symmetry deduced from the ^{1}H NMR spectra of **11a–c** and **12a,b** did not show the useful information for the assignments, because all of **11a–c** and **12a,b** gave only the C_1 symmetrical splitting pattern arising from their asymmetrical templates. The black rectangle in Scheme 2 denotes that the head-to-tail structure is not clarified in these bisadducts.

In the ^{1}H NMR spectra, the characteristic high magnetic field shift of the bridging CH_2 proton peaks in the *cis*-3 and *e* isomers and the lower magnetic field shift of the aromatic proton peaks in the *cis*-2 isomer were always observable, which were very useful signs as the criterion for the assignment.[10] An *equatorial* bridging CH_2 proton H^a in the *e* isomers **11a** (δ 3.17 ppm), **11b** (δ 3.16 ppm), and **12a** (δ 3.23 ppm) was shifted to

higher magnetic field (Δδ 0.7–1.5 ppm) compared to other bridging CH_2 protons (Scheme 2). Probably, the high magnetic field shift is due to the ring current effect of the facing benzene ring A of the H^a proton. The similar high field shift was found in an *equatorial* bridging CH_2 proton H^b (δ 3.57 ppm) in the *cis*-3 isomer **13a**, although the shift (Δδ 0.4–0.9 ppm) was smaller than those of the *e* isomers. In the preceding references of the bis(methano[1,2]benzenomethano)[60]fullerenes bearing a template moiety, we also found the high magnetic field shift of the *equatorial* bridging CH_2 protons in the *cis*-3 and *e* isomers.[10,19]

In *cis*-2 isomer **13b**, the two aromatic proton peaks H^c and $H^{c'}$ (δ 8.58 and 8.67 ppm) were shifted to lower magnetic field (Δδ 0.6–0.9 ppm) than those of other isomers (Scheme 2). This result indicates that **13b** adopts an in-in form but not in-out and out-out forms owing to the direction of the ester groups in the benzene ring, because the significant lower magnetic field shift due to the steric compression can be found only in the in-in *cis*-2 isomer as reported by Nishimura and his co-workers.[10] On the other hand, another *cis*-2 isomer **12b** did not show such a significant lower magnetic field shift for H^c and $H^{c'}$ (δ 8.21 and 8.25 ppm), suggesting the in-out form as **12bB** or the out-out form as **12bC** rather than the in-in form as **12bA** (Fig. 2). Similarly, three isomers, in-in, in-out, and out-out isomers, in *cis*-3 **13a** and *trans*-4 **11c** are available. Only the in-in isomer in the *cis*-3 and *trans*-4 could be proposed judging from the size of the diol templates in **11c** and **13a** and the splitting pattern of the ^1H NMR spectrum of **13a**.

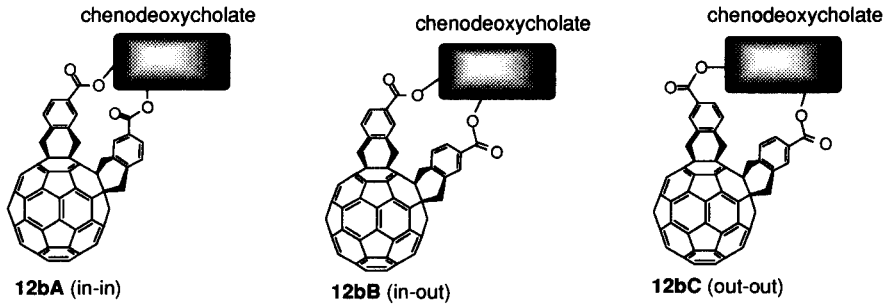


Fig. 2 Three possible structures, **12bA** (in-in), **12bB** (in-out), and **12bC** (out-out), in *cis*-2 isomer **12b**.

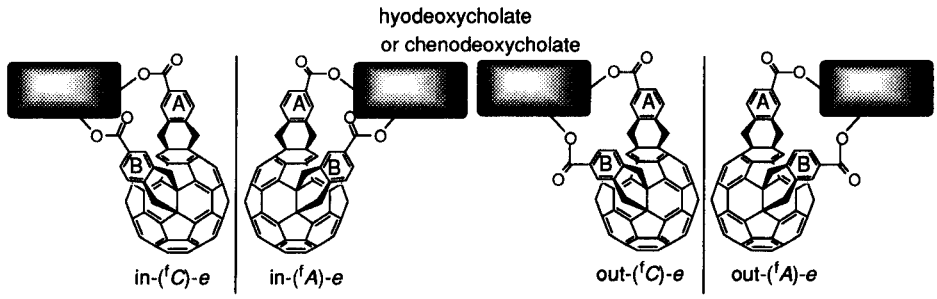


Fig. 3 Four diastereoisomers in *e* isomers **11a**, **11b**, and **12a**.

Theoretically, four diastereoisomers in-(^fC)-*e*, in-(^fA)-*e*, out-(^fC)-*e*, and out-(^fA)-*e* of *e* isomers are available in **11a**, **11b**, and **12a** owing to the direction of the ester groups in the benzene rings A and B (Fig. 3). By sterical reason, out-isomers (out-(^fC)-*e* and out-(^fA)-*e*) can be excluded and the *e* isomers isolated here are

in-isomers (in-(^{f}C)-*e* and in-(^{f}A)-*e*). As described below (see a section of CD spectra), comparison of the CD spectra among **11a**, **11b**, and **12a** indicates that *e*-isomer **11a** and *ent-e* isomers **11b** and **12a** have the opposite chirality (^{f}C) or (^{f}A) to each other. Although both of the two double additions utilizing **3** and **4** as templates occur on *e* location regioselectively, the stereochemistry in major *e* isomers **11a** and **12a** inverts depending on the position of the second OH group in the template diols **3** bearing 3,6-OH groups and **4** bearing 3,7-OH groups. The chiroselectivity was also achieved in the reaction of **9** leading to (^{f}C)-*cis*-3 isomer **13a** as a single diastereoisomer, in which the absolute configuration (^{f}C) was deduced from the CD spectrum as indicated below (see a section of CD spectra) (Scheme 2). Opposite diastereoisomer *ent*-**13a** with (^{f}A) chirality could be scarcely formed, therefore, judging from the result of the HPLC analysis (Table 1).

There are two isomers, 3,6- or 3,7-isomer and 6,3- or 7,3-isomer, in principle, owing to the orientation of the template moiety in **11a–c** with 3,6-ester groups and **12a,b** with 3,7-ester groups (Fig. 4). The bisadducts **11a–c** and **12a,b** obtained here were the single orientational isomers but not the mixtures, although the assignment in the head-to-tail orientation of the template moiety in **11a–c** and **12a,b** has not yet been attained. Thus, the three selectivities in the orientation of the template moiety as well as the addition pattern and the stereochemistry were achieved in the double cycloadditions between [60]fullerene and steroid–appended dibenzoates **7** and **8**.

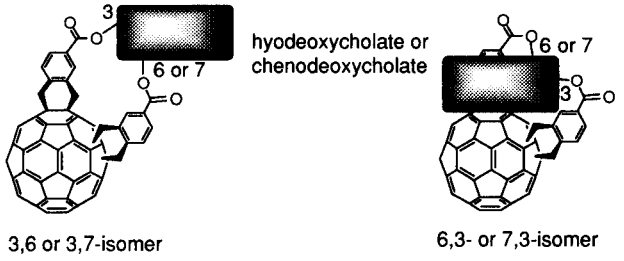


Fig. 4 Two orientational isomers 3,6- or 3,7-isomer and 6,3- or 7,3-isomer in **11a–c** with a methyl hyodeoxycholate template and in **12a,b** with a methyl chenodeoxycholate template.

CD Spectra.

Recently, chiral fullerene derivatives have attracted attention and their chiroptical properties have been studied on the basis of CD spectroscopy.[20] The [60]fullerene–bisadducts **11a–c**, **12a,b**, and **13a,b** bearing chiral templates were optically active and were distinguished into the three chiral groups, i) C_2-symmetrical (^{f}C)-*cis*-3 **13a** with a chiral addition pattern, ii) C_1-symmetrical *e* **11a**, **11b**, and **12b** with a locally symmetrical addition pattern, and iii) C_1-symmetrical *cis*-2 and *trans*-4 **11c**, **12b**, and **13b** with an achiral addition pattern.

The CD spectrum of **13a** in dichloromethane gave the pronounced *Cotton* effects ($\Delta\varepsilon$ <160) due to the chiroptical contribution of the chirally functionalized fullerene chromophore, showing the similar trend with the chirally functionalized [60]fullerene–bisadducts reported previously (Fig. 5).[5,6,8,12,19,21] The absolute configuration of **13a** can be assigned to be (^{f}C) on the basis of the sign of the *Cotton* effects.[22]

Although *e* isomers **11a**, **11b**, and **12a** were also CD-active, the $\Delta\varepsilon$ values of **11a**, **11b**, and **12a** were smaller by 1 or 2 orders of magnitude compared to those of **13a** (Figs. 5 and 6). The weak *Cotton* effects in **11a**, **11b**, and **12a** are assigned to the induced CD arising from the perturbation of the achiral fullerene chromophore by two effects: that is i) the local asymmetry based on the *e*-addition pattern,[12,19] and ii) the

chirality of the template moiety.[23] The former effect mainly contributes to the generation of the induced CD as discussed below. The CD spectra of [CD(-)421]-**11b** and [CD(-)421]-**12a** were similar in shape to each other and showed a mirror image shape compared to that of [CD(+)421]-**11a**, indicating that **11a** and **11b/12a** have the opposite chirality (^{f}C) or (^{f}A) to each other (Fig. 6). The sign of the *Cotton* effect at 421 nm, which is arising from the characteristic absorption maximum found in all *e* isomers,[17,18] can be applied to assign the absolute configurations (^{f}C)-*e* and (^{f}A)-*e* (Fig. 3).

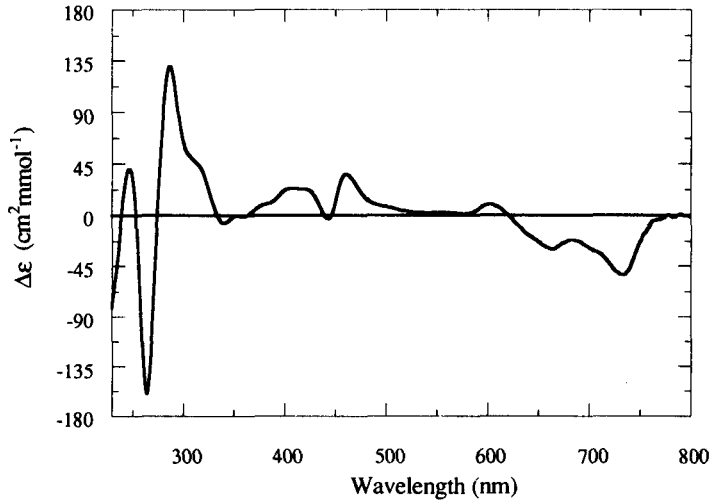


Fig. 5 CD spectrum of **13a** in dichloromethane (2×10^{-5} mol dm^{-3}, 10 mm cell).

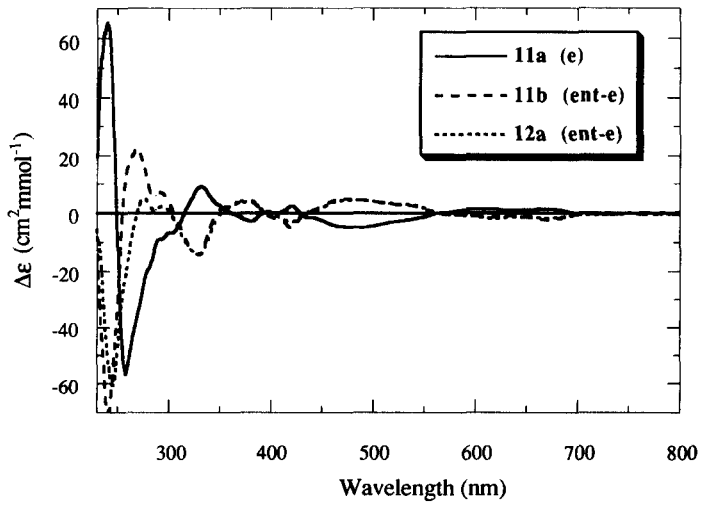


Fig. 6 CD spectra of **11a**, **11b**, and **12a** in dichloromethane (2×10^{-4} mol dm^{-3}, 1 mm cell in 230–400 nm, 10 mm cell in 400–800 nm).

The CD spectra of **11c**, **12b**, and **13b** with the achiral addition pattern were shown in Fig. 7. Although the intensities of the CD spectra in **11c** and **12b** with steroid templates were very weak ($\Delta\varepsilon$ <1.5 between 400–800 nm), the *Cotton* effects can be detected reproducibly. On the other hand, the *Cotton* effects in **13b** with a butanediol template were too weak to be detected except the range of 230–300 nm.[6]

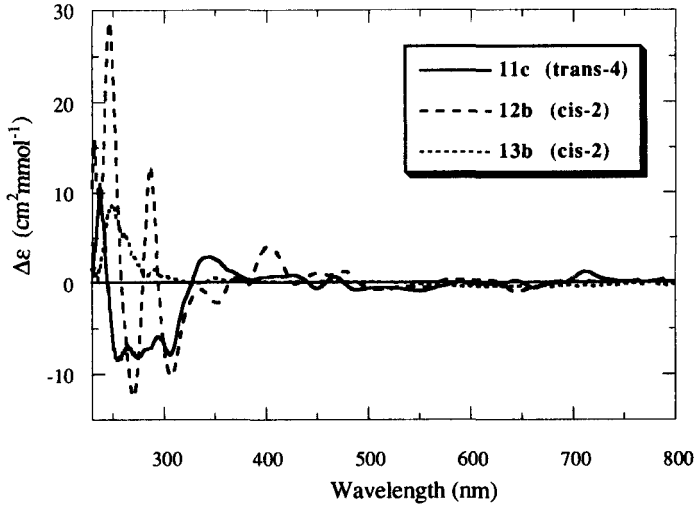


Fig. 7 CD spectra of **11c**, **12b**, and **13b** in dichloromethane (2×10^{-4} mol dm^{-3}, 1 mm cell in 230–400 nm, 10 mm cell in 400–800 nm).

The finding that the *Cotton* effects in the *e* **11a**, **11b**, and **12a** were 5–6 times stronger than those in the *trans*-4 **11c** and *cis*-2 **12b** indicates that the induced CD effects found in **11a**, **11b**, and **12a** are mainly due to the local asymmetry based on the *e*-addition pattern whereas the effect of the chiral template moiety is very weak. However, it should be emphasized that the steroid template in **11c** and **12b** can perturb the achiral [60]fullerene chromophore to generate the detectable induced CD. By comparison of the CD spectra of **13b** bearing a butanediol template with **11c**/**12b** bearing a steroid template, it becomes clear that the magnitude of the induced CD effects in the *cis*-2 and *trans*-4 isomers increases with the increase in the size and the number of chiral centers of the template moiety.[24]

CONCLUSION

In this study, we have demonstrated that diols including steroid derivatives are useful as a potential template family for regio- and chiroselective introduction of two functional groups into [60]fullerene. The addition patterns in the double additions between [60]fullerene and diol–dibenzoates faithfully reflect the diol-containing steroid structures used as template molecules. In particular, the inherent chirality of diol templates plays a decisive role in the chiroselective double additions leading to chiral [60]fullerene–bisadducts. Furthermore, when the steroidal diols are used as template molecules, the three selectivities (the addition pattern, the stereochemistry, and the orientation of the template moiety) are achieved at one time.

The [60]fullerene–bisadducts obtained here have various kinds of chiral structures whose differences are reflected by the CD spectra. The magnitude of the *Cotton* effects in the [60]fullerene–bisadducts increases in the order of *cis*-3 isomer (with the chirally functionalized fullerene chromophore) >> *e* isomer (with the local asymmetry in bis(methano[1,2]benzenomethano)[60]fullerene moiety and the very large chiral template (steroid)) > *cis*-2 and *trans*-4 isomers (with the very large chiral template (steroid)) >> *cis*-2 isomer (with only the small chiral template).

In the [60]fullerene–bisadducts with chiral steroid templates, the half hemisphere of the parent [60]fullerene is covered with the chiral template. The partially surrounded [60]fullerene structures with the chiral templates resemble the supramolecular structures of [60]fullerene found in the complexation with γ-cyclodextrin[25] and in the interaction with hydrophobic grooves of DNA.[26] Thus, it is expected that CD spectroscopic study can play an important role to elucidate the supramolecular structures of [60]fullerene and its homologues in near future. We believe that this study provides fruitful information not only on the chiral fullerene chemistry but also on the biological applications of fullerene.

EXPERIMENTAL

All melting points were uncorrected. IR spectra were recorded on a SHIMADZU FT-IR 8100M and measured as KBr pellets. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ with a BRUKER ARX300. Mass spectra (negative SIMS) were measured on a HITACHI M-2500 Mass Spectrometer. UV–vis spectra were measured on a JASCO V-570 spectrophotometer. CD spectra were measured on a JASCO J-720WI spectropolarimeter. HPLC was performed on a WATERS 600E-MSDS and detected on a WATERS 490E multiwavelength detector. The isomer distribution was determined by using COSMOSIL 5PBB column (10 × 250 mm) eluting with *n*-hexane/toluene (3:7 (v/v), 1.0 mL/min). Column chromatography was carried out on silica gel (Wako C-300). Compounds **1**[27] and **4**[28] were prepared according to methods decribed previously. [60]Fullerene (>99.5%) was purchased from Southern Chemical Group. Methyl deoxycholate (**2**) and methyl hyodeoxycholate (**3**) were purchased from SIGMA Co., Ltd. (2*R*,3*R*)-Butanediol was purchased from Aldrich Chemical Co., Inc.

Methyl 3α,12α-bis{[-3,4-bis(bromomethyl)phenyl]methanoyloxy}-5β-cholan-24-oate (6).

A mixture of **1** (308 mg, 1.0 mmol) and thionyl chloride (1.19 g, 0.73 mL, 10.0 mmol) was heated at the reflux temperature for 2 h under a nitrogen atmosphere. The formation of the aroyl chloride was check by ^{1}H NMR [$CDCl_3$, δ 4.64, 4.67 (s, each 2 H, CH_2Br), 7.54 (d, J = 8.1 Hz, 1 H, ArH), 8.06 (dd, J = 1.9, 8.1 Hz, 1 H, ArH), 8.11 (d, J = 1.9 Hz, 1 H, ArH)]. After the mixture was cooled to room temperature, the excess thionyl chloride was removed *in vacuo* to dryness. To a solution of the oily residue in dry toluene (10 mL) were added methyl deoxycholate (**2**) (163 mg, 0.4 mmol) and $KHCO_3$ (80 mg, 0.8 mmol) and the mixture was heated at the reflux temperature for 23 h under a nitrogen atmosphere. The reaction mixture was washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to dryness. The residue was purified by silica gel column chromatography eluting with dichloromethane/hexane (3:1 v/v) to give **6** in 34% yield (135 mg, 0.137 mmol) as white powder: mp 74–76 °C; IR (KBr) ν_{max} 2948, 2869, 1735 (sh, ν_{CO}), 1717 (ν_{CO}), 1277, 1215, 1184, 1107, 760, 619 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80 (d, J = 6.6 Hz, 3 H, Me), 0.82, 0.97 (s, each 3 H, Me), 1.01–2.35 (m, 26 H), 3.62 (s, 3 H, COOMe), 4.63, 4.64, 4.65, 4.68 (s, each 2 H, CH_2Br),

4.81–4.94 (m, 1 H, OCH-3), 5.37 (br-s, 1 H, OCH-12), 7.40, 7.48 (d, J = 7.9 Hz, each 1 H, ArH), 7.84, 8.00 (dd, J = 1.6, 7.9 Hz, each 1 H, ArH), 7.93, 8.07 (d, J = 1.6 Hz, each 1 H, ArH). Anal. Calcd for $C_{43}H_{54}Br_4O_6 \cdot 0.5C_6H_{14}$: C, 53.66; H, 5.97. Found: C, 53.35; H, 5.69.

Methyl 3α,6α-bis{[-3,4-bis(bromomethyl)phenyl]methanoyloxy}-5β-cholan-24-oate (7).

According to the same procedure used for the preparation of **6**, **7** was obtained from **1** (308 mg, 1.0 mmol), thionyl chloride (1.19 g, 0.73 mL, 10.0 mmol), dry toluene (10 mL), methyl hyodeoxycholate (**3**) (163 mg, 0.4 mmol), and $KHCO_3$ (80 mg, 0.8 mmol). The reaction mixture was purified by silica gel column chromatography eluting with dichloromethane/toluene (1:1 v/v) to give **7** in 29% yield (113 mg, 0.115 mmol) as white powder: mp 88–90 °C; IR (KBr) ν_{max} 2946, 2869, 1735 (sh, ν_{CO}), 1717 (ν_{CO}), 1277, 1215, 1182, 1105, 760, 617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.69, 1.08 (s, each 3 H, Me), 0.93 (d, J = 6.3 Hz, 3 H, Me), 1.04–2.43 (m, 26 H), 3.67 (s, 3 H, COOMe), 4.65, 4.66, 4.67, 4.70 (s, each 2 H, CH_2Br), 4.92–5.07 (m, 1 H, OCH-3), 5.39–5.49 (m, 1 H, OCH-6), 7.42, 7.45 (d, J = 8.0 Hz, each 1 H, ArH), 7.92, 7.99 (dd, J = 1.6, 8.0 Hz, each 1 H, ArH), 7.98, 8.05 (d, J = 1.6 Hz, each 1 H, ArH). Anal. Calcd for $C_{43}H_{54}Br_4O_6$: C, 52.35; H, 5,52. Found: C, 52.59; H, 5.58.

Methyl 3α,7α-bis{[-3,4-bis(bromomethyl)phenyl]methanoyloxy}-5β-cholan-24-oate (8).

According to the same procedure used for the preparation of **6**, **8** was obtained from **1** (4.62 g, 15.0 mmol), thionyl chloride (17.8 g, 10.9 mL, 150 mmol), dry toluene (100 mL), methyl chenodeoxycholate (**4**) (2.44 g, 6.0 mmol), and $KHCO_3$ (1.20 g, 12.0 mmol). The reaction mixture was purified by silica gel column chromatography eluting with hexane/dichloromethane (1:3 v/v) to give **8** in 22% yield (1.30 g, 1.32 mmol) as white powder: mp 80–81 °C; IR (KBr) ν_{max} 2942, 2869, 1735 (sh, ν_{CO}), 1717 (ν_{CO}), 1277, 1215, 1184, 1107, 760, 619 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.69, 1.03 (s, each 3 H, Me), 0.93 (d, J = 6.4 Hz, 3 H, Me), 0.99–2.41 (m, 26 H), 3.63 (s, 3 H, COOMe), 4.60, 4.63 (s, each 2 H, CH_2Br), 4.66 (s, 4 H, CH_2Br), 4.76–4.92 (m, 1 H, OCH-3), 5.19–5.26 (m, 1 H, OCH-7), 7.42, 7.43 (d, J = 8.0 Hz, each 1 H, ArH), 7.88, 7.95 (dd, J = 1.6, 8.0 Hz, each 1 H, ArH), 7.94, 8.04 (d, J = 1.6 Hz, each 1 H, ArH). Anal. Calcd for $C_{43}H_{54}Br_4O_6$: C, 52.35; H, 5,52. Found: C, 52.71; H, 5.62.

2,3-Bis{[-3,4-bis(bromomethyl)phenyl]methanoyloxy}-(2*R*,3*R*)-butane (9).

To a suspension of **1** (308 mg, 1.0 mmol) and (2*R*,3*R*)-butanediol (**5**) (45 mg, 0.5 mmol) in dry dichloromethane (3 mL) were added DMAP (4-(*N*,*N*-dimethylamino)pyridine) (6 mg, 0.05 mmol) and DCC (dicyclohexylcarbodiimide) (206 mg, 1.0 mmol) at 0 °C under a nitrogen atmosphere. After the mixture was stirred at room temperature for 1 h, the reaction mixture was filtered off to remove dicyclohexylurea. The filtrate was washed with 0.6 mol dm^{-3} HCl and aqueous 10 wt-% NaCl solution. The organic phase was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to dryness. The residue was purified by silica gel column chromatography eluting with hexane/toluene (1:4 v/v) to give **9** in 28% yield (92 mg, 0.137 mmol): colorless needles (dichloromethane/hexane); mp °C 121–122 °C; IR (KBr) ν_{max} 2977, 1719, 1707 (ν_{CO}), 1266, 1215, 758, 615, 558 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (d, J = 5.9 Hz, 6 H, Me), 4.63, 4.64 (s, each 4 H, CH_2Br), 5.29–5.42 (m, 2 H, OCH), 7.41 (d, J = 7.9 Hz, 2 H, ArH), 7.92 (dd, J = 1.5, 7.9 Hz, 2 H, ArH), 7.99 (d, J = 1.5 Hz, 2 H, ArH). Anal. Calcd for $C_{22}H_{22}Br_4O_4 \cdot 0.1C_6H_{14}$: C, 40.00; H, 3.48. Found: C, 40.04; H, 3.36.

General Procedure for Double Addition between [60]Fullerene and 6–9.

To a solution of [60]fullerene (72 mg, 0.1 mmol), 18-crown-6 (1.06 g, 4.0 mmol), and potassium iodide (166 mg, 1.0 mmol) in dry toluene (200 mL) was added **6–9** (0.1 mmol) under a nitrogen atmosphere. The mixture was heated at the reflux temperature for 40 h. After the reaction mixture was cooled to room temperature, it was filtered off and washed with toluene. The filtrate was evaporated *in vacuo* to dryness. The residue was suspended into aqueous 1 wt-% $NaHSO_3$ solution (50 mL) and stirred at room temperature for 30 min under a nitrogen atmosphere. The insoluble brown solid was collected by filtration and washed with water. The obtained brown solid was dissolved in toluene, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to dryness. The residue was purified by silica gel column chromatography eluting with toluene to give unreacted [60]fullerene and with toluene/ethyl acetate to give bisadducts **10–13** as isomeric mixtures. The isomeric mixtures of **11–13** were separated by silica gel column chromatography eluting with toluene/ethyl acetate to give the major isomers **11a–c**, **12a,b**, and **13a,b**.

(Methyl 3α,5β,6α-cholan-24-oate)-3,6-diyl 1,2:18,36-bis(methano[1,2]benzenomethano)-[60]fullerene-64,72-dicarboxylate (11a).

An analytical sample of **11a** was obtained as a reddish brown solid by recrystallization from dichloromethane/hexane: mp >450°C; IR (KBr) ν_{max} 2946, 2867, 1721 (ν_{CO}), 1267, 1217, 1179, 1096, 764, 527 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66, 1.05 (s, each 3 H, Me), 0.90 (d, J = 6.3 Hz, 3 H, Me), 0.90–2.40 (m, 26 H), 3.17 (d, J = 13.7 Hz, 1 H, CH_2-69-*eq*), 3.63 (s, 3 H, COOMe), 3.96–4.17 (m, 4 H, CH_2), 4.31 (d, J = 13.7 Hz, 1 H, CH_2), 4.48 (d, J = 12.9 Hz, 1 H, CH_2), 4.59 (d, J = 13.4 Hz, 1 H, CH_2), 5.10–5.26 (m, 2 H, OCH), 7.52, 7.58 (d, J = 7.8 Hz, each 1 H, ArH), 7.80, 7.97 (d, J = 1.5 Hz, each 1 H, ArH), 8.04, 8.19 (dd, J = 1.5, 7.8 Hz, each 1 H, ArH); MS (negative SIMS, NBA) m/z 1386 [(M–1)$^-$]; UV/Vis (dichloromethane) λ_{max} (ε) 423 (5603), 397 (sh, 6124), 341 (26 316), 320 (35 407), 242 (117 220) nm; CD (dichloromethane) λ_{max} (Δε) 676 (1.500), 637 (0.994), 604 (1.484), 490 (-4.775), 421 (2.543), 405 (0.220), 397 (0.564), 380 (-2.708), 331 (8.979), 258 (-56.76), 241 (65.19) nm. Anal. Calcd for $C_{103}H_{54}O_6$•0.1CH_2Cl_2: C, 88.70; H, 3.83. Found: C, 88.41; H, 4.26.

(Methyl 3α,5β,6α-cholan-24-oate)-3,6-diyl 1,2:18,36-bis(methano[1,2]benzenomethano)-[60]fullerene-64,72-dicarboxylate (11b).

An analytical sample of **11b** was obtained as a reddish brown solid by recrystallization from dichloromethane/hexane: mp >450°C; IR (KBr) ν_{max} 2946, 2865, 1721 (ν_{CO}), 1267, 1219, 1177, 1098, 764, 527 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68, 1.04 (s, each 3 H, Me), 0.81–2.50 (m, 25 H), 0.94 (d, J = 6.1 Hz, 3 H, Me), 2.68 (q, J = 12.1 Hz, 1 H, CH-4'-*ax*), 3.16 (d, J = 14.1 Hz, 1 H, CH_2-69-*eq*), 3.67 (s, 3 H, COOMe), 3.97 (d, J = 13.2 Hz, 1 H, CH_2), 4.03 (d, J = 13.2 Hz, 1 H, CH_2), 4.05 (d, J = 14.1 Hz, 1 H, CH_2), 4.10 (d, J = 13.2 Hz, 1 H, CH_2), 4.21 (d, J = 14.1 Hz, 1 H, CH_2), 4.36–4.62 (m, 3 H, CH_2 and OCH-3'), 5.40 (quint, J = 5.8 Hz, 1 H, OCH-6'), 7.50, 7.59 (d, J = 7.8 Hz, each 1 H, ArH), 7.91, 7.93 (d, J = 1.2 Hz, each 1 H, ArH), 8.01, 8.05 (dd, J = 1.2, 7.8 Hz, each 1 H, ArH); MS (negative SIMS, NBA) m/z 1386 [(M–1)$^-$]; UV/Vis (dichloromethane) λ_{max} (ε) 423 (5482), 397 (sh, 5892), 341 (25 654), 320 (37 958), 242 (120 160) nm; CD (dichloromethane) λ_{max} (Δε) 671 (-2.117), 634 (-0.726), 621 (-1.265), 473 (4.850), 421 (-5.145),

377 (4.404), 330 (-14.34), 291 (7.019), 268 (22.13) nm. Anal. Calcd for $C_{103}H_{54}O_6 \cdot 0.5CH_2Cl_2$: C, 86.93; H, 3.88. Found: C, 86.85; H, 4.26.

(Methyl 3α,5β,6α-cholan-24-oate)-3,6-diyl 1,2:34,35-bis(methano[1,2]benzenomethano)-[60]fullerene-64,72-dicarboxylate (11c).

An analytical sample of **11c** was obtained as a greenish brown solid by recrystallization from dichloromethane/hexane: mp >450°C; IR (KBr) ν_{max} 2946, 2867, 1717 (ν_{CO}), 1271, 1215, 1179, 1096, 766, 525 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68, 1.09 (s, each 3 H, Me), 0.92 (d, J = 6.3 Hz, 3 H, Me), 1.04–2.43 (m, 26 H), 3.66 (s, 3 H, COOMe), 3.94 (d, J = 12.8 Hz, 1 H, CH_2), 4.02 (d, J = 13.5 Hz, 1 H, CH_2), 4.20 (d, J = 13.5 Hz, 1 H, CH_2), 4.24 (d, J = 13.5 Hz, 1 H, CH_2), 4.45 (d, J = 12.8 Hz, 1 H, CH_2), 4.46 (d, J = 13.5 Hz, 1 H, CH_2), 4.54–4.67 (m, 1 H, OCH-3'), 4.62 (d, J = 13.5 Hz, 1 H, CH_2), 4.72 (d, J = 13.5 Hz, 1 H, CH_2), 5.27–5.39 (m, 1 H, OCH-6'), 7.51, 7.57 (d, J = 7.7 Hz, each 1 H, ArH), 7.75, 7.91 (d, J = 1.5 Hz, each 1 H, ArH), 8.04, 8.06 (dd, J = 1.5, 7.7 Hz, each 1 H, ArH); MS (negative SIMS, NBA) m/z 1387 (M^-); UV/Vis (dichloromethane) λ_{max} (ε) 708 (556), 644 (749), 450 (sh, 3439), 309 (41 180), 265 (sh, 90 100), 238 (121 400) nm; CD (dichloromethane) λ_{max} (Δε) 712 (1.143), 661 (-0.705), 643 (0.160), 626 (-0.371), 603 (-0.316), 591 (-0.045), 551 (-1.008), 517 (-0.654), 488 (-0.900), 467 (0.590), 450 (-0.739), 427 (0.772), 384 (0.246), 346 (2.834), 307 (-7.892), 295 (-5.909), 275 (-8.200), 265 (-6.833), 255 (-8.507) nm. Anal. Calcd for $C_{103}H_{54}O_6 \cdot 0.5CH_2Cl_2$: C, 86.93; H, 3.88. Found: C, 87.30; H, 4.18.

(Methyl 3α,5β,7α-cholan-24-oate)-3,7-diyl 1,2:18,36-bis(methano[1,2]benzenomethano)-[60]fullerene-64,72-dicarboxylate (12a).

An analytical sample of **12a** was obtained as a reddish brown solid by recrystallization from dichloromethane/hexane: mp >450°C; IR (KBr) ν_{max} 2930, 2867, 1735 (sh), 1717 (ν_{CO}), 1269, 1179, 1098, 764, 527 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.67, 1.06 (s, each 3 H, Me), 0.89 (d, J = 6.4 Hz, 3 H, Me), 0.96–2.42 (m, 26 H), 3.23 (d, J = 14.1 Hz, 1 H, CH_2-69-*eq*), 3.64 (s, 3 H, COOMe), 3.97 (d, J = 12.7 Hz, 1 H, CH_2), 4.01 (d, J = 12.7 Hz, 1 H, CH_2), 4.18 (d, J = 14.1 Hz, 1 H, CH_2), 4.20 (d, J = 14.1 Hz, 1 H, CH_2), 4.22 (d, J = 14.1 Hz, 1 H, CH_2), 4.56 (d, J = 12.7 Hz, 1 H, CH_2), 4.58 (d, J = 12.7 Hz, 1 H, CH_2), 4.85–4.98 (m, 1 H, OCH-3'), 5.45–5.51 (m, 1 H, OCH-7'), 7.44, 7.63 (d, J = 7.6 Hz, each 1 H, ArH), 7.68, 7.87 (d, J = 1.5 Hz, each 1 H, ArH), 7.89, 8.05 (dd, J = 1.5, 7.6 Hz, each 1 H, ArH); MS (negative SIMS, NBA) m/z 1387 (M^-); UV/Vis (dichloromethane) λ_{max} (ε) 423 (5626), 397 (sh, 6182), 323 (41 176), 242 (119 520) nm; CD (dichloromethane) λ_{max} (Δε) 670 (-1.651), 637 (-1.178), 623 (-1.716), 476 (4.495), 421 (-3.029), 379 (3.967), 329 (-14.02), 293 (2.288), 286 (0.994), 276 (5.190), 245 (-60.76) nm. Anal. Calcd for $C_{103}H_{54}O_6$: C, 89.16; H, 3.92. Found: C, 88.69; H, 4.21.

(Methyl 3α,5β,7α-cholan-24-oate)-3,7-diyl 1,2:7,21-bis(methano[1,2]benzenomethano)-[60]fullerene-dicarboxylate (12b).

An analytical sample of **12b** was obtained as a brown solid by recrystallization from dichloromethane/hexane: mp >450°C; IR (KBr) ν_{max} 2944, 2867, 1736 (sh), 1711 (ν_{CO}), 1269, 1181, 1098, 760, 527 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.74, 1.09 (s, each 3 H, Me), 0.85–2.43 (m, 25 H), 0.96 (d, J = 6.4 Hz, 3 H, Me), 2.99 (q, J = 12.3 Hz, 1 H, CH-4'-*ax*), 3.65 (s, 3 H, COOMe), 3.85 (d, J = 13.8 Hz, 1 H, CH_2), 3.97–4.09 (m, 3 H, CH_2), 4.15 (d, J = 15.0 Hz, 1 H, CH_2), 4.21 (d, J = 13.8 Hz, 1 H, CH_2), 4.63 (d, J =

13.8 Hz, 1 H, CH_2), 4.82 (d, J = 15.0 Hz, 1 H, CH_2), 4.84–4.97 (m, 1 H, OCH-3'), 5.23–5.28 (m, 1 H, OCH-7'), 7.42, 8.17 (d, J = 7.8 Hz, each 1 H, ArH), 8.09, 8.56 (dd, J = 1.2, 7.8 Hz, each 1 H, ArH), 8.21, 8.25 (d, J = 1.2 Hz, each 1 H, ArH); MS (negative SIMS, NBA) m/z 1387 (M^-); UV/Vis (dichloromethane) λ_{max} (ε) 450 (sh, 4813), 249 (101 440), 233 (106 460) nm; CD (dichloromethane) λ_{max} ($\Delta\varepsilon$) 644 (-1.151), 579 (0.310), 555 (-0.658), 536 (-0.489), 519 (-0.870), 478 (1.153), 462 (0.777), 451 (0.963), 429 (-0.225), 402 (4.009), 381 (-0.512), 371 (0.445), 353 (-2.340), 337 (-0.845), 308 (-10.28), 287 (12.85), 270 (-12.56), 248 (28.76), 238 (8.274), 233 (15.66) nm. Anal. Calcd for $C_{103}H_{54}O_6$: C, 89.16; H, 3.92. Found: C, 88.83; H, 4.16.

(2*R*,3*R*)-Butane-2,3-diyl (^{f}C)-1,2:16,17-bis(methano[1,2]benzenomethano)[60]fullerene-65,73-dicarboxylate (13a).

An analytical sample of **13a** was obtained as a dark brown solid by recrystallization from dichloromethane/hexane: mp >450°C; IR (KBr) ν_{max} 1717 (ν_{CO}), 1310, 1281, 1267, 1218, 1096, 758, 527 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57 (d, J = 5.4 Hz, 6 H, Me), 3.57 (d, J = 14.1 Hz, 2 H, CH_2-68,76-*eq*), 3.97 (d, J = 14.1 Hz, 2 H, CH_2), 4.13, 4.50 (d, J = 13.9 Hz, each 2 H, CH_2), 5.36–5.45 (m, 2 H, OCH), 7.50 (d, J = 7.7 Hz, 2 H, ArH), 7.70 (d, J = 1.1 Hz, 2 H, ArH), 8.24 (dd, J = 1.1, 7.7 Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$) δ 17.70 (CH_3), 41.72, 45.68 (CH_2), 59.96, 64.15 (C), 73.32 (CH), 127.54, 127.66 (CH), 128.49, 129.48 (C), 130.50 (CH), 131.76, 135.13, 136.71, 137.37, 138.56, 140.08, 141.59, 141.80, 141.87, 142.02, 142.04, 144.03, 144.25, 144.74, 145.05, 145.07, 145.18, 145.98, 146.21, 146.25, 146.58, 147.65, 148.11, 148.34, 148.62, 149.14, 149.54, 151.23, 152.91 (C), 167.06 (CO); MS (negative SIMS, NBA) m/z 1070 [(M-1)$^-$]; UV/Vis (dichloromethane) λ_{max} (ε) 738 (526), 665 (647), 395 (sh, 7809), 261 (105 350), 232 (105 810) nm; CD (dichloromethane) λ_{max} ($\Delta\varepsilon$) 735 (-53.01), 683 (-21.51), 664 (-30.31), 601 (9.534), 578 (1.567), 461 (35.46), 443 (-3.061), 407 (23.30), 340 (-7.021), 287 (129.8), 265 (-160.2), 247 (40.23) nm. Anal. Calcd for $C_{82}H_{22}O_4$: C, 91.95; H, 2.07. Found: C, 92.16; H, 1.99.

(2*R*,3*R*)-Butane-2,3-diyl 1,2:7,21-bis(methano[1,2]benzenomethano)[60]fullerene-64,72-dicarboxylate (13b).

An analytical sample of **13b** was obtained as a brown solid by recrystallization from dichloromethane/hexane: mp >450°C; IR (KBr) ν_{max} 1721 (ν_{CO}), 1279, 1096, 760, 527 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65, 1.69 (d, J = 6.6 Hz, each 3 H, Me), 3.94, 3.97, 4.15, 4.16, 4.81, 4.83 (d, J = 14.4 Hz, each 1 H, CH_2), 4.06 (d, J = 14.4 Hz, 2 H, CH_2), 4.96, 5.69 (dq, J = 3.6, 6.6 Hz, each 1 H, OCH), 7.52, 7.54 (d, J = 7.7 Hz, each 1 H, ArH), 8.10, 8.19 (dd, J = 1.1, 7.7 Hz, each 1 H, ArH), 8.58, 8.67 (d, J = 1.1 Hz, each 1 H, ArH); ^{13}C NMR ($CDCl_3$) δ 18.19, 18.47 (CH_3), 43.03, 43.35, 45.07, 45.17 (CH_2), 62.30, 62.41, 62.65, 62.82 (C), 71.98, 76.16 (CH), 127.50, 127.63, 128.20, 129.00, 129.45 (CH), 129.67 (C), 129.87 (CH), 130.50, 131.05, 132.82, 133.14, 133.49, 137.61, 137.70, 137.84, 138.54, 138.61, 141.21, 141.28, 141.29, 141.39, 141.52, 141.54, 142.72, 142.75, 142.82, 143.02, 143.05, 143.84, 143.92, 144.07, 144.42, 144.45, 144.49, 144.54, 144.57, 144.63, 144.80, 145.00, 145.03, 145.20, 145.23, 145.36, 145.65, 145.67, 145.69, 146.09, 146.42, 146.96, 147.03, 147.17, 147.28, 147.39, 147.41, 147.62, 149.04, 149.37, 149.69, 153.68, 155.29, 158.88, 158.92, 158.95, 160.14, 160.24 (C), 165.67, 165.89 (CO); MS (negative SIMS, NBA) m/z 1070 [(M-1)$^-$]; UV/Vis (dichloromethane) λ_{max} (ε) 450 (sh, 4262), 405 (sh, 6700), 254 (99 465),

231 (101 070) nm; CD (dichloromethane) λ_{max} ($\Delta\varepsilon$) 289 (1.47), 283 (0.686), 249 (8.52), 235 (0.135) nm. Anal. Calcd for $C_{82}H_{22}O_4$: C, 91.95; H, 2.07. Found: C, 91.83; H, 2.30.

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15. The ^{1}H NMR and mass spectra of the isomeric mixtures of **10**–**13** indicated that **11**–**13** were mostly composed of the closed bisadducts whereas **10** contained small amount of the open mono- and bisadducts. The ^{1}H NMR spectra of **10**–**13** afforded the sharp peaks in the region of the bridging CH_2 protons, indicating that the mixtures of **10**–**13** consist of the closed bisadducts. If the mixtures **10**–**13** contained the opened mono-, bis-, and polyadducts, these ^{1}H NMR spectra should be broadened due to the slow slipping motion around the cyclohexene rings in the open adducts. In the mass spectra of **11**–**13**, the parent ion peaks for the open adducts were scarcely observed. In contrast, the mass spectrum of **10** afforded the parent ion peaks in the region of the open mono- and bisadducts, although the intensities of the peaks were relatively weak. The foregoing findings imply that the cyclic bisadduct of **10** is less stable than those of **11**–**13**.

16. The nonselective cycloaddition between [60]fullerene and **6** was also supported by the ^{1}H NMR spectrum of **10**, which gave the 6–7 proton peaks with same intensity for the COOMe group indicating the formation of the 6–7 isomers of **10**.
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22. Recently, Harada and Diederich's group assigned the absolute configurations of chiral fullerene derivatives based on the comparison between the theoretical and the experimental CD spectra: Goto, H.; Harada, N.; Crassous, J.; Diederich, F. *J. Chem. Soc. Perkin Trans. 2*, **1998**, 1719–1723. For example, a chiral *cis*-3 isomer of [60]fullerene–bisadduct with the plus sign of a band around 490 nm can be identified to be (^{f}*C*)-configuration. The CD spectrum of **13a** obtained here was very similar to this typical (^{f}*C*)-pattern.
23. The Cotton effects due to induced CD were found in some [60]fullerene derivatives having a chiral substituent. For example: a) Bianco, A.; Maggini, M.; Scorrano, G.; Toniolo, C.; Marconi, G.; Villani, C.; Prato, M. *J. Am. Chem. Soc.*, **1996**, *118*, 4072–4080. b) Wilson, S. R.; Lu, Q.; Cao, J.; Wu, Y.; Welch, C. J.; Schuster, D. I. *Tetrahedron*, **1996**, *52*, 5131–5142.
24. Recently, Diederich and his co-workers reported that the *Cotton* effects in *cis*-2 [60]fullerene–bisadducts with a chiral template were too weak to be detected (see ref. 6). It was concluded that the chiral template in the *cis*-2 bisadducts is too far from the achiral fullerene chromophore to generate the induced CD. The *cis*-2 bisadducts had only two chiral centers in the template part, however, the contribution of the number of the chiral centers was not discussed.
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