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Resolution of inherently chiral *anti*-*O*,*O*′-dialkylated calix[4]arenes and determination of their absolute stereochemistries by CD and X-ray methods

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Abstract—Inherently chiral *anti*-*O*,*O*′-dibenzyl-*p*-*tert*-butylcalix[4]arene **1** was resolved as the (*S*)-2-methoxy-2-(naphthalen-1-yl)propionic ester by flash chromatography. Conversely, the *anti*-*O*,*O*′-dibutyl analogue **2** was resolved as the (S_a)-2′-methoxy-1,1′-binaphthalene-2-carboxylic ester by crystallization combined with flash chromatography. CD analysis of these compounds indicated the absolute stereochemistries to be (S_a)-(+)-**1** and (S_a)-(+)-**2**, respectively, the former of which was confirmed by X-ray crystallographic analysis.

1. Introduction

Over the past decade, there has been increasing interest in the development of chiral host molecules having a calixarene skeleton.[1] A variety of chiral calixarenes have been prepared by introducing chiral substituents at the lower rim through the phenolic oxygens or at the *para* positions, and applied to chromogenic receptors,[2] additives in capillary electrophoresis,[3] chiral stationary phases for GC and HPLC,[4] chiral solvating agents for NMR,[5] and so on.[6] On the other hand, although considerable efforts have been paid to the preparation of inherently chiral calixarenes,[1] only a small number of this type of compound have so far been resolved by using chiral HPLC[7] or other methods,[8–10] which hinders their applications to chiral receptors.[10,11] In addition, few reports have dealt with the absolute configurations of the inherently chiral calixarenes.[9–11] We have recently reported an efficient method for a net proximal dialkylation of calix[4]arenes at the lower rim via the dialkylation of readily available *O*,*O*′-disiloxane-1,3-diyl-bridged calix[4]arenes and subsequent desilylation,[12] which provides easy access to inherently chiral *anti*-*O*,*O*′-dialkylated calix[4]arenes. Herein, we report the resolution of *anti*-*O*,*O*′-dialkylated calix[4]arenes **1** and **2** prepared by this method[13] and the determination of their absolute stereochemistries by X-ray crystallographic analysis and the CD exciton chirality method.[14]

2. Results and discussion

2.1. Resolution of *anti*-*O*,*O*′-dialkylated calix[4]arenes 1 and 2

The resolution of *anti*-*O*,*O*′-dibenzyl ether **1**[12] could be achieved by flash column chromatography after conversion into diastereomeric esters **3** (Scheme 1). Thus, treatment of dibenzyl ether **1** with (*S*)-2-methoxy-2-(naphthalen-1-yl)propionic acid [(*S*)-MNPA][15] in dichloromethane in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) gave a mixture of four possible diastereomeric monoesters **3a**–**d** as shown by HPLC analysis (Fig. 1). The mixture was separated by flash chromatography on silica gel with hexane–diethyl

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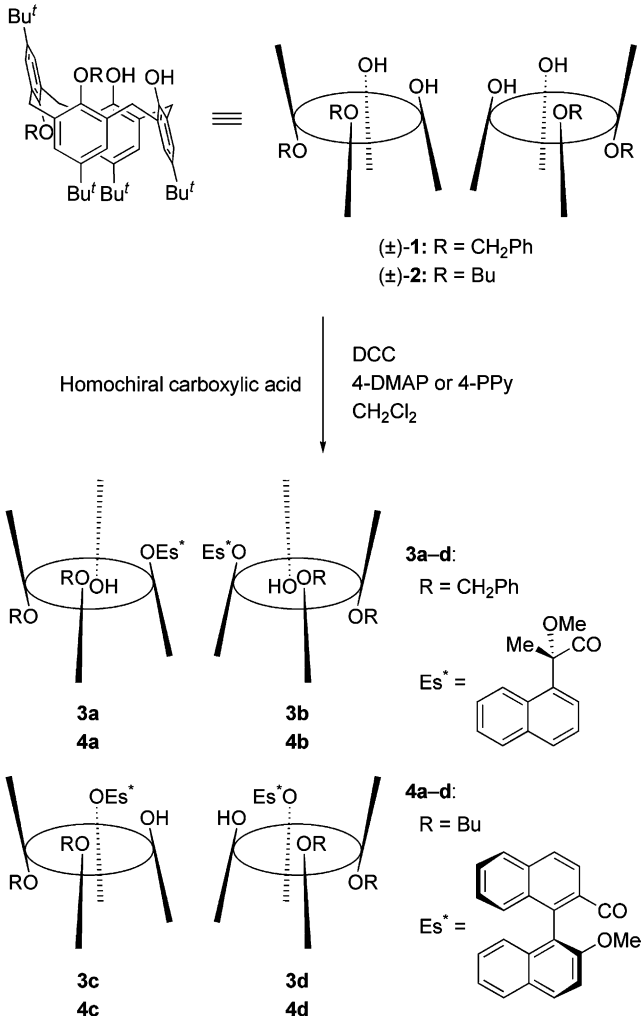

Scheme 1.

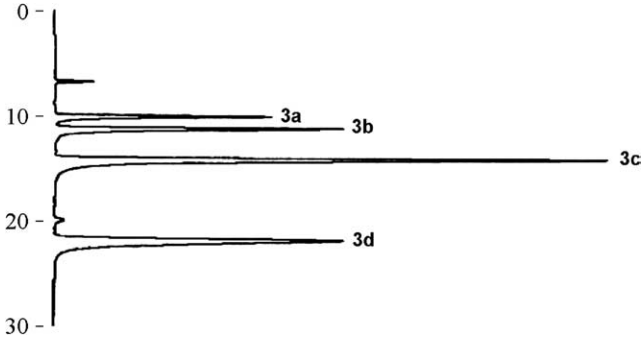

Figure 1. HPLC analysis of a mixture of diastereomeric esters **3a**–**d**. Column: Mightysil Si 60 (4.6 × 250 mm, Kanto Chemical Co., Inc.); eluent: hexane–ether (95:5); flow rate: 1 mL min^{-1}.

ether (19:1) as an eluent. The first-eluted fraction gave a mixture of **3a** and **3b**, while the second and third fractions gave **3c** and **3d** as pure substances in 38% and 29% yields, respectively. The mixture was reloaded on a silica gel column and eluted with hexane–dichloromethane (1:1) to give **3a** and **3b** in 9% and 13% yields, respectively.

It has been reported that the conformation of calix[4]-arenes can be deduced from the ^{13}C NMR chemical shifts of the methylene signals.[16] Thus, the methylene carbon between two adjacent phenol units of *syn* conformation, which is abbreviated hereafter as a *syn*-methylene carbon, resonates at δ 30–32 ppm, whereas that between the units of *anti* conformation (an *anti*-methylene carbon) at δ 37–39 ppm. All the diastereomeric esters **3a**–**d** showed two signals at each magnetic field (δ 28.9–33.3 and 38.5–39.6 ppm) for the bridging methylene carbons, indicating that they adopted a partial cone or 1,2-alternate conformation. In the ROESY spectra[17] of compounds **3a** and **3b**, one aromatic proton of each phenol unit was correlated with a *syn*-methylene proton (C^1–H or C^3–H), while another aryl proton of the same phenol unit with an *anti*-methylene proton (C^2–H or C^4–H), which corresponds to the *syn–anti–syn–anti* arrangement of the four methylene groups (Fig. 2a). Thus, the conformations of **3a** and **3b** were established to be 1,2-alternate. On the other hand, the ROESY spectra of compounds **3c** and **3d** revealed the presence of phenol units between *syn*- and *anti*- (A or C ring), *anti*- and *anti*- (B ring), *anti*- and *syn*- (A or C ring), and *syn*- and *syn*-methylene groups (D ring), indicating the *syn–anti–anti–syn* arrangement of the four methylene groups, which assigned the conformations of **3c** and **3d** to partial cone (Fig. 2b).

Transesterification of compounds **3a** and **3c** with sodium methoxide, followed by hydrolysis of the resulting methyl esters, gave enantiopure diether (+)-**1** in almost quantitative yields, while the same treatment of **3b** and **3d** gave the (−)-counterpart. As mentioned below, the absolute configuration of compound **3c** was determined to be S_a by X-ray crystallographic analysis, which, combined with the observations so far mentioned, allowed the assignment of the absolute configurations of **3a**, **3b**, and **3d** as shown in Scheme 1.

An attempted resolution of *anti*-*O*,*O*′-dibutyl ether **2**[12] by employing the same procedure as used for compound **1** failed because of the low efficiency of the chromatographic separation of the diastereomeric esters. We then turned our attention to 2′-methoxy-1,1′-binaphthalene-2-carboxylic acid,[18] which has been shown to be a useful chiral derivatizing agent for the discrimination of chiral alcohols and amines.[19] Esterification of racemic **2** with (S_a)-2′-methoxy-1,1′-binaphthalene-2-carboxylic acid with the aid of DCC gave a mixture of four possible diastereomeric monoesters **4a**–**d** as shown by an HPLC analysis (Scheme 1, Fig. 3). Crystallization of the mixture from diethyl ether–hexane gave a colorless powder, which was further purified by flash chromatography on silica gel eluting with hexane–diethyl ether (19:1) to give **4a** and **4b** in 15% and 9% yields, respectively. HPLC analysis of the samples showed that **4a** and **4b** corresponded to the fourth- and first-eluted components, respectively. On the other hand, the mother liquor was evaporated to leave a residue, which was crystallized from 2-propanol to give the second-eluted component **4c** in 27% yield. As in the case of compounds **3a**–**d**, detailed NMR analysis of these compounds revealed that **4a** and **4b** adopted a 1,2-alternate conformation, while

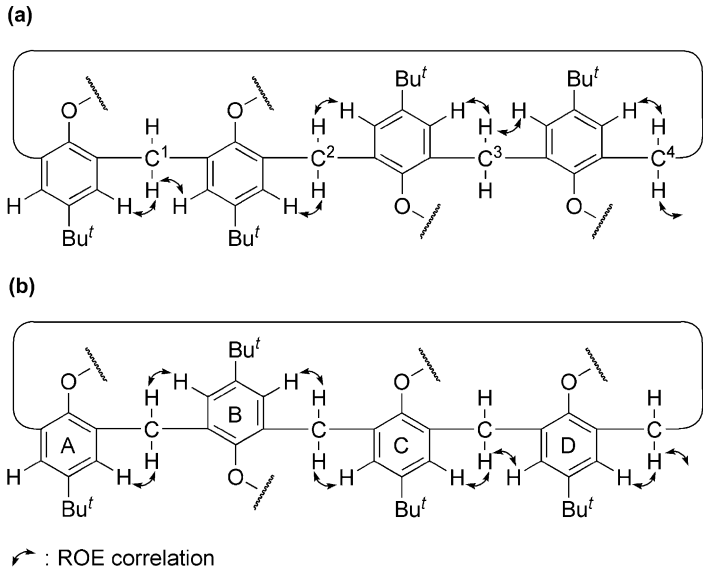

Figure 2. ROE correlations observed in the ROESY spectra of esters **3a** and **3b** (a) and **3c** and **3d** (b).

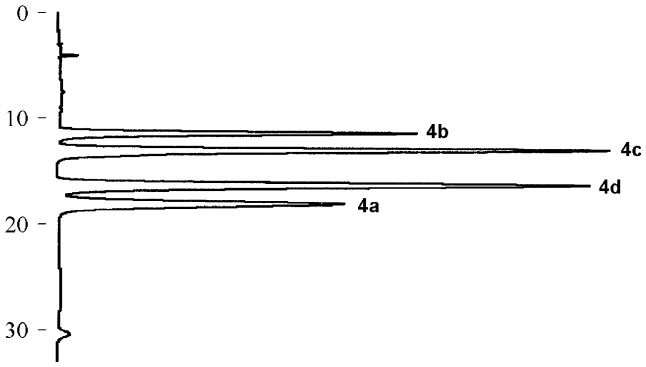

Figure 3. HPLC analysis of a mixture of diastereomeric esters **4a**–**d**. Column: Mightysil Si 60 (4.6 × 250 mm, Kanto Chemical Co., Inc.); eluent: cyclohexane–diethyl ether (95:5); flow rate: 1 mL min^{-1}.

4c adopted a partial-cone conformation. Hydrolysis of **4a** and **4c** gave (+)-**2**, while that of **4b** gave the (−)-counterpart. These observations, combined with the assignment of the absolute stereochemistry of (+)-**2** to S_a by the CD exciton chirality method (vide infra), determined the absolute configurations of compounds **4a**, **4b**, and **4c** as shown in Scheme 1. The evaporation residue of the mother liquid of the second crystallization contained another ester as a main component, which was adequately assigned to ester **4d** by ^{1}H and ^{13}C NMR analyses of the crude mixture. However, it could not be isolated by recrystallization or flash chromatography.

2.2. Determination of the absolute configurations of compounds 1 and 2 by X-ray and CD methods

Crystallization of ester **3c** from hexane gave colorless plates, one of which was subjected to X-ray crystallographic analysis (Fig. 4). The compound was found to adopt a partial-cone conformation similar to that in the solution (vide supra). The axial chirality of the *anti*-*O*,*O*′-dialkylated calix[4]arenes can be defined by the spatial arrangement of four aromatic carbons at

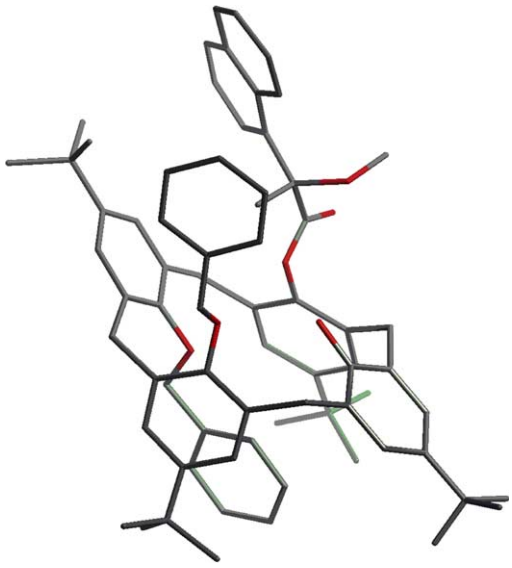

Figure 4. X-ray structure of diastereomeric ester **3c**.

the *ortho* positions to the methylene bridge between the two etherified phenol units. The absolute stereochemistry of **3c** was determined to be S_a by using the (*S*)-MNPA moiety as an internal reference. Thus, the S_a absolute configuration of dibenzyl ether (+)-**1** was established.

We next carried out the CD analysis of dibenzyl ether **1** (Fig. 5).[20] The CD spectra of (+)- and (−)-**1** are mirror images of each other and showed an exciton split CD pattern at the UV band of ~230 nm, which was assigned to the $^{1}L_a$ transition of the four phenol units with a long axis polarization. We reported that the *anti*-*O*,*O*′-dialkylated calix[4]arenes rapidly interconvert between two partial-cone conformations in the solution via the oxygen-through-the-annulus rotation.[12,21] Therefore, it is easily conceivable that the CD signals originating from the disposition of the free phenol units, are

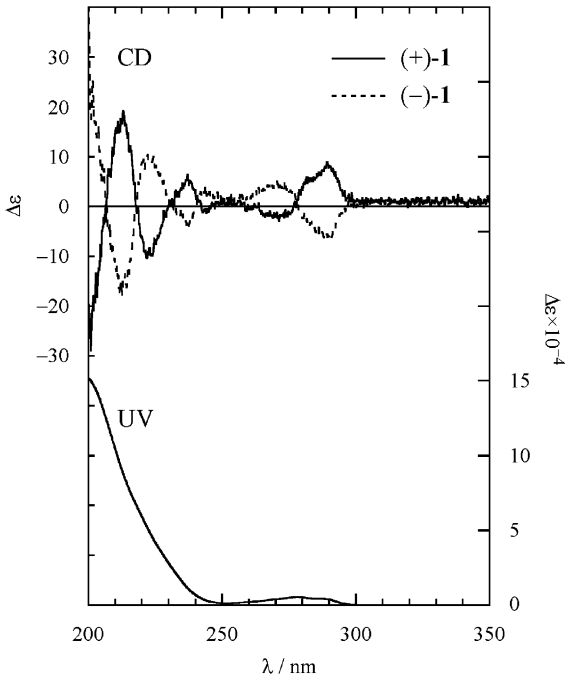

Figure 5. CD and UV spectra of dibenzyl ethers (+)- and (−)-**1** in ethanol at 25 °C. Concn: (+)-**1**, 0.101 mM; (−)-**1**, 0.103 mM.

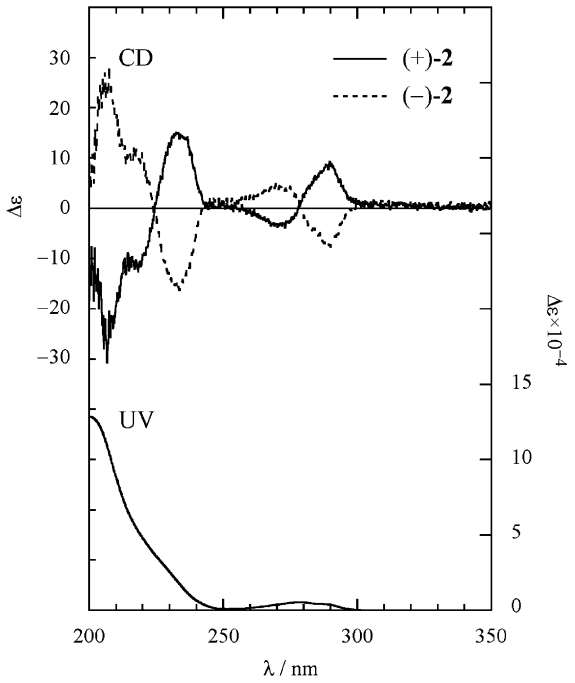

Figure 6. CD and UV spectra of dibutyl ethers (+)- and (−)-**2** in ethanol at 25 °C. Concn: (+)-**2**, 0.133 mM; (−)-**2**, 0.134 mM.

cancelled by the equilibrium and that the observed Cotton effects are due to the exciton interaction between the two etherified benzene chromophores of a fixed conformation. The CD spectrum of (+)-**1** showed the positive first and the negative second Cotton effects at the ^1L_a absorption band, indicating that the two long axes of the etherified phenol units twisted clockwise. This unambiguously established the absolute stereochemistry of (+)-**1** to be S_a, which coincided with the assignment by the X-ray analysis (vide supra).

The CD exciton chirality method could be advantageously utilized for the determination of the absolute stereochemistry of dibutyl ether **2** (Fig. 6). As in the case of (+)-**1**, the CD spectrum of (+)-**2** showed the positive first and the negative second Cotton effects at the ^1L_a absorption band, indicating that the two long axes of the etherified phenol units twisted clockwise. Thus, the absolute configuration of (+)-**2** was assigned to S_a.

3. Conclusion

Inherently chiral *anti-O,O′*-dibenzyl- **1** and *anti-O,O′*-dibutyl-*p-tert*-butylcalix[4]arene **2** were resolved by diastereomer formation methods. Their absolute configurations were determined to be (S_a)-(+)-**1** and (S_a)-(+)-**2** by CD and X-ray analyses.

4. Experimental

4.1. General

Melting points were taken using a Yamato IA-9000 apparatus. Microanalyses were carried out in the Microanalytical Laboratory of the Institute of Multidisciplinary Research for Advanced Materials, Tohoku University. Optical rotations were measured on a JASCO DIP-1000 polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a JEOL JIR-3510 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400, DRX-500 or JEOL JNM-ECA300 spectrometer using tetramethylsilane (^{1}H NMR) or chloroform (^{13}C NMR) as an internal standard and $CDCl_3$ as a solvent. *J*-Values are given in hertz. Open columns and flash columns were prepared by use of Kanto Kagaku silica gel 60 (spherical, 63–210 μm) and silica gel 60 N (spherical, neutral, 40–50 μm), respectively. Dichloromethane and THF were distilled from calcium hydride and sodium diphenylketyl, respectively. Compounds **1** and **2** were prepared as described previously.[12] Other materials were used as purchased.

4.2. Resolution of *anti-O,O′*-dibenzyl ether 1

4.2.1. Esterification of ether 1 to diastereomeric monoesters 3a–d. To an ice-cold solution of *anti-O,O′*-dibenzyl ether **1** (414 mg, 501 μmol) in dichloromethane (5 mL) were added (*S*)-MNPA (172 mg, 747 μmol), 4-(dimethylamino)pyridine (4-DMAP) (245 mg, 1.84 mmol), and DCC (1.03 g, 5.01 mmol) under nitrogen. After stirring at room temperature for 24 h, the mixture was cooled to 0 °C and quenched with 2 M HCl. The mixture was extracted with dichloromethane and the extract washed with water, dried over $MgSO_4$, and evaporated. The residue was passed through a silica gel column with hexane–diethyl ether (1:4) as an eluent to give a mixture of diastereomeric monoesters, which was resolved into a mixture of **3a** and **3b**, diastereomerically pure **3c** (196 mg, 38%) and **3d** (153 mg, 29%) by flash column

chromatography on silica gel with hexane–diethyl ether (19:1) as an eluent. The mixture was then separated by flash column chromatography with hexane–dichloromethane (1:1) as an eluent to give **3a** (44 mg, 9%) and **3b** (70 mg, 13%). Ester **3a**: as a colorless powder, mp 218.9–220.9 °C (decomp.) (dichloromethane–methanol) (Found: C, 83.01; H, 7.94. Calcd for $C_{72}H_{80}O_6$: C, 83.04; H, 7.74%); $[\alpha]_D^{29} = -111.6$ (*c* 1.09, chloroform); δ_H (500 MHz) 0.75 (3H, s, CH_3), 0.80 [9H, s, $C(CH_3)_3$], 1.14 [9H, s, $C(CH_3)_3$], 1.24 [9H, s, $C(CH_3)_3$], 1.36 [9H, s, $C(CH_3)_3$], 2.98 (3H, s, OCH_3), 3.15 (1H, d, *J* 13.8, $ArCH_2Ar$), 3.30 (1H, d, *J* 14.0, $ArCH_2Ar$), 3.44 (1H, d, *J* 16.4, $ArCH_2$ Ar), 3.50 (1H, d, *J* 13.8, $ArCH_2Ar$), 3.68 (1H, d, *J* 16.4, $ArCH_2Ar$), 3.74–3.82 (2H, m, $ArCH_2Ar$), 4.11 (1H, d, *J* 13.0, $ArCH_2Ar$), 4.29 (1H, d, *J* 11.7, OCH_2Ph), 4.51 (1H, d, *J* 11.9, OCH_2Ph), 4.80 (1H, d, *J* 11.7, OCH_2Ph), 4.97 (1H, d, *J* 11.9, OCH_2Ph), 6.32 (1H, s, OH), 6.52 (1H, d, *J* 2.2, ArH), 6.54 (2H, d, *J* 7.3, OCH_2Ph), 6.84 (1H, d, *J* 2.3, ArH), 6.87 (1H, d, *J* 2.4, ArH), 6.90 (1H, d, *J* 2.3, ArH), 6.93 (2H, d, *J* 7.2, OCH_2Ph), 7.00–7.03 (3H, m, OCH_2Ph, ArH), 7.06 (1H, d, *J* 2.3, ArH), 7.10 (1H, t, *J* 7.4, OCH_2Ph), 7.15 (2H, t, *J* 7.5, OCH_2Ph), 7.22 (1H, d, *J* 6.8, Nap), 7.26 (1H, t, *J* 7.5, OCH_2Ph), 7.36–7.43 (5H, m, Nap, ArH), 7.75 (1H, d, *J* 8.1, Nap), 7.78–7.81 (1H, m, Nap), and 8.53–8.55 (1H, m, Nap); δ_C (75 MHz) 22.61, 29.95, 31.01, 31.19, 31.33, 31.42, 31.65, 31.91, 33.33, 33.99, 34.11, 34.26, 38.49, 39.31, 52.68, 74.19, 75.01, 85.03, 124.59, 124.63, 124.69, 125.00, 125.09, 125.20, 125.31, 125.38, 125.73, 126.07, 126.85, 126.16, 126.98, 127.47, 127.53, 127.59, 127.77, 128.09, 128.71, 129.11, 129.59, 131.41, 132.34, 132.71, 133.07, 133.16, 133.25, 134.21, 134.42, 135.37, 135.89, 137.48, 141.29, 144.71, 145.38, 146.78, 147.36, 150.63, 150.76, 152.64, and 170.51. Ester **3b**: as a colorless powder, mp 201.9–203.0 °C (dichloromethane–methanol) (Found: C, 83.05; H, 7.87. Calcd for $C_{72}H_{80}O_6$: C, 83.04; H, 7.74%); $[\alpha]_D^{29} = +87.2$ (*c* 1.06, chloroform); δ_H (500 MHz) 0.84 (3H, s, CH_3), 1.07 [9H, s, $C(CH_3)_3$], 1.15 [9H, s, $C(CH_3)_3$], 1.32 [9H, s, $C(CH_3)_3$], 1.36 [9H, s, $C(CH_3)_3$], 3.00 (1H, d, *J* 11.6, $ArCH_2Ar$), 3.01 (3H, s, OCH_3), 3.12–3.15 (2H, m, $ArCH_2Ar$), 3.41–3.51 (3H, m, $ArCH_2Ar$, OCH_2Ph), 3.80 (1H, d, *J* 12.9, $ArCH_2Ar$), 3.87 (1H, d, *J* 12.1, OCH_2Ph), 3.92 (1H, d, *J* 16.7, $ArCH_2Ar$), 4.03 (1H, d, *J* 16.8, $ArCH_2Ar$), 4.30 (1H, d, *J* 11.8, OCH_2Ph), 4.62 (1H, d, *J* 11.8, OCH_2Ph), 6.21 (2H, d, *J* 7.5, OCH_2Ph), 6.39–6.41 (3H, m, OH, ArH), 7.00–7.15 (8H, m, OCH_2Ph, ArH, Nap), 7.22 (1H, t, *J* 7.6, Nap), 7.29–7.32 (2H, m, ArH), 7.42–7.46 (2H, m, Nap), 7.64 (1H, d, *J* 8.1, Nap), 7.72–7.74 (1H, m, Nap), 8.48–8.50 (1H, m, Nap); δ_C (75 MHz) 22.51, 28.93, 31.28, 31.35, 31.47, 31.63, 32.15, 33.87, 33.89, 33.96, 34.21, 39.13, 39.41, 52.66, 74.47, 75.08, 84.25, 124.41, 124.70, 124.94, 125.03, 125.31, 125.43, 125.48, 126.03, 126.22, 126.27, 126.44, 126.52, 126.56, 126.84, 127.10, 127.46, 127.50, 127.69, 128.14, 128.18, 128.63, 129.32, 131.45, 131.70, 132.58, 132.68, 133.09, 133.72, 133.86, 134.33, 135.42, 135.77, 137.20, 141.68, 144.05, 145.22, 146.58, 147.06, 150.52, 150.85, 153.05, 171.89. Ester **3c**: as a colorless powder, mp 164.5–166.3 °C (hexane) (Found: C, 83.10; H, 7.80. Calcd for $C_{72}H_{80}O_6$: C, 83.04; H, 7.74%); $[\alpha]_D^{29} = -8.5$ (*c* 1.04, chloroform); δ_H (500 MHz) 0.66 [9H, s, $C(CH_3)_3$], 0.76 [9H, s, $C(CH_3)_3$], 0.85 [9H, s, $C(CH_3)_3$], 1.38 [9H, s, $C(CH_3)_3$], 1.58 (3H, s, CH_3), 3.20 (1H, d, *J* 13.7, $ArCH_2Ar$), 3.27 (3H, s, OCH_3), 3.32 (1H, d, *J* 12.8, $ArCH_2Ar$), 3.74 (1H, d, *J* 13.7, $ArCH_2Ar$), 3.86–3.90 (2H, m, $ArCH_2Ar$), 3.95 (1H, d, *J* 17.0, $ArCH_2Ar$), 4.03 (1H, d, *J* 16.3, $ArCH_2Ar$), 4.09 (1H, d, *J* 12.5, OCH_2Ph), 4.17 (1H, d, *J* 12.7, $ArCH_2Ar$), 4.24 (1H, d, *J* 12.4, OCH_2Ph), 4.63 (1H, d, *J* 11.1, OCH_2Ph), 4.80 (1H, d, *J* 11.2, OCH_2Ph), 5.74 (2H, d, *J* 7.8, OCH_2Ph), 6.43 (2H, d, *J* 7.5, OCH_2Ph), 6.62 (1H, d, *J* 1.9, ArH), 6.66 (1H, d, *J* 2.0, ArH), 6.72 (1H, t, *J* 7.4, OCH_2Ph), 6.81–6.83 (2H, m, ArH), 6.91 (1H, d, *J* 2.0, ArH), 7.04–7.07 (2H, m, ArH), 7.21 (1H, d, *J* 2.1, ArH), 7.21–7.30 (5H, m, OCH_2Ph, Nap), 7.46–7.55 (5H, m, OCH_2Ph, Nap), 7.72 (1H, s, OH), 7.10 (1H, t, *J* 8.3, OCH_2Ph), 8.68 (1H, d, *J* 8.5, Nap); δ_C (75 MHz) 23.96, 30.60, 30.76, 30.94, 31.80, 32.39, 32.76, 33.49, 33.57, 33.67, 33.95, 39.31, 53.50, 69.28, 76.77, 86.00, 124.39, 124.43, 124.67, 125.18, 125.39, 125.45, 125.76, 125.85, 125.92, 126.20, 126.41, 126.53, 126.94, 127.33, 128.57, 128.84, 129.30, 129.52, 129.56, 130.52, 131.50, 132.12, 132.32, 132.54, 132.83, 133.27, 134.82, 135.61, 136.28, 137.32, 141.52, 144.45, 145.36, 147.15, 147.33, 150.35, 150.55, 153.40, 171.47. Ester **3d**: as a colorless powder, mp 215.6–216.5 °C (hexane) (Found: C, 83.08; H, 7.87. Calcd for $C_{72}H_{80}O_6$: C, 83.04; H, 7.74%); $[\alpha]_D^{29} = -86.8$ (*c* 1.03, chloroform); δ_H (500 MHz) 0.52 [9H, s, $C(CH_3)_3$], 0.70 [9H, s, $C(CH_3)_3$], 1.29 (3H, s, CH_3), 1.33 [9H, s, $C(CH_3)_3$], 1.48 [9H, s, $C(CH_3)_3$], 2.34 (1H, d, *J* 12.4, $ArCH_2Ar$), 3.02 (1H, d, *J* 12.4, $ArCH_2Ar$), 3.02 (3H, s, OCH_3), 3.37 (1H, d, *J* 13.5, $ArCH_2Ar$), 3.81 (1H, d, *J* 16.8, $ArCH_2Ar$), 3.96–4.00 (2H, m, $ArCH_2Ar$), 4.10 (1H, d, *J* 12.7, OCH_2Ph), 4.13–4.18 (2H, m, $ArCH_2Ar$), 4.23 (1H, d, *J* 12.6, OCH_2Ph), 4.76 (1H, d, *J* 10.6, OCH_2Ph), 4.95 (1H, d, *J* 10.6, OCH_2Ph), 5.46 (2H, d, *J* 7.7, OCH_2Ph), 6.24 (2H, t, *J* 7.5, OCH_2Ph), 6.47 (1H, d, *J* 2.1, ArH), 6.56–6.60 (2H, m, OCH_2Ph, ArH), 6.64 (1H, d, *J* 2.1, ArH), 6.83 (1H, d, *J* 2.2, ArH), 6.96 (1H, d, *J* 2.2, ArH), 7.06 (1H, d, *J* 2.3, ArH), 7.26–7.46 (9H, m, OCH_2Ph, ArH, Nap), 7.49 (2H, d, *J* 7.6, OCH_2Ph), 7.72 (d, *J* 8.0, 1H, Nap), 7.76 (1H, d, *J* 8.2, Nap), 7.86 (1H, s, OH), 8.97 (d, *J* 8.7, 1H, Nap); δ_C (75 MHz) 21.02, 30.04, 30.48, 30.67, 31.71, 31.74, 33.05, 33.27, 33.51, 33.90, 34.32, 39.42, 39.56, 50.88, 68.41, 77.16, 83.43, 123.75, 124.14, 124.24, 124.89, 125.04, 125.26, 125.37, 125.61, 125.82, 125.89, 126.11, 126.47, 126.90, 127.12, 128.31, 128.53, 128.74, 128.88, 129.50, 129.62, 130.18, 131.73, 131.91, 132.07, 132.88, 133.21, 134.01, 135.74, 137.03, 141.10, 143.94, 145.70, 146.93, 147.52, 150.62, 153.38, 170.18.

4.2.2. Hydrolysis of ester 3c to *anti-O,O′*-dibenzyl ether (+)-1. To a 28% solution of sodium methoxide in methanol (15 mL) was added ester **3c** (737 mg, 709 μmol) under nitrogen and the mixture refluxed for 4 h. After addition of water (1 mL), the mixture was refluxed for a further 30 min and then cooled to room temperature. After most of the methanol was evaporated, the residue was extracted with diethyl ether, and the extract washed with 2 M HCl and water, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel with hexane–dichloromethane (1:1) as an eluent to give diether (+)-**1** (571 mg, 97%,) as a colorless solid, $[\alpha]_D^{25} = +23.6$ (*c*

1.01, chloroform). The enantiomeric excess of the sample was determined to be 100% ee by HPLC on a Sumika SUMICHIRAL OA-2000 column (4.6 mm i.d. × 25 cm) with hexane–ethanol (99.8:0.2) as the eluent. The spectral data of the sample were identical with those of the racemate.[12]

4.2.3. Hydrolysis of ester 3d to *anti*-*O*,*O*′-dibenzyl ether (−)-1. Ester **3d** (802 mg, 770 μmol) was hydrolyzed by the same procedure as above to give diether (−)-**1** of 100% ee (654 mg, 98%) as a colorless solid, $[\alpha]_D^{25} = -23.6$ (*c* 1.02, chloroform).

4.3. Resolution of *anti*-*O*,*O*′-dibutyl ether 2

4.3.1. Esterification of ether 2 to diastereomeric monoesters 4a–d. To an ice-cold solution of *anti*-*O*,*O*′-dibutyl ether **2** (1.53 g, 2.00 mmol) in dichloromethane (20 mL) were added (*S*)-2′-methoxy-1,1′-binaphthalene-2-carbonic acid (697 mg, 2.12 mmol), 4-pyrrolidinopyridine (4-PPy) (593 mg, 4.00 mmol), and DCC (821 g, 3.98 mmol) under nitrogen and the mixture stirred at room temperature for 6 h. After being cooled to 0 °C, the mixture was quenched with 2 M HCl and extracted with dichloromethane. The extract was washed with water, dried over $MgSO_4$, and evaporated to leave a residue, which was passed through a silica gel column with hexane–diethyl ether (1:5) as an eluent to give a mixture of four diastereomeric monoesters. Crystallization of the mixture from diethyl ether–hexane gave a mixture of two diastereomers, which was resolved into **4a** (329 mg, 15%) and **4b** (201 mg, 9%) by flash column chromatography on silica gel with hexane–diethyl ether (19:1) as an eluent. The filtrate was evaporated to leave a residue, which was crystallized from 2-propanol to give **4c** (586 mg, 27%). Ester **4a**: as a colorless powder, mp 276.8–278.5 °C (decomp.) (diethyl ether–hexane) (Found: C, 82.89; H, 8.25. Calcd for $C_{74}H_{86}O_6$: C, 82.95; H, 8.09%); $[\alpha]_D^{29} = -124.8$ (*c* 1.06, chloroform); δ_H (300 MHz) 0.06 (3H, t, *J* 7.2, CH_2CH_3), 0.41–0.81 (4H, m, $CH_2CH_2CH_3$), 0.68 (3H, t, *J* 7.6, CH_2CH_3), 0.81 [9H, s, $C(CH_3)_3$], 0.91–1.06 (2H, m, CH_2CH_3), 0.91–1.35 (2H, m, OCH_2CH_2), 1.25 [9H, s, $C(CH_3)_3$], 1.30 [9H, s, $C(CH_3)_3$], 1.59 [9H, s, $C(CH_3)_3$], 3.04 (1H, d, *J* 12.7, $ArCH_2Ar$), 3.11–3.26 (2H, m, OCH_2), 3.49–3.58 (1H, m, OCH_2), 3.56 (1H, d, *J* 13.7, $ArCH_2Ar$), 3.66–3.74 (1H, m, OCH_2), 3.77 (3H, s, OCH_3), 3.80 (1H, d, *J* 17.2, $ArCH_2Ar$), 3.86 (1H, d, *J* 13.4, $ArCH_2Ar$), 3.92 (1H, d, *J* 17.2, $ArCH_2Ar$), 3.96 (1H, d, *J* 17.5, $ArCH_2Ar$), 4.02 (1H, d, *J* 13.0, $ArCH_2Ar$), 4.06 (1H, d, *J* 16.8, $ArCH_2Ar$), 6.22 (1H, d, *J* 8.6, Nap), 6.68 (1H, d, *J* 1.7, ArH), 6.86 (1H, d, *J* 8.6, Nap), 6.96–7.02 (3H, m, ArH × 2, Nap), 7.04 (1H, d, *J* 8.9, Nap), 7.12–7.23 (6H, m, ArH × 3, Nap × 3), 7.26 (1H, s, OH), 7.32 (1H, d, *J* 1.7, ArH), 7.37–7.43 (2H, m, Nap × 2), 7.57 (1H, d, *J* 2.1, ArH), 7.68 (1H, d, *J* 8.2, Nap), 7.76 (1H, d, *J* 8.3, Nap), 7.86 (1H, d, *J* 9.3, Nap); δ_C (75 MHz) 13.04, 13.78, 18.33, 18.68, 29.65, 30.23, 30.96, 31.41, 31.53, 31.59, 31.82, 32.70, 33.41, 34.02, 34.11, 34.46, 39.16, 39.75, 73.21, 73.88, 113.88, 122.39, 123.00, 124.15, 124.26, 124.67, 124.76, 124.91, 125.03, 125.60, 126.21, 126.31, 126.88, 127.02, 127.15, 127.37, 127.50, 127.95, 128.07, 128.49, 129.01, 129.07, 131.00, 132.48, 132.79, 132.82, 133.67, 133.41, 134.16, 134.28, 134.94, 137.98, 142.47, 144.35, 144.66, 146.45, 147.02, 150.45, 151.41, 153.98, 154.51, 163.14. Ester **4b**: as a colorless powder, mp 286.4–289.1 °C (decomp.) (diethyl ether–hexane) (Found: C, 82.74; H, 8.19. Calcd for $C_{74}H_{86}O_6$: C, 82.95; H, 8.09%); $[\alpha]_D^{29} = +62.2$ (*c* 0.95, chloroform); δ_H (300 MHz) −0.13 (3H, t, *J* 7.2, CH_2CH_3), 0.27–0.36 (2H, m, CH_2CH_3), 0.44–0.54 (2H, m, OCH_2CH_2), 0.68 (3H, t, *J* 7.2, CH_2CH_3), 0.90 [9H, s, $C(CH_3)_3$], 0.92–1.05 (2H, m, CH_2CH_3), 1.18–1.37 (2H, m, OCH_2CH_2), 1.26 [9H, s, $C(CH_3)_3$], 1.31 [9H, s, $C(CH_3)_3$], 1.58 [9H, s, $C(CH_3)_3$], 3.06 (2H, dd, *J* 6.9, 9.3, OCH_2), 3.23 (1H, d, *J* 12.4, $ArCH_2Ar$), 3.50–3.74 (2H, m, OCH_2), 3.57 (1H, d, *J* 13.1, $ArCH_2Ar$), 3.62 (3H, s, OCH_3), 3.69 (1H, d, *J* 16.5, $ArCH_2Ar$), 3.86 (1H, d, *J* 17.2, $ArCH_2Ar$), 3.94 (1H, d, *J* 17.2, $ArCH_2Ar$), 4.01–4.10 (3H, m, $ArCH_2Ar \times 3$), 6.11 (1H, d, *J* 8.6, Nap), 6.65 (1H, d, *J* 2.1, ArH), 6.86 (1H, d, *J* 8.3, Nap), 6.97 (1H, d, *J* 1.7, ArH), 7.00 (1H, d, *J* 2.0, ArH), 7.04 (1H, d, *J* 8.6, Nap), 7.04–7.17 (3H, m, Nap × 3), 7.16 (1H, d, *J* 2.4, ArH), 7.22–7.31 (4H, m, ArH × 2, Nap × 2), 7.33 (1H, s, OH), 7.35–7.42 (2H, m, ArH, Nap), 7.57 (1H, d, *J* 2.1, ArH), 7.68 (1H, d, *J* 8.2, Nap), 7.77 (1H, d, *J* 7.9, Nap), 7.85 (1H, d, *J* 8.9, Nap); δ_C (75 MHz) 12.64, 13.80, 18.30, 18.69, 29.76, 30.25, 30.74, 31.25, 31.56, 31.61, 31.81, 32.73, 33.57, 34.03, 34.14, 34.46, 38.99, 39.75, 55.63, 73.20, 74.19, 122.06, 123.12, 124.20, 124.78, 125.07, 125.35, 125.49, 125.81, 126.04, 126.19, 126.77, 126.89, 127.04, 127.12, 127.50, 127.57, 127.72, 127.86, 128.07, 128.47, 128.75, 128.92, 131.02, 132.42, 132.80, 132.93, 133.17, 134.01, 134.13, 134.85, 137.48, 142.32, 144.46, 144.54, 146.47, 147.09, 150.60, 151.41, 153.06, 154.37, 163.49. Ester **4c**: as colorless crystals, mp 185.5–187.8 °C (2-propanol) (Found: C, 82.68; H, 8.15. Calcd for $C_{74}H_{86}O_6$: C, 82.95; H, 8.09%); $[\alpha]_D^{29} = -20.5$ (*c* 1.09, chloroform); δ_H (300 MHz) 0.68–0.84 (5H, m, CH_2CH_3), 0.89 [9H, s, $C(CH_3)_3$], 0.99 [9H, s, $C(CH_3)_3$], 1.17 [9H, s, $C(CH_3)_3$], 1.18–1.30 (5H, m, OCH_2CH_2, CH_2CH_3), 1.28 [9H, s, $C(CH_3)_3$], 1.61 (2H, td, *J* 7.2, 22.7, CH_2CH_3), 1.86–2.17 (2H, m, OCH_2CH_2), 2.95 (1H, td, *J* 8.3, 8.2, OCH_2), 3.00 (1H, d, *J* 12.7, $ArCH_2Ar$), 3.14 (1H, td, *J* 8.3, 8.2, OCH_2), 3.39 (1H, d, *J* 13.7, $ArCH_2Ar$), 3.68 (2H, s, $ArCH_2Ar$), 3.68–3.76 (1H, m, OCH_2), 3.88 (2H, s, $ArCH_2Ar$), 3.95–3.99 (2H, m, $ArCH_2Ar \times 2$), 3.95 (3H, s, OCH_3), 4.11–4.19 (1H, m, OCH_2), 6.73 (1H, d, *J* 2.4, ArH), 6.82 (1H, d, *J* 8.2, Nap), 6.87 (1H, d, *J* 2.0, ArH), 6.97 (1H, d, *J* 2.1, ArH), 6.98–7.04 (4H, m, ArH × 4), 7.06–7.12 (1H, m, Nap), 7.15 (1H, d, *J* 2.1, ArH), 7.20–7.26 (3H, m, Nap × 3), 7.29 (1H, s, OH), 7.46 (1H, d, *J* 8.9, Nap), 7.53 (1H, td, *J* 3.8, 8.3, Nap), 7.78 (1H, d, *J* 7.9, Nap), 7.85 (1H, d, *J* 8.9, Nap), 7.88 (1H, d, *J* 8.3, Nap), 7.93 (1H, d, *J* 9.3, Nap), 8.43 (1H, d, *J* 8.6, Nap); δ_C (75 MHz) 13.84, 14.27, 18.47, 19.23, 25.34, 30.99, 31.12, 31.24, 31.37, 31.60, 31.67, 31.86, 32.27, 33.70, 33.79, 34.03, 38.31, 38.82, 56.31, 71.01, 74.12, 113.28, 122.03, 123.29, 124.25, 125.06, 125.15, 125.80, 125.95, 126.23, 126.53, 127.48, 127.56, 127.68, 127.75, 127.93, 128.04, 128.91, 129.16, 129.43, 132.00, 132.19, 132.67, 132.93, 133.24, 133.38, 133.66, 134.15, 135.40, 138.99, 141.51, 144.35, 144.90, 145.88, 146.68, 150.43, 150.71, 153.38, 154.56, 164.35.

4.3.2. Hydrolysis of ester 4c to *anti-O,O′*-dibutyl ether (+)-2. To a solution of ester **4c** (550 mg, 513 μmol) in THF (5 mL) were added a 28% solution of sodium methoxide in methanol (10 mL) under nitrogen and the mixture refluxed for 2 h before addition of water (1 mL). The mixture was refluxed for a further 30 min and cooled to room temperature. After the organic solvents were evaporated, the residue was extracted with diethyl ether and the extract washed successively with 2 M HCl and water, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel with hexane–ethyl acetate (15:1) as an eluent to give diether (+)-**2** (362 mg, 93%) as a colorless solid, $[\alpha]_D^{25} = +4.1$ (*c* 1.02, ethanol). The enantiomeric excess of the sample was determined to be 99.9% by HPLC on a Daicel CHIRALCEL OD-H column (4.6 mm i.d. × 25 cm) with hexane–2-propanol (99.7:0.3) as the eluent. The spectral data of the sample were identical with those of the racemate.[12]

4.3.3. Hydrolysis of ester 4b to *anti-O,O′*-dibutyl ether (−)-2. Ester **4b** (214 mg, 200 μmol) was hydrolyzed by the same procedure as above to give diether (−)-**2** of 99% ee (138 mg, 91%) as a colorless solid, $[\alpha]_D^{25} = -4.0$ (*c* 1.02, ethanol).

4.4. X-ray analysis of ester 3c

Data were collected on a Rigaku/MSC Mercury CCD diffractometer using Cu Kα radiation ($\lambda = 0.71069$ Å). The calculation was performed using the software package TeXsan (v. 1.11).[22] The structure was solved by the direct methods with SIR2002[23] and refined by full-matrix least squares methods with SHELXL-97.[24] Crystal data and refinement statistics are as follows: $C_{168}H_{216}O_{12}$, $M = 2427.55$, monoclinic, $a = 9.884(4)$, $b = 18.813(4)$, $c = 41.209(8)$ Å, $\beta = 103.816(6)°$, $V = 7440.7(3)$ Å^3, $T = 223$ K, space group $P2_1$, $Z = 2$, μ(Cu Kα) = 0.509 mm^{-1}, 39,768 reflections measured, 19,282 unique ($R_{int} = 0.060$). Final $R_1 = 0.067$ for 17,258 data [$I > 2\sigma(I)$] and $wR_2 = 0.208$ for all data, $GOF = 0.998$. The details of the crystal data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no CCDC 251444. The absolute stereochemistry of ester **3c** was assigned to S_a by using the (*S*)-MNPA moiety as an internal reference.

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