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Synthesis of Chiral and Modifiable Hexahydroxydiphenoyl Compounds

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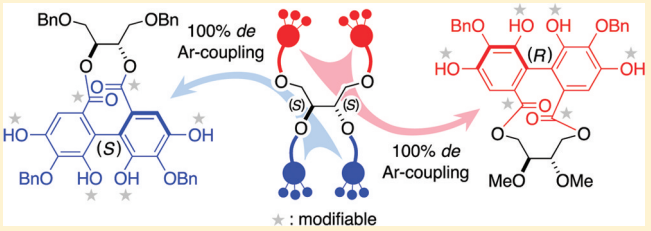
Supporting Information

ABSTRACT: A reliable method for synthesizing each enantiomer of the hexahydroxydiphenoyl (HHDP) compounds has been developed. The synthesis involved atropselective construction of the aryl−aryl bond of the HHDP compounds. This construction relied on the $CuCl_2$·*n*-$BuNH_2$-mediated intramolecular coupling of bis(4-*O*-benzylgallate) on two simple chiral auxiliaries, both of which were derived from L-(+)-tartaric acid. The coupling reaction realized complete or near-perfect atropselectivity. The two auxiliaries induced opposite axial chirality despite their identical origin. The diastereoselectivities of these couplings were probably controlled kinetically. Modifications of the free phenolic hydroxy groups and the carbonyl groups in the resulting HHDP compounds demonstrated the potential derivatization of a wide variety of HHDP analogues.



INTRODUCTION

The hexahydroxydiphenoyl (HHDP) group is a motif component of ellagitannins, exemplified by (−)-corilagin (**1**) (Figure 1), a class of polyphenolic natural products with a broad range of biological activities.[1−3] Interestingly, several activities have been attributed to the HHDP moiety,[4,5] including inhibitions of recombinant rat squalene epoxidase[6] and of protein kinase C[4] and anti-HIV activities.[7−9] Additionally, HHDP compounds with axial chirality have attracted much attention as possible asymmetric catalysts.[10−15] The easily modifiable phenolic hydroxy groups of the HHDP group allow potential derivatization of a wide variety of systematically designed analogues. Despite the biological and chemosynthetic importance of the chiral HHDP compounds, their availability from natural sources is low because the isolation of a substantial amount of pure ellagitannin is generally difficult.[16] Although many methods for synthesizing chiral HHDP compounds have been studied,[17−30] most of them adopt methyl groups to protect the phenolic hydroxy groups despite their difficult removal. Application of removable protecting groups on the HHDP compounds has been carried out in total syntheses of natural ellagitannins.[31−34] However, an effective and usable method of synthesizing both enantiomers of chiral HHDP was not presented in these works. An accessible method of synthesizing chiral HHDP compounds including a wide variety of derivatives would contribute not only to structure−activity relationship studies to aid understanding of the bioactivity of ellagitannins but also to the development of novel asymmetric catalysts.

There are many methods of synthesizing axially chiral biaryl compounds, but methods that allow the coupling of gallates to provide the HHDP compounds are less common.[35] Lipshutz and co-workers reported the atropselective intramolecular oxidative coupling of two biaryl parts connected to a simple chiral auxiliary via higher order cyanocuprate intermediates. They applied this method to the construction of the axially chiral HHDP part of an ellagitannin.[24,36] Their work demonstrates that asymmetric induction by chiral auxiliaries is effective for the atropselective biaryl bond formation, and they extended this strategy to versatile preparations of axially chiral biaryl compounds.[37,38] However, ether linkages are used to connect the aryl parts and the auxiliary. This linkage causes a loss of ability to recover the chiral auxiliaries when releasing them from the biaryl parts. Furthermore, unremovable methyl groups have been applied to protect the phenolic hydroxy groups of the HHDP group, and thus limit its derivatization. In our studies on the synthesis of **1**,[34] we discovered that 4-*O*-benzylated gallates were efficiently coupled to furnish the HHDP moiety by $CuCl_2$·*n*-$BuNH_2$ reagents. Such a reagent system was originally developed by Brussee and co-workers for the preparation of binaphthol.[39] The biaryl bond formation proceeded atropselectively and with good yield. However, in terms of the ease of synthesizing the chiral HHDP compounds, the D-glucose-derived auxiliary in **2** was inefficient because it required nine steps for its preparation. Therefore, we sought a simpler auxiliary suitable for our substrate (Figure 1). In this paper, we describe an accessible method of synthesizing chiral HHDP compounds using two simple chiral auxiliaries prepared from a single chiral source. The chiral auxiliaries were **3**[40] and

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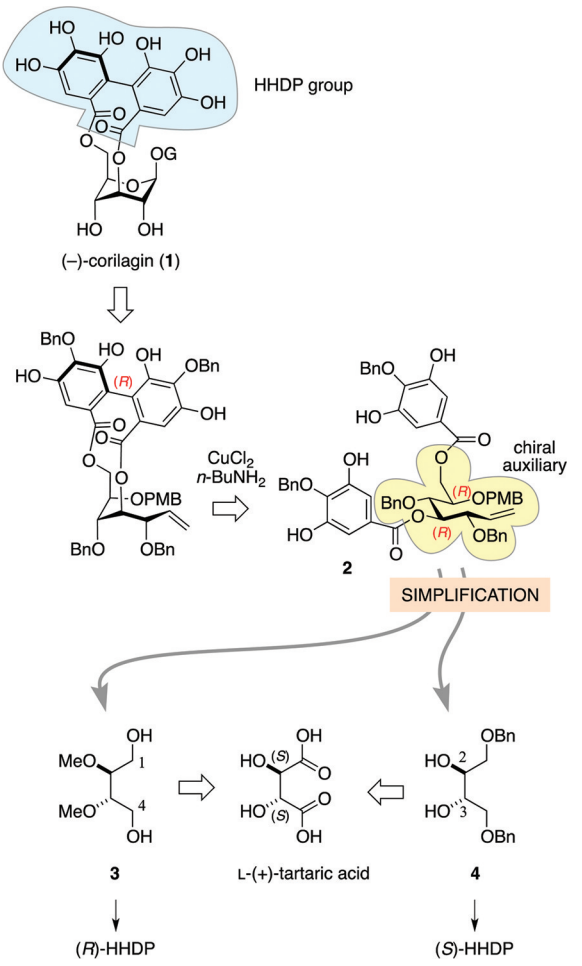


Figure 1. Idea and outline of this work.

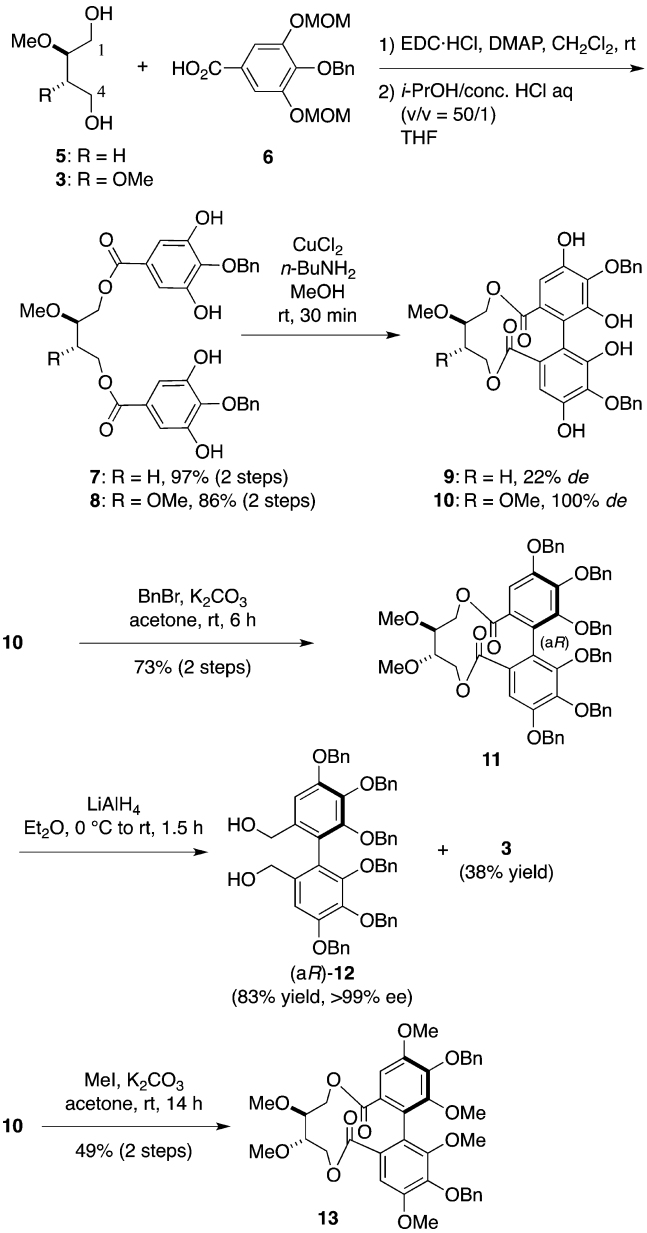
4,[41] and both were derived from L-(+)-tartaric acid. Intramolecular coupling of the two 4-*O*-benzylated gallates on the chiral auxiliaries provided the HHDP products diastereoselectively with opposite axial chirality.

RESULTS AND DISCUSSION

The complete central-to-axial chirality transfer required at least two stereogenic centers, as illustrated by the studies using **5**[42] and **3** as the chiral auxiliaries (Scheme 1), which have one and two asymmetric carbons, respectively. Auxiliaries **5** and **3** were prepared individually from D-(+)-malic acid in three steps and from L-(+)-tartaric acid dimethyl ester in two steps. The esterification of **5** and **3** with **6** followed by the removal of the MOM groups furnished the coupling precursors **7** and **8**. Intramolecular oxidative phenol coupling of **7** with $CuCl_2$·*n*-$BuNH_2$ gave the cyclic biaryl **9** as a mixture of diastereomers. The ^1H NMR spectrum indicated the ratio of 61:39 for the diastereomers (22% de). On the other hand, a similar coupling of **8** afforded the cyclic biaryl **10** as a single diastereomer (100% de). An increase of the *gauche* steric hindrance would result in high atropselectivity.

Tetraphenolic **10** decomposed slowly in air and on silica gel, whereas treatment in air and quick chromatography on silica gel made it possible to isolate the pure compound. To ensure easy handling, the phenolic hydroxy groups were protected with benzyl groups soon after the phenol coupling. This treatment provided the hexabenzyl ether **11**, which was stable under the

Scheme 1. Aryl Coupling on the 1,4-Diol Chiral Auxiliaries and Related Transformations[a]



[a]EDC·HCl = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride.

circumstances mentioned above. Reduction of **11** with lithium aluminum hydride easily removed the chiral auxiliary to produce the HHDP compounds (a*R*)-**12** (>99% ee)[43] and **3** in 83% and 38% yields, respectively. Methylation of **10** gave the tetra-*O*-methylated cyclic biaryl **13**; X-ray crystallographic analysis of **13** confirmed the atrop-*R* (a*R*) configuration of **10**.[44]

The adoption of the chiral auxiliary **4** provided another enantiomer, (a*S*)-**12** (Scheme 2). L-(+)-Tartaric acid was the source of the auxiliary **4** as well as the source of the diol **3**, but the connecting sites of the gallates were altered to positions 2 and 3. In Lipshutz's work, they used the auxiliary **4** for the intramolecular oxidative coupling via higher order cyanocuprate intermediates, in which they adopted ether linkages to connect the aryl parts and the auxiliary **4**.[36] In contrast, we linked our

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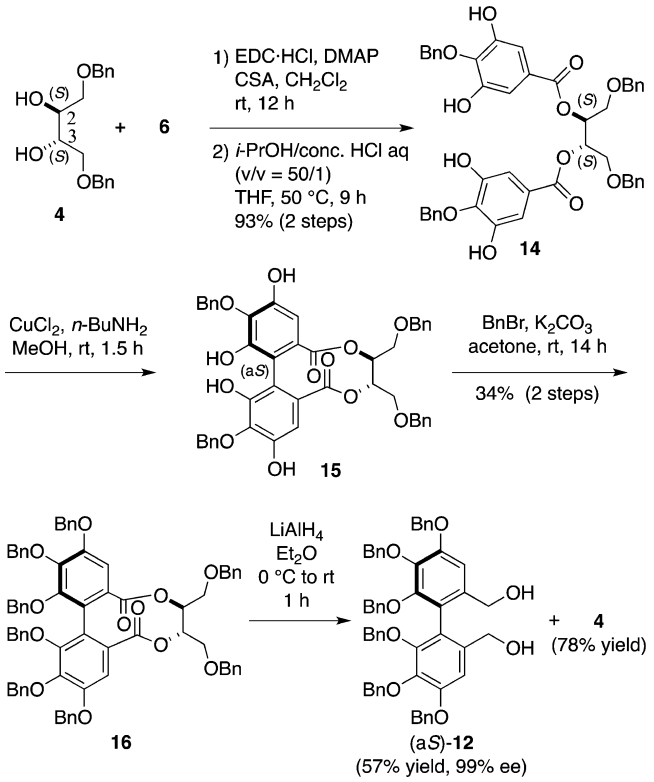
Scheme 2. Aryl Coupling on the 2,3-Diol Chiral Auxiliaries and Related Transformations[a]

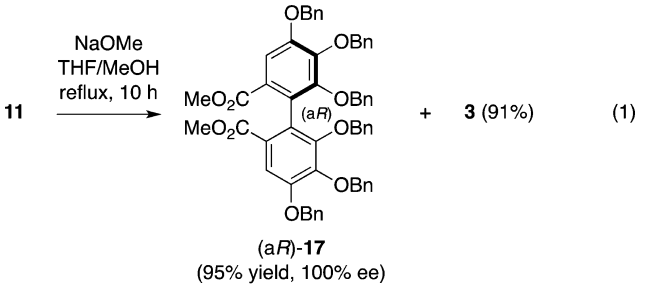


[a]CSA = (±)-camphor-10-sulfonic acid.

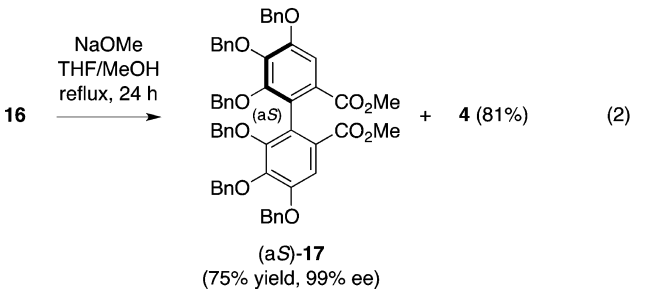
substrates to the auxiliary **4** via ester linkage because it permitted easy cleavage and recovery of the auxiliary **4**. The esterification of **4** with **6** followed by the removal of the MOM groups furnished the coupling precursor **14**. Intramolecular phenol coupling of **14** produced **15**. Benzylation of **15** afforded the hexabenzylated **16** in 34% yield in two steps. Monitoring of the coupling reaction using mass spectra suggested that solvolysis of the galloyl ester was competed as a side reaction. The greater strain in the ten-membered ring of **15** than in the twelve-membered ring of **10** would slow the coupling, emphasizing the side reaction. In addition, the strained structure was likely to affect the stability of the coupled compound, thus, unidentified degradation products were observed during the full benzylation of **15**. Removal of the chiral auxiliary gave the HHDP compound (a*S*)-**12** in 57% yield (99% ee),[43] and **4** was recovered in 78% yield. The similar polarity of the two diols meant that they required iterative chromatography for their separation,[45] which resulted in low yield of **12** although the reduction itself proceeded cleanly. Comparing the optical rotation of (a*S*)-**12** ($[\alpha]^{25}_{D}$ −78.2) with (a*R*)-**12** ($[\alpha]^{25}_{D}$ +77.2) confirmed the atrop-*S* configuration.

The diastereoselectivity of these couplings was probably controlled kinetically. Smrčina and Kočovský divided the factors determining the axial chirality in the Cu(II)-mediated aryl−aryl couplings into three groups, which were (i) the diastereoselective crystallization, (ii) the second order asymmetric transformation, and (iii) the enantioselective (or diastereoselective) coupling.[46] The first factor appears when a diastereomer crystallizes more easily than the others. This phenomenon often accompanies the second factor, which is the rotation of the aryl−aryl bond that produces a thermodynamically more stable diastereomer.[39,46,47] In addition, several racemic 2,2′-dihydroxybiphenyl compounds deracemize under treatment of the bisphenols with Cu(II) ion and chiral amines.[48,49] The third is the kinetic control, which has been observed in the use of chiral amine as the reagent system.[50,51] In our experiment, nothing precipitated during the coupling reactions, and retreatment of the separated major diastereomer of **9** with the coupling conditions ($CuCl_2$ and *n*-$BuNH_2$ in MeOH) did not rotate the biaryl axis. Accordingly, the first and second factors had no effect. As a result kinetic diastereoselectivity was induced in these reactions. Therefore, we should correct our previous description stating that the axial diastereoselectivity was thermodynamically controlled.[34]

Whereas the reductive treatment of **11** and **16** reproduced the chiral auxiliaries **3** and **4** as previously described (Schemes 1 and 2), methanolysis allowed efficient recovery of the chiral auxiliaries (eqs 1 and 2). The methanolysis of **11** proceeded



(1)



(2)

cleanly without byproduct, although the reduction of **11** gave unidentified byproduct whose polarity was similar to that of **3**. Furthermore, the reduction products of **16**, which are (a*S*)-**12** and **4**, represented a pair of diols whose polarities were similar, and this hindered a straightforward separation.[45] In contrast, methanolysis of **11** gave a pair of products, a diester **17** and the diol **3**, separation of which was quick and easy. Thus, treatment of **11** with NaOMe in THF/MeOH provided diester (a*R*)-**17** in 95% yield (100% ee)[43,45] and the chiral diol **3** was recovered in 91% yield. Similarly, methanolysis of **16** afforded (a*S*)-**17** in 75% yield (99% ee)[43] along with recovered **4** in 81% yield.

The following conversions demonstrated the potential derivatization of the chiral HHDP compounds. Allylation of **10** gave the tetra-*O*-allylated cyclic biaryl **18** (eq 3). This result, and methylation of **10** (Scheme 1) demonstrate the ease of regioselective modification of the phenolic hydroxy groups in the HHDP compounds, which is a remarkable advantage of the production of HHDP analogues over the previous methods. Hydrolytic cleavage was possible, as well as the methanolysis of the cyclic biaryls, and thus **11** liberated the dicarboxylic acid **19** (88% yield, 100% ee) (eq 4).[43] Oxidation of **12** with Dess-Martin periodinane (DMP) easily provided the corresponding dialdehyde **20** (100% ee)[43] maintaining complete axial chirality

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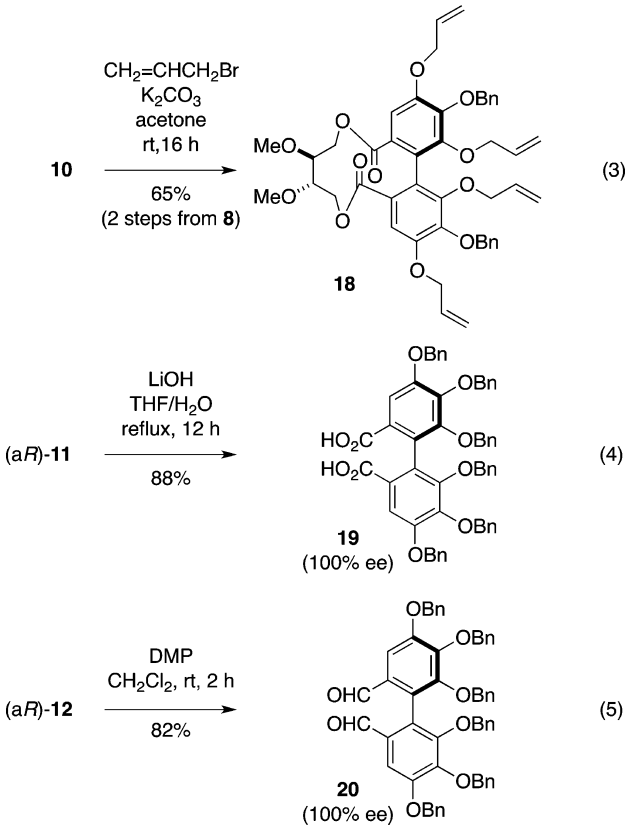

(eq 5). These derivatives are also the prospective substrates for a range of versatile and optically active biaryls.

■ CONCLUSION

In summary, we have developed a method of synthesizing chiral HHDP derivatives. They were synthesized with complete or near perfect atropselectivity using $CuCl_2$·*n*-$BuNH_2$ complex-mediated oxidative phenol coupling of bis(4-*O*-benzylgallate) with two simple chiral auxiliaries that were prepared from a single starting material, L-(+)-tartaric acid. Note that each chiral auxiliary introduced opposite axial chirality, and the derived chiral HHDP compounds were readily modifiable. Because of the improved availability of the chiral HHDP substrates, these methods may advance the biological and synthetic applications of this class.

■ EXPERIMENTAL SECTION

General Methods. All commercially available reagents were used without further purification. All moisture- and air-sensitive reactions were performed under a positive pressure of argon or nitrogen. The substrates were azeotropically dried if needed by evaporation of their MeCN or C_6H_6 solution several times to remove trace H_2O that may be contained to the substrate. Proceedings of reactions were monitored by TLC and MS. Anhydrous $MgSO_4$ was used to dry organic layers after extraction, and it was removed by filtration through a cotton pad. The filtrate was evaporated and subjected to further purification protocols if necessary. This sequence was represented as "the general drying procedure" in the following experimental methods.

TLC was performed on Merck precoated silica gel 60 F_{254}. Spots were visualized by exposure to UV light or by immersion into a solution of 2% anisaldehyde, 5% H_2SO_4 in ethanol, or a solution of 10% phosphomolybdic acid in ethanol followed by heating at ca. 200 °C. Commercially available PLC plates (20 × 20 cm, Silicagel 60 F_{254}, 2 mm) were used for preparative purposes. Column chromatography was performed on silica gel 60 (70−230 mesh).

Specific optical rotations were determined using a polarimeter with a 100 mm cell at 589 nm in chloroform. Enantiomeric purities of the compds after cleavage of the auxiliaries were determined by HPLC with a Daicel CHIRALPAK AD-3 column (4.6 × 250 mm) and with detection at 254 nm. Eluant, flow rate, and t_R are described individually in the following sections.

NMR spectra were recorded at 400 and 100 MHz for ^1H and ^{13}C NMR, respectively, and with either TMS or residual proton of deuterated solvent as internal reference. The ^1H NMR data are indicated by a chemical shift with the multiplicity, the coupling constants, and the integration in parentheses in this order. The multiplicities are abbreviated as s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, and br: broad. The ^{13}C NMR data are reported as the chemical shift with the hydrogen multiplicity obtained from the DEPT spectra in parentheses. The multiplicities are abbreviated as s: C, d: CH, t: CH_2, and q: CH_3. When the number of the carbon was more than one, the number was added in the parentheses.

Regarding IR spectra, the major absorbance bands are all reported in wavenumbers (cm^{-1}). HRMS were obtained for ESI and are reported in units of mass to charge.

(*R*)-2-Methoxy-1,4-butandiyl Bis(4-*O*-benzylgallate) (7). (*R*)-2-Methoxy-1,4-butanediol (**5**) (1.00 g, 8.32 mmol) was dried using C_6H_6 before use. It was then dissolved in CH_2Cl_2 (80 mL). To the solution were added 4-*O*-benzyl-3,5-di-*O*-methoxymethylgallic acid (**6**) (7.24 g, 20.8 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl) (9.58 g, 50.0 mmol), and DMAP (9.14 g, 74.8 mmol), and the mixture was stirred for 1 h at rt under an Ar atmosphere. After addition of H_2O, the aq mixture was extracted with AcOEt, and the combined organic layer was successively washed with saturated aq $NaHCO_3$, H_2O, and brine. After the general drying procedure, the mixture was purified by column chromatography (281 g of SiO_2, *n*-hexane/AcOEt = 3/1 to 1/1) to afford (*R*)-2-methoxy-1,4-butandiyl bis(4-*O*-benzyl-2,3-di-*O*-methoxymethylgallate) (6.34 g, 98% yield) as a colorless oil: $[\alpha]^{26}_D$ +3.9 (*c* 1.26, $CHCl_3$); IR (ZnSe, thin film) 3033, 2955, 2828, 2061, 1717, 1591, 1499, 1453, 1433, 1393, 1327, 1219, 1196, 1156, 1109, 1048, 1005, 924, 762, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 2H), 7.53 (s, 2H), 7.47−7.45 (m, 4H), 7.37−7.28 (m, 6H), 5.18 (s, 4H), 5.18 (s, 4H), 5.13 (s, 4H), 4.50−4.44 (m, 3H), 4.29 (dd, *J* = 11.7, 5.8 Hz, 1H), 3.73−3.68 (m, 1H), 3.50 (s, 3H), 3.47 (s, 12H), 2.11−1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0 (s), 165.9 (s), 151.1 (s, 4C), 143.4 (s), 143.4 (s), 137.5 (s, 2C), 128.6 (d, 4C), 128.5 (d, 4C), 128.3 (d, 2C), 125.9 (s), 125.9 (s), 112.5 (d, 2C), 112.3 (d, 2C), 95.7 (t, 2C), 95.7 (t, 2C), 76.4 (d), 75.4 (t, 2C), 66.5 (t), 61.7 (t), 58.5 (q), 56.6 (q, 4C), 31.3 (t); ESIHRMS (*m*/*z*) calcd for $C_{41}H_{48}O_{15}Na$ $[M + Na]^+$ 803.2891, found 803.2865.

To a solution of (*R*)-2-methoxy-1,4-butandiyl bis(4-*O*-benzyl-2,3-di-*O*-methoxymethylgallate) (500 mg, 0.640 mmol) in THF (3 mL), a mixture of *i*-PrOH (100 mL) and concd hydrochloric acid (2 mL) were added. The mixture was stirred for 21 h at 60 °C. The mixture was cooled to 0 °C, and saturated aq $NaHCO_3$ was added. After removal of *i*-PrOH by evaporation, the aq mixture was extracted with AcOEt. The combined organic layer was successively washed with H_2O and brine. After the general drying procedure, the mixture was purified by column chromatography (3.0 g of SiO_2, $CHCl_3$) to afford **7** (384 mg, 99% yield) as a colorless oil: $[\alpha]^{26}_D$ −4.6 (*c* 0.64, $CHCl_3$); IR (ZnSe, thin film) 3568, 3398, 2966, 1701, 1597, 1524, 1453, 1350, 1237, 1057, 995, 756, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.32 (m, 10H), 7.20 (s, 2H), 7.19 (s, 2H), 5.14 (s, 2H), 5.13 (s, 2H), 4.46−4.40 (m, 3H), 4.30 (dd, *J* = 11.7, 5.1 Hz, 1H), 3.73−3.67 (m, 1H), 3.45 (s, 3H), 2.07−1.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7 (s, 2C), 149.3 (s, 4C), 137.9 (s), 137.8 (s), 136.7 (s, 2C), 129.0 (d, 5C), 128.9 (d, 5C), 125.8 (s), 125.5 (s), 110.0 (d, 2C), 109.9 (d, 2C), 76.5 (d), 75.6 (t, 2C), 66.1 (t), 61.9 (t), 58.0 (q), 30.9 (t); ESIHRMS (*m*/*z*) calcd for $C_{33}H_{32}O_{11}Na$ $[M + Na]^+$ 627.1842, found 627.1847.

(*R*)-2-Methoxy-1,4-butandiyl 5,5′-bis(benzyloxy)-4,4′,6,6′-tetrahydroxy-1,1′-biphenyl-2,2′-dicarboxylate (9). The substrate **7** (230 mg, 0.380 mmol) was dried using MeCN before use. It was then dissolved in MeOH (10 mL). To the other flask were

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added $CuCl_2$ (258 mg, 1.92 mmol) and *n*-$BuNH_2$ (559 mg, 7.64 mmol). To the mixture was added MeOH (22 mL), and the resulting mixture was stirred for 20 min at rt under an Ar atmosphere to prepare a blue solution of $CuCl_2$·*n*-$BuNH_2$ complex. Then the solution of **7** in MeOH was added to the blue solution, and the mixture was stirred for 30 min at rt. The reaction mixture was diluted with Et_2O (20 mL), and quenched by addition of saturated aq NH_4Cl and 1 M hydrochloric acid. After evaporation to remove MeOH, the aq mixture was extracted with Et_2O, and the combined organic layer was successively washed with 1 M hydrochloric acid, saturated aq $NaHCO_3$, H_2O, and brine. After the general drying procedure, evaporation of the filtrate afforded **9** as a diastereomeric mixture with 22% de. The mixture was separated by silica gel column chromatography (5.0 g of SiO_2, *n*-hexane/AcOEt = 2/1 to 1/1) to afford one of the diastereomer **9** (93.1 mg, 41% yield) and another diastereomer **9** (12.2 mg, 5% yield), each as a yellow amorphous solid.

Data for one of the diastereomer **9**: $[\alpha]^{26}_D$ −4.6 (*c* 1.8, $CHCl_3$); IR (ZnSe, thin film) 3501, 3400, 3032, 2953, 2363, 2253, 1780, 1608, 1499, 1453, 1394, 1238, 1190, 1062, 980, 912, 857, 754, 700 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.56−7.53 (m, 4H), 7.38−7.29 (m, 6H), 6.67 (s, 1H), 6.66 (s, 1H), 5.19 (d, *J* = 11.0 Hz, 1H), 5.18 (d, *J* = 11.0 Hz, 1H), 5.14 (d, *J* = 11.0 Hz, 1H), 5.13 (d, *J* = 11.0 Hz, 1H), 4.56−4.51 (m, 1H), 4.39 (dd, *J* = 11.9, 2.5 Hz, 1H), 4.09 (dd, *J* = 11.9, 3.9 Hz, 1H), 3.96−3.90 (m, 1H), 3.69−3.64 (m, 1H), 3.36 (s, 3H), 2.32−2.23 (m, 1H), 1.87−1.80 (m, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 168.3 (s), 168.1 (s), 150.4 (s), 150.3 (s), 150.2 (s, 2C), 138.8 (s), 138.8 (s), 136.9 (s), 136.8 (s), 131.3 (s), 131.2 (s), 129.3 (d, 4C), 129.1 (d, 4C), 128.7 (d, 2C), 115.4 (s), 115.3 (s), 108.6 (d), 108.3 (d), 77.0 (d), 74.8 (t, 2C), 65.3 (t), 62.3 (t), 56.6 (q), 30.1 (t); ESIHRMS (*m*/*z*) calcd for $C_{33}H_{30}O_{11}Na$ $[M + Na]^+$ 625.1686, found 625.1680.

Data for the other diastereomer of **9**: mp 99.5−100.9 °C; IR (ZnSe, thin film) 3501, 3401, 3033, 2957, 1719, 1607, 1499, 1453, 1366, 1238, 1192, 1063, 965, 916, 855, 756, 700 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.56−7.52 (m, 4H), 7.38−7.29 (m, 6H), 6.65 (s, 2H), 5.18 (d, *J* = 11.0 Hz, 1H), 5.18 (d, *J* = 11.0 Hz, 1H), 5.14 (d, *J* = 11.0 Hz, 1H), 5.13 (d, *J* = 11.0 Hz, 1H), 4.40−4.35 (m, 1H), 4.11−4.02 (m, 3H), 3.69−3.63 (m, 1H), 3.40 (s, 3H), 2.32−2.26 (m, 1H), 1.81−1.73 (m, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 168.2 (s), 167.9 (s), 150.5 (s), 150.4 (s), 150.3 (s), 150.3 (s), 138.8 (s, 2C), 136.8 (s, 2C), 131.6 (s), 131.0 (s), 129.4 (d, 2C), 129.3 (d, 2C), 129.1 (d, 4C), 128.7 (d, 2C), 115.4 (s), 115.3 (s), 108.6 (d), 107.9 (d), 77.7 (d), 74.8 (t, 2C), 66.2 (t), 61.7 (t), 57.3 (q), 30.8 (t); ESIHRMS (*m*/*z*) calcd for $C_{33}H_{30}O_{11}Na$ $[M + Na]^+$ 625.1686, found 625.1676.

(2*S*,3*S*)-Dimethoxy-1,4-butandiyl bis(4-*O*-benzylgallate) (8). (2*S*,3*S*)-Dimethoxy-1,4-butanediol (**3**) (2.81 g, 18.7 mmol) was dried using C_6H_6 before use. It was then dissolved in CH_2Cl_2 (187 mL). To the solution were added **6** (15.0 g, 43.1 mmol), EDC·HCl (21.5 g, 112 mmol), and DMAP (20.6 g, 169 mmol), and the mixture was stirred for 1.5 h at rt under an Ar atmosphere. Addition of 1 M hydrochloric acid quenched the reaction, and the separated organic layer was successively washed with 1 M hydrochloric acid, saturated aq $NaHCO_3$, H_2O, and brine. After the general drying procedure, the mixture was purified by column chromatography (534 g of SiO_2, *n*-hexane/AcOEt = 6/1 to 1/1) to afford (2*S*,3*S*)-dimethoxy-1,4-butandiyl bis(4-*O*-benzyl-2,3-di-*O*-methoxymethylgallate) (13.1 g, 86% yield) as a white solid: mp 78.5−80.5 °C; $[\alpha]^{24}_D$ +1.7 (*c* 1.00, $CHCl_3$); IR (ZnSe, thin film) 2955, 2830, 1719, 1592, 1499, 1453, 1393, 1329, 1194, 1156, 1109, 1049, 924, 760, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 4H), 7.47−7.45 (m, 4H), 7.37−7.30 (m, 6H), 5.18 (s, 8H), 5.13 (s, 4H), 4.58 (dd, *J* = 11.5, 6.0 Hz, 2H), 4.46 (dd, *J* = 11.5, 4.0 Hz, 2H), 3.75−3.71 (m, 2H), 3.56 (s, 6H), 3.46 (s, 12H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8 (s, 2C), 151.1 (s, 4C), 143.4 (s, 2C), 137.4 (s, 2C), 128.5 (d, 4C), 128.5 (d, 4C), 128.3 (d, 2C), 125.5 (s, 2C), 112.4 (d, 4C), 95.7 (t, 4C), 79.0 (d, 2C), 75.4 (t, 2C), 64.0 (t, 2C), 59.6 (q, 2C), 56.5 (q, 4C); ESIHRMS (*m*/*z*) calcd for $C_{42}H_{50}O_{16}Na$ $[M + Na]^+$ 833.2997, found 833.3002.

To a solution of (2*S*,3*S*)-dimethoxy-1,4-butandiyl bis(4-*O*-benzyl-2,3-di-*O*-methoxymethylgallate) (1.70 g, 2.10 mmol) in THF (20 mL) was added a mixture of *i*-PrOH (105 mL) and concd hydrochloric acid (2.1 mL). The mixture was stirred for 20 h at 50 °C. To this, a mixture of *i*-PrOH (100 mL) and concd hydrochloric acid (2.0 mL) was added, and it was stirred for additional 1 h at 60 °C. To this, a mixture of *i*-PrOH (100 mL) and concd hydrochloric acid (2.0 mL) were added again, and it was stirred for 11 h at 60 °C. The mixture was cooled to 0 °C, and then, saturated aq $NaHCO_3$ was added. After removal of *i*-PrOH by evaporation, the aq mixture was extracted with AcOEt. The combined organic layer was successively washed with H_2O, and brine. After the general drying procedure, the mixture was purified by column chromatography (17 g of SiO_2, $CHCl_3$ only, then $CHCl_3$/MeOH = 100/1 to 50/1) to afford **8** (1.33 g, 100% yield) as a colorless amorphous solid: $[\alpha]^{24}_D$ −25.5 (*c* 1.00, $CHCl_3$); IR (ZnSe, thin film) 3387, 2955, 2835, 1699, 1599, 1522, 1454, 1352, 1223, 1096, 1057, 1003, 914, 870, 756, 698 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.53−7.51 (m, 4H), 7.37−7.28 (m, 6H), 7.15 (s, 4H), 5.19 (s, 4H), 4.56 (dd, *J* = 11.5, 3.2 Hz, 2H), 4.37 (dd, *J* = 11.5, 5.8 Hz, 2H), 3.83−3.81 (m, 2H), 3.52 (s, 6H); ^{13}C NMR (100 MHz, acetone-d_6) δ 166.4 (s, 2C), 151.5 (s, 4C), 139.1 (s, 2C), 138.6 (s, 2C), 129.4 (d, 4C), 129.1 (d, 4C), 128.9 (d, 2C), 126.4 (s, 2C), 110.0 (d, 4C), 79.8 (d, 2C), 74.6 (t, 2C), 64.4 (t, 2C), 59.4 (q, 2C); ESIHRMS (*m*/*z*) calcd for $C_{34}H_{34}O_{12}Na$ $[M + Na]^+$ 657.1948, found 657.1946.

(2*S*,3*S*)-Dimethoxy-1,4-butandiyl (*R*)-5,5′-Bis(benzyloxy)-4,4′,6,6′-tetrahydroxy-1,1′-biphenyl-2,2′-dicarboxylate (10). The substrate **8** (2.00 g, 3.15 mmol) was used as the starting material of the transformation. Because use of more than 1 g of **8** decreased the yield of product **10** in our preliminary investigations, the starting material was divided into two equal parts (1.00 g × 2), and two reactions were run in parallel. After the end of the reaction, the two batches were combined, and the following workups were performed together.

A mixture of $CuCl_2$ (530 mg each, total 1.06 g, 7.88 mmol) and *n*-$BuNH_2$ (1.16 g each, total 2.32 g, 31.7 mmol) was dissolved into MeOH (35 mL each) and stirred for 30 min at rt under an Ar atmosphere to prepare a blue solution of $CuCl_2$·*n*-$BuNH_2$ complex. Meanwhile, the starting material **8** was azeotropically dried using MeCN before use. It was dissolved in MeOH (35 mL each) and added to the solutions of the $CuCl_2$·*n*-$BuNH_2$ complex. The mixtures were then stirred for 30 min at rt. The reaction mixtures were diluted with Et_2O (20 mL each) and quenched with 1 M hydrochloric acid, and then, these two mixtures were combined. After evaporation to remove MeOH, the aq mixture was extracted with Et_2O. The combined organic layer was successively washed with 1 M hydrochloric acid, H_2O, and brine. After the general drying procedure, evaporation of the filtrate afforded crude **10** as a yellow amorphous solid. Chromatographic purification was possible using silica gel under rapid elution ($CHCl_3$ only, then $CHCl_3$/MeOH = 100/1). The isolated **10** was unstable after prolonged storage in air.

Data for **10**: $[\alpha]^{25}_D$ +14.2 (*c* 1.00, $CHCl_3$); IR (ZnSe, thin film) 3107, 2953, 1717, 1603, 1506, 1456, 1375, 1354, 1219, 1102, 1063, 970, 854, 754, 700 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.55−7.53 (m, 4H), 7.38−7.31 (m, 6H), 6.63 (s, 2H), 5.18 (d, *J* = 17.7 Hz, 2H), 5.13 (d, *J* = 17.7 Hz, 2H), 4.41−4.38 (m, 2H), 4.13−4.09 (m, 2H), 3.58−3.57 (m, 2H), 3.45 (s, 6H); ^{13}C NMR (100 MHz, acetone-d_6) δ 168.3 (s, 2C), 150.4 (s, 2C), 150.2 (s, 2C), 138.9 (s, 2C), 136.8 (s, 2C), 131.4 (s, 2C), 129.3 (d, 4C), 129.1 (d, 4C), 128.7 (d, 2C), 115.0 (s, 2C), 108.4 (d, 2C), 78.9 (d, 2C), 74.8 (t, 2C), 61.2 (t, 2C), 57.8 (q, 2C); ESIHRMS (*m*/*z*) calcd for $C_{34}H_{32}O_{12}Na$ $[M + Na]^+$ 655.1791, found 655.1786.

(2*S*,3*S*)-Dimethoxy-1,4-butandiyl (*R*)-4,4′,5,5′,6,6′-Hexakis-(benzyloxy)-1,1′-biphenyl-2,2′-dicarboxylate (11). According to the procedure described above, **8** (2.00 g, 3.15 mmol) was transformed to **10**, which was used for the next step without purification.[52] K_2CO_3 (1.31 g, 9.48 mmol) and BnBr (1.61 g, 9.41 mmol) were added in this order to a solution of crude **10** in acetone (15 mL). The mixture was stirred for 3 h at rt under an Ar atmosphere. To the mixture were added further acetone (15 mL), K_2CO_3 (1.00 g, 7.24 mmol), and BnBr (1.44 g, 8.42 mmol), and it was stirred for additional 3 h at rt. The reaction mixture was filtrated through a cotton−Celite pad, and the filtrate was evaporated. The

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resulting residue was diluted with AcOEt (40 mL), and it was successively washed with saturated aq NH_4Cl, H_2O, and brine. After the general drying procedure, the crude product was purified by column chromatography (57 g of SiO_2, *n*-hexane/AcOEt = 4/1 to 3/2) to afford **11** (2.28 g, 73% yield for two steps) as a yellow oil: $[\alpha]^{24}_D$ +33.3 (*c* 1.21, $CHCl_3$); IR (ZnSe, thin film) 3032, 2982, 2878, 2828, 1734, 1592, 1497, 1455, 1366, 1331, 1246, 1196, 1157, 1096, 1013, 978, 911, 847, 739, 696 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.60−7.58 (m, 4H), 7.46−7.38 (m, 10H), 7.28−7.27 (m, 6H), 7.22 (s, 2H), 7.18−7.16 (m, 6H), 7.01−6.99 (m, 4H), 5.28 (d, J = 16.6 Hz, 2H), 5.24 (d, J = 16.6 Hz, 2H), 5.03−4.96 (m, 6H), 4.80 (d, J = 10.8 Hz, 2H), 4.48 (d, J = 11.9 Hz, 2H), 4.23−4.20 (m, 2H), 3.66−3.64 (m, 2H), 3.49 (s, 6H); ^{13}C NMR (100 MHz, acetone-d_6) δ 168.4 (s, 2C), 153.5 (s, 2C), 153.0 (s, 2C), 145.2 (s, 2C), 138.9 (s, 2C), 138.8 (s, 2C), 138.0 (s, 2C), 130.5 (s, 2C), 129.4 (d, 4C), 129.1 (d, 8C), 129.0 (d, 6C), 128.9 (d, 4C), 128.8 (d, 4C), 128.7 (d, 2C), 128.4 (d, 2C), 124.2 (s, 2C), 109.7 (d, 2C), 78.7 (d, 2C), 76.1 (t, 2C), 75.6 (t, 2C), 71.9 (t, 2C), 61.7 (t, 2C), 58.0 (q, 2C); ESIHRMS (*m*/*z*) calcd for $C_{62}H_{56}O_{12}Na$ $[M + Na]^+$ 1015.3669, found 1015.3626.

(*R*)-4,4′,5,5′,6,6′-Hexakis(benzyloxy)-2,2′-bis-(hydroxymethyl)-1,1′-biphenyl [(a*R*)-12]. To a stirred mixture of LAH (9.1 mg, 0.24 mmol) in Et_2O (1.0 mL) under an Ar atmosphere was dropwise added a solution of **11** (80.3 mg, 80.9 μmol) in Et_2O (1.5 mL) at 0 °C. After being stirred at 0 °C to rt for 45 min, the reaction mixture was cooled to 0 °C again. Additional LAH (7.7 mg, 0.20 mmol) was added to the mixture, and it was stirred at 0 °C to rt for 45 min. The reaction mixture was diluted with Et_2O (3.0 mL) and quenched with H_2O (minimal required amount). Anhydrous $MgSO_4$ and Celite were added to the wet mixture, and it was filtered through a cotton−Celite pad. After evaporation of the filtrate, the resulting residue was purified by silica gel column chromatography (5.0 g of SiO_2, *n*-hexane/AcOEt = 9/1, then AcOEt only) to afford (a*R*)-**12** (57.4 mg, 83% yield, >99% ee) and **3** (4.6 mg, 38% yield) both as a colorless oil. Unidentified byproducts whose polarity was similar to that of **3** decreased the isolation yield of **3**. ^1H NMR data for (a*R*)-**12** were identical to the literature data.[4] The ee value was determined by HPLC with the chiral column (eluant: *n*-hexane/ethanol = 9/1, flow rate: 1.0 mL/min, t_R: 12.2 min). Data for (a*R*)-**12**: $[\alpha]^{25}_D$ −78.2 (*c* 0.85, $CHCl_3$); IR (ZnSe, thin film) 3391, 3063, 2876, 1595, 1455, 1123, 1098, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (br d, J = 6.9 Hz, 4H), 7.46−7.34 (m, 10H), 7.31−7.24 (m, 6H), 7.21−7.12 (m, 6H), 7.06 (s, 2H), 6.83 (br d, J = 6.6 Hz, 4H), 5.25 (d, J = 11.7 Hz, 2H), 5.21 (d, J = 11.7 Hz, 2H), 5.07 (d, J = 10.8 Hz, 2H), 5.02 (d, J = 10.8 Hz, 2H), 4.98 (d, J = 11.0 Hz, 2H), 4.60 (d, J = 11.0 Hz, 2H), 4.19 (br s, 4H), 2.68 (br s, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 153.5 (s, 2C), 151.5 (s, 2C), 141.8 (s, 2C), 139.0 (s, 2C), 138.7 (s, 2C), 138.2 (s, 2C), 137.8 (s, 2C), 129.3 (d, 4C), 129.1 (d, 4C), 128.9 (d, 4C), 128.8 (d, 4C), 128.7 (d, 2C), 128.6 (d, 2C), 128.5 (d, 4C), 128.1 (d, 2C), 128.1 (d, 4C), 122.9 (s, 2C), 110.1 (d, 2C), 75.8 (t, 2C), 75.2 (t, 2C), 71.5 (t, 2C), 62.8 (t, 2C); ESIHRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{56}H_{50}O_8$ 873.3403, found 873.3382.

(2*S*,3*S*)-Dimethoxy-1,4-Butandiyl (*R*)-5,5′-bis(benzyloxy)-4,4′,6,6′-tetrakis(methyloxy)-1,1′-biphenyl-2,2′-dicarboxylate (13). According to the procedure described in the synthesis of **10**, **8** (200 mg, 0.315 mmol) was transformed to **10**, which was used for the next step without purification.[52] To a solution of crude **10** in acetone (9.5 mL) were added MeI (447 mg, 3.2 mmol) and K_2CO_3 (653 mg, 4.72 mmol) under an Ar atmosphere. The mixture was stirred for 14 h at rt. It was then filtrated through a cotton−Celite pad and evaporated. The residue was dissolved in CH_2Cl_2 (80 mL), and the solution was successively washed with H_2O and brine. After the general drying procedure, the mixture was purified by preparative TLC ($CHCl_3$/MeOH = 30/1) to give **13** (106 mg, 49% yield for two steps) as a yellow solid, which was recrystallized from a mixture of CH_2Cl_2 and *n*-hexane to afford single crystals: mp 202.2−202.7 °C; $[\alpha]^{25}_D$ +101 (*c* 1.00, $CHCl_3$); IR (ZnSe, thin film) 2961, 2936, 2851, 1736, 1593, 1497, 1485, 1395, 1337, 1206, 1103, 1059, 1026, 986, 754, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50−7.48 (m, 4H), 7.37−7.27 (m, 6H), 6.86 (s, 2H), 5.18 (d, J = 11.2 Hz, 2H), 5.10 (d, J = 11.2 Hz, 2H), 4.47 (br d, J = 11.9 Hz, 2H), 4.17−4.13 (m, 2H), 3.85 (s, 6H), 3.64 (s, 6H), 3.59−3.58 (m, 2H), 3.51 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9 (s, 2C), 153.2 (s, 2C), 152.8 (s, 2C), 143.3 (s, 2C), 137.7 (s, 2C), 128.6 (s, 2C), 128.6 (d, 4C), 128.4 (d, 4C), 128.1 (d, 2C), 122.8 (s, 2C), 107.0 (d, 2C), 78.4 (d, 2C), 75.1 (t, 2C), 61.8 (t, 2C), 61.0 (q, 2C), 58.7 (q, 2C), 56.3 (q, 2C); ESIHRMS (*m*/*z*) calcd for $C_{38}H_{40}O_{12}Na$ $[M + Na]^+$ 711.2417, found 711.2398.

(2*S*,3*S*)-1,4-Dibenzyloxy-2,3-butandiyl Bis(4-*O*-benzylgallate) (14). (2*S*,3*S*)-1,4-Bis(benzyloxy)-2,3-butanediol (**4**) (1.00 g, 3.31 mmol) was azeotropically dried using C_6H_6 before use. It was then dissolved in CH_2Cl_2 (10 mL). To the solution were added **6** (2.59 g, 7.44 mmol), (±)-camphor-10-sulfonic acid (384 mg, 1.65 mmol), EDC·HCl (2.54 g, 13.3 mmol), and DMAP (404 mg, 3.31 mmol) under an Ar atmosphere, and the mixture was stirred for 12 h at rt. After addition of 1 M aq H_3PO_4 until pH of the mixture changed to ∼2, the aq mixture was extracted with AcOEt. The combined organic layer was successively washed with H_2O, and brine. After the general drying procedure, evaporation of the filtrate afforded crude (2*S*,3*S*)-1,4-dibenzyloxy-2,3-butandiyl bis(4-*O*-benzyl-2,5-di-*O*-methoxymethylgallate) as a colorless oil: $[\alpha]^{23}_D$ +12.1 (*c* 1.12, $CHCl_3$); IR (ZnSe, thin film) 3033, 2905, 1721, 1590, 1329, 1217, 1194, 1048, 758, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 4H), 7.46−7.44 (m, 4H), 7.36−7.20 (m, 16H), 5.70−5.65 (m, 2H), 5.15 (d, J = 8.4 Hz, 4H), 5.13 (d, J = 8.4 Hz, 4H), 5.10 (s, 4H), 4.56 (d, J = 11.9 Hz, 2H), 4.47 (d, J = 11.9 Hz, 2H), 3.80−3.72 (m, 4H), 3.43 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3 (s, 2C), 151.0 (s, 4C), 143.5 (s, 2C), 137.9 (s, 2C), 137.5 (s, 2C), 128.5 (d, 4C), 128.4 (d, 8C), 128.2 (d, 2C), 127.9 (d, 4C), 127.8 (d, 2C), 125.5 (s, 2C), 112.6 (d, 4C), 95.7 (t, 4C), 75.4 (t, 2C), 73.5 (t, 2C), 72.2 (d, 2C), 68.4 (t, 2C), 56.5 (q, 4C); ESIHRMS (*m*/*z*) calcd for $C_{54}H_{58}O_{16}Na$ $[M + Na]^+$ 985.3623, found 985.3642.

To a solution of the crude (2*S*,3*S*)-1,4-dibenzyloxy-2,3-butandiyl bis(4-*O*-benzyl-2,5-di-*O*-methoxymethylgallate) in THF (8 mL) was added a mixture of *i*-PrOH containing 5 v/v% of concd hydrochloric acid (25 mL), and it was stirred for 9 h at 50 °C. The mixture was cooled to rt, and saturated aq $NaHCO_3$ was added until the pH of the mixture became ∼7. After removal of *i*-PrOH by evaporation, the aq mixture was extracted with AcOEt. The combined organic layer was successively washed with saturated aq $NaHCO_3$, H_2O, and brine. After the general drying procedure, the mixture was purified by column chromatography (100 g of SiO_2, *n*-hexane/AcOEt = 6/1 to 1/1) to afford **14** (2.41 g, 93% yield for two steps) as a colorless amorphous solid: $[\alpha]^{25}_D$ +13.4 (*c* 1.52, $CHCl_3$); IR (ZnSe, thin film) 3424, 1707, 1597, 1455, 1364, 1215, 1055, 754, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.34 (m, 10H), 7.28−7.22 (m, 10H), 7.17 (s, 4H), 6.09 (br s, 4H), 5.65−5.62 (m, 2H), 5.11 (s, 4H), 4.53 (d, J = 12.1 Hz, 2H), 4.44 (d, J = 12.1 Hz, 2H), 3.70 (br d, J = 3.9 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9 (s, 2C), 149.2 (s, 4C), 137.9 (s, 2C), 137.5 (s, 2C), 136.7 (s, 2C), 129.0 (d, 6C), 128.8 (d, 4C), 128.6 (d, 4C), 128.1 (d, 4C), 128.0 (d, 2C), 125.4 (s, 2C), 110.1 (d, 4C), 75.6 (t, 2C), 73.5 (t, 2C), 71.9 (d, 2C), 68.3 (t, 2C); ESIHRMS (*m*/*z*) calcd for $C_{46}H_{42}O_{12}Na$ $[M + Na]^+$ 809.2574, found 809.2560.

(2*S*,3*S*)-1,4-Dibenzyloxy-2,3-butandiyl (*S*)-5,5′-bis-(benzyloxy)-4,4′,6,6′-tetrahydroxy-1,1′-biphenyl-2,2′-dicarboxylate (15). The substrate **14** (76.1 mg, 96.7 μmol) was azeotropically dried using MeCN before use. It was then dissolved in MeOH (3.0 mL). To the other flask were added $CuCl_2$ (68.3 mg, 0.508 mmol) and *n*-$BuNH_2$ (146 mg, 2.00 mmol) under a N_2 atmosphere. To the mixture was added MeOH (7.0 mL), and it was stirred for 20 min at rt to prepare a blue solution of $CuCl_2$·*n*-$BuNH_2$ complex. To this mixture was added the solution of **14** in MeOH. The mixture was stirred for 1.5 h at rt. The reaction was quenched with 1 M hydrochloric acid and saturated aq NH_4Cl. The aq mixture was extracted by AcOEt. The combined organic layer was successively washed with 1 M hydrochloric acid, saturated aq $NaHCO_3$, H_2O, and brine. After the general drying procedure, evaporation of the filtrate afforded crude **15** as a yellow amorphous solid. The isolated **15** was unstable in air to prolonged storage, which was used for the next step without purification. Data for **15**: $[\alpha]^{25}_D$ +11.1 (*c* 0.19, $CHCl_3$); IR (ZnSe, thin film) 3063, 3032, 2923, 2361, 1750, 1607, 1584, 1497, 1455, 1368, 1177, 1132, 1061, 737, 700 cm^{-1}; ^1H NMR (400 MHz,

acetone-d_6) δ 7.56−7.54 (m, 4H), 7.40−7.28 (m, 16H), 6.59 (s, 2H), 5.39 (m, 2H), 5.18 (d, J = 11.0 Hz, 2H), 5.13 (d, J = 11.0 Hz, 2H), 4.63 (d, J = 12.1 Hz, 2H), 4.54 (d, J = 12.1 Hz, 2H), 3.82 (m, 4H); ^{13}C NMR (100 MHz, acetone-d_6) δ 168.6 (s, 2C), 150.5 (s, 2C), 150.2 (s, 2C), 139.3 (s, 2C), 138.9 (s, 2C), 136.6 (s, 2C), 132.1 (s, 2C), 129.4 (d, 4C), 129.3 (d, 4C), 129.1 (d, 4C), 128.8 (d, 2C), 128.7 (d, 4C), 128.6 (d, 2C), 112.8 (s, 2C), 106.1 (d, 2C), 75.1 (d, 2C), 74.0 (t, 2C), 73.0 (t, 2C), 68.9 (t, 2C); ESIHRMS (m/z) calcd for $C_{46}H_{40}O_{12}Na$ $[M + Na]^+$ 807.2417, found 807.2401.

(2*S*,3*S*)-1,4-Dibenzyloxy-2,3-butandiyl (*S*)-4,4′,5,5′,6,6′-Hexakis(benzyloxy)-1,1′-biphenyl-2,2′-dicarboxylate (16). K_2CO_3 (82.9 mg, 0.600 mmol) and BnBr (103 mg, 0.602 mmol) were added in this order to a solution of crude **15** in acetone (2 mL) under a N_2 atmosphere. The mixture was stirred for 14 h at rt. The reaction mixture was filtrated through a cotton−Celite pad. The filtrate was diluted with AcOEt (10 mL), and the solution was successively washed with saturated aq NH_4Cl, H_2O, and brine. After the general drying procedure, the crude product was purified by silica gel column chromatography (3.0 g of SiO_2, *n*-hexane/AcOEt = 20/1 to 1/1) to afford **16** (37.6 mg, 34% yield for two steps) as a yellow amorphous solid: $[\alpha]^{25}_D$ −16.9 (c 0.955, $CHCl_3$); IR (ZnSe, thin film) 3063, 2926, 1746, 1593, 1372, 1192, 1097, 737, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.43 (m, 4H), 7.42−7.21 (m, 26H), 7.13−7.07 (m, 6H), 7.01−6.96 (m, 4H), 6.90 (s, 2H), 5.49 (s, 2H), 5.18 (d, J = 11.3 Hz, 2H), 5.08 (d, J = 11.3 Hz, 2H), 4.98 (d, J = 10.9 Hz, 2H), 4.95 (d, J = 11.0 Hz, 2H), 4.80 (d, J = 10.9 Hz, 2H), 4.64 (d, J = 11.0 Hz, 2H), 4.62 (d, J = 12.2 Hz, 2H), 4.48 (d, J = 12.2 Hz, 2H), 3.79−3.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0 (s, 2C), 152.7 (s, 2C), 152.5 (s, 2C), 144.1 (s, 2C), 137.7 (s, 2C), 137.6 (s, 2C), 137.5 (s, 2C), 136.5 (s, 2C), 129.7 (s, 2C), 128.6 (d, 4C), 128.5 (d, 4C), 128.4 (d, 4C), 128.2 (d, 4C), 128.1 (d, 2C), 128.0 (d, 4C), 127.9 (d, 6C), 127.9 (d, 4C), 127.8 (d, 2C), 127.6 (d, 4C), 127.4 (d, 2C), 121.5 (s, 2C), 107.0 (d, 2C), 75.5 (t, 2C), 75.4 (t, 2C), 75.3 (d, 2C), 73.3 (t, 2C), 71.2 (t, 2C), 67.7 (t, 2C); ESIHRMS (m/z) calcd for $C_{74}H_{64}O_{12}Na$ $[M + Na]^+$ 1167.4295, found 1167.4281.

(*S*)-4,4′,5,5′,6,6′-Hexakis(benzyloxy)-2,2′-bis-(hydroxymethyl)-1,1′-biphenyl [(a*S*)-12]. To a stirred mixture of LAH (2.8 mg, 83 μmol) in Et_2O (500 μL) under an Ar atmosphere was added dropwise a solution of **16** (23.8 mg, 21 μmol) in Et_2O (1.50 mL) at 0 °C. The mixture was stirred for an additional 30 min at 0 °C to rt. Further LAH (4.2 mg, 0.13 mmol) was slowly added at 0 °C, and the mixture was stirred for an additional 30 min at rt. The reaction was quenched by successive addition of H_2O (7.0 μL), AcOH (7.0 μL), 1 M aq NaOH (7.0 μL), and H_2O (21.0 μL). Then $MgSO_4$ was added to the wet mixture, and it was filtered through a cotton−Celite pad to remove aluminum salts and $MgSO_4$. After evaporation of the filtrate, the resulting residue was purified by silica gel column chromatography (5 g of SiO_2, *n*-hexane/AcOEt = 7/1 to 2/1) to afford (a*S*)-**12**, **4**, and their mixture. The mixture part was then separated by preparative TLC (*n*-hexane/AcOEt 2/1, run three times) to afford (a*S*)-**12** and **4**, but each of which contained small amount of another. Therefore, they were further purified by silica gel chromatography (5 g of SiO_2, *n*-hexane/AcOEt = 7/1 to 1/1) to afford (a*S*)-**12** (10.1 mg, 57% yield, 99% ee) and **4** (4.9 mg, 78% yield) both as a colorless oil. ^{1}H NMR data for (a*S*)-**12** was identical to literature data.[4] The ee value was determined by HPLC with the chiral column (eluant: *n*-hexane/ethanol =9/1, flow rate: 1.0 mL/min, t_R: 26.1 min). Data for (a*S*)-**12**: $[\alpha]^{25}_D$ +77.2 (c 0.94, $CHCl_3$).

Dimethyl (*R*)-4,4′,5,5′,6,6′-Hexakis(benzyloxy)-1,1′-biphenyl-2,2′-dicarboxylate [(a*R*)-17]. To a solution of **11** (63.7 mg, 64.4 μmol) in MeOH (5 mL) and THF (1 mL) was added NaOMe (173.9 mg, 3.22 mmol). The mixture was refluxed for 10 h, and then the reaction mixture was cooled to rt. Protic ion-exchange resin, IR-120 PLUS (H), was added to the reaction mixture and stirred. Then it was filtered through a cotton pad, and the filtrate was evaporated. The resulting residue was purified by column chromatography (4.0 g of SiO_2, *n*-hexane only then *n*-hexane/AcOEt = 3/1 to 1/9) to afford (a*R*)-**17** (55.6 mg, 95% yield, 100% ee) as a yellow amorphous solid and **3** (8.8 mg, 91% yield) as a colorlees oil. ^{1}H NMR data for (a*R*)-**17** were identical to the literature data.[4] The ee value was determined by HPLC with the chiral column (eluant: *n*-hexane/*i*-PrOH/TFA = 95/5/0.1, flow rate: 1.5 mL/min, t_R: 11.1 min). Data for (a*R*)-**17**: $[\alpha]^{25}_D$ −46.2 (c 1.00, $CHCl_3$); IR (ZnSe, thin film) 3031, 2876, 1698, 1591, 1564, 1497, 1455, 1414, 1366, 1325, 1279, 1217, 1161, 1096, 970, 910. 739, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 2H), 7.52−7.50 (m, 4H), 7.44−7.37 (m, 6H), 7.34−7.32 (m, 4H), 7.28−7.21 (m, 6H), 7.17−7.09 (m, 6H), 6.88−6.85 (m, 4H), 5.22 (d, J = 11.4 Hz, 2H), 5.18(d, J = 11.4 Hz, 2H), 5.00 (d, J = 10.8 Hz, 2H), 4.96 (d, J = 10.8 Hz, 2H), 4.89 (d, J = 11.2 Hz, 2H), 4.76 (d, J = 11.2 Hz, 2H), 3.57 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9 (s, 2C), 151.8 (s, 2C), 151.1 (s, 2C), 145.6 (s, 2C), 137.9 (s, 2C), 137.4 (s, 2C), 136.8 (s, 2C), 128.7 (d, 4C), 128.7 (d, 4C), 128.4 (d, 4C), 128.2 (d, 2C), 128.1 (d, 6C), 127.9 (d, 4C), 127.7 (s, 2C), 127.6 (d, 4C), 127.5 (d, 2C), 125.6 (s, 2C), 111.2 (d, 2C), 75.5 (t, 2C), 74.7 (t, 2C), 71.2 (t, 2C), 52.0 (q, 2C); ESIHRMS (m/z) calcd for $C_{58}H_{50}O_{10}Na$ $[M + Na]^+$ 929.3302, found 929.3286.

Dimethyl (*S*)-4,4′,5,5′,6,6′-Hexakis(benzyloxy)-1,1′-biphenyl-2,2′-dicarboxylate [(a*S*)-17]. To a solution of **16** (21.9 mg, 19.0 μmol) in MeOH (2 mL) and THF (500 μL) was added NaOMe (2.6 mg, 48 μmol). The mixture was stirred for 24 h at reflux. The reaction mixture was cooled to rt, and protic ion-exchange resin, IR-120 PLUS (H), was added. The mixture was filtered through a cotton pad, and the filtrate was evaporated. The resulting residue was purified by silica gel column chromatography (6.0 g of SiO_2, *n*-hexane/AcOEt = 7/1 to 1/1) to afford (a*S*)-**17** (13.0 mg, 75% yield, 99% ee) and **4** (4.7 mg, 81% yield) both as a colorless oil. ^{1}H NMR data for (a*S*)-**17** were identical to the literature data.[4] The ee value was determined by HPLC with the chiral column (eluant: *n*-hexane/*i*-PrOH/TFA = 95/5/0.1, flow rate: 1.5 mL/min, t_R 24.3 min). Data for (a*S*)-**17**: $[\alpha]^{25}_D$ +30.0 (c 5.30, $CHCl_3$).

(2*S*,3*S*)-Dimethoxy-1,4-butandiyl (*R*)-4,4′,6,6′-Tetrakis-(allyloxy)-5,5′-bis(benzyloxy)-1,1′-biphenyl-2,2′-dicarboxylate (18). According to the procedure described in the synthesis of **10**, **8** (800 mg, 1.26 mmol) was transformed to **10** (804 mg, quant), a part of which (26 mg, 41.1 μmol) was used for the next step without purification.[52] K_2CO_3 (227 mg, 1.64 mmol) and allyl bromide (21.9 mg, 181 μmol) were added in this order to a solution of crude **10** in acetone (4 mL) under an Ar atmosphere. The mixture was stirred for 16 h at rt. The reaction mixture was filtrated through a cotton−Celite pad. The filtrate was evaporated, and then the residue was diluted with AcOEt (10 mL) and successively washed with saturated aq NH_4Cl, H_2O, and brine. After the general drying procedure, the crude product was purified by silica gel column chromatography (1.0 g of SiO_2, *n*-hexane/AcOEt = 2/1 to 1/1) to afford **18** (21.2 mg, 65% yield for two steps) as a colorless oil: $[\alpha]^{26}_D$ +60.9 (c 0.685, $CHCl_3$); IR (ZnSe, thin film) 2932, 2880, 2830, 2361, 1736, 1593, 1497, 1482, 1455, 1408, 1331, 1246, 1196, 1157, 1096, 1013, 994, 926, 851, 743, 698 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.57−7.54 (m, 4H), 7.40−7.30 (m, 6H), 7.00 (s, 2H), 6.13 (dddd, J = 16.0, 10.6, 5.3, 5.3 Hz, 2H), 5.76 (dddd, J = 16.0, 10.8, 5.3, 5.3 Hz, 2H), 5.49 (ddd, J = 17.2, 1.6, 1.6 Hz, 2H), 5.29 (ddd, J = 10.5, 1.6, 1.6 Hz, 2H), 5.18 (d, J = 11.1 Hz, 2H), 5.09 (d, J = 11.1 Hz, 2H), 5.09 (dq, J = 17.2, 1.6, 1.6 Hz, 2H), 4.96 (dq, J = 10.5, 1.6, 1.6 Hz, 2H), 4.69−4.60 (m, 4H), 4.48 (ddt, J = 12.6, 5.5, 1.6 Hz, 2H), 4.42 (d, 2H), 4.35 (ddt, J = 12.6, 5.5, 1.6 Hz, 2H), 4.19−4.15 (m, 2H), 3.61−3.60 (m, 2H), 3.46 (s, 6H) ; ^{13}C NMR (100 MHz, acetone-d_6) δ 168.3 (s, 2C), 153.1 (s, 2C), 152.8 (s, 2C), 144.5 (s, 2C), 138.9 (s, 2C), 135.7 (d, 2C), 134.4 (d, 2C), 130.3 (s, 2C), 129.2 (d, 8C), 128.8 (d, 2C), 123.9 (s, 2C), 118.0 (t, 2C), 116.7 (t, 2C), 109.3 (d, 2C), 78.7 (d, 2C), 75.8 (t, 2C), 74.7 (t, 2C), 70.5 (t, 2C), 61.5 (t, 2C), 57.9 (q, 2C); ESIHRMS (m/z) calcd for $C_{46}H_{48}O_{12}Na$ $[M + Na]^+$ 815.3043, found 815.3017.

(*R*)-4,4′,5,5′,6,6′-Hexakis(benzyloxy)-1,1′-biphenyl-2,2′-dicarboxylic Acid (19). To a solution of (a*R*)-**11** (1.10 g, 1.10 mmol) in THF (20 mL) was added $LiOH·H_2O$ (46.5 mg, 11.0 mmol) in H_2O (5 mL). The mixture was refluxed for 12 h, and then 1 M hydrochloric acid was added until pH of the mixture became ∼1 to quench the reaction. THF was removed from the reaction mixture by evaporation, and the remained aq mixture was extracted with AcOEt. The combined organic layer was successively washed with 1 M hydrochloric acid, H_2O and brine. After the general drying procedure, the

mixture was purified by recrystallization (AcOEt/*n*-hexane) to afford **19** (850 mg, 88% yield, 100% ee) as a white powder whose ^{1}H NMR data were identical to the literature data.[4] The ee value was determined by HPLC with the chiral column (eluant: *n*-hexane/*i*-PrOH/TFA = 93/7/0.1, flow rate: 2.0 mL/min, t_R: 10.1 min). Data for **19**: mp 147−148 °C; $[\alpha]^{25}_D$ −61.2 (*c* 1.08, $CHCl_3$); IR (ZnSe, thin film) 3031, 2876, 1698, 1591, 1564, 1497, 1455, 1414, 1366, 1325, 1279, 1217, 1161, 1096, 970, 910. 739, 696 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.65 (s, 2H), 7.62 (s, 2H), 7.60 (s, 2H), 7.47−7.43 (m, 4H), 7.40−7.37 (m, 6H), 7.28−7.25 (m, 6H), 7.18−7.16 (m, 6H), 6.94−6.91 (m, 4H), 5.30 (s, 4H), 5.06 (d, *J* = 11.0 Hz, 2H), 4.99 (d, *J* = 11.0 Hz, 2H), 4.95 (d, *J* = 11.0 Hz, 2H), 4.88 (d, *J* = 11.0 Hz, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 168.0 (s, 2C), 152.6 (s, 2C), 151.9 (s, 2C), 146.4 (s, 2C), 139.0 (s, 2C), 138.7 (s, 2C), 138.2 (s, 2C), 129.4 (d, 4C), 129.2 (d, 5C), 129.1 (d, 4C), 129.0 (s, 2C), 128.9 (d, 5C), 128.7 (d, 6C), 128.3 (d, 6C), 127.2 (s, 2C), 112.3 (d, 2C), 75.9 (t, 2C), 75.1 (t, 2C), 71.8 (t, 2C); ESIHRMS (*m*/*z*): $[M - H]^+$ calcd for $C_{56}H_{45}O_{10}$ 877.3013, found 877.2982.

(*R*)-4,4′,5,5′,6,6′-Hexakis(benzyloxy)-2,2′-diformyl-1,1′-biphenyl (20). Dess−Martin periodinane (55.6 mg, 131 μmol) was added to a solution of (a*R*)-**12** (37.1 mg, 43.5 μmol) in CH_2Cl_2 (3.0 mL) at rt. After stirring for 2 h under a N_2 atmosphere, the reaction was quenched by addition of saturated aq $Na_2S_2O_3$ (1.5 mL) and $NaHCO_3$ (1.5 mL). The mixture was extracted with CH_2Cl_2. The extract was successively washed with saturated aq $NaHCO_3$, H_2O, and brine. After the general drying procedure, the crude product was purified by column chromatography (10 g of SiO_2, 10% to 30% AcOEt in *n*-hexane) to afford **20** (30.1 mg, 82%, 100% ee) as a pale yellow solid. The ee value was determined by HPLC with the chiral column (eluant: *n*-hexane/ethanol/TFA = 95/5/0.1, flow rate: 1.5 mL/min, t_R: 17.2 min). Data for **20**: mp 132−134 °C; $[\alpha]^{25}_D$ −24.4 (*c* 1.02, $CHCl_3$); IR (ZnSe, thin film) 3033, 2872, 1686, 1584, 1455, 1320, 1098, 970, 739, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 2H), 7.54−7.08 (m, 22H), 6.83 (br d, *J* = 7.6 Hz, 4H), 5.24 (s, 4H), 5.14 (d, *J* = 11.0 Hz, 2H), 5.08 (d, *J* = 11.0 Hz, 2H), 4.82 (d, *J* = 11.2 Hz, 2H), 4.62 (d, *J* = 11.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0 (d, 2C), 153.3 (s, 2C), 151.1 (s, 2C), 146.5 (s, 2C), 136.9 (s, 2C), 136.5 (s, 2C), 136.1 (s, 2C), 131.0 (s, 2C), 128.7 (d, 8C), 128.3 (d, 8C), 128.1 (d, 4C), 127.8 (d, 2C), 127.7 (d, 4C), 127.5 (d, 4C), 124.8 (s, 2C), 107.1 (d, 2C), 75.4 (t, 2C), 74.7 (t, 2C), 71.0 (t, 2C); ESIHRMS (*m*/*z*) calcd for $C_{56}H_{46}O_8Na$ $[M + Na]^+$ 869.3090, found 869.3057.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra, chromatograms, ORTEP diagram of **13**, and X-ray data of **13** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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