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SYNTHESIS OF HIGHLY OXYGENATED BIPHENYL DERIVATIVE IN AN OPTICALLY ACTIVE FORM THROUGH PALLADIUM-MEDIATED INTRAMOLECULAR BIARYL COUPLING REACTION

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Abstract – Optically active 6,6'-dihydroxymethyl-2,2'-3,3'-4,4'-hexamethoxybiphenyl (**1**) was prepared *via* the Pd-mediated biaryl coupling reaction of a phenyl benzoate derivative and the following enantioselective lactone opening reaction.

INTRODUCTION

Biaryl compounds with an axial chirality exhibit interesting and important properties in various fields of chemistry.¹ Many kinds of optically active biaryl compounds have been developed as chiral ligands² or Brønsted acid,³ and have demonstrated that they are practically efficient for a variety of catalytic asymmetric reactions.⁴

The chiral biaryl structure is also found in several classes of natural products such as lignans, alkaloids, etc.⁵ Some of them exhibit unique biological activities, therefore, the synthetic investigations have been considered as important studies.

In this report, we focused on the asymmetric synthesis of 6,6'-dihydroxymethyl-2,2'-3,3'-4,4'-hexamethoxybiphenyl (**1**), which is significantly related to the ellagitannin chemistry.⁶ To our knowledge, this molecule in a non-racemic form has been prepared only in a diastereoselective manner or by an optical resolution,⁷ while no enantioselective preparation of this compound has been reported. Thus we envisioned that the Bringmann's "*lactone concept*" would be effective for the preparation of **1** in

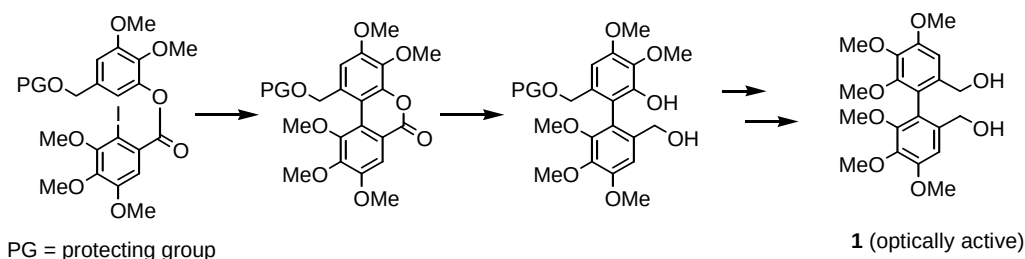
an optically active form.^{8,9}

The alternative preparation of **1** is also described, which involves an optical resolution using a chiral alkoxide derived from glucose.

RESULTS AND DISCUSSION

Synthetic Outline

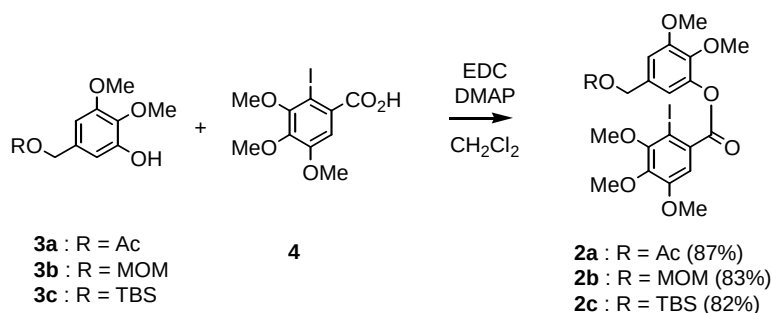
Our synthetic plan for **1** is depicted in Scheme 1. The palladium-mediated biaryl coupling reaction of phenyl benzoates has been known as a good method for the preparation of dibenzopyranones.¹⁰ The enantioselective reduction of the lactone ring would be expected to generate the biphenyl compound in a non-racemic form, which can then be transformed into **1**.



Scheme 1 Synthetic outline for optically active **1**

Biaryl coupling reaction of phenyl benzoate

We initially prepared the phenyl benzoate derivatives (**2a-2c**) as the precursors of the 6*H*-dibenzo[*b,d*]pyran-6-ones. A simple condensation reaction using EDC successfully produced the corresponding esters (**2a-2c**) from the phenols (**3a-3c**)¹¹ and benzoic acid (**4**)^{7b} (Scheme 2).



Scheme 2 Preparation of esters **2a-2c**

The palladium-mediated coupling reaction of the prepared esters (**2a-2c**) was examined under various conditions (Table 1). We first tried 10 mol% Pd(OAc)₂ with *n*Bu₃P or Ph₃P as a ligand at high temperature (runs 1-3). In these cases, the desired lactone (**5a**) was obtained in low yields, and an

unexpected tetracyclic compound **6** was isolated as a by-product. When 25 mol% of the Pd catalysts were employed at a lower temperature, better results were observed without the generation of **6** (runs 4 and 5). Both changing the base from NaOAc to K₂CO₃ and changing the ligand from Ph₃P to *n*Bu₃P were not effective (runs 6 and 8). When using 10 mol% of Pd(OAc)₂, the reactivity was dramatically reduced (run 7).

Table 1 Pd-mediated biaryl coupling reaction of **2a-2c**

5a : R = Ac
5b : R = MOM
5c : R = TBS

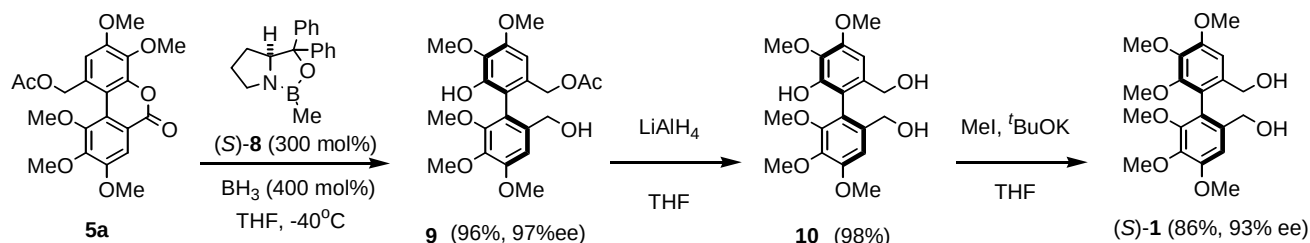
run	ester	Pd [mol%]	ligand [mol%]	base [mol%]	bath temp. (°C)	time	product (Yield, %)
1	2a	Pd(OAc) ₂ [10]	<i>n</i> Bu ₃ P [20]	NaOAc [200]	200	15 min	5a (19) 6 (6)
2	2a	Pd(OAc) ₂ [10]	Ph ₃ P [20]	NaOAc [200]	180	30min	5a (34) 6 (15)
3	2a	Pd(OAc) ₂ [10]	Ph ₃ P [20]	K ₂ CO ₃ [100]	170	30 min	5a (26) 6 (19)
4	2a	PdCl ₂ (Ph ₃ P) ₂ [25]	---	NaOAc [200]	120	3 h	5a (88)
5	2a	Pd(OAc) ₂ [25]	Ph ₃ P [50]	NaOAc [200]	120	3 h	5a (82)
6	2a	Pd(OAc) ₂ [25]	Ph ₃ P [50]	K ₂ CO ₃ [100]	120	2 h	5a (37)
7	2a	Pd(OAc) ₂ [10]	Ph ₃ P [20]	NaOAc [200]	120	24 h	5a (45) 6 (8)
8	2a	Pd(OAc) ₂ [25]	<i>n</i> Bu ₃ P [50]	NaOAc [200]	120	8 h	5a (35)
9	2b	PdCl ₂ (Ph ₃ P) ₂ [25]	---	NaOAc [200]	120	5 h	5b (80)
10	2b	Pd(OAc) ₂ [25]	Ph ₃ P [50]	NaOAc [200]	120	4 h	5b (76)
11	2c	PdCl ₂ (Ph ₃ P) ₂ [25]	---	NaOAc [200]	120	3 h	7 (25)
12	2c	Pd(OAc) ₂ [25]	Ph ₃ P [50]	NaOAc [200]	120	3 h	5c (62) 7 (18)

The MOM-protected substrate **2b** was also transformed into **5b** in good yields using 25 mol% Pd(OAc)₂ or PdCl₂(Ph₃P)₂ at 120 °C. On the other hand, the reaction of the siloxy compound **2c** did not give a satisfactory result; an aldehyde **7** was unexpectedly generated (runs 11-12).

Enantioselective synthesis of optically active **1**

Since the key intermediate lactone was successfully obtained, we next examined the further transformation of the optically active biaryl compound using **5a** (Scheme 3). The enantioselective reduction of **5a** was performed with the combination of the chiral oxazaborolidine (*S*)-**8** and borane.¹² This reductive lactone-ring opening produced the biphenyl **9** in a high enantioselectivity. The reduction of the acetoxy group in **9** and the successive methylation of the phenolic hydroxy group in **10** gave (*S*)-**1** with a slight loss of enantiomeric purity.

The absolute configuration of the product was determined by comparison of the sign of the optical rotation with the reported data.^{7i, 7h}

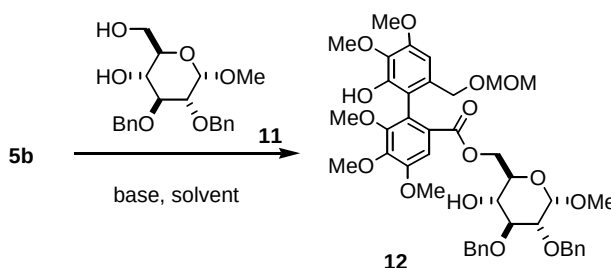


Scheme 3 Transformation of **5a** into (S)-**1**

Lactone ring opening with sugar alkoxide

As an alternative method for the preparation of the optically active **1**, we attempted a diastereoselective manner using a glucose derivative as the chiral auxiliary. The sugar alkoxide, which was easily derived from glucose, was employed as a nucleophile. Table 1 summarizes the results of the reaction between **5b** and the sugar alkoxide which was prepared from **11**¹³ and base. Although several conditions were investigated, no diastereoselectivity was observed except for the case when using DMF as the solvent (run 3) in which a slight selectivity was recognized.

Table 2 Lactone ring opening of **5b** with sugar alkoxide

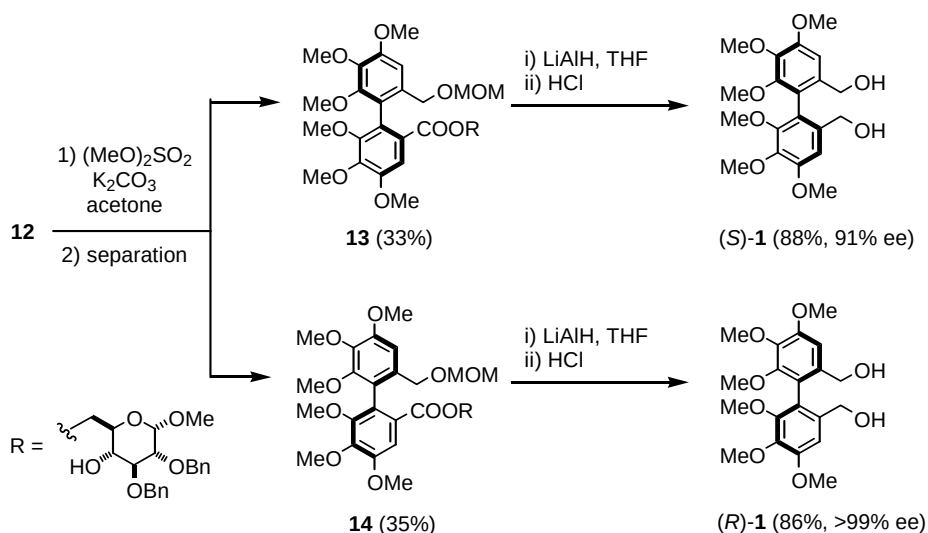


run	base (eq.)	solvent	temp. (°C)	yield (%)	d.r. ^{a)}
1	NaH (1.0)	THF	0	88	1.0 : 1.0
2	NaH (1.0)	THF	-80	89	1.0 : 1.0
3	NaH (1.0)	DMF	0	94	1.4 : 1.0
4	ⁿ BuLi (1.0)	toluene	0	89	1.0 : 1.0

a) Determined by ¹H-NMR: see the experimental section.

The inseparable 1:1 mixture of **12** was methylated to produce the hexamethoxy compounds **13** and **14** by treatment with dimethyl sulfate (Scheme 4). Fortunately, **13** and **14** could be separated from each other

by silica gel column chromatography. One diastereomer **13** was transformed into (*S*)-**1** by the reduction with LiAlH₄ and successive hydrolysis. The other isomer **14** was also subjected to the same process and (*R*)-**1** was produced.



Scheme 4 Transformation of **12** into (*S*)- and (*R*)-**1**

CONCLUSION

The asymmetric synthesis of 6,6'-dihydroxymethyl-2,2'-3,3'-4,4'-hexamethoxybiphenyl (**1**) was demonstrated using the Pd-mediated biaryl coupling reaction of phenyl benzoate followed by the enantioselective reduction of the lactone ring. Also, (*S*)- and (*R*)-**1** were separately prepared through the nucleophilic lactone ring opening reaction using a sugar alkoxide.

EXPERIMENTAL

The melting points were measured using a Yanagimoto micro melting point hot-plate apparatus and are uncorrected. The IR spectra were recorded using a JASCO FTIR-350 spectrophotometer. The NMR spectra were taken by a Varian VXR-500 (500 MHz) or MERCURY (300 MHz) instrument. The chemical shifts are given in δ ppm with TMS as the internal standard. The MS was obtained using a VG-Autospec instrument. The optical rotations were determined by a Shimadzu SPD-6A polarimeter. The elemental analysis was performed by a Yanaco MT-5 instrument. The silica gel column chromatography was carried out using 9385 Kieselgel 60 (Merck). The TLC analysis was performed on Kieselgel 60 F₂₅₄ (Merck) plates.

5-Acetoxymethyl-2,3-dimethoxyphenyl 2-iodo-3,4,5-trimethoxybenzoate (**2a**)

Under an argon atmosphere, a solution of **3a** (3.50 g, 15.5 mmol), ^{11a} **4** (5.78 g, 17.1 mmol), ^{7b,14} EDC

(4.92 g, 26.7 mmol), and DMAP (418 mg, 3.42 mmol) in CH_2Cl_2 (MeOH-free, 100 mL) was stirred for 6 h at rt. The reaction mixture was poured into water and then extracted with CH_2Cl_2 . The organic layer was washed with brine, dried over MgSO_4 , and evaporated to give a residue which was subjected to silica gel column chromatography with Et_2O -hexane (2:1).

Colorless needles, mp 89-91 °C (CH_2Cl_2 -hexane).

^1H -NMR (300 MHz, CDCl_3) δ : 2.12 (3H, s, OCOCH_3), 3.88 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 5.06 (2H, s, OCH_2Ar), 6.86 (1H, d, $J=2.0$ Hz), 6.87 (1H, d, $J=2.0$ Hz), 7.49 (1H, s).

^{13}C -NMR (75 MHz, CDCl_3) δ : 21.1, 56.2, 56.4, 60.90, 60.95, 61.1, 65.8, 85.1, 110.5, 111.3, 115.1, 129.2, 131.4, 140.9, 143.7, 145.5, 153.2, 153.5, 154.0, 164.1, 170.6.

IR (KBr) cm^{-1} : 2940, 1745 ($\text{C}=\text{O}$), 1510, 1480, 1430, 1380, 1330, 1230, 1165, 1140, 1100, 1000.

Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{IO}_9$: C, 46.17; H, 4.24. Found: C, 46.17; H, 4.22.

2,3-Dimethoxy-5-methoxymethoxymethylphenyl 2-iodo-3,4,5-trimethoxybenzoate (2b)

Under an argon atmosphere, a solution of **3b** (3.80 g, 16.6 mmol), ^{11}b **4** (6.19 g, 18.3 mmol), 7b,14 EDC (5.26 g, 27.5 mmol), and DMAP (450 mg, 3.66 mmol) in CH_2Cl_2 (MeOH-free, 100 mL) was stirred for 6 h at rt. The reaction mixture was poured into water and then extracted with CH_2Cl_2 . The organic layer was washed with brine, dried over MgSO_4 , and evaporated to give a residue which was subjected to silica gel column chromatography with Et_2O - CHCl_3 (1:20).

Pale yellow oil.

^1H -NMR (500 MHz, CDCl_3) δ : 3.42 (3H, s, CH_2OCH_3), 3.87 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.57 (2H, s, ArCH_2O), 4.72 (2H, s, OCH_2O), 6.85 (1H, d, $J=2.0$ Hz, phenol-4 or 6-H), 6.87 (1H, d, $J=2.0$ Hz, phenoxy-4 or 6-H), 7.49 (1H, s, benzoyl-6-H).

IR (neat) cm^{-1} : 1750 ($\text{C}=\text{O}$), 1500, 1480, 1460, 1430, 1380, 1340, 1200, 1170, 1140, 1100, 1050, 1000.

FAB-Mass (positive ion mode) m/z : 548 $[\text{M}]^+$.

5-tert-Butyldimethylsilyloxymethyl-2,3-dimethoxyphenyl 2-iodo-3,4,5-trimethoxybenzoate (2c)

Under an argon atmosphere, a solution of **3c** (550 mg, 1.84 mmol), ^{11}b **4** (653 mg, 1.93 mmol), 7b,14 EDC (555 mg, 2.90 mmol), and DMAP (47.2 mg, 0.386 mmol) in CH_2Cl_2 (MeOH-free, 20 mL) was stirred for 1 h at rt. The reaction mixture was poured into water and then extracted with CH_2Cl_2 . The organic layer was washed with brine, dried over MgSO_4 , and evaporated to give a residue which was subjected to silica gel column chromatography with AcOEt - CHCl_3 (1:4).

Colorless oil.

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.12 (6H, s, $\text{Si}(\text{CH}_3)_2$), 0.96 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 3.87 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.71 (2H, s, ArCH_2O), 6.79 (1H, d, $J=1.95$ Hz, phenoxy-4 or 6-H), 6.88 (1H, d, $J=1.95$ Hz, phenoxy-4 or 6-H), 7.48 (1H, s, benzoyl-6-H).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ : -5.14, 18.4, 26.0, 56.0, 56.3, 60.9, 61.1, 64.3, 84.8, 107.8, 111.1, 112.1, 129.6, 137.2, 139.4, 143.6, 145.3, 153.2, 153.3, 153.9, 164.3.

IR (neat) cm^{-1} : 1750 ($\text{C}=\text{O}$), 1500, 1480, 1460, 1430, 1390, 1340, 1200, 1170, 1140, 1100, 1080, 1000.

FAB-Mass (positive ion mode) m/z : 618 $[\text{M}]^+$.

HRMS (FAB) calcd for $\text{C}_{25}\text{H}_{35}\text{IO}_8\text{Si}$ $[\text{M}]^+$: 618.1145. Found: 618.1097.

General procedure for the coupling reaction (Table 1)

A mixture of **2** (0.183 mmol), palladium reagent, ligand, base, and DMA (2 mL) was heated in an oil bath. After cooling, the solid material was removed by filtration. The filtrate was poured into water and then extracted with CH_2Cl_2 . The organic layer was washed with brine, dried with MgSO_4 , and evaporated to give a residue which was subjected to silica gel column chromatography with AcOEt-hexane.

1-Acetoxymethyl-3,4,8,9,10-pentamethoxy-6H-dibenzo[b,d]pyran-6-one (5a)

Colorless prisms, mp 168-169 $^\circ\text{C}$ (CH_2Cl_2 -hexane).

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 2.03 (3H, s, OCOCH_3), 3.56 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 4.08 (3H, s, OCH_3), 5.23 (2H, s, ArCH_2O), 6.96 (1H, s, 2-H), 7.66 (1H, s, 7-H).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ : 21.1, 56.3, 56.4, 61.4, 61.5, 61.6, 65.9, 107.9, 108.9, 109.8, 117.9, 122.8, 129.5, 135.5, 144.2, 148.2, 149.1, 152.7, 153.2, 160.4, 170.5.

IR (KBr) cm^{-1} : 1740 ($\text{C}=\text{O}$), 1730 ($\text{C}=\text{O}$), 1600, 1480, 1380, 1350, 1330, 1230, 1100.

FAB-Mass (positive ion mode) m/z : 418 $[\text{M}]^+$, 419 $[\text{M}+1]^+$.

HRMS (FAB) calcd for $\text{C}_{21}\text{H}_{22}\text{O}_9$ $[\text{M}]^+$: 418.1264. Found: 418.1254.

Anal. Calcd for $\text{C}_{21}\text{H}_{22}\text{O}_9$: C, 60.28; H, 5.30. Found: C, 60.20; H, 5.30.

3,4,8,9,10-Pentamethoxy-1-methoxymethoxymethyl-6H-dibenzo[b,d]pyran-6-one (5b)

Colorless prisms, mp 145-147 $^\circ\text{C}$ (CH_2Cl_2 -hexane).

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 3.33 (3H, s, OCH_2OCH_3), 3.53 (3H, s, 10- OCH_3), 3.99 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 4.86 (3H, s, OCH_3), 4.59 (2H, s, CH_2O), 4.70 (2H, s, OCH_2OCH_3), 7.17 (1H, s, 2-H), 7.67 (1H, s, 7-H).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ : 55.5, 56.1, 56.3, 61.3, 61.4, 61.5, 68.9, 96.1, 108.0, 108.7, 109.5, 117.9,

123.1, 131.9, 135.1, 144.1, 148.2, 149.3, 152.8, 153.1, 160.7.

IR (KBr) cm^{-1} : 1730 (C=O), 1480, 1350, 1330, 1150, 1120, 1005, 1050, 1000.

Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{O}_9$: C, 59.99 ; H, 5.75. Found : C, 59.78 ; H, 5.68

1-*tert*-Butyldimethylsilyloxymethyl-3,4,8,9,10-pentamethoxy-6*H*-dibenzo[*b,d*]pyran-6-one (5c)

Colorless needles, mp 165-167 °C (Et_2O).

^1H -NMR (300 MHz, CDCl_3) δ : -0.04 (6H, s, $\text{Si}(\text{CH}_3)_2$), 0.87 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 3.50 (3H, s, 10- OCH_3), 3.97 (3H, s, OCH_3), 3.999 (3H, s, OCH_3), 4.003 (3H, s, OCH_3), 4.08 (3H, s, OCH_3), 4.75 (2H, s, ArCH_2O), 7.27 (1H, s, 2-H), 7.68 (1H, s, 7-H).

^{13}C -NMR (75 MHz, CDCl_3) δ : -5.4, 18.3, 25.8, 55.9, 56.4, 61.2, 61.4, 61.6, 64.2, 107.95, 108.04, 108.6, 117.9, 123.1, 134.7, 135.2, 143.9, 148.3, 149.3, 152.8, 153.0, 160.8.

IR (KBr) cm^{-1} : 1735 (C=O), 1480, 1340, 1120, 1080.

Anal. Calcd for $\text{C}_{25}\text{H}_{34}\text{O}_8\text{Si}$: C, 61.20 ; H, 6.99. Found : C, 61.35 ; H, 6.86.

2,3,7,8-Tetramethoxy-5*H*,10*H*-chromeno[6,5,4,3-*c,d,e*]chromen-5-one (6)

Colorless needles, mp 244-246 °C (CH_2Cl_2 -hexane).

^1H -NMR (300 MHz, CDCl_3) δ : 3.93 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 5.44 (2H, s, ArCH_2O), 6.60 (1H, s, 1-H), 7.34 (1H, s, 6-H).

^{13}C -NMR (75 MHz, CDCl_3) δ : 56.4, 56.6, 61.3, 61.6, 67.7, 77.2, 103.8, 104.1, 105.9, 112.5, 116.7, 121.8, 142.2, 142.3, 142.5, 153.8, 153.9, 160.1.

IR (KBr) cm^{-1} : 1730 (C=O), 1610, 1490, 1400, 1380, 1330, 1240, 1110, 1000.

FAB-Mass (positive ion mode) m/z : 345 $[\text{M}+1]^+$.

HRMS (FAB) calcd for $\text{C}_{18}\text{H}_{16}\text{O}_7$ $[\text{M}]^+$: 344.0896. Found : 344.0864.

Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{O}_7$: C, 62.79 ; H, 4.68. Found : C, 62.70 ; H, 4.68.

1-Formyl-3,4,8,9,10-pentamethoxy-6*H*-dibenzo[*b,d*]pyran-6-one (7)

Colorless needles, mp 218-224 °C (CH_2Cl_2 - Et_2O).

^1H -NMR (300 MHz, CDCl_3) δ : 3.54 (3H, s, 10- OCH_3), 4.01 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 4.08 (3H, s, OCH_3), 4.09 (3H, s, OCH_3), 7.41 (1H, s, 2 or 7-H), 7.73 (1H, s, 2 or 7-H), 9.86 (1H, s, CHO).

^{13}C -NMR (75 MHz, CDCl_3) δ : 56.3, 56.5, 60.2, 61.5, 61.7, 108.1, 108.5, 111.0, 117.5, 121.2, 128.3, 139.5, 144.6, 148.6, 148.8, 152.9, 154.1, 160.0, 187.3.

IR (KBr) cm^{-1} : 1730 (C=O), 1690 (C=O), 1600, 1480, 1350, 1330, 1100.

(*S*)-6-Acetoxymethyl-2-hydroxy-6'-hydroxymethyl-2',3,3',4,4'-pentamethoxy-1,1'-biphenyl (9)

To a solution of (*S*)-**8** (596 mg, 2.15 mmol) in THF (20 mL), a BH₃-THF solution (2.87 mmol) was added at 0 °C under an argon atmosphere. The mixture was warmed to rt, stirred for 30 min, and then cooled to -40 °C. A solution of **5a** (300 mg, 0.717 mmol) in THF (40 mL) was dropwise added to the mixture. After 12 h, the entire mixture whole was poured into water and extracted with Et₂O. The organic layer was washed with brine, dried over MgSO₄, and the solvent evaporated. The resulting residue was purified by silica gel column chromatography using AcOEt.

Colorless needles, mp 129-130 °C (CH₂Cl₂-hexane).

¹H-NMR (300 MHz, CDCl₃) δ: 1.87 (1H, bs, CH₂OH), 1.98 (3H, s, OCOCH₃), 3.58 (3H, s, 2'-OCH₃), 3.90 (3H, s, OCH₃), 3.93 (6H, s, 2 × OCH₃), 3.95 (3H, s, OCH₃), 4.28 (2H, s, ArCH₂OH), 4.71 (1H, d, A of AB, *J*=12.5 Hz, ArCH_AH_BOAc), 4.79 (1H, d, B of AB, *J*= 12.5 Hz, ArCH_AH_BOAc), 5.88 (1H, br, OH), 6.63 (1H, s, 5 or 5'-H), 6.94 (1H, s, 5 or 5'-H).

¹³C-NMR (75 MHz, CDCl₃) δ: 21.0, 55.8, 55.9, 60.8, 61.0, 61.1, 63.5, 64.5, 94.8, 104.5, 108.0, 115.27, 119.9, 131.2, 135.0, 135.8, 141.6, 146.7, 151.5, 153.4, 170.4.

IR (KBr) cm⁻¹: 3460 (OH), 3140 (OH), 1735 (C=O), 1240, 1110.

Anal. Calcd for C₂₁H₂₆O₉: C, 59.71; H, 6.20. Found: C, 59.88; H, 6.35.

[α]_D²² = -7.0°(CHCl₃, *c* 0.490) [97% ee]. The ee was determined by HPLC analysis.

HPLC conditions: column, CHIRALPACK AD; eluent, IPA:hexane = 1:4; flow rate, 1.0 mL/min; wavelength, 254 nm; retention time, 20.2 min. [(*R*)-form: 14.6 min.]

(*S*)-2-Hydroxy-6,6'-dihydroxymethyl-2',3,3',4,4'-pentamethoxy-1,1'-biphenyl (**10**)

To a suspension of LiAlH₄ (17.0 mg, 0.473 mmol) and THF (5 mL), a solution of **9** (100 mg, 0.237 mmol, 97%ee) in THF (5 mL) was dropwise added at 0 °C, and then the mixture was stirred for 12 h at -10 °C. The reaction was quenched with a 10% NaOH aqueous solution. After extraction with ether, the organic layer was dried over MgSO₄ and the solvent was evaporated to give a residue which was subjected to silica gel column chromatography using AcOEt-hexane (5:1).

Colorless needles, mp 154-155 °C (CH₂Cl₂-hexane).

¹H-NMR (300 MHz, CDCl₃) δ: 3.20 (2H, br, CH₂OH exchange with D₂O), 3.57 (3H, s, 2'-OCH₃), 3.91 (3H, s, OCH₃), 3.93 (3H, s, OCH₃), 3.94 (3H, s, OCH₃), 3.94 (3H, s, OCH₃), 4.17 (2H, s, 6-CH₂OH), 4.24 (1H, d, A of AB, *J*=11.7 Hz, 6'-CH_AH_BOH), 4.24 (1H, d, A of AB, *J*=11.7 Hz, 6'-CH_AH_BOH), 6.70 (1H, s, 5 or 5'-H), 6.92 (1H, s, 5 or 5'-H).

¹³C-NMR (75 MHz, CDCl₃) δ: 55.7, 55.9, 61.4, 63.4, 63.7, 105.4, 108.7, 114.7, 121.1, 134.9, 135.7, 135.9, 141.9, 146.7, 151.2, 151.8, 153.3.

IR (KBr) cm⁻¹: 3480 (OH), 3320 (OH), 3160 (OH), 1600, 1460, 1400, 1320, 1100, 1000.

Anal. Calcd for C₁₉H₂₄O₈: C, 59.99; H, 6.36. Found: C, 59.92; H, 6.40.

$[\alpha]_D^{24} +19.8^\circ$ (CHCl₃, *c* 0.540) [96% ee]. The ee was determined by HPLC analysis.

HPLC conditions : column, CHIRALPACK AD; eluent, IPA:hexane = 1:4; flow rate, 1.0 mL/min; wavelength, 254 nm; retention time, 16.6 min. [(*R*)-form: 13.8 min.]

(*S*)- 6,6'-Dihydroxymethyl-2,2',3,3',4,4'-hexamethoxy-1,1'-biphenyl ((*S*)-1)⁷

To a stirring solution of **10** (55 mg, 0.145 mmol) in THF (10 mL), MeI (9.28 μ L, 0.149 mmol) and ^tBuOK (16.8 mg, 0.149 mmol) were successively added at 0 °C. The mixture was allowed to warm to rt. After 72 h, the mixture was poured into water and extracted with Et₂O. The organic layer was washed with brine, dried over MgSO₄, and the solvent evaporated to give a residue which was subjected to silica gel column chromatography using AcOEt-CHCl₃ (1:1).

Colorless needles, mp 127-128 °C (CH₂Cl₂-hexane).

¹H-NMR (300 MHz, CDCl₃) δ : 2.25 (2H, br, CH₂OH), 3.67 (6H, s, 2,2'-OCH₃), 3.89 (6H, s, OCH₃), 3.94 (6H, s, OCH₃), 4.19 (4H, s, 6,6'-CH₂OH), 6.89 (2H, s, 5,5'-H).

¹³C-NMR (75 MHz, CDCl₃) δ : 56.0, 60.92, 60.93, 63.7, 108.7, 121.5, 135.5, 141.5, 150.8, 153.1.

IR (KBr) cm⁻¹: 3500 (OH), 3400 (OH), 1600, 1460, 1400, 1120, 1100.

Anal. Calcd for C₂₀H₂₆O₈ : C, 60.90 ; H, 6.64. Found : C, 60.98 ; H, 6.49.

$[\alpha]_D^{26} = +43.1^\circ$ (CHCl₃, *c* 0.490) [93% ee]. The ee was determined by HPLC analysis.

HPLC conditions : column, CHIRALCELL OD; eluent, IPA:hexane = 1:4; flow rate, 1.0 mL/min; wavelength, 254 nm; retention time, 8.1 min. [(*R*)-**1**, 5.9 min.]

General procedure for Table 2

To a mixture of **11** (116 mg, 0.309 mmol), NaH (60% in mineral oil) (12.4 mg, 0.309 mmol), and THF (10 mL), a solution of **5b** (130 mg, 0.309 mmol) in THF (5 mL) was dropwise added at 0 °C. After check of TLC, the mixture was poured into water and extracted with AcOEt. The organic layer was washed with brine, dried over MgSO₄, and evaporated to give a residue which was subjected to silica gel column chromatography using AcOEt-hexane (1:1). An inseparable diastereomeric mixture of **12** (216 mg) was obtained. The ratio of diastereomers was determined by ¹H-NMR analysis after the next transformation.

Methyl 2,3-di-O-benzyl-6-O-[(*S*)-3,4,5-trimethoxy-2-(2,3,4-trimethoxy-6-methoxymethoxymethylphenyl)-benzoyl]- α -D-glucopyranoside (13**) and Methyl 2,3-di-O-benzyl-6-O-[(*R*)-3,4,5-trimethoxy-2-(2,3,4-trimethoxy-6-methoxymethoxymethylphenyl)-benzoyl]- α -D-glucopyranoside (**14**)**

A mixture of **12** (1:1 mixture of diastereomers, 216 mg, 0.271 mmol), (MeO)₂SO₂ (28 μ L, 0.298 mmol), K₂CO₃ (37 mg, 0.271 mmol), and acetone (10 mL) was heated under reflux for 5 h, and then poured into

water. After extraction with ether, the organic layer was washed with brine, dried over MgSO_4 , and the solvent evaporated. Purification with silica gel column chromatography using AcOEt-hexane (1:1) gave **14** (76.7 mg, 35%) and **13** (72.3 mg, 33%).

13: Colorless oil.

^1H -NMR (500 MHz, CDCl_3) δ : 2.75 (1H, dd, $J=9.5$, 9.5 Hz), 3.25 (3H, s, OCH_3), 3.30 (3H, s, OCH_3), 3.31 (1H, dd, $J=3.8$, 9.8 Hz), 3.56 (3H, s, OCH_3), 3.59 - 3.90 (3H, m), 3.65 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.93 (6H, s, $2 \times \text{OCH}_3$), 4.06 (1H, d, A of AB, $J=11.3$ Hz), 4.11 (1H, dd, $J=1.8$, 12.3 Hz), 4.24 (1H, d, B of AB, $J=11.3$ Hz), 4.43 (1H, d, $J=3.5$ Hz), 4.44 (1H, d, A of AB, $J=6.3$ Hz), 4.52 (1H, d, B of AB, $J=6.3$ Hz), 4.51 (1H, dd, $J=3.5$, 9.0 Hz), 4.66 (1H, d, A of AB, $J=12.0$ Hz), 4.83 (1H, d, B of AB, $J=12.0$ Hz), 4.78 (1H, d, A of AB, $J=11.3$ Hz), 4.89 (1H, d, B of AB, $J=11.3$ Hz), 6.75 (1H, s), 7.28 - 7.45 (11H, m).

^{13}C -NMR (75 MHz, CDCl_3) δ : 55.1, 55.3, 56.0, 60.50, 60.53, 60.6, 60.8, 63.9, 68.2, 69.0, 73.5, 75.7, 80.0, 81.4, 96.2, 98.3, 107.9, 109.8, 123.4, 124.7, 125.6, 127.5, 127.7, 127.96, 127.99, 128.1, 128.2, 130.5, 138.4, 139.0, 141.3, 145.6, 151.0, 151.4, 152.1, 152.4, 167.1.

IR (CHCl_3) cm^{-1} : 3500 (OH), 1720 (C=O), 1590, 1485, 1460, 1390, 1330, 1100.

FAB-Mass (positive ion mode) m/z : 809 $[\text{M}+1]^+$.

14: Colorless oil.

^1H -NMR (500 MHz, CDCl_3) δ : 3.17 (1H, dd, $J=9.3$, 9.3 Hz), 3.20 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 3.42 (1H, dd, $J=3.5$, 9.5 Hz), 3.56 - 3.65 (2H, m), 3.59 (3H, s, OCH_3), 3.63 (3H, s, OCH_3), 3.71 (1H, dd, $J=9.3$, 9.3 Hz), 3.82 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.12 (1H, d, A of AB, $J=12.5$ Hz), 4.21 (1H, d, B of AB, $J=12.5$ Hz), 4.24 (1H, s), 4.25 (1H, d, $J=1.5$ Hz), 4.46 (2H, s), 4.56 (1H, d, $J=3.5$ Hz), 4.66 (1H, d, A of AB, $J=12.3$ Hz), 4.73 (1H, d, A of AB, $J=11.5$ Hz), 4.75 (1H, d, B of AB, $J=12.3$ Hz), 4.96 (1H, d, B of AB, $J=11.5$ Hz), 6.82 (1H, s), 7.29 - 7.38 (11H, m).

^{13}C -NMR (75 MHz, CDCl_3) δ : 55.1, 55.2, 55.7, 56.0, 60.5, 60.6, 60.7, 60.8, 63.4, 67.2, 69.2, 69.7, 73.1, 75.5, 79.5, 81.2, 95.7, 98.0, 106.4, 109.3, 122.4, 124.8, 125.8, 127.6, 127.8, 127.9, 127.9, 128.2, 128.3, 131.4, 137.9, 138.7, 140.9, 145.5, 150.8, 151.6, 152.1, 152.5, 166.6.

IR (CHCl_3) cm^{-1} : 3480 (OH), 1700 (C=O), 1590, 1490, 1480, 1395, 1330, 1230, 1155, 1100.

FAB-Mass (positive ion mode) m/z : 831 $[\text{M}+\text{Na}]^+$.

Transformation of **13** into (S)-1

To a suspension of LiAlH_4 (6.0 mg, 0.161 mmol) and THF (1 mL), a solution of **13** (65.2 mg, 0.081 mmol) in THF (2 mL) was dropwise added at 0 °C, and then the mixture was stirred for 1 h at the same temperature. The reaction was quenched with a 5N HCl aqueous solution, and then the mixture was stirred for 4 h at 50 °C. After extraction with Et_2O , the organic layer was dried over MgSO_4 and the

solvent was evaporated to give a residue which was subjected to silica gel column chromatography using AcOEt-hexane (2:1). Thus (*S*)-**1** (55.9 mg, 88%, 91%ee) was obtained.

Transformation of **14** into (*R*)-**1**

Using a method similar to the one just described, (*R*)-**1** was obtained from **14**.

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