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Intramolecular biaryl coupling reaction of benzyl benzoate and phenyl benzoate derivatives, and its application to the formal synthesis of (−)-steganone

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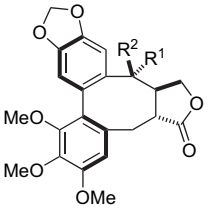
Abstract—Construction of the biaryl moiety of stegane and related compounds through an intramolecular biaryl coupling reaction is described. Undesired products were obtained by the intramolecular coupling reaction of benzyl benzoates (**8**, **13**, and **14**) because of their steric and electrostatic properties, and only that of phenyl benzoates (**26b** and **26c**) afforded the desired biaryl lactones in good yields. An asymmetric formal synthesis of the title compound has been achieved using an enantioselective lactone-opening reaction followed by a four-step conversion to the known compound.

1. Introduction

Stegane (**1**) and its related compounds (**2**, **3**) are dibenzocyclooctadiene lignans isolated from *Steganotaenia araliacea* in 1973 (Fig. 1).[1] They have attracted considerable synthetic interest because of their significant biological activities, such as antileukemic property,[2] and their structurally unique features. One of the most outstanding features in their structures is an unsymmetrical biaryl moiety with an axial chirality. To date, various strategies have been attempted to form a biaryl system in the synthesis of stegane and related compounds, such as photocyclization,[3] Suzuki–Miyaura coupling,[4] oxidative biaryl coupling,[5] the S_NAr reaction,[6] Ullmann coupling,[7] and the [2+2+2] three-component cyclization reaction.[8] In general, their axial chirality has been formed in a diastereoselective manner, whereas the enantioselective formation of these targets has not been reported.



$R^1 = R^2 = H$: (-)-stegane (**1**)
R^1, $R^2 = O$: (-)-steganone (**2**)
$R^1 = OAc$, $R^2 = H$: (-)-steganacin (**3**)

Figure 1.

On the other hand, Bringmann has proposed a 'lactone strategy' for the enantioselective preparation of axially chiral biaryl compounds, which is quite an effective method to synthesize the biaryl-type natural products involving axial chirality in an optically active form.[9]

In this report, we investigated the intramolecular biaryl coupling reaction of benzyl benzoate and phenyl benzoate derivatives to provide the biaryl part of stegane and its related compounds. Also we extended Bringmann's 'lactone strategy' to the first enantioselective formation of this axial chirality.[10]

2. Results and discussion

2.1. Coupling reaction of benzyl benzoate derivatives[11]

Initially, we examined the Pd-mediated intramolecular coupling reaction of benzyl benzoate (**8**). Benzoic acid (**6**) was readily prepared from piperonyl alcohol by iodination[12] of **4** followed by a two-step oxidization, and then esterification of **6** with 3,4,5-trimethoxybenzylalcohol (**7**) afforded the coupling precursor (**8**) in good yield (Scheme 1). Although the

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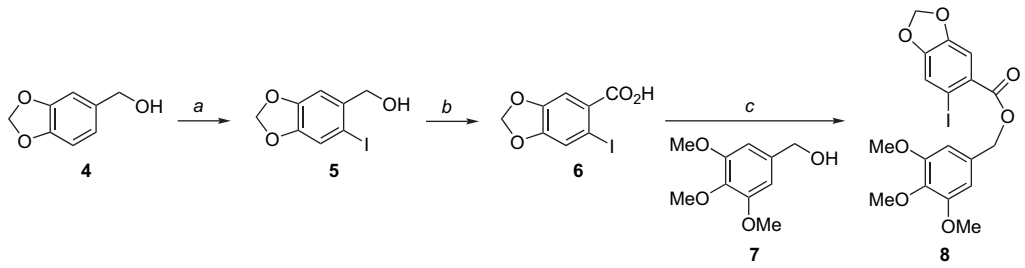
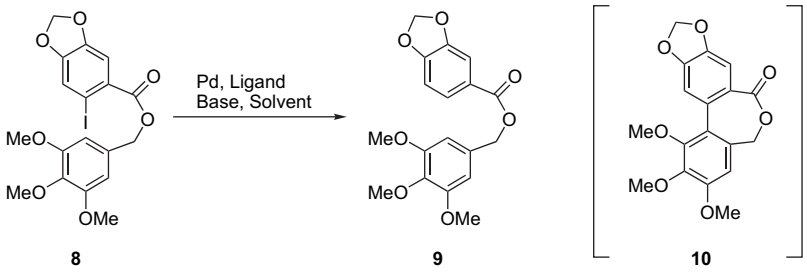


Scheme 1. (a) I_2, CF_3CO_2Ag, $CHCl_3$, −5 °C, 10 min, 83%; (b) (i) CrO_3, *c*-H_2SO_4, H_2O, acetone, 0–5 °C, 5 min; (ii) H_2O_2, NaH_2PO_4, $HClO_2$, MeCN, H_2O, rt, 2 h, 73%; (c) **7**, EDC, DMAP, CH_2CI_2, rt, 1 h, 66%.

coupling reaction of **8** under various reaction conditions was investigated, the desired biaryl lactone (**10**) could not be obtained; thus dehalogenation mainly occurred to give ester (**9**) (Table 1). Especially, using a non-polar solvent and an amine, such as toluene and $^{i}Pr_2NEt$, afforded the dehalogenated product in high yield (Table 1, run 1).

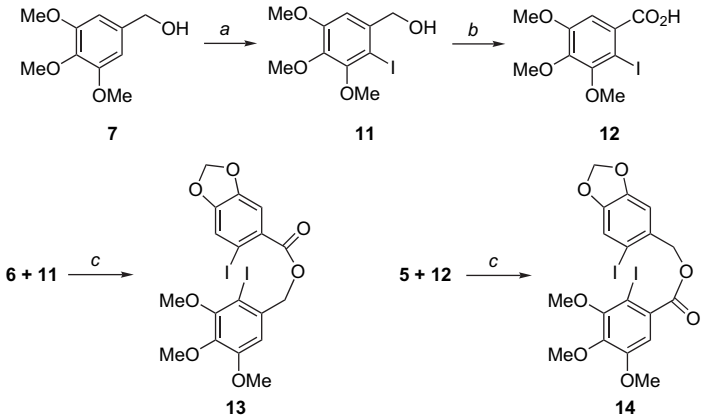
Because the Pd-mediated intramolecular coupling reaction of monoiodide **8** was not successful, we attempted the Ullmann coupling reaction of benzyl benzoate derivatives. This method is a conventional technique for the formation of a biaryl component; however, this process is generally ineffective for unsymmetrical biaryl compounds because a competitive homo-coupling cannot be avoided.[13] Bisiodides **13** and **14** as coupling precursors were prepared via esterification between the corresponding 2-iodo benzoic acids **6** and **12**, and 2-iodo benzylalcohols **11** and **5**, respectively (Scheme 2). Alcohol (**11**) and benzoic acid (**12**) were synthesized through a procedure similar to the synthesis of **5** and **6**. As shown in runs 1–3 of Table 2, the Ullmann coupling reaction of **13** produced only the homo-coupling product (**15**) and dehalogenated ester (**16**) without the desired

Table 1. Pd-catalyzed aryl–aryl coupling reaction of **8**



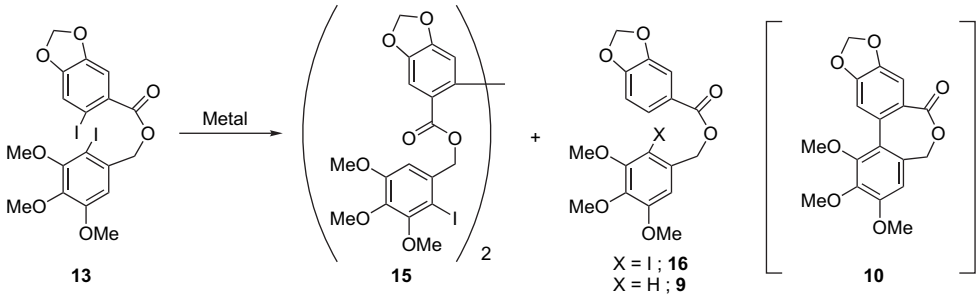
Run	Pd (mol %)	Ligand (mol %)	Base (mol %)	Solvent	Temp (°C)	Time (h)	Yield (%)	
							9	**10**
1	$Pd(OAc)_2$ (20)	PPh_3 (60)	$^{i}Pr_2NEt$ (200)	Toluene	Reflux	2.5	84	N.D.[a]
2	$Pd(acac)_2$ (100)	POT (300)	K_2CO_3 (200)	DMF	130	2.5	—[b]	N.D.[a]
3	$Pd(PPh_3)_2Cl_2$ (20)	—	AcONa (200)	DMA	Reflux	1.5	—[b]	N.D.[a]
4	$Pd(PPh_3)_4$ (20)	—	Ag_2CO_3 (200)	MeCN	Reflux	9	—[c]	

[a] N.D., not detected.
[b] Compound **9** was the major product on TLC analysis.
[c] Many spots were observed on TLC.



Scheme 2. (a) I_2, CF_3CO_2Ag, $CHCl_3$, −5 °C, 1 h, 79%; (b) (i) CrO_3, *c*-H_2SO_4, H_2O, acetone, 0–5 °C, 5 min; (ii) H_2O_2, NaH_2PO_4, $HClO_2$, MeCN, H_2O, rt, 1 h, 92%; (c) EDC, DMAP, CH_2Cl_2, rt, **13**: 1 h, 79%; **14**: 2 h, 80%.

Table 2. Ullmann-type coupling reaction of **13**



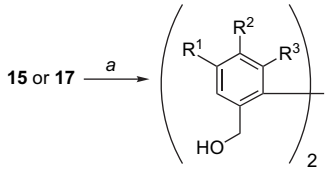
13 **15** X = I ; **16** X = H ; **9** **10**

Run	Conditions (mol %)	Yield (%)			
		15	**16**	**9**	**10**
1	Cu (800), DMF, reflux, 2 h	52	16	—	—
2	Cu (800), DMA, reflux, 2 h	25	49	—	—
3	Cu (800), DMSO, reflux, 2 h	—[a]			
4	$Pd(OAc)_2$ (20), PPh_3 (40), $^iPr_2NEt$ (200), xylene, reflux, 2 h	—	18	75	—
5	$Pd(acac)_2$ (20), DPPP (40), $^iPr_2NEt$ (200), DMA, reflux, 1 h	—	15	33	—
8	$Pd(PPh_3)_2Cl_2$ (20), $(Bu_3Sn)_2$ (100), Bu_4NBr (150), Li_2CO_3 (200), toluene, reflux, 5 h	—	—	41	—
6	$Ni(PPh_3)Cl_2$ (20), PPh_3 (200), Zn (100), KI (100), DMF, reflux 5 h	—[a]			
7	Zn (200), DMF, reflux, 4 h	—	28	72	—

[a] Many spots were observed on TLC.

lactone (**10**) being isolated, when DMF or DMA was used as a reaction medium (runs 1 and 2). DMSO gave only a complex mixture (run 3). On the other hand, the Ullmann coupling reaction of **14** in DMF produced a result nearly similar to that above, namely, dimerization and dehalogenation of the starting material predominantly occurred (Table 3, run 1). In this case, the desired lactone (**20**) was fortunately isolated although the yield was quite low. Here, we carried out the degradation experiment of dimers **15** and **17** in order to confirm their structures (Scheme 3). Reduction of **15** and **17** with DIBAL produced the known bisbenzylalcohols **21**[14] and **22**[15] as the main products. We also examined the coupling reaction of bisiodides **13** and **14** using some other metal reagents (Table 2, runs 4–7, and Table 3, runs 2 and 3);[14,16] however, they produced only the dehalogenated products **9**, **16**, **18**, and **19**.

As mentioned above, the biaryl coupling reaction of benzyl benzoate derivatives was not suitable for the preparation of dibenzoxepinone skeleton. It was thought that the steric



21 : R^1, R^2 = -OCH_2O-; R^3 = H
22 : R^1 = R^2 = R^3 = -OMe

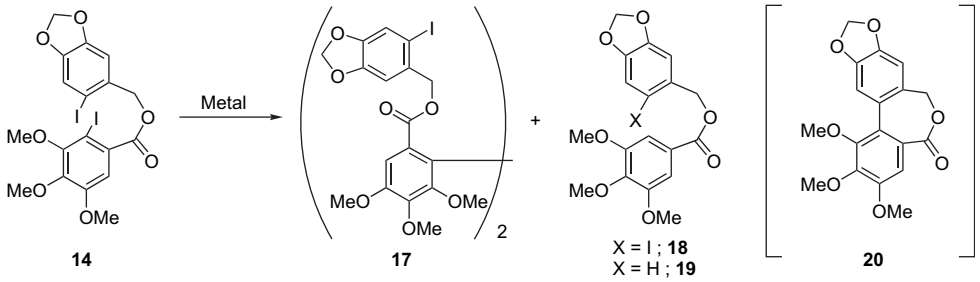
Scheme 3. (a) DIBAL, toluene, −78 °C, 1 h, **21**: 68%; **22**: 74%.

factor interfered with these reactions. Thus, we intended to investigate the next class of substrates, phenyl benzoate derivatives.

2.2. Intramolecular biaryl coupling reaction of phenyl benzoate derivatives

Contrary to the benzyl benzoate derivatives, the Pd-mediated intramolecular biaryl coupling reaction[17] of phenyl

Table 3. Ullmann-type coupling reaction of **14**

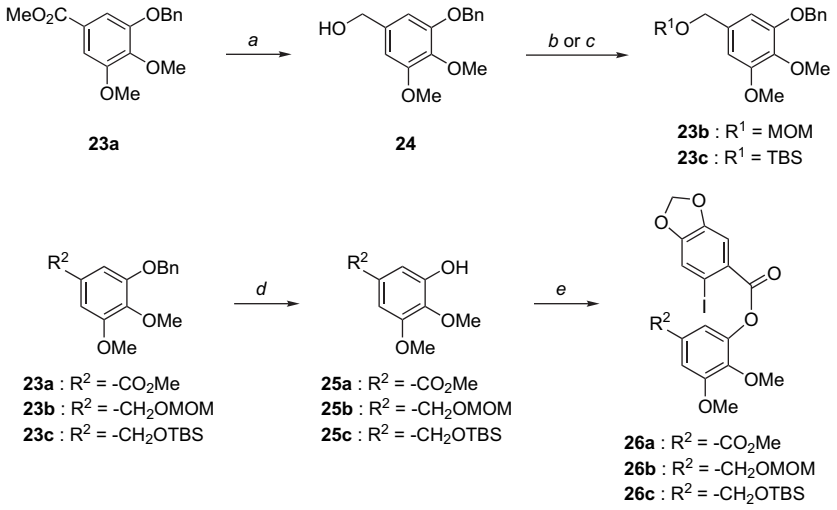


14 **17** X = I ; **18** X = H ; **19** **20**

Run	Conditions (mol %)	Yield (%)			
		17	**18**	**19**	**20**
1	Cu (800), DMF, reflux, 2 h	62	25	—	5
2	$Pd(OAc)_2$ (20), PPh_3 (40), $^iPr_2NEt$ (200), xylene, reflux, 0.5 h	—	—	78	—
3	$Ni(PPh_3)_4$ (100), DMF, reflux, 10 h	—[a]			

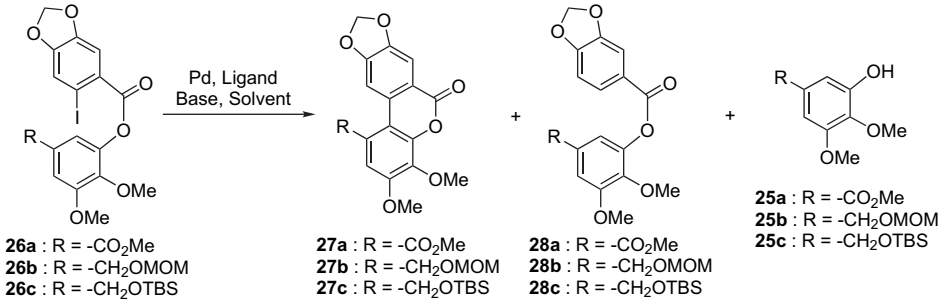
[a] Many spots were observed on TLC.

benzoate derivatives has been studied well.[18] This reaction is a very effective method for the preparation of various dibenzopyranones, so we planned to apply this method to phenyl benzoate **26a** at first. Ester **26a** was prepared from the known phenol **25a**[19] via a simple esterification with **6** (Scheme 4). Although the coupling reaction of **26a** was investigated intensively, the desired lactone **27a** could not be isolated, and the dehalogenated product **28a** and the hydrolyzed product **25a** were obtained instead (Table 4, runs 1 and 2). We assumed that the methoxycarbonyl group on the aromatic ring interfered with this reaction because of its electron-withdrawing property. Accordingly, we selected phenyl benzoates **26b** and **26c**, which possess a benzyl ether group instead of a methoxycarbonyl group, as coupling precursors. Both **26b** and **26c** were prepared as follows: **23a** was reduced with DIBAL to benzylalcohol (**24**), which was subsequently protected with a MOM or TBS group. After that, the resulting protected benzylalcohols **23b** and **23c** were reduced to **25b** and **25c**, finally condensation with **6** was carried out to afford the corresponding esters **26b** and **26c**, respectively. The esters were intensively investigated for the Pd-mediated biaryl coupling reaction under various conditions. Runs 3–10 of Table 4 demonstrate that the reaction of **26b** and **26c** proceeded to form the desired lactones **27b** and **27c** in good yield. Moreover, we confirmed the ability to apply this reaction to a gram-scale (~20 g) synthesis.



Scheme 4. (a) DIBAL, toluene, −78 °C, 1 h, 96%; (b) MOMCl, $^{i}Pr_2NEt$, DMF, 60 °C, 1 h, 96% for **23b**; (c) TBSCI, imidazole, CH_2Cl_2, rt, 5 min, quant. for **23c**; (d) H_2, Pd–C, MeOH or AcOEt, rt, 83–100%; (e) **6**, EDC, DMAP, CH_2Cl_2, rt, 84–100%.

Table 4. Pd-catalyzed aryl–aryl coupling reaction of **26**



Substrate	Run	Pd (mol %)	Ligand (mol %)	Base (mol %)	Solvent	Temp (°C)	Time (min)	Yield (%)		
								27	**28**	**25**
26a	1	$Pd(OAc)_2$ (200)	PPh_3 (60)	K_2CO_3 (200)	DMF	130	540	—	—	19
	2	$Pd(OAc)_2$ (100)	DPPP (100), $^{n}Bu_3P$ (100)	$^{i}Pr_2NEt$ (200)	DMF	130	180	—	40	19
26b	3	$Pd(acac)_2$ (20)	PPh_3 (40)	AcONa (200)	Toluene	Reflux	210	—[a]		
	4	$Pd(OAc)_2$ (20)	PPh_3 (40)	$^{i}Pr_2NEt$ (200)	DMF	Reflux	90	—	54	—
	5	$Pd(PPh_3)_4$ (20)	—	Ag_2CO_3 (200)	DMF	Reflux	90	25	14	—
	6	$Pd(OAc)_2$ (10)	$^{n}Bu_3P$ (20)	K_2CO_3 (100)	DMA	Reflux	30	71	Trace	—
	7	$Pd(OAc)_2$ (30)	—	K_2CO_3 (100)	DMA	130	30	77	—	—
26c	8	$Pd(OAc)_2$ (30)	—	K_2CO_3 (100)	DMA	130	20	53	—	Trace
	9	$Pd(OAc)_2$ (10)	$^{n}Bu_3P$ (20)	K_2CO_3 (100)	DMA	130	360	31[b]	—	49[b]
	10	$Pd(OAc)_2$ (10)	$^{n}Bu_3P$ (20)	K_2CO_3 (100)	DMA	Reflux	10	63	—	Trace

[a] No reaction on TLC.
[b] Determined by ^{1}H NMR.

Because, we could obtain the desired lactones in satisfactory yield through the Pd-mediated intramolecular biaryl coupling reaction of **26b** and **26c**, we next attempted the asymmetric lactone-opening reaction of **27b** and **27c**.

2.3. Asymmetric lactone-opening reaction and determination of the absolute configuration

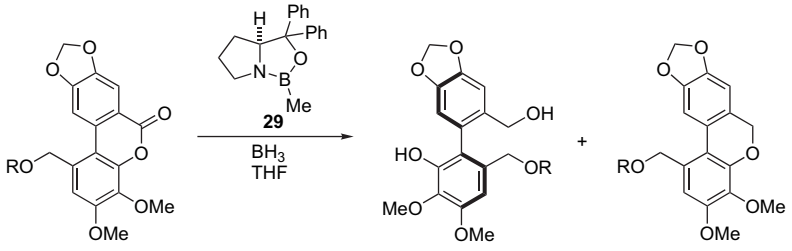
First, we investigated a dynamic kinetic resolution of **27b** and **27c** through reduction with a chiral oxazaborolidine (**29**)–borane complex.[9,20] As shown in Table 5, asymmetric reduction of **27b** produced a lactone-opened product **30b** in good enantioselectivity (run 1) with moderate yield. When this reaction was carried out at 0 °C, the ee of **30b** was only 47% although the reaction rate was accelerated (run 2). Using a lower amount of the reducing agent (**29**–borane) led to a moderate yield and ee (run 3). Generation of by-product **31b** was observed in each case. On the other hand, asymmetric reduction of **27c** afforded **30c** in excellent yield and good enantioselectivity (run 4). Under this reaction condition, by-product **31c** was not detected in contrast to the case of **27b**. However, undesired **31c** was obtained in 51% yield when the reaction was conducted at higher temperature (run 5). We also examined another condition of dynamic kinetic resolution, using BINAL[9] or lithium menthoxide,[9] which has been developed by Bringmann and co-workers. However, in spite of our intensive efforts, we could not obtain any fruitful results.

In order to determine the absolute configuration of **30c**, we converted it into the known compound **33** (Scheme 5).[4a] Methylation of the phenolic hydroxyl group followed by oxidation with PDC afforded aldehyde **32** without racemization. The treatment of **32** with methyl lithium at −78 °C produced about a 5.5:1 diastereoisomeric mixture, which was easily separated by column chromatography. O-Allylation of the major diastereomer afforded **33**, whereas the configuration at the benzylic position was not determined. The ee of the resulting **33** was 80% by HPLC analysis. All spectral data for **33** including optical rotation were consistent with those of the reported compound;[4a] therefore, the absolute configuration of **30c** was determined to be *R*.

3. Conclusion

We investigated the intramolecular biaryl coupling reaction of benzyl benzoate and phenyl benzoate derivatives and the enantioselective lactone-opening reaction using chiral oxazaborolidine–borane complex in order to provide the biaryl moiety of the stegane families. The coupling reaction of benzyl benzoate derivatives was not suitable for this purpose, whereas the Pd-mediated coupling reaction of phenyl benzoate followed by asymmetric reduction successfully produced a key intermediate of these targets. The synthesis of (−)-steganone from **33** has already been reported.[4a] Thus, we accomplished the formal total synthesis of (−)-steganone.

Table 5. Asymmetric lactone-opening reaction of **27** with a chiral oxazaborolidine–BH_3 complex



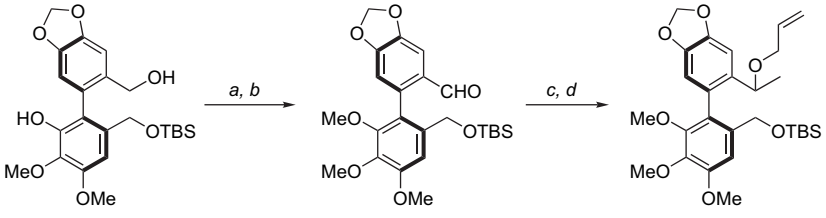
27b : R = MOM
27c : R = TBS

30b : R = MOM
30c : R = TBS

31b : R = MOM
31c : R = TBS

Substrate	Run	BH_3 (mol %)	**29** (mol %)	Temp (°C)	Time (h)	Yield (%)		ee of **30**[a] (%)
						30	**31**	
27b	1	400	300	−78 to rt	8	59	16	86
	2	400	300	0	1.5	67	26	47
	3	200	50	−40	40	55	11	68
27c	4	400	300	−78 to −40	17	97	—	83
	5	400	300	−78 to 0	17	49	51	78

[a] Determined by HPLC analysis using CHIRALCEL OD.



30c : 83%ee

32

33 : 80%ee

Scheme 5. (a) MeI, ^{t}BuOK, THF, rt, 48 h, 88%; (b) PDC, CH_2CI_2, rt, 12 h, 77%; (c) MeLi, THF, −78 °C, 0.5 h, 55%; (d) allyl bromide, NaH, DMF, rt, 37 h, 66%.

4. Experimental

4.1. General

Melting points were measured using a Yanagimoto micro melting point hot-plate apparatus and are uncorrected. IR spectra were recorded on a Jasco FTIR-350 spectrophotometer. NMR spectra were taken with a Varian VXR-500 (500 MHz), MERCURY (300 MHz), VXR-200 (200 MHz), or JNM-MY60FT (60 MHz) instrument. Chemical shifts are given in δ parts per million with TMS as an internal standard. FABMS was obtained with a VG-70SE instrument using *m*-nitrobenzyl alcohol as the matrix. Optical rotations were determined on a JASCO Dip-4 digital polarimeter. Elemental analysis was performed with a Yanaco MT-5 analyzer. Silica gel column chromatography was carried out using Wakogel C-200 (Wako) or 9385 Kieselgel 60 (Merck). TLC analysis was performed on Kieselgel 60 F_{254} (Merck) plates.

4.1.1. 5-Hydroxymethyl-6-iodo-1,3-benzodioxole (5).[12] I_2 (27.9 g, 0.110 mol) and CF_3CO_2Ag (24.1 g, 0.109 mol) were added at −5 °C to a solution of **4** (12.6 g, 82.8 mmol) in $CHCl_3$ (200 mL). After stirring at −5 °C for 10 min, the mixture was filtered with Celite, and the filtrate was washed with saturated aqueous $Na_2S_2O_3$ solution. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was recrystallized from $CHCl_3$ to afford **5** as colorless needles (19.0 g, 83%), mp 107.5–109 °C [lit.[12] 108–109 °C ($CHCl_3$)]. IR (KBr) cm^{-1}: 3270, 1500, 1480, 1450, 1240, 1100, 1040, 925, 860. ^1H NMR (60 MHz, DMSO-d_6) δ: 4.33 (2H, d, J=5.5 Hz, ArCH_2OH), 5.34 (1H, t, J=5.5 Hz, OH), 6.03 (2H, s, OCH_2O), 7.04 (1H, s, Ar-4-H), 7.31 (1H, s, Ar-7-H).

4.1.2. 6-Iodo-1,3-benzodioxole-5-carboxylic acid (6).[21] To a solution of **5** (1.00 g, 3.60 mmol) in acetone (5 mL), Jones reagent (2.02 mL, 5.39 mmol for CrO_3) was added dropwise at 0–5 °C. After stirring at 0 °C for 5 min, the resulting mixture was quenched with $NaHSO_3$ solution, poured into water, and extracted with AcOEt. The organic layer was successively washed with saturated aqueous $NaHCO_3$ solution and brine, and it was dried over anhydrous $MgSO_4$. After evaporation, the residue (1.03 g) was dissolved in MeCN–H_2O (20:1) (21 mL), and $NaH_2PO_4\cdot 2H_2O$ (116 mg, 0.744 mmol), 31% H_2O_2 (0.550 mL, 5.61 mmol), and 80% $NaClO_2$ (632 mg, 5.59 mmol) in H_2O (1 mL) were added at 0–5 °C. After stirring at rt for 2 h, aqueous $NaHSO_3$ solution was added to the reaction mixture and extracted with AcOEt. The organic layer was collected, washed with brine, and dried over anhydrous $MgSO_4$. After evaporation, the residue was recrystallized from AcOEt to afford **6** as colorless prisms (767 mg, 73%), mp 216.5–219 °C [lit.[21] 218.5–221 °C (MeOH)]. IR (KBr) cm^{-1}: 2700, 1710, 1620, 1500, 1490, 1420, 1350, 1280, 1250, 1145, 1040, 920. ^1H NMR (60 MHz, $CDCl_3$) δ: 6.13 (2H, s, OCH_2O), 7.32 (1H, s, Ar-7-H), 7.49 (1H, s, Ar-4-H), 13.06 (1H, s, COOH). FABMS (positive ion mode) *m/z*: 292 $[M]^+$, 293 $[M+1]^+$.

4.1.3. 3,4,5-Trimethoxybenzyl 6-iodo-1,3-benzodioxole-5-carboxylate (8). To a solution of **6** (713 mg, 2.44 mmol) and **7** (481 mg, 2.43 mmol) in CH_2Cl_2 (30 mL), EDC (702 mg, 3.66 mmol) and DMAP (45.0 mg, 0.368 mmol) were added. The mixture was stirred for 1 h at rt, washed with water and brine, and dried over anhydrous $MgSO_4$. After evaporation, the residue was recrystallized from CH_2Cl_2–Et_2O to afford **8** as colorless needles (754 mg, 66%), mp 119–121 °C. IR (KBr) cm^{-1}: 1715, 1590, 1500, 1245, 1130, 1030. ^1H NMR (200 MHz, $CDCl_3$) δ: 3.85 (3H, s, Ar-4-OCH_3), 3.88 (6H, s, Ar-3,5-OCH_3), 5.26 (2H, s, OCH_2Ar), 6.04 (2H, s, OCH_2O), 6.67 (2H, s, benzylalcohol-2,6-H), 7.37 (1H, s, 1,3-benzodioxole-7-H), 7.41 (1H, s, 1,3-benzodioxole-4-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 56.15, 60.80, 67.45, 84.95, 102.41, 105.70, 111.04, 120.89, 127.41, 131.11, 138.01, 148.09, 151.13, 153.29, 165.26. Anal. Calcd for $C_{18}H_{17}IO_7$: C, 45.78; H, 3.63. Found: C, 45.61; H, 3.75.

4.2. Typical procedure for the Pd-mediated coupling reaction of benzyl benzoate 8 (Table 1, run 1)

To a solution of **8** (63.3 mg, 0.134 mmol) in toluene (3 mL), PPh_3 (21.1 mg, 0.0804 mmol), $^iPr_2NEt$ (47.0 μL, 0.270 mmol), and $Pd(OAc)_2$ (6.0 mg, 0.027 mmol) were successively added, and the mixture was refluxed for 2.5 h under argon atmosphere. After cooling, the mixture was filtered, and the filtrate was diluted with ether, washed with brine, and dried over anhydrous $MgSO_4$. After evaporation, the resulting oil was subjected to silica gel column chromatography with AcOEt–*n*-hexane (1:5) to produce **9** (38.9 mg, 84%).

4.2.1. 3,4,5-Trimethoxybenzyl 1,3-benzodioxole-5-carboxylate (9). Colorless needles, mp 118–119.5 °C (CH_2Cl_2–Et_2O). IR (KBr) cm^{-1}: 1715, 1600, 1445, 1330, 1280, 1125, 1030, 760. ^1H NMR (200 MHz, $CDCl_3$) δ: 3.85 (3H, s, Ar-4-OCH_3), 3.88 (6H, s, Ar-3,5-OCH_3), 5.25 (2H, s, OCH_2Ar), 6.04 (2H, s, OCH_2O), 6.66 (2H, s, benzylalcohol-2,6-H), 6.84 (1H, d, J=8.2 Hz, 1,3-benzodioxole-7-H), 7.49 (1H, d, J=1.6 Hz, 1,3-benzodioxole-4-H), 7.69 (1H, dd, J=8.2, 1.6 Hz, 1,3-benzodioxole-6-H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 56.03, 60.71, 66.76, 101.73, 105.36, 107.87, 109.42, 123.92, 125.36, 131.58, 137.82, 147.63, 151.62, 153.21, 165.63. FABMS (positive ion mode) *m/z*: 346 $[M]^+$, 347 $[M+1]^+$. Anal. Calcd for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24. Found: C, 62.26; H, 4.98.

4.2.2. 2-Iodo-3,4,5-trimethoxybenzylalcohol (11).[13] I_2 (3.00 g, 11.8 mmol) and CF_3CO_2Ag (2.60 g, 11.8 mmol) were added at −5 °C to a solution of **7** (2.01 g, 10.1 mmol) in $CHCl_3$ (100 mL). After stirring at −5 °C for 1 h, the mixture was filtered, and the filtrate was washed with saturated aqueous $Na_2S_2O_3$ solution. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated off. The resulting residue was subjected to silica gel column chromatography with AcOEt–*n*-hexane (1:3) to produce **11** (2.59 g, 79%). Colorless needles, mp 51–53 °C (Et_2O–*n*-hexane) [lit.[13] 56.5–57.7 °C (hexane)]. IR (KBr) cm^{-1}: 3270, 1565, 1480, 1445, 1390, 1325, 1200, 1150, 1100, 1020. ^1H NMR (60 MHz, $CDCl_3$) δ: 3.87 (9H, s), 4.66 (2H, s), 6.94 (1H, s).

4.2.3. 2-Iodo-3,4,5-trimethoxybenzoic acid (12).[22] To a solution of **11** (9.98 g, 30.8 mmol) in acetone (100 mL), Jones reagent (10.0 mL, 26.7 mmol for CrO_3) was added dropwise at 0–5 °C. After stirring at 0 °C for 5 min, the reaction

mixture was quenched with aqueous $NaHSO_3$ solution, poured into water, and extracted with ether. The organic layer was successively washed with saturated aqueous $NaHCO_3$ solution and brine, and it was dried over anhydrous $MgSO_4$. After evaporation, the residue (10.8 g) was dissolved in MeCN–H_2O (25:1) (104 mL). To the mixture, $NaH_2PO_4 \cdot 2H_2O$ (480 mg, 3.08 mmol), 31% H_2O_2 (3.00 mL, 30.8 mmol), and 80% $NaClO_2$ (3.48 g, 30.8 mmol) in H_2O (4 mL) were added at 0–5 °C. After stirring at rt for 1 h, to the reaction mixture was added aqueous $NaHSO_3$ solution and extracted with ether. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After evaporation, the residue was recrystallized from Et_2O–*n*-hexane to afford **12** as colorless needles (9.52 g, 91%), mp 147–148 °C [lit.[22] 135–142 °C]. IR (KBr) cm^{-1}: 2960, 1700, 1580, 1480, 1410, 1380, 1335, 1235, 1110, 1000. ^1H NMR (60 MHz, $CDCl_3$) δ: 3.90–4.00 (9H, s, Ar-3,4,5-OCH_3), 6.60 (1H, br, COOH), 7.45 (1H, s, Ar-6-H).

4.2.4. 2-Iodo-3,4,5-trimethoxybenzyl 6-iodo-1,3-benzodioxole-5-carboxylate (13). To a solution of **6** (2.80 g, 9.59 mmol) and **11** (1.82 g, 5.62 mmol) in CH_2Cl_2 (100 mL), EDC (1.89 g, 9.86 mmol) and DMAP (145 mg, 1.19 mmol) were successively added. The mixture was stirred for 3 h at rt, washed with water and brine, and dried over anhydrous $MgSO_4$. After evaporation, the residue was recrystallized from CH_2Cl_2–Et_2O to afford **13** as colorless needles (2.67 g, 79%), mp 102–104 °C. IR (KBr) cm^{-1}: 1730, 1480, 1380, 1240, 1135, 1030, 1000. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.87 (3H, s, $ArOCH_3$), 3.88 (3H, s, $ArOCH_3$), 3.90 (3H, s, $ArOCH_3$), 5.35 (2H, s, OCH_2Ar), 6.04 (2H, s, OCH_2O), 6.92 (1H, s, benzylalcohol-6-H), 7.42 (1H, s, 1,3-benzodioxole-7-H), 7.45 (1H, s, 1,3-benzodioxole-4-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 56.25, 60.78, 60.93, 71.09, 85.16, 86.80, 102.40, 109.84, 111.23, 120.91, 127.00, 133.52, 142.09, 148.06, 151.19, 153.32, 153.68, 164.87. Anal. Calcd for $C_{18}H_{15}IO_8$: C, 36.14; H, 2.70. Found: C, 36.02; H, 2.85.

4.2.5. 6-Iodo-1,3-benzodioxole-5-ylmethyl 2-iodo-3,4,5-trimethoxybenzoate (14). To a solution of **5** (2.50 g, 8.99 mmol) and **12** (3.95 g, 11.7 mmol) in CH_2Cl_2 (100 mL), EDC (2.76 g, 14.4 mmol) and DMAP (176 mg, 1.44 mmol) were successively added. After stirring for 2 h at rt, **12** (608 mg, 1.80 mmol) and EDC (517 mg, 2.70 mmol) were added again to the mixture. The reaction mixture was stirred for an additional 1 h at the same temperature. The whole mixture was then washed with water and brine, and dried over anhydrous $MgSO_4$. After evaporation, the resulting residue was subjected to silica gel column chromatography with AcOEt–*n*-hexane (1:2) to produce a colorless solid. Recrystallization from Et_2O–*n*-hexane afforded pure **14** as colorless needles (4.32 g, 80%) mp 125–126 °C. IR (KBr) cm^{-1}: 2940, 1735, 1480, 1380, 1330, 1240, 1215, 1100, 1040, 1010, 925, 865. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.87 (3H, s, $ArOCH_3$), 3.89 (3H, s, $ArOCH_3$), 3.91 (3H, s, $ArOCH_3$), 5.30 (2H, s, OCH_2Ar), 5.99 (2H, s, OCH_2O), 7.05 (1H, s, 1,3-benzodioxole-7-H), 7.30 (2H, s, 1,3-benzodioxole-4-H and benzoic acid-6-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 56.28, 60.80, 61.01, 71.05, 84.13, 87.49, 101.86, 110.76, 110.89, 118.82, 130.36, 131.26, 145.00, 148.39, 148.60, 153.27, 153.84, 165.89. FABMS (positive ion mode) *m/z*: 598 $[M]^+$. Anal. Calcd for $C_{18}H_{16}I_2O_7$: C, 36.14; H, 2.70. Found: C, 36.40; H, 2.76.

4.3. Typical procedure for Ullmann coupling reaction (Table 2, run 1)

Copper was purified by a published method.[23] Under argon atmosphere, a mixture of Cu (170 mg, 2.68 mmol) and DMF (2 mL) was refluxed for 30 min, and a solution of **13** (200 mg, 0.334 mmol) in DMF (2 mL) was added via syringe; the mixture was then refluxed for a further 2 h. After cooling, the mixture was filtered, and the filtrate was diluted with ether. The solution was successively washed with 28% aqueous ammonia solution, water, and brine and dried over anhydrous $MgSO_4$. After evaporation, the resulting oil was subjected to silica gel column chromatography with ether–chloroform (1:100) to produce **15** (81.6 mg, 52%) and **16** (24.4 mg, 16%).

4.3.1. 6,6′-Bis(2-iodo-3,4,5-trimethoxybenzyl 1,3-benzodioxole-5-carboxylate) (15). Colorless prisms, mp 150.5–152.5 °C (CH_2Cl_2–Et_2O). IR (KBr) cm^{-1}: 2950, 1690, 1480, 1330, 1255, 1105, 1035, 1000. ^1H NMR (200 MHz, $CDCl_3$) δ: 3.85 (6H, s, $ArOCH_3$), 3.89 (6H, s, $ArOCH_3$), 3.91 (6H, s, $ArOCH_3$), 4.99 (2H, d, J=12.0 Hz, OC*H*HAr), 5.09 (2H, d, J=12.0 Hz, OCH*H*Ar), 5.98 (2H, d, J=1.4 Hz, OC*H*HO), 6.00 (2H, d, J=1.4 Hz, OCH*H*O), 6.49 (2H, s, 1,3-benzodioxole-7 and 7′-H), 6.64 (2H, s, benzylalcohol-6 and 6′-H), 7.30 (2H, s, 1,3-benzodioxole-4 and 4′-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.88, 56.14, 60.70, 60.90, 70.70, 87.66, 101.99, 109.56, 110.01, 121.91, 133.46, 139.60, 141.98, 146.36, 150.13, 153.03, 153.39, 165.53. Anal. Calcd for $C_{36}H_{32}I_2O_{14}$: C, 45.88; H, 3.42. Found: C, 46.05; H, 3.37.

4.3.2. 2-Iodo-3,4,5-trimethoxybenzyl 1,3-benzodioxole-5-carboxylate (16). Colorless prisms, mp 120–122 °C (CH_2Cl_2–hexane). IR (KBr) cm^{-1}: 1705, 1500, 1330, 1280, 1260, 1105, 770. ^1H NMR (200 MHz, $CDCl_3$) δ: 3.85 (3H, s, $ArOCH_3$), 3.87 (3H, s, $ArOCH_3$), 3.89 (3H, s, $ArOCH_3$), 5.32 (2H, s, OCH_2Ar), 6.03 (2H, s, OCH_2O), 6.83 (1H, d, J=8.2 Hz, 1,3-benzodioxole-7-H), 6.88 (1H, s, benzylalcohol-6-H), 7.50 (1H, d, J=1.7 Hz, 1,3-benzodioxole-4-H), 7.70 (1H, dd, J=8.2, 1.7 Hz, 1,3-benzodioxole-6-H). ^{13}C NMR (125 Hz, $CDCl_3$) δ: 56.14, 60.77, 60.91, 70.42, 86.68, 101.77, 107.97, 109.54, 109.58, 123.80, 125.53, 133.98, 141.99, 147.68, 151.71, 153.30, 153.63, 165.43. FABMS (positive ion mode) *m/z*: 472 $[M]^+$. Anal. Calcd for $C_{18}H_{17}IO_7$: C, 45.78; H, 3.63. Found: C, 45.50; H, 3.56.

4.3.3. 2,2′-Bis(6-iodo-1,3-benzodioxole-5-ylmethyl 3,4,5-trimethoxybenzoate) (17). Colorless prisms, mp 131–133 °C (CH_2Cl_2–Et_2O–hexane). IR ($CHCl_3$) cm^{-1}: 3020, 1710, 1480, 1325, 1220, 1205, 1100, 1040. ^1H NMR (200 MHz, $CDCl_3$) δ: 3.55 (6H, s, $ArOCH_3$), 3.85 (6H, s, $ArOCH_3$), 3.92 (6H, s, $ArOCH_3$), 4.99 (4H, d, J=1.4 Hz, OCH_2Ar), 5.97 (4H, s, OCH_2O), 6.57 (2H, s, 1,3-benzodioxole-7 and 7′-H), 7.18 (2H, s, 1,3-benzodioxole-4 and 4′-H), 7.38 (2H, s, benzoic acid-6 and 6′-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.71, 60.49, 60.61, 70.55, 87.06, 101.72, 109.27, 110.01, 118.31, 124.51, 126.39, 131.37, 145.43, 148.16, 148.19, 150.88, 151.86, 166.19. Anal. Calcd for $C_{36}H_{32}I_2O_{14}$: C, 45.88; H, 3.42. Found: C, 46.08; H, 3.62.

4.3.4. 6-Iodo-1,3-benzodioxole-5-ylmethyl 3,4,5-trimethoxybenzoate (18). Colorless needles, mp 152–153.5 °C (CH_2Cl_2–Et_2O). IR (KBr) cm^{-1}: 2940, 1720, 1590, 1505, 1480, 1460, 1420, 1340, 1230, 1135. ^1H NMR (200 MHz, $CDCl_3$) δ: 3.91 (6H, s, Ar-3,5-OCH_3), 3.91 (3H, s, Ar-4-OCH_3), 5.29 (2H, s, OCH_2Ar), 5.99 (2H, s, OCH_2O), 6.98 (1H, s, 1,3-benzodioxole-7-H), 7.30 (1H, s, 1,3-benzodioxole-4-H), 7.35 (2H, s, benzoic acid-2,6-H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 56.21, 60.85, 70.35, 87.14, 101.82, 106.95, 110.25, 118.85, 124.81, 131.74, 142.31, 148.37, 148.47, 152.88, 165.74. Anal. Calcd for $C_{18}H_{17}IO_7$: C, 45.78; H, 3.63. Found: C, 45.93; H, 3.91.

4.3.5. 1,2,3-Trimethoxy-9,10-methylenedioxy-7*H*-dibenzo[*c*,*e*]oxepine-7-one (20). Colorless needles, mp 162–166 °C (CH_2Cl_2–Et_2O). IR (KBr) cm^{-1}: 2950, 1710, 1600, 1510, 1490, 1410, 1330, 1250, 1110, 1040, 930, 890. ^1H NMR (200 MHz, $CDCl_3$) δ: 3.65 (3H, s, $ArOCH_3$), 3.95 (3H, s, $ArOCH_3$), 3.99 (3H, s, $ArOCH_3$), 4.80 (1H, d, J=12.0 Hz, OC*H*HAr), 4.94 (1H, d, J=12.0 Hz, OCH*H*Ar), 6.02 (1H, d, J=1.4 Hz, OC*H*HO), 6.07 (1H, d, J=1.4 Hz, OCH*H*O), 6.92 (1H, s, Ar-11-H), 7.62 (1H, s, Ar-4-H), 7.62 (1H, s, Ar-8-H). FABMS (positive ion mode) *m*/*z*: 344 $[M]^+$. HRMS (FAB) Calcd for $C_{18}H_{16}O_7$ $[M]^+$: 344.0896. Found: 344.0858.

4.3.6. 1,3-Benzodioxole-5-ylmethyl 3,4,5-trimethoxybenzoate (19). PPh_3 (35.1 mg, 0.134 mmol), $^iPr_2NEt$ (116 μL, 0.666 mmol), and $Pd(OAc)_2$ (15.0 mg, 0.0668 mmol) were successively added to a solution of **14** (200 mg, 0.334 mmol) in xylene (3 mL), and the mixture was refluxed for 2.5 h under argon atmosphere. After cooling, the mixture was filtered, and the filtrate was diluted with AcOEt, washed with brine, and dried over anhydrous $MgSO_4$. After evaporation, the resulting oil was subjected to silica gel column chromatography with AcOEt–*n*-hexane (1:3.5) to produce **19** (89.9 mg, 78%). Colorless prisms, mp 141.5–143 °C (Et_2O–*n*-hexane). IR (KBr) cm^{-1}: 2950, 1695, 1585, 1505, 1435, 1415, 1330, 1225, 1125, 1035, 1000, 965, 860, 760. ^1H NMR (200 MHz, $CDCl_3$) δ: 3.90 (9H, s, Ar-3,4,5-OCH_3), 5.26 (2H, s, OCH_2Ar), 5.98 (2H, s, OCH_2O), 6.78–6.95 (3H, m, 1,3-benzodioxole-4,6,7-H), 7.31 (2H, s, benzoic acid-2,6-H). ^{13}C NMR (125 Hz, $CDCl_3$) δ: 56.16, 60.82, 66.73, 101.10, 106.78, 108.16, 108.98, 122.23, 125.04, 129.72, 142.16, 147.57, 147.73, 152.82, 165.99. Anal. Calcd for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24. Found: C, 62.20; H, 5.07.

4.4. Reduction of dimers 15 and 17

To a solution of **15** (100 mg, 0.106 mmol) in toluene (2 mL), DIBAL (1.0 M toluene solution, 0.530 mL, 0.530 mmol) was added dropwise at −78 °C, and the mixture was then stirred for 1 h at the same temperature. A sodium hydroxide aqueous solution (1.0 M, 10 mL) was added, and the mixture was stirred for 30 min at rt. After extraction with ether, the organic layer was washed with brine, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The residue was subjected to silica gel column chromatography with ether–chloroform (1:20) to give **21** (21.9 mg, 68%) and alcohol **11** (46.0 mg, 67%). Reduction of **17** (200 mg, 0.212 mmol) using the same procedure employed for **15** was carried out to afford **22** (62.0 mg, 74%) and alcohol **5** (111 mg, 94%).

4.4.1. 6,6′-Bis(hydroxymethyl)-5,5′-bi-1,3-benzodioxole (21).[14] Colorless needles, mp 182–182.5 °C ($CHCl_3$). IR (KBr) cm^{-1}: 3300, 2900, 1500, 1480, 1245, 1065, 1040, 930, 860. ^1H NMR (200 MHZ, $CDCl_3$–acetone) δ: 4.22 (2H, br, OH, exchangeable with D_2O), 4.22 (4H, s, OCH_2Ar), 6.01 (4H, s, OCH_2O), 6.58 (2H, s, Ar-4, 4′-H), 7.01 (2H, s, Ar-7, 7′-H). Anal. Calcd for $C_{16}H_{14}O_6 \cdot 0.5H_2O$: C, 61.73; H, 4.86. Found: C, 61.75; H, 4.69.

4.4.2. 6,6′-Hydroxymethyl-1,1′,2,2′,3,3′-hexamethoxy-1,1′-biphenyl (22).[15] Colorless prisms, mp 96.5–97.5 °C (Et_2O–hexane) [lit.[15] 106–108 °C (Et_2O–hexane); optically active form]. IR (KBr) cm^{-1}: 3400, 2950, 1600, 1490, 1460, 1400, 1325, 1195, 1130, 1105, 1010, 980. ^1H NMR (200 MHz, $CDCl_3$) δ: 3.67 (6H, s, $ArOCH_3$), 3.89 (6H, s, Ar-OCH_3), 3.93 (6H, s, $ArOCH_3$), 4.18 (4H, s, ArCH_2OH), 6.89 (2H, s, Ar-H). FABMS (positive ion mode) *m*/*z*: 394 $[M]^+$. Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64. Found: C, 60.56; H, 6.86.

4.4.3. 3-Benzyloxy-4,5-dimethoxybenzylalcohol (24).[24] To a solution of **23a** (50.0 g, 0.165 mol) in toluene (300 mL), DIBAL (1.0 M toluene solution, 500 mL, 0.500 mol) was added dropwise, and the mixture was then stirred for 1 h at −78 °C. A sodium hydroxide aqueous solution (1.0 M, 450 mL) was added, and the mixture was stirred for 30 min at rt. After extraction with ether, the organic layer was washed with brine, dried over anhydrous $MgSO_4$, and the solvent was evaporated to give **24** as a yellow oil (43.5 g, 96%). IR (neat) cm^{-1}: 3440, 2950, 1735, 1590, 1505, 1480, 1430, 1380, 1330, 1240, 1120, 1010, 825, 740, 700. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.71 (1H, t, J=6.0 Hz, OH, exchangeable with D_2O), 3.87 (3H, s, $ArOCH_3$), 3.87 (3H, s, $ArOCH_3$), 4.59 (2H, d, J=6.0 Hz, ArCH_2OH), 5.14 (2H, s, $ArOCH_2Ph$), 6.62 (1H, s, Ar-2 or 6-H), 6.63 (1H, s, Ar-2 or 6-H), 7.30–7.47 (5H, m, C_6H_5). FABMS (positive ion mode) *m*/*z*: 274 $[M]^+$.

4.4.4. 1-Benzyloxy-2,3-dimethoxy-5-methoxymethoxymethylbenzene (23b). $^iPr_2NEt$ (66.9 mL, 0.384 mol) and MOMCl (29.2 mL, 0.384 mol) were successively added to a solution of **24** (35.0 g, 0.128 mol) in DMF (250 mL) at 0 °C. The mixture was stirred for 1 h at 60 °C and poured into water. After extraction with ether, the organic layer was successively washed with 10% HCl solution, saturated aqueous $NaHCO_3$ solution, and brine. The solution was dried over anhydrous $MgSO_4$ and the solvent was evaporated to give **23b** as a pale yellow oil (39.2 g, 96%). IR (neat) cm^{-1}: 2950, 1590, 1510, 1455, 1430, 1380, 1330, 1240, 1120, 1055, 920, 825, 740. ^1H NMR (200 MHz, $CDCl_3$) δ: 3.40 (3H, s, CH_2OCH_3), 3.87 (3H, s, $ArOCH_3$), 3.87 (3H, s, $ArOCH_3$), 4.50 (2H, s, $ArCH_2O$), 4.68 (2H, s, OCH_2O), 5.14 (2H, s, $ArOCH_2Ph$), 6.60 (1H, d, J=1.6 Hz, Ar-2 or 6-H), 6.63 (1H, d, J=1.6 Hz, Ar-2 or 6-H), 7.30–7.48 (5H, m, C_6H_5). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 55.34, 56.03, 60.82, 69.16, 70.96, 95.51, 105.10, 106.96, 127.22, 127.78, 128.45, 133.29, 137.05, 138.10, 152.34, 153.38. FABMS (positive ion mode) *m*/*z*: 318 $[M]^+$. Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.90; H, 6.97. Found: C, 67.99; H, 7.08.

4.4.5. 1-Benzyloxy-5-*tert*-butyldimethylsilyl-2,3-dimethoxybenzene (23c). To a solution of TBSCl (2.16 g, 14.3 mmol) in CH_2Cl_2 (10 mL), a mixture of **24** (3.03 g,

11.0 mmol) and imidazole (1.12 g, 16.5 mmol) in CH_2Cl_2 (10 mL) was added. The reaction mixture was stirred for 5 min at rt, washed with water and brine, and dried over anhydrous $MgSO_4$. After evaporation, the resulting oil was subjected to silica gel column chromatography with AcOEt–*n*-hexane (1:10) to produce **23c** as a colorless oil (4.29 g, quant). IR (neat) cm^{-1}: 2940, 1590, 1510, 1460, 1430, 1370, 1330, 1255, 1235, 1120, 1010, 840, 780. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.08 (6H, s, $Si(CH_3)_2$), 0.93 (9H, s, $SiC(CH_3)_3$), 3.86 (3H, s, $ArOCH_3$), 3.87 (3H, s, $ArOCH_3$), 4.64 (2H, s, $ArCH_2OTBS$), 5.14 (2H, s, $ArOCH_2Ph$), 6.58 (1H, s, Ar-2 or 6-H), 6.59 (1H, s, Ar-2 or 6-H), 7.30–7.48 (5H, m, C_6H_5). ^{13}C NMR (50 MHz, $CDCl_3$) δ: −5.32, 18.32, 25.88, 55.93, 60.83, 64.77, 70.86, 103.06, 104.88, 127.11, 127.71, 128.45, 136.98, 137.20, 137.33, 152.23, 153.23. Anal. Calcd for $C_{22}H_{32}O_4Si$: C, 68.00; H, 8.30. Found: C, 68.02; H, 8.27.

4.4.6. Methyl 3-hydroxy-4,5-dimethoxybenzoate (25a).[19] A mixture of **23a** (10.2 g, 33.7 mmol) and 10% Pd–C (108 mg) in MeOH (100 mL) was stirred under an H_2 atmosphere for 24 h at rt. Pd–C was filtered off and the filtrate was evaporated. The resulting residue was recrystallized from AcOEt to afford **25a** as colorless prisms (6.00 g, 83%), mp 72–74 °C [lit.[19] 72.5–73 °C (AcOEt–hexane)]. IR (KBr) cm^{-1}: 3405, 1710, 1600, 1505, 1435, 1360, 1275, 1200, 1165, 1115, 1010. ^1H NMR (60 MHz, $CDCl_3$) δ: 3.89 (3H, s, $ArOCH_3$), 3.91 (3H, s, $ArOCH_3$), 3.96 (3H, s, $COOCH_3$), 5.89 (1H, s, OH), 7.20 (1H, d, J=1.8 Hz, Ar-2-H), 7.32 (1H, d, J=1.8 Hz, Ar-6-H).

4.4.7. 2,3-Dimethoxy-5-methoxymethoxymethylphenol (25b). The mixture of **23b** (35.1 g, 0.110 mol) and 5% Pd–C (1.76 g) in MeOH (350 mL) was stirred under an H_2 atmosphere for 32 h at rt. Pd–C was filtered off and the filtrate was evaporated to give **25b** as a pale brown oil (26.8 g, quant). IR (neat) cm^{-1}: 3260, 2940, 1600, 1510, 1460, 1430, 1380, 1350, 1235, 1200, 1145, 1100, 1045, 1000, 920, 825, 780, 700. ^1H NMR (200 MHz, $CDCl_3$) δ: 3.42 (3H, s, OCH_2OCH_3), 3.87 (3H, s, $ArOCH_3$), 3.88 (3H, s, $ArOCH_3$), 4.49 (2H, s, $ArCH_2O$), 4.70 (2H, s, OCH_2O), 5.79 (1H, s, OH, exchangeable with D_2O), 6.49 (1H, d, J=1.8 Hz, Ar-4 or 6-H), 6.60 (1H, d, J=1.8 Hz, Ar-4 or 6-H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 55.30, 55.75, 60.82, 69.00, 95.49, 103.55, 107.72, 133.90, 134.96, 149.22, 152.37. FABMS (positive ion mode) *m/z*: 228 $[M]^+$. HRMS (FAB) Calcd for $C_{11}H_{16}O_5$ $[M]^+$: 228.0998. Found: 228.0969.

4.4.8. 5-*tert*-Butyldimethylsiloxymethyl-2,3-dimethoxyphenol (25c). The mixture of **23c** (38.9 mg, 0.100 mmol) and 5% Pd–C (1.3 mg) in AcOEt (1 mL) was stirred under an H_2 atmosphere for 10 h at rt. Pd–C was filtered off, and the filtrate was evaporated. The resulting oil was subjected to silica gel column chromatography with AcOEt–*n*-hexane (1:3) to produce **25c** (25.1 mg, 84%) as a pale yellow oil. IR (neat) cm^{-1}: 3440, 2940, 1600, 1510, 1460, 1435, 1380, 1350, 1260, 1200, 1140, 1100, 1000, 940, 840, 780. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.10 (6H, s, $Si(CH_3)_2$), 0.95 (9H, s, $SiC(CH_3)_3$), 3.86 (3H, s, $ArOCH_3$), 3.88 (3H, s, $ArOCH_3$), 4.64 (2H, s, $ArCH_2O$), 5.76 (1H, s, OH, exchangeable with D_2O), 6.50 (1H, d, J=1.6 Hz, Ar-4 or 6-H), 6.55 (1H, d, J=1.8 Hz, Ar-4 or 6-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.33, 18.34, 25.88, 55.66, 60.86, 64.68, 101.68, 105.48, 134.20, 137.68, 149.06, 152.21. FABMS (positive ion mode) *m/z*: 297 $[M-1]^+$, 298 $[M]^+$, 299 $[M+1]^+$. HRMS (FAB) Calcd for $C_{15}H_{26}O_4Si$ $[M-1]^+$: 297.1522. Found: 297.1522. $[M+1]^+$: 299.1679. Found: 299.1651.

4.4.9. 2,3-Dimethoxy-5-methoxycarbonylphenyl 6-iodo-1,3-benzodioxole-5-carboxylate (26a). To a solution of **6** (10.0 g, 34.2 mmol) and **25a** (6.05 g, 28.5 mmol) in CH_2Cl_2 (300 mL), EDC (9.84 g, 51.3 mmol) and DMAP (3.48 g, 28.5 mmol) were successively added. The mixture was stirred for 1 h at rt, washed with water and brine, and dried over anhydrous $MgSO_4$. After evaporation, the resulting residue was recrystallized from CH_2Cl_2–Et_2O to afford **26a** as colorless needles (12.7 g, 91%), mp 119–121 °C. IR (KBr) cm^{-1}: 1745, 1720, 1615, 1580, 1500, 1480, 1430, 1400, 1380, 1335, 1230, 1120, 1090, 1050, 1000, 940, 870, 760. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.91 (3H, s, $ArOCH_3$), 3.93 (3H, s, $ArOCH_3$), 3.95 (3H, s, $COOCH_3$), 6.10 (2H, s, OCH_2O), 7.49 (1H, s, 1,3-benzodioxole-7-H), 7.52 (1H, d, J=1.5 Hz, phenol-4-H), 7.55 (1H, d, J=1.5 Hz, phenol-6-H), 7.65 (1H, s, 1,3-benzodioxol-4-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.25, 56.22, 60.96, 86.21, 102.59, 111.41, 111.57, 117.09, 121.28, 125.06, 125.80, 143.41, 145.27, 148.20, 151.73, 153.20, 163.24, 165.97. Anal Calcd for $C_{18}H_{15}IO_8$: C, 44.46; H, 3.11. Found: C, 44.43; H, 3.36.

4.4.10. 2,3-Dimethoxy-5-methoxymethoxymethylphenyl 6-iodo-1,3-benzodioxole-5-carboxylate (26b). To a solution of **6** (8.67 g, 29.7 mmol) and **25b** (4.52 g, 19.8 mmol) in CH_2Cl_2 (200 mL), EDC (6.83 g, 35.6 mmol) and DMAP (435 mg, 3.56 mmol) were successively added. The mixture was stirred for 2 h at rt, washed with water and brine, and dried over anhydrous $MgSO_4$. After evaporation, the resulting oil was subjected to silica gel column chromatography with ether–chloroform (1:20) to give a yellow solid (9.75 g), and it was recrystallized from CH_2Cl_2–Et_2O–*n*-hexane to afford **26b** as colorless prisms (8.33 g, 84%), mp 82–85 °C. IR (KBr) cm^{-1}: 1740, 1500, 1480, 1380, 1350, 1325, 1240, 1220, 1130, 1090, 1045, 1005, 920. ^1H NMR (200 MHz, $CDCl_3$) δ: 3.42 (3H, s, OCH_2OCH_3), 3.85 (3H, s, $ArOCH_3$), 3.91 (3H, s, $ArOCH_3$), 4.56 (2H, s, OCH_2Ar), 4.71 (2H, s, OCH_2OCH_3), 6.09 (2H, s, $ArOCH_2OAr$), 6.81 (1H, d, J=2.0 Hz, phenol-4-H), 6.86 (1H, d, J=2.0 Hz, phenol-6-H), 7.49 (1H, s, 1,3-benzodioxole-7-H), 7.65 (1H, s, 1,3-benzodioxole-4-H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 55.36, 56.04, 60.83, 68.50, 85.98, 95.58, 102.52, 109.59, 111.51, 114.30, 121.15, 126.13, 133.51, 140.40, 143.77, 148.13, 151.55, 153.56, 163.39. Anal. Calcd for $C_{19}H_{19}IO_8$: C, 45.44; H, 3.81. Found: C, 45.13; H, 3.84.

4.4.11. 5-*tert*-Butyldimethylsiloxymethyl-2,3-dimethoxyphenyl 6-iodo-1,3-benzodioxole-5-carboxylate (26c). To a solution of **6** (117 mg, 0.401 mmol) and **25c** (101 mg, 0.338 mmol) in CH_2Cl_2 (3 mL), EDC (96.3 mg, 0.502 mmol) and DMAP (6.1 mg, 0.0499 mmol) were successively added. The mixture was stirred for 2 h at rt, washed with water and brine, and dried over anhydrous $MgSO_4$. After evaporation, the resulting residue was subjected to silica gel column chromatography with ether–chloroform (1:100) to produce **26c** (194 mg, 100%). Colorless prisms, mp 70–74 °C (*n*-hexane). IR (KBr) cm^{-1}: 1730, 1600, 1470, 1360,

1320, 1250, 1140, 1035, 1005, 860, 840, 780. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.11 (6H, s, $Si(CH_3)_2$), 0.95 (9H, s, $SiC(CH_3)_3$), 3.84 (3H, s, $ArOCH_3$), 3.89 (3H, s, $ArOCH_3$), 4.70 (2H, s, $ArCH_2OTBS$), 6.09 (2H, s, $ArOCH_2OAr$), 6.73 (1H, d, J=2.0 Hz, phenol-4-H), 6.87 (1H, d, J=2.0 Hz, phenol-6-H), 7.48 (1H, s, 1,3-benzodioxole-7-H), 7.64 (1H, s, 1,3-benzodioxole-4-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.29, 18.35, 25.89, 55.96, 60.87, 64.29, 85.93, 102.51, 107.86, 111.55, 112.23, 121.15, 126.38, 137.20, 139.63, 143.73, 148.16, 151.52, 153.45, 163.58. Anal. Calcd for $C_{23}H_{29}IO_7Si$: C, 48.26; H, 5.11. Found: C, 47.98; H, 4.94.

4.5. Pd-catalyzed aryl–aryl coupling reaction of 26a (Table 4, run 2)

The mixture of **26a** (100 mg, 0.206 mmol), DPPP (84.8 mg, 0.206 mmol), ^{n}Bu$_3$P (51.5 μL, 0.207 mmol), ^{i}Pr$_2$NEt (71.8 μL, 0.412 mmol), and $Pd(OAc)_2$ (46.3 mg, 0.206 mmol) in DMF (3 mL) was stirred for 3 h at 130 °C under argon atmosphere. After cooling, the mixture was diluted with ether and filtered. The filtrate was washed with water and brine, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The resulting residue was subjected to silica gel column chromatography with AcOEt–*n*-hexane (1:5) to give **28a** (29.5 mg, 40%) and alcohol **25a** (8.4 mg, 19%).

4.5.1. 2,3-Dimethoxy-5-methoxycarbonylphenyl 1,3-benzodioxole-5-carboxylate (28a). Colorless prisms, mp 109–111 °C (CH_2Cl_2–Et_2O). IR (KBr) cm^{-1}: 1720, 1605, 1505, 1450, 1340, 1260, 1230, 1155, 1120, 1090, 1040, 1000, 755. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.89 (3H, s, $ArOCH_3$), 3.90 (3H, s, $ArOCH_3$), 3.95 (3H, s, $COOCH_3$), 6.09 (2H, s, OCH_2O), 6.91 (1H, d, J=8.0 Hz, 1,3-benzodioxole-7-H), 7.51 (1H, d, J=2.0 Hz, phenol-4-H), 7.54 (1H, d, J=2.0 Hz, phenol-6-H), 7.62 (1H, d, J=2.0 Hz, 1,3-benzodioxole-4-H), 7.83 (1H, dd, J=8.0, 2.0 Hz, 1,3-benzodioxole-6-H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 52.19, 56.19, 60.84, 101.95, 108.13, 109.94, 111.15, 117.27, 122.74, 125.03, 126.34, 143.71, 145.37, 147.86, 152.27, 153.19, 163.98, 165.98. Anal. Calcd for $C_{18}H_{16}O_8$: C, 60.00; H, 4.48. Found: C, 60.03; H, 4.58.

4.6. Pd-catalyzed aryl–aryl coupling reaction of 26b (Table 4, run 7)

The mixture of **26b** (181 mg, 0.360 mmol), K_2CO_3 (49.8 mg, 0.360 mmol), and $Pd(OAc)_2$ (24.2 mg, 0.108 mmol) in DMA (5 mL) was stirred for 30 min at 130 °C under argon atmosphere. After cooling, the mixture was diluted with AcOEt and filtered. The filtrate was washed with water and brine, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The resulting residue was subjected to silica gel column chromatography with AcOEt–*n*-hexane (1:1) and then ether–chloroform (1:10) to produce **27b** (104 mg, 77%).

4.6.1. 3,4-Dimethoxy-1-methoxymethoxymethyl-8,9-methylenedioxybenzo[*c*]chromen-6-one (27b). Colorless prisms, mp 161–163 °C (CH_2Cl_2–Et_2O). IR (KBr) cm^{-1}: 2940, 1730, 1600, 1485, 1325, 1260, 1140, 1040, 1000, 930. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.52 (3H, s, OCH_2OCH_3), 3.98 (3H, s, $ArOCH_3$), 4.00 (3H, s, $ArOCH_3$), 4.85 (2H, s, $ArCH_2O$), 4.90 (2H, s, OCH_2OCH_3), 6.16 (2H, s, $ArOCH_2OAr$), 7.00 (1H, s, Ar-2-H), 7.81 (1H, s, Ar-11-H), 7.89 (1H, s, Ar-7-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 56.04, 56.16, 61.36, 68.95, 95.66, 102.34, 105.44, 108.47, 112.53, 112.75, 115.56, 128.53, 132.09, 136.51, 145.82, 147.45, 152.03, 153.67, 160.10. Anal. Calcd for $C_{19}H_{18}O_8$: C, 60.96; H, 4.85. Found: C, 60.83; H, 4.84.

4.6.2. 2,3-Dimethoxy-5-methoxymethoxymethylphenyl 1,3-benzodioxole-5-carboxylate (28b). Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.42 (3H, s, OCH_2OCH_3), 3.81 (3H, s, $ArOCH_3$), 3.90 (3H, s, $ArOCH_3$), 4.55 (2H, s, $ArCH_2O$), 4.71 (2H, s, OCH_2OCH_3), 6.08 (2H, s, $ArOCH_2OAr$), 6.79 (1H, d, J=1.8 Hz, phenol-4-H), 6.86 (1H, d, J=1.8 Hz, phenol-6-H), 6.91 (1H, d, J=8.2 Hz, 1,3-benzodioxole-7-H), 7.62 (1H, d, J=1.8 Hz, 1,3-benzodioxole-4-H), 7.83 (1H, dd, J=8.2, 1.8 Hz, 1,3-benzodioxole-6-H).

4.7. Pd-catalyzed aryl–aryl coupling reaction of 26c (Table 4, run 10)

The mixture of **26c** (100 mg, 0.175 mmol), ^{n}Bu$_3$P (8.7 μL, 0.0349 mmol), K_2CO_3 (24.2 mg, 0.175 mmol), and $Pd(OAc)_2$ (3.9 mg, 0.0173 mmol) in DMA (3 mL) was refluxed for 10 min under argon atmosphere. After cooling, the mixture was diluted with ether and filtered. The filtrate was washed with water and brine, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The resulting residue was subjected to silica gel column chromatography with ether–chloroform (1:50) to give a pale yellow solid (68.7 mg), and it was recrystallized from $CHCl_3$–*n*-hexane to afford **27c** as colorless prisms (49.3 mg, 63%).

4.7.1. 1-*tert*-Butyldimethylsilyloxymethyl-3,4-dimethoxy-8,9-methylenedioxybenzo[*c*]chromen-6-one (27c). Colorless prisms, mp 142–143 °C ($CHCl_3$–*n*-hexane). IR (KBr) cm^{-1}: 2960, 1740, 1500, 1480, 1380, 1240, 1220, 1120, 1090, 1060, 1040, 840. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.18 (6H, s, $Si(CH_3)_2$), 0.96 (9H, s, $SiC(CH_3)_3$), 3.97 (3H, s, $ArOCH_3$), 4.00 (3H, s, $ArOCH_3$), 4.97 (2H, s, $ArCH_2OTBS$), 6.15 (2H, s, $ArOCH_2OAr$), 7.03 (1H, s, Ar-2-H), 7.81 (1H, s, Ar-11-H), 7.91 (1H, s, Ar-7-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.06, 18.19, 25.76, 56.09, 61.40, 65.26, 102.31, 105.82, 108.52, 110.71, 112.25, 115.54, 132.30, 132.42, 136.09, 145.83, 147.38, 152.12, 153.75, 160.28. Anal. Calcd for $C_{23}H_{28}O_7Si$: C, 62.14; H, 6.35. Found: C, 61.92; H, 6.19.

4.8. Asymmetric lactone-opening reaction of 27b (Table 5, run 1)

To the solution of (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (**29**, 111 mg, 0.400 mmol) in THF (2 mL), 1.15 M BH_3·THF solution (0.465 mL, 0.535 mmol) was added dropwise at −78 °C under an argon atmosphere. After stirring for 5 min, the solution of **27b** (50 mg, 0.134 mmol) in THF (1 mL) was added dropwise, and the mixture was allowed to warm to 0 °C. After stirring for 8 h, the resulting mixture was quenched with water and extracted with ether. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The resulting oil was subjected to silica gel column chromatography with AcOEt–*n*-hexane (1:2) to give **30b** as a colorless solid (30.0 mg, 59%, 86% ee) and **31b** (7.6 mg, 16%).

4.8.1. (−)-2-Hydroxy-2′-hydroxymethyl-3,4-dimethoxy-6-methoxymethoxymethyl-4′,5′-methylenedioxy-1,1′-biphenyl (30b). $[\alpha]_D^{24}$ −5.8 (*c* 0.432, $CHCl_3$) [91.0% ee]. Mp 101–101.5 °C ($CHCl_3$–hexane). IR (KBr) cm^{-1}: 3490, 3150 (OH), 2900, 1610, 1485, 1460, 1230, 1140, 1110, 1050, 990, 925, 880. ^1H NMR (200 MHZ, $CDCl_3$) δ: 2.78 (1H, br, OH, exchangeable with D_2O), 3.22 (3H, s, OCH_2OCH_3), 3.93 (3H, s, $ArOCH_3$), 3.94 (3H, s, $ArOCH_3$), 4.22 (1H, d, *J*=7.0 Hz, $ArCHHOCH_2$), 4.23 (2H, s, $ArCH_2OH$), 4.27 (1H, d, *J*=7.0 Hz, $ArCHHOCH_2$), 4.49 (1H, d, *J*=6.8 Hz, $OCHHOCH_3$), 4.49 (1H, d, *J*=6.8 Hz, $OCHHOCH_3$), 5.84 (1H, s, OH, exchangeable with D_2O), 5.99 (1H, d, *J*=1.4 Hz, ArOCHHOAr), 6.02 (1H, d, *J*=1.4 Hz, ArOCHHOAr), 6.61 (1H, s, Ar-6′-H), 6.65 (1H, s, Ar-5-H), 7.04 (1H, s, Ar-3′-H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 55.27, 55.78, 60.91, 63.12, 67.38, 95.78, 101.14, 105.05, 109.62, 110.26, 119.81, 127.36, 131.90, 134.18, 135.06, 146.76, 147.07, 147.48, 151.58. Anal. Calcd for $C_{19}H_{22}O_8$: C, 60.31; H, 5.86. Found: C, 60.12; H, 5.83. HPLC condition: column, CHIRALCEL OD; solvent, IPA/*n*-hexane=1:9; flow rate, 1.0 mL/min; wavelength, 254 nm; retention time, 45.8 min [(+)-**30b**, 36.0 min].

4.8.2. 3,4-Dimethoxy-1-methoxymethoxymethyl-8,9-methylenedioxy-6*H*-benzo[*c*]chromen (31b). Colorless prisms, mp 120–123 °C (CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ: 3.51 (3H, s, OCH_2OCH_3), 3.88 (3H, s, $ArOCH_3$), 3.92 (3H, s, $ArOCH_3$), 4.72 (2H, s, $ArCH_2O$), 4.84 (2H, s, $ArCH_2O$), 4.87 (2H, s, OCH_2OCH_3), 5.99 (2H, s, $ArOCH_2OAr$), 6.73 (1H, s, Ar-H), 6.75 (1H, s, Ar-H), 7.40 (1H, s, Ar-H).

4.9. Asymmetric lactone-opening reaction of 27c (Table 5, run 4)

To a solution of (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (**29**, 402 mg, 1.45 mmol) in THF (5 mL), 1.15 M $BH_3\cdot$THF solution (1.69 mL, 1.94 mmol) was added dropwise at −78 °C under an argon atmosphere. After stirring for 5 min, the solution of **27c** (215 mg, 0.484 mmol) in THF (2 mL) was added dropwise, and the mixture was allowed to warm to −40 °C. After stirring for 17 h, the resulting mixture was quenched with water and extracted with ether. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The resulting oil was subjected to silica gel column chromatography with AcOEt–*n*-hexane (1:2) to give **30c** as a colorless solid (210 mg, 97%, 83% ee).

4.9.1. (*R*)-(−)-6-*tert*-Butyldimethylsiloxymethyl-2-hydroxy-2′-hydroxymethyl-3,4-dimethoxy-4′,5′-methylenedioxy-1,1′-biphenyl (30c). $[\alpha]_D^{21}$ −10.5 (*c* 0.732, $CHCl_3$) [83% ee]. Mp 140–141 °C ($CHCl_3$–hexane). IR (KBr) cm^{-1}: 3460, 3120, 2950, 1615, 1580, 1480, 1375, 1340, 1225, 1140, 1040, 990, 840. ^1H NMR (200 MHZ, $CDCl_3$) δ: 0.01 (6H, s, $Si(CH_3)_2$), 0.88 (9H, s, $SiC(CH_3)_3$), 2.52 (1H, br, OH, exchangeable with D_2O), 3.92 (3H, s, $ArOCH_3$), 3.93 (3H, s, $ArOCH_3$), 4.23 (2H, br s, $ArCH_2OH$), 4.28 (1H, d, *J*=13.0 Hz, ArCHHOTBS), 4.35 (1H, d, *J*=13.0 Hz, ArCHHOTBS), 5.83 (1H, s, OH, exchangeable with D_2O), 5.99 (1H, d, *J*=1.4 Hz, ArOCHHOAr), 6.03 (1H, d, *J*=1.4 Hz, ArOCHHOAr), 6.60 (1H, s, Ar-6′-H), 6.73 (1H, s, Ar-5-H), 7.04 (1H, s, Ar-3′-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.46, −5.44, 18.30, 25.85, 55.68, 60.95, 62.96, 63.37, 101.14, 103.50, 109.63, 110.32, 118.02, 127.34, 133.91, 134.44, 135.27, 146.35, 147.19, 147.50, 151.58. Anal. Calcd for $C_{23}H_{32}O_7Si$: C, 61.58; H, 7.19. Found: C, 61.50; H, 7.02. HPLC condition: column, CHIRALCEL OD; solvent, IPA/*n*-hexane=1:7; flow rate, 1.0 mL/min; wavelength, 254 nm; retention time, 15.8 min [(*S*)-**30c**, 11.6 min].

4.9.2. 1-*tert*-Butyldimethylsilyloxymethyl-3,4-dimethoxy-8,9-methylenedioxy-6*H*-benzo[*c*]chromen (31c). IR (KBr) cm^{-1}: 2920, 1600, 1480, 1325, 1240, 1140, 1120, 1040, 990, 835, 780. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.17 (6H, s, $Si(CH_3)_2$), 0.98 (9H, s, $SiC(CH_3)_3$), 3.89 (3H, s, $ArOCH_3$), 3.92 (3H, s, $ArOCH_3$), 4.83 (2H, s, $ArCH_2O$), 4.87 (2H, s, $ArCH_2O$), 6.00 (2H, s, OCH_2O), 6.73 (1H, s, Ar-H), 6.80 (1H, s, Ar-H), 7.38 (1H, s, Ar-H).

4.9.3. (*R*)-6-*tert*-Butyldimethylsiloxymethyl-2′-hydroxymethyl-2,3,4-trimethoxy-4′,5′-methylenedioxy-1,1′-biphenyl. To a solution of **30c** (200 mg, 0.446 mmol, 83% ee) in THF (3 mL), ^{t}BuOK (55.0 mg, 0.491 mmol) and MeI (30.0 μL, 0.490 mmol) were successively added. The mixture was stirred for 48 h at rt, poured into ice-water, and neutralized with 10% HCl solution. After extraction with ether, the organic layer was washed with brine, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The resulting oil was subjected to silica gel column chromatography with AcOEt–*n*-hexane (1:2) to give the title compound (181 mg, 88%, 83% ee), and the starting material **31c** (23.2 mg, 12%, 86% ee) was recovered. $[\alpha]_D^{21}$ +19.4 (*c* 3.792, $CHCl_3$) [83% ee]. IR (KBr) cm^{-1}: 3520, 2960, 1480, 1400, 1320, 1230, 1140, 1105, 1040, 1005, 850. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.00 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 2.92 (1H, br, OH, exchangeable with D_2O), 3.60 (3H, s, Ar-2-OCH_3), 3.90 (3H, s, $ArOCH_3$), 3.93 (3H, s, $ArOCH_3$), 4.16 (2H, br s, $ArCH_2OH$), 4.23 (1H, d, *J*=13.0 Hz, ArCHHOTBS), 4.38 (1H, d, *J*=13.0 Hz, ArCHHOTBS), 6.02 (1H, d, *J*=1.4 Hz, ArOCHHOAr), 6.04 (1H, d, *J*=1.4 Hz, ArOCHHOAr), 6.61 (1H, s, Ar-6′-H), 6.95 (1H, s, Ar-5-H), 7.03 (1H, s, Ar-3′-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.48, −5.46, 18.26, 25.81, 55.80, 60.99, 61.17, 62.78, 63.54, 101.12, 106.99, 109.84, 109.99, 124.93, 127.95, 133.68, 135.06, 140.97, 146.89, 147.28, 150.55, 152.87. Anal. Calcd for $C_{24}H_{34}O_7Si$: C, 62.31; H, 7.41. Found: C, 62.18; H, 7.07. HPLC condition: column, CHIRALCEL OD; solvent, IPA/*n*-hexane=1:15; flow rate, 1.0 mL/min; wavelength, 254 nm; retention time, 9.8 min [(*S*)-**36**, 7.4 min].

4.9.4. (*R*)-6-*tert*-Butyldimethylsiloxymethyl-2′-formyl-2,3,4-trimethoxy-4′,5′-methylenedioxy-1,1′-biphenyl (32). The starting alcohol (181 mg, 0.391 mmol) in CH_2Cl_2 (1.5 mL) was added to a solution of PDC (294 mg, 0.781 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C, and the mixture was stirred for 12 h at rt. The mixture was filtered with Celite, and the filtrate was washed with water and brine, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The resulting oil was subjected to silica gel column chromatography with AcOEt–*n*-hexane (1:3) to give **32** (138 mg, 77%). $[\alpha]_D^{21}$ −1.2 (*c* 2.080, $CHCl_3$). IR (KBr) cm^{-1}: 2920, 1680, 1610, 1480, 1400, 1325, 1270, 1240, 1140, 995, 850, 780. ^1H NMR (500 MHz, $CDCl_3$) δ: −0.03 (3H, s,

$SiCH_3$), −0.02 (3H, s, $SiCH_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 3.62 (3H, s, Ar-2-OCH_3), 3.88 (3H, s, $ArOCH_3$), 3.92 (3H, s, $ArOCH_3$), 4.25 (1H, d, J=13.0 Hz, ArC*H*HOTBS), 4.34 (1H, d, J=13.0 Hz, ArCH*H*OTBS), 6.10 (1H, d, J=1.5 Hz, ArOC*H*HOAr), 6.12 (1H, d, J=1.5 Hz, ArOCH*H*OAr), 6.68 (1H, s, Ar-6′-H), 6.96 (1H, s, Ar-5-H), 7.46 (1H, s, Ar-3′-H), 9.50 (1H, s, CHO). ^{13}C NMR (50 MHz, $CDCl_3$) δ: −5.47, 18.23, 25.80, 55.86, 60.77, 60.88, 62.78, 102.03, 105.89, 106.23, 110.77, 121.59, 129.48, 135.37, 137.02, 140.73, 147.88, 151.18, 152.21, 153.56, 190.29. Anal. Calcd for $C_{24}H_{32}O_7Si$: C, 62.58; H, 7.00. Found: C, 62.60; H, 6.68.

4.9.5. (+)-6-*tert*-Butyldimethylsiloxymethyl-2′-(1-hydroxyethyl)-2,3,4-trimethoxy-4′,5′-methylenedioxy-1,1′-biphenyl. To a solution of **32** (135 mg, 0.293 mmol) in THF (2 mL), 2.2 mol/L MeLi in Et_2O solution (187 μL, 0.411 mmol) was added dropwise at −78 °C under an argon atmosphere. After stirring for 30 min, the resulting mixture was quenched with saturated aqueous NH_4Cl solution and extracted with ether. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The resulting oil was subjected to silica gel column chromatography with Et_2O–*n*-hexane (1:1) to give the title compound (76.5 mg, 55%, 79% ee). $[\alpha]_D^{21}$ +33.9 (*c* 1.342, $CHCl_3$) [79% ee]. IR (KBr) cm^{-1}: 3390, 2940, 1480, 1235, 1140, 1110, 1085, 1040, 840. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.01 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.33 (3H, d, J=6.3 Hz, CH(OH)CH_3), 3.56 (3H, s, Ar-2-OCH_3), 3.90 (3H, s, $ArOCH_3$), 3.92 (3H, s, $ArOCH_3$), 4.16 (1H, d, J=13.5 Hz, ArC*H*HOTBS), 4.43 (1H, q, J=6.3 Hz, C*H*(OH)CH_3), 4.45 (1H, d, J=13.5 Hz, ArCH*H*OTBS), 6.01 (1H, d, J=2.0 Hz, OC*H*HO), 6.02 (1H, d, J=2.0 Hz, OCH*H*O), 6.55 (1H, s, Ar-H), 7.02 (1H, s, Ar-H), 7.11 (1H, s, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: −5.31, −5.27, 18.36, 21.97, 25.91, 55.81, 61.10, 61.24, 62.61, 66.29, 101.05, 105.77, 106.21, 109.64, 124.32, 126.73, 135.26, 137.65, 140.57, 146.40, 147.48, 150.13, 152.70. FABMS (positive ion mode) *m/z*: 476 $[M]^+$, 475 $[M-1]^+$. Anal. Calcd for $C_{25}H_{36}O_7Si$: C, 63.00; H, 7.61. Found: C, 63.18; H, 7.54. HPLC condition: column, CHIRALCEL OD; solvent, IPA/*n*-hexane=1:31; flow rate, 1.0 mL/min; wavelength, 254 nm; retention time, 16.5 min [(−)-form, 13.7 min].

The diastereoisomer was obtained by further purification of another fraction as a colorless solid (14.3 mg, 10%, 85% ee).

4.9.6. (+)-6-*tert*-Butyldimethylsiloxymethyl-2′-(1-allyloxyethyl)-2,3,4-trimethoxy-4′,5′-methylenedioxy-1,1′-biphenyl (33).[4a,c] To a solution of the secondary alcohol (64.0 mg, 0.134 mmol) in DMF (2 mL), NaH (6.4 mg, 0.160 mmol) and allyl bromide (23.2 μL, 0.268 mmol) were added at 0 °C. The resulting mixture was allowed to warm to rt, and the addition of NaH (6.4 mg, 0.160 mmol) and allyl bromide (23.2 μL, 0.268 mmol) at 0 °C was repeated a further three times. At 6 h after the final addition of the reagents, the resulting mixture was quenched with pH 6.86 phosphate buffer and extracted with ether. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The resulting oil was subjected to silica gel column chromatography with ether–*n*-hexane (1:4) to give **33** as a colorless oil (45.7 mg, 66%, 80% ee). $[\alpha]_D^{20}$ +1.8 (*c* 2.285, $CHCl_3$) [80% ee] [lit.[4a] $[\alpha]_D^{25}$ +2.3 (*c* 1.18, $CHCl_3$)]. IR (KBr) cm^{-1}: 2930, 1600, 1480, 1400, 1235, 1140, 1040, 1000, 940, 840. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.01 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.14 (3H, d, J=6.3 Hz, CH(OAllyl)CH_3), 3.60 (3H, s, Ar-2-OCH_3), 3.75–3.81 (1H, m, OC*H*HCH=CH_2), 3.88 (3H, s, $ArOCH_3$), 3.85–3.93 (1H, m, OCH*H*CH=CH_2), 3.92 (3H, s, $ArOCH_3$), 4.14 (1H, d, J=13.5 Hz, ArC*H*HOTBS), 4.15 (1H, q, J=6.3 Hz, C*H*(OAllyl)CH_3), 4.37 (1H, d, J=13.5 Hz, ArCH*H*OTBS), 5.08 (1H, ddd, J=8.7, 3.0, 2.5 Hz, OCH_2CH=C*H*H), 5.23 (1H, ddd, J=15.6, 3.0, 2.5 Hz, OCH_2CH=CH*H*), 5.80–5.95 (1H, m), 6.01 (2H, s, OCH_2O), 6.52 (1H, s, Ar-H), 6.98 (1H, s, Ar-H), 7.10 (1H, s, Ar-H). HPLC condition: column, CHIRALCEL AD; solvent, IPA/*n*-hexane=1:400; flow rate, 0.2 mL/min; wavelength, 254 nm; retention time, 38.0 min [(−)-**33**, 32.3 min].

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