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TOTAL SYNTHESIS OF CORIARIIN B

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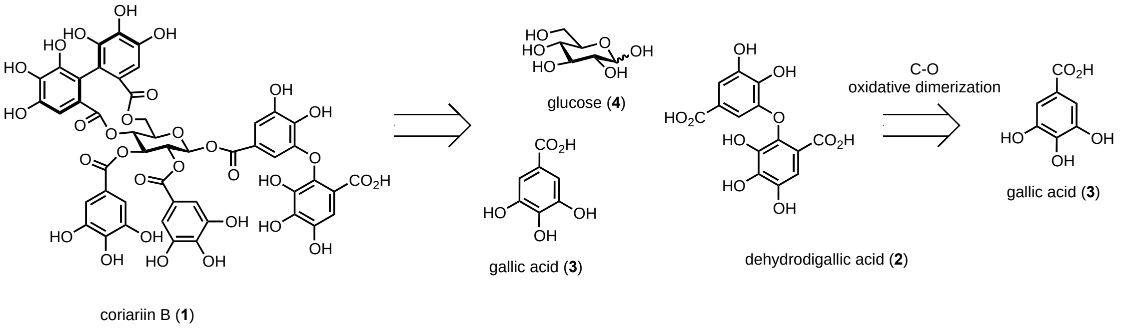
Abstract – The total synthesis of coriariin B (**1**), which is a type of ellagitannin, and originally obtained from the leaves of *Coriaria japonica*, was achieved by esterification between the glucose derivative and partially protected dehydrodigallic acid (**5**). The HHDP (hexahydroxydiphenoyl) unit was constructed by the oxidative phenol coupling reaction in a stereoselective manner.

Coriariin B (**1**) was isolated from the leaves of *Coriaria japonica* by Okuda and co-workers and its structure was determined in 1986.[1] The structural feature of **1** is the two characteristic aromatic ring moieties, i.e., a dehydrodigalloyl group at the anomeric position of the glucose core and an axially chiral hexahydroxydiphenoyl (HHDP) unit combined with the 4- and 6-hydroxy groups. Naturally occurring polyphenolic compounds like **1** are well known as ellagitannins,[2] and are expected to be new drug candidates.[3] Thus, the synthetic studies of ellagitannins are attracting the attention of many organic chemists[4] whereas there is no report on the total synthesis of coriariin B (**1**).

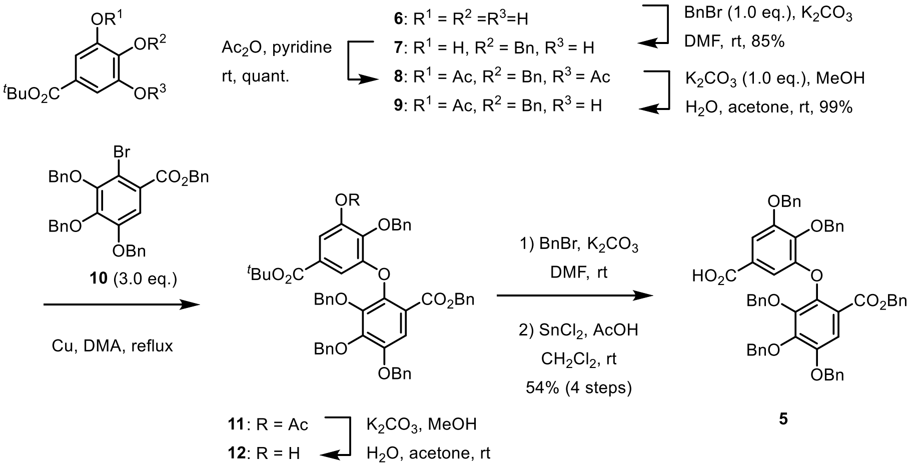
Recently, we demonstrated the facile preparation of dehydrodigallic acid (**2**) via the Ullmann condensation reaction, which would be applicable to the total synthesis of ellagitannins possessing the dehydrodigalloyl unit as part of the structure.[5] In this report, we present the improved preparation of the partially protected dehydrodigallic acid derivative and the total synthesis of **1**.

In Scheme 1, a simple synthetic plan is summarized in which the target molecule (**1**) should be constructed through sequential esterification of the hydroxy groups of glucose (**4**) with gallic acid (**3**) and **2**. The HHDP group should be formed by Yamada's protocol[4e,6] during the final stage (*vide infra*). The oxidative dimerization of **3** would be necessary for preparation of **2**.

Our total synthesis commenced with the preparation of the partially protected dehydrodigallic acid derivative (**5**) (Scheme 2). Since the two carboxy groups of **2** must be differentiated for the total synthesis, the *tert*-butyl ester **6**[5] was chosen as the starting material. Selective monobenzylation of **6** for forming **7** and the next acetylation of the remaining hydroxy groups generated **8** which was subjected to careful hydrolysis to afford the phenol **9**. The following diaryl ether synthesis was performed using the Ullmann condensation conditions between **9** and an excess amount of bromide **10**.[5] Although, during this step, generation of the homo-dimerized product from **10** could not be avoided, the next hydrolysis of the acetoxy group of **11** was carried out without purification to remove the by-products involving the dimerized material. The obtained phenol **12** was benzylated again followed by deprotection of the *tert*-butyl group for forming the desired carboxylic acid **5**.[5]



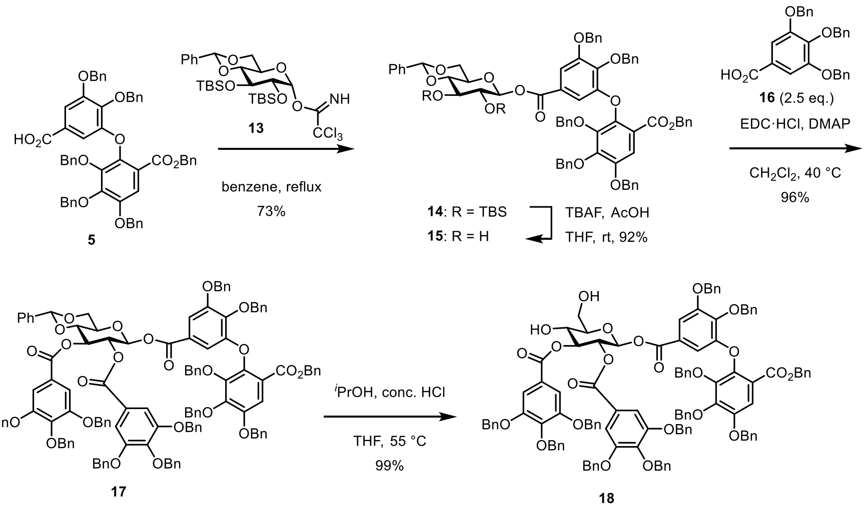
Scheme 1. Synthesis Plan of Coriariin B (**1**)



Scheme 2. Preparation of Dehydrodigallic Acid Derivative (**5**)

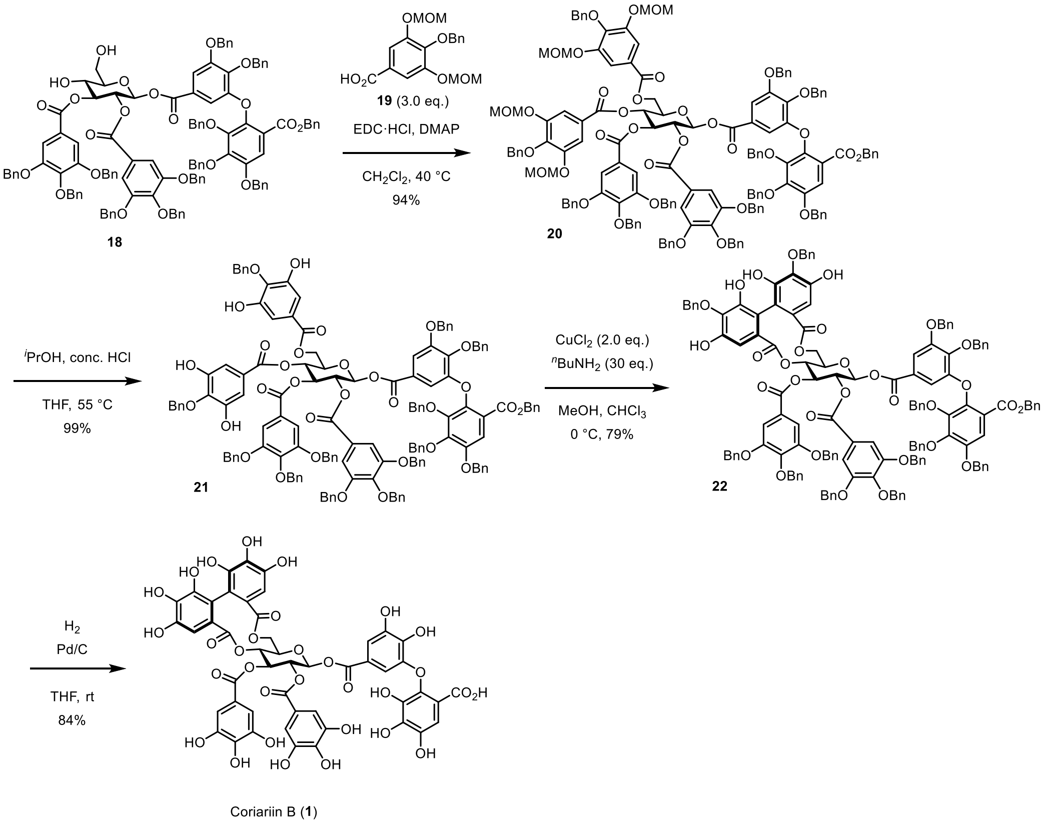
According to Feldman's method,[7] the glycosylation reaction was carried out between **5** and the glucose derivative (**13**) to afford the 1-dehydrodigalloyl compound (**14**) in a *β*-selective manner (Scheme 3). After desilylation of the 2- and 3-hydroxy positions with TBAF, the condensation reaction of **15** with the benzyl-protected gallic acid (**16**)[8] was conducted for producing **17**. Removal of the benzylidene group of **17** by the acid hydrolysis conditions led to forming **18** in a sufficient yield.

Finally, in order to complete the synthesis, we applied Yamada's HHDP construction method in our challenge (Scheme 4). Namely, installation of the gallic acid derivatives (**19**)[9] at the 4- and 6-hydroxy groups was conducted by the conventional condensation reaction. Removal of the MOM group of the obtained pentaester (**20**) was necessary to prepare the precursor for the oxidative biphenyl coupling reaction. For realizing the C-C coupling between the two aromatic rings of **21**, Yamada's system ($CuCl_2$-$^{n}BuNH_2$) was employed for forming the axially chiral biphenyl (**22**) in a diastereoselective manner. Consequently, the synthesis of the objective molecule, coriariin B (**1**), was accomplished after debenzylation of **22** under the catalytic hydrogenolysis conditions.



Scheme 3. Preparation of Intermediate (**18**)

The ^{1}H- and ^{13}C-NMR data of the synthetic material were consistent with the data of the authentic sample. In conclusion, we could synthesize the ellagitannin, coriariin B (**1**), in 16 steps from gallic acid (**3**).



Scheme 4. Synthesis of Coriariin B (**1**)

EXPERIMENTAL

General Information

Melting points were measured using a Yanagimoto micro-melting point hot-plate and are uncorrected. The IR spectra were recoded using a Shimadzu FTIR-8400 spectrophotometer. The NMR spectra were obtained using a JEOL α-400 (400 MHz) or JNX-ECX500 (500 MHz) instrument. The chemical shifts are given in δ parts per million with TMS as an internal standard. The elemental analyses were performed using an Elementar vario MICRO cube or Thermo Fisher Scientific Flash EA 1112 analyzer. The FABMS was obtained using a JEOL JMS-AX505HAD instrument. Silica gel column chromatography was carried out using wakogel® C-200 or 60N. TLC analysis was performed on Kieselgel 60 F_{254} (Merck) plates. Solvents were dried with a standard procedure.

***tert*-Butyl 4-benzyloxy-3,5-dihydroxybenzoate (7)**

To a mixture of **6** (1.00g, 4.42 mmol), K_2CO_3 (611 mg, 4.42 mmol), and DMF (40 mL) was slowly added BnBr (0.53 mL, 4.42 mmol) at rt, then the mixture was stirred for 5 h. The mixture was acidified with 10% HCl aqueous solution, and diluted with water (150 mL). After extraction with AcOEt, 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/hexane = 1/5. The title compound **7** (1.19 g, 85%) was obtained as light yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.58 (9H, s, ^{t}Bu), 5.18 (2H, s, CH_2), 6.40 (2H, s, OH), 7.35-7.40 (5H, m, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.3, 75.4, 81.8, 109.7, 127.6, 128.8, 129.0, 136.7, 137.2, 149.1, 166.2. IR ($CHCl_3$): 3526, 1706, 1602, 1522, 1455, 1369, 1252, 1162, 1057, 967 cm^{-1}. HRMS (EI) Calcd for $C_{18}H_{20}O_5$ $[M]^+$: 316.1311; found: 316.1288 $[M]^+$.

***tert*-Butyl 3,5-diacetoxy-4-benzyloxybenzoate (8)**

A mixture of **7** (1.00 g, 3.16 mmol), pyridine (10 mL), and Ac_2O (0.74 mL, 7.95 mmol) was stirred for 30 min at rt. The mixture was acidified with 10% HCl aqueous solution, and diluted with water (80 mL). After extraction with AcOEt, 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/hexane = 1/3. The title compound **8** (1.27 g, 100%) was obtained. An analytical sample of **8** was obtained after recrystallization from Et_2O-hexane. Colorless solid, mp 72.0-72.1 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.56 (9H, s, ^{t}Bu), 2.20 (6H, s, CH_3), 5.03 (2H, s, CH_2), 7.33-7.38 (5H, m, Ar-H), 7.61 (2H, s, Ar-H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.6, 28.1, 75.7, 81.6, 122.4, 127.66, 127.70, 128.3, 128.5, 136.7, 144.0, 147.0, 163.7, 168.6. IR (KBr): 1781, 1765, 1710, 1370, 1325, 1223, 1197, 1188, 1165, 1045, 961, 761 cm^{-1}. HRMS (EI) Calcd for $C_{22}H_{24}O_7$ $[M]^+$: 400.1522; found: 400.1527 $[M]^+$.

tert-Butyl 3-acetoxy-4-benzyloxy-5-hydroxybenzoate (9)

To a mixture of **8** (4.85 g, 12.1 mmol), acetone (50 mL), MeOH (25 mL), and water (25 mL) was added K_2CO_3 (1.67 g, 12.1 mmol) at rt, then the mixture was stirred for 1 h. After AcOEt (50 mL) was added, the mixture was acidified with 10% HCl aqueous solution, and poured into water (150 mL). The organic layer was separated, washed with brine, and dried over $MgSO_4$ to give a pale yellow residue of **9** (4.30 g, 99%). Analytical sample was obtained after recrystallization from AcOEt-hexane. Colorless solid, mp 130.5-130.8 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.56 (9H, s, ^{t}Bu), 2.27 (3H, s, CH_3), 5.05 (2H, s, CH_2), 5.54 (1H, s, OH), 7.29-7.44 (7H, m, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.8, 28.2, 76.0, 81.6, 109.6, 115.0, 116.5, 128.1, 128.3, 128.88, 128.90, 136.4, 141.7, 143.1, 149.0, 149.8, 164.7, 168.9. IR (KBr): 3436, 2360, 1765, 1704, 1587, 1355, 1230, 1158, 1058, 961 cm^{-1}. HRMS (EI) Calcd for $C_{20}H_{22}O_6$ $[M]^+$: 358.1416; found: 358.1465 $[M]^+$.

Benzyl 3,4,5-tris(benzyloxy)-2-(2-benzyloxy-5-*tert*-butoxycarbonyl-3-hydroxy)phenoxybenzoate (12) and 3,4-dibenzyloxy-5-(2,3,4-tribenzyloxy-6-benzyloxycarbonylphenoxy)benzoic acid (5)

A mixture of **9** (1.00 g, 2.79 mmol), **10** (5.10 g, 8.37 mmol), Cu powder (1.06 g, 16.7 mmol), and DMA (10 mL) was heated at 160 °C for 75 min. After cooling, the mixture was filtered through Celite^{TM} pad, then the filtrate was concentrated *in vacuo* to give a residue (14.7 g). The crude oil was dissolved in acetone (75 mL), MeOH (25 mL), and water (25 mL), then K_2CO_3 (771 mg, 5.58 mmol) was added to the mixture which was stirred at rt for 12 h. The solvent was removed *in vacuo*, then the residual oil was acidified with 10% HCl aqueous solution and diluted with water (200 mL). After extraction with AcOEt, the organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a black residue which was subjected to silica gel column chromatography with AcOEt/hexane/CH_2Cl_2 = 0.25/3/1. Yellow amorphous of **12** (6.76 g) was obtained. IR ($CHCl_3$): 3524, 1706, 1595, 1438, 1345, 1072, 968 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.51 (9H, s, ^{t}Bu), 2.19 (3H, s, CH_3), 4.97 (2H, s, CH_2), 5.04 (2H, s, CH_2), 5.13 (2H, s, CH_2), 5.14 (2H, s, CH_2), 5.20 (2H, s, CH_2), 7.07 (1H, d, *J* = 2.0 Hz, Ar-H), 7.14-7.47 (17H, m, Ar-H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.7, 28.2, 67.2, 71.4, 75.1, 75.7, 75.9, 81.3, 111.2,113.2, 117.5, 120.1, 127.0, 127.8, 127.9, 128.1, 128.2, 128.3, 128.48, 128.53, 128.75, 128.79, 135.6, 136.4, 136.6, 136.9, 137.8, 142.1, 143.6, 144.2, 146.6, 147.2, 150.3, 152.7, 164.6, 168.9. HRMS (FAB) Calcd for $C_{53}H_{49}O_{10}$ $[M]^+$: 845.33253; found: 845.33376 $[M]^+$.

To a solution of **12** (6.00 g) in CH_2Cl_2 (15 mL), AcOH (1.60 mL, 28 mmol) and $SnCl_2$ (2.65 g, 14.0 mmol) were added, then the mixture was stirred for 105 h at rt. After filtration, the solvent was removed *in vacuo* to give a residue which was subjected to silica gel chromatography with AcOEt/hexane = 1/2. Pale yellow solid of **5** (1.17 g, 54%) was obtained by recrystallization from AcOEt-hexane, mp 126.4-128.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.92 (2H, s, CH_2), 4.96 (2H, s, CH_2), 5.11 (2H, s, CH_2), 5.12 (4H, s, CH_2), 5.15 (2H, s, CH_2), 6.90 (1H, d, *J* = 1.6 Hz, ArH), 7.07-7.45 (32H, m, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 67.3, 71.2, 71.4, 75.0, 75.6, 75.7, 109.6, 109.9, 111.0, 120.1, 123.9, 127.6, 127.8, 127.9, 128.0, 128.1, 128.17, 128.24, 128.28, 128.29, 128.4, 128.5, 128.68, 128.72, 128.8, 135.5, 136.4, 136.7, 136.8, 136.9, 138.0, 142.4, 142.6, 146.6, 147.0, 150.1, 152.7, 152.8, 164.9, 171.7.

4,6-*O*-Benzylidene-2,3-di-*O*-(*tert*-butyldimethylsilyl)-1-*O*-[3,4-dibenzyloxy-5-(2,3,4-tribenzyloxy-6-benzyloxycarbonylphenoxy)galloyl]-*β*-D-glucopyranoside (14)

To a solution of **5** (900 mg, 1.14 mmol) in benzene (15 mL) was added a solution of **13**[7] (878 mg, 1.37 mmol) in benzene (20 mL). After the mixture was heated under reflux for 25 h, the solvent was removed *in vacuo* to give a residue which was subjected to column chromatography with AcOEt/hexane = 1/8, producing amorphous powder of **14** (1.21 g, 73%), mp 43.2-45.1 °C, $[\alpha]_D^{21}$ -27.6 (c 1.0, $CHCl_3$). ^1H-NMR (400 MHz, $CDCl_3$) δ: -0.024 (6H, s), 0.004 (3H, s), 0.058 (3H, s), 0.758 (9H, s), 0.764 (9H, s), 3.58 (2H, t, *J* = 10.0 Hz, H-4, H-6), 3.71 (1H, dt, *J* = 4.4, 9.6 Hz, H-5), 3.79 (1H, t, *J* = 6.0 Hz, H-2), 3.87 (1H, dd, *J* = 6.0, 8.0 Hz, H-3), 4.29 (1H, dd, *J* = 4.4, 10.4 Hz, H-6), 4.87 (2H, s), 4.94 (2H, dd, *J* = 10.8, 33.2 Hz), 5.06-5.14 (6H, m), 5.17 (2H, s), 5.39 (1H, s), 5.86 (1H, d, *J* = 6.4 Hz, H-1), 7.00 (1H, d, *J* = 2.0 Hz), 7.08-7.47 (37H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: -3.91, -3.60, -3.32, 18.1, 18.4, 25.9, 26.2, 65.9, 67.3, 69.2, 71.49, 71.54, 74.9, 75.1, 75.7, 75.8, 75.9, 81.7, 95.6, 102.3, 109.9, 110.0, 111.2, 120.0, 124.2, 126.5, 127.6, 127.7, 127.8, 128.0, 128.1, 128.16, 128.21, 128.27, 128.34, 128.46, 128.50, 128.7, 128.8, 129.2, 135.6, 136.4, 136.8, 136.86, 136.94, 137.2, 138.0, 142.58, 142.61, 146.7, 147.2, 150.1, 152.86, 152.91, 164.7, 164.9. IR (KBr): 3065, 3032, 2953, 2929, 2882, 2855, 1735, 1711, 1592, 1500, 1454, 1426, 1374, 1214, 1200, 1090, 1075, 837, 695 cm^{-1}. *Anal.* Calcd for $C_{81}H_{88}O_{15}Si_2$: C, 71.65; H, 6.53. Found: C, 71.31; H, 6.59.

4,6-*O*-Benzylidene-1-*O*-[3,4-di-*O*-benzyl-5-*O*-(2,3,4-tribenzyloxy-6-benzyloxycarbonylphenoxy)galloyl]-*β*-D-glucopyranoside (15)

AcOH (0.0850 mL, 1.49 mmol) and tetra-*n*-butylammonium fluoride (1M in THF) (2.36 mL, 2.36 mmol) were added dropwise to a solution of **14** (400 mg, 0.295 mmol) in THF (3 mL), then the mixture was stirred for 49 h at rt. To the reaction mixture, AcOEt (15 mL) and H_3PO_4 aqueous solution (1M, 9 mL) were added. After the mixture was poured into water (10 mL), extraction with AcOEt was carried out. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a residue which was subjected to column chromatography with AcOEt/hexane = 1/1. Colorless amorphous powder of **15** (305 mg, 92%) was obtained, mp 60.5-62.1 °C, $[\alpha]_D^{21}$ -5.5 (c 1.0, $CHCl_3$). ^1H-NMR (400 MHz, $CDCl_3$) δ: 2.62 (1H, brs), 2.81 (1H, brs), 3.58 (1H, t, *J* = 9.2 Hz, H-4), 3.64 (1H, dt, *J* = 4.8, 9.2 Hz, H-5), 3.71-3.76 (2H, m, H-2, H-6), 3.90 (1H, t, *J* = 9.2 Hz, H-3), 4.36 (1H, dd, *J* = 4.8, 10.4 Hz, H-6), 4.95 (2H, s), 4.96 (2H, dd, *J* = 10.4, 15.2 Hz), 5.08-5.19 (8H, m), 5.52 (1H, s), 5.76 (1H, d, *J* = 8.0 Hz, H-1), 6.96 (1H, d, *J* = 1.6 Hz), 7.11-7.51 (37H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 67.1, 67.3, 68.5, 71.5, 73.5, 73.7, 75.0, 75.77, 75.82, 80.2, 94.8, 102.1, 109.8, 111.0, 120.2, 123.5, 126.4, 127.7, 127.8, 127.9, 128.1, 128.2, 128.26, 128.30, 128.4, 128.5, 128.7, 128.77, 128.81, 129.5, 135.4, 136.3, 136.7, 136.8, 136.9, 137.9, 142.3, 142.6, 146.6, 147.1, 150.1, 152.7, 152.8, 164.3, 165.1. IR (KBr): 3478, 3063, 3032, 2932, 2873, 2359, 2322, 1730, 1591, 1427, 1340, 1199, 1087, 1016, 696 cm^{-1}. *Anal.* Calcd for $C_{69}H_{60}O_{15}$: C, 73.39; H, 5.36. Found: C, 73.12; H, 5.07.

4,6-*O*-Benzylidene-2,3-di-*O*-(3,4,5-tri-*O*-benzylgalloyl)-1-*O*-[3,4-di-*O*-benzyl-5-*O*-(2,3,4-tribenzyloxy-6-benzyloxycarbonylphenoxy)galloyl]-*β*-D-glucopyranoside (17)

A solution of **15** (700 mg, 0.620 mmol), **16**[8] (683 mg, 1.55 mmol), DMAP (30.3 mg, 0.248 mmol), and EDC·HCl (297 mg, 1.55 mmol) in CH_2Cl_2 (25 mL) was heated under reflux for 12 h, then the mixture was poured into water (40 mL). After the mixture was extracted with AcOEt, the orgnic solvent was successively washed with sat. NH_4Cl aq., sat. K_2CO_3 aq., and brine, dried over $MgSO_4$, and evaporated to give a residue which was subjected to column chromatography with CH_2Cl_2/hexane/AcOEt = 1/3/0.25. Pale yellow amorphous powder of **17** (1.17 g, 96%) was obtained, mp 54.6-56.8 °C, $[\alpha]_D^{21}$ +26.8 (c 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.88 (1H, t, *J* = 10.0 Hz, H-6), 3.92 (1H, dt, *J* = 3.2, 9.2 Hz, H-5), 4.01 (1H, t, *J* = 10.0 Hz, H-4), 4.48 (1H, d, *J* = 6.4 Hz, H-6), 4.79-5.15 (24H, m), 5.57 (1H, s), 5.73 (1H, dd, *J* = 8.0, 10.0 Hz, H-2), 5.91 (1H, t, *J* = 10.0 Hz, H-3), 6.09 (1H, d, *J* = 8.0 Hz, H-1), 6.93 (1H, d, *J* = 1.6 Hz), 6.99-7.48 (71H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 67.1, 67.5, 68.4, 71.1, 71.2, 71.3, 71.9, 72.2, 74.9, 75.09, 75.13, 75.6, 75.7, 78.5, 93.3, 101.6, 109.2, 109.3, 109.4, 109.8, 111.0, 120.0, 123.0, 123.7, 124.3, 126.2, 127.6, 127.66, 127.70, 127.86, 127.91, 127.98, 128.04, 128.1, 128.17, 128.23, 128.3, 128.37, 128.43, 128.5, 128.6, 128.7, 129.2, 135.4, 136.3, 136.4, 136.5, 136.55, 136.62, 136.8, 137.36, 137.38, 137.8, 142.3, 142.6, 142.9, 143.1, 146.5, 147.0, 150.1, 152.5, 152.6, 152.7, 152.9, 164.0, 164.7, 165.1, 165.3. IR (KBr): 3065, 3031, 2931, 2873, 1734, 1589, 1499, 1429, 1336, 1195, 1097, 910, 750, 695 cm^{-1}. *Anal.* Calcd for $C_{125}H_{104}O_{23}$: C, 76.05; H, 5.31. Found: C, 75.80; H, 5.19.

2,3-Di-*O*-(3,4,5-tri-*O*-benzylgalloyl)-1-*O*-[3,4-di-*O*-benzyl-5-*O*-(2,3,4-tribenzyloxy-6-benzyloxycarbonylphenoxy)galloyl]-*β*-D-glucopyranoside (18)

To a solution of **17** (1.10 g, 0.557 mmol) in THF (25 mL), a mixture of ^{i}PrOH and conc. HCl aq. (v/v = 50/1, 5.0 mL) was added. The reaction mixture was heated at 55 °C for 6 h, then the solvent was removed in *vacuo*. After the residue was poured into sat. $NaHCO_3$ aq. (80 mL), the mixture was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a crude residue which was subjected to column chromatography with AcOEt/hexane = 1/1. Colorless amorphous powder of **18** (1.04 g, 99%) was obtained, mp 55.4-57.0 °C; $[\alpha]_D^{21}$ +37.5 (c 1.0, $CHCl_3$); ^1H-NMR (400 MHz, $CDCl_3$ + D_2O) 3.78-3.82 (1H, m, H-5), 3.92 (1H, dd, *J* = 4.0, 12.0 Hz, H-6), 4.00-4.08 (2H, m, H-4, H-6), 4.79-5.13 (24H, m), 5.45 (1H, t, *J* = 9.2 Hz, H-3), 5.69 (1H, dd, *J* = 8.4, 9.2 Hz, H-2), 6.05 (1H, d, *J* = 8.4 Hz, H-1), 6.93 (1H, d, *J* = 1.6 Hz), 6.99-7.46 (66H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) 61.8, 67.1, 69.4, 71.0, 71.09, 71.14, 71.3, 74.9, 75.1, 75.2, 75.6, 75.7, 92.7, 109.16, 109.22, 109.4, 109.8, 111.0, 119.9, 123.2, 123.7, 123.8, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.57, 128.64, 128.7, 135.4, 136.3, 136.35, 136.43, 136.5, 136.6, 136.8, 137.29, 137.34, 137.8, 142.3, 142.5, 143.0, 143.2, 146.5, 147.0, 150.1, 152.55, 152.64, 152.7, 152.9, 164.1, 164.8, 165.1, 167.0; IR (KBr): 3484, 3065, 3032, 2917, 1729, 1589, 1498, 1427, 1338, 1213, 1104, 1002, 909, 861 cm^{-1}. *Anal.* Calcd for $C_{118}H_{100}O_{23}$: C, 75.15; H, 5.34. Found: C, 75.14; H, 5.42.

2,3-Di-*O*-(3,4,5-tri-*O*-benzylgalloyl)-4,6-di-*O*-(4-*O*-benzyl-3,5-di-*O*-methoxymethylgalloyl)-1-*O*-[3,4-di-*O*-benzyl-5-*O*-(2,3,4-tribenzyloxy-6-benzyloxycarbonylphenoxy)galloyl]-*β*-D-glucopyranoside (20)

A solution of **18** (100 mg, 0.0530 mmol), **19**[9] (55.8 mg, 0.160 mmol), DMAP (7.0 mg, 0.057 mmol), and EDC·HCl (61.7 mg, 0.322 mmol) in CH_2Cl_2 (1.5 mL) was allowed to stand for 17 h, then the mixture was acidified (pH = ca. 1) with 10% HCl aq. The mixture was poured into water (10 mL). After extraction with AcOEt, the orgnic solvent was washed with brine, dried over $MgSO_4$, and evaporated to give a residue which was subjected to column chromatography with CH_2Cl_2/hexane/AcOEt = 1/2/0.5. Pale yellow amorphous powder of **20** (126 mg, 94%) was obtained, mp 41.8-43.0 °C; $[\alpha]_D^{21}$ +22.5° (c 1.0, $CHCl_3$). ^1H-NMR (400 MHz, $CDCl_3$) δ: 3.40 (6H, s), 3.43 (6H, s), 4.35 (1H, t, *J* = 5.6 Hz, H-6), 4.41 (1H, dt, *J* = 2.0, 5.6 Hz, H-5), 4.76 (1H, dd, *J* = 2.8, 12.8 Hz, H-6), 4.81-5.16 (36H, m), 5.76 (1H, t, *J* = 9.6 Hz, H-4), 5.78 (1H, t, *J* = 9.6 Hz, H-2), 6.00 (1H, t, *J* = 9.6 Hz, H-3), 6.15 (1H, d, *J* = 8.4 Hz, H-1), 6.90 (1H, d, *J* = 1.6 Hz), 6.97-7.48 (78H, m), 7.54 (2H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 56.4, 56.5, 63.0, 67.2, 69.3, 71.1, 71.2, 71.4, 73.3, 73.4, 74.9, 75.1, 75.2, 75.3, 75.6, 75.7, 92.8, 95.47, 95.51, 109.1, 109.3, 109.5, 109.8, 111.0, 112.4, 112.5, 120.0, 123.2, 123.8, 123.9, 124.1, 125.1, 127.6, 127.7, 127.8, 127.89, 127.93, 128.0, 128.1, 128.17, 128.23, 128.3, 128.35, 128.45, 128.48, 128.52, 128.66, 128.70, 135.3, 136.3, 136.5, 136.63, 136.65, 136.8, 137.3, 137.41, 137.45, 137.9, 142.3, 142.5, 142.9, 143.1, 143.5, 143.8, 146.5, 147.0, 150.1, 150.9, 151.0, 152.56, 152.65, 152.9, 163.9, 164.75, 164.78, 164.9, 165.47, 165.52. IR (KBr): 3065, 3032, 2950, 2913, 1734, 1590, 1499, 1429, 1333, 1194, 1109, 1003, 910, 751, 695 cm^{-1}. *Anal.* Calcd for $C_{154}H_{136}O_{35}$: C, 72.63; H, 5.38. Found: C, 72.46; H, 5.27.

2,3-Di-*O*-(3,4,5-tri-*O*-benzylgalloyl)-4,6-di-*O*-(4-*O*-benzylgalloyl)-1-*O*-[3,4-di-*O*-benzyl-5-*O*-(2,3,4-tribenzyloxy-6-benzyloxycarbonylphenoxy)galloyl]-*β*-D-glucopyranoside (21)

To a solution of **20** (100 mg, 0.0393 mmol) in THF (1 mL), a mixture of ^{i}PrOH and conc. HCl aq. (v/v = 50/1, 3.0 mL) was added. The reaction mixture was heated at 55 °C for 6 h, then the solvent was removed in *vacuo*. After the residue was poured into sat. $NaHCO_3$ aq. (2 mL), the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a crude oil which was subjected to column chromatography with CH_2Cl_2/hexane/AcOEt = 1/1/0.5. Colorless amorphous powder of **21** (91.8 mg, 99%) was obtained, mp 57.0-59.3 °C; $[\alpha]_D^{21}$ +20.9 (c 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$ + D_2O) δ: 4.29-4.33 (1H, m, H-5), 4.52 (1H, dd, *J* = 4.8, 12.0 Hz, H-6), 4.63 (1H, d, *J* = 10.4 Hz, H-6), 4.85-5.18 (28H, m), 5.72 (1H, t, *J* = 9.6 Hz, H-4), 5.83 (1H, dd, *J* = 8.4, 9.6 Hz, H-2), 5.96 (1H, t, *J* = 9.6 Hz, H-3), 6.14 (1H, d, *J* = 8.4 Hz, H-1), 6.93 (1H, d, *J* = 1.6 Hz), 7.01-7.50 (80H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 61.8, 67.3, 68.2, 71.1, 71.2, 71.4, 71.5, 73.1, 73.6, 74.9, 75.0, 75.1, 75.2, 75.6, 75.8, 93.2, 109.0, 109.3, 109.6, 109.9, 110.0, 110.1, 111.1, 120.0, 123.1, 123.59, 123.63, 123.7, 124.1, 127.6, 127.76, 127.82, 127.9, 128.0, 128.1, 128.2, 128.28, 128.31, 128.37, 128.41, 128.47, 128.49, 128.6, 128.7, 128.78, 128.83, 135.4, 136.3, 136.35, 136.45, 136.66, 136.68, 136.8, 136.9, 137.37, 137.41, 137.9, 138.1, 138.5, 142.3, 142.6, 142.9, 143.2, 146.6, 147.1, 149.1, 149.2, 150.1, 152.6, 152.7, 152.8, 153.0, 164.2, 165.0, 165.7, 165.9, 166.6. IR (KBr): 3435, 3064, 3031, 2945, 2874, 2359, 1730, 1591, 1500, 1454, 1429, 1339, 1198, 1076, 1003, 912, 752, 695 cm^{-1}. *Anal.* Calcd for $C_{146}H_{120}O_{31}$: C, 73.98; H, 5.10. Found: C, 73.88; H, 4.96.

2,3-Di-*O*-(3,4,5-tri-*O*-benzylgalloyl)-4,6-*O*-(*S*)-[4,4',6,6'-tetrahydroxy-5,5'-dibenzyloxy-1,1'-biphenyl-2,2'-dicarboxylate]-1-*O*-[3,4-di-*O*-benzyl-5-*O*-(2,3,4-tribenzyloxy-6-benzyloxycarbonylphenoxy)-galloyl]-*β*-D-glucopyranoside (22)

Under N_2, a mixture of $CuCl_2$ (22.8 mg, 0.170 mmol), ^{n}BuNH_2 (0.250 mL, 2.53 mmol), and MeOH (20 mL) was added dropwise to a solution of **21** (200 mg, 0.0844 mmol) in $CHCl_3$ (20 mL) at 0 °C. The mixture was stirred for 3 h at the same temperature, then poured into sat. NH_4Cl aqueous solution (40 mL). After extraction with $CHCl_3$, the organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a residue which was subjected to column chromatography with CH_2Cl_2/AcOEt = 20/1. Brown amorphous powder of **22** (158 mg, 79%) was obtained, mp 82.8-84.6 °C; $[\alpha]_D^{21}$ +44.5 (c 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, acetone-d_6 + D_2O) δ: 3.96 (1H, d, *J* = 12.8 Hz, H-6), 4.67 (1H, dd, *J* = 6.8, 10.0 Hz, H-5), 4.76 (2H, s), 4.87-5.17 (20H, m), 5.20 (2H, s), 5.23 (2H, s), 5.24 (2H, s), 5.36 (1H, t, *J* = 9.6 Hz, H-4), 5.39 (1H, t, *J* = 6.8 Hz, H-6), 5.75 (1H, t, *J* = 9.2 Hz, H-2), 5.98 (1H, t, *J* = 9.2 Hz, H-3), 6.35 (1H, d, *J* = 8.0 Hz, H-1), 6.55 (1H, s), 6.69 (1H, s), 6.95 (1H, d, *J* = 1.6 Hz), 6.97-7.41 (66H, m), 7.50-7.55 (10H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 62.5, 67.2, 70.3, 70.6, 70.8, 71.1, 71.2, 72.6, 73.3, 74.96, 75.02, 75.3, 75.5, 75.6, 75.7, 93.6, 107.3, 108.3, 109.0, 109.3, 109.5, 110.0, 111.1, 113.5, 114.3, 119.8, 122.6, 123.1, 123.4, 127.3, 127.4, 127.7, 127.8, 128.0, 128.2, 128.4, 128.7, 128.8, 128.9, 129.5, 135.3, 135.4, 136.3, 136.4, 136.58, 136.63, 136.8, 137.4, 137.5, 137.7, 142.2, 143.0, 143.3, 146.5, 147.0, 147.3, 147.5, 148.96, 149.02, 150.1, 152.4, 152.6, 152.8, 153.0, 164.69, 164.72, 166.2, 166.5, 166.8. IR (KBr): 3427, 3063, 3032, 1728, 1589, 1499, 1454, 1429, 1371, 1338, 1195, 1094, 1075, 1029, 1003, 911, 752, 737, 695 cm^{-1}. *Anal.* Calcd for $C_{146}H_{118}O_{31}$: C, 74.04; H, 5.02. Found: C, 74.22; H, 5.05.

Coriariin B (1)

To a suspension of 10% Pd/C (37.8 mg) in THF (20 mL), a solution of **22** (144 mg, 0.0608 mmol) in THF (10 mL) was added and the mixture was stirred under the H_2 atmosphere for 14 h. After filtration using Celite™, the solvent of the filtrate was removed under reduced pressure. The concentrated residue was subjected to column chromatography using Sephadex™ LH-20 with acetone-H_2O (1:4 to 1:2) to produce the gray powder of **1** (56.3 mg, 84%); mp >250 °C, $[\alpha]_D^{20}$ +63.9 (c = 0.1, acetone) [lit. $[\alpha]_D$ +66 (c 0.1, acetone)][1a]; ^{1}H-NMR (500 MHz, acetone-*d*$_6$) 3.85 (1H, d, *J* = 13.0 Hz, H-6), 4.51 (1H, dd, *J* = 6.0, 10.0 Hz, H-5), 5.19 (1H, t, *J* = 10.0 Hz, H-4), 5.34 (1H, dd, *J* = 6.0, 13.0 Hz, H-6), 5.54 (1H, t, *J* = 8.5 Hz, H-2), 5.82 (1H, t, *J* = 10.0 Hz, H-3), 6.13 (1H, d, *J* = 8.5 Hz, H-1), 6.45 (1H, s), 6.65 (1H, s), 6.82 (1H, d, *J* = 1.5 Hz), 6.97 (2H, s), 6.99 (2H, s), 7.18 (1H, s), 7.23 (1H, d, *J* = 1.5 Hz); ^{13}C-NMR (125 MHz, acetone-*d*$_6$) 63.0, 70.7, 71.6, 73.0, 93.7, 107.8, 108.2, 108.4, 110.2, 110.3, 112.3, 115.2, 115.5, 115.7, 119.5, 120.4, 120.5, 125.9, 126.5, 136.47, 136.52, 137.2, 139.1, 139.2, 139.8, 140.3, 141.0, 143.3, 144.4, 144.5, 145.2, 145.3, 145.8, 145.9, 146.4, 148.2, 164.8, 165.3, 166.2, 166.4, 167.6, 168.0; IR (KBr): 3355, 1727, 1701, 1616, 1521, 1448, 1345, 1198, 1095, 1069, 1034, 1011, 756 cm^{-1}. HRMS-FAB (*m/z*): Calcd for $C_{48}H_{35}O_{31}$ $[M+H]^+$ 1107.1162; Found, 1107.1202.

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