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SYNTHESIS OF LACTONIZED VALONEOYL GROUP-CONTAINING ELLAGITANNINS, OENOTHEIN C AND CORNUSIIN B

Hitoshi Abe,[a]* Haruka Imai,[b] Daichi Ogura,[a] and Yoshikazu Horino[a]

a) Graduate School of Science and Engineering, University of Toyama, Gofuku, Toyama 930-8555, Japan. b) Graduate School of Innovative Life Science, University of Toyama, Gofuku, Toyama 930-8555, Japan.
E-mail: abeh@eng.u-toyama.ac.jp

Dedicated to Professor Kaoru Fuji on the occasion of his 80th birthday

Abstract – The total synthesis of two ellagitannins, oenothein C and cornusiin B, which involve a lactonized valoneoyl group (LVG) in the molecules, was accomplished starting from glucose and gallic acid. Classical Ullmann coupling reactions were effective for preparation of the key intermediate, the lactonized valoneic acid derivative, which was subjected to a condensation reaction with glucose, and finally converted to the ellagitannins.

INTRODUCTION

Ellagitannins are widely distributed in the plant world, and are very interesting compounds because of their variety of biological activities such as antioxidant, antiviral, antitumor, etc.[1] Since the 1970s, many reports have been published dealing with their isolation and structure characterization, and currently, over 500 ellagitannin structures have been elucidated.[2] In spite of the numerous studies about their structure determinations and biological investigations, only a limited number of studies of ellagitannin synthesis has been reported.[3] Based on this information, several research groups have challenged the total synthesis of ellagitannins using their unique strategies, and some total syntheses of the ellagitannins have been performed.[4]

A lactonized valoneoyl group (LVG) (**1**) is often found as part of the structure in the ellagitannins,[5] which involves the C-C and C-O-C connections between two aromatic rings, and the two fused lactone rings similar to ellagic acid (**2**) (Figure 1). As already mentioned, some total syntheses of the ellagitannins have been reported, however, we can find no report for the synthesis of the LVG-containing ellagitannins. Both oenothein C (**3**)[6] and cornusiin B (**4**)[7] possess the VLG connecting to the 2-position of glucose (**5**).

Recently, we demonstrated the preparation of lactonized valoneic acid using the classical Ullmann reaction for the C-C and C-O bond formation.[8] As an extension of our previous study, in this article, we present the first synthesis of the VLG-containing ellagitannins, oenothein C and cornusiin B, by utilizing the Ullmann biaryl coupling and the aryl ether synthesis.[9,10]

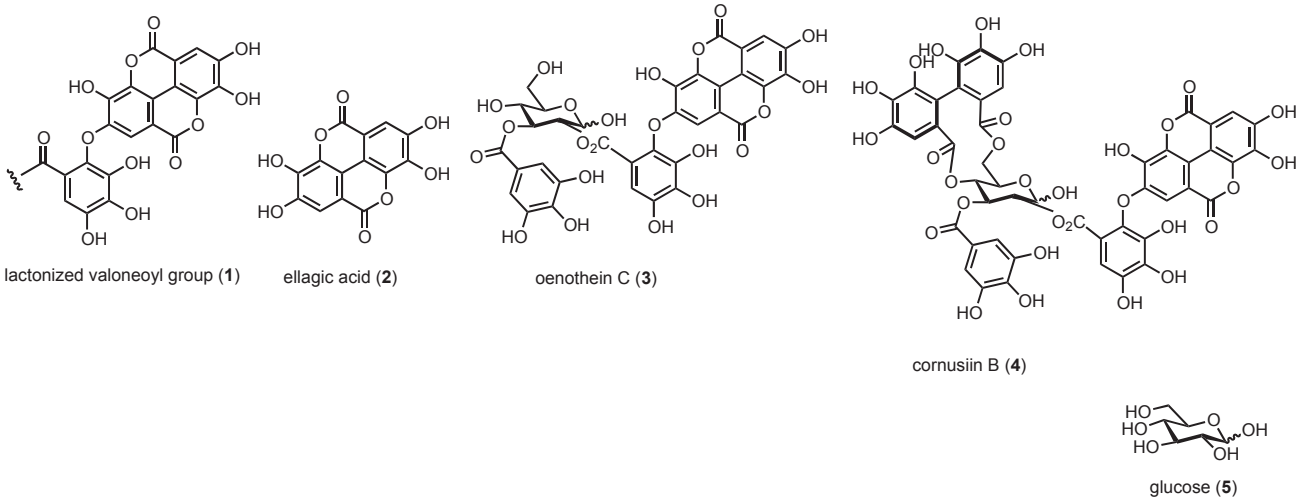


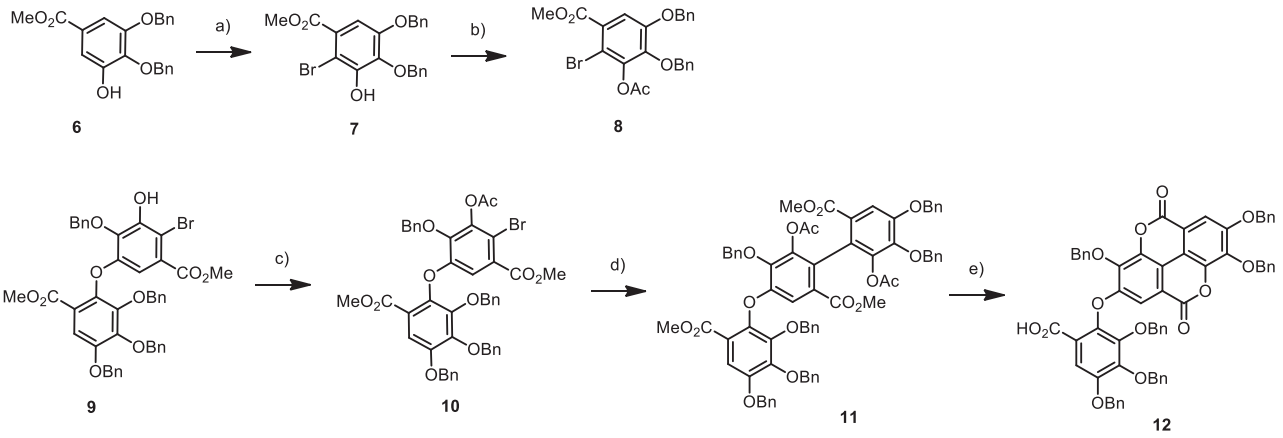
Figure 1. Structures of ellagitannin related compounds

RESULTS AND DISCUSSION

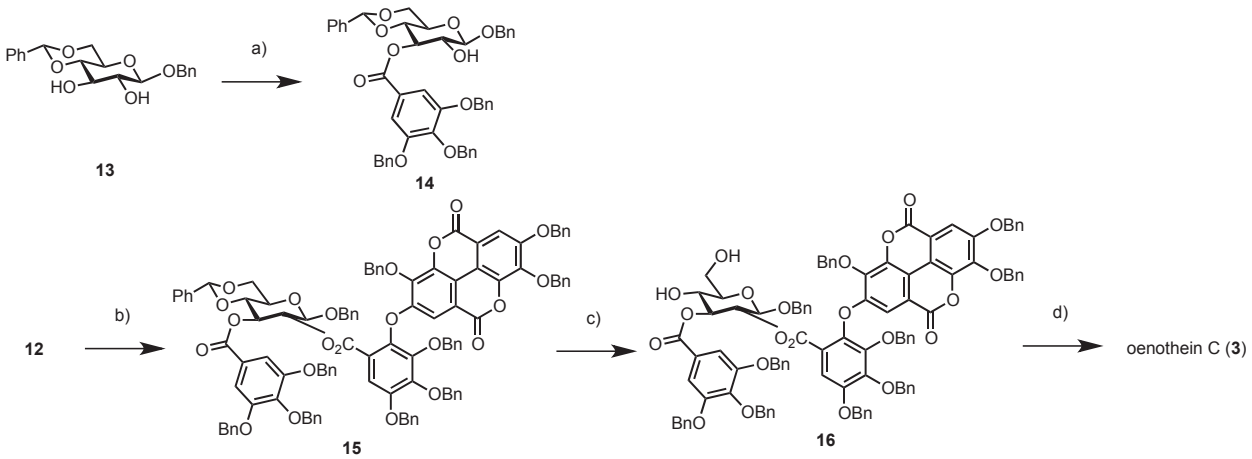
Initially, we started the preparation of the LVD congener using the gallic acid derivative (**6**)[11] which was easily obtained from commercially-available gallic acid through a short-step transformation (Scheme 1). The regioselective bromination of **6** with DBDMH (1,3-dibromo-5,5-dimethylhydantoin) was successfully carried out for forming the bromide **7**, and the acetylation of the remaining hydroxy group gave the acetate **8**. On the other hand, it was necessary to prepare the coupling partner for the intermolecular Ullmann coupling reaction, thus the known compound **9**[8] was transformed into **10** by acetylation of the phenolic hydroxy group. Employing 3.0 equivalents of **8**, the intermolecular reaction afforded the biaryl compound **11** using an excess amount of copper dust[12] in DMF (*N*,*N*-dimethylformamide) by heating. Fortunately, in this step, the dimerization product of **10** was not detected whereas **8** dimerized to afford the undesired by-product.[13] Saponification of the three methoxycarbonyl groups and the two acetyl groups in **11** followed by acid treatment was effective for the formation of the dilactone structure of **12**.

According to the reported method, the glucose derivative **13** was prepared,[14] and galloylation of the 3-hydroxy group was attempted (Scheme 2). All efforts were unsuccessful for selective esterification of the 3-position, as a result, **14** was prepared only in 25% yield. The following esterification between **12** and **14** smoothly proceeded to afford **15** which equals the all-protected oenothein C. The benzylidene

group of the sugar could be removed by acid hydrolysis to form **16**, and finally, catalytic hydrogenolysis for debenzylation of all the *O*-protecting groups produced oenothein C (**3**).



Scheme 1. Synthesis of LVG derivative (**12**). a) DBDMH (0.52 eq.), $CHCl_3$, rt, 3 h (77%); b) Ac_2O (4.0 eq.), pyridine, rt, 1.5 h (81%); c) Ac_2O (4.0 eq.), pyridine, rt, 2 h (96%); d) **8** (3.0 eq.), Cu (12.0 eq.), DMF, 180 °C (bath temp.), 1.5 h (69%); e) (i) 10% KOH aq., THF, 90 °C, 14 h; (ii) TFA (25 eq.), $CHCl_3$, 60 °C, 3 h (70%).

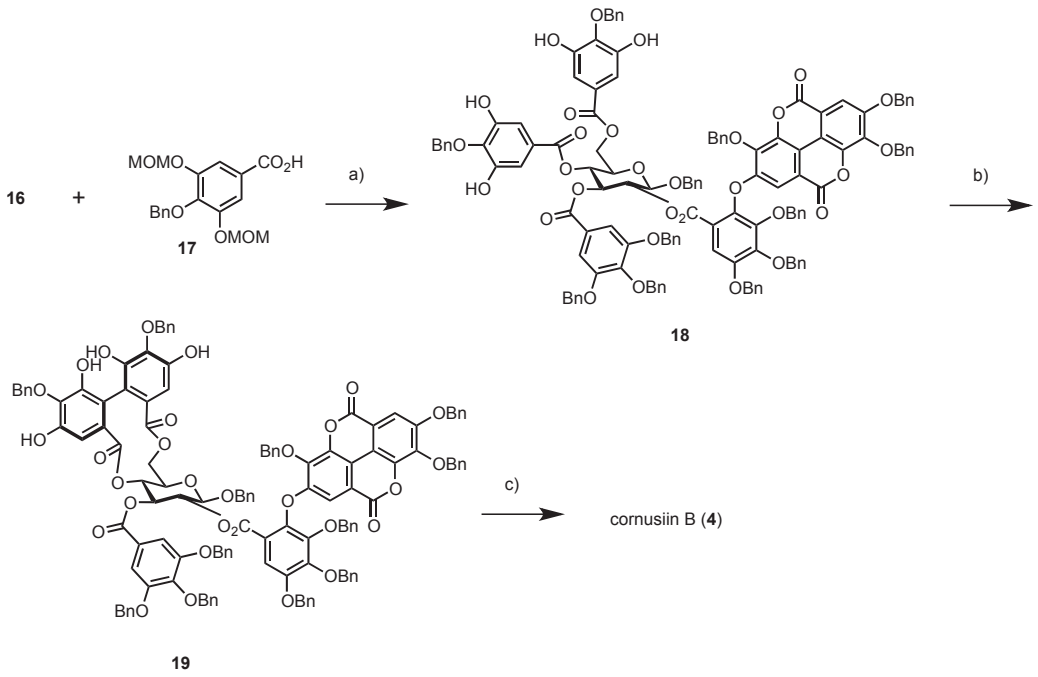


Scheme 2. Synthesis of oenothein C (**3**). a) 3,4,5-tribenzyloxybenzoic acid (1.5 eq.), EDC (2.0 eq.), DMAP (0.25 eq.), CH_2Cl_2, rt, 14 h (25%); b) **14** (1.2 eq.), EDC (1.2 eq.), DMAP (0.25 eq.), CH_2Cl_2, rt, 4 h (81%); c) ^{i}PrOH/conc. HCl, THF, 55 °C, 3 h (96%); d) H_2, Pd/C, THF, rt, 23 h (74%).

As the next stage of our synthetic study of the ellagitannins, we considered that **16** can be applied to the synthesis of cornusiin B (**4**) as the key intermediate, thus, the galloylation with **17** at both the 4- and 6-positions in glucose was carried out (Scheme 3). For construction of the HHDP (hexahydroxydiphenoyl) group in an enantiomerically-pure form, the copper-mediated oxidative coupling reaction is recognized as an excellent method, which was developed by Yamada and co-workers.[15] In our synthetic scheme, we utilized Yamada's method for the formation of the HHDP group, therefore, **18** was treated with the

combination of copper(II) chloride and *n*-butylamine. The final deprotection by the conventional hydrogenolysis method was also successful to complete the synthesis of cornisiin B (**4**).

The NMR data of the synthetic **3** and **4** were consistent with the reported data.



Scheme 3. Synthesis of cornusiin B (**4**). a) (i) 4-benzyloxy-3,5-di(methoxymethoxy)benzoic acid (**17**) (2.05 eq.), EDC (2.8 eq.), DMAP (0.5 eq.), CH_2Cl_2, rt, 6.5 h (83%); (ii) ^{i}PrOH/conc. HCl, THF, 55 °C, 14 h (92%); b) $CuCl_2$ (2 eq.), $^{n}BuNH_2$ (3 eq.), MeOH, $CHCl_3$, 0 °C (59%); c) H_2, Pd/C, THF, rt, 25 h (87%).

CONCLUSION

We succeeded in the syntheses of two ellagitannins, oenothein C (**3**) and cornusiin B (**4**), which incorporate the LVG in their molecules. The investigation of their biological activities and further extension of this study are currently underway in our research group.

EXPERIMENTAL

General information: Melting points were measured using a Yanagimoto micro-melting point hot plate apparatus and are uncorrected. Optical rotations were determined by a Horiba SEPA-500 polarimeter. The IR spectra were recorded using a Shimadzu FTIR-8400 spectrophotometer. The NMR spectra were taken using a JEOL α-400 or JNX-ECX500 instrument. The chemical shifts are given in δ ppm with a solvent peak as the internal standard. The elemental analyses were performed using an Elementar Vario MICRO Cube or Thermo Fisher Scientific Flash EA 1112 analyzer. The MS were measured in the positive ion mode using a JEOL JMS-AX505HAD instrument. Silica gel column chromatography was carried out

using Wakogel® C-200 or C-400. The reaction solvents were used after purification with a standard method.

Methyl 4,5-bis(benzyloxy)-2-bromo-3-hydroxybenzoate (**7**)

DBDMH (1,3-dibromo-5,5-dimethylhydantoin) (0.335 g, 1.17 mmol) was portionwise added to a solution of ester **6** (0.822 g, 2.26 mmol) in $CHCl_3$ (80 mL) over 1 h, then the mixture was stirred for 3 h. After evaporation of the solvent, recrystallization from hexane-AcOEt was carried out to give the colorless solid of **7** (0.761 g, 77%), mp 102.8-103.4 °C (AcOEt-hexane). IR (KBr) cm^{-1}: 3630, 3502, 3066, 1733, 1432, 1341, 1205, 960, 738, 701. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.92 (3H, s), 5.15 (2H, s), 5.16 (2H, s), 6.18 (1H, s), 7.16 (1H, s), 7.28 (5H, s), 7.36-7.46 (5H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 52.6, 71.4, 75.8, 101.7, 108.6, 127.8, 128.5, 128.7, 128.9 (x2), 136.1, 148.0, 150.2, 166.4. HRMS calcd for $C_{22}H_{20}O_5Br$ $[M+1]^+$: 443.0494; Found: 443.0479.

Methyl 3-acetoxy-4,5-bis(benzyloxy)-2-bromobenzoate (**8**)

Acetic anhydride (0.646 mL, 6.87 mmol) was added to a solution of phenol **7** (0.761 g, 1.72 mmol) in pyridine (20 mL), then the mixture was stirred for 1.5 h. After the addition of toluene to the mixture, the volatile materials were removed under reduced pressure. The resulting yellow solid (0.926 g) was subjected to column chromatography with AcOEt-hexane (1:5) to give the colorless solid of **8** (0.667 g, 81%), mp 93.0-93.6 °C. IR (KBr) cm^{-1}: 3108, 2950, 1765, 1740, 1723, 1437, 1346, 1199, 1092, 738, 696. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.25 (3H, s), 3.92 (3H, s), 5.10 (2H, s), 5.15 (2H, s), 7.32 (5H, s), 7.36-7.45 (5H, m), 7.48 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.5, 52.7, 71.6, 75.5, 109.5, 114.4, 126.9, 127.8, 128.4, 128.5, 128.8, 135.8, 136.9, 144.8, 151.3, 165.8, 168.1. Anal. Calcd for $C_{24}H_{21}BrO_6$: C, 59.40; H, 4.36. Found: C, 59.42; H, 4.17.

Methyl 3-acetoxy-4-(benzyloxy)-2-bromo-5-(2,3,4-tris(benzyloxy)-6-(methoxycarbonyl)-phenolxy)-benzoate (**10**)

Acetic anhydride (0.190 mL, 2.02 mmol) was added to a solution of phenol **9** (0.429 g, 0.532 mmol) in pyridine (6 mL), then the mixture was stirred for 2 h. After the addition of toluene to the mixture, the volatile materials were removed under reduced pressure. The resulting residue was subjected to column chromatography with AcOEt-hexane (1:5) to give the colorless solid of **10** (0.430 g, 96%), mp 117.0-117.8 °C. IR (KBr) cm^{-1}: 3033, 2948, 1774, 1730, 1717, 1589, 1482, 1437, 1366, 1328, 1206, 1073, 1018, 973, 752, 695. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.25 (3H, s), 3.76 (3H, s), 3.81 (3H, s), 5.00 (2H, s), 5.16 (4H, s), 5.18 (2H, s), 6.93 (1H, s), 7.13-7.49 (21H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.5, 52.58, 52.63, 71.5, 75.65, 75.72, 76.0, 109.8, 111.0, 114.5, 120.0, 126.7, 127.9, 128.2, 128.3, 128.4, 128.5, 128.6,

128.8, 136.2, 136.5, 136.8, 137.4, 141.5, 143.7, 144.1, 146.6, 146.9, 150.4, 151.4, 165.1, 165.6, 167.8. Anal. Calcd for $C_{46}H_{39}BrO_{11}$: C, 65.18; H, 4.64. Found: C, 64.98; H, 4.58.

Dimethyl 6,6'-diacetoxy-4,5,5'-tris(benzyloxy)-4'-(2,3,4-tris(benzyloxy)-6-(methoxycarbonyl)-phenoxy)-[1,1'-biphenyl]-2,2'-dicarboxylate (11)

Under an N_2 atmosphere, a mixture of **10** (1.00 g, 1.18 mmol), **8** (1.71 g, 3.54 mmol), copper powder (0.900 g, 14.2 mmol), and DMF (2 mL) was heated at 180 °C with stirring. After 1.5 h, the mixture was diluted with AcOEt, and filtered with Celite. The volatile materials were evaporated and the residue was acidified with a 10% HCl aqueous solution to pH 1. The mixture was poured into water (40 mL), then extracted with AcOEt. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. The crude residue was subjected to silica gel column chromatography with AcOEt-hexane (1:3) to give a yellow amorphous **11** (0.945 g, 69%).[16] IR (KBr) cm^{-1}: 3032, 2950, 1773, 1730, 1719, 1603, 1482, 1434, 1368, 1323, 1200, 1071, 743, 697. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.71 (3H, s), 1.83 (3H, s) 3.44 (3H, s), 3.46 (3H, s), 3.77 (3H, s), 5.00 (2H, m), 5.13 (2H, m), 5.16 (2H, s), 5.17 (2H, s), 5.21 (2H, s), 5.28 (2H, s), 7.09 (1H, s), 7.22-7.49 (31H, m), 7.64 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.0, 20.2, 51.9, 52.0, 52.4, 71.1, 71.4, 74.6, 74.9, 75.7, 76.1, 111.2, 113.0, 113.3, 119,8, 124.6, 125.2, 125.3, 125.6, 127.8, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.3, 128.4, 128.5, 128.6, 128.7, 128.7, 136.2, 136.7, 136.9, 137.3, 137.7, 142.0, 142.5, 142.7, 143.1, 143.7, 146.8, 147.0, 150.2, 151.1, 151.4, 165.2, 165.9, 166.3, 167.8 (x2). Anal. calcd for $C_{70}H_{60}O_{17}$: C, 71.66; H, 5.15. Found: C, 71.42; H, 5.28.

3,4,5-tris(Benzyloxy)-2-((3,7,8-tris(benzyloxy)-5,10-dioxo-5,10-dihydrochromeno[5,4,3-*cde*]chromen-2-yl)oxy)benzoic acid (12)

To a solution of **11** (0.400 g, 0.341 mmol) in THF (15 mL) was added a 10% KOH aqueous solution (15 mL), then the mixture was heated at 90 °C for 14 h. After adjusting the pH to 1 with a 10% HCl aqueous solution, the mixture was poured into water and extracted with AcOEt. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated to leave a solid residue (0.355 g) which was dissolved in $CHCl_3$ (15 mL). After TFA (0.640 mL, 8.52 mmol) was added to the solution, the mixture was heated at 60 °C for 3 h. Water was added for quenching the reaction, and an extractive work-up with $CHCl_3$ was carried out. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. Purification by silica gel column chromatography with AcOEt-hexane (1:1) was carried out to give a yellow amorphous **12** (0.238 g, 70%). IR (KBr) cm^{-1}: 3032, 2953, 2927, 1739, 1690, 1609, 1480, 1454, 1414, 1351, 1222, 1173, 1084, 913, 738, 697. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.93 (2H, s), 5.168 (2H, s), 5.173 (2H, s), 5.27 (2H, s), 5.44 (4H, s), 6.94-7.00 (5H, m), 7.27-7.53 (28H, m), 7.75 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 71.5, 71.8, 75.8, 76.00, 76.04, 109.4, 110.7, 111.3, 112.7, 112.8, 113.5,

113.9, 118.1, 127.8, 127.89, 127.95, 128.01, 128.1, 128.35, 128.43, 128.47, 128.52, 128.57, 128.60, 128.7, 128.8, 128.9, 135.6, 136.1, 136.4, 136.5, 136.6, 136.7, 140.7, 140.9, 141.9, 142.0, 142.5, 146.2, 147.7, 150.5, 153.8, 154.0, 158.6, 158.8, 168.7. HRMS (FAB) calcd for $C_{63}H_{47}O_{13}Na$ $[M+Na]^+$: 1034.2914; Found: 1034.2975.

Benzyl 4,6-*O*-benzylidene-3-(3,4,5-tribenzyloxy)benzoyl-2-hydroxy-*β*-D-glucopyranoside (14)

To a mixture of **13** (0.500 g, 1.40 mmol), EDC (0.537 g, 2.80 mmol), DMAP (42.7 mg, 0.35 mmol), and CH_2Cl_2 (110 mL), 3,4,5-tribenzyloxybenzoic acid (0.925 g, 2.10 mmol) was portionwise added over 3 h. After the reaction mixture was allowed to stand for 14 h, the volatile materials were removed. Purification by silica gel column chromatography with CH_2Cl_2-AcOEt (60:1) was carried out to give a colorless solid of **14** (0.264 g, 25%). Colorless amorphous, mp 158.0-159.0 °C, $[\alpha]_D^{24}$ -51 (*c* 1.0, $CHCl_3$). IR (KBr) cm^{-1}: 3504, 3032, 2867, 1706, 1589, 1500, 1454, 1429, 1371, 1339, 1210, 1101, 1002, 748, 696. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.63 (1H, d, *J* = 2.8 Hz), 3.57-3.63 (1H, m), 3.75 -3.90 (3H, m), 4.43 (1H, dd, *J* = 4.8 Hz, 10.4 Hz), 4.64 (1H, d, *J* = 7.2 Hz), 4.70 (1H, d, *J* = 11.6 Hz), 4.98 (1H, d, *J* = 11.6 Hz), 5.10 (2H, s), 5.11 (4H, s), 5.42 (1H, dd, *J* = 9.6 Hz, 18.8 Hz), 5.54 (1H, s), 7.22-7.43 (25H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 66.5, 68.7, 71.3, 71.6, 73.5, 74.4, 75.1, 78.5, 101.5, 102.5, 109.6, 124.6, 126.1, 127.5, 127.9, 128.0, 128.1, 128.1, 128.2, 128.5, 128.6, 129.0, 136.6, 136.8, 137.3, 142.7, 152.5, 166.0. HRMS (FAB) calcd for $C_{48}H_{45}O_{10}$ $[M+1]^+$: 781.3012; Found: 781.3025.

Benzyl 4,6-*O*-benzylidene-2-(3,7,8-tris(benzyloxy))-2-(3,4,5-tris(benzyloxy)-2-((3,7,8-tris(benzyloxy)-5,10-dioxo-5,10-dihydrochromeno[5,4,3-*cde*]chromen-2-yl)oxy)benzoyl)-*β*-D-glucopyranoside (15)

To a mixture of **12** (0.200 g, 0.198 mmol), EDC (44.0 mg, 0.237 mmol), DMAP (6 mg, 0.0495 mmol), and CH_2Cl_2 (6 mL), **14** (0.185 g, 0.237 mmol) was added. After the reaction mixture was allowed to stand for 4 h, the volatile materials were removed. Purification by silica gel column chromatography with CH_2Cl_2-hexane-AcOEt (1:3:0.4) to produce a yellow amorphous **15** (0.284 g, 81%), $[\alpha]_D^{23}$ +80 (*c* 1.0, $CHCl_3$). IR (KBr) cm^{-1}: 2960, 2926, 1734, 1719, 1608, 1455, 1340, 1215, 1086, 1005, 735, 697. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.46 (1H, m), 3.77-3.84 (2H, m), 4.36-4.40 (1H, dd, *J* = 5.2 Hz, 10.8 Hz), 4.51 (1H, d, *J* = 12 Hz), 4.79 (1H, d, *J* = 7.2 Hz), 4.82 (1H, d, *J* = 12 Hz), 4.90-5.15 (14H, m), 5.36-5.49 (7H, m), 6.93-7.64 (60H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 66.5, 66.6, 68.67, 68.73, 70.8, 71.0, 71.5, 71.6, 72.8, 75.2, 75.7, 75.78, 75.82, 76.0, 77.4, 79.0, 101.5, 109.0, 109.2, 110.2, 110.6, 112.7 (x2), 113.6, 113.9, 116.3, 120.0, 124.3, 126.2, 126.5, 127.4, 127.6, 127.8 (x2), 127.9, 128.0, 128.1 (x2), 128.2, 128.3, 128.4, 128.5, 128.6, 128.8 (x2), 129.1, 135.7, 136.1, 136.6 (x2), 136.7, 136.9 (x2), 137.0, 137.7, 140.3, 140.8,

141.5, 141.7, 141.9, 142.6, 146.3, 146.9, 150.6, 152.5, 153.8, 158.3, 158.9, 163.5, 165.1. Anal. Calcd for $C_{111}H_{88}O_{22}$: C, 75.16; H, 5.00. Found: C, 74.83; H, 5.04.

Benzyl 2-(3,4,5-tris(benzyloxy)-2-((3,7,8-tris(benzyloxy)-5,10-dioxo-5,10-dihydrochromeno[5,4,3-*cde*]chromen-2-yl)oxy)benzoyl)-4,6-dihydroxy-*β*-D-glucopyranoside (16)

To a solution of **15** (0.284 g, 0.160 mmol) in THF (8.5 mL), ^{i}PrOH/conc. HCl aq. (1:1, 1.5 mL) was added and the mixture was heated at 55 °C for 23 h. After neutralization with a sat. $NaHCO_3$ aqueous solution, extraction with AcOEt was carried out. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated to give a residue which was subjected to silica gel column chromatography with AcOEt-hexane (1:1). A yellow amorphous **16** (0.258 g, 96%) was obtained. $[\alpha]_D^{24}$ +3 (*c* 1.0, $CHCl_3$). IR (KBr) cm^{-1}: 3436, 3031, 2927, 1744, 1608, 1454, 1430, 1340, 1216, 1115, 1087, 910, 734, 695. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.27 (1H, br), 3.71-3.94 (3H, m), 4.52 (1H, d, *J* = 12.4 Hz), 4.59 (1H, d, *J* = 7.6 Hz), 4.78-5.15 (21H, m), 6.99-7.39 (52H, m), 7.53-7.55 (2H, m), 7.71 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 62.2, 70.3, 70.8, 71.3, 71.5, 71.9, 75.2, 75.7, 75.8, 76.1, 77.3, 99.9, 109.1, 110.0, 112.7, 113.4, 113.9, 119.2, 127.0, 127.6, 127.8, 127.9, 128.0 (x2), 128.2 (x2), 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 135.6, 136.0, 136.5, 136.6 (x2), 136.8, 137.2, 137.6, 140.0, 140.9, 141.5, 141.8, 141.9, 142.9, 1467.0, 150.7, 152.4, 153.9, 158.0, 159.0, 164.0, 167.9. Anal. Calcd for $C_{104}H_{84}O_{22}$: C, 74.10; H, 5.02. Found: C, 73.73; H, 5.04.

Oenothein C (3)

To a suspension of 10% Pd/C (50 mg) in THF (20 mL) was added a solution of **16** (0.135 g, 0.225 mmol) in THF (20 mL), and the reaction mixture was vigorously stirred for 23 h at rt under a hydrogen atmosphere. The mixture was filtered using a Celite pad and the filtrate was concentrated. The resulting residue was purified by reverse phase column chromatography (Sephadex LH-20) with MeOH:H_2O (1:1) to give **3** (46 mg, 74%) as a grayish amorphous material, mp > 250 °C (decomp.). $[\alpha]_D^{25}$ +70 (*c* 0.5, MeOH). IR (KBr) cm^{-1}: 3429-3300, 1718, 1705, 1617, 1362, 1349, 1340, 1216, 1211, 1106, 1046. ^{1}H-NMR (500 MHz, acetone-d_6 + D_2O) δ: 3.35-3.38 (1H, m), 3.63-3.81 (6H, m), 3.89-3.92 (1H, m), 4.56 (β-isomer, 1H, d, *J* = 8.0 Hz), 4.87 (α-isomer, 1H, dd, *J* = 4.0, 10.0 Hz), 4.97 (β-isomer, 1H, dd, *J* = 8.0, 9.5 Hz), 5.15 (β-isomer, 1H, t, *J* = 10.0 Hz), 5.19 (α-isomer, 1H, d, *J* = 3.5 Hz), 5.66 (α-isomer, 1H, t, *J* = 10.0 Hz), 6.92 (β-isomer, 2H, s), 7.01 (α-isomer, 2H, s), 7.03 (β-isomer, 1H, s), 7.04 (α-isomer, 1H, s), 7.12 (β-isomer, 1H, s), 7.14 (α-isomer, 1H, s), 7.576 (β-isomer, 1H, s), 7.579 (α-isomer, 1H, s). ^{13}C-NMR (125 MHz, acetone-d_6 + D_2O) δ: 62.0, 62.1, 69.6, 69.7, 72.6, 73.1, 73.9, 74.2, 77.2, 77.4, 90.5, 95.6, 108.9, 109.1, 109.2, 109.3, 110.0, 110.1, 110.2, 110.4, 111.4, 113.4, 113.9, 114.4, 115.3, 120.9,

121.2, 136.1, 136.5, 137.5, 137.61, 137.65, 137.70, 138.9, 139.0, 139.82, 139.85, 140.2, 140.3, 140.5, 140.7, 141.4 143.7, 143.8, 145.76, 145.82, 148.9, 149.0, 149.8, 149.9, 159.7, 159.8, 160.0, 164.4, 164.5, 167.2, 167.3.

Benzyl 2-(3,4,5-tris(benzyloxy)-2-((3,7,8-tris(benzyloxy)-5,10-dioxo-5,10-dihydrochromeno[5,4,3-*cde*]chromen-2-yl)oxy)benzoyl)-4,6-bis(4-(benzyloxy)-3,5-bis(methoxymethoxy))-*β*-D-glucopyranoside

To a mixture of **16** (0.236 g, 0.140 mmol), EDC (75.1 mg, 0.392 mmol), DMAP (8.5 mg, 0.07 mmol), and CH_2Cl_2 (5 mL), 4-benzyloxy-3,5-di(methoxymethoxy)benzoic acid (**17**, 0.100 g, 0.287 mmol) was added. After the reaction mixture was allowed to stand for 6.5 h, a 10% HCl aqueous solution was added for adjusting the pH to 1. The mixture was extracted with AcOEt, then the organic layer was washed with brine, dried over magnesium sulfate, and concentrated. Purification by silica gel column chromatography with hexane- AcOEt (2:1) was carried out to produce the yellow amorphous title compound (0.270 g, 83%). $[\alpha]_D^{17}$ -5 (*c* 1.0, $CHCl_3$). IR (KBr) cm^{-1}: 3030, 2951, 2901, 1732, 1607, 1589, 1499, 1481, 1454, 1433, 1412, 1393, 1333, 1215, 1192, 1155, 1107, 1086, 1047, 1003, 910, 853, 754, 735, 696. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.42 (6H, s), 3.44 (6H, s), 3.81-3.85 (1H, m, 3.27 (1H, dd, *J* = 6.8, 12.8 Hz), 4.25-4.30 (1H, m), 4.63-4.70 (2H, m), 4.80-5.53 (34H, m), 6.90-7.64 (69H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 56.47, 56.51, 63.4, 70.3, 71.0, 71.47, 71.53, 72.2, 72.3, 75.1, 75.3, 75.6, 75.7, 75.8, 76.0, 95.5, 99.5, 108.8, 109.1, 110.1, 110.7, 112.3, 112.5, 112.7, 113.5, 113.8, 119.4, 123.8, 124.2, 125.3, 126.8, 127.4, 127.7, 127.76, 127.83, 127.9, 128.0, 128.1, 128.17, 128.21, 128.3, 128.4, 128.47, 128.5, 128.6, 128.7, 128.8, 135.7, 136.1, 136.6, 136.8, 137.2, 137.4, 137.6, 140.8, 141.5, 141.7, 141.9, 142.7, 143.3, 143.8, 146.3, 146.9, 150.6, 150.99, 151.02, 152.4, 153.6, 153.7, 158.2, 158.9, 163.3, 164.8, 165.4, 165.5. Anal. Calcd for $C_{140}H_{120}O_{34}$: C, 71.66; H, 5.15. Found: C, 71.89; H, 4.93.

Benzyl 2-(3,4,5-tris(benzyloxy)-2-((3,7,8-tris(benzyloxy)-5,10-dioxo-5,10-dihydrochromeno[5,4,3-*cde*]chromen-2-yl)oxy)benzoyl)-4,6-bis(4-(benzyloxy)-3,5-dihydroxybenzoyl)-*β*-D-glucopyranoside (18)

To a THF (6 mL) solution of tetra(methoxymethylether) (0.100 g, 0.0426 mmol), which was prepared by the above procedure, ^{i}PrOH/conc. HCl aq. (1:1, 2 mL) was added and the mixture was heated at 55 °C for 14 h. After neutralization with a sat. $NaHCO_3$ aqueous solution, extraction with AcOEt was carried out. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated to give a residue which was subjected to silica gel column chromatography with AcOEt-hexane (1:6). A yellow amorphous **18** (85 mg, 92%) was obtained. $[\alpha]_D^{17}$ +26 (*c* 1.0, $CHCl_3$). IR (KBr) cm^{-1}: 3514, 3404, 3381, 3063, 3032, 2945, 1728, 1604, 1522, 1499, 1481, 1454, 1431, 1412, 1340, 1198, 1105, 1086, 1078, 1057,

1028, 1001, 910, 868, 853, 750, 735, 696. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.67-3.73 (1H, m), 4.28-4.31 (1H, m), 4.38-4.41 (2H, m), 4.71-5.51 (27H, m), 6.98-7.55 (69H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 63.2, 71.0, 71.3, 71.7, 72.5, 75.1, 75.2, 75.4, 75.7, 75.8, 76.2, 108.5, 109.1, 109.8, 109.9, 112.5, 123.5, 124.3, 125.1, 127.0, 127.5, 127.8, 127.9, 127.9, 128.0, 128.1, 128.2, 128.3, 128.37, 128.43, 128.49, 128.54, 128.6, 128.70, 128.74, 128.8, 128.9, 135.5, 136.0, 136.4, 136.56, 136, 59, 136.7, 136.75, 136.81, 137.6, 137.7, 138.2, 140.1, 141.7, 141.8, 142.7, 147.1, 149.1, 150.7, 152.4, 153.9, 154.1, 158.2, 163.6, 165.0, 165.9. Anal. Calcd for $C_{132}H_{102}O_{30}$: C, 73.05; H, 4.83. Found: C, 72.78; H, 4.68.

Benzyl 2-(3,4,5-tris(benzyloxy)-2-((3,7,8-tris(benzyloxy)-5,10-dioxo-5,10-dihydrochromeno[5,4,3-*cde*]chromen-2-yl)oxy)benzoyl)-4,6-(*S*)-(3,3',5,5'-tetrahydroxy-4,4'-dibenzyloxy-6,6'-diphenoyl)-*β*-D-glucopyranoside (19)

Under a nitrogen atmosphere, a mixture of $CuCl_2$ (10 mg, 0.0756 mmol), $^{n}BuNH_2$ (0.112 mL, 1.13 mmol), and MeOH (8 mL) was stirred at 0 °C for 30 min. To the mixture, a solution of **18** (82 mg, 0.0378 mmol) in $CHCl_3$ was added at 0 °C, then the mixture was stirred at the same temperature for 4.5 h. To adjust the pH to 1, 10% HCl aq. was added and the mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. Purification by silica gel column chromatography with CH_2Cl_2-AcOEt (20:1) was carried out to give a yellow amorphous **19** (0.048 g, 59%). $[\alpha]_D^{16}$ +29 (*c* 1.0, $CHCl_3$). IR (KBr) cm^{-1}: 3503, 3422, 3063, 3032, 2936, 1747, 1720, 1607, 1587, 1499, 1479, 1454, 1433, 1412, 1340, 1213, 1171, 1107, 1076, 1028, 1003, 986, 910, 735, 696. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.57-3.66 (1H, m), 3.82-3.85 (1H, m), 4.49-5.72 (29H, m), 6.69 (1H, s), 6.94-7.82 (66H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 60.6, 70.6, 70.7, 71.2, 71.8, 72.2, 75.2, 75.5, 75.6, 75.7, 75.9, 76.1, 76.3, 99.8, 108.8, 109.0, 112.5, 112.9, 114.0, 127.7, 127.8, 127.9, 127.96, 128.01, 128.1, 128.3, 128.36, 128.40, 128.55, 128.61, 128.7, 128.75, 128.8.0, 128.9, 129.0, 135.3, 135.4, 136.0, 136.5, 136.57, 136.63, 136.7, 136.9, 137.0, 137.1, 137.8, 141.68, 141.74, 142.9, 146.9, 147.2, 149.0, 149.1, 150.8, 152.4, 153.9, 163.9, 165.4, 167.2, 171.3.

Cornusiin B (4)

Under a hydrogen atmosphere, a suspension of **19** (0.135 g, 0.225 mmol) and 10% Pd/C in THF (15 mL) was stirred for 25 h. After removing the undissolved materials by filter paper, the mixture was concentrated to give a residue which was purified by reverse phase column chromatography (Sephadex LH-20) with MeOH-H_2O (1:6 to 1:1) as the eluent. Cornusiin B (**4**, 46 mg, 87%) was obtained as a brown amorphous powder. $[\alpha]_D^{25}$ +67 (*c* 0.5, $CHCl_3$). IR (KBr) cm^{-1}: 3067-3487, 1718, 1616, 1448, 1348, 1197, 1105, 1043, 758. ^{1}H-NMR (500 MHz, acetone-d_6 + D_2O) δ: 3.67-3.74 (2H, m, β-glu H-6, α-glu H-6), 4.06-4.09 (1H, m, β-glu H-5), 4.55-4.58 (1H, m, α-glu H-5), 4.72 (1H, d, *J* = 8 Hz, β-glu H-1), 4.60-5.08

(3H, m, α-glu H-2, α-glu H-4, β-glu H-4), 5.15-5.25 (3H, m, β-glu H-2, α-glu H-6, β-glu H-6), 5.34-5.40 (2H, m, β-glu H-3, α-glu H-1), 5.77 (1H, t, J = 10 Hz, α-glu H-3), 6.44 (1H, s, β-HHDP), 6.48 (1H, s, α-HHDP), 6.59 (1H, s, β-HHDP), 6.60 (1H, s, α-HHDP), 6.74 (1H, s, β-galloyl), 6.86 (1H, s, α-galloyl), 7.04 (1H, s, β-LVG-H_B), 7.06 (1H, s, α-LVG-H_B), 7.17 (2H, s, α-LVG-H_C, β-LVG-H_C), 7.61 (2H, s, α-LVG-H_A, β-LVG-H_A). ^{13}C-NMR (125 MHz, acetone-d_6 + D_2O) δ: 63.4, 67.1, 71.09, 71.12, 71.5, 72.0, 73.0, 73.9, 74.0, 90.9, 96.6, 107.9, 108.1, 109.1, 109.2, 109.3, 110.0, 110.1, 110.4, 110.5, 111.5, 113.5, 113.6, 114.1, 114.6, 115.3, 115.38, 115.44, 115.7, 120.5, 120.6, 126.1, 126.2, 126.6, 126.7, 136.1, 136.2, 136.3, 136.5, 137.67, 137.73, 137.75, 137.78, 138.9, 138.9, 139.7, 139.8, 140.2, 140.3, 140.6, 140.7, 141.3, 143.7, 143.8, 144.3, 144.4, 145.07, 145.15, 145.5, 145.6, 148.9, 149.0, 149.9, 159.4, 159.6, 160.1, 160.3, 164.1, 164.3, 166.3, 166.6, 167.5, 167.5, 168.0, 168.1. HRMS (FAB) calcd for $C_{48}H_{45}O_{10}$ $[M+1]^+$: 1087.0900; Found: 1087.0839.

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