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TOTAL SYNTHESIS OF OENOTHEIN C

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Abstract – The simple total synthesis of oenothein C (**1**), ellagitannin, originally isolated from the leaves of *Oenothera erythrosepala*, was achieved by successive esterification of the glucose derivative with the protected valoneic acid dilactone (**2**) and gallic acid (**3**). The lactonized valoneic acid (**11**), which is the key structural part, was prepared by the intermolecular Ullmann cross coupling reaction.

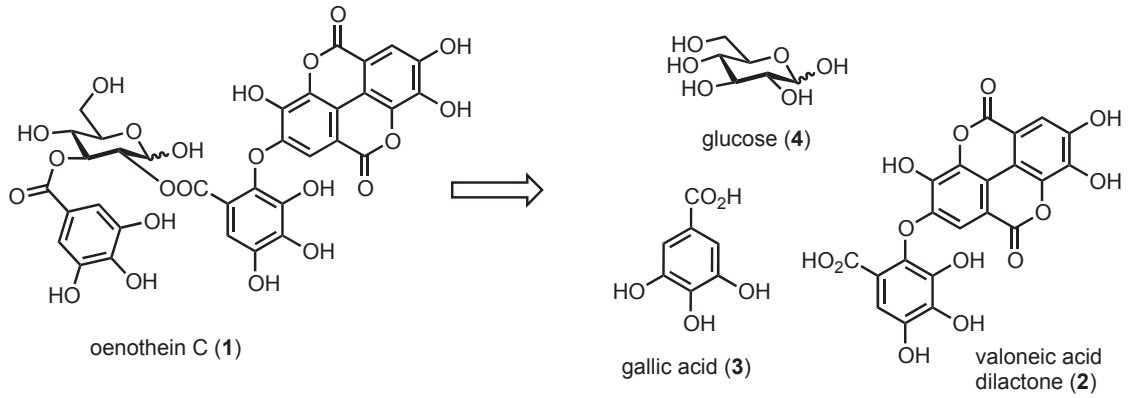
Ellagitannins are often found in the dicotyledonous plants and this class of compounds has attracted much attention as a medical resource since they have interesting biological activities such as anti-tumor, anti-oxidant, and antiviral activities, etc.[1] In 1984, oenothein C (**1**) was isolated from leaves of *Oenothera erythrosepala* by Okuda *et al.*[2] They determined its structure to be a disubstituted glucose derivative as an anomeric mixture. Namely, a lactonized valoneoyl group and a galloyl group are combined at the 2- and 3-positions, respectively, of the glucose core.[3] Although the synthetic challenges of the ellagitannins have been actively studied by many chemists since the 1990s,[4,5] there has been no report about the synthesis of ellagitannins which possess the lactonized valoneoyl unit such as oenothein C (**1**).

Recently, we reported the synthesis of the lactonized valoneoyl unit,[6] which was performed by using both the Ullmann condensation and Ullmann coupling reactions for formation of the C-O and C-C bonds between two aromatic rings.[7] As an extension of our synthetic research, we describe the first total synthesis of the lactonized valoneoyl group-containing ellagitannin, oenothein C (**1**). In order to perform the synthesis, we needed to prepare the valoneic acid dilactone derivative which is protected on all phenolic hydroxy groups before esterification with the sugar.

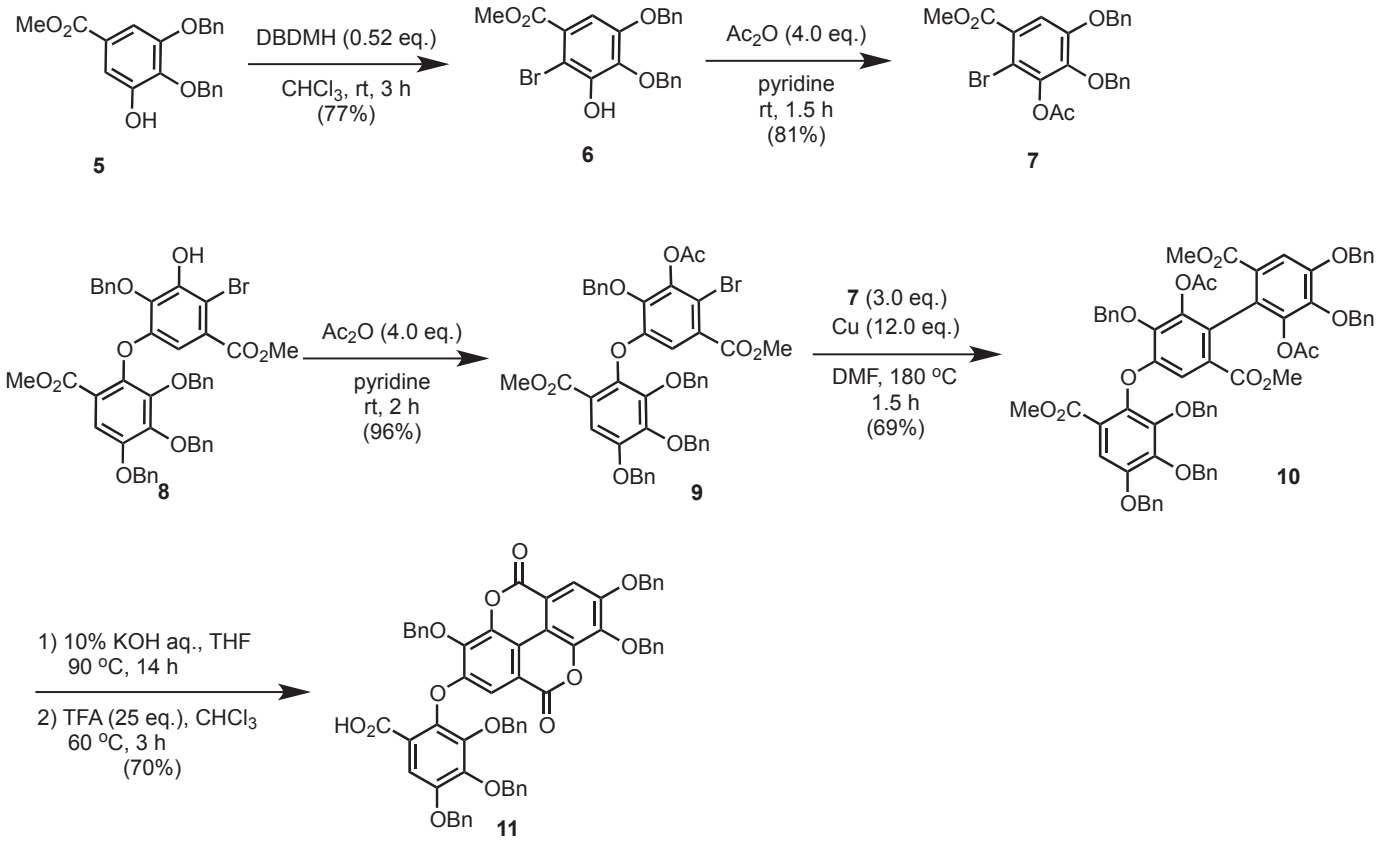
The synthesis plan is simply outlined in Scheme 1 in which the target molecule (**1**) could be constructed by successive esterification between the valoneic acid dilactone (**2**), gallic acid (**3**), and glucose (**4**). We postulated that the preparation of **2** could be realized by the application of the reported method.[6]

As shown in Scheme 2, the synthesis commenced with the preparation of the aryl bromide **7** via a two-step conversion from the protected methyl gallate **5**.[8] Bromination of **5** with

1,3-dibromo-5,5-dimethylhydantoin (DBDMH) produced **6** followed by conventional acetylation to form **7**. As a coupling partner in the intermolecular Ullmann reaction, we needed the other aryl bromide **9** which was easily obtained from the known **8**[6] by a normal acetylating system. The coupling reaction between **7** and **9** successfully proceeded to generate **10** using 3 equiv. of **7** and an excess amount of copper dust.[9] Alkaline hydrolysis of the esters and concomitant lactonization with trifluoroacetic acid (TFA) produced the all-benzylated valoneic acid dilactone **11**.[10]

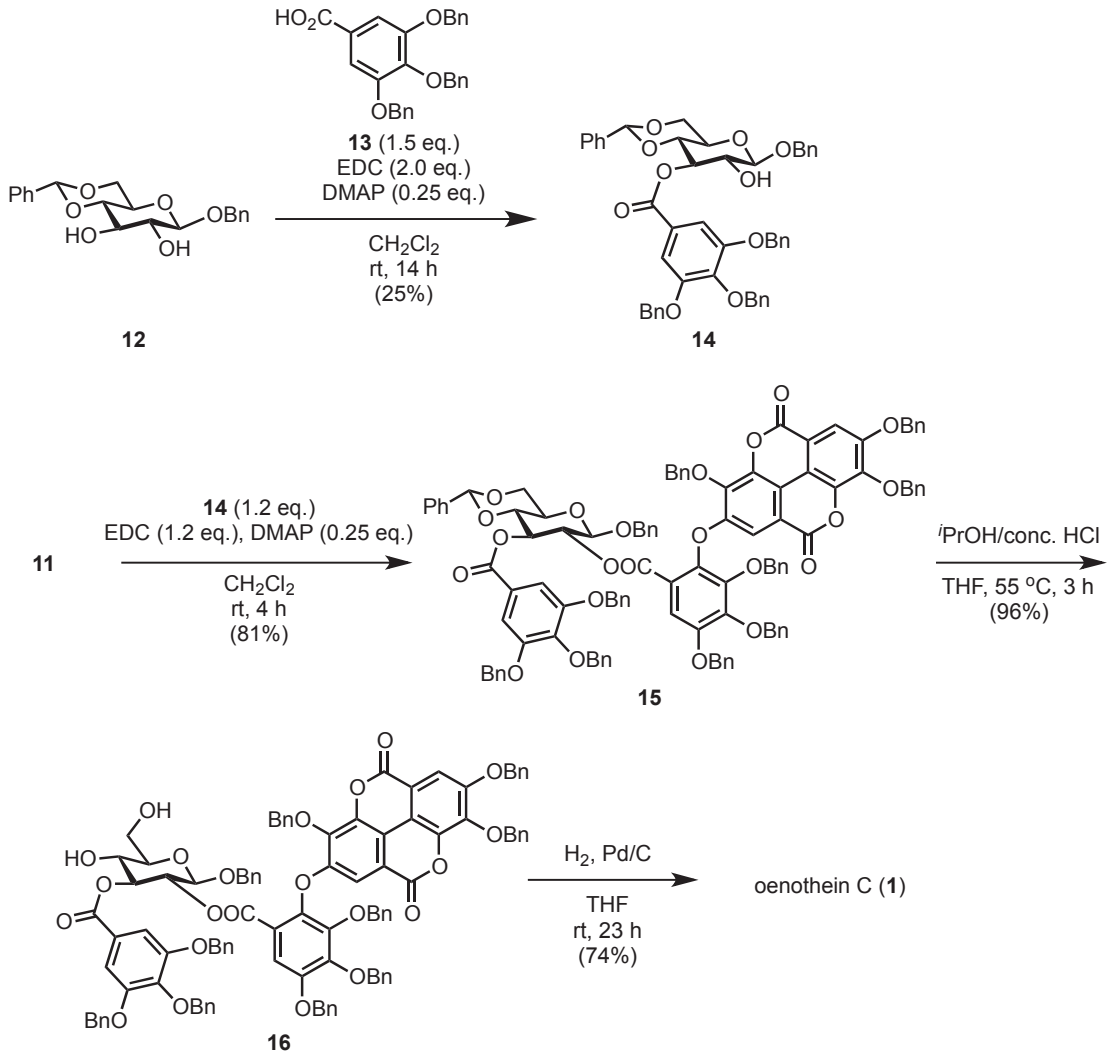


Scheme 1. Synthesis Plan for Oenothein C (**1**)



Scheme 2. Preparation of Lactonized Valoneoyl Unit (**11**)

For the sugar moiety, we chose the glucose derivative (**12**)[11] as the starting material, which was protected by the benzylidene group at the 4- and 6-position hydroxy groups, and the benzyl group at the 1-position (Scheme 3). The selective galloylation at the 3-position with **13**[12] was unsuccessful, thus the desired **14** was produced in only 25% yield.[13] In spite of the low yield of **14**, further transformation was examined so that the esterification between **11** and **14** provided **15**. The benzylidene protection was removed by an acid treatment to form **16**, which was subjected to catalytic hydrogenolysis for deprotection of all the benzyl groups on the phenolic hydroxy groups. Finally, we obtained the target molecule, oenothein C (**1**).[14] The comparison of the NMR data is depicted in Figure 1 in which both the proton and carbon NMR spectra are identical between the authentic and synthetic data.



Scheme 3. Completion of the Synthesis of Oenothein C (**1**)

In conclusion, the first total synthesis of ellagitannin, which involves the valoneic acid dilactone moiety in the molecule, was performed.

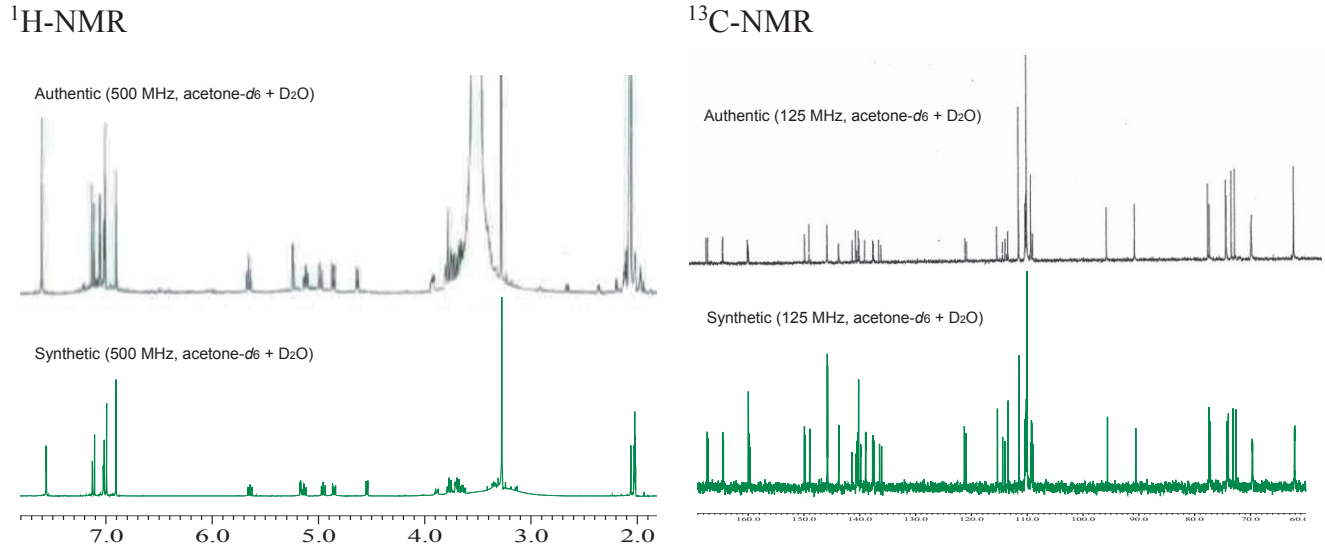


Figure 1. Comparison of NMR Spectra between Authentic and Synthetic Samples

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10. **Valoneic acid dilactone derivative (11):** A mixture of **10** (0.400 g, 0.341 mmol), 10% KOH aq. (15 mL), and THF (15 mL) was heated at 90 °C. After 14 h, the mixture was acidified by addition of 10% HCl aqueous solution, and then extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed to give a solid residue which was dissolved in $CHCl_3$ (15 mL). TFA (0.640 mL, 8.52 mmol) was added to the mixture and heated at 60 °C for 3 h. The mixture was diluted with water (30 mL) and extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a residue, which was subjected to a column chromatography (Wakogel™ C-400) with AcOEt:hexane = 1:1. Yellow amorphous of **11** (0.238 g, 70%) was obtained, mp 172.7-173.2 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.93 (2H, s, CH_2), 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, 142.6, 146.2, 147.7, 150.5, 153.8, 154.0, 158.6, 158.8, 168.7. IR (KBr) cm^{-1}: 3032, 2953, 2927, 1739, 1690, 1609, 1480, 1454, 1414, 1351, 1222, 1173, 1084, 913, 738, 697.
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13. All trials to improve the yield in the transformation to **14** from **12** were unsuccessful.
14. **Oenothein C (1):** To a suspension of 10% Pd/C (50 mg) in THF (20 mL) was added a solution of **14** (0.135 g, 0.225 mmol) in THF (20 mL), and the reaction mixture was vigorously stirred for 23 h at rt

under H_2 atmosphere. The mixture was filtered with a Celite™ pad and the filtrate was concentrated. The resulting residue was purified by a reverse phase column chromatography (Sephadex™ LH-20) with MeOH:H_2O = 1:1 as an eluent to give oenothein C (**1**, 0.046 g, 74%) as a grayish amorphous, mp > 250 °C (decomp.). $[\alpha]_D^{25}$ +70 (*c* 0.5, MeOH). ^{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. IR (KBr) cm^{-1}: 3429-3300, 1718, 1705, 1617, 1362, 1349, 1340, 1216, 1211, 1106, 1046.