

HETEROCYCLES, Vol. 95, No. 1, 2017, pp. 131-136. © 2017 The Japan Institute of Heterocyclic Chemistry  
Received, 5th June, 2016, Accepted, 28th July, 2016, Published online, 27th October, 2016  
DOI: 10.3987/COM-16-S(S)6

## TOTAL SYNTHESIS OF OENOTHEIN C

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**Abstract** – The simple total synthesis of oenothain 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.

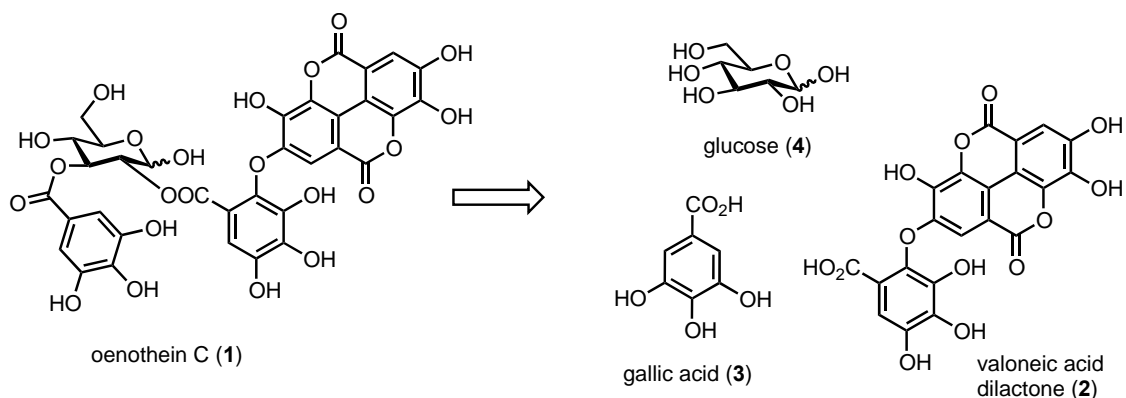
Ellagitannins are often found in the dicotyledonous plants and this class of compounds has attracted much attention as a medical resource since they have interesting biological activities such as anti-tumor, anti-oxidant, and antiviral activities, etc.<sup>1</sup> In 1984, oenothain C (**1**) was isolated from leaves of *Oenothera erythrosepala* by Okuda *et al.*<sup>2</sup> 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.<sup>3</sup> Although the synthetic challenges of the ellagitannins have been actively studied by many chemists since the 1990s,<sup>4,5</sup> there has been no report about the synthesis of ellagitannins which possess the lactonized valoneoyl unit such as oenothain C (**1**).

Recently, we reported the synthesis of the lactonized valoneoyl unit,<sup>6</sup> 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.<sup>7</sup> As an extension of our synthetic research, we describe the first total synthesis of the lactonized valoneoyl group-containing ellagitannin, oenothain 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.

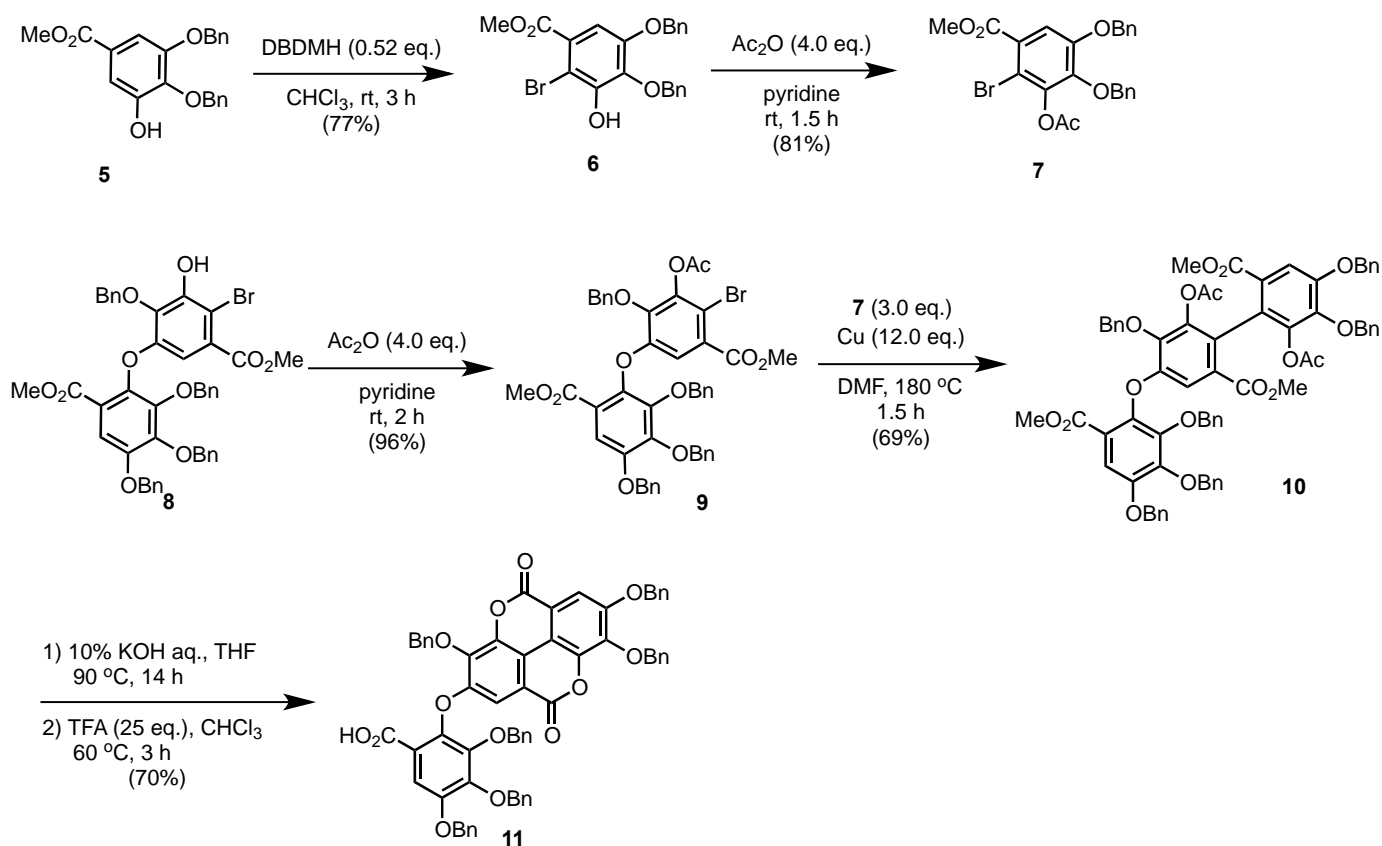
The synthesis plan is simply outlined in Scheme 1 in which the target molecule (**1**) could be constructed by successive esterification between the valoneic acid dilactone (**2**), gallic acid (**3**), and glucose (**4**). We postulated that the preparation of **2** could be realized by the application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

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**.<sup>8</sup> 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**<sup>6</sup> 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.<sup>9</sup> Alkaline hydrolysis of the esters and concomitant lactonization with trifluoroacetic acid (TFA) produced the all-benzylated valoneic acid dilactone **11**.<sup>10</sup>

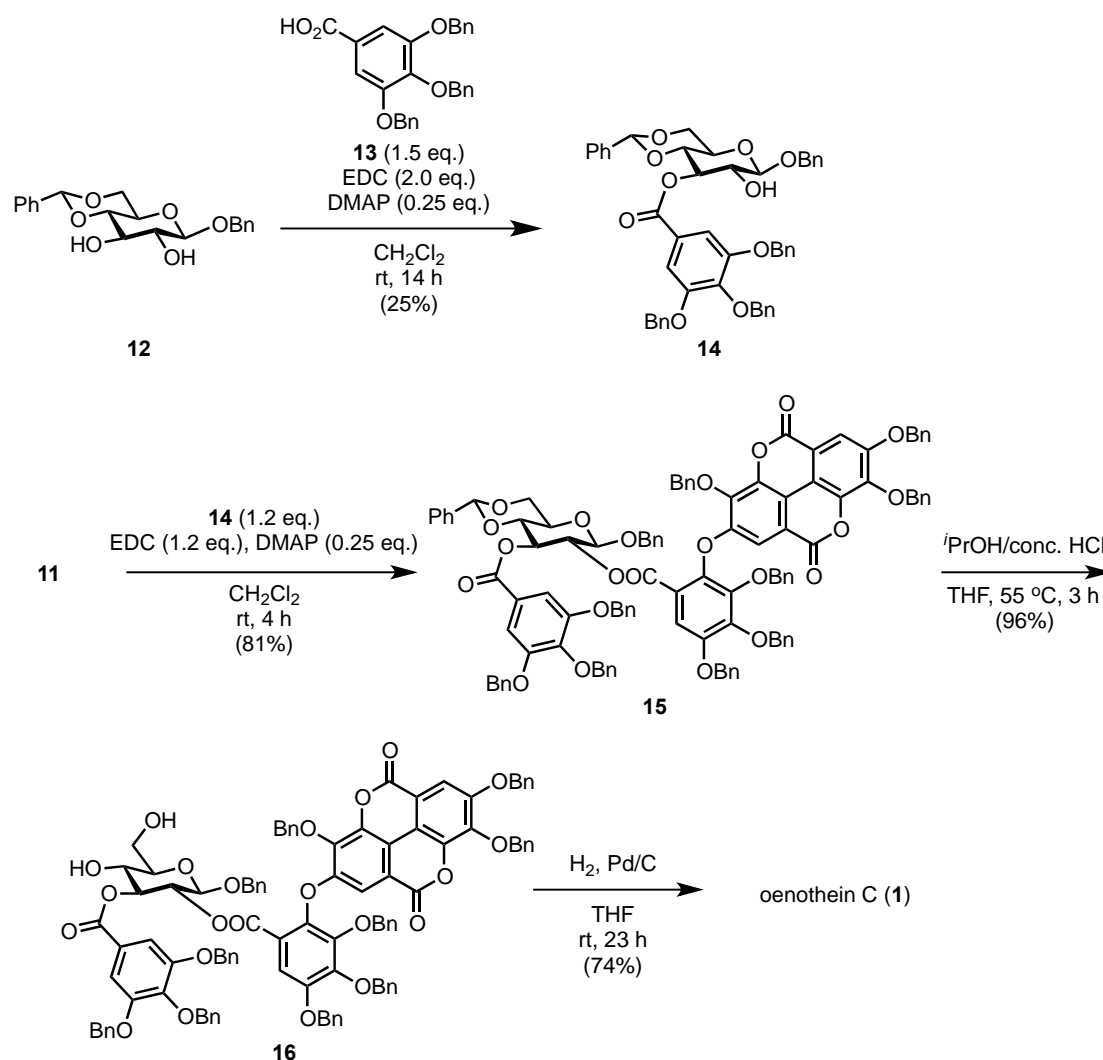


**Scheme 1.** Synthesis Plan for Oenothien C (1)



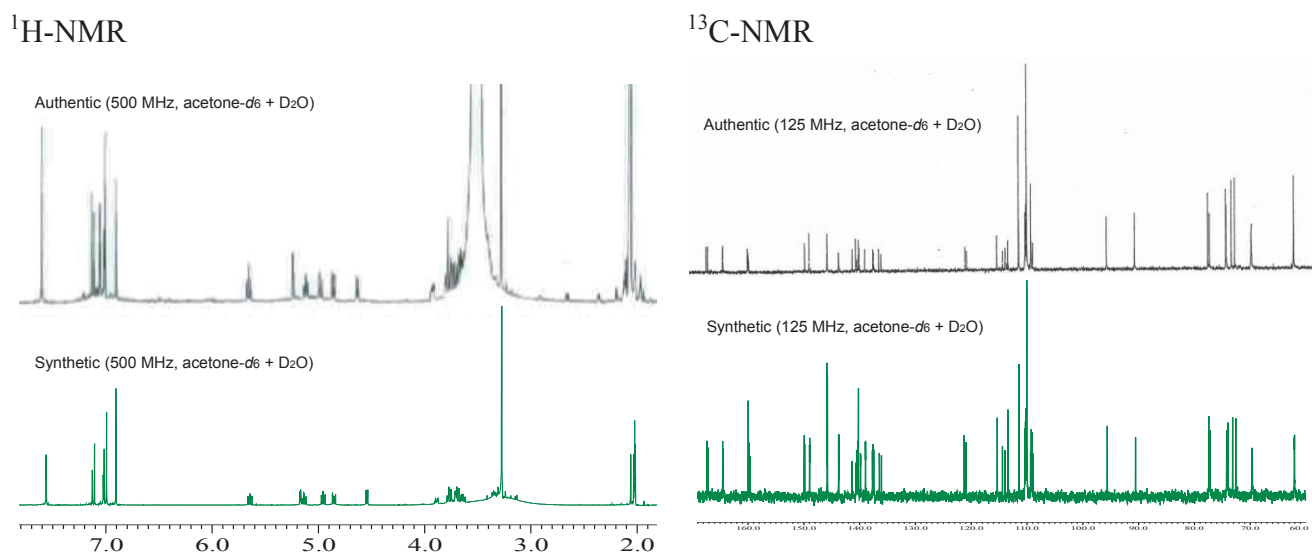
**Scheme 2.** Preparation of Lactonized Valoneoyl Unit (11)

For the sugar moiety, we chose the glucose derivative (**12**)<sup>11</sup> 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**<sup>12</sup> was unsuccessful, thus the desired **14** was produced in only 25% yield.<sup>13</sup> 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, oenothain C (**1**).<sup>14</sup> 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 Oenothain 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

## ACKNOWLEDGEMENTS

We thank Professors T. Hatano and S. Taniguchi (Okayama University) for their helpful discussions and for providing the spectral data of oenothin C. This study was financially supported by the JSPS KAKENHI (Grant Number 15K07854 for H. A.).

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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<sub>4</sub>. The solvent was removed to give a solid residue which was dissolved in CHCl<sub>3</sub> (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<sub>3</sub>. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, 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. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 4.93 (2H, s, CH<sub>2</sub>), 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). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>: 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. **Oenothien 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<sub>2</sub> 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<sub>2</sub>O = 1:1 as an eluent to give oenothien C (**1**, 0.046 g, 74%) as a grayish amorphous, mp > 250 °C (decomp.).  $[\alpha]_D^{25} +70$  (*c* 0.5, MeOH). <sup>1</sup>H-NMR (500 MHz, acetone-*d*<sub>6</sub> + D<sub>2</sub>O) 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). <sup>13</sup>C-NMR (125 MHz, acetone-*d*<sub>6</sub> + D<sub>2</sub>O) 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<sup>-1</sup>: 3429-3300, 1718, 1705, 1617, 1362, 1349, 1340, 1216, 1211, 1106, 1046.