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Enantioselective synthesis of valoneic acid derivative

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Abstract

The enantioselective synthesis of trimethyl octa-*O*-methylvaloneate (**1**) was accomplished using the Bringmann's 'lactone concept', which involves the intramolecular biaryl coupling reaction of a phenyl benzoate derivative and the asymmetric lactone-opening reaction.

Ellagitannins are natural polyphenolic compounds, which are widely distributed in many kinds of higher plants.[1] Because of their interesting biological activities based on an antioxidant property, this class of compounds has been expected for medicinal use.[2] A valoneoyl group is commonly observed in some class of ellagitannins, especially in its oligomers. Typical examples of some ellagitannins, which possess the valoneoyl group in the molecule, are shown in Figure 1.[3] In the course of the studies for structure determination, trimethyl octamethylvaloneate (**1**) has often been isolated during experiments involving the solvolysis and methylation process.[4] To date, the synthesis of **1** has never been performed, although it is an important part structure of ellagitannin family.[5]

In this Letter, we describe the enantioselective synthesis of the valoneic acid derivative, trimethyl octamethylvaloneate (**1**).

The synthetic plan is outlined in Scheme 1. Since we envisioned that Bringmann's 'lactone concept' would be a useful method[6] for the construction of the axially chiral biphenyl moiety, lactone **2** should be a key intermediate in this synthesis. As an appropriate precursor of lactone **2**, ester **3** should be realized by a simple esterification between the corresponding phenol **4** and carboxylic acid **5**. Phenol **4** was expected to be prepared by the Ullmann type coupling[7] between phenol **6**[8] and bromide **7**.[9]

Based on the above synthetic plan, we initially prepared ester **3** as depicted in Scheme 2. The Ullmann coupling of phenol **6**,[8] which was easily prepared by the reported method, and bromide **7**[9] produced the desired biphenyl ether **8**. The deprotection under hydrogenolysis conditions led to phenol **4**, which was coupled with benzoic acid **5**[10] using EDC.

Unfortunately, all attempts for the intramolecular biaryl coupling reaction[11] of **3** were unsuccessful. This result is similar to the previously reported ones,[11b] in which the neighboring ester group to the reacting position gives a negative effect in the Pd-mediated biaryl coupling reaction.

Thus, we thought that the ester groups should be converted into a protected carbinol function such as the acetoxymethyl group (Scheme 3). Two ester groups in **8** were reduced with $LiAlH_4$ to afford bisalcohol **9**, followed by acetylation. The debenzylation of **10** was carried out to form phenol **11**, which was coupled with **5**[10] using the usual esterification process.

Scheme 4 demonstrates the transformation of ester **12** into the axially chiral biphenyl derivative **15** using Bringmann's 'lactone concept'. The intramolecular biaryl coupling reaction using $Pd(OAc)_2$, Ph_3P, and NaOAc successfully produced lactone **13**. In the next step for the lactone-opening reaction of **13**, the combination of the borane and chiral oxazaborolidine (CBS reagent, **14**)[12]

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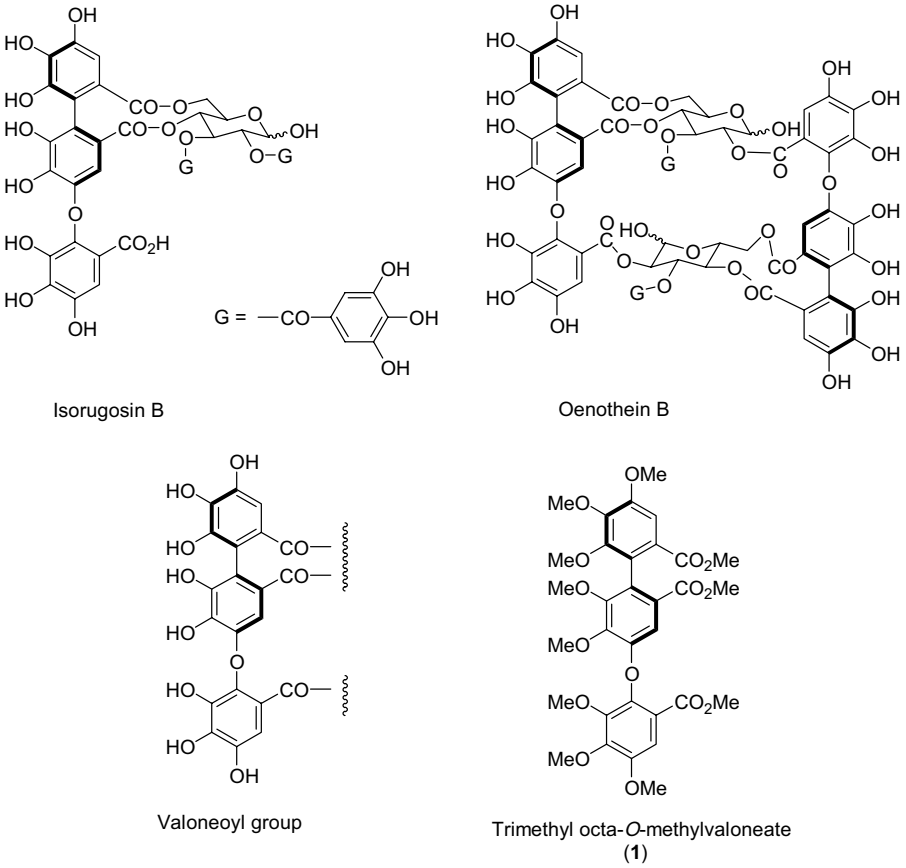
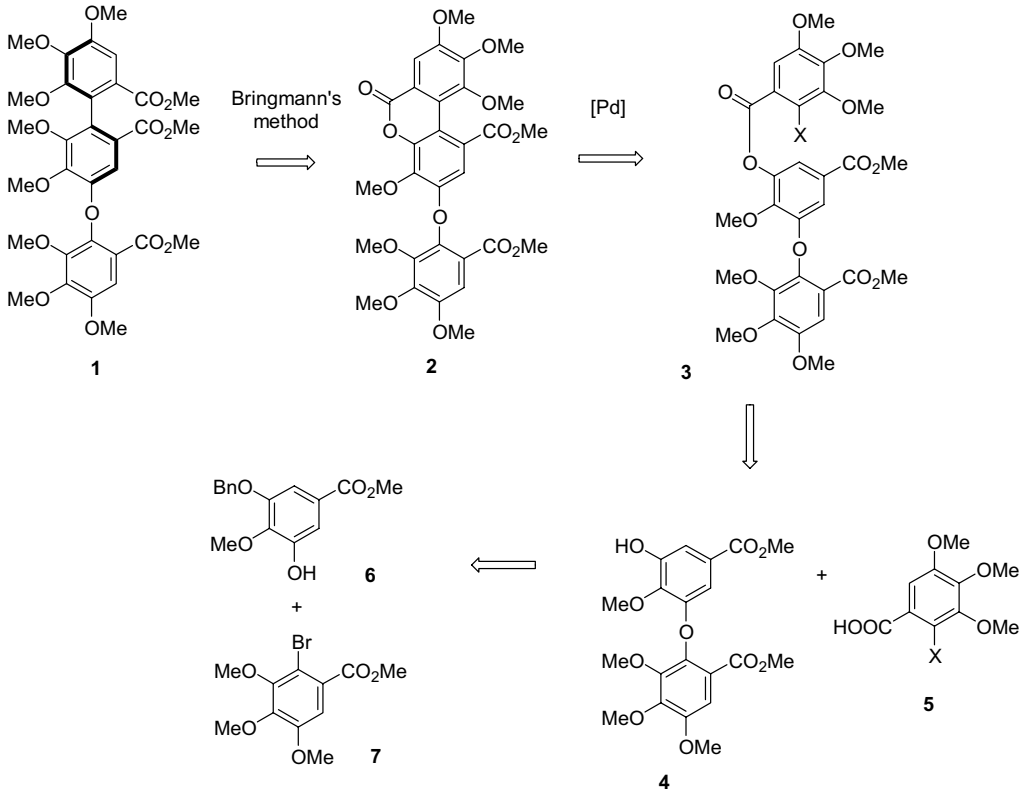
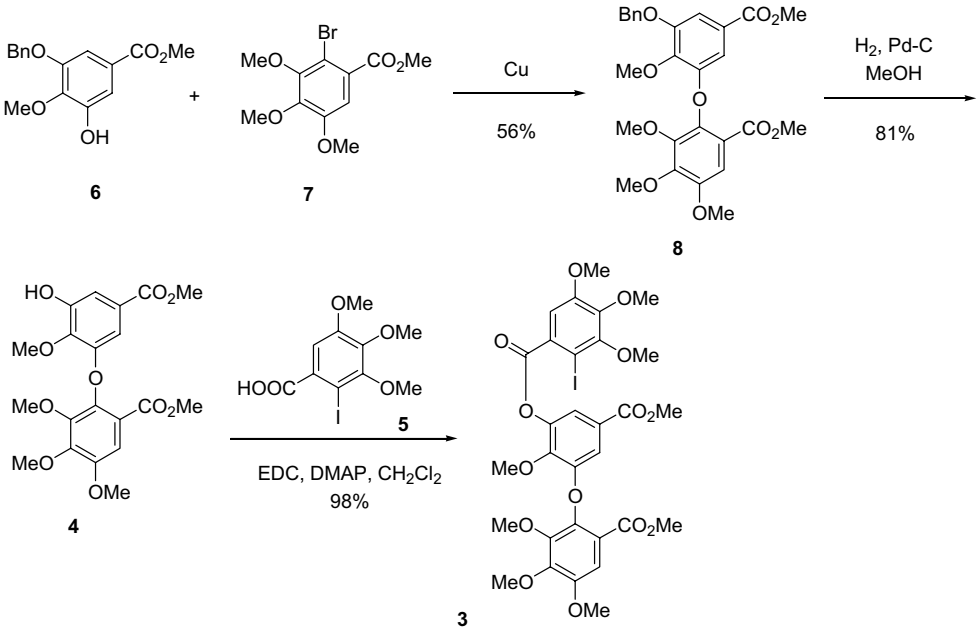


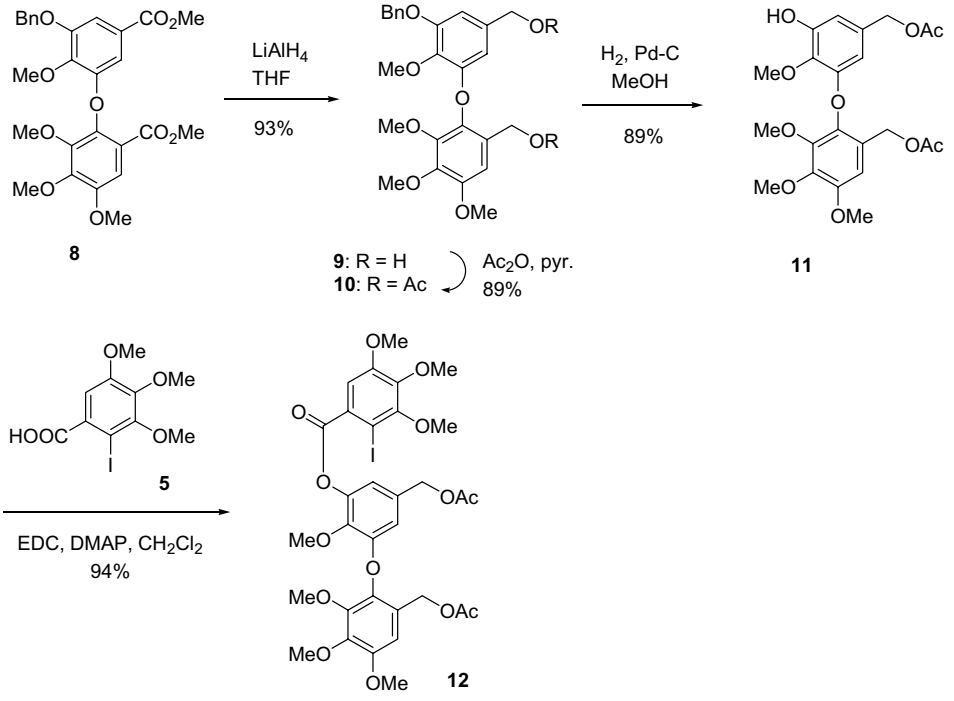
Fig. 1. Examples of valoneoyl group-containing ellagitannins.



Scheme 1. Synthetic outline of **1**.



Scheme 2. Synthesis of ester **3**.

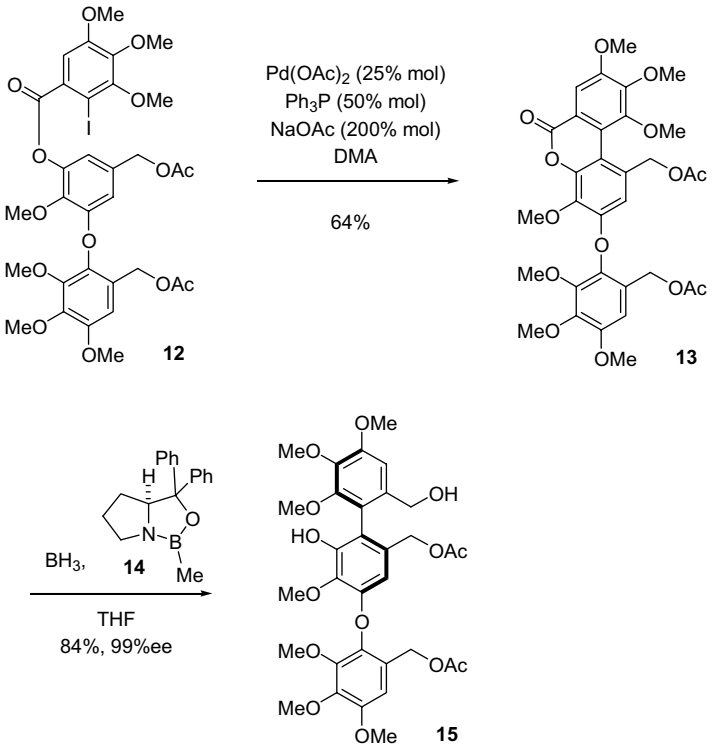


Scheme 3. Synthesis of ester **12**.

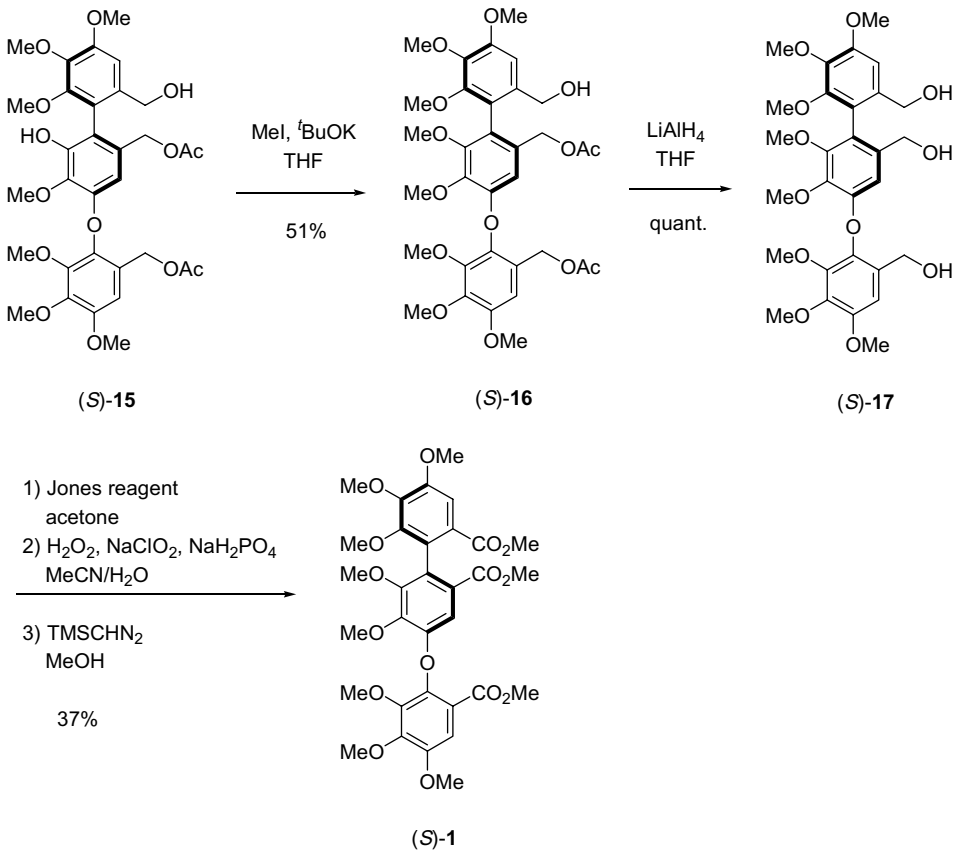
succeeded in the generation of the optically active (*S*)-**15** in an enantiomerically pure form.[13]

The phenolic hydroxyl group of (*S*)-**15** was methylated, and successive reduction of the two acetoxy groups produced triol (*S*)-**17**. Finally, the two-step oxidation of three hydroxyl groups and the methylation of the generating carboxylic acids led to the complete synthesis of (*S*)-**1** (Scheme 5). The absolute configuration of the synthetic compound was determined by the comparison of the optical rotation sign with the reported data.[14]

In conclusion, we synthesized the valoneic acid derivative (*S*)-**1**, an important part of the structure of the ellagitannins. Further transformation toward natural ellagitannins, involving manipulation of the protecting groups on phenolic OH, is now underway in our laboratory.



Scheme 4. Construction of axially chiral biphenyl compound **15** by Bringmann's method.



Scheme 5. Synthesis of (*S*)-**1**.

Acknowledgments

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13. The experimental method for transformation of **12** into **15**: A mixture of **12** (1 g, 1.3 mmol), $Pd(OAc)_2$ (72 mg, 0.32 mmol), NaOAc (213 mg, 2.6 mmol), and DMA (65 ml) was heated under reflux. After 15 min, the mixture was diluted with AcOEt and filtrated. The filtrate was washed with water and brine, and then the organic layer was dried over $MgSO_4$. After evaporation of the solvent, a residue was purified with silica gel column chromatography to afford **13** (534 mg, 64%) as colorless needles.
BH_3–THF (1.03 M, 0.96 ml) was added to a solution of **14** (266 mg, 0.96 mmol) in THF (10 ml) at 0 °C, and then the mixture was warmed to rt. After 30 min, a solution of **13** (100 mg, 0.16 mmol) was added dropwise at −40 °C and stirred for 72 h at the same temperature. The mixture was poured into water and extracted with AcOEt. The organic solution was washed with brine, dried, and evaporated to give a residue. Silica gel column chromatography affords pure **15** (85 mg, 84%, 99% ee) as amorphous substance. The ee was determined by HPLC analysis with Daicel Chiralcel AD.
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