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Total Synthesis of (−)-Corilagin

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Ellagitannins are a biologically and structurally diverse class of natural products.[1] The structure typically consists of galloyl and hexahydroxydiphenoyl (HHDP) group(s) esterified to a glucose (Figure 1), and the structural diversity arises from the number and location of the ester substituents, modification of the substituents, oligomerization, and ring-opening of the pyranose. The pyranose ring of the glucose moiety can even be in the axial-rich conformation, which is the flipped chair ($^1C_4$) or a twist-boat (B) form, when an HHDP group bridges two discontiguous hydroxy groups. Hence, the ellagitannins possessing the axial-rich glucose have been termed $^1C_4$/B-ellagitannins. Corilagin (**1**), one of the $^1C_4$/B-ellagitannins, is the first discovered natural product containing stable axial-rich glucose. It was isolated from dividivi (*Caesalpina coriaria*) by Schmidt and co-workers in 1951.[2] The HHDP group bridges the 3- and 6-oxygens of the glucose,[3] and its axial chirality is *R*.[4] Recently, a wide range of biological activities has been reported for **1**, for example, the potentiation of β-lactam antibiotics against MRSA, antiviral and antimicrobial activities, inhibition of TNF-α release, antihypertensive effect, and inhibition of a chitin synthase.[5] We now describe the synthesis **1**, which is also the first total synthesis of a $^1C_4$/B-ellagitannin.

Two main efforts in the synthesis of **1** were the strategy to build the 3,6-bridged bis-macrolactone structure, which is holding the glucose ring in the contra-thermodynamic conformation, and the development of an efficient synthetic method for the HHDP group. As the retrosynthetic perspective in scheme 1, we constructed the bicyclic ring system by synthesizing the floppy bis-macrolactone ring first then the more rigid six-membered ring (Scheme 1), that is (i) ring-opening of the pyranose; (ii) preparation of the HHDP group by coupling of the two gallates on the 3- and 6-oxygens; and (iii) reconstruction of the pyranose, since the formation of the bis-macrolactone involving ring-flip of the pyranose was difficult. Although we once achieved the skeleton by this three-step sequence, the unattainable complete demethylation of nonamethylcorilagin (**2**) prevented the total synthesis.[6] Further, difficulty of the iodination of corresponding tri-*O*-benzyl- or MOM-protected gallates forced us to abandon the use of Ullmann coupling for the HHDP-preparation. Previously, two methods for the HHDP-preparation have contributed to the total syntheses of ellagitannins.[7] One of them, Feldman's method, involves the intramolecular oxidative phenol coupling of diphenylmethylene-protected gallates.[8] This method provides a mixture of regioisomers due to the asymmetry of the protecting groups, which require subsequent deprotection/protection steps to afford a single synthetic intermediate.[9] Consequently, development of an effective coupling of symmetrically protected gallates should advance the synthetic approach in ellagitannin chemistry.

To develop an effective synthetic method for the HHDP group, symmetrically designed methyl 4-*O*-benzylgallate (**3**)[10] was applied in the known phenol coupling methods.[11] This preliminary investigation revealed that utilization of the $CuCl_2$·amine complex was promising. This reagent was originally developed by Brussee and co-workers for the coupling reactions required for the preparation of binaphthols.[12] In this synthesis, ethylamine or amphetamine were the most effective compounds for the amine part of the reagent when the substrate is 2-naphthol. We also found that the use of primary amines was effective for the intermolecular coupling of **3**. Thus, the coupling of **3** was successful when using not only ethylamine, but also *n*-butyl- and *n*-hexylamines to give the corresponding dimer in 35, 52, and 49% yield, respectively, along with the trimer and lager oligomers (Scheme 2). The reaction conditions could be applied to the intramolecular case with a digallate **4**, in which the four-carbon-linker corresponds to the 3- to 6-positions of glucose in **1**. The yields of the intramolecular couplings were better than those of the intermolecular cases providing **5** in 77−85% yield.

The $CuCl_2$·amine mediated coupling was applied to **6** to afford the bridged synthetic intermediate **7** as the sole coupled product (Scheme 3). The coupling precursor **6** was prepared by the esterification of the ring-opened **8** (seven steps from D-glucose)[6] with **9**, followed by the removal of the MOM groups. For the oxidative intramolecular coupling of **6**, the use of *n*-butylamine was optimal for constructing the 3,6-HHDP-bridge to afford **7** in 76% yield. In contrast, the operations with ethyl- and *n*-hexylamines decreased the yield to 30% and trace, respectively. The coupled product **7** was a single diastereomer, with the sugar-derived sp^3 asymmetries being completely transferred to the axial site. This

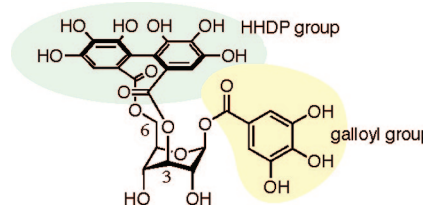
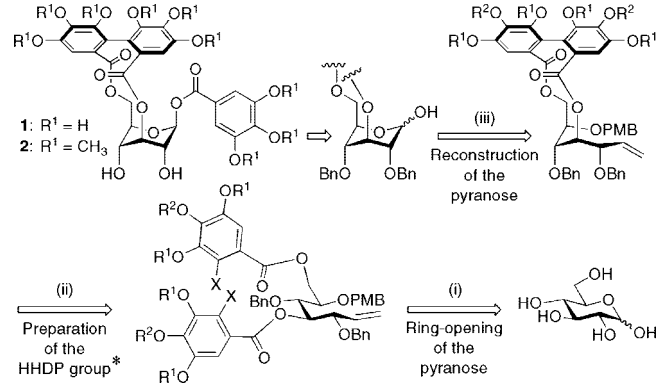


Figure 1. Structure of corilagin (**1**).

Scheme 1. Retrosynthetic Approach to Corilagin (**1**)[a]



[a] This work: $R^1 = X = H$, $R^2 = Bn$, (*) oxidative phenol coupling. Our previous approach: $R^1 = R^2 = CH_3$, X = I, (*) Ullmann coupling.[6]

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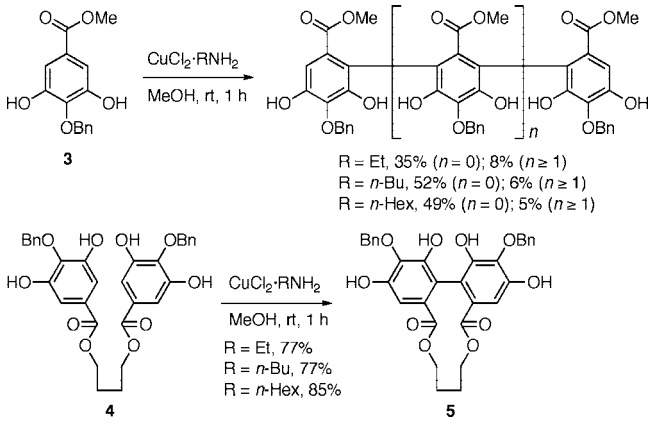
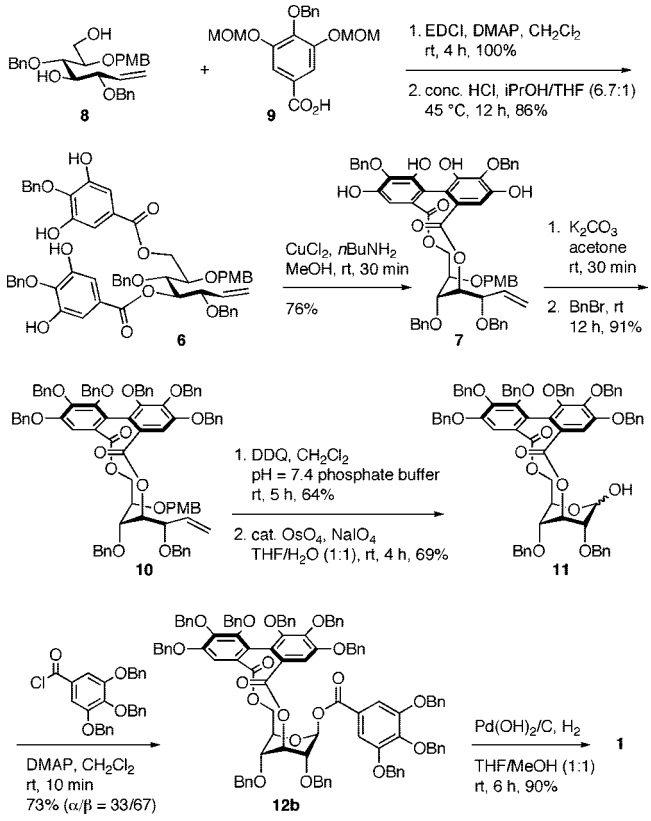
Scheme 2. Coupling of 4-*O*-Benzylgallates by $CuCl_2$·amine Complex



Scheme 3. Synthesis of Corilagin (**1**)[a]



[a] DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride, MOM = methoxymethyl.

axial diastereoselectivity would be thermodynamically controlled because the bond between the two aryl groups rotates as their copper salts. For example, certain racemic 1,1′-biaryl-2,2′-diols deracemize by treatment with CuCl or $CuCl_2$ and chiral amines.[13] In addition, $CuCl_2$·amine-mediated phenol couplings accompany similar deracemizations by the support of the chirality of the amines or the substrates.[12,14] The atrop-*R* configuration in **7** was ultimately confirmed by the total synthesis of **1**.

The subsequent five steps following the synthesis of key intermediate **7** achieved the total synthesis (Scheme 3). Thus, the benzyl protection of **7** followed by the cleavage of the PMB group afforded **10** whose double-bond was then oxidatively cleaved to reconstruct the pyranose ring providing **11**. Introduction of the galloyl group to the anomeric position afforded **12** (α/β = 33/67). Hydrogenolysis of the β-isomer **12b** cleaved eleven benzyl groups to provide **1** whose physical and spectral data (optical rotation, ^1H and ^{13}C NMR, IR) were identical with those of the natural corilagin.

In summary, the total synthesis of **1** was achieved by the integration of the development of the oxidative coupling of the symmetrically protected gallates and the temporarily ring-opened synthetic route for the 3,6-HHDP bridge. This first total synthesis of a $^1C_4$/B-ellagitannin reveals that the combination of the 4-*O*-benzyl gallate and the $CuCl_2$·amine complex allows efficient preparation of the HHDP group. Because of the structural resemblance in ellagitannins, this new method would be applicable for the syntheses of the other natural ellagitannins and their artificial analogues.

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Supporting Information Available: Complete ref 11, experimental procedures, characterization of new compounds, ^1H and ^{13}C NMR spectra for compound **5**−**7**, **9**−**11**, **12ab**, and natural and synthetic **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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