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# Total Synthesis of the Proposed Structure of Roxbin B; the Nonidentical Outcome

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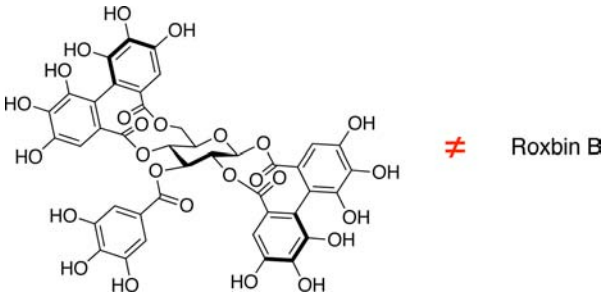
## ABSTRACT




**A proposed structure of roxbin B was synthesized. For the synthesis, a new synthetic method for the preparation of the hexahydroxydiphenoyl (HHDP) bridge was developed that involved the stepwise esterification of axially chiral HHDP acid anhydride. The synthesized compound was not identical to the natural roxbin B.**

Natural ellagitannin is a structurally diverse class of hydrolyzable tannins,[1] the structures of which typically include glucose bearing hexahydroxydiphenoyl (HHDP) group(s) (Figure 1). Among the 10 combinations ($_5C_2$) of the potential positions in the case of HHDP-bridged $\beta$-glucopyranose, natural products possessing a bridge structure between O-1 and O-4, between O-2 and O-6, and between O-1 and O-2 of glucose have been quite rare.[2] Among the three rare positions, the structural difficulty in the first and the second positions can be easily understood, but it is strange that ellagitannin bearing the HHDP bridge at the third position is rare. (−)-Roxbin B is a natural ellagitannin possessing the 1,2-HHDP bridge, which was isolated from the unripe fruits of *Rosa roxburghii* TRATT by Okuda and co-workers in 1987.[3] The structure was characterized as 3-*O*-galloyl-1,2;4,6-bis-*O*-(*S*)-HHDP-$\beta$-D-glucose (**1**).

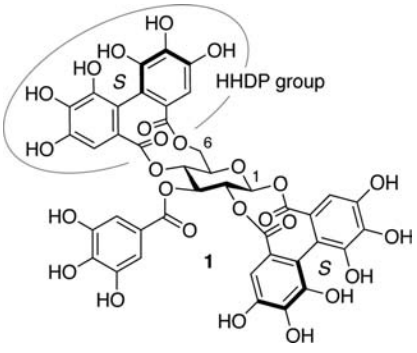



**Figure 1.** Proposed structure of roxbin B (**1**).

We recently reported a reliable method for synthesizing the chiral HHDP compounds.[4] The method involved intramolecular aryl−aryl coupling of 4-*O*-benzylated gallates on simple chiral auxiliaries derived from L-tartaric acid. The coupling was induced by $CuCl_2$−*n*-$BuNH_2$ with

(1) (a) Gross, G. G.; Hemingway, R. W.; Yoshida, T. *Plant Polyphenol 2. Chemistry, Biology, Pharmacology and Ecology*; Kluwer Academic/Pleum Publishers: New York, 1999. (b) Yoshida, T.; Hatano, T.; Ito, H.; Okuda, T. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science B. V.: Amsterdam, 2000; Vol. 23, pp 395−453.

(2) (a) The 1,2-HHDP structure (CAS No. 1173170-86-9) written in the following paper is unsubstantial. The structure is drawn as just a conceptual scheme of ellagitannins: Hanhineva, K.; Kokko, H.; Siljanen, H.; Rogachev, I.; Aharoni, A.; Kärenlampi, S. O. *J. Exp. Bot.* **2009**, *60*, 2093–2106. (b) The 1,2-HHDP structure of CAS No. 82576-46-3 should be revised to 1,3-HHDP: Malhotra, S.; Misra, K. *Curr. Sci.* **1983**, *52*, 583–585.

(3) Yoshida, T.; Chen, X.-M.; Hatano, T.; Fukushima, M.; Okuda, T. *Chem. Pharm. Bull.* **1987**, *35*, 1817–1822.

(4) Asakura, N.; Fujimoto, S.; Michihata, N.; Nishii, K.; Imagawa, H.; Yamada, H. *J. Org. Chem.* **2011**, *76*, 9711–9719.

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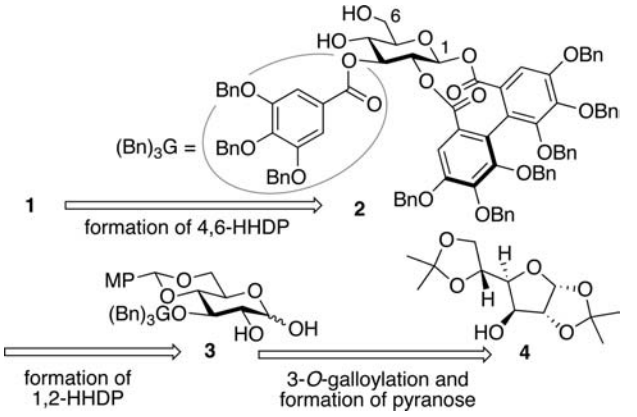
complete or near-perfect diastereoselectivity to provide each enantiomer of the HHDP compounds. The easy availability of the chiral HHDP compounds potentially improves the synthesis of natural ellagitannins; herein we describe a concrete application, namely the first total synthesis of the proposed structure of roxbin B (**1**). From the synthesis, we demonstrated that **1** was not roxbin B.

**Scheme 1.** Retrosynthesis of **1**

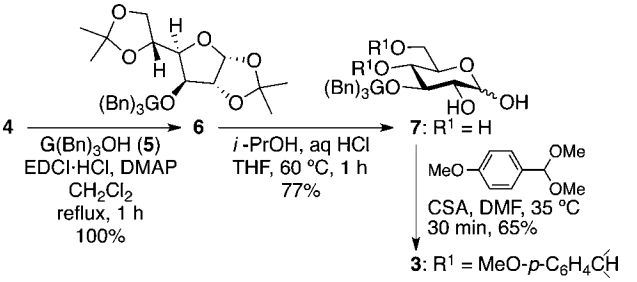



Scheme 1 outlines the strategy for the total synthesis of **1**. The retrosynthetic analysis started with the disconnection of the 4,6-HHDP group of **1**, which would be formed in the final stage of the synthesis. To form the 1,2-HHDP group of **2**, the 4,6- and 1,2-diols should be protected and unmasked, respectively, as **3**. In this communication, we discuss three different methods for the formation of the 1,2-HHDP bridge. For 3-*O*-gallate **3**, diacetone-D-glucose (**4**) would be the applicable starting material.

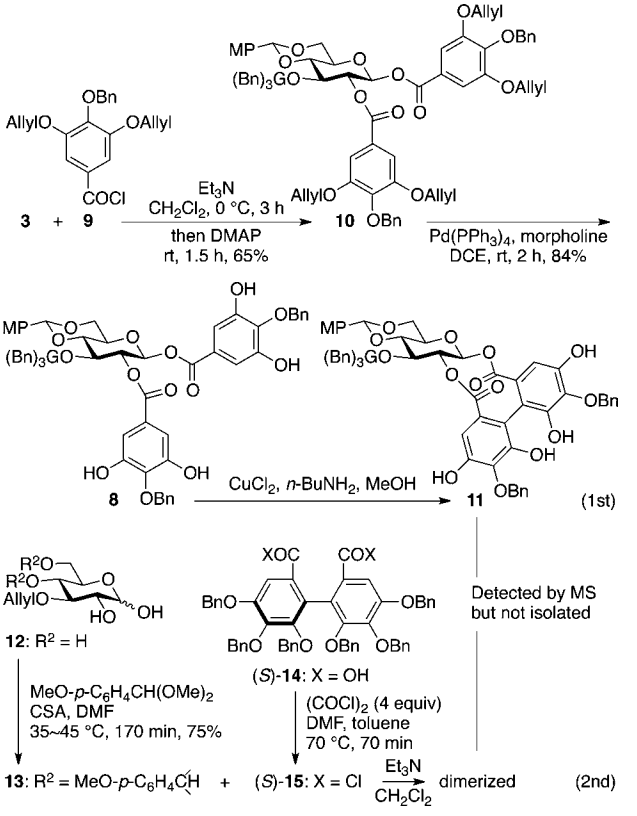
Synthesis of compound **3** was successful despite the choice of a considerably short path (Scheme 2). Thus, 3-*O*-galloylation of **4** with 3,4,5-tri-*O*-benzylgallic acid (**5**) under the modified Steglich's conditions[5] gave **6** quantitatively. The galloyl ester of **6** survived under the acidic reaction conditions for removal of the acetonide groups to provide tetraol **7** in 77% yield.[6] The 4,6-selective formation of *p*-methoxybenzylidene acetal was possible, affording the desired 1,2-diol **3** in 65% yield.[7]

To construct the 1,2-HHDP bridge, we investigated three methods. First, intramolecular coupling of 4-*O*-benzylated digallates on **8** was attempted (Scheme 3).[4,9] The digallate **8** was prepared through acylation of the 1,2-diol **3** with 3,5-di-*O*-allyl-4-*O*-benzylgalloyl chloride (**9**) followed by

**Scheme 2.** Synthesis of 1,2-Diol **3**[8]




**Scheme 3.** Attempts To Prepare the 1,2-HHDP Bridge




deallylation[10] of **10**. In the anomeric acylation, use of the $Et_3N$ induced the $\beta$-selectivity.[11] The employment of the partly allyl protected derivative of gallic acid was unprecedented in ellagitannin synthesis. The treatment of **8** with $CuCl_2$–*n*-$BuNH_2$ in MeOH provided a complex mixture. Although the mass spectrum indicated the formation of the desired **11** [$m/z$ 1201.5 $(M - H)^-$] in trace proportions, we could not isolate **11**. The intramolecular aryl–aryl coupling was therefore ineffective in this case. In the second method,

(5) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed.* **1978**, *17*, 569–583.
(6) Schmidt, O. T.; Schach, A. *Ann.* **1951**, *571*, 29–41.
(7) Evans, D. A.; Ng, H. P. *Tetrahedron Lett.* **1993**, *34*, 2229–2232.
(8) Abbreviations: CSA, 10-camphorsulfonic acid; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. The other abbreviations are listed in The Journal of Organic Chemistry Guidelines for Authors (Updated January 2012).
(9) (a) Yamada, H.; Nagao, K.; Dokei, K.; Kasai, Y.; Michihata, N. *J. Am. Chem. Soc.* **2008**, *130*, 7566–7567. (b) Kasai, Y.; Michihata, N.; Nishimura, H.; Hirokane, T.; Yamada, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 8026–8029.
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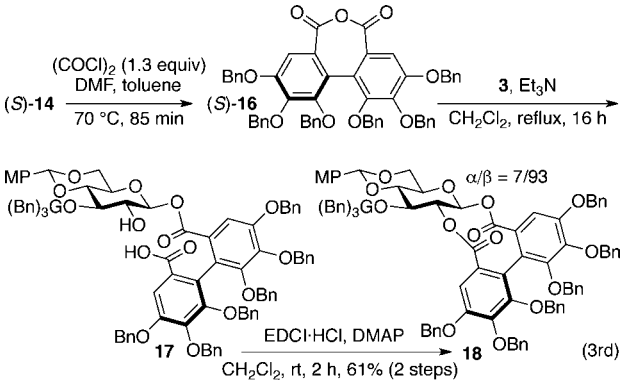
we attempted double esterification,[12] which is the formation of the bislactone starting from a diol (**13** in this work) and a diacid (diacid chloride (*S*)-**15** in this work), first through intermolecular but subsequently through intramolecular esterifications. However, this approach produced a dimer (not isolated), of which the mass spectrum indicated the production of a compound in which the two sugar moieties were esterified to one HHDP group (*m*/*z* 1541.5, M + Na). Diol **13** was prepared by introduction of *p*-methoxybenzylidene acetal on the 4,6-diol of known **12**.[13] Diacid chloride (*S*)-**15** was obtained by chlorination of the diacid (*S*)-**14** (98% ee)[4,14] using 4 equiv of $(COCl)_2$.

To avoid the formation of the dimer, we applied the corresponding acid anhydride (*S*)-**16** as the third approach (Scheme 4). The acid anhydride (*S*)-**16** was obtained by

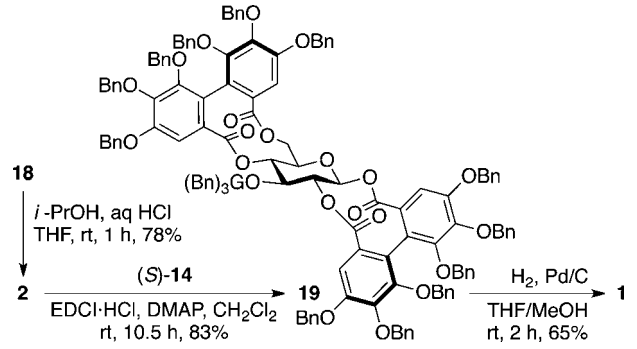
**Scheme 4.** Construction of the 1,2-HHDP Bridge




treatment of diacid (*S*)-**14** with 1.3 equiv of $(COCl)_2$. The aryl−aryl bond of (*S*)-**16** did not rotate at rt for a week, maintaining the axial chirality.[15] The 1,2-(*S*)-HHDP bridge was constructed by stepwise diacylation. Specifically, regioselective esterification of diol **3** with acid anhydride (*S*)-**16** in the presence of $Et_3N$, followed by lactonization of the furnished $\beta$-glycosyl ester **17**, afforded the 1,2-bridged **18** in 61% yield from **3** as an $\alpha/\beta$ = 7/93 mixture of anomers. The high regioselectivity of the esterification was due to the higher reactivity of the anomeric hydroxy group compared to the sterically more hindered 2-OH.

The following three steps transformed **18** to the proposed structure of roxbin B (**1**) (Scheme 5). Acid hydrolysis of the *p*-methoxybenzylidene acetal of **18** provided the corresponding 4,6-diol **2** in 78% yield. The double esterification of the 4,6-diol of **2** was effectively possible with (*S*)-HHDP dicarboxylic acid (*S*)-**14**, thus obtaining 1,2-(*S*)- and 4,6-(*S*)-bridged **19** in 83% yield. Khanbabaee and co-workers reported the formation of the 4,6-(*S*)-HHDP

**Scheme 5.** Synthesis of the Proposed Structure of Roxbin B (**1**)




bridge through the double esterification strategy with racemic **14** via kinetic resolution.[16] In this transformation, the unnecessary (*R*)-HHDP dicarboxylic acid also reacts by producing oligomers, which wastes the diol, the base of the bridge.[17] Adoption of the chiral HHDP donor removed this problem and improved the efficiency of the double esterification step, including isolation of the desired bislactone compounds. Finally, hydrogenolytic cleavage of the 15 benzyl groups of **19** gave **1**. The purification of **1** was performed by Sephadex LH-20 column chromatography. Toyopearl HW-40, which has often been used as a column packing material for purification of many natural ellagitannins,[18] decomposed **1**, suggesting the instability of the 1,2-HHDP bridged ellagitannin.

The synthetically obtained **1** was not identical to the naturally occurring roxbin B (see Supporting Information). Thus, the proposed structure **1** must be revised.

In conclusion, we achieved the first total synthesis of the proposed structure for roxbin B, but the synthesized compound was not identical to the natural product. In these synthetic studies, we newly obtained an effective strategy for the synthesis of natural ellagitannins, which was the stepwise construction of the HHDP-bridge with the corresponding acid anhydride. This strategy was useful when the desired double esterification was ineffective. Application of the strategy would expand the range of synthetically available ellagitannins. Structural reconsideration of roxbin B including total synthesis is currently underway.

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**Supporting Information Available.** Synthesis of 3,5-di-*O*-allyl-4-*O*-benzylgalloyl chloride (**9**), comparison of $^{1}H$ and $^{13}C$ NMR spectra of natural roxbin B and synthetic **1**, and experimental section and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.