Total Synthesis of Phyllanemblinin B

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Abstract A total synthesis was developed of phyllanemblinin B, a natural ellagitannin containing 1-O-galloyl and 2,4-O-hexahydroxydiphenoyl groups on a d-glucose scaffold. The use of a µ-hydroxocopper(II) complex resulted in a completely stereoselective oxidative coupling of the galloyl groups on the open-chain glucose moiety and facilitated the first total synthesis of phyllanemblinin B.

Key words total synthesis, natural products, ellagitannins, phyllanemblinin B, oxidative coupling

Phyllanemblinin B (1) is an ellagitannin first isolated in 2001 by Tanaka, Kouno, and co-workers from the fruit juice of Phyllanthus emblica L., also known as the Malacca tree (Figure 1, left).\textsuperscript{1} The tree’s fruits and their juice have been widely used as antiinflammatory and antipyretic agents. The authors reported the \textsuperscript{1}H and \textsuperscript{13}C NMR spectra of 1 (Figure 1, left). 1 The tree’s fruits and their juice have been widely used as antiinflammatory and antipyretic agents. The authors reported the \textsuperscript{1}H and \textsuperscript{13}C NMR spectra of 1, which showed the presence of a β-galloyl group at the 1-oxygen position (O-1) and a hexahydroxydiphenoyl (HHDP) group bridging the O-2 and O-4 atoms of the d-glucose unit. They also reported that the coupling constant between H-1 and H-2 in the \textsuperscript{1}H NMR spectrum ($J_{H1,H2} = 6.0$ Hz) indicated a skew-boat conformation of the glucopyranose scaffold [also refer to our determination of $S_1$ as reported in the Supporting Information (SI) SI-03]. Moreover, based on the circular dichroism (CD) spectrum of 1, including the observation of a positive Cotton effect at 267 nm and a negative one at 230 nm, the axial chirality of the 2,4-O-HHDP groups was determined to be R. Furthermore, the group also found that hydrogenation of fucosin (2)\textsuperscript{2} in the presence of palladium on carbon afforded 1 in 14% yield; fucosin (2) contains a dehydrohexahydroxydiphenoyl (DH-HDPP) group instead of the HHDP group between O-2 and O-4 (Figure 1, right). Although 1 and 2 both contain a similar 11-membered ring, the slight difference in the number of sp\textsuperscript{3} carbon atoms in the ring (three for 1 versus four for 2) affects the shapes of these structures.

The 2,4-O-HHDP bridge is an unusual motif for a natural ellagitannin. In relation to the biosynthesis of ellagatannins, Schmidt, Haslam, and co-workers proposed the oxidation of the 1,2,3,4,6-penta-O-galloyl-β-d-glucopyranose (β-PGG; 3), which results in the formation of the HHDP group and the generation of basic ellagitannins (Scheme 1).\textsuperscript{3} For example, the oxidative coupling of the galloyl groups at O-4 and O-6 in 3 affords the 4,6-O-HHDP bridge, thus resulting in the biosynthesis of tellimagrandin II (4). Oxidative coupling between discontinuous positions, such as O-1 and O-6, is also possible and results in the generation of davidin (5). In the case of coupling at O-3 and O-6, followed by the hydrolysis of the galloyl groups at O-2 and O-4, the construction of 3,6-O-HHDP group permits the synthesis of corilagin (6). Thus, for the initial construction of the HHDP group, a total of eight combinations exist, which involve a choice of two out of five galloyl groups in 3. Two research groups have investigated the possible combination tendencies. Niemetz, Gross, and co-workers conducted biological evaluations and discovered an oxidase that is involved in the coupling of the galloyl groups between O-4 and O-6 in 3.\textsuperscript{5,7} An enzyme extracted from Telima grandiflora leaves

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permitted the biosynthesis of 4; however, no further evaluation has been reported. In 2017, we conducted a nonenzymatic study that involved the investigation of the chemical oxidation of 7 possessing partially protected galloyl groups.\textsuperscript{8} The study established that the galloyl groups tended to couple in the following order: O-4/O-6, O-1/O-6, O-1/O-2, O-2/O-3, and O-3/O-6. Notably, the formation of a 2,4-O-HHDP group was not observed. Phyllanemblinin B (1) is the only natural ellagitannin possessing a 2,4-O-HHDP group, although numerous ellagitannins containing a DHHP group at O-2 and O-4 have been isolated [e.g. fucosin (2)].

Previously, the Martin and Feldman groups have both reported studies on the construction of the 2,4-O-HHDP group. Although there are a number of reports concerning the chemical syntheses of natural ellagitannins containing 1,6-, 9 2,3-, 10–13 3,4-, 14,15 3,6-, 16,17 or 4,6-O-HHDP groups,\textsuperscript{10,11,18–22} on D-glucose, the synthesis of phyllanemblinin B (1) has not been described. In 1998, prior to the isolation of 1, Martin and co-workers investigated an Ullman coupling reaction in the presence of a copper compound in refluxing DMF for the coupling of 2-iodo-3,4,5-trimethoxybenzoyl groups on a carbohydrate derivative (Scheme 2a).\textsuperscript{10} The lead(IV) acetate-mediated conversion of the partially protected galloyl groups of 10 led to the formation of the HHDP-containing product 11 as a complex mixture of diastereomers, in addition to the generation of diphenyl ketal regioisomers. The silylation of the free hydroxy groups in 11 gave a crude mixture of four isomers. Purification of the crude product by flash chromatography and further thin-layer chromatography provided (R)-12 and (S)-12 in yields of 40 and 36%, respectively. The axial chirality of (R)-12 was established by a comparison of its CD spectrum with that of 1. Consequently, the complexity arising from the presence of both diastereomers as well as regioisomers differing in the position of the protective groups makes the chemical synthesis of such natural products challenging.

In the present study, we developed a total synthesis of phyllanemblinin B (1). Our synthetic approach was based on our previous study on the synthesis of corilagin (6) by using a symmetry-protected galloyl group on the flexible open-chain glucose derivative 13 as the coupling precursor (Scheme 2c).\textsuperscript{17} In the study, the oxidation of 13 by a compositional study that involved the investigation of the chemical oxidation of 7 possessing partially protected galloyl groups.\textsuperscript{8} The study established that the galloyl groups tended to couple in the following order: O-4/O-6, O-1/O-6, O-1/O-2, O-2/O-3, and O-3/O-6. Notably, the formation of a 2,4-O-HHDP group was not observed. Phyllanemblinin B (1) is the only natural ellagitannin possessing a 2,4-O-HHDP group, although numerous ellagitannins containing a DHHP group at O-2 and O-4 have been isolated [e.g. fucosin (2)].

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Scheme 1 Proposed biosynthesis of basic ellagitannins

![Scheme 1 Proposed biosynthesis of basic ellagitannins](image)

| a. Martin’s method [Cu, DMF, reflux] |
| b. Feldman’s method [Pd(OAc)\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, –38 °C] |
| c. Our previous work [CuCl\textsubscript{2}, BuNH\textsubscript{2}, MeOH] |
| d. This work [β-hydroxy Cu\textsuperscript{II} complex, CH\textsubscript{3}CH\textsubscript{2}OH] |

Scheme 2 Previous methods for the construction of the HHDP group and the approach developed in this study

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plex of copper(II) chloride and butylamine resulted in the stereoselective construction of the HHDP group and afforded 14. To provide the 2,4-O-HHD2D group for phyllanemblin B (1), the oxidation of 15 by using a μ-hydroxo copper(II) complex resulted in the formation of 16 with a complete diastereoselectivity (Scheme 2d). Consequently, the outcomes of this work permitted an effective synthesis of 1. Moreover, the glucopyranose conformation, which was bridged by the 2,4-O-HHD2D group, was analyzed, and the axial chiralities of both the constructed and the naturally occurring HHDP group of 1 were confirmed.

The 2,4-O-HHD2D bridge on the open-chain glucose derivative was constructed from a known compound 17 (Scheme 3). Subsequent protection of the two hydroxy groups at O-2 and O-4 in 17 with methoxymethyl (MOM) moieties provided 18 (SI; SI-04). Consecutive hydrolysis of the thioacetal functionality in 18 by N-bromosuccinimide and water, Wittig olefination of the hemiacetal group, and p-methoxybenzyl-protection of the resulting hydroxy moiety provided 19 in 50% yield in three steps (SI; SI-05). Treatment of 19 with hydrochloric acid removed the MOM groups to provide 20 in 69% yield (SI; SI-06). Subsequent esterification of the hydroxy groups in 20 by using a galloyl acid derivative protected with benzyl and MOM groups,17 followed by acid treatment, provided the coupling precursor 15 (SI; SI-07 and SI-08). Notably, for the construction of the desired (R)-HHDP group from 15, the μ-hydroxo copper(II) complex [Cu(OH)(TMEDA)]2Cl2, previously reported by Koga and co-workers,26 was effective in generating 16.

For the intramolecular oxidative coupling of the galloyl motifs, a μ-hydroxo copper(II) complex was used to construct the HHDP group. Initially, we used the reaction conditions previously reported by our group. Combining copper(II) chloride and butylamine in methanol17 gave 16 in a low yield of 6% (SI; SI-09). As a result of a screening of the oxidizing reagent, we found that the oxidation of 15 with [Cu(OH)(TMEDA)]2Cl2 in dichloromethane resulted in a considerable improvement in the yield of 16 to 82%.27 We suspect that this marked improvement in the yield originates from inhibition of solvolysis of the ester as a result of replacing methanol with dichloromethane. In addition, our study also found that the μ-hydroxo copper(II) reagent was useful in constructing HHDP groups between O-2 and O-3 or between O-4 and O-6 in the glucopyranose derivatives, which are the common components of ellagitannins (see also the additional experiments described in the SI; SI-14). Notably, no reaction occurred when a combination of copper(II) chloride and butylamine with dichloromethane as the sole solvent was used. By the extension of the usable solvent system for the oxidative coupling of the galloyl groups, this alternative method permits the installation of a HHDP moiety in a manner that cannot be achieved by using the conventional method.

We subsequently established the constructed axial chirality of 16. In the coupling reaction that we conducted, 16 was obtained as a single diastereomer. Benzyl protection of 16 followed by solvolysis afforded 21 in 37% yield over two steps (Scheme 3; see also SI; SI-10). Comparison of the optical rotary dispersion data of the prepared sample of 21 with previously reported data28,29 suggested an (R)-axial chirality; we therefore inferred that the oxidative coupling of the galloyl groups on the flexible open-chain glucose scaffold in 15 progressed with complete (R)-selectivity.

The final steps of the total synthesis of 1 involved a ring-closing reaction to provide the glucopyranose scaffold (Scheme 3). Following protection of the hydroxy groups in 16 with benzyl groups, treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded 22 in 75% yield from 16 (SI; SI-11 and SI-12). Dihydroxylation and oxidative cleavage by using a combination of osmium(VIII) oxide and sodium periodate converted the exo-olefin functionality in 22 into an aldehyde moiety. To reconstruct the pyranose ring, acylation at O-1 by using fully O-benzylated gallic acid anhydride30 effectively afforded 23 (SI; SI-13). Finally, hydrogenolysis of the benzyl groups in 23 generated 1.31

However, the 1H and 13C NMR data for 1 were not identical to those reported in the literature.1 Such trends are fre-
In summary, we have effectively accomplished the first total synthesis of phyllanemblinin B (1) in three key steps: (i) ring-opening of a glucopyranose moiety, (ii) preparation of a HHDP group by the oxidative coupling of the two galacto moieties at O-2 and O-4, and (iii) reconstruction of the glucopyranose moiety. The comprehensive evaluation of each step, including the development of an alternative coupling method, confirmation of the axial chirality, and determination of the glucopyranose conformation has advanced the chemistry of the key scaffolds of ellagitannins containing components at O-2 and O-4.

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**Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707812.

**References and Notes**


(27) **Product 16**

[Cu(OH)2(TMEDA)]Cl2 (231 mg, 498 μmol) was added to a solution of 15 (150 mg, 156 μmol) in CH2Cl2 (7.8 mL) at r.t., and the mixture was stirred at r.t. for 1 h. Sat. aq NH4Cl was added and the aqueous mixture was extracted with EtOAc. The organic layers were combined, washed successively with 1 M aq HCl and brine, and dried (MgSO4). The residue was purified by column chromatography [silica gel (14 g), hexane-EtOAc (9:1 to 1:3) to give an amorphous yellow solid; yield: 123 mg (128 μmol, 82%)].

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(126 MHz, CDCl3, 24.5 °C): δ = 169.7 (s, 1 C, HHDP), 166.7 (s, 1 C, HHDP), 159.2 (s, 1 C, PMB), 149.0 (s, 1 C, HHDP), 148.1 (s, 1 C, HHDP), 147.7 (s, 1 C, HHDP), 138.8 (s, 1 C, Bn), 137.7 (s, 1 C, Bn), 136.7 (s, 1 C, Bn), 136.5 (s, 1 C, Bn), 135.7 (s, 1 C, HHDP), 135.1 (s, 1 C, HHDP), 133.2 (d, 1 C, C-2), 131.2 (s, 1 C, HHDP), 130.8 (s, 1 C, PMB), 129.2 (d, 2 C, PMB), 129.1 (d, 1 C, Bn), 129.0 (d, 2 C, Bn), 128.92 (d, 3 C, Bn), 128.90 (d, 3 C, Bn), 128.88 (d, 3 C, Bn), 128.5 (d, 2 C, Bn), 128.4 (s, 1 C, HHDP), 127.9 (d, 2 C, Bn), 127.8 (d, 2 C, Bn), 127.6 (d, 1 C, C-1), 113.8 (d, 2 C, PMB), 112.7 (s, 1 C, HHDP), 111.9 (s, 1 C, HHDP), 110.4 (d, 1 C, HHDP), 106.8 (d, 1 C, HHDP), 76.2 (d, 1 C, C-3), 76.10 (d, 1 C, C-4), 76.05 (d, 1 C, C-6), 75.8 (d, 1 C, C-5), 75.5 (t, 1 C, Bn), 75.4 (t, 1 C, Bn), 73.5 (t, 1 C, Bn), 73.0 (t, 1 C, Bn), 72.2 (t, 1 C, PMB), 71.2 (t, 1 C, C-7), 55.4 (q, 1 C, PMB). HRMS (ESI) m/z [M + Na]+ calcd for C57H52NaO14: 983.3255; found: 983.3274.

(31) Phyllanemblinin B (1)
A mixture of 23 (47.2 mg, 28.9 μmol) and Pd/C (wetted with ~55% H2O, 10 wt% on C: 56.0 mg; 3.08 mg as Pd, 28.9 μmol) in MeOH (1.5 mL) and THF (1.5 mL) was stirred for 2 h at r.t. under H2. The mixture was then filtered through a cotton–Celite pad to remove the catalyst and carbon, and the filtrate was concentrated. The resulting residue was purified by column chromatography [Sephadex LH-20 (3 g), acetone] to afford an amorphous yellow solid; yield: 16.2 mg (25.5 μmol, 88%); [α]D25 −32 (c 0.95, MeOH).
IR (ATR): 3331, 2926, 2851, 1688, 1612, 1516, 1445, 1312, 1186, 1024, 872, 752 cm−1. 1H NMR (500 MHz, acetone-d6, 22.3 °C): δ = 7.39 (s, 1 H, HHDP), 7.12 (s, 2 H, G), 6.90 (s, 1 H, HHDP), 6.10 (d, J = 5.9 Hz, 1 H, H-1), 5.33 (ddd, J = 5.9, 1.0, 1.0 Hz, 1 H, H-2), 4.88 (br dd, J = 3.7, 1.0 Hz, 1 H, H-4), 4.39 (br d, J = 3.7 Hz, 1 H, H-3), 4.33 (dd, J = 5.4, 4.5 Hz, 1 H, H-5), 3.93 (dd, J = 11.5, 5.4 Hz, 1 H, H-6), 3.88 (dd, J = 11.5, 4.5 Hz, 1 H, H-6). 13C NMR (126 MHz, acetone-d6, 22.3 °C): δ = 168.4 (s, 1 C, HHDP), 167.9 (s, 1 C, HHDP), 165.0 (s, 1 C, galloyl), 146.1 (s, 2 C, galloyl), 145.6 (s, 1 C, HHDP), 145.0 (s, 1 C, HHDP), 144.8 (s, 1 C, HHDP), 144.7 (s, 1 C, HHDP), 139.9 (s, 1 C, galloyl), 138.8 (s, 1 C, HHDP), 136.4 (s, 1 C, HHDP), 127.1 (s, 1 C, HHDP), 121.5 (s, 1 C, HHDP), 120.5 (s, 1 C, galloyl), 117.2 (s, 1 C, HHDP), 115.6 (s, 1 C, HHDP), 113.1 (d, 1 C, HHDP), 110.1 (d, 2 C, galloyl), 107.9 (d, 1 C, HHDP), 92.9 (d, 1 C, C-1), 81.0 (d, 1 C, C-5), 78.9 (d, 1 C, C-2), 72.7 (d, 1 C, C-4), 66.9 (d, 1 C, C-3), 52.8 (t, 1 C, C-6). HRMS (ESI) m/z [M + H]+ calcd for C37H32O14: 635.2328; found: 635.2328.