


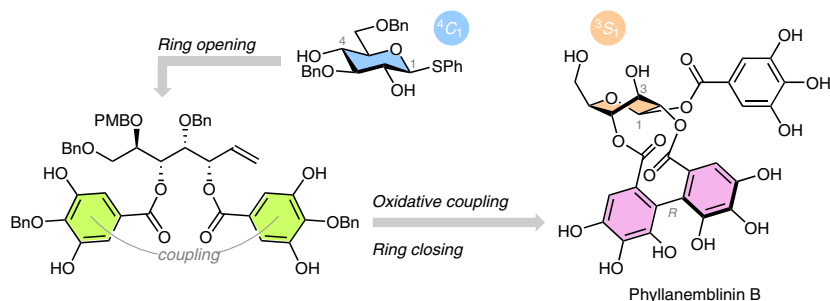
# Total Synthesis of Phyllanemblinin B

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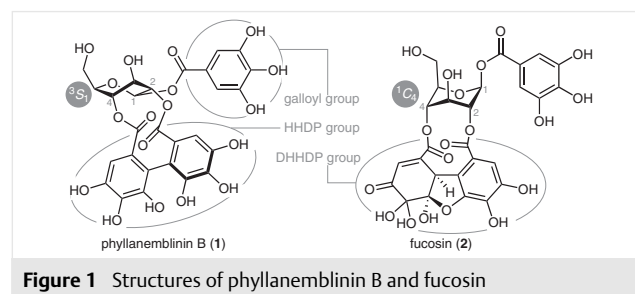
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**Abstract** A total synthesis was developed of phyllanemblinin B, a natural ellagitannin containing 1-*O*-galloyl and 2,4-*O*-hexahydroxydiphenoyl groups on a *D*-glucose scaffold. The use of a  $\mu$ -hydroxo copper(II) complex resulted in a completely 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).<sup>1</sup> The tree's fruits and their juice have been widely used as antiinflammatory and antipyretic agents. The authors reported the <sup>1</sup>H and <sup>13</sup>C NMR spectra of **1**, which showed the presence of a  $\beta$ -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 <sup>1</sup>H NMR spectrum ( $J_{H-1,H-2} = 6.0$  Hz) indicated a skew-boat conformation of the glucopyranose scaffold [also refer to our determination of <sup>3</sup>S<sub>1</sub> 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**) in the presence of palladium on carbon afforded **1** in 14% yield; fucosin (**2**) contains a dehydrohexahydroxydiphenoyl (DHHP) group instead of the HHDP group between O-2 and O-4 (Figure 1, right). Although **1** and **2** both contain a similar

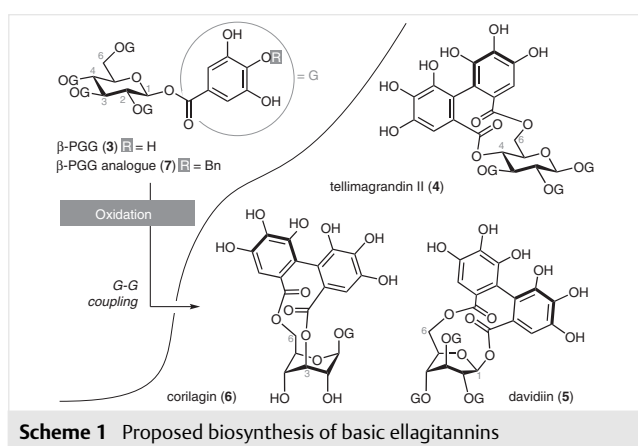
11-membered ring, the slight difference in the number of sp<sup>3</sup> carbon atoms in the ring (three for **1** versus four for **2**) affects the shapes of these structures.



**Figure 1** Structures of phyllanemblinin B and fucosin

The 2,4-*O*-HHDP bridge is an unusual motif for a natural ellagitannin. In relation to the biosynthesis of ellagitannins, Schmidt, Haslam, and co-workers proposed the oxidation of the 1,2,3,4,6-penta-*O*-galloyl- $\beta$ -*D*-glucopyranose ( $\beta$ -PGG; **3**), which results in the formation of the HHDP group and the generation of basic ellagitannins (Scheme 1).<sup>3–5</sup> 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 davidiin (**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**.<sup>6,7</sup> An enzyme extracted from *Telima grandiflora* leaves

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.<sup>8</sup> 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 DHHDP group at O-2 and O-4 have been isolated [e.g. fucosin (**2**)].

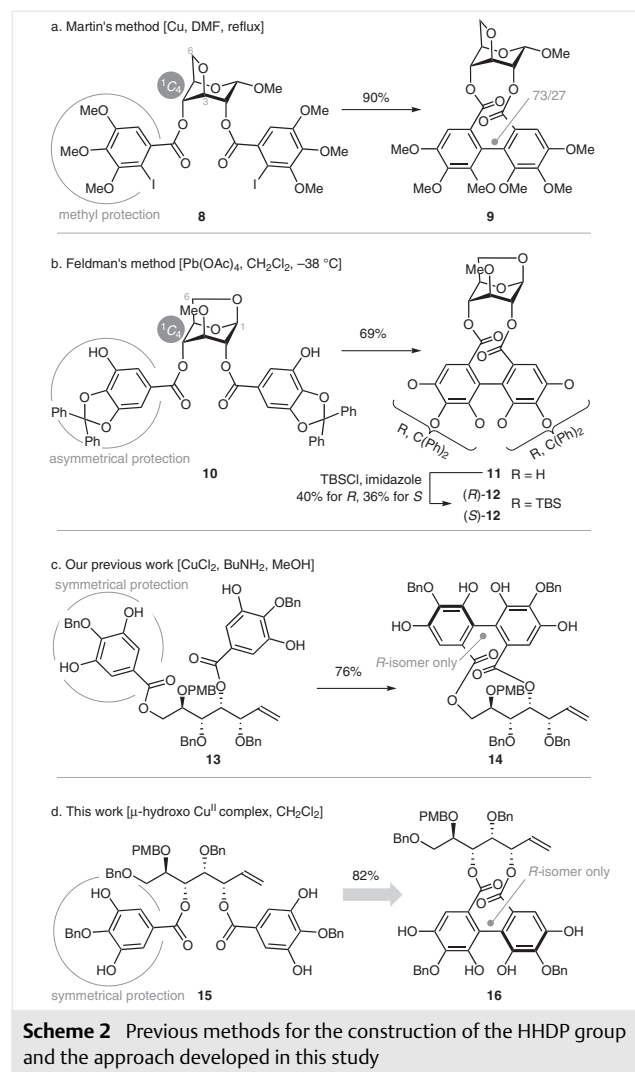


Previously, the Martin and Feldman groups have both reported studies on the construction of the 2,4-*O*-HHDP group. Although there are a number of reports concerning the chemical syntheses of natural ellagitannins containing 1,6-,<sup>9</sup> 2,3-,<sup>10–13</sup> 3,4-,<sup>14,15</sup> 3,6-,<sup>16,17</sup> or 4,6-*O*-HHDP groups<sup>10,13,18–22</sup> 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).<sup>10</sup> With the 3,6-anhydro glucose derivative **8** as a substrate containing two iodobenzoyl functionalities at O-2 and O-4, the coupling reaction resulted in the construction of a fully *O*-methylated HHDP group, providing **9** in 90% yield as a 73:27 mixture of diastereomers. The axial chirality was not determined in the study. The authors speculated that the conformational flexibility around the C–O–C(O) bonds of the ester linkage in **8** controlled the stereoselectivity of the coupling reaction. Although this approach is an effective method for the construction of the 2,4-*O*-HHDP group, per-*O*-methyl ethers are not considered to be useful moieties in natural-product synthesis.<sup>23</sup>

Five years later, Feldman and co-workers investigated the stability and reactivity of the 2,4-*O*-HHDP group (Scheme 2b).<sup>24</sup> The lead(IV) acetate-mediated conversion<sup>23</sup> of the partially protected galloyl groups of **10** led to the for-

mation 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).<sup>17</sup> In the study, the oxidation of **13** by a com-



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*-HHDP group for phyllanemblinin B (**1**), the oxidation of **15** by using a  $\mu$ -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*-HHDP 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*-HHDP bridge on the open-chain glucose derivative was constructed from a known compound **17**<sup>25</sup> (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,<sup>17</sup> 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  $\mu$ -hydroxo copper(II) complex [Cu(OH)(TMEDA)]<sub>2</sub>Cl<sub>2</sub>, previously reported by Koga and co-workers,<sup>26</sup> was effective in generating **16**.

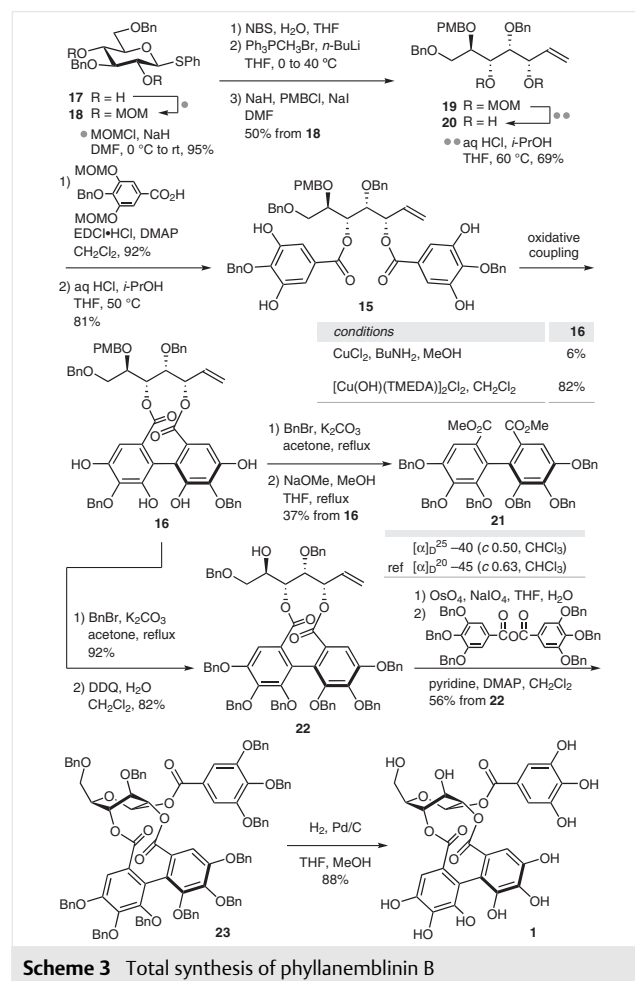
For the intramolecular oxidative coupling of the galloyl motifs, a  $\mu$ -hydroxo copper(II) complex was used to construct the HHDP group. Initially, we used the reaction conditions previously reported by our group. Combining copper(II) chloride and butylamine in methanol<sup>17</sup> gave **16** in 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)]<sub>2</sub>Cl<sub>2</sub> in dichloromethane resulted in a considerable improvement in the yield of **16** to 82%.<sup>27</sup> 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  $\mu$ -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 data<sup>28,29</sup> 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 anhydride<sup>30</sup> effectively afforded **23** (SI; SI-13). Finally, hydrogenolysis of the benzyl groups in **23** generated **1**.<sup>31</sup>

However, the <sup>1</sup>H and <sup>13</sup>C NMR data for **1** were not identical to those reported in the literature.<sup>1</sup> Such trends are fre-



quently observed for ellagitannins because their NMR chemical shifts are sensitive to the measurement conditions, and often vary depending on the temperature, concentration, and the amount of water contamination. Therefore, to match the measurement conditions, the NMR spectra of the synthesized product **1** were directly compared with those of **1** obtained from natural fucosin (**2**) measured by using the same NMR instrument under identical conditions (SI; SI-01). The established data were identical. We therefore concluded that we had achieved the first total synthesis of **1**. As a result, it is noteworthy that our synthesis starting from **16** chemically confirmed the axial chirality of **1** as *R*. Furthermore, our method for determining the pyranose conformation<sup>32</sup> established that glucopyranose ring of both **23** and **1** containing 2,4-*O*-HHDP groups exhibited an <sup>3</sup>S<sub>1</sub> conformation (SI; SI-02 and SI-03).

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 galate 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

- Zhang, Y. J.; Abe, T.; Tanaka, T.; Yang, C. R.; Kouno, I. *J. Nat. Prod.* **2001**, *64*, 1527.
- Haddock, E. A.; Gupta, E. R. K.; Haslam, E. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2535.
- Schmidt, O. T.; Mayer, W. *Angew. Chem.* **1956**, *68*, 103.
- Haslam, E. In *Plant Polyphenols: Synthesis, Properties, Significance*; Hemingway, R. W.; Laks, P. E., Ed.; Springer US: Boston, **1992**, 169.
- Haslam, E. In *Plant Polyphenols 2: Chemistry, Biology, Pharmacology, Ecology*; Gross G. G., Hemingway R. W., Yoshida T., Branham S. J., Ed.; Springer US: Boston, MA, **1999**.
- Niemetz, R.; Schilling, G.; Gross, G. G. *Chem. Commun.* **2001**, 35.
- Niemetz, R.; Gross, G. G. *Phytochemistry* **2003**, *62*, 301.
- Ashibe, S.; Ikeuchi, K.; Kume, Y.; Wakamori, S.; Ueno, Y.; Iwashita, T.; Yamada, H. *Angew. Chem. Int. Ed.* **2017**, *56*, 15402.
- Kasai, Y.; Michihata, N.; Nishimura, H.; Hirokane, T.; Yamada, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 8026.
- Dai, D.; Martin, O. R. *J. Org. Chem.* **1998**, *63*, 7628.
- Su, X.; Surry, D. S.; Spandl, R. J.; Spring, D. R. *Org. Lett.* **2008**, *10*, 2593.
- Richieu, A.; Peixoto, P. A.; Pouységu, L.; Deffieux, D.; Quideau, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 13833.
- Takeuchi, H.; Ueda, Y.; Furuta, T.; Kawabata, T. *Chem. Pharm. Bull.* **2017**, *65*, 25.
- Yamada, H.; Ohara, K.; Ogura, T. *Eur. J. Org. Chem.* **2013**, 7872.
- Shibayama, H.; Ueda, Y.; Kawabata, T. *Chem. Lett.* **2020**, *49*, 182.
- Ikeda, Y.; Nagao, K.; Tanigakiuchi, K.; Tokumaru, G.; Tsuchiya, H.; Yamada, H. *Tetrahedron Lett.* **2004**, *45*, 487.
- Yamada, H.; Nagao, K.; Dokei, K.; Kasai, Y.; Michihata, N. *J. Am. Chem. Soc.* **2008**, *130*, 7566.
- Feldman, K. S.; Ensel, S. M.; Minard, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 1742.
- Feldman, K. S.; Lawlor, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7396.
- Zheng, S.; Laraia, L.; O'Connor, C. J.; Sorrell, D.; Tan, Y. S.; Xu, Z.; Venkataraman, A. R.; Wu, W.; Spring, D. R. *Org. Biomol. Chem.* **2012**, *10*, 2590.
- Michihata, N.; Kaneko, Y.; Kasai, Y.; Tanigawa, K.; Hirokane, T.; Higasa, S.; Yamada, H. *J. Org. Chem.* **2013**, *78*, 4319.
- Takeuchi, H.; Mishiro, K.; Ueda, Y.; Fujimori, Y.; Furuta, T.; Kawabata, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 6177.
- Feldman, K. S.; Ensel, S. M. *J. Am. Chem. Soc.* **1994**, *116*, 3357.
- Feldman, L. S.; Iyer, M. R.; Liu, Y. *J. Org. Chem.* **2003**, *68*, 7433.
- Bourdreux, Y.; Lemétais, A.; Urban, D.; Beau, J.-M. *Chem. Commun.* **2011**, 47, 2146.
- Noji, M.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1994**, *35*, 7983.
- Product 16**  
[Cu(OH)(TMEDA)]<sub>2</sub>Cl<sub>2</sub> (231 mg, 498 μmol) was added to a solution of **15** (150 mg, 156 μmol) in CH<sub>2</sub>Cl<sub>2</sub> (7.8 mL) at r.t., and the mixture was stirred at r.t. for 1 h. Sat. aq NH<sub>4</sub>Cl 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 (MgSO<sub>4</sub>). 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%); [α]<sub>D</sub><sup>24</sup> +26 (c 0.61, CHCl<sub>3</sub>). IR (ATR): 3406, 3030, 2936, 2874, 1717, 1599, 1514, 1454, 1346, 1215, 1175, 1053, 986, 750, 696 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 24.6 °C): δ = 7.40–7.33 (m, 10 H, Bn), 7.32–7.22 (m, 10 H, Bn), 7.18–7.14 (m, 2 H, PMB), 6.82–6.79 (m, 2 H, PMB), 6.77 (s, 1 H, HHDP), 6.73 (s, 1 H, HHDP), 5.75 (ddd, *J* = 17.2, 10.3, 8.3 Hz, 1 H, H-2), 5.50 (dddd, *J* = 8.3, 6.5, 0.9, 0.9 Hz, 1 H, H-3), 5.24 (dd, *J* = 8.6, 4.3 Hz, 1 H, H-5), 5.18 (d, *J* = 11.4 Hz, 1 H, Bn), 5.152 (d, *J* = 11.4 Hz, 1 H, Bn), 5.147 (ddd, *J* = 17.2, 0.9, 0.9 Hz, 1 H, H-1), 5.11 (d, *J* = 11.4 Hz, 1 H, Bn), 5.09 (d, *J* = 11.4 Hz, 1 H, Bn), 5.08 (ddd, *J* = 10.3, 0.9, 0.9 Hz, 1 H, H-1), 4.75 (d, *J* = 11.0 Hz, 1 H, PMB), 4.58 (d, *J* = 11.0 Hz, 1 H, PMB), 4.52 (d, *J* = 12.0 Hz, 1 H, Bn), 4.47 (d, *J* = 12.0 Hz, 1 H, Bn), 4.42 (d, *J* = 11.0 Hz, 1 H, Bn), 4.32 (d, *J* = 11.0 Hz, 1 H, Bn), 4.24 (dd, *J* = 6.5, 4.3 Hz, 1 H, H-4), 4.20 (ddd, *J* = 8.6, 6.4, 2.4 Hz, 1 H, H-6), 3.85 (dd, *J* = 10.7, 2.4 Hz, 1 H, H-7), 3.77 (s, 3 H, PMB), 3.69 (dd, *J* = 10.7, 6.4 Hz, 1 H, H-7). <sup>13</sup>C NMR

(126 MHz, CDCl<sub>3</sub>, 24.5 °C):  $\delta$  = 169.7 (s, 1 C, HHDP), 166.7 (s, 1 C, HHDP), 159.2 (s, 1 C, PMB), 149.4 (s, 1 C, HHDP), 149.0 (s, 1 C, HHDP), 148.1 (s, 1 C, HHDP), 147.7 (s, 1 C, HHDP), 138.5 (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, 3 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, Bn), 120.9 (t, 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]<sup>+</sup> calcd for C<sub>57</sub>H<sub>52</sub>NaO<sub>14</sub>: 983.3255; found: 983.3274.

- (28) Kashiwada, Y.; Huang, L.; Ballas, L. M.; Jiang, J. B.; Janzen, W. P.; Lee, K.-H. *J. Med. Chem.* **1994**, *37*, 195.
- (29) Asakura, N.; Fujimoto, S.; Michihata, N.; Nishii, K.; Imagawa, H.; Yamada, H. *J. Org. Chem.* **2011**, *76*, 9711.
- (30) Armitage, R.; Bayliss, G. S.; Gramshaw, J. W.; Haslam, E.; Haworth, R. D.; Jones, K.; Rogers, H. J.; Searle, T. *J. Chem. Soc.* **1961**, 1842.
- (31) **Phyllanemblinin B (1)**  
A mixture of **23** (47.2 mg, 28.9  $\mu$ mol) and Pd/C (wetted with ~55% H<sub>2</sub>O, 10 wt% on C: 56.0 mg; 3.08 mg as Pd, 28.9  $\mu$ mol) in MeOH (1.5 mL) and THF (1.5 mL) was stirred for 2 h at r.t. under

H<sub>2</sub>. 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  $\mu$ mol, 88%);  $[\alpha]_D^{25}$  –32 (c 0.95, MeOH).

IR (ATR): 3331, 2926, 2851, 1688, 1612, 1516, 1445, 1312, 1186, 1024, 872, 752 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, acetone-*d*<sub>6</sub>, 22.3 °C):  $\delta$  = 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). <sup>13</sup>C NMR (126 MHz, acetone-*d*<sub>6</sub>, 22.3 °C):  $\delta$  = 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), 139.5 (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), 62.8 (t, 1 C, C-6). HRMS (ESI)  $m/z$  [M – H]<sup>-</sup> calcd for C<sub>27</sub>H<sub>21</sub>O<sub>18</sub>: 633.0728; found: 633.0708.

- (32) Ikuta, D.; Hirata, Y.; Wakamori, S.; Shimada, H.; Tomabechei, Y.; Kawasaki, Y.; Ikeuchi, K.; Hagimori, T.; Matsumoto, S.; Yamada, H. *Science* **2019**, *364*, 674.