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The first construction of a 3,6-bridged ellagitannin skeleton with $^1C_4$/B glucose core; synthesis of nonamethylcorilagin

Yasunori Ikeda, Kohei Nagao, Koki Tanigakiuchi, Go Tokumaru, Hitoshi Tsuchiya and Hidetoshi Yamada*

School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda 669-1337, Japan

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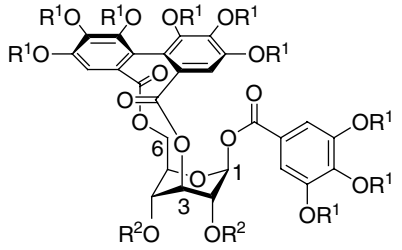
Abstract—The synthesis of nonamethylcorilagin is described. In the synthesis, the intramolecular Ullmann coupling afforded the (*R*)-hexahydroxydiphenoyl part—a characteristic bridge structure of the target molecule—when the glucopyranose ring was opened in advance. This synthesis demonstrates the first synthetic approach to a 3,6-bridged ellagitannin skeleton whose conformation of the D-glucose core is $^1C_4$ or skew boat.

Ellagitannins—a family of the polyphenolic plant metabolites—have hexahydroxydiphenoyl (HHDP)[1] and/or analogous group(s) esterified to the hydroxyl groups of a glucose core.[2] Among the ellagitannins, there is a subclass of compounds whose HHDP group bridges the nonadjacent hydroxyl groups in the glucose core, and thus the conformation of the pyranose ring is bound to be in the $^1C_4$ or skew boat form ($^1C_4$/B).[3] The interests in such compounds have recently grown, because of their wide range of activities. For example, corilagin (**1**) (Fig. 1)—one of the most classic and simplest 3,6-bridged ellagitannins[4]—shows potentiation of β-lactam antibiotics against MRSA,[5] antifungal,[3b] antimicroviral,[6] and antiviral activities,[7] antihypertensive effect in rats,[8] and a cancer preventive effect.[9]

Total syntheses of the 3,6-bridged ellagitannins have not been accomplished despite the fact that more than a dozen ellagitannins have been synthesized after the pioneering synthesis of a 4,6-HHDP-containing ellagitannin, tellimagrandin I, by Feldman and co-workers.[10] Even the HHDP bridge over the northern hemisphere of the $^1C_4$/B glucose core has not been synthesized.[11] This communication reports the first synthetic approach to the 3,6-bridged HHDP group through the synthesis of nonamethylcorilagin (**2**).



1: $R^1 = R^2 = H$
2: $R^1 = CH_3$, $R^2 = H$

Figure 1. Structure of corilagin (**1**) and nonamethylcorilagin (**2**).

As our preliminary attempts, construction of the 3,6-HHDP bridge was investigated by the intramolecular Ullmann coupling of **3** (Fig. 2) according to Dai and Martin's report.[11a] However, the coupling was ineffective in producing the corresponding annulated product. Intermolecular diesterification of **4** with **5** was also ineffective. These direct formations of the 3,6-HHDP bridge require a ring flip of the pyranose into the axial-rich chair or skew boat. This would be the main reason for these failures.

Preparation of the (*R*)-HHDP-3,6-bridge has been realized using the following sequence: opening of a

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* Corresponding author. Tel.: +81-79-565-8342; fax: +81-79-565-9077; e-mail: hidetosh@kwansei.ac.jp

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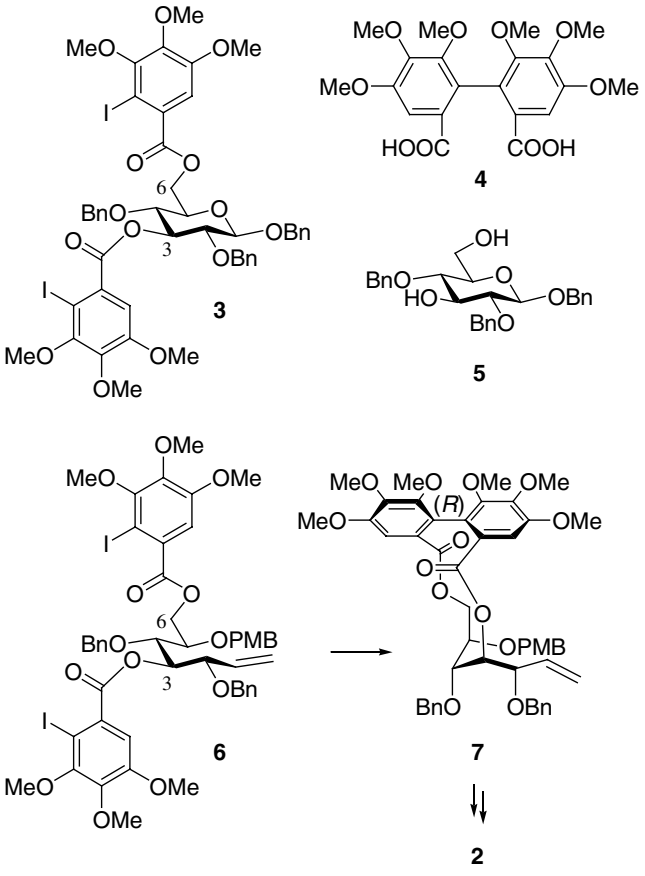
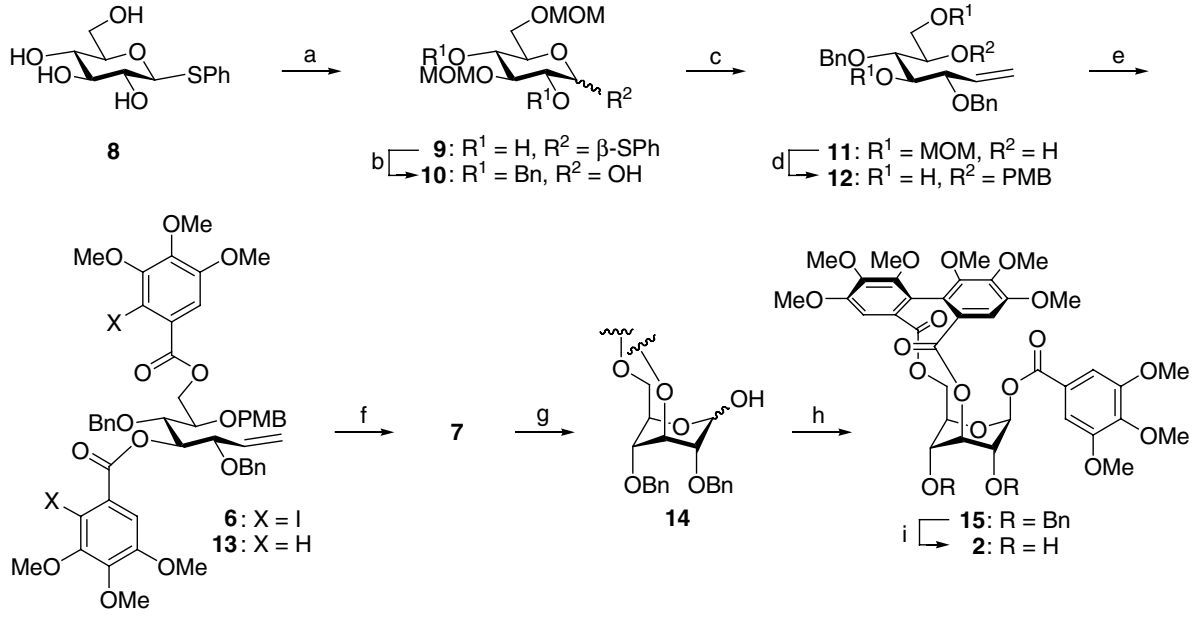


Figure 2.

pyranose ring, stereoselective intramolecular Ullmann coupling of **6**, then reproduction of the pyranose ring from **7**. Adopting this 'indirect' approach, synthesis of **2** was achieved.

The synthesis of **2** started from phenyl 1-thio-β-D-glucopyranoside (**8**) (Scheme 1).[12] Treatment of **8** with methoxymethyl (MOM) chloride discriminated the 2,4- and 3,6-positions to protect the 3,6-hydroxyl groups and selectively give **9** in 64% yield.[13] Dibenzylation of the unprotected 2,4-positions of **9** followed by hydrolysis of the phenylthio group furnished a glucopyranose **10**. Wittig olefination of **10** opened the pyranose ring to obtain **11**, which was introduced to a diol **12** by way of *p*-methoxybenzyl (PMB) protection and cleavage of the MOM groups. Installations of the two 2-iodo-3,4,5-trimethoxybenzoyl esters to the resulting diol furnished the precursor of the Ullmann coupling, **6**.[11a] The slow addition of **6** in DMF to refluxing DMF containing pretreated Cu-dust afforded the desired intramolecular annulated compound **7** as the sole diastereomer along with the reduced **13**. The yield of **7** was 48% when the final concentration of the products was 3 mM. An increase in the concentration decreased the yield. The biaryl asymmetry was not clear at this stage. Successive oxidative treatments of **7** deprotected the PMB group and cleaved the double bond to reproduce the glucopyranose ring in **14** whose conformation was $^{1}C_{4}$/B that has more axial substituents. Introduction of the trimethylgalloyl ester to the anomeric hydroxyl group gave a 4:6 mixture of the corresponding α- and β-isomers. Debenzylation of the separated β-isomer **15** furnished nonamethylcorilagin (**2**). All the spectral data (^{1}H and ^{13}C NMR, IR, MS, and optical rotation) of synthetic **2** were in agreement with those obtained from the



Scheme 1. Reagents and conditions: (a) MOMCl, *i*-Pr_2NEt, DMF, 0 °C to rt, 1 day, 64%; (b) (1) NaH, 0 °C, 30 min, then BnBr, DMF, 0 °C to rt, 2.5 h, (2) NBS, THF/H_2O (7:1), 0 °C, 20 min, 69% (two steps); (c) $Ph_3P{=}CH_2$, THF, −50 °C to rt, overnight, 82%; (d) (1) NaH, rt, 1 h, then PMBCl, DMF, rt, 7 h, (2) HCl, *i*-PrOH, 60 °C, 3 h, 65% (two steps); (e) 2-iodo-3,4,5-trimethoxybenzoic acid, EDCl (WSC), DMAP, CH_2Cl_2, rt, 10 h, 94%; (f) Cu-dust, DMF, reflux, 22 h, 48%; (g) (1) DDQ, CH_2Cl_2/H_2O (10:1), rt, 1 h, 85%, (2) cat OsO_4, $NaIO_4$, THF/H_2O (1:1), rt, 6 h, 70%; (h) 3,4,5-trimethoxybenzoyl chloride, Et_3N, CH_2Cl_2, rt, 15 h, 93% (α/β = 4:6); (i) 20% $Pd(OH)_2$ on C, H_2, THF, 4 h, 92%.

methylated natural product,[14,15] and this revealed the (*R*)-configuration of the biaryl moiety in the synthetic compound. Cleavage of the methyl ethers of **2** under several reaction conditions was pointless because the cleavage of the anomeric ester competed against the demethylations.[16]

In conclusion, nonamethylcorilagin was synthesized, which contains a 3,6-bridged HHDP group with a $^1C_4$/B glucose core, one of the common structures in the ellagitannin family. The construction of the 3,6-bridged biaryl moiety required pre-opening of the pyranose ring. The Ullmann coupling took place in a highly stereoselective manner to give the (*R*)-HHDP moiety.

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References and Notes

1. Hexahydroxydiphenoyl group is a trivial name of 6,6′-dicarbonyl-2,2′,3,3′,4,4′-hexahydroxydiphenoyl group.
2. Okuda, T.; Yoshida, T.; Hatano, T. Hydrolyzable Tannins and Related Polyphenols. In *Progress in the Chemistry of Organic Natural Products*, Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, Ch. Eds.; Springer: Wein, 1995; Vol. 66; pp 1–117.
3. (a) Jochims, J. C.; Taigel, G.; Schmidt, O. T. *Justus Liebigs Ann. Chem.* **1968**, *717*, 169–185; (b) Latté, K. P.; Kolodziej, H. *Phytochemistry* **2000**, *54*, 701–708; (c) Gaudreaut, R.; Van, D. V.; Theo, G. M.; Whitehead, M. A. *J. Mol. Model.* **2002**, *8*, 73–80.
4. (a) Schmidt, O. T.; Lademann, R. *Justus Liebigs Ann. Chem.* **1951**, *571*, 232–237; (b) Schmidt, O. T.; Schmidt, D. M.; Herok, J. *Justus Liebigs Ann. Chem.* **1954**, *587*, 67–74; (c) Okuda, T.; Yoshida, T.; Hatano, T. *Tetrahedron Lett.* **1980**, *21*, 2561–2564.
5. Shimizu, M.; Shiota, S.; Mizushima, T.; Ito, H.; Hatano, T.; Yoshida, T.; Tsuchiya, T. *Antimicrob. Agents Chemother.* **2001**, 3198–3201.
6. (a) Burapadaja, S.; Bunchoo, A. *Planta Med.* **1995**, *61*, 365–366; (b) Adesina, S. K.; Idowu, O.; Ogundaini, A. O.; Oladimeji, H.; Olugbade, T. A.; Onawunmi, G. O.; Pais, M. *Phytother. Res.* **2000**, *14*, 371–374.
7. (a) Liu, K. C.; Lin, M.; Lee, S.; Chiou, J.; Ren, S.; Lien, E. J. *Planta Med.* **1999**, *65*, 43–46; (b) Lim, Y. A.; Mei, M. C.; Kusumoto, I. T.; Miyashiro, H.; Hattori, M.; Gupta, M. P.; Correa, M. *Phytother. Res.* **1997**, *11*, 22–27.
8. (a) Cheng, J.; Lin, T.; Hsu, F. *Can. J. Physiol. Pharmacol.* **1995**, *73*, 1425–1429; (b) Lin, T. C.; Hsu, F. L.; Cheng, J. T. *J. Nat. Prod.* **1993**, *56*, 629–632.
9. Okabe, S.; Suganuma, M.; Imayoshi, Y.; Taniguchi, S.; Yoshida, T.; Fujiki, H. *Biol. Pharm. Bull.* **2001**, *24*, 1145–1148.
10. (a) Feldman, K. S.; Ensel, S. M.; Minard, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 1742–1745; (b) Quideau, S.; Feldman, K. S. *Chem. Rev.* **1996**, *96*, 475–503; (c) Khanbabaee, K.; van Ree, T. *Synthesis* **2001**, 1585–1610.
11. Formations of 2,4-HHDP bridge have been reported starting from substrates whose ring conformation are prefixed with the 1,6- or 3,6-ethereal bridge structures. (a) Dai, D.; Martin, O. R. *J. Org. Chem.* **1998**, *63*, 7628–7633; (b) Feldman, K. S.; Iyer, M. R.; Liu, Y. *J. Org. Chem.* **2003**, *68*, 7433–7438.
12. Motawia, M. S.; Olsen, C. E.; Enevoldsen, K.; Marcussen, J.; Møller, B. L. *Carbohydr. Res.* **1995**, *277*, 109–123.
13. Although we reported the similar 3,6-selective protection of **8** with bulky silyl protecting groups, the following benzylation of the 2,4-hydroxyl groups was difficult due to the bulkiness of the protections. Ikeda, Y.; Furukawa, K.; Yamada, H. *Carbohydr. Res.* **2002**, *337*, 1499–1501.
14. (a) Yoshida, T.; Okuda, T. *Heterocycles* **1980**, *14*, 1743–1749; (b) Tanaka, T.; Nonaka, G.; Nishioka, I. *Phytochemistry* **1985**, *24*, 2075–2078; (c) Saijo, R.; Nonaka, G.; Nishioka, I. *Chem. Pharm. Bull.* **1989**, *37*, 2624–2630.
15. As a supplement for the partial lack of detailed spectral data in the literature, the following data should be listed. $[\alpha]_D^{22}$ −154.7° (*c* 0.10, $CHCl_3$), lit.[14c] $[\alpha]_D^{22}$ −166.9° (*c* 0.8, $CHCl_3$); IR (ZnSe) 3441, 2944, 2847, 1744, 1709, 1591, 1462, 1338, 1209, 1167, 1121, 1101 cm^{-1}; ^1H NMR (400 MHz in acetone-d_6) δ 7.23 (2H, s), 6.92 (1H, s), 6.88 (1H, s), 6.46 (1H, dd, $J = 1.0$, 1.0 Hz, H-1), 5.24 (1H, d, $J = 6.9$ Hz, 4-OH), 5.23 (1H, d, $J = 8.6$ Hz, 2-OH), 5.08 (1H, dd, $J = 11.6$, 10.4 Hz, H-6), 4.87 (1H, dddd, $J = 3.4$, 2.5, 1.0, 1.0, H-3), 4.62 (1H, dddd, $J = 11.6$, 7.8, 1.1, 1.0 Hz, H-5), 4.54 (1H, dddd, $J = 6.9$, 3.4, 1.4, 1.1 Hz, H-4), 4.33 (1H, dd, $J = 10.4$, 7.8 Hz, H-6), 4.18 (1H, dddd, $J = 8.6$, 2.5, 1.4, 1.0 Hz, H-2), 3.91 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.67 (2×3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.20 (3H, s, OCH_3); ^{13}C NMR (100 MHz in acetone-d_6) δ 168.4 (C), 166.7 (C), 165.1 (C), 154.4 (2×C), 154.3 (C), 153.6 (C), 153.4 (C), 153.3 (C), 145.8 (C), 144.9 (C), 144.0 (C), 129.9 (C), 128.1 (C), 125.0 (C), 124.6 (C), 123.0 (C), 108.8 (CH), 107.8 (2×CH), 106.0 (CH), 96.7 (CH), 75.1 (CH), 69.5 (CH), 67.6 (CH), 64.7 (CH_2), 61.7 (CH), 61.0 (CH_3), 60.9 (CH_3), 60.7 (CH_3), 60.6 (CH_3), 56.9 (2×CH_3), 56.5 (CH_3), 55.6 (2×CH_3); HRMS (ESI) *m*/*z* calcd for $C_{36}H_{40}O_{18}$ (M^++Na) 783.2112, found 783.2124.
16. Khanbabaee, K.; Lötzerich, K. *Tetrahedron* **1997**, *53*, 10725–10732.