Synthesis of All-Methylated Isorugosin B

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All-methylated isorugosin B was synthesized *via* two-step esterification between optically active valoneic acid and glucose derivatives.

Key words ellagitannin; palladium; coupling reaction; natural product; glucose derivative

Ellagitannins are a class of polyphenols that are suspected of being useful medically, as they are strong antioxidants[1—3]; however, compared to other polyphenols, few synthetic studies of ellagitannins[4—8] have been conducted because of their chemical instability and structural intricacy. Within the ellagitannin family, compounds that contain valoneoyl groups are frequently found in natural products.[9—13] Despite this, the complete synthesis of an ellagitannin containing a valoneoyl group has not yet been reported.

Recently, we reported the stereoselective synthesis of a valoneic acid derivative, in which Bringmann's "lactone concept"[14—18] was used to form its optically active biphenyl moiety.[19] In this paper, based on our previous work, we report the synthesis of all-methylated isorugosin B (**1**)[20—23] (Fig. 1).

The retrosynthetic analysis of **1** is depicted in Chart 1. Two ester functions would be formed in the final stage of the synthetic scheme, leading to the valoneic acid derivative (**2**) and sugar moiety (**3**).[24] The optically active valoneoyl group **2** would be formed by Bringmann's method[4] which involves the intramolecular biaryl coupling reaction[25] of **4**, followed by enantioselective lactone ring opening. The key intermediate **4** would be derived from the corresponding phenol **5** and carboxylic acid **6**.

Initially, we attempted to prepare the biphenyl ether from the Ullmann condensation reaction[26] between methyl *o*-bromobenzoate **7** and (siloxymethyl)phenol **8**.[27] Because the only compound isolated in the reaction between **7** and **8** was the unexpected aldehyde **9**, accompanied by many by-products, we postulated that the formyl compound **10**[27] could be used in the same reaction. Based on this, the desired ether compound **9** was obtained successfully. The reduction of the formyl group and deprotection of the benzyl group afforded the benzyl alcohol **11** (Chart 2).

Protection of the benzylic hydroxyl group of **11** using the *tert*-butyldimethylsilyl chloride (TBSCl)-imidazole system was effective for preparing the phenol fragment **5**. The simple esterification between **5** and the corresponding benzoic

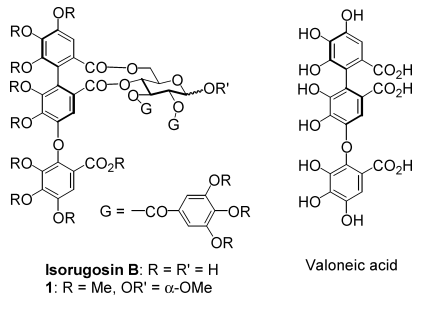

Fig. 1. Structure of Isorugosin B and Its Related Compounds

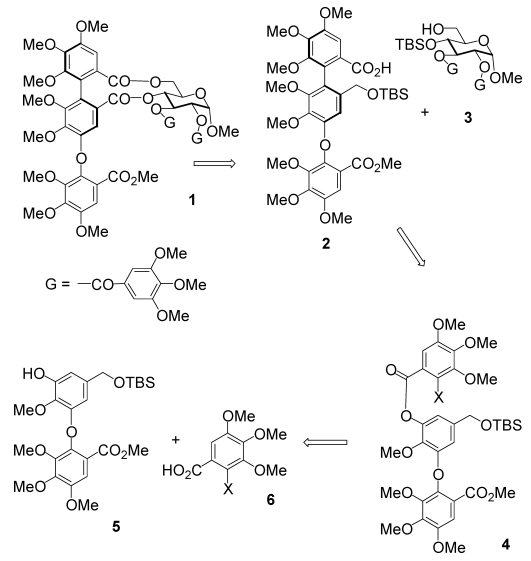

Chart 1. Synthetic Plan for **1**

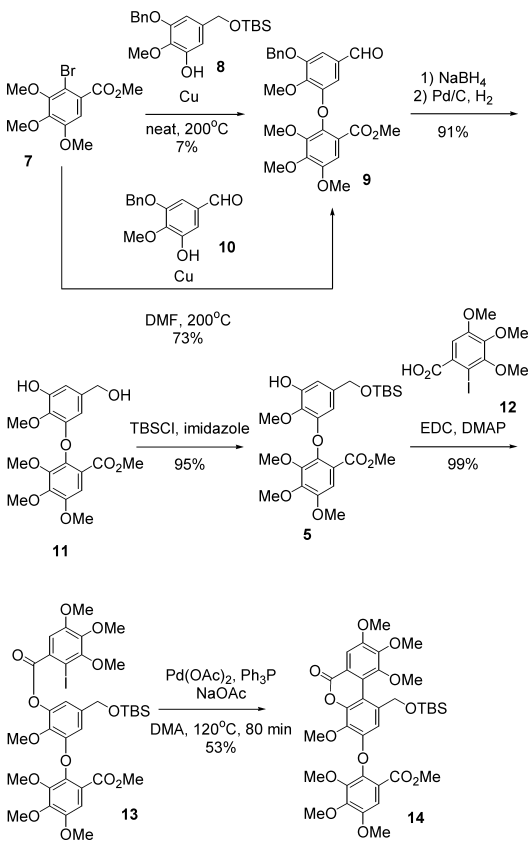

Chart 2. Synthesis of **14**

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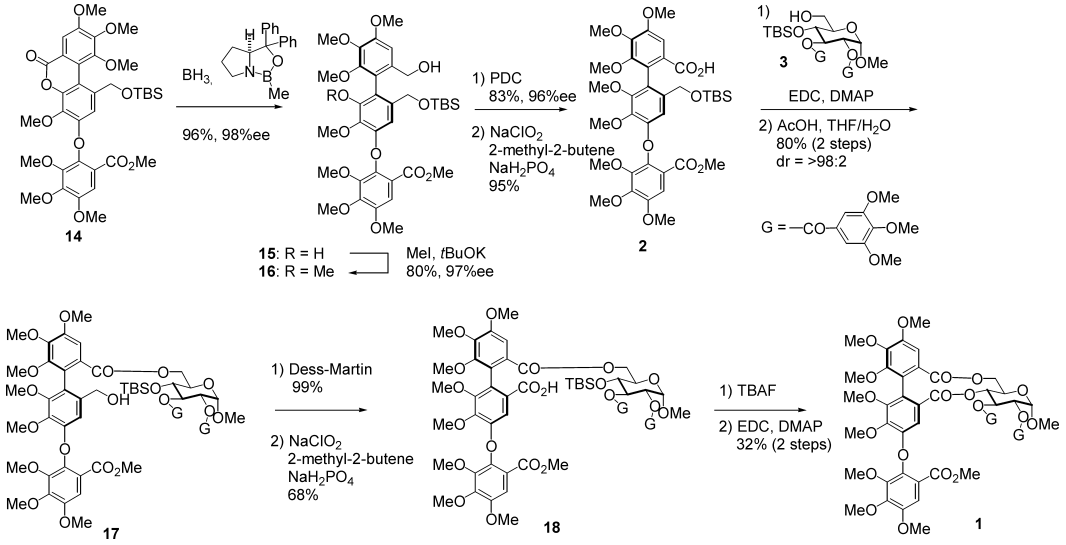

Chart 3. Synthesis of All-Methylated Isorugosin B (**1**)

acid **12** successfully afforded the precursor **13** for the intramolecular biaryl coupling reaction. The reaction of **13** with $Pd(OAc)_2$, Ph_3P, and NaOAc proceeded smoothly, resulting in the lactone compound **14** in moderate yield.

The enantioselective lactone-opening reaction of **14** using Bringmann's method, the borane-CBS reagent system,[28] proceeded efficiently to generate the biphenyl compound **15**[29] in an enantioselective form.[30] The methylation of the resulting phenolic hydroxy group followed by two-step oxidation (pyridinium dichromate (PDC) oxidation and Pinnick oxidation[31]) of the benzylic hydroxy group formed the optically active valoneic acid derivative **2** (Chart 3).[30]

To complete the synthesis of **1**, we needed to form the eleven-membered ring *via* double esterification between **2** and the glucose derivative **3**. The first ester condensation between **2** and **3**, and the selective desilylation of the primary alcohol yielded the desired alcohol **17**. This compound was successively subjected to the usual manipulation involving the two-step oxidation leading to the carboxylic acid **18**. Finally, the silyl group on the sugar moiety was deprotected, and this was followed by the second esterification[32] of the hydroxyl group at the 4-position of the sugar with the carboxylic acid of the valoneoyl group, resulting in the synthesis of **1**.[20,33]

The NMR data of the synthetic **1** were identical with the authentic chart.

In conclusion, we succeeded in the first synthesis of the valoneoyl group-containing ellagitannin derivative **1**. Based on this work, our laboratory is attempting to synthesize natural isorugosin B.

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References and Notes

1) Miyamoto K., Nomura M., Murayama T., Furukawa T., Hatano T., Yoshida T., Koshiura R., Okuda T., *Biol. Pharm. Bull.*, **16**, 379—387 (1993).
2) Aoki K., Nishimura K., Abe H., Maruta H., Sakagami H., Hatano T., Okuda T., Yoshida T., Tsai Y. J., Uchiumi F., Tanuma S., *Biochem. Biophys. Acta*, **1158**, 251—256 (1993).
3) Okuda T., Kimura Y., Yoshida T., Hatano T., Okuda H., Arichi S., *Chem. Pharm. Bull.*, **31**, 1625—1631 (1983).
4) Several total syntheses of simple ellagitannins have been reported: Quideau S., Feldman K. S., *Chem. Rev.*, **96**, 475—503 (1996) and references cited therein.
5) Khanbabaee K., van Ree T., *Synthesis*, **2001**, 1585—1610 (2001).
6) Feldman K. S., *Phytochemistry*, **66**, 1984—2000 (2005).
7) Ikeda Y., Nagao K., Tanigakiuchi K., Tokumaru G., Tsuchiya H., Yamada H., *Tetrahedron Lett.*, **45**, 487—489 (2004).
8) Yamada H., Nagao K., Dokei K., Kasai Y., Michihana N., *J. Am. Chem. Soc.*, **130**, 7566—7567 (2008).
9) Hatano T., Yasuhara T., Matsuda M., Yazaki K., Yoshida T., Okuda T., *Chem. Pharm. Bull.*, **37**, 2269—2271 (1989).
10) Hatano T., Ogawa N., Kira R., Yasuhara T., Okuda T., *Chem. Pharm. Bull.*, **37**, 2083—2090 (1989).
11) Hatano T., Yasuhara T., Matsuda M., Yazaki K., Yoshida T., Okuda T., *J. Chem. Soc., Perkin Trans. 1*, **1990**, 2735—2743 (1990).
12) Yoshida T., Hatano T., Ahmed A. F., Okonogi A., Okuda T., *Tetrahedron*, **47**, 3575—3584 (1991).
13) Santos S. C., Waterman P. G., *Fitoterapia*, **72**, 95—97 (2001).
14) Bringmann G., Breuning M., Tasler S., *Synthesis*, **1999**, 525—558 (1999).
15) Bringmann G., Menche D., *Acc. Chem. Res.*, **34**, 615—624 (2001).
16) Bringmann G., Breuning M., Pfeifer R.-M., Schenk W. A., Kamikawa K., Uemura M., *J. Organomet. Chem.*, **661**, 31—47 (2002).
17) Bringmann G., Tasler S., Pfeifer R. M., Breuning M., *J. Organomet. Chem.*, **661**, 49—65 (2002).
18) Bringmann G., Mortimer A. J. P., Keller P. A., Gresser M. J., Garner J., Breuning M., *Angew. Chem. Int. Ed.*, **44**, 5384—5427 (2005).
19) Abe H., Sahara Y., Matsuzaki Y., Takeuchi Y., Harayama T., *Tetrahedron Lett.*, **49**, 605—609 (2008).
20) Yoshida T., Chou T., Maruyama Y., Okuda T., *Chem. Pharm. Bull.*, **38**, 2681—2686 (1990).
21) Yoshida T., Chou T., Haba K., Okano Y., Shingu T., Miyamoto K., Koshiura R., Okuda T., *Chem. Pharm. Bull.*, **37**, 3174—3176 (1989).
22) Hatano T., Kira R., Yasuhara T., Okuda T., *Heterocycles*, **27**, 2081—2085 (1988).
23) Hatano T., Kira R., Yasuhara T., Okuda T., *Chem. Pharm. Bull.*, **36**, 3920—3927 (1988).
24) Compound **3** was prepared easily from the known compound: Nelson T. D., Meyers A. I., *J. Org. Chem.*, **59**, 2577—2588 (1994).
25) Abe H., Harayama T., *Heterocycles*, **75**, 1305—1320 (2008).
26) For a recent review on Ullmann condensation reaction, see; Ley S. V., Thomas A. W., *Angew. Chem. Int. Ed.*, **42**, 5400—5449 (2003).
27) Compounds **8** and **10** were obtained by two-step transformation from methyl 3-benzyloxy-5-hydroxy-4-methoxybenzoate: Tanaka M., Ikeya Y., Mitsuhashi H., Maruno M., Wakamatsu T., *Tetrahedron*, **51**,

11703—11742 (1995).
28) Cho B. T., *Tetrahedron*, **62**, 7621—7643 (2006).
29) The *S*-configuration was confirmed by comparison of the optical rotation of the known compound which has been synthesized in our labolatory.[19)]
30) The ee was determined by HPLC analysis using Daicel CHIRALPAK AD or CHIRALCEL OD.
31) Bal B. S., Childers W. E. Jr., Pinnick H. W., *Tetrahedron*, **37**, 2091—2096 (1981).
32) The low yield of this step may be due to the low reactivity of the secondary hydroxyl group.
33) The $[\alpha]_D$ value of the synthetic sample did not match the reported value (synthetic $[\alpha]_D$ $+28°$ ($c=1.52$, acetone); reported $[\alpha]_D$ $-7°$ ($c=0.3$, acetone)[20)]). We speculate that this discrepancy was due to impurities in the reported sample, as many unidentified peaks are seen in the authentic NMR data.