Regioselective Catalysis

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Total Synthesis of Ellagitannins through Regioselective Sequential Functionalization of Unprotected Glucose**

*Hironori Takeuchi, Kenji Mishiro, Yoshihiro Ueda, Yusuke Fujimori, Takumi Furuta, and Takeo Kawabata**

Dedicated to Professor Emeritus Kaoru Fuji on the occasion of his 77th birthday (Kiju)

Abstract: *Short total syntheses of natural glycosides (ellagitannins) were performed through sequential and regioselective functionalization of the hydroxy groups of unprotected glucose. The key reactions are β-selective glycosidation of a gallic acid derivative by using unprotected glucose as a glycosyl donor and catalyst-controlled regioselective introduction of a galloyl group into the inherently less reactive hydroxy group of the glucoside.*

Natural glycosides are known to exhibit a wide range of biological activities. Owing to their pharmaceutical potential, considerable efforts have been devoted to their synthesis.[1–4] However, the synthesis of carbohydrates including glycosides is always associated with difficulties in the selective manipulation of multiple hydroxy groups, and has so far been achieved through multistep protection/deprotection procedures. We developed an extremely short total synthesis of ellagitannins by eliminating the use of protective groups for glucose.

Ellagitannins are a large class of plant polyphenols with a wide variety of biological activities, such as antitumor and antiviral activities, and specific polyphenol–protein interactions.[1,2] While ellagitannins have been known for a long time,[5] recent disclosure of the attractive biological activities of this class of natural glycosides has generated increased interest in their chemical synthesis.[1–4] Among the ellagitannins, we chose strictinin (**1**)[6] and tellimagrandin II (**2**, eugeniin)[7] as synthetic targets (Figure 1). These compounds show anti-HSV,[8] antitumor,[9] anti-influenza virus,[10] and antiallergic activities.[11] Their structures basically consist of a central sugar core, typically glucose (D-glucose), to which

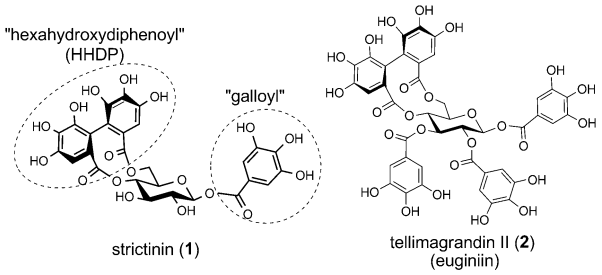
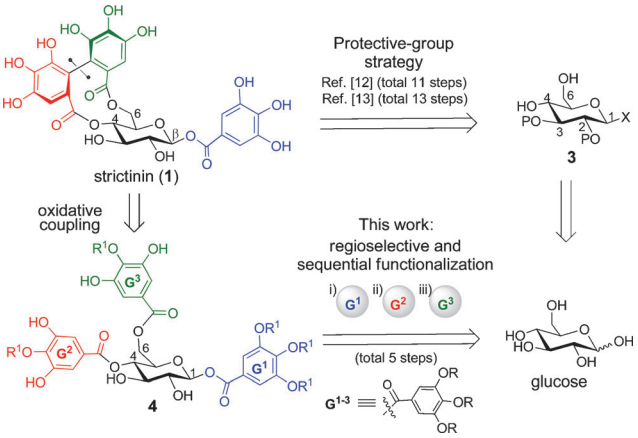


Figure 1. Target ellagitannins.

esterified gallic acid (galloyl) and hexahydroxy diphenoic acid (HHDP) groups are added.

Retrosynthetic analyses for strictinin (**1**) are shown in Scheme 1. A rational retrosynthetic analysis should lead to suitably protected precursor **3**, which possesses free C(4)-OH, C(6)-OH, and C(1)-X (X = activating group for glycosidation), C(2)-OP (P = protective group), and C(3)-OP to enable the introduction of an HHDP group at C(4)-O and C(6)-O of the glucopyranose skeleton. Pioneering studies on the total synthesis of strictinin (**1**) via precursors depicted as **3** have been reported by Khanbabaee and co-workers,[12] as well as by Yamada and co-workers.[13]



Scheme 1. Retrosynthetic analysis for strictinin (**1**). P = protective group. X = activating group for glycosylation.

In contrast to these approaches, we envisaged that strictinin (**1**) could be synthesized in short steps from

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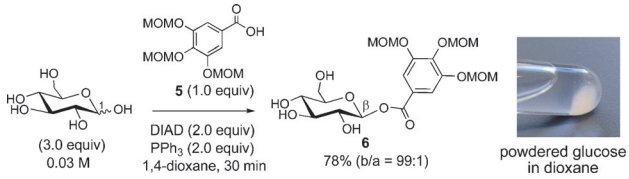
unprotected glucose if galloyl(oxy) groups (G^1, G^2, G^3) could be introduced to unprotected glucose sequentially and in a regioselective manner. Oxidative phenol coupling[13] between the 4- and 6-gallate of **4** was expected to construct the HHDP moiety of **1**. In the sequence toward **4**, three galloyl(oxy) groups were planned to be regioselectively and sequentially introduced to unprotected glucose in the order C(1) (blue galloyloxy group), C(4)-OH (red galloyl group), and C(6)-OH (green galloyl group). After the introduction of the first galloyloxy group at C(1), introduction of the second and third galloyl groups in the order C(4)-OH and then C(6)-OH was expected to be critical to obtain 1,4,6-trigallate **4** because once the second galloyl group was introduced at C(4)-OH, the third one was assumed to be readily introduced at C(6)-OH based on the inherently higher reactivity of the C(6)-OH among the remaining three free hydroxy groups at C(2), C(3), and C(6). On the other hand, if the second galloyl group was introduced at C(6)-OH, the third one was expected to be introduced selectively at C(3)-OH[14] or in a nonselective manner. Total synthesis of tellimagrandin II (**2**) was also planned through the regioselective and sequential introduction of five galloyl(oxy) groups to unprotected glucose. If this strategy could be realized, we should be able to eliminate several steps that would otherwise be required for the introduction and removal of the protective groups for glucose. Thus, the synthetic strategy proposed herein is expected to provide a ground-breaking new route to the synthesis of natural glycosides, considering that the only reliable approach to date for the synthesis of glycosides has included the use of suitably protected intermediates such as **3**.

The first problem is the stereoselective glycosidation of unprotected glucose (Scheme 2). While protected glucose derivatives have generally been used as glycosyl donors for glycosidation,[1–4,15] methods for the glycosidation of an acidic

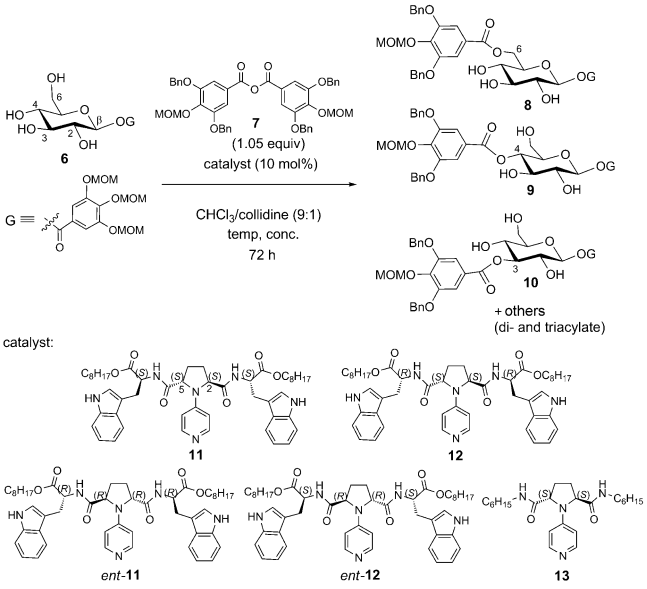


Scheme 2. Direct stereoselective glycosidation.

nucleophile with unprotected glucose have been reported.[16,17] Shoda and co-workers reported the glycosidation of phenol derivatives with unprotected glucose under Mitsunobu conditions.[16] While the reaction took place regioselectively at the anomeric carbon, it gave an α/β (1:3) mixture of the glycosides. Aime and co-workers also reported that an α/β mixture (α/β = 41/59) of glycosides was obtained through the treatment of carboxylic acid with unprotected glucose under Mitsunobu conditions.[17] We examined the glycosidation of gallic acid trimethoxymethyl ether (**5**) with unprotected glucose as a glycosyl donor (Scheme 2). After a thorough screening of the conditions (see the Supporting Information), we obtained highly stereoselective glycosidation. Treatment of a suspension of glucose (0.03 M) and **5** in 1,4-dioxane with diisopropyl azodicarboxylate (DIAD) and PPh_3 at room temperature for 30 min gave the desired product **6** with high stereoselectivity (β/α = 99/1) and in 78% yield. The use of finely ground glucose powder and ultrasonication of the powder suspension in 1,4-dioxane prior to the addition of the Mitsunobu reagents were found to be crucial for the smooth progression of the glycosylation. Although glucose did not dissolve initially in 1,4-dioxane, it did dissolve gradually and the reaction proceeded within 30 min to give **6** in a stereoselective manner.

With β-glycoside **6** in hand, we next investigated the regioselective introduction of a galloyl group to C(4)-OH of **6** (Table 1). We previously developed catalyst **11**, which enabled the highly regioselective acylation of octyl β-D-glucopyr-

Table 1: Optimization of organocatalytic regioselective acylation of **6**.



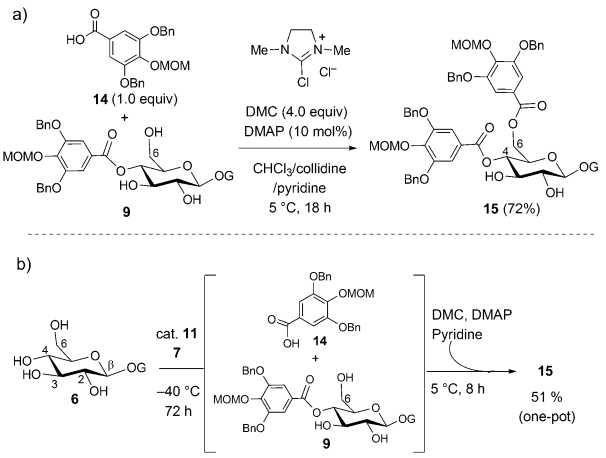
Entry	Catalyst	*T* [°C]	Conc. [M]	Product [%][a]			
				8	**9**	**10**	others
1[b]	**11**	−45	0.03	3	18	6	ca. 0[c]
2[d]	**11**	20	0.02	0	54	21	6
3	**11**	−40	0.02	1	83	4	3
4	**11**	−40	0.04	0	91	6	0
5	*ent*-**11**	−40	0.04	21	3	6	21
6	**12**	−40	0.04	15	35	10	16
7	*ent*-**12**	−40	0.04	11	14	4	16
8	**13**	−40	0.04	11	42	15	15

[a] Yields were determined by ^{1}H NMR with 1,3-dinitrobenzene as an internal standard. [b] Run in $CHCl_3$ in the presence of 1.5 equiv of 2,4,6-collidine. [c] 70% of the starting material was recovered. [d] Run for 24 h.

anose.[18,19] The catalytic regioselective introduction of a galloyl group with electron-withdrawing acetoxy groups to C(4)-OH of octyl β-D-glucopyranose was also achieved.[20] Treatment of **6** with anhydride **7** in the presence of catalyst **11** under the previously optimized conditions,[20] however, gave the desired 1,4-digallate **9** in only 18% yield even after 72 h (entry 1) owing to the low reactivity of anhydride **7** with the electron-donating OBn and OMOM groups. The use of

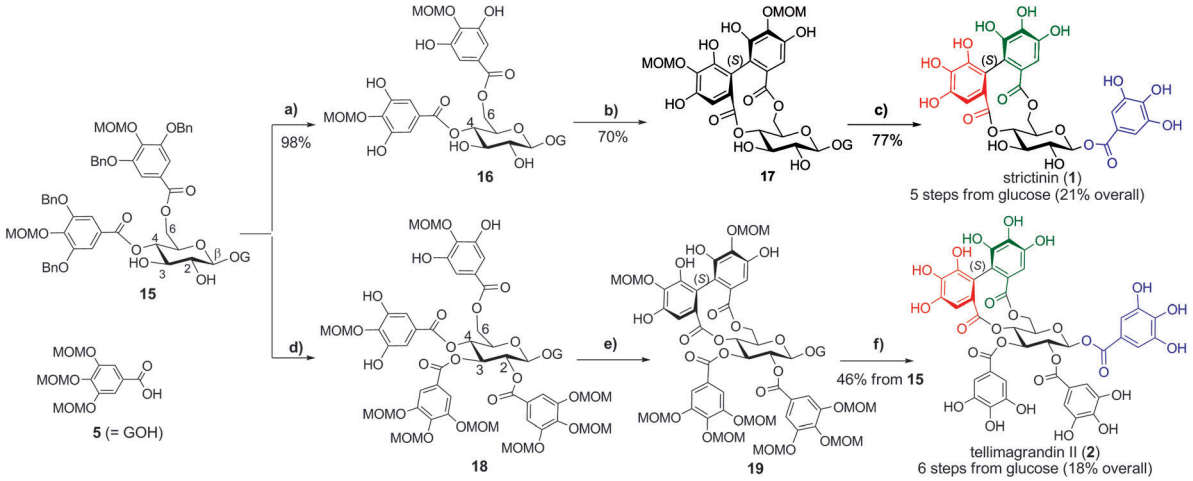
$CHCl_3$/collidine (9:1) instead of $CHCl_3$ as a solvent gave much better results. 1,4-Digallate **9** was obtained as the major product in 54% yield when the reaction was performed at 20°C (entry 2). The corresponding reaction at −40°C gave **9** in 83% yield with much improved regioselectivity (entry 3). The observed strong temperature dependence of the regioselectivity indicates that the $\Delta S^{\ddagger}$ term significantly contributes to the regioselective reaction, thus suggesting that hydrogen-bonding interaction between the catalyst and the substrate may be responsible for the high regioselectivity, as previously proposed for the regioselective acylation of carbohydrates.[18,20,21] The best result was obtained in the reaction at a substrate concentration of 0.04 M, which gave **9** in 91% yield (entry 4). Use of catalysts *ent*-**11** and *ent*-**12** with the (2*R*,5*R*)-pyrrolidine skeleton resulted in unselective reactions (entries 5 and 7). On the other hand, catalysts **12** and **13** with the same (2*S*,5*S*)-pyrrolidine skeleton as catalyst **11** gave **9** as the major regioisomer in moderate yields (entries 6 and 8). These results indicate that the stereochemistry of the pyrrolidine skeleton of the catalysts has the major effects on the regiochemistry of acylation, while the structure and stereochemistry of the amide side chains has only minor effects. Thus, catalyst **11** was found to enable the conventionally difficult molecular transformation with a significant reversal of the innate reactivity of the substrate through fine molecular recognition of the substrate structure.

We next examined the introduction of a galloyl group to the primary C(6)-OH, which seems to be the most reactive hydroxy group among three free hydroxy groups of glycoside **9** (Scheme 3a). The regioselective introduction of a galloyl group to the C(6)-OH of **9** was readily accomplished through treatment with gallic acid derivative **14** and 2-chloro-1,3-dimethylimidazolinium chloride (DMC) to give **15** in 72% yield. Since **14** was expected to be generated in situ from anhydride **7** and catalyst **11**, a one-pot procedure for the sequential introduction of two galloyl groups at C(4)-OH and C(6)-OH of **6** was examined (Scheme 3b). The catalyst-controlled regioselective C(4)-O-galloylation of **6** with **7** in the presence of catalyst **11** followed by substrate-controlled C(6)-O-galloylation with in situ generated **14** took place successfully to give **15** in 51% yield in a one-pot reaction (53 mg of **15** from 40 mg of **6**). This key transformation could be scalable to give 1.07 g of **15** in 50% yield from **6** with sufficient reproducibility.



Scheme 3. a) Substrate-controlled regioselective acylation of C(6)-OH in **9**. b) One-pot regioselective diacylation of **6** through catalyst-controlled regioselective C(4)-*O*-galloylation followed by substrate-controlled C(6)-*O*-galloylation.

The conversion of **15** into strictinin (**1**) is shown in Scheme 4. Removal of the benzyl groups of **15** through hydrogenation proceeded smoothly to give **16** in 98% yield. The oxidative phenol coupling of the resulting phenol derivative **16** was accomplished according to the method developed by Yamada and co-workers.[13] When treating **16** with $CuCl_2$/*n*$BuNH_2$, intramolecular oxidative phenol coupling between the 4- and 6-gallate took place to give the corresponding HHDP derivative **17** with complete control of the newly formed chiral axis (*S*) in the HHDP moiety. Removal of the MOM groups of **17** completed the total



Scheme 4. Total syntheses of strictinin (**1**) and tellimagrandin II (**2**). Reagents and conditions: a) H_2, $Pd(OH)_2$/C, THF, RT; b) $CuCl_2$, *n*$BuNH_2$, MeOH/$CHCl_3$ (1:1), RT; c) conc. HCl/*i*PrOH/THF (1:50:50), RT; d) **5**, EDCI·HCl, DMAP, CH_2Cl_2, RT and then H_2, $Pd(OH)_2$/C, THF, RT; e) same as b); f) same as c). THF = tetrahydrofuran, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.

synthesis of strictinin (**1**) in five overall steps and 21% overall yield from naturally abundant glucose. The overall number of the steps in the present synthesis is much fewer than for the previously reported syntheses (11 and 13 steps from glucose, respectively[12,13]).

We next examined the total synthesis of tellimagrandin II (**2**) by using the present strategy (Scheme 4 d–f). The introduction of two additional galloyl groups at C(2)-OH and C(3)-OH of diol **15** through the reaction with **5** in the presence of EDCI·HCl, followed by hydrogenolysis of the resulting 1,2,3,4,6-pentagallate gave **18**. Pentagallate **18** was transformed into tellimagrandin II through the same procedure used for the transformation of **16** to strictinin. Tellimagrandin II (eugeniin) was synthesized from glucose in six steps overall and in 18% overall yield. The number of synthetic steps from glucose is much less than that for the previous total synthesis of tellimagrandin II (14 steps[22]).

Since carbohydrate synthesis has been developed in parallel with the development of protective groups, the current strategies for carbohydrate synthesis still rely largely on the use of protective groups.[23] On the other hand, approaches to the direct regioselective manipulation of carbohydrates have recently been reported.[24–26] We developed a de novo synthetic route to natural glycosides of an ellagitannin family through the sequential and regioselective introduction of galloyl(oxy) groups to unprotected glucose. The present strategy would provide a new retrosynthetic approach to a limited class of natural glycosides. We expect that the concept of catalyst-controlled regioselective functionalization[27] will stimulate the further development of direct methods for the synthesis of complex natural products with minimal use of protective groups.

Keywords: ellagitannin · glycosidation · organocatalysis · regioselectivity · total synthesis

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Communications

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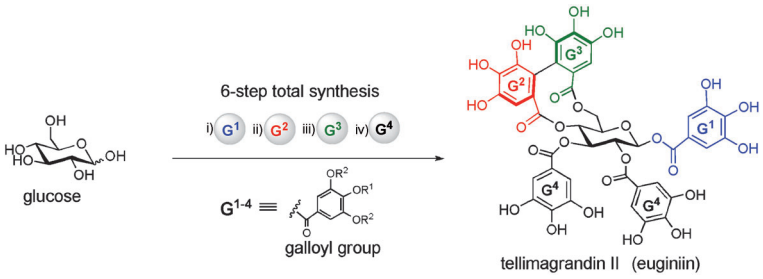
Total Synthesis of Ellagitannins through Regioselective Sequential Functionalization of Unprotected Glucose



Short and sweet: Very short total syntheses of ellagitannins were achieved through sequential and regioselective functionalization of the hydroxy groups of unprotected glucose.