

Final-Stage Site-Selective Acylation for the Total Syntheses of Multifidosides A-C by Organocatalysis

Yoshihiro Ueda, Takumi Furuta, and Takeo Kawabata*

Abstract: The first total syntheses of multifidosides A-C have been achieved. The synthetic strategy is characterized by catalytic site-selective acylation of protecting-group-free precursors **5a-c** (also natural glycosides) at the final stage. High functional-group-tolerance of the site-selective acylation promoted by organocatalyst **4** enabled conventionally difficult molecular transformation in a predictable and reliable manner. An advantage of this strategy is to avoid the risks of undesired side reactions during the removal of the protecting groups at the final stage of the total synthesis, which we actually encountered in our attempted total synthesis and also have been reported in the literature.

Predictability is one of the most important factors for designing the strategy of target-oriented synthesis^[1] because rational retrosynthesis relies on the chemical transformations with predictable selectivity. Retrosynthetic analyses have been proposed based on the expected chemo-, diastereo-, and/or enantioselectivity of the corresponding reactions. In addition to these selectivities, site-selectivity has been a current focus as a key factor to streamline the synthetic routes to complex molecules^[2-4]. Recently, we reported total synthesis of natural glycosides of an ellgitannin family based on site-selective introduction of galloyl groups to unprotected glucose at an early stage of the total synthesis^[5]. Here we report the first total syntheses of natural glycosides, multifidosides A, B, and C, via final-stage site-selective acylation (Figure 1). In the most cases of total syntheses, the final step is employed for deprotection of the protective groups. It has been believed that the key reaction should not be run at the final step because synthetic efforts may be hampered by the final step if the key reaction did not take place in the expected manner. On the other hand, the present site-selective acylation was found to be suitable to be performed at the final stage of the total synthesis, because the site-selectivity was maintained throughout the acylation of various natural glycosides precursors without exception, and thus, this site-selective molecular transformation seems predictable and reliable^[6]. Recently, late-stage site-selective functionalization of biologically active compounds has been receiving increasing attention because it enables diversification of biologically active compounds retaining their original activity^[7]. Final-stage site-selective functionalization is expected to be a more promising entry to conveniently providing natural products and their derivatives with the related biological activity.

Synthetic targets **1-3** (Figure 1) were isolated in 2008 by Zhao

and co-workers from whole plants of *Pteris multifida* used for a traditional Chinese medicine^[8]. Compounds **1** and **2** were reported to have significant cytotoxicity against HepG2 tumor cells. These glycosides possess a *p*-coumaroyl group at C(4)-OH of the glucopyranose moiety. A retrosynthetic analysis of **1** and **2** is shown in Figure 1. While properly protected precursor **6** with the free C(4)-OH (route 2) is a rational precursor for the synthesis of **1** and **2** based on the conventional protection/deprotection strategy, we envisioned to introduce the *p*-coumaroyl group directly onto the C(4)-OH of the protecting-group-free precursor **5** by site-selective acylation with organocatalyst **4** (route 1). In light of high functional-group-tolerance observed in the previously reported site-selective acylation reactions,^[5,6] we anticipated that the desired 4-O-acylation would take place through the hypothetical transition state (Figure 1) in the presence of otherwise more reactive primary hydroxy group(s) and other hydrogen-bond acceptors. The expected advantages of the present strategy would involve (1) a proposal of an unconventional retrosynthetic route to natural glucosides with C(4)-O-acylated glucopyranose substructure, (2) shorter synthetic steps by streamlining the synthetic scheme, and (3) avoidance of the risks of the undesired side reactions during the removal of the protecting groups (PGs) at the later stage, which we actually encountered in our attempted total synthesis (see Scheme 3). The examples of undesired side reactions at the late-stage deprotection have also been reported toward the synthesis of phenylethanoid glycosides, which include acyl migration, over reduction, and isomerization of the double bond^[9]. Notably, the proposed synthetic scheme realizes an one-step conversion from a natural glycoside to other natural glycoside, since precursor **5** is also a naturally occurring glycoside, wallichoside^[10].

A retrosynthetic analysis for natural glycosides **5a-c** (**5a**: (2*S*,3*S*)-wallichoside, **5b**: (2*R*,3*S*)-wallichoside, **5c**: pteroside B),

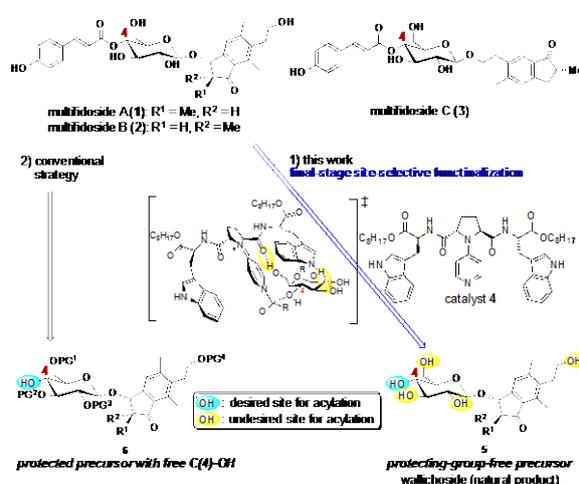


Figure 1. Structures of multifidosides A-C and synthetic strategy: route 1 (this work); organocatalytic final-stage site-selective acylation of the protecting-group-free precursor, **5** and route 2; conventional strategy using a properly protected precursor, **6**.

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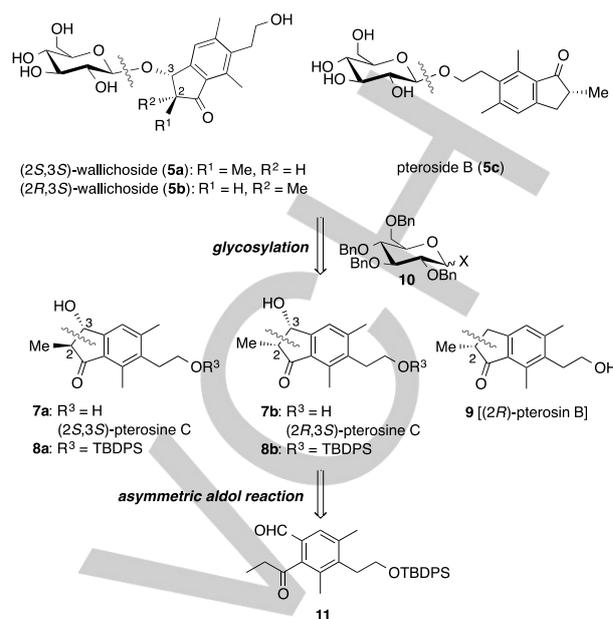
[**] This work was financially supported by Grant-in-Aids for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" and for Scientific Research (S) from MEXT. We are grateful to Prof. W.-M. Zhao at the Chinese Academy of Sciences for providing NMR spectra of natural multifidosides A-C. Supporting Information for this article is given via a link at the end of the document.

the precursors of target natural glycosides **1-3**, is shown in Scheme 1. Glycosides **5a-c** would be obtained by β -selective glycosylation of aglycons **8a**, **8b**, and **10** with commercially available glycosyl donor **11** followed by debenzoylation. Aglycons **8a**, **8b**, and **10** are also natural products known as (2*S*,3*S*)-pterisin C, (2*R*,3*S*)-pterisin C, and (2*R*)-pterisin B^[10], respectively. The β -hydroxyketone moiety of **8a** and **8b** would be constructed by an organocatalytic intramolecular asymmetric aldol reaction of aromatic ketoaldehyde **12**. Although the relative stereochemistry of the aldol reaction could not be predicted at this stage, both the *syn*- and *anti*- isomers were required because they both are constituents of the natural products, and the interconversion between them seemed possible by epimerization at C(2). Aglycon **10** would be readily obtained by reductive removal of the hydroxy group of **8b**^[11].

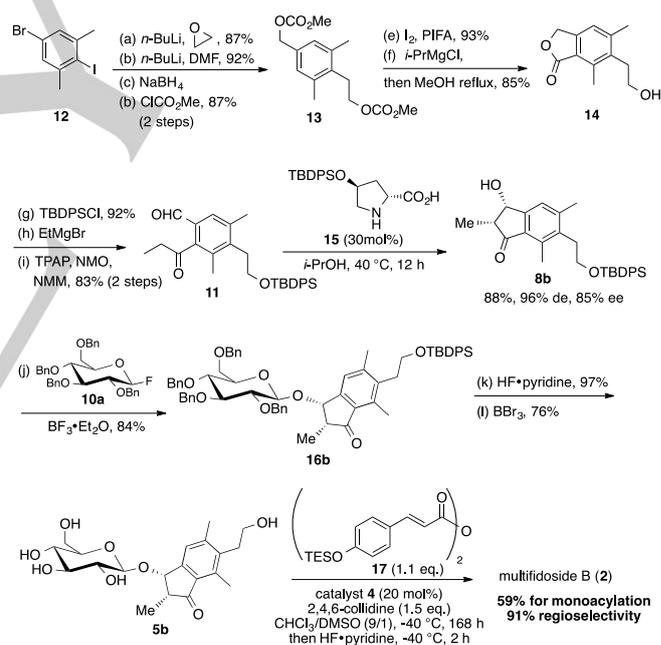
Total synthesis of **2** was investigated at first (Scheme 2). The aldol precursor **12** was prepared from commercially available *tetra*-substituted benzene **13**. Consecutive lithium-halogen exchange of **13** followed by hydroxyethylation and formylation of the respective aryl lithium species afforded a *tri*-substituted benzaldehyde derivative, which was then converted to **14** by reduction of the formyl group and methoxycarbonylation of the resulting alcohol. After iodination of **14** with I₂ and PIFA^[12], intramolecular O to C acyl migration of the aryl magnesium species generated by iodine-magnesium exchange of the resulting aryl iodine followed by methanolysis gave lactone **15**. Protection of the primary hydroxy group of **15** with a TBDPS group, addition of a Grignard reagent to the lactone, followed by Ley oxidation^[13] of the resulting lactol gave aldol precursor **12**.

Then, the asymmetric intramolecular aldol reaction of ketoaldehyde **12** was investigated. Since List, Lerner, and Barbas reported the direct asymmetric aldol reaction between aliphatic ketones and aldehydes catalyzed by L-proline^[14], a tremendous number of organocatalytic asymmetric aldol reactions and related reactions have been reported^[15]. However, there are only limited examples of direct aldol reactions using arylalkylketones as aldol donors because of the poor reactivity^[16]. After thorough screening of catalysts and the conditions (Table S1), we found that proline derivative **16**^[17] has reactivity sufficient to give **9b** with the desired absolute and relative configuration (88% yield, *syn*:*anti*=98:2, 85% ee for the *syn* isomer). To the best of our knowledge, this is the first successful example of the asymmetric intramolecular aldol reaction of aromatic ketoaldehydes catalyzed by proline or its analogues. β -Selective glycosylation of **9b** (85% ee) took place by treatment with commercially available glycosyl donor **11a** and BF₃·Et₂O in EtCN^[18] to give a diastereomeric mixture of the β -glycosides resulting from a 92.5 : 7.5 enantiomeric mixture of **9b**. Diastereomerically pure **17b**, obtained by the removal of the minor diastereomer, was subjected to the removal of TBDPS and Bn groups to afford **5b**, the proposed precursor for **2**.

Organocatalytic site-selective coumaroylation of **5b** was next investigated toward the total synthesis of **2**. The use of less-coordinating solvents such as CHCl₃ or toluene was claimed to be critical for achieving high site-selectivity of the acylation of glycopyranoses catalyzed by **4**^[6], which was assumed to be due to the effective hydrogen-bonding interaction in these solvents as shown in Figure 1. However, **5b**, the substrate for the *p*-



Scheme 1. Retrosynthetic analysis for **5a-c**.



Scheme 2. Total synthesis of multifidocide B (**2**). Reagents and conditions: a) *n*-BuLi, Et₂O, -78 °C; ethylene oxide, -78 °C to r.t., 87%; b) *n*-BuLi, THF, -78 to -30 °C; DMF, -78 °C to r.t., 92%; c) NaBH₄, MeOH, 0 °C; d) methyl chloroformate, pyridine, DMAP (5 mol%), DCM, r.t., 87% (2 steps); e) I₂, PIFA, CH₂Cl₂, r.t., 93%; f) *i*-PrMgCl, THF, 0 °C; MeOH, reflux, 85%; g) TBDPSCI, imidazole, r.t., 92%; h) EtMgBr, THF, 0 °C; i) TPAP (5 mol%), NMO, NMM, MS 4Å, DCM, r.t., 83% (2 steps); j) **10a** (X = β -F), BF₃·Et₂O, MS 4Å, EtCN, -78 to 0 °C, 84%; k) HF·pyridine, THF, r.t., 97% l) BBr₃, DCM, -78 °C, 76%.

coumaroylation possessing five free hydroxy groups, was totally insoluble in CHCl₃ or toluene. Instead of these solvents, CHCl₃/DMSO (9/1) was found to be effective for the

site-selective acylation at the C(4)-OH of the glucopyranose derivative irrespective of the strongly hydrogen-bond accepting nature of DMSO^[19]. TES-protected anhydride **18** was employed as an acylating reagent because the use of acid anhydrides rather than acid chlorides was critical for the site-selectivity^[6a] and the TES group was expected to be readily removed at the work-up process. As expected, site-selective acylation of **5b** catalyzed by **4** took place at the desired site to give natural glycoside **2** directly in 54% isolated yield (91% site-selectivity among the monoacylates obtained in 59% yield). This result showed that the site-selective acylation is highly functional-group tolerant in the presence of many potentially nucleophilic hydroxy groups, hydrogen-bond donors (-OH) and acceptors (ketone, etheral oxygen). The surprising functional-group tolerance of the site-selective acylation makes the present strategy reliable and predictable^[20].

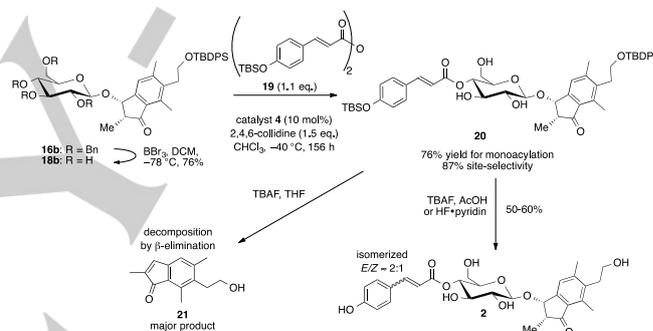
This strategy provides additional advantages in the total synthesis by avoiding the risks of undesired side reactions (Scheme 3). For example, attempted total synthesis of **2** using partially protected precursor **18b** resulted in the double-bond isomerization to give an *E/Z* (2/1) mixture of **2** by the final-step deprotection of the OTBDPS group in **20** with TBAF/AcOH or HF/pyridine. Whereas the double bond in the hydroxy cinnamoyl group of the natural products has been reported to easily undergo *E,Z*-isomerization^[9c,21], only a small extent of *E,Z*-isomerization of **2** was observed (*E/Z* = 20~10/1) in our strategy shown in Scheme 2 (Natural products **1**, **2**, and **3** also contain a small amount of the *Z*-isomer, see Supporting information Figure S1-S3). Another attempt to obtain **2** by treatment of **20** with TBAF hampered the efforts to the total synthesis, and gave decomposed product **21** as the major product by β -elimination of the glucose moiety^[22]. In the literature for the total synthesis of 4-*O*-acylated glycoside natural products, undesired side reactions such as acyl migration from the desired 4-*O*-acylate to the undesired 6-*O*-acylate and over-reduction and isomerization of the cinnamoyl moiety by the final-step deprotection have been reported^[9]. These problems could be avoided when the present strategy with protecting-group-free precursors is employed.

Total syntheses of **1** and **3** were performed by the similar procedure to that for the synthesis of **2** (Scheme 4). Epimerization at the carbonyl α -carbon of **17b** took place by the careful basic treatment at 0 °C to give a 86:14 mixture of **17a** and **17b** without β -elimination of the glucose moiety (Scheme 4A). Separation of the resulting diastereomers gave **17a** as a pure diastereomer in 70% yield. (2*S*,3*S*)-Wallichoside (**5a**) was obtained by removal of the protective groups of **17a**. Organocatalytic site-selective coumaroylation of **5a** with five free hydroxy groups took place also in a predictable manner to give a natural product, multifidoside A (**1**), in 54% isolated yield (Scheme 4A, 84% site-selectivity among the monoacylates obtained in 64% yield). Aglycon **10**, the proposed precursor of **3**, was prepared by Barton-McComby deoxygenation^[23] of **9b** followed by desilylation (Scheme 4B). Glycosylation of **10** by Schmidt's procedure^[18b,24] followed by hydrogenation of the resulting glycoside gave pteroside B (**5c**). Total synthesis of multifidoside C (**3**) was achieved by catalytic site-selective coumaroylation of **5c** in 70% isolated yield (90% site-selectivity among the monoacylates obtained in 78% yield). Thus, total syntheses of natural glycosides, multifidosides A, B, and C, were

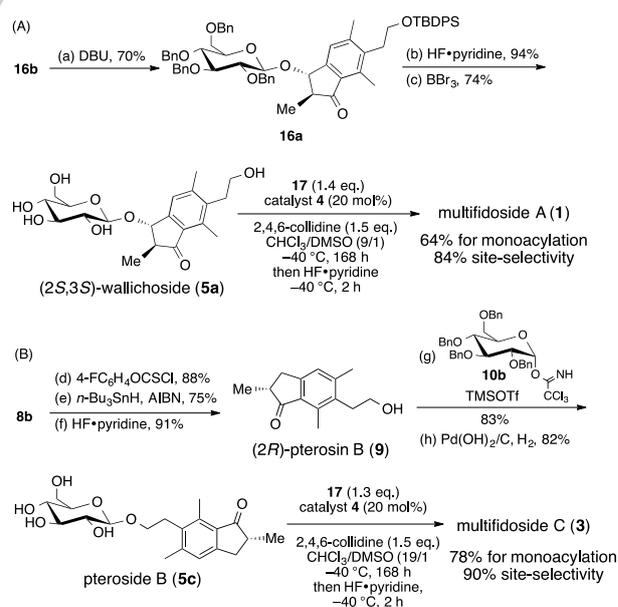
accomplished via final-stage organocatalytic site-selective coumaroylation of the precursors with multiple free hydroxyl groups.

The desired site-selectivity was maintained throughout the acylation of the glycosides with various aglycon moieties. Another advantage of this strategy is the direct and facile diversification of natural glycosides (Scheme 5). Isobutyryl, benzoyl, and *N*-Cbz- α -aminoacyl groups were introduced to the expected hydroxy group of a natural glycoside, (2*R*,3*S*)-wallichoside (**5b**), in up to 97% site-selectivity by the protocol described above. The biological activity of carbohydrates possessing acyl group(s) often depends on the position and structure of the acyl group(s)^[25,26]. Therefore, the site-selective introduction of various acyl groups at the final stage of the synthesis may be applicable to searching for the biologically active analogues.

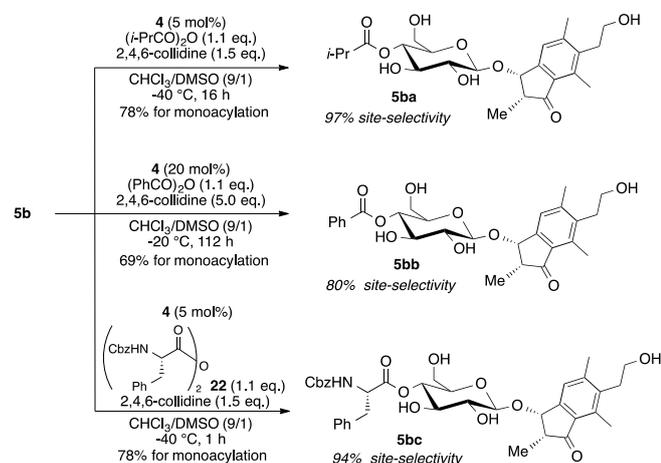
In conclusion, the first total syntheses of multifidosides A (**1**), B (**2**) and C (**3**) have been accomplished in 15 steps (8.2% overall yield), 14 steps (12% overall yield), and 16 steps (11% overall yield), respectively, from commercially available reagents.



Scheme 3. Our problems encountered at the later-stage deprotection toward total synthesis of **2**.



Scheme 4. Total syntheses of (A) **1** and (B) **3**. Reagents and Conditions: a) DBU, toluene, 0 °C, 70%; b) HF-pyridine, THF, r.t., 94%; c) BBr₃, DCM, -78 °C, 74%; d) **22**, **4** (20 mol%), collidine, CHCl₃/DMSO (9/1), -40 °C, 16 h; HF-pyridine, -40 °C, 2 h; e) 4-FC₆H₄OCSCI, DMAP, DCM, r.t., 88%; f) *n*-Bu₃SnH, AIBN (20 mol%), benzene, 100 °C, 75%; g) HF-pyridine, THF, r.t., 91%; h) **11b**, TMSOTf (10 mol%), CH₃CN, -40 °C, 83%, (s) Pd(OH)₂/C, H₂, AcOEt/MeOH (1/1), r.t., 82%.



Scheme 5. Final-stage site-selective diversification of a natural product, (2R,3S)-wallichoside (**5b**).

The key step is the final-stage site-selective acylation of the protecting-group-free precursors by organocatalysis. Because of the predictability and reliability of the catalytic site-selective introduction of the various functionalized acyl groups, this synthetic strategy would provide a new retrosynthetic route to 4-O-acylglucosides such as phenylethanoid glycosides^[27] and ellagitannins^[28] of biological interest.

Keywords: acylation • natural glycoside • organocatalyst • site-selectivity • retrosynthesis

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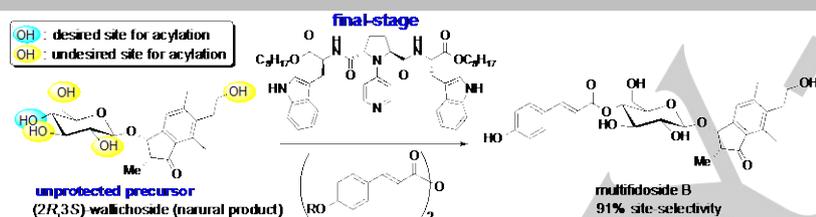
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**Final-Stage Site-Selective Acylation
for the Total Syntheses of
Multifidosides A-C by
Organocatalysis**

A new retrosynthetic route to 4-*O*-acylated natural and unnatural glycosides was proposed. Organocatalytic site-selective coumaroylation of the protective-group-free precursors possessing multiple hydroxy groups was performed successfully at the final-stage of the total syntheses of multifidosides A, B, and C. The site-selectivity was found to be predictable and reliable throughout the acylation of the various protective-group-free precursors.