Unconventional Retrosynthesis

International Edition: DOI: 10.1002/anie.201504729
German Edition: DOI: 10.1002/ange.201504729

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

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Abstract: *The first total syntheses of multifidosides A–C have been achieved. The synthetic strategy is characterized by catalytic site-selective acylation of unprotected glycoside precursors in the final stage of the synthesis. High functional-group tolerance of the site-selective acylation, promoted by an organocatalyst, enabled the 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.*

Predictability is one of the most important factors for designing the strategy of target-oriented synthesis[1] because rational retrosynthesis relies on 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 the total synthesis of natural glycosides of an ellgitannin family and it was based on site-selective introduction of galloyl groups to unprotected glucose at an early stage of the total synthesis.[5] Herein we report the first total syntheses of natural glycosides, multifidosides A, B, and C, by final-stage site-selective acylation (Figure 1). In most cases of total syntheses, the final step is employed for removal of the protecting groups. It is believed that the key reaction should not be used as the final step because synthetic efforts may be hampered if the key reaction does not proceed in the expected manner. In contrast, the present site-selective acylation was found to be suitable for the final stage of a 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 received an increasing amount of attention because it enables diversification of biologically active compounds which retain 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.

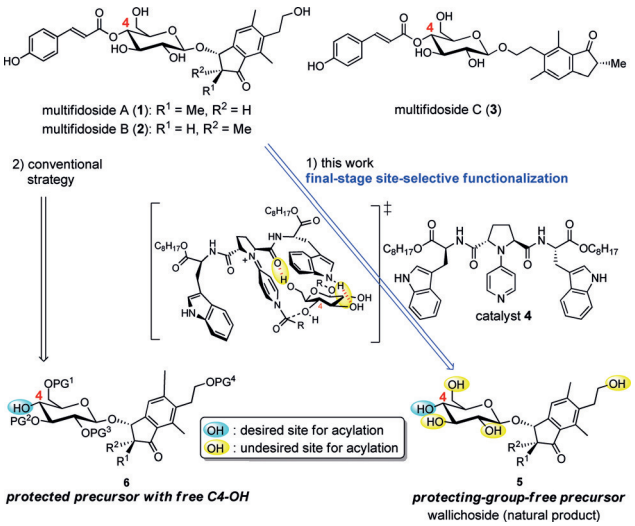

Figure 1. Structures of multifidosides A–C and two synthetic strategies. Route 1 (this work): an organocatalyzed final-stage site-selective acylation of the precursor **5**. Route 2: conventional strategy using the protected precursor **6**. PG = protecting group.

The synthetic targets **1**–**3** (Figure 1) were isolated in 2008 by Zhao and co-workers from whole plants of *Pteris multifida*, which are used for a traditional Chinese medicine.[8] The compounds **1** and **2** were reported to have significant cytotoxicity against HepG2 tumor cells. These glycosides possess a *p*-coumaroyl group at C4 of the glucopyranose moiety. A retrosynthetic analysis of **1** and **2** is shown in Figure 1. Although the properly protected precursor **6**, having a free C4–OH (route 2) is a rational precursor for the synthesis of **1** and **2** based on the conventional protection/deprotection strategy, we envisioned the introduction of the *p*-coumaroyl group directly to C4 of the unprotected precursor **5** by site-selective acylation with the organocatalyst **4** (route 1). In light of the 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, shown in Figure 1, even in the presence of 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 a C4-O-acylated glucopyranose substructure, 2) fewer 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 a later stage of the synthesis. Such side

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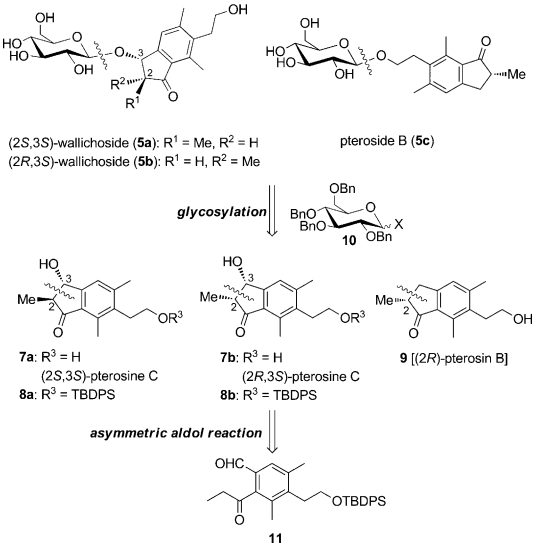
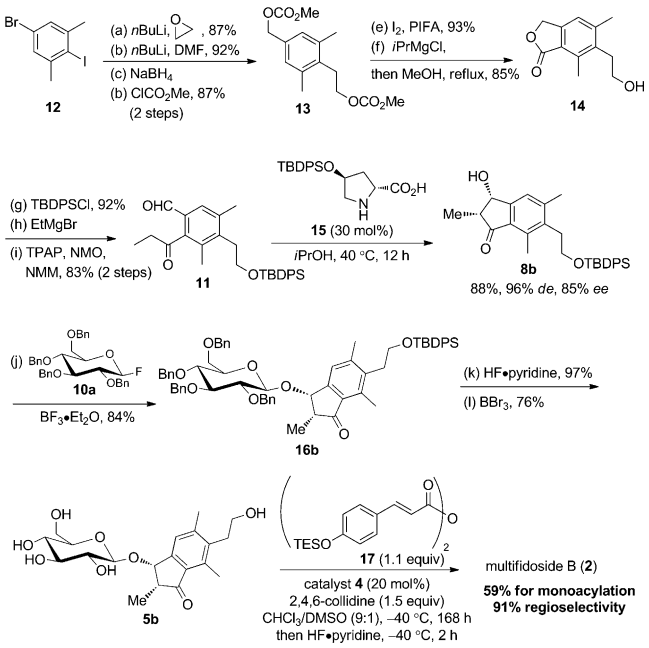
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201504729.

reactions were in fact encountered in our attempted total synthesis (see Scheme 3). Examples of undesired side reactions at a late-stage deprotection have also been reported for the synthesis of phenylethanoid glycosides, and include acyl migration, over reduction, and isomerization of the double bond.[9] Notably, the proposed synthetic scheme realizes a one-step conversion from a natural glycoside, as **5** is also a naturally occurring glycoside, wallichoside, into other natural glycosides.[10]

A retrosynthetic analysis for natural glycosides **5a–c** [**5a**: (2*S*,3*S*)-wallichoside, **5b**: (2*R*,3*S*)-wallichoside, **5c**: pteroside B], the precursors of the target natural glycosides **1–3**, is shown in Scheme 1. The glycosides **5a–c** could be obtained by



Scheme 1. Retrosynthetic analyses for **5a–c**. TBDPS = *tert*-butyldiphenylsilyl.



Scheme 2. Total synthesis of multifidoside B (**2**). Reagents and conditions: a) *n*BuLi, Et_2O, −78 °C; ethylene oxide, −78 °C to RT, 87%; b) *n*BuLi, THF, −78 to −30 °C; DMF, −78 °C to RT, 92%; c) $NaBH_4$, MeOH, 0 °C; d) methyl chloroformate, pyridine, DMAP (5 mol%), CH_2Cl_2, RT, 87% (2 steps); e) I_2, PIFA, CH_3CN, RT, 93%; f) *i*PrMgCl, THF, 0 °C; MeOH, reflux, 85%; g) TBDPSCl, imidazole, RT, 92%; h) EtMgBr, THF, 0 °C; i) TPAP (5 mol%), NMO, NMM, 4 Å M.S., CH_2Cl_2, RT, 83% (2 steps); j) **10a** (X = β-F), $BF_3{\cdot}Et_2O$, 4 Å M.S., EtCN, −78 to 0 °C, 84%; k) HF·pyridine, THF, RT, 97% l) BBr_3, CH_2Cl_2, −78 °C, 76%. DMAP = 4-(*N*,*N*-dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, M.S. = molecular sieves, NMM = 4-methylmorpholine, NMO = *N*-methylmorpholine oxide, PIFA = phenyliodine(III) bis(trifluoroacetate), THF = tetrahydrofuran, TPAP = tetra-*n*-propylammonium perruthenate.

β-selective glycosylation of the aglycons **7a**, **7b**, and **9**, respectively, with a commercially available glycosyl donor (**10**), and subsequent debenzylation. The aglycons **7a**, **7b**, and **9** are also natural products known as (2*S*,3*S*)-pterosin C, (2*R*,3*S*)-pterosin C, and (2*R*)-pterosin B,[10] respectively. The β-hydroxyketone moieties of **7a** and **7b** could be constructed by an organocatalytic intramolecular asymmetric aldol reaction of the aromatic ketoaldehyde **11**. 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 are both constituents of the natural products, and the interconversion between them seemed possible by epimerization at C2. The aglycon **9** would be readily obtained by reductive removal of the hydroxy group of **7b**.[11]

The total synthesis of **2** was investigated first (Scheme 2). The aldol precursor **11** was prepared from the commercially available tetrasubstituted benzene **12**. Consecutive lithium–halogen exchange/hydroxyethylation and lithium–halogen exchange/formylation of **12** afforded a trisubstituted benzaldehyde derivative, which was then underwent reduction of the formyl group and methoxycarbonylation of the resulting alcohol to give **13**. After iodination of **13** with I_2 and PIFA,[12] intramolecular O to C acyl migration of the aryl magnesium species, generated by iodine–magnesium exchange of the resulting aryl iodine, and subsequent methanolysis gave the lactone **14**. Protection of the primary hydroxy group of **14** with a TBDPS group, addition of a Grignard reagent to the lactone, and Ley oxidation[13] of the resulting lactol gave **11**.

The asymmetric intramolecular aldol reaction of **11** was then 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 asymmetric organocatalytic aldol reactions and related reactions have been reported.[15] However, there are only a limited number of examples of direct aldol reactions using arylalkylketones as aldol donors, because of the poor reactivity.[16] After thorough screening of catalysts and the reaction conditions (see Table S1 in the Supporting Information), we found that the proline derivative **15**[17] has reactivity sufficient to give **8b** with the desired absolute and relative configuration (88% yield, *syn*/*anti* = 98:2, 85% *ee* for the *syn* isomer; Scheme 2). 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 **8b** (85% *ee*;

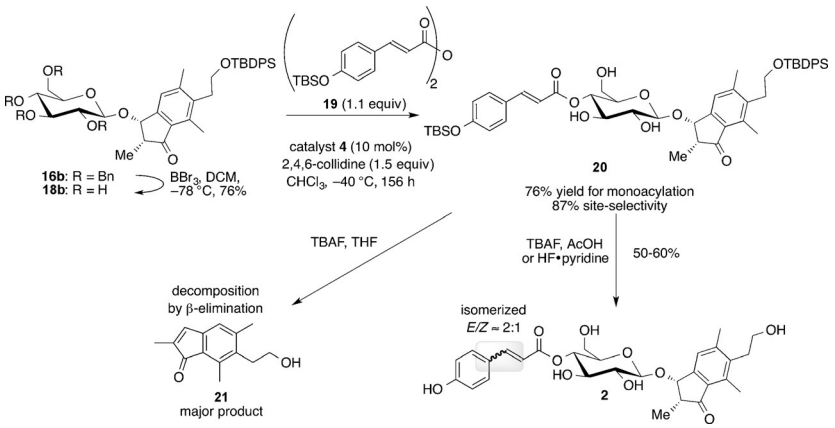
92.5:7.5 enantiomeric mixture) took place by treatment with the commercially available glycosyl donor **10a** and $BF_3{\cdot}Et_2O$ in EtCN[18] to give a diastereomeric mixture of the β-glycosides. Diastereomerically pure **16b**, obtained by the removal of the minor diastereomer resulting from the minor enantiomer of **8b**, 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 for the total synthesis of **2**. The use of less-coordinating solvents such as either $CHCl_3$ or toluene was claimed to be critical for achieving high site-selectivity of the acylation of glycopyranoses catalyzed by **4**,[6] and was assumed to be due to the effective hydrogen-bonding interactions in these solvents (Figure 1). However, **5b**, the substrate for the *p*-coumaroylation, possessing five free hydroxy groups, was totally insoluble in either $CHCl_3$ or toluene. Instead of these solvents, $CHCl_3$/DMSO (9:1) was found to be effective for the site-selective acylation at C4 of the glucopyranose derivative irrespective of the strongly hydrogen-bond accepting nature of DMSO.[19] The TES-protected anhydride **17** 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 during the work-up. As expected, site-selective acylation of **5b**, catalyzed by **4**, took place at the desired site to give the natural glycoside **2** in 54% yield (91% site-selectivity among the monoacylates obtained in a combined yield of 59%). This result showed that the site-selective acylation is highly functional-group tolerant in the presence of many potentially nucleophilic hydroxy groups, as well as hydrogen-bond donors (OH) and acceptors (ketone and ethereal oxygen atoms). The surprising functional-group tolerance of the site-selective acylation makes the present strategy reliable and predictable.[20]

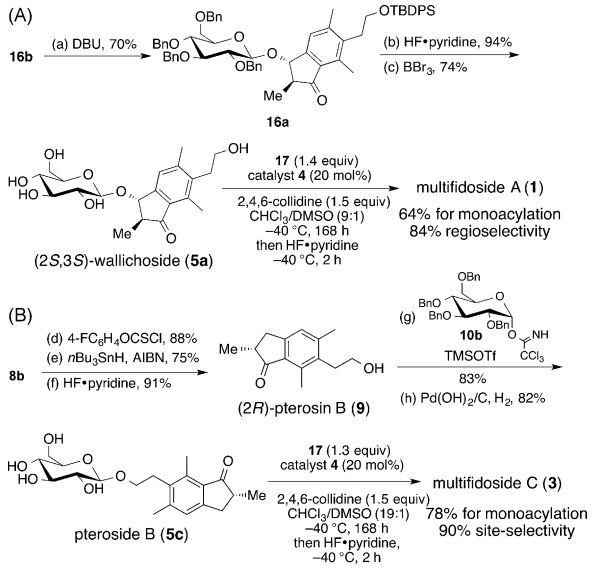
This strategy provides additional advantages in total synthesis by avoiding the risks of undesired side reactions (Scheme 3). For example, an attempted total synthesis of **2**, using the partially protected precursor **18b**, resulted in double-bond isomerization to give an *E*/*Z* (2:1) mixture of **2** in the final removal of the TBDPS group in **20** with either TBAF/AcOH or HF/pyridine. Although 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 current work (Scheme 2; natural products **1**, **2**, and **3** also contain a small amount of the *Z* isomer; see Figures S1–S3 in the Supporting Information). Another attempt to obtain **2** by treatment of **20** with TBAF hampered the efforts of the total synthesis, and gave the decomposed product **21** as the major product by β-elimination of the glucose moiety (Scheme 3).[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 in the final deprotection step have been reported.[9] These problems were avoided when the present strategy, with protecting-group-free precursors, was employed.

The total syntheses of **1** and **3** were performed by a similar procedure to that used for **2** (Scheme 4). Epimerization at the carbonyl α-carbon atom of **16b** proceeded with careful basic treatment at 0°C to give a 86:14 mixture of **16a** and **16b** without β-elimination of the glucose moiety (Scheme 4A). Separation of the resulting diastereomers gave **16a** as a pure diastereomer in 70% yield. (2*S*,3*S*)-Wallichoside (**5a**) was obtained by removal of the protecting groups of **16a**. Organocatalytic site-selective coumaroylation of **5a**, with five free hydroxy groups, took place in a predictable manner to give the natural product multifidoside A (**1**) in 54% yield (84% site-selectivity among the monoacylates obtained in a combined yield of 64%). The aglycon **9**, the proposed precursor of **3**, was prepared by Barton–McComby deoxygenation[23] of **8b** followed by desilylation (Scheme 4B). Glycosylation of **9** by Schmidt's procedure[18b,24] and subsequent hydrogenation of the resulting glycoside gave pteroside B[10] (**5c**). Total synthesis of multifidoside C (**3**) was achieved by catalytic site-selective coumaroylation of **5c** in 70% yield (90% site-selectivity among the monoacylates obtained in a combined yield of 78%). Thus, the total syntheses of the natural glycosides **1**–**3**, were accomplished by final-stage organocatalytic site-selective coumaroylation of precursors having multiple free hydroxy groups.

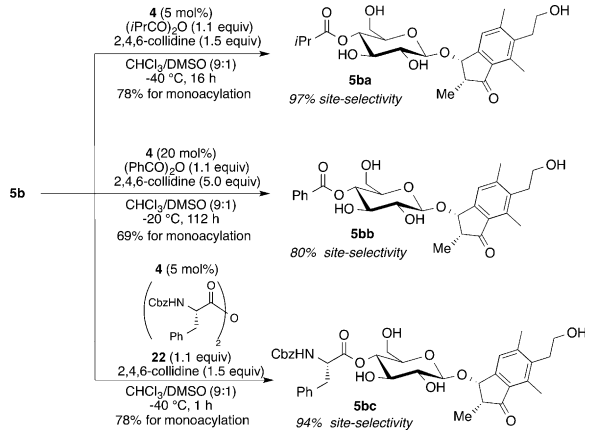
The desired site-selectivity was maintained for the acylation of glycosides with various aglycon moieties. Another advantage of this strategy is the direct and facile diversification of natural glycosides (Scheme 5). Isobutyryl, benzoyl, and *N*-Cbz-α-aminoacyl groups were introduced to the desired hydroxy group of the natural glycoside (2*R*,3*S*)-wallichoside (**5b**) in up to 97% site-selectivity when using 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 present method for 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.



Scheme 3. Problems encountered during the late-stage deprotection toward the total synthesis of **2**. TBAF = tetra-*n*-butylammonium fluoride.



Scheme 4. Total syntheses of multifidoside A (**1**) and B (**3**). Reagents and conditions: a) DBU, toluene, 0 °C, 70%; b) HF·pyridine, THF, RT, 94%; c) BBr_3, CH_2Cl_2, −78 °C, 74%; d) 4-FC_6H_4OCSCl, DMAP, CH_2Cl_2, RT, 88%; e) nBu_3SnH, AIBN (20 mol%), benzene, 100 °C, 75%; f) HF·pyridine, THF, RT, 91%; g) **10b**, TMSOTf (10 mol%), CH_3CN, −40 °C, 83%, h) Pd(OH)$_2$/C, H_2, AcOEt/MeOH (1:1), RT, 82%. AIBN = α,α′-azobis(isobutyronitrile), DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.



Scheme 5. Final-stage site-selective diversification of (2*R*,3*S*)-wallichoside (**5b**). Cbz = carboxybenzyl.

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. 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 various functionalized acyl groups, this synthetic strategy could provide a new retrosynthetic route to 4-O-acylglycosides, such as phenylethanoid glycosides[27] and ellagitannins,[28] which are of biological interest.

Acknowledgements

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 naturally occuring multifidosides A–C.

Keywords: acylation · glycosides · natural products · organocatalysis · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 11966–11970
Angew. Chem. **2015**, *127*, 12134–12138

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Received: May 25, 2015
Published online: August 28, 2015

