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Efficient Synthesis of Lupane-Type Saponins via Gold(I)-Catalyzed Glycosylation with Glycosyl *ortho*-Alkynylbenzoates as Donors

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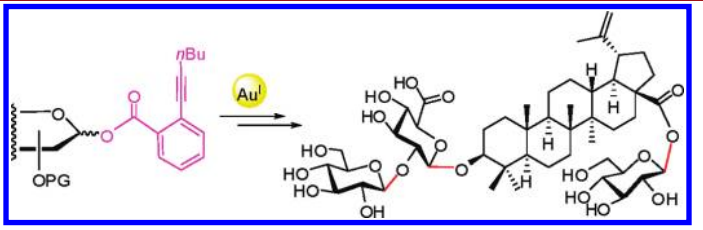
ABSTRACT



Glycosylation of the acid labile betulin and betulinic acid derivatives was achieved with glycosyl *ortho*-hexynylbenzoates as donors under the catalysis of PPh_3AuNTf_2; this enabled the efficient synthesis of lupane-type saponins, as exemplified by the total synthesis of the proposed betulinic acid trisaccharide from *Bersama engleriana*.

More than 70 lupane-type saponins have to date been identified from plants;[1] some of them show potent bioactivities, including anticancer,[2] anti-inflammatory,[3] and pancreatic lipase inhibitory activities.[4] These plant glycoconjugates occur as minor components and in a heterogeneous manner, which makes them difficult to isolate in sufficient quantities for biological and pharmacological studies. Nevertheless, lupanes such as betulinic acid (which is the most frequent aglycone) and betulin are abundantly available from plants;[5] attachment of sugars chemically onto these aglycones would provide an easy access to the diverse lupane-type saponins.[1,6] Earlier efforts on the glycosylation of betulinic acid and betulin relied on the Koenigs–Knorr method with glycosyl bromides as donors and a heavy metal salt (e.g., Ag_2O) as a promoter to provide simple glycosides in moderate yields.[7] Recently, higher glycosylation yields have been achieved with glycosyl trichloroacetimidates as donors under the catalysis of TMSOTf or $BF_3 \cdot OEt_2$, which has enabled the synthesis of a series of the lupane-type saponins.[8,9] With these synthetic compounds Pichette and co-workers found that some members of the lupane-type saponins possessed good anticancer activity while being devoid of hemolytic

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(7) (a) Odinokova, L. E.; Oshitok, G. I.; Denisenko, V. A.; Afufriev, V. F.; Tolkach, A. M.; Uvarova, N. I. *Khim. Prir. Soedin.* **1984**, 182. *Chem. Abstr.* **1985**, *102*, 24940. (b) Odinokova, L. E.; Denisenko, M. V.; Denisenko, V. A.; Uvarova, N. I. *Khim. Prir. Soedin.* **1988**, 212. *Chem. Abstr.* **1988**, *109*, 231406. (c) Klinotova, E.; Krecek, V.; Klinot, J.; Endova, M.; Eisenreichova, J.; Budesinsky, M.; Sticha, M. *Collect. Czech. Chem. Commun.* **1997**, *62*, 1776. (d) Samoshina, N. F.; Denisenko, M. V.; Denisenko, V. A.; Uvarova, N. I. *Chem. Nat. Compd.* **2003**, *39*, 575. (e) Ohara, S.; Ohira, T. *J. Wood Sci.* **2003**, *49*, 59.

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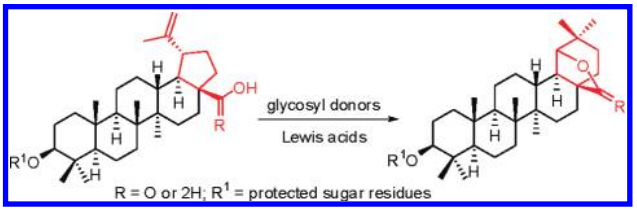
activity,[8a,10] which is of particular interest for the development of saponins as potential therapeutic agents.

During these syntheses, it was found that glycosylation of the 28-OH of betulin derivatives and the 28-COOH of betulinic acid derivatives proceeded with difficulty due to Wagner–Meerwein rearrangements taking place easily under the acidic glycosylation conditions (Scheme 1).[8b,d] Herein we report an efficient solution to this problem by glycosylation of betulin and betulinic acid derivatives with our newly developed gold(I)-catalyzed glycosylation protocol.[11]

Scheme 1. Wagner–Meerwein Rearrangements of Betulin and Betulinic Acid Derivatives during Glycosylation



A prominent feature of the gold(I)-catalyzed glycosylation protocol with glycosyl *ortho*-alkynylbenzoates as donors is that the reaction proceeds under neutral conditions. This point has been clearly proven by a recent finding of the isochromen-4-yl-gold(I) intermediate and the importance of its protodeauration for the catalytic cycle of the glycosylation.[12] Thus, extremely acid-labile aglycones, such as the *N*-Boc-protected purine derivatives and the dammarane derivatives, could be glycosylated effectively with this method.[13]

Glycosylation of the 3-OH of betulin and betulinic acid derivatives (i.e., **2a**,[8d] **2b**, **2c**[8d]) was examined first with a panel of the readily available glycosyl *ortho*-hexynylbenzoates (**1a**–**d**)[11,13,14] under normal conditions (0.1 equiv of PPh_3AuNTf_2, CH_2Cl_2, 4 Å MS, rt). The results are summarized in Table 1. Coupling of 28-*O*-TBDPS-betulin **2a** with perbenzoyl rhamnosyl *ortho*-hexynylbenzoate **1a** gave the desired 3-*O*-α-L-rhamnoside **3**[8d] in a good (83%) yield (entry 1). Coupling of 28-*O*-TBDPS-betulinate **2b** with the orthogonally protected glucopyranosyl *ortho*-hexynylbenzoate **1b** led to the desired 3-*O*-*β*-glucoside **4** in an even higher yield (entry 2). It has been reported that glycosylation of the betulinic acid derivative **2c**, which bears a perbenzoyl glucose residue on the 28-COOH, with glycosyl trichloroacetimidates is problematic.[8d] A good coupling yield (86%) was registered with perbenzoyl rhamnosyl trichloroacetimidate as the donor; glycosylation with perbenzoyl arabinopyranosyl trichloroacetimidate led to the coupling product in only 63% yield. Moreover, no coupling product was obtained when perbenzoyl glucopyranosyl trichloroacetimidate was used as the donor.[8d] Gratifyingly, the coupling efficiency was significantly enhanced when the corresponding glycosyl *ortho*-hexynylbenzoates were used as donors under the gold(I)-catalyzed conditions (entries 3–5). Thus, the glycosylation of **2c** with perbenzoyl rhamnosyl and arabinopyranosyl *ortho*-hexynylbenzoates **1a** and **1c** afforded the desired glycosides **5** and **6** in 90% and 84% yield, respectively. With perbenzoyl glucopyranosyl *ortho*-hexynylbenzoate **1d** as the donor, the reaction led only to the corresponding orthoester. Nevertheless, upon raising the amount of PPh_3AuNTf_2 to 0.5 equiv, the desired glycoside **7**[8d] could be obtained in a high (83%) yield (entry 5).

More difficult was the reported glycosylation of the 28-OH of betulin and the 28-COOH of betulinic acid derivatives, which undergo Wagner–Meerwein rearrangement easily in the presence of Lewis acids.[8b,d] Especially, betulin derivatives bearing a protected sugar residue at the 3-OH (e.g., **2d**) could not be glycosylated with glycosyl trichloroacetimidates at all.[8d] In contrast to these precedents, glycosylation of **2d** with perbenzoyl rhamnosyl and arabinopyranosyl *ortho*-hexynylbenzoates **1a** and **1c** under the catalysis of PPh_3AuNTf_2 led to the corresponding glycosides **8** and **10** in 83% and 87% yield, respectively (Table 2, entries 1 and 3). The byproduct of the Wagner–Meerwein rearrangement was not detected. Glycosylation of **2d** with perbenzoyl glucopyranosyl donor **1d** again required 0.5 equiv of PPh_3AuNTf_2 to secure a satisfactory yield of the product **12** (82%, entry 5). With the superarmed glucopyranosyl *ortho*-hexynylbenzoate **1e**[14] as the donor, 0.1 equiv of PPh_3AuNTf_2 was sufficient to yield the coupled product **14** in a high 91% yield (entry 7). Glycosylation of the 28-COOH of betulinic acid derivative **2e**[8b] with glycosyl *ortho*-hexynylbenzoates (**1a**, **1c**, and **1d**) met with no accident, leading to the desired glycosyl betulinates (**9**, **11**, and **13**) in high yields (entries 2, 4, and 6). Again, no product derived from the Wagner–Meerwein rearrangement was detected.

With these glycoside derivatives of betulin and betulinic acid easily available, access to lupane-type saponins became an easy task. This is exemplified by our further elaboration of the betulinic acid 3-*O*-glucoside **4** into the trisaccharide **21**, which was identified as a minor component from *Bersama engleriana* (Scheme 2).[15] Thus, the 28-*O*-TBDPS and 2′-*O*-benzoyl esters on **4** were cleaved under

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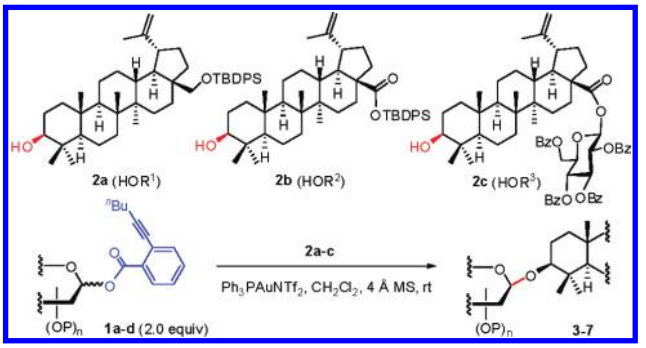
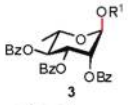
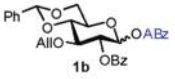
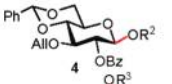
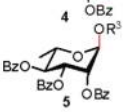
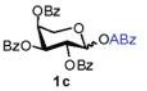
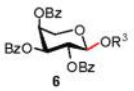
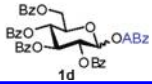
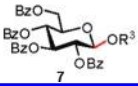
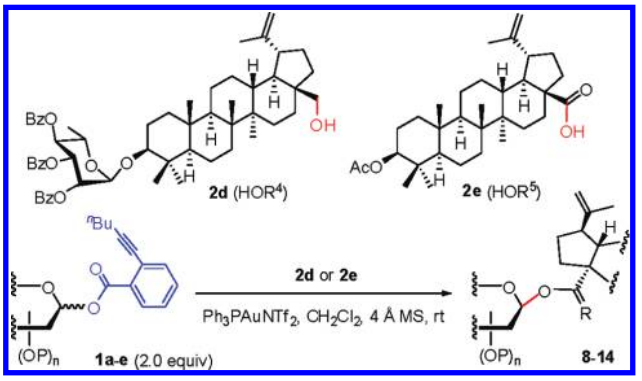
Table 1. Glycosylation of the 3-OH of Betulin and Betulinic Acid Derivatives with Glycosyl *ortho*-Hexynylbenzoates as Donors[a]

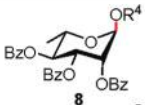
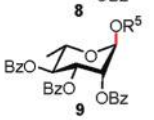
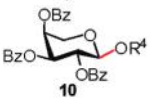
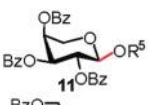
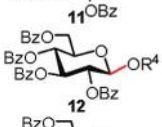
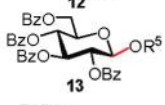
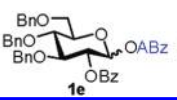
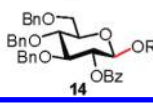


entry	donor	acceptor	catalyst (equiv)	product	yield[b]
1	 1a	2a	0.1	 3	83%
2	 1b	2b	0.1	 4	93%
3	1a	2c	0.1	 5	90%
4	 1c	2c	0.1	 6	84%
5	 1d	2c	0.5	 7	83%

[a] A typical procedure: A solution of **2a** (34 mg, 0.05 mmol) and **1a** (66 mg, 0.1 mmol) in anhydrous CH_2Cl_2 was stirred at room temperature in the presence of 4 Å molecular sieves for 30 min. Then, $Ph_3PAuNTf_2$ (7 mg, 0.01 mmol) was added, and the resulting mixture was stirred for another 1.5 h under an argon atmosphere at room temperature. Filtration through a pad of Celite and concentration yielded a residue, which was purified by silica gel column chromatography (petroleum ether/EtOAc, 15:1) to provide **3** (47 mg, 83%) as a white solid. [b] Isolated yield.

Table 2. Glycosylation of the 28-OH of Betulin and the 28-COOH of Betulinic Acid Derivatives with Glycosyl *ortho*-Hexynylbenzoates as Donors



entry	donor	acceptor	catalyst (equiv)	product	yield[a]
1	1a	2d	0.1	 8	83%
2	1a	2e	0.1	 9	94%
3	1c	2d	0.1	 10	87%
4	1c	2e	0.1	 11	85%
5	1d	2d	0.5	 12	82%
6	1d	2e	0.5	 13	83%
7	 1e	2d	0.1	 14	91%

[a] Isolated yield.

basic conditions to afford **15** (86%), which was subjected to glycosylation with perbenzoyl glucopyranosyl *ortho*-hexynylbenzoate **1d** (3.0 equiv). In the presence of 0.5 equiv of PPh_3AuNTf_2 under normal conditions, the 28-COOH and 2′-OH on **15** were glycosylated simultaneously to afford trisaccharide **16** in an excellent 92% yield. The 3′-*O*-allyl and 4′,6′-*O*-benzylidene groups on **16** were then removed with $PdCl_2$ and TsOH subsequently to provide triol **17** in high yield (80% in two steps). At this stage we attempted the selective oxidation of the primary 6′-OH in triol **17** via the modified Anelli oxidation (TEMPO, $Ca(OCl)_2$, KBr, Bu_4NBr).[16] However, it was found that the double bond in the betulinic acid aglycone did not survive these conditions, and a complex mixture resulted.[17] Therefore, the 3′,4′-hydroxyls of **17** were blocked via a three-step protecting group transformation, i.e., selective silylation of the primary 6′-OH, acetylation of the remaining 3′,4′-OH, and selective removal of the 6′-*O*-TBS group, to furnish **19** (95% in three steps). Alcohol **19** was subjected to oxidation with PCC and $NaClO_2$ subsequently to provide the corresponding glucuronic acid derivative in good yield (64% in two steps), which was further transformed into the methyl ester **20** to facilitate purification and characterization. During the PCC oxidation of the primary 6′-OH in **19**, it was found that the oxidation proceeded sluggishly. Nevertheless, the reaction rate could be enhanced dramatically by the addition of activated 3 Å MS.[18] Finally, hydrolysis

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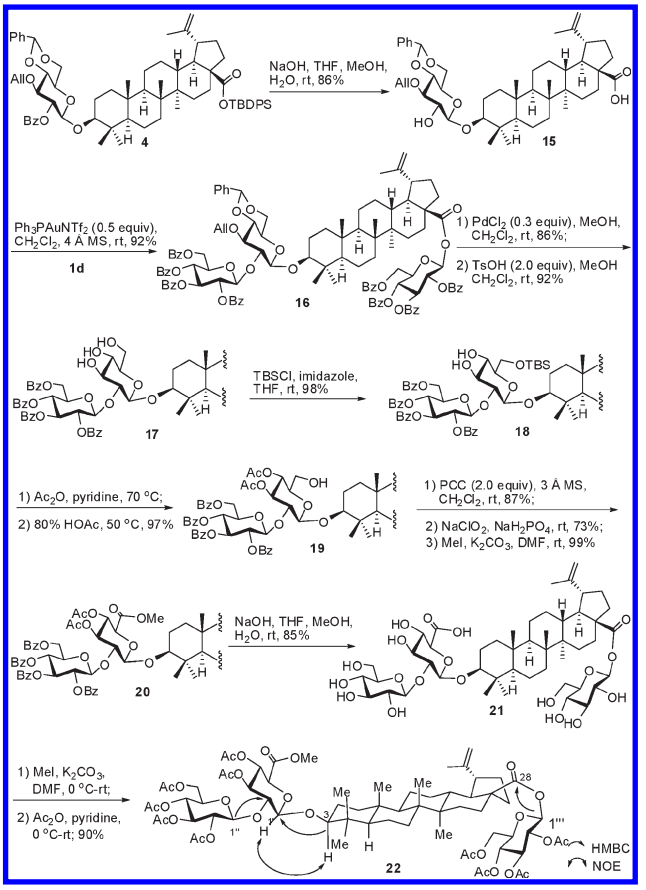
(17) Tojo, G.; Fernandez, M. In *Oxidation of Primary Alcohols to Carboxylic Acids: A Guide to Current Common Practice*; Tojo, G., Ed.; Springer: Berlin, 2007; p 79.

Scheme 2. Synthesis of the Proposed Lupane-Type Saponin **21** from *Bersama engleriana*



of all the ester protecting groups on **20** afforded the target trisaccharide saponin **21** in a good 85% yield.

Unexpectedly, the physical and analytical data (^{13}C NMR and $[\alpha]_D$ value) of **21** were not in agreement with those reported for the natural product.[15,19] To validate the structure of the synthetic compound **21**, this trisaccharide was converted to the fully protected derivative **22**, which provided well assignable NMR spectra. Extensive NMR analyses (^{1}H, ^{13}C, DEPT-135, COSY, NOESY, HMQC, and HMBC) led to the conclusion of the structure of **22**; thus the structure of **21** was correct (Scheme 2). Additional support was also obtained from the assignment of the intermediate trisaccharide **16**.[19]

In summary, taking advantage of the mild promotion conditions associated with PPh_3AuNTf_2 as the catalyst, glycosyl *ortho*-alkynylbenzoates have been successfully applied to the glycosylation of betulin and betulinic acid derivatives, which could otherwise undergo Wagner–Meerwein rearrangement under the classical glycosylation conditions with Lewis acids as promoters. The present glycosylation method has enabled the facile synthesis of lupane-type saponins, as exemplified by the efficient assembly of the betulinic acid trisaccharide **21**, which could be conducted at a 5−10 g scale with excellent yields.

Acknowledgment. This work was financially supported by the National Basic Research Program of China (2010CB833202) and the National Natural Science Foundation of China (90713003 and 20932009).

Supporting Information Available. Experimental details, copies of ^{1}H and ^{13}C NMR spectra of all new compounds, and 2D NMR spectra of compounds **16** and **22** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) See Supporting Information for details.