# First Synthesis of a Bidesmosidic Triterpene Saponin by a Highly Efficient Procedure

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Saponins comprise a diverse class of plant glycosides which possess a broad range of interesting biological activities.[1] The structural diversity of saponins lies mainly in their "glycoforms" (a term which is used to describe a set of oligosaccharides of a special pattern being attached to a same peptide chain). It is noteworthy that more than half of the triterpene saponins are glycosides of oleanolic acid or its derivatives, with one sugar chain attached through an ether linkage at C-3 and another through an ester linkage at C-28 (a so-called "bidesmosidic saponin").[1b] The isolation of individual saponins from a plant species presents a formidable task, which hinders the further development of this important group of natural products. Chemical synthesis could remove this bottleneck; however, to date only a few studies on the chemical synthesis of saponins have been reported, and none of these addresses the construction of a bidesmosidic triterpene saponin.[2] Herein we report the first such synthesis of a bidesmosidic triterpene saponin (**1**), a compound first isolated from the leaves of a commonly used Chinese medicinal herb *Acanthopanax senicosus*.[3]

The recent development of glycosylation procedures and sophisticated protecting group strategies has enabled the syntheses of a number of naturally existing oligosaccharides and glycoconjugates.[4] However, the laborious protecting group manipulation required between each glycosylation step results in notorious low efficiency. To address this problem, the "one-pot sequential glycosylation" procedure has been developed, which depends on sufficiently disparate reactivities of a set of carefully designed carbohydrate building blocks.[5] Most of the reported one-pot protocols have been achieved by tuning the reactivities of the glycosyl donors through selective introduction of different protecting groups or leaving groups. Differences in reactivities of the hydroxyl groups or their masked forms (silyl ethers and trityl ethers) on the saccharide acceptors have also been exploited to steer the sequential glycosylations,[5a,f,6] in a strategy called "two-

**Scheme 1.** Retrosynthesis of Saponin **1**
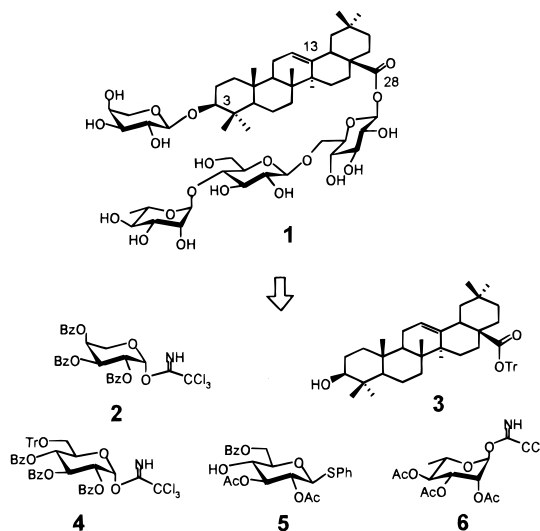


**Scheme 2.** Preparation of the Monosaccharide Building Blocks **2**, **4**, and **5**[a]
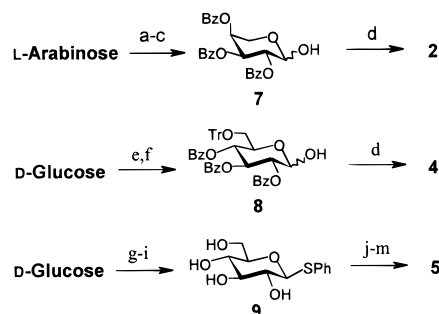


[a] Conditions: (a) BzCl, pyridine, 0 °C, 96%; (b) 33% HBr/HOAc, CH$_2$Cl$_2$, 1 h; (c) Ag$_2$CO$_3$, acetone, H$_2$O, 89% (two steps); (d) Cl$_3$CCN, DBU, CH$_2$Cl$_2$, ~90%; (e) TrCl, pyridine, 80 °C, 10 h, then BzCl, 0 °C, 96%; (f) H$_2$NNH$_2$·HOAc, DMF, 79%; (g) Ac$_2$O, pyridine, 100%; (h) PhSH, SnCl$_4$, CH$_2$Cl$_2$, 79%; (i) NaOMe, HOMe, 100%; (j) PhCH(OMe)$_2$, CSA (0.06 equiv), DMF; (k) Ac$_2$O, pyridine; (l) 80% HOAc, 50 °C, 75% (three steps); (m) BzCl, pyridine, −10 °C, 93%.

directional glycosylation".[6a−c] Thus in designing our synthesis of **1** we planned to use both the one-pot glycosylation[5] on the donor side and the two-directional glycosylation[6a−c] on the acceptor side.

As shown in Scheme 1, saponin **1** was disconnected into five readily accessible building blocks (**2**−**6**). The trityl ester **3** was easily prepared in quantitative yield by treating oleanolic acid with triphenylmethyl chloride (TrCl) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in refluxing tetrahydrofuran (THF). 2,3,4-Tri-*O*-benzoyl-β-L-arabinopyranosyl trichloroacetimidate (**2**), 2,3,4-tri-*O*-benzoyl-6-*O*-trityl-α-D-glucopyranosyl trichloroacetimidate (**4**), and phenyl 2,3-di-*O*-acetyl-6-*O*-benzoyl-1-thio-β-D-glucopyranoside (**5**) were readily synthesized using routine transformations (Scheme 2). 2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl trichloroacetimidate (**6**) is a known compound.[7]

As shown in Scheme 3, assembly of the acyl-protected saponin **14** was achieved by four successive glycosylation steps: (1) The

(1) (a) Rouhi, A. M. *Chem. Eng. News* **1995**, *73* (Sept 11), 28−35. (b) Hostettmann, K.; Marston, A. *Saponins*; Cambridge University Press: Cambridge, UK, 1995. (c) *Saponins Used in Traditional and Modern Medicine*; Waller, G. R., Yamasaki, K., Eds.; Advances in Experimental Medicine and Biology 404; Plenum Press: New York, 1996.

(2) For previous efforts on the total synthesis of saponins, see: (a) Randolph, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5693−5700. (b) Nishizawa, M.; Yamada, H. *Synlett* **1995**, 785−793. (c) Deng, S.; Yu, B.; Hui, Y. *Tetrahedron Lett.* **1998**, *39*, 6511−6514. (d) Deng, S.; Yu, B.; Lou, Y.; Hui, Y. *J. Org. Chem.* **1999**, *64*, 202−208.

(3) (a) Shao, C. J.; Kasai, R.; Xu, J. D.; Tanaka, O. *Chem. Pharm. Bull.* **1988**, *36*, 601−608. (b) Reference 1b, pp 337−341.

(4) (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155−173. (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212−235. (c) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531. (d) Boons, G.-J. *Contemp. Org. Synth.* **1996**, 173−200.

(5) For "one-pot glycosylation", see: (a) Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580−1581. (b) Yamada, H.; Harada, T.; Takahashi, T. *J. Am. Chem. Soc.* **1994**, *116*, 7919−7920. (c) Chenault, H. K.; Castro, A. *Tetrahedron Lett.* **1994**, *35*, 9145−9148. (d) Ley, S. V.; Priepke, H. W. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2292−2294. (e) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734−753. (f) Yamada, H.; Kato, T.; Takahashi, T. *Tetrahedron Lett.* **1999**, *40*, 4581−4584.

(6) For "two-directional glycosylation", see: (a) Zhu, T.; Boons, G.-J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1898−1900. (b) Zhu, T.; Boons, G.-J. *Tetrahedron Lett.* **1998**, *39*, 2187−2190. (c) Zhu, T.; Boons, G.-J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 857−861. (d) Boons, G.-J.; Bowers, S.; Coe, D. M. *Tetrahedron Lett.* **1997**, *38*, 3773−3776. (e) Boons, G.-J.; Zhu, T. *Synlett* **1997**, 809−811.

(7) Kitagawa, I.; Baek, N. I.; Ohashi, K.; Sakagami, M.; Yoshikawa, M.; Shibuya, H. *Chem. Pharm. Bull.* **1989**, *37*, 1131−1133.

**Scheme 3.** Assembly of Saponin **1** by Successive Glycosylation[a]
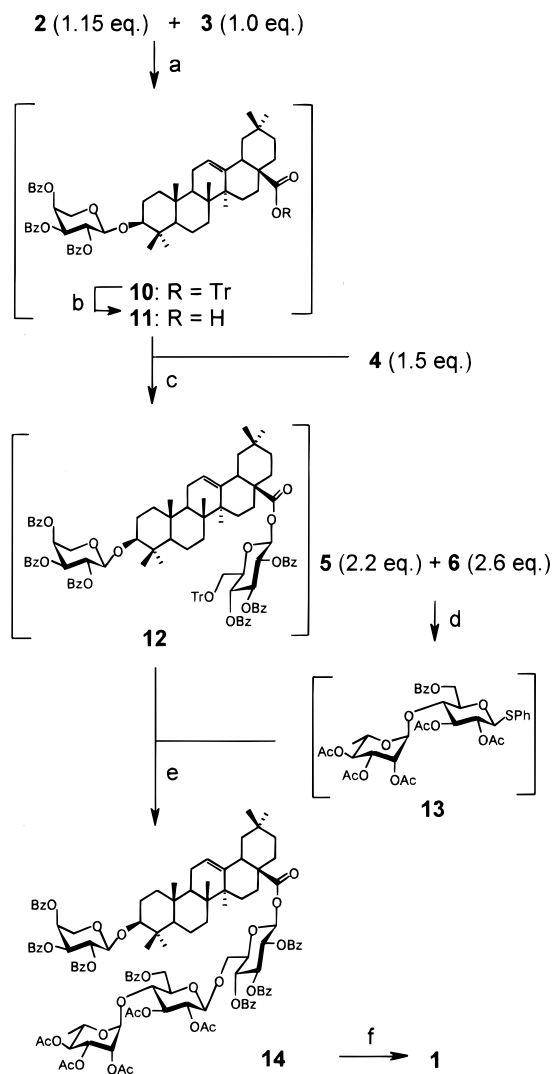


[a] The equivalents of the reactants and reagents were based on oleanolic ester **3**. Conditions: (a) TMSOTf (0.3 equiv), CH₂Cl₂, 4-Å MS, −60 °C, 20 min; (b) room temperature, 20 min; (c) 0 °C, 20 min; (d) TMSOTf (0.2 equiv), CH₂Cl₂, 4-Å MS, −70 °C to room temperature; (e) TMSOTf (1.5 equiv), NIS (3 equiv), CH₂Cl₂, 4-Å MS, −15 °C, 15 min, 62% (overall yields based on **3**); (f) 0.2% NaOMe, MeOH, CH₂Cl₂, room temperature, 2 h, 73%.

coupling of oleanolic ester **3** (1.0 equiv) with trichloroacetimidate **2** (1.15 equiv) was completed within 20 min in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.3 equiv) at low temperature (−60 °C), providing the desired glycoside **10**,[8] which was readily converted into the acid **11** upon warming to room temperature for 20 min. (2) Addition of a CH₂Cl₂ solution of the trichloroacetimidate **4** (1.5 equiv) into the above mixture at 0 °C resulted in the complete consumption of the reactants (**11** and **4**) within 20 min, affording

(8) The present conditions used for glycosylation of a sapogenin have been found to be ideal, see: Deng, S.; Yu, B.; Xie, J.; Hui, Y. *J. Org. Chem.* **1999**, *64*, 7265−7266.

**12**. (3) In the second flask, the phenyl thio-disaccharide **13** had been prepared during steps 1 and 2 by glycosylation of the thioglycoside **5** (2.2 equiv) with trichloroacetimidate **6** (2.6 equiv) under the promotion of TMSOTf (0.2 equiv).[5b] (4) Addition of the mixture in the second flask into the first, followed by addition of TMSOTf (1.5 equiv) and *N*-iodosuccinimide (NIS) (3.0 equiv)[6d] at −15 °C and stirring at this temperature for 15 min, led to the desired protected saponin **14** in 62% yield (after chromatography on silica gel, based on the oleanolic ester **2**). Remarkably, only 3 h was required to accomplish the four glycosylation steps and one chromatographic purification, and a per glycosylation yield of 89% was achieved. Selective removal of the acetate and benzoate protections in the presence of the C-28 ester glycosidic linkage (0.2% NaOMe/HOMe/CH₂Cl₂, room temperature) afforded the target saponin **1** in 73% yield.[9] The physical data obtained were essentially identical to those reported for the natural product.[3]

Progress of the successive glycosylation was conveniently monitored by thin-layer chromatography (TLC). On TLC plates, each desired intermediate (**10**−**14**) appeared as the dominant spot and was well separated from less mobile spots resulting from decomposition of the excess donors (**2**, **4**, **6**, **13**). The trityl group (Tr), which has seldom been used to protect a carboxylic acid,[10] appeared to have a pivotal role in the success of these transformations. Direct glycosylation of oleanolic acid (without the trityl ester protection) with various glycosyl donors resulted in a mixture of products, with the 13β,28-lactones being significant byproducts. Other protecting groups were found to be either too labile (e.g., trimethylsilyl, triethylsilyl) or too robust (e.g., *tert*-butyldimethyl silyl, allyl) for the protection of the 28-COOH, requiring an additional step for deprotection. Finally, the trityl ether on trichloroacetimidate **4** was stable under the conditions for the coupling with acid **11**, yet subsequently served as an acceptor under stronger conditions (TMSOTf/NIS, Scheme 3, step e).[6d]

In conclusion, the first chemical synthesis of a bidesmosidic triterpene saponin (**1**) was efficiently carried out using four successive glycosylation steps. The method used represents a conceptual advance in its use of two flasks[11] and the combination of one-pot glycosylation[5] and two-directional glycosylation[6] strategies. The present glycosylation procedure that has emerged should provide an efficient entry into not only related bidesmosidic saponins but also other complex glycoconjugates and their libraries.

**Supporting Information Available:** Experimental details and spectral/ analytical data for all new compounds (**2**−**14**) and saponin **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The ester glycosidic linkage at C-28 of a pentacyclic triterpene has been found to be rather resistant to basic hydrolysis. See ref 1b, pp 185, and references cited therein.

(10) (a) Murata, S.; Noyori, R. *Tetrahedron Lett.* **1981**, 22, 2107−2108. (b) Berlin, K. D.; Gower, L. H.; White, J. W.; Gibbs, D. E.; Sturm, G. P. *J. Org. Chem.* **1962**, *27*, 3595−3597.

(11) Zhu and Boons also employed two flasks in their sequential glycosylation, see ref 6e.