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Synthesis of a group of diosgenyl saponins by a one-pot sequential glycosylation

Biao Yu,[a,*] Hai Yu,[b] Yongzheng Hui[a,*] and Xiuwen Han[b]

[a]*State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

[b]*State Key Laboratory of Catalyst, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China*

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Abstract

A group of natural diosgenyl saponins was synthesized in a highly efficient manner employing the 'one-pot sequential glycosylation' protocol with the combined use of glycosyl trichloroacetimidates and thioglycosides.

Saponins are a structurally diverse class of plant glycosides, which have attracted much attention in recent years because of the host of biological activities they exhibit.[1] The structural diversity of saponins lies mainly in their sugar moieties which results in the extreme difficulty in isolation of these compounds.[1] Application of contemporary synthetic carbohydrate chemistry would provide a realistic route to this important group of natural products.[2]

As a result of the development of various glycosylation procedures and sophisticated protecting group strategies, it is now no longer a problem whether a naturally existing oligosaccharide can be synthesized;[3] and the new challenge is the efficiency of the oligosaccharide assembly. To tackle this challenge, the 'one-pot sequential glycosylation' strategy has recently been developed,[4–7] which performs two or more steps of glycosylation sequentially in one-pot, without the need for intermediate purification and protecting group manipulation between each glycosylation step. This one-pot approach has been achieved by taking advantage of the sufficient disparity between the reactivities of a set of glycosyl donors: either a set of donors with different protecting groups (armed or disarmed),[5,7] or a set of donors with different leaving groups.[4,6,7] The one-pot protocol developed by Takahashi et al. employed glycosyl trichloroacetimidates and thioglycosides as sequential glycosyl donors.[6] The first step of the coupling was between glycosyl trichloroacetimidate (Donor I) and thioglycoside (Donor II, which was actually an acceptor in this step) and was promoted by TMSOTf; then the resulting thiodisaccharide acted as a glycosyl donor upon addition of the second promoter (NIS) and the acceptor. The elegance of this protocol is: (1) glycosyl trichloroacetimidates and thioglycosides are the two most commonly used synthons in oligosaccharide synthesis and are readily accessible; (2) the activation of glycosyl trichloroacetimidates with TMSOTf

* Corresponding author.

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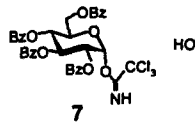
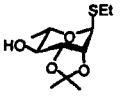
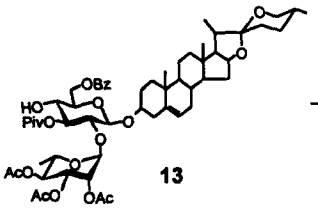
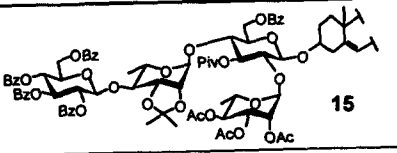
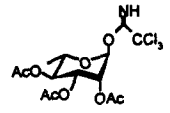
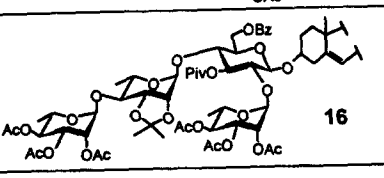
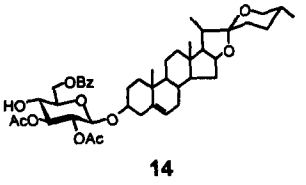
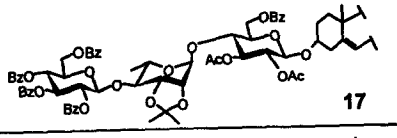
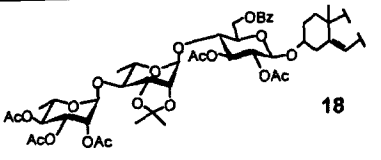
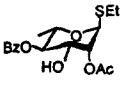
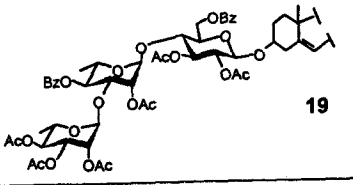
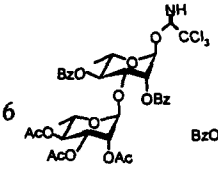
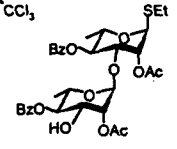
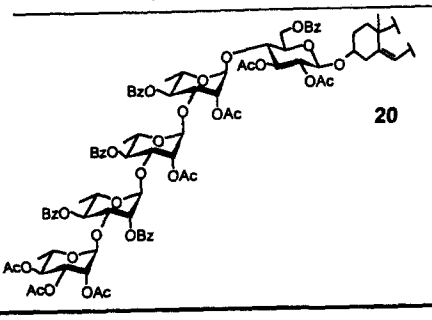
Table 1
One-pot synthesis of a group of diosgenyl saponins[12]

Entry	Donor I	Donor II	Acceptor	Product	Yield
1	 7	 10	 13	 15	96
2	 8	10		 16	98
3	7	10	 14	 17	90
4	8	10		 18	91
5	8	 11		 19	61
6	 9	 12		 20	62

and the activation of thioglycosides with NIS and TfOH (which is generated from the first step via TMSOTf hydrolysis) are distinguishable, with no need to control carefully the one-pot conditions. However, since the advent of this protocol, no further application has been reported. Herein, we report the synthesis of a group of diosgenyl saponins (**1–6**)[8–11] by utilization of this efficient protocol.

1 Gluβ-(1→4)-Rhaα-(1→4)-[Rhaα-(1→2)]-Gluβ-(1→3)-Diosgenin
2 Rhaα-(1→4)-Rhaα-(1→4)-[Rhaα-(1→2)]-Gluβ-(1→3)-Diosgenin
3 Gluβ-(1→4)-Rhaα-(1→4)-Gluβ-(1→3)-Diosgenin
4 Rhaα-(1→4)-Rhaα-(1→4)-Gluβ-(1→3)-Diosgenin
5 Rhaα-(1→3)-Rhaα-(1→4)-Gluβ-(1→3)-Diosgenin
6 Rhaα-(1→3)-Rhaα-(1→3)-Rhaα-(1→3)-Rhaα-(1→4)-Gluβ-(1→3)-Diosgenin

As shown in Table 1, readily accessible trichloroacetimidates (**7**,[13] **8**,[14] **9**[15]) (2 equiv.), thioglycosides (**10**,[16] **11**,[17] **12**[17]) (1.5 equiv.), and acceptors (**13**,[2a] **14**[18]) (1.0 equiv.) were used in the one-pot synthesis of the corresponding protected saponins (**15–20**).[12] The first step was carried out at a low temperature (–70°C) with a catalytic amount of TMSOTf (0.1 equiv.); a higher temperature (–10°C) resulted mainly in the intermolecular ethylthio group transfer.[19] In the second step, 1.0 equivalent of NIS was found enough to complete the coupling reaction (in Takahashi's report,[6] 5 equiv. of NIS was used). The yields were very high for the one-pot preparation of **15–18** (90–98% based on acceptors, entries 1–4), but moderate for the preparation of **19** and **20** (61% and 62%, respectively, entries 5–6). This is because the coupling of the trichloroacetimidate (**8**, **9**) with thioglycoside (**11**, **12**) through 1→3 linkage was relatively difficult: glycosylation of **8** with **11** led to the corresponding thiodisaccharide in 85% isolated yield. Treatment of **15–18** with 80% HOAc to cleave the propylidene group, followed with NaOH to remove the acyl protecting groups (Ac, Bz, and Piv) afforded the desired saponins **1–4** in good yields (81–87%). Treatment of **19** and **20** with NaOMe in HOMe to remove the Ac and Bz groups provided saponins **5** and **6** in 90% yields. The synthetic saponins **1–6** gave satisfactory data compared with those reported.[8–11]

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12. A typical procedure for the one-pot synthesis of saponins. To a stirred mixture of imidate **8** (220 mg, 0.30 mmol), thioglycoside **10** (50 mg, 0.20 mmol) and 4Å MS in dry CH_2Cl_2 (5 mL) at –70°C, was added a CH_2Cl_2 solution of TMSOTf (0.05 M, 0.4 mL) dropwise. After being stirred for 0.5 h, the acceptor **14** (100 mg, 0.13 mmol) was added, and the reaction temperature was elevated to –20°C, and then NIS (48 mg, 0.21 mmol) was added. The resulting mixture was stirred at –20°C for another 0.5 h, before the addition of Et_3N to quench the reaction. The mixture was filtered through a

pad of Celite. The filtrates were concentrated and applied to a silica gel column chromatography (petroleum ether:EtOAc 4:1) to provide the desired saponin **18** as a white solid (181 mg, 91% based on acceptor **14**).

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15. Trichloroacetimidate **9** was prepared as follows: glycosylation of allyl 2,4-di-*O*-benzoyl-α-L-rhamnopyranoside [see: Aspinall, G. O.; Crane, A. M.; Gammon, D. M.; Ibrahim, I. H.; Khare, N. K.; Chatterjee, D.; Rivoire, B.; Brennan, P. J. *Carbohydr. Res.* **1991**, *216*, 337] with 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl trichloroacetimidate (**8**) under the promotion of TMSOTf provided allyl 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→3)-2,4-di-*O*-benzoyl-α-L-rhamnopyranoside (88%), which was treated with $PdCl_2$ in dry MeOH to remove the anomeric allyl group [see: Liao, W.; Lu, D. *Carbohydr. Res.* **1996**, *296*, 171] followed by addition with Cl_3CCN,[3b] to furnish **9** in 50% yield.
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