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Synthetic Investigation toward QS-21 Analogues

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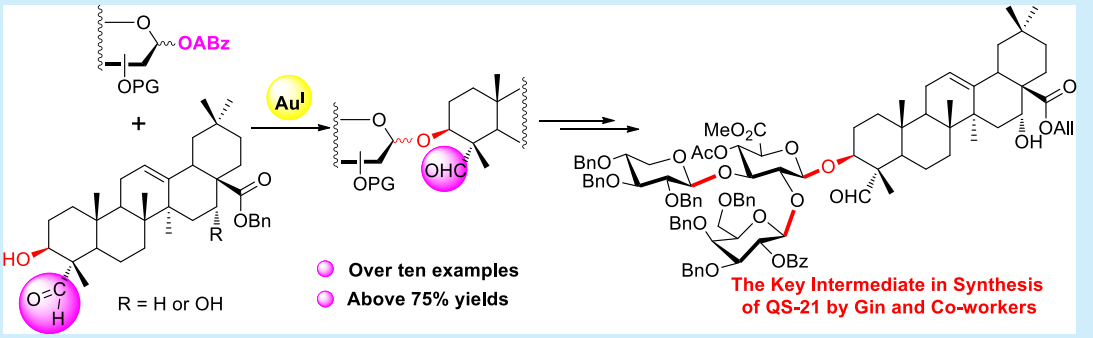

ABSTRACT: With glycosyl *o*-alkynylbenzotes as donors, a highly efficient protocol to construct the challenging glycosidic linkages at C3-OH of C23-oxo oleanane triterpenoids is disclosed, on the basis of which different strategies for the highly efficient synthesis of QS-21 analogues with the west-wing trisaccharide of QS-21 have been established.

The naturally occurring triterpene saponin QS-21, isolated from *Quillaja saponaria* tree bark, has proven to be one of the most potent vaccine adjuvants and has now been clinically evaluated in over 100 vaccines (Figure 1).[1−3] Despite the remarkable potency and extensive clinical studies, the evident drawbacks inherent to QS-21, including chemical instability,[4] limited supply,[5] and clinical toxicity,[2b] prevent its wide use. To tackle these problems, a highly efficient route to chemically synthesize QS-21 has to be established. Although extensive investigations have led to the successful synthesis of QS-21 and its analogues,[6−9] accessing these bioactive compounds is still by no means a trivial problem, as efficiency-limiting steps are encompassed in the established synthetic protocols, among which the most prominent one is the inefficient incorporation of the west-wing trisaccharide to the quillaic acid core via C3-OH because of the strong electron-withdrawing effect of the C23 carbonyl group (59% yield, α/β = 1:7).[7] The efficiency-limiting glycosylation step impairs the overall efficiency of QS-21 and analogues thereof synthesis, thereby retarding the progress of searching for new adjuvant candidates as well.[8,9] Moreover, the C3 *O*-glycosidic linkages of C23-oxo oleanane triterpene are widely spread in other naturally occurring bioactive saponins.[10] Thus, a protocol for the efficient installation of sugar substituents to 3-OH groups of gypsogenin/quillaic acid is highly demanded.

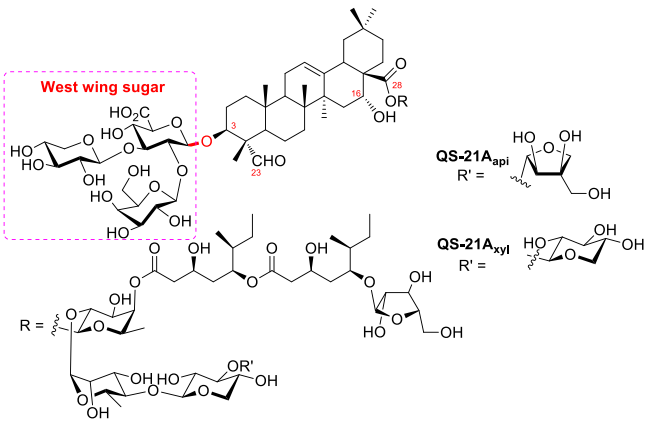

Figure 1. Chemical structures of QS-21.

The Yu glycosylation[11] was selected to forge the challenging glycosidic linkages of C3-OH groups of C23-oxo oleanane triterpenoids because it has exhibited excellent glycosylation capability.[12] Pleasantly, the coupling between benzyl gypsogenin ester **2**[13] and perbenzoylated glucosyl *o*-alkynylbenzoate (ABz) donor **1a**[14] provided the desired glycoside **3a** smoothly in 83% yield under the catalysis of $Ph_3PAuNTf_2$ (0.3 equiv) at 65 °C (Scheme 1, entry 1). Incorporation of an electron-donating silyl protecting group[14] (PG) or adoption of a superarmed protection pattern[15] led to more reactive donors **1b** and **1c**; their couplings with **2** proceeded efficiently even

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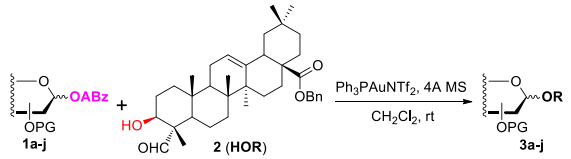
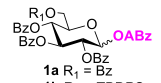
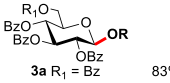
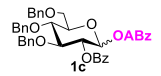
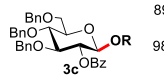
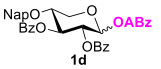
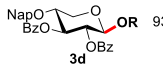
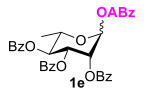
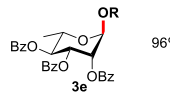
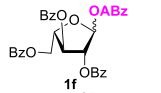
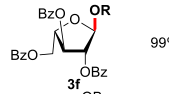
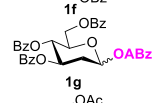
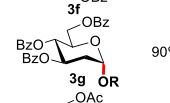
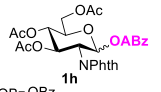
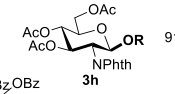
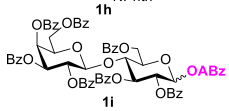
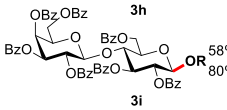
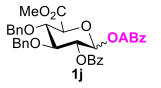
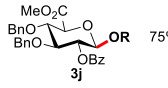
Scheme 1. Glycosylation of Gypsogenin 3-OH with Glycosyl *o*-Alkynylbenzoates as Donors



Entries	Donor	Catalyst (equiv)	Product	Yield (%)[a]
1				
2	**1a** R_1 = Bz **1b** R_1 = TBDPS	0.3 0.25	**3a** R_1 = Bz **3b** R_1 = TBDPS	83% (only β)[b,c] 92% (only β) 89% (only β)[d]
3		0.25		98% (only β)
4		0.25		93% (only β)
5		0.25		96% (only α)
6		0.25		99% (only α)
7		0.25		90% (only α)
8		0.25		91% (only β)
9		0.25 0.3		58% (only β)[e] 80% (only β)[c]
10		0.25		75% (only β)

[a]Isolated yields. [b]When conducted at room temperature under the effect of 0.25 equiv of Au(I) complex, the ortho ester was the only detected product at room temperature. [c]The reaction was conducted at 65 °C. [d]Yield obtained in a gram-scale synthesis. [e]21% of **2** was recovered.

under the standard conditions, that is, 0.25 equiv of $Ph_3PAuNTf_2$ at room temperature (**3b** in 92% yield and **3c** in 98% yield; entries 2 and 3).[16] Of note, **3b** could be prepared on a gram scale, and only a slight drop in yield was observed (89%). Similarly, the pentose donors **1d** and **1f** were also viable donors for the protocol,[17] and the desired products **3d** and **3f** were obtained in excellent yields (entries 4 and 6). The rhamnosyl donor **1e**[17] was also competent to condense with **2** under the standard conditions, furnishing **3e** in 96% yield without any event (entry 5). Moreover, with 2-deoxyglucosyl ABz **1g** as the donor, the more challenging 2-deoxyglycosidic linkage was forged stereoselectively and efficiently to afford **3g** in 90% yield (entry 7), as is the case for **1h**, which provided glucosamine-decorated gypsogein **3h** in high yield (91%; entry 8). However, with disaccharide ABz **1i** as donor, disaccharide saponin **3i** was isolated in only 58% yield under the standard conditions (entry 9). As in the case of donor **1a**, the condensation yield was eventually improved to 80% by elevating the reaction temperature to 65 °C and increasing the amount of catalyst to 0.3 equiv (entry 9). Finally, the reaction of glucuronyl ABz donor **1j**[18] with **2** was examined since a glucuronyl moiety constitutes the core sugar of the left-wing trisaccharide of QS-21 and its analogues. Pleasantly, when the glycosylation between **2** and inert donor **1j**[18] was carried out under the standard conditions, the glycosylation product **3j** was isolated in a respectable 75% yield (entry 10), verifying the robustness of the established protocol.

With the protocol to forge the challenging glycosidic linkages at 3-OH of C23-oxo oleanane-type triterpenoids fixed, we then set out to investigate the strategies for the efficient synthesis of C23-oxo oleanane triterpene saponins bearing the left-wing trisaccharide of QS-21. To this end, trisaccharide saponins **4** and **5**, with gypsogenin and quillaic acid as aglycones, were chosen as the target molecules (Figure 2). The promising vaccine adjuvant bioactivity of compounds

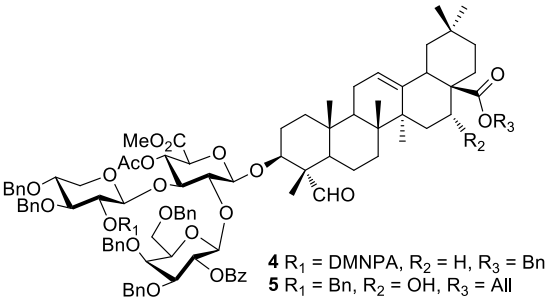


Figure 2. Chemical structures of **4** and **5**.

derived from truncated QS-21 and modified gypsogenin saponins[19] warrants the synthetic study of **4** and **5**, through which analogues with more structural variations than those derived directly from naturally occurring QS-21 could be obtained. In addition, the highly efficient synthesis of **5** holds the promise to improve the overall synthetic efficiency of QS-21 because it was used as an advanced intermediate in the first total synthesis of QS-21.[7]

The synthetic investigation commenced with the preparation of glycosyl ABz donors **10**, **13**, and **15** required for the fabrication of the west-wing trisaccharide of QS-21 (Scheme 2). Selective oxidation of diol intermediate **6**[20,21] and subsequent carboxylic group methylation delivered **7** (75% over two steps), which was followed by acetylation and deallylation under conventional conditions to afford **8** (82% over two steps). Silylation of **8** provided **9** (89% yield), which was then subjected to anomeric ABz installation to finish the preparation of glucuronyl donor **10** (80% over two steps). Under the effect of DMNPAA and TMSOTf,[22] **11**[23] was converted to **12** (93%), which was then transformed to **13** via a sequence of $PdCl_2$-mediated deallylation and dehydrative acylation (82% over two steps). Following procedures similar to those used for the synthesis of **13**, the preparation of galactosyl ABz donor **15** was straightforward with **14**[24] as the starting material (85% over two steps). All three Yu donors were equipped with acyl groups at the C2-OH, whereby the neighboring group participation effect could be exploited to secure the 1,2-*trans* stereoselectivity in the ensuing glycosylation reactions. Moreover, the mutual orthogonality of the DMNPA group to the generally applied PGs including AZMB, Bz, and Ac could simplify the protecting group manipulations, thus potentially further improving the efficiency of the synthesis.

To secure both structural variations and high overall efficiency, different strategies were investigated during the

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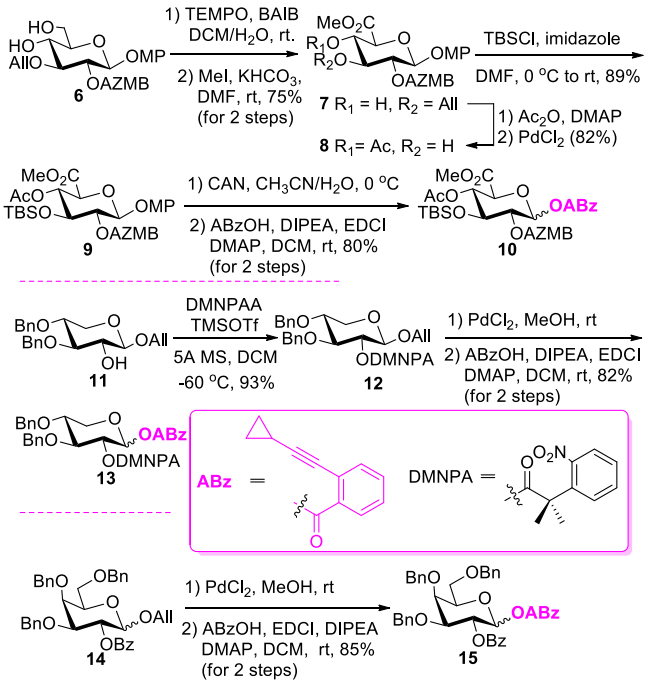
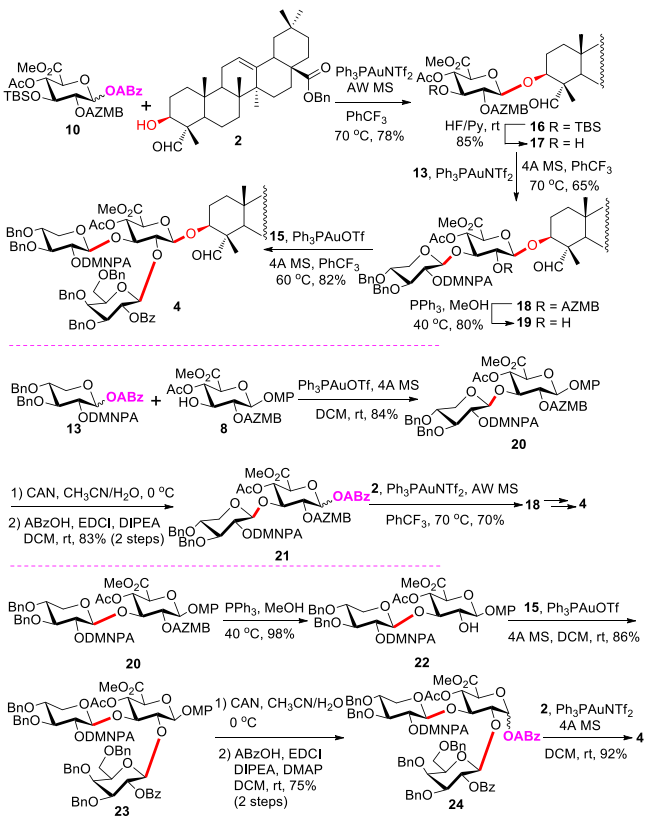
Scheme 2. Synthesis of Glycosyl *o*-Alkynylbenzoate Donors



synthetic investigation toward **4** (Scheme 3).[25] However, a problem was encountered in the first step of the linear strategy. Although an electron-donating TBS group was installed in donor **10**, an evident reactivity drop was still observed in comparison with **1j**. Thus, efficient glycosylation was achieved only at low concentration (0.002 M) and elevated temperature (70 °C) with AW MS as the desiccant and benzotrifluoride (BTF)[26] as the solvent (**15**, 78% yield).[27] Removal of the TBS group in **15** generated **17** (85%), which was ready for sugar chain elongation. As the C3-OH was flanked by two electron-withdrawing acyl groups,[28] acceptor **17** exhibited diminished reactivity. Thus, the coupling between **17** and **13** was carried out under the effect of 0.3 equiv of Au(I) complex at 70 °C to provide **18** (65%). Cleavage of the AZMB group in **18** resulted in disaccharide acceptor **19**; the subsequent condensation between **19** and **15** furnished the desired trisaccharide saponin **4** under the catalysis of $Ph_3PAuOTf$ (82%).[29] The ^{13}C signals of the anomeric carbons of **4** residing at 100.6, 100.1, and 99.3 ppm verified the *β*-configuration of all freshly constructed glycosidic linkages.[30] Thus, counting from building blocks **2**, **10**, **13**, and **15**, **4** was obtained in 28% overall yield by the linear strategy.

Scheme 3. Synthesis of 4 via Different Strategies



To ensure high efficiency, accessing **5** via a convergent strategy was also attempted (Scheme 4). Similarly, the glycosylation of quillaic acid derivative **25** with trisaccharide donor **24** proceeded smoothly to give trisaccharide saponin **26** stereoselectively and efficiently (88%). It is worth mentioning that the stereoselectivity and chemical yield obtained here are much better than those reported in the literature.[7] Compound **26** was then exposed to saponification and benzylation[32] to afford **5** (60% over two steps), the key intermediate in the synthesis of QS-21 by Gin and co-workers. A comparison of the spectroscopic data of **5** with those reported in the literature was made, and a good accordance was observed.[27]

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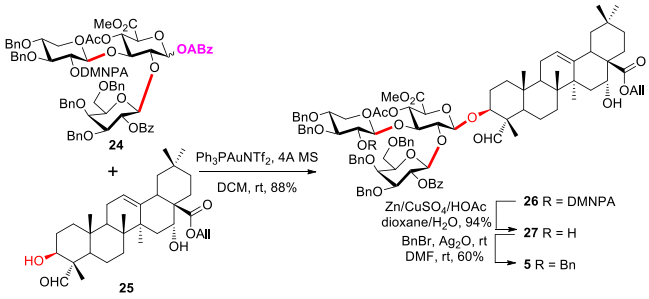
Scheme 4. Synthesis of the Key Intermediate 5 via a Convergent Strategy



In summary, a protocol featuring the Yu glycosylation has been discovered to construct the challenging 3-*O*-glycosidic linkages of C23-oxo oleanane triterpenenoids. The protocol enjoys a broad substrate scope and high efficiency, on the basis of which the highly efficient synthesis of gypsogenin/quillaic acid saponins bearing the west-wing trisaccharide of QS-21 has been achieved. Therefore, this provides a solution to break the chronic bottleneck restricting easy access to 3-*O*-glycosides of C23-oxo oleanane triterpenoids, including QS-21, which will facilitate access to these biologically relevant compounds and accordingly expedite the process of searching for novel and ideal adjuvant candidates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03185.

Experimental procedures, analytical data, and copies of 1D and 2D NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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