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Simple Glycosylation Reaction of Allyl Glycosides

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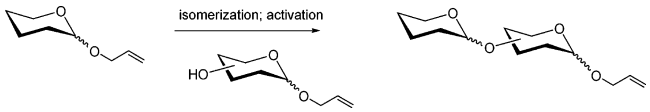

A simple glycosylation strategy employing only allyl glycosides is described. In a one-pot fashion, an allyl glycoside is first isomerized to the reactive 1-prop-en-yl glycoside intermediate, which subsequently undergoes glycosylation with a glycosyl acceptor, promoted by NIS at room temperature.

Chemical synthesis of structurally well-defined olio- or polysaccharides and glycoconjugates is of the utmost importance to life sciences.[1] Numerous efforts have been devoted to the development of novel glycosylation methodologies during the last several decades;[2] however, despite progress in the field, the synthesis of complex carbohydrates in an efficient fashion remains a challenging task.

Ideally, in the preparation of glycosylation building blocks, the group first installed at the anomeric position of an unprotected free sugar unit should remain at that position as a protecting group (PG) against further functional group adjustment on this glycosyl building block. At the glycosylation step, this same anomeric PG should serve as a latent leaving group (LG). In this manner, time-consuming anomeric group replacement (i.e., from PG to LG) and intermediate purification frequently encountered in a conventional carbohydrate synthesis can be avoided, dramatically improving the overall efficiency of an oligosaccharide synthesis. However, this straightforward strategy is difficult to execute due to the fact that commonly utilized LGs are not stable enough to be anomeric PGs. Although thio[3] and *n*-pentyl[4] groups merit themselves as anomeric PGs as well as anomeric LGs, consecutive utilization of thioglycosides or *n*-pentyl glycosides in an oligosaccharide synthesis from the reducing end often requires the anomeric group in the glycosyl acceptors to be properly disarmed to avoid undesired activation. This reactivity tuning process involves extensive protecting group manipulations and/or anomeric group modifications.[5,6]

Here, we report a simple glycosylation strategy wherein the anomeric PG placed in the very first step of a glycosylation building block preparation also acts as a latent LG. We envision that the widely used allyl group is ideal in serving this dual role (i.e., as a PG and LG) (Scheme 1). Thus, the readily available allyl glycoside **1** can be isomerized to the prop-1-enyl glycoside **2** that should be a reactive intermediate under certain activation conditions.[7] With the glycosyl acceptor **3**, a new saccharide **4** will form that can serve as a glycosyl donor for the next round of glycosylation also with an allyl glycoside acceptor. This iterative process may continue until the targeted oligosaccharide is synthesized. With this novel glycosylation strategy, preparation of an oligosaccharide can start from either the reducing end or the non-reducing end without any reactivity tuning of the anomeric group.

O-Allyl 2,3,4-tri-*O*-benzyl-D-xylopyranoside **5** ($\beta/\alpha = 3:1$) was first chosen as the donor to test the new approach (Scheme 2). Clean isomerization of **5** to the prop-1-enyl glycoside **6** was achieved in the presence of 1 mol % of $[Ir(COD)(PMePh_2)_2]$-PF_6, pre-activated with hydrogen, in THF at room temperature.[8] Upon completion of the isomerization in 90 min, THF was removed, and the glycosyl acceptor (NuH) in acetonitrile was

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(6) Several iterative glycosylation methods employing thioglycosides, which do not require anomeric group reactivity tuning, have been recently published: (a) Yamago, S.; Yamada, T.; Maruyama, T.; Yoshida, J.-I. *Angew. Chem., Int. Ed*. **2004**, *43*, 2145. (b) Huang, X.; Huang, L.; Wang, H.; Ye, X.-S. *Angew. Chem., Int. Ed*. **2004**, *43*, 5221. (c) Yamada, T.; Takemura, K.; Yoshida, J.-I.; Yamago, S. *Angew. Chem., Int. Ed*. **2006**, *45*, 7575.

(7) (a) The only known case of utilizing a prop-1-enyl glycoside as the glycosyl donor was reported by Sinaÿ and coworkers.[7c] In their procedure, a stoichiometric amount of TMSOTf was used as the promoter. (b) Sinaÿ et al.,[7c] Boons and Isles,[7d] and Chenault et al.[7e] also explored using other vinyl glycosides as glycosyl donors. (c) Marra, A.; Esnault, J.; Veyrieres, A.; Sinaÿ, P. *J. Am. Chem. Soc*. **1992**, *114*, 6354. (d) Boons, G.-J.; Isles, S. *J. Org. Chem*. **1996**, *61*, 4262. (e) Chenault, H. K.; Castro, A.; Chafin, L. F.; Yang, J. *J. Org. Chem*. **1996**, *61*, 5024.

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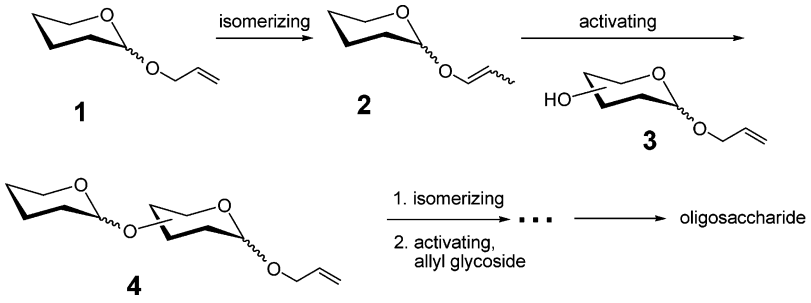
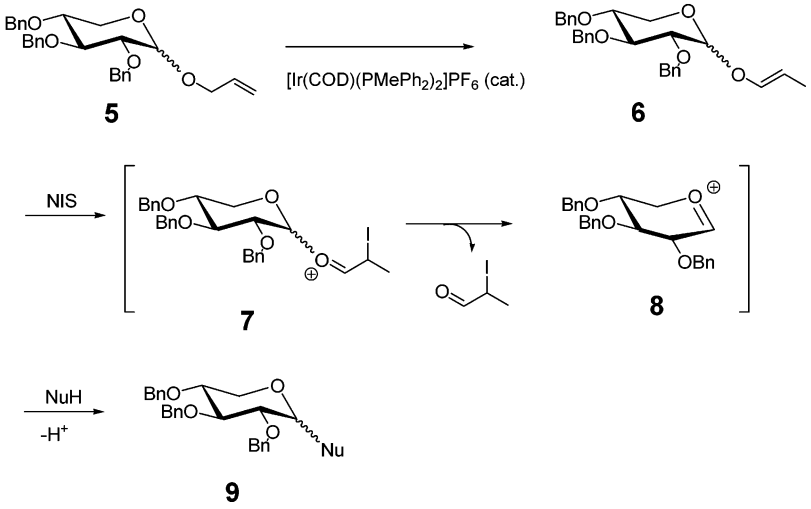
SCHEME 1



SCHEME 2



introduced. Treatment of the glycosyl donor and acceptor with NIS at room temperature afforded the desired glycosylation product within a few minutes.[9] Presumably, reaction of **6** with NIS led to the formation of the iodo oxocarbenium intermediate **7** and subsequently to the oxocarbenium **8**. In the presence of a glycosyl acceptor (NuH), a new glycoside **9** formed. With 1 equiv of allyl rhamnoside **10** as the glycosyl acceptor, disaccharide **11** was obtained in 74% yield with a β/α ratio of 1.6:1 after treatment of 1 equiv of NIS. The yield was further improved to 83% by increasing the donor/NIS/acceptor ratio from 1:1:1 to 1.5:1.5:1 (Table 1, entry 1). With acceptors **12** and **13**, the desired disacchrides **14** and **15** both were obtained in 85% yields by using 1.5 equiv of donors (Table 1, entries 2 and 3). The β/α ratios varied with different acceptors under the same reaction conditions, but the β anomers were always favored.

The same protocol was also extended to the glycosyl donor **16**. Thus, isomerization of **16** (β/α = 1:3) with 3% of the catalyst was completed in 90 min at room temperature. Subsequent glycosylation with acceptors **10**, **12**, or **17** afforded the disaccharides **18**−**20** in good yields (Table 1, entries 4−6). It is worth noting that acid sensitive isopropylidene groups in the products survived the reaction conditions (Table 1, entries 1, 3, and 4). Most importantly, the anomeric allyl protecting groups in the products remained intact (Table 1, entries 1, 2, and 4−6),[10] which will allow an iterative glycosylation approach to oligosaccharides with only allyl glycosides.

The new approach was further tested in the synthesis of a protected trisaccharide fragment of QS-21A$_{xyl}$, a powerful and frequently used immune adjuvant (Scheme 3).[11] The new glycosylation procedure with the glycosyl donor **14**β and the glycosyl donor **10** afforded the trisaccharide in 67% yield with a β/α ratio of 1.3:1 at the new bond formation site, favoring the desired **21**$\beta\beta$. With the three allyl building blocks **5**, **10**, and **12**, the protected trisaccharide fragment of QS-21A$_{xyl}$ was prepared in seven steps from unprotected D-xylose and L-rhamnose.

Alternatively, synthesis of the same trisaccharide was performed starting from the non-reducing end of the rhamnoside **10** (Scheme 3). Thus, the allyl xyloside **12** was first protected with a PMB group and then isomerized to the corresponding anomeric enol ether in the presence of 1 mol % of [Ir(COD)(PMePh$_2$)$_2$]PF$_6$ for 15 h at room temperature. Subsequent glycosylation with the acceptor **10** in acetonitrile activated by NIS provided the disaccharide **22** in 72% yield as a 1:1.6 α,β mixture, favoring the desired **22**β. Removal of the PMB group with DDQ afforded the glycosyl acceptor **23**β in 83% yield. The final step of glycosylation of **23**β with the donor **5** generated the trisaccharide in 75% yield as a 1:2 α,β mixture, favoring the desired anomer **21**$\beta\beta$.

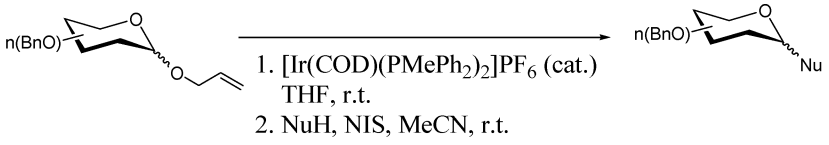
(8) (a) Baudry, D.; Ephritikhine, M.; Felkin, H. J. *Chem. Commun*. **1978**, 694. (b) [Ir(COD)(PMePh$_2$)$_2$]PF$_6$ is commercially available (CAS number: 38465-86-0). Other catalysts were not screened for the isomerization step.

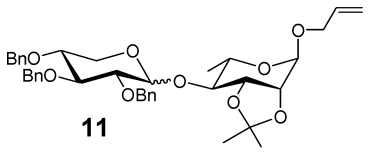
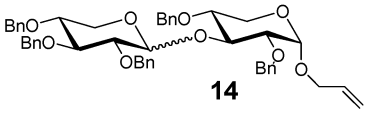
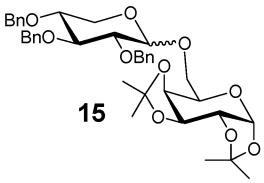
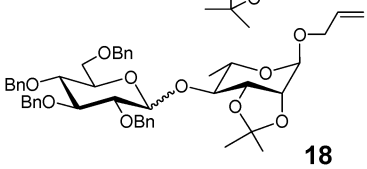
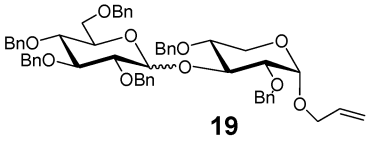
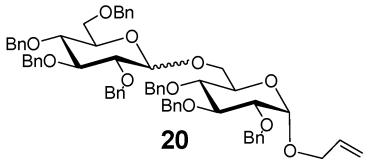
(9) (a) Treatment of prop-1-enyl glycosides with NIS or NBS in the presence of water has been used in removing allyl protecting groups in a two-step sequence.[9b] Interestingly, the replacement of water with other nucleophiles in this protocol for oligosaccharide synthesis had never been explored. (b) Halkes, K. M.; Slaghek, T. M.; Vermeer, H. J.; Kamerling, J. P.; Vliegenthart, J. F. G. *Tetrahedron Lett.* **1995**, *36*, 6137.

(10) Prolonged reaction time did not lead to observable isomerization of the allyl group in the products in the presence of the iridium catalyst residue.

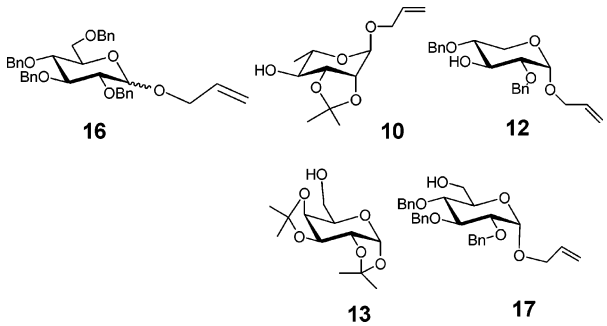
(11) Wang, P.; Kim, Y.-J.; Navarro-Vallalobos, M.; Rohde, B. D.; Gin, D. Y. *J. Am. Chem. Soc*. **2005**, *127*, 3256 and references cited therein.

TABLE 1. One-Pot Glycosylation of Allyl Glycosides



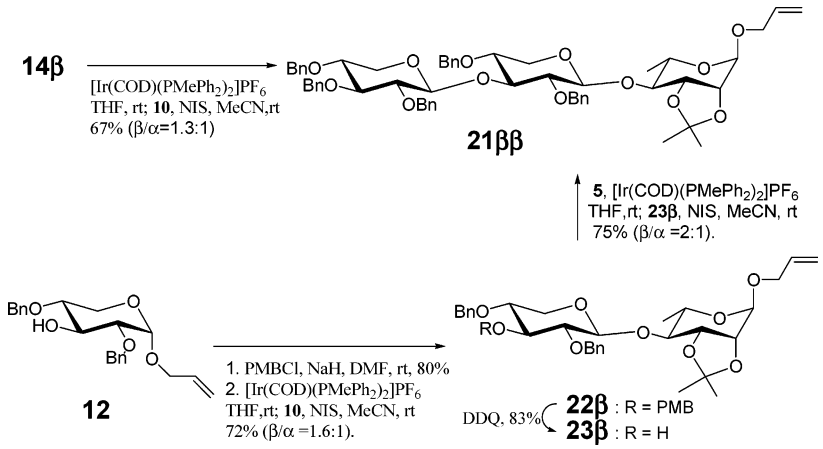
Entry	Donor	Acceptor	Product	Yield (β/α)[a]
1	**5**	**10**	 **11**	74% (1.6:1) [b] 83% (1.6:1) [c]
2	**5**	**12**	 **14**	85% (2.1:1)[c]
3	**5**	**13**	 **15**	85% (3.2:1) [c]
4	**16**	**10**	 **18**	68% (1.7:1)[d]
5	**16**	**12**	 **19**	62% (2.7:1)[d]
6	**16**	**17**	 **20**	65% (4:1)[d]

[a] Two anomers were separated by flash column chromatography. [b] Donor/NIS/acceptor = 1:1:1. [c] Donor/NIS/acceptor = 1.5:1.5:1. [d] Donor/NIS/acceptor = 2:2:1.



In summary, a simple glycosylation strategy employing only allyl glycosides was described. In a one-pot fashion, an allyl glycoside was first isomerized to the reactive 1-prop-en-yl glycoside intermediate that subsequently underwent glycosylation promoted by NIS at room temperature. This single procedure can be repeatedly used to prepare oligosaccharides.

SCHEME 3



However, with NIS as the activator, disarmed glycosides did not undergo the desired glycosylation. Further exploration to expand the application scope of this method is in progress.

Experimental Section

General Procedure for the Glycosylation Reaction (Synthesis of Disaccharide 14[12]). $[Ir(COD)(PMePh_2)_2]PF_6$ (13 mg, 0.015 mmol) in 1.0 mL of THF was degassed and stirred under hydrogen atmosphere for 15 min at room temperature. The clear solution obtained was injected to *O*-allyl 2,3,4-tir-*O*-benzylxylopyranoside **5** ($\beta/\alpha = 4:1$) (622 mg, 1.35 mmol) in 10 mL of THF under nitrogen at room temperature. The reaction mixture was stirred for 90 min, and THF was removed. The residue was azeotroped with toluene and then was treated with *O*-allyl 2,4-di-*O*-benzyl-α-D-xylopyranoside **12** (370 mg, 1.0 mmol) in 5.0 mL of acetonitrile, followed by NIS (304 mg, 1.5 mmol). The reaction was stirred under argon at room temperature for 15 min. The reaction solution was then concentrated and purified with flash column chromatography (eluted with benzene/ethyl acetate 19:1) to afford a mixture of **14***β* and **14**α, 641 mg (85%), R_f 0.24. The mixture of anomers was separated by a second flash column and eluted with petroleum ether/ethyl acetate 7:1.

Disaccharide 14*β*. R_f 0.4 (petroleum ether/ethyl acetate 7:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.15 (m, 25H), 5.87 (m, 1 H), 5.27 (dq, J = 17.2, 1.5 Hz, 1 H), 5.20 (ddt, J = 10.3, 1.6, 1.1 Hz, 1 H), 4.96 (AB, J = 11.6 Hz, 1 H), 4.95 (d, J = 7.5 Hz, 1 H), 4.91 (AB, J = 11.0 Hz, 2 H), 4.86−4.80 (m, 2 H), 4.72 (AB, J = 11.7 Hz, 1 H), 4.65 (AB, J = 12.0 Hz, 1 H), 4.62 (AB, J = 11.5 Hz, 1 H), 4.60 (AB, J = 10. 7 Hz, 1 H), 4.57 (d, J = 3.5 Hz, 1 H), 4.36 (AB, J = 11.7 Hz, 1 H), 4.26 (t, J = 9.1 Hz, 1 H), 4.09 ($ABMX_2$, J = 12.8, 5.1, 1.4 Hz, 1 H), 3.94 (dd, J = 11.5, 4.9 Hz, 1 H), 3.90 ($ABMX_2$, J = 12.8, 5.8, 1.1 Hz, 1 H), 3.67−3.50 (m, 4 H), 3.48−3.34 (m, 3 H), 3.16 (dd, J = 11.6, 10.0 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.0, 138.9, 138.8, 138.4, 138.3, 133.8, 128.7, 128.5, 128.5, 128.5, 128.2, 128.2, 128.0, 128.0, 128.0, 127.8, 127.8, 127.7, 118.5, 103.2, 95.4, 84.2, 83.0, 81.1, 78.5, 75.9, 75.8, 75.2, 73.6, 73.6, 73.5, 68.2, 63.9, 60.2; FTIR (neat) cm^{-1} 3062, 3030, 2886, 1496, 1363, 1076; HRMS (ESI) *m*/*z*: Calcd for $C_{48}H_{52}O_9Na$ (M + Na) 795.3509, found 795.3531.

Disaccharide 14α. R_f 0.30 (petroleum ether/ethyl acetate 7:1); ^{1}H NMR (400 MHz, CDCl3) δ 7.45−7.15 (m, 25 H), 5.60 (d, J = 3.5 Hz, 1 H), 5.30 (dq, J = 17.2, 1.6 Hz, 1 H), 5.22 (ddt, J = 10.3, 1.7, 1.1 Hz, 1 H), 4.92 (s, 2 H), 4.76−4.71 (m, 2 H), 4.68−4.52 (m, 7 H), 4.19 (t, J = 9.2 Hz, 1 H), 4.12 ($ABMX_2$, J = 11.5, 5.1, 1.4 Hz, 1 H), 4.10−4.04 (m, 1 H), 4.00−3.92 (m, 2 H), 3.59−3.46 (m, 5 H), 3.44 (dd, J = 9.7, 3.6 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2, 138.8, 138.4, 138.3, 138.0, 134.0, 128.8, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.8, 127.7, 127.7, 127.2, 118.6, 97.0, 95.2, 81.4, 80.0, 79.4, 78.8, 78.1, 75.8, 74.8, 73.6, 73.2, 73.0, 72.5, 68.2, 60.4, 59.6; FTIR (neat) cm^{-1} 3030, 2873, 1032; HRMS (ESI) *m*/*z*: Calcd for $C_{48}H_{52}O_9Na$ (M + Na) 795.3509, found 795.3537.

Acknowledgment. This work was supported by the University of Alabama at Birmingham. We thank Dr. M. Renfrow of the UAB Biomedical FT-ICR MS Laboratory for assistance in mass spectroscopy.

Supporting Information Available: General information, spectroscopic data, and NMR spectra for glycoside products **11**, **14**, **15**, **18**−**21**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Known compounds but no detailed spectroscopic data were reported. See: Fukase, K.; Hase, S.; Ikenaka, T.; Kusumoto, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 436.