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Stereoselective Glycosylation of *exo*-Glycals Accelerated by Ferrier-Type Rearrangement

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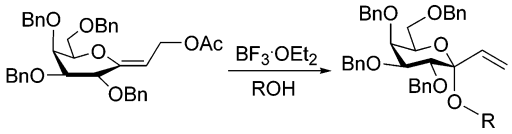
ABSTRACT



Owing to the driving force of the Ferrier-type rearrangement, the *exo*-glycals are highly reactive with various alcohols to afford glycosides and glycoconjugates with exclusive α-configuration. The resulting vinyl group in these glycosylation products can be further elaborated for general applications, including the synthesis of spiro derivatives and glycosylation of 2-ketoaldonic acids.

Glycosidic bond formation is the prerequisite to incorporate appropriate glycoforms into various biomolecules. It is well-known that *endo*-glycals (1,2-unsaturated sugars) are utilized as versatile building blocks in chemical glycosylations such as the Ferrier reaction and Danishefsky's glycal assembly procedure. Both methods have been developed as effective methods to synthesize various glycoconjugates, including Lewis and blood group determinants, gangliosides, and tumor-associated antigens,[1−5] as well as many bioactive natural products (e.g., forskolin[6] and cyclophellitol[7,8]). A Michael addition to 2-nitrogalactal, recently demonstrated by Schmidt et al., is another example to utilize *endo*-glycal for the synthesis of T_N, ST_N antigens, and other glycopeptides.[9] Therefore, it is reasonable that *exo*-glycals should be also synthetically valuable because these molecules can not only generate C-glycosidic linkages but also serve as useful glycosyl donors as aforementioned *endo*-glycals. However, the chemistry of *exo*-glycals is either rare or tedious in comparison with *endo*-glycals.[10] In search of a way to solve this problem, a general and efficient method has been devised by our group to prepare *exo*-glycals based on a nucleophilic

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(1) Williams, L. J.; Garbaccio, R. M.; Danishefsky, S. J. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2000; Vol. 1, pp 61−92.
(2) Seeberger, P. H.; Danishefsky, S. J. *Acc. Chem. Res.* **1998**, *31*, 685.
(3) (a) Zheng, C.; Seeberger, P. H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 786. (b) Zheng, C.; Seeberger, P. H.; Danishefsky, S. J. *J. Org. Chem.* **1998**, *63*, 1126. (c) Seeberger, P. H.; Eckhardt, M.; Gutteridge, C. E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10064.
(4) (a) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443. (b) Ciment, D. M.; Ferrier, R. J. *J. Chem. Soc. C* **1966**, 441.
(5) Danishefsky, S.; Kato, N.; Askin, D.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 360.
(6) Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1992**, *57*, 1065.
(7) (a) Vite, G. D.; Alonso, R.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 2268. (b) Henry, K. J.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 5128.
(8) (a) McDevitt, R. E.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 3250. (b) For a detailed review, please see: Fraser-Reid, B. *Acc. Chem. Res.* **1996**, *29*, 57.
(9) (a) Winterfeld, G. A.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2654. (b) Winterfeld, G. A.; Ito, Y.; Ogawa, T.; Schmidt, R. R. *Eur. J. Org. Chem.* **1999**, 1167. (c) Das, J.; Schmidt, R. R. *Eur. J. Org. Chem.* **1998**, 1609.
(10) (a) Praly, J.-P.; Chen, G.-R.; Gola, J.; Hetzer, G. Raphoz, C. *Tetrahedron Lett.* **1997**, *38*, 8185. (b) Molina, A.; Czernecki, S.; Xie, J. *Tetrahedron Lett.* **1998**, *39*, 7507. (c) Alcaraz, M.-L.; Griffin, F. K.; Paterson, D. E.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 8183. (d) Griffin, F. K.; Murphy, P. V.; Paterson, D. E., Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 8179. (e) Griffin, F. K.; Paterson, D. E.; Murphy, P. V.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2002**, 1305. (f) Belica, P. S.; Franck, R. W. *Tetrahedron Lett.* **1998**, *39*, 8225. (g) Yang, G.; Franck, R. W.; Bittman, R.; Samadden, P.; Arthur, G. *Org. Lett.* **2001**, *3*, 197.

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addition of sugar lactones and the subsequent dehydration,[11] which was found to be applicable to various saccharide precursors (including *gluco*-, *galacto*-, *manno*-, and *fuco*-types) and stereoselective to give the products of (*Z*)-configuration.[11c]

In our previous study,[12] *exo*-glycosyl ester **1** (Figure 1) reacted with several primary alcohols (e.g., allyl, ethyl, and

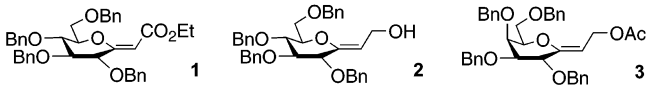


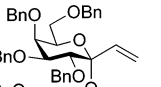
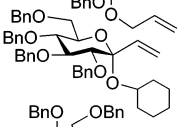
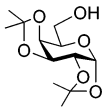
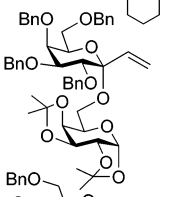
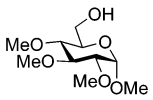
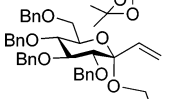
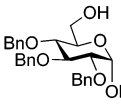
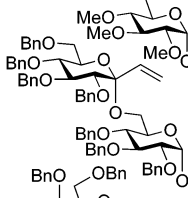
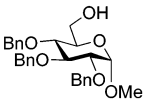
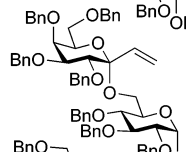
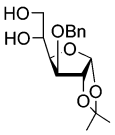
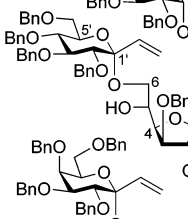
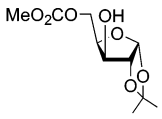
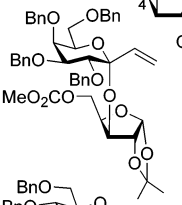
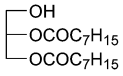
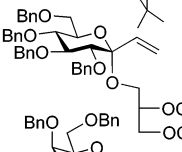
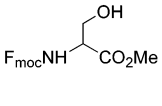
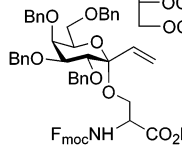
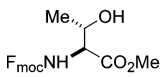
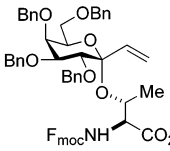
Figure 1. Structures of *exo*-glycals **1**−**3**.

benzyl alcohols) to afford unusual glycosides with both O- and C-glycosidic linkages. However, the yields of such Michael reactions with more hindered nucleophiles (e.g., cyclohexanol) decreased dramatically. Fortunately, we found that *exo*-glycosyl alcohol **2** (85% yield obtained from the reduction of **1**) and acetate **3** (derived from galactonolactone) were superior glycosyl donors. Herein we demonstrate that such *exo*-glycals undergo glycosylation reactions to give novel glycosides and glycoconjugates with excellent stereoselectivity.

In the presence of $BF_3{\cdot}OEt_2$, *exo*-glycals **2** and **3** reacted smoothly with a variety of alcohols ranging from simple to hindered ones to give exclusively α-glycosidation products **4**−**14** (Table 1). It is noted that all the products contain a vinyl group at the anomeric positions as characterized by the chemical shifts in their ^1H and ^{13}C NMR spectra. Therefore, the glycosylations of **2** and **3** should proceed via allylic rearrangement, reminiscent of the Ferrier reaction in the glycosylation of *endo*-glycals. All reactions led to the same stereochemical outcome at the anomeric centers, consistent with a nucleophilic attack from the bottom face of the sugar ring. All product structures were rigorously determined by DEPT and NOESY spectra in addition to other spectroscopic properties.[13] The three-bond carbon-proton coupling constant $^3J_{C,H}$ (∼1.6 Hz), related to the orientation of the H2′ and vinyl carbon (−*C*H═), supported the anomeric configuration of keto-glycosides in solution.[14] The structure of **8** was also corroborated by comparison with the reported NMR spectral data.[14b]

The cross-coupling of acetate **3** was relatively clean in comparison with the reaction of alcohol **2**, which might be

Table 1. Glycosylations of *exo*-Glycals **2** and **3** with Various Alcohols

entry	substrate	nucleophile	product (yield)
a	**3**		 **4** (95%)
b	**2**		 **5** (80%)
c	**3**		 **6** (90%)
d	**2**		 **7** (80%)
e	**2**		 **8** (68%)
f	**3**		 **9** (75%)
g	**2**		 **10** (72%)
h	**3**		 **11** (65%)
i	**2**		 **12** (65%)
j	**3**		 **13** (83%)
k	**3**		 **14** (70%)

[a] All reactions were carried out at 0 °C in CH_2Cl_2 with the alcohol nucleophile (1−2 equiv) in the presence of BF_3OEt_2 (1 equiv) and molecular sieves (4 Å).

accompanied by small amounts (∼10%) of the rearranged product **15** and the self-coupling product **16** (Figure 2). Glycosylation of **15** has been carried out to give **8**.[15]

(11) (a) Yang, W.-B.; Chang, C.-F.; Wang, S.-H.; Teo, C.-F.; Lin, C.-H. *Tetrahedron Lett.* **2001**, *42*, 4657. (b) Yang, W.-B.; Wu, C.-Y.; Chang, C.-C.; Wang, S.-H.; Teo, C.-F.; Lin, C.-H. *Tetrahedron Lett.* **2001**, *42*, 6907. (c) Yang, W.-B.; Yang, Y.-Y.; Gu, Y.-F.; Wang, S.-H.; Chang, C.-C.; Lin, C.-H. *J. Org. Chem.* **2002**, *67*, 3773.

(12) Chang, C.-F.; Yang, W.-B.; Chang, C.-C.; Lin, C.-H. *Tetrahedron Lett.* **2002**, *43*, 6515.

(13) For instance, the NOESY spectra of product **10** indicated the cross-peaks among H5′ (δ 3.89), H6a (δ 3.50), and H6b (δ 3.65). The data thus verified that the *C*-vinyl group is located at the β-position.

(14) (a) Tvaroska, I.; Taravel, F. R. *Adv. Carbohydr. Chem. Biochem.* **1995**, *51*, 15.(b) Li, X.; Ohtake, H.; Takahashi, H.; Ikegami, S. *Tetrahedron* **2001**, *57*, 4297. (c) Li, X.; Takahashi, H.; Ohtake, H.; Shiro, M.; Ikegami, S. *Tetrahedron* **2001**, *57*, 8053. (d) Schlesselmann, P.; Fritz, H.; Lehmann, J.; Uchiyama, T.; Brewer, C. F.; Hehre, E. J. *Biochemistry* **1982**, *21*, 6606.

(15) Some keto-glycosides including compound **8** have been studied for the glycosylation. Please see ref 14b for the details.

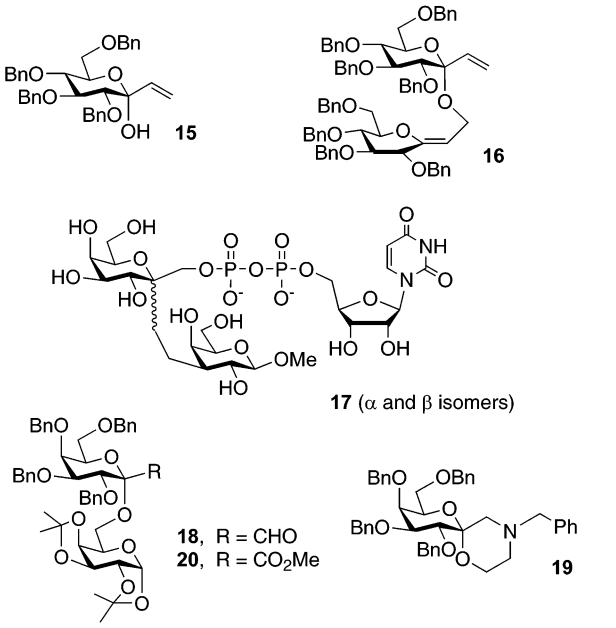


Figure 2. Structures of compounds **15**−**20**.

Nevertheless, under the same condition, in our hands the glycosylation of **15** with cyclohexanol in the presence of BF_3·OEt_3 only afforded a low yield (<15%) of glycosylation product **5**, in contrast to the high yielding (80%) reaction of **2** (entry b of Table 1). This example demonstrated that the Ferrier-type rearrangement greatly facilitated the glycosylations of the *exo*-glycal alcohol **2**, in comparison with an analogous mixed ketalization.[16]

Our current method is applicable to the synthesis of disaccharides (e.g., **6**−**11**), glycolipids (e.g., **12**), and glycopeptides (e.g., **13** and **14**) having quaternary anomeric centers,[17] which have exerted difficulty in the preparation of spiro compounds and carbohydrate synthesis. In the development of glycosyltransferase inhibitors, for instance, it is synthetically challenging to accommodate both glycosyl donor and acceptor. Schmidt and co-workers reported a new type of disubstrate-analogue inhibitors **17**.[18] Despite the potent inhibition exhibited by their molecules, the preparation was laborious. Furthermore, our results also show other significant features besides the high efficiency of the glycosylation reactions. Glycopeptides **13** and **14** mimic the essential core structure of T_N antigen.[19] The vinyl-containing products **5**−**14** are ready for further transformations. For instance, compound **6** was subjected to ozonolysis and followed by the treatment of Me_2S to generate aldehyde **18** (80% yield from **6**, Figure 2). This aldehyde provides a good opportunity for conjugation with biomolecules and attachment to solid supports. In addition to metathesis,[20] compound **4** was also subjected to ozonolysis and a subsequent reductive amination to afford a novel spiro molecule **19** (70% yield from **4**). Our method can be considered a way to achieve α-glycosylation reactions of 2-ketoaldonic acids (e.g., sialic acids[21] and KDO) because the vinyl group in the products can be converted to an ester via the intermediacy of aldehyde. For example, disaccharide ester **20** was obtained by oxidation of **18** with Ag_2O in MeOH.

In conclusion, this report represents the first investigation to apply the Ferrier reaction for the glycosidic bond formation of *exo*-glycals. The glycosylation of *exo*-glycals is successfully established to prepare various glycosides and glycoconjugates with the enhanced reactivity. The efficient glycosylations, even with hindered alcohol substrates, usually complete within 1 h at 0 °C. All functional groups on the sugar ring remain intact, contrary to the analogous reactions of *endo*-glycals in which two chiral centers at C2 and C3 are always missing. The glycosylation product contains a vinyl group that can be further elaborated for general purposes, such as in the preparation of spiro derivatives and glycosides of 2-ketoaldonic acid conjugates. At this stage, the latter application provides the products with O-glycosidic linkage in the axial position that is the same as KDO-containing glycosides but opposite to sialosides. It is possible to obtain the other stereochemical outcome by manipulating factors such as neighboring group participation and solvent effect. The investigation is currently in progress.

Acknowledgment. The authors thank Prof. Jim-Min Fang at National Taiwan University for his critical reading of this manuscript, and the financial support from the National Science Council of Taiwan and Academia Sinica, Taiwan.

Supporting Information Available: ^{1}H NMR spectra of compounds **1**−**16** and **18**−**20** and NOESY spectra of compounds **6**, **8**, and **10** to indicate the correlation in space of H2′ and the vinyl proton (−C*H*═CH_2), as well as H5′ and H6. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For representative examples, please see: (a) Trost, B. M.; Edstrom, E. D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 520. (b) Trost, B. M.; Edstrom, E. D.; Carter-Petillo, M. B. *J. Org. Chem.* **1989**, *54*, 4489.

(17) **Typical Glycosylation Procedure.**To a stirred solution of a glycosyl acceptor (1.0−2.0 equiv) and *exo*-glycal **2** or **3** (1.0 equiv) in anhydrous CH_2Cl_2 at 0 °C was added dropwise BF_3·OEt_2 (1.0 equiv) in the presence of 4 Å molecular sieves. The reaction was usually complete within 1 h. The reaction mixture was quenched by addition of saturated $NaHCO_3$ and extracted with CH_2Cl_2 for three times. The collected organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The resulting residue was subjected to silica gel chromatography (with hexanes and EtOAc) to afford the product.

(18) Waldscheck, B.; Streiff M.; Notz, W.; Kinzy, W.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 4007.

(19) (a) Hirohashi, S.; Clausen, H.; Yamada, T.; Shimosato, Y.; Hakamori, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7039. (b) Takahashi, H. K.; Metoki, R.; Hakamori, S. *Cancer Res.* **1988**, *48*, 4361.

(20) van Boom et al. also synthesized a series of spiroacetals by ring-closing metathesis of compound **4** and analogues. Please see: van Hooft, P. A. V.; Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 6061.

(21) (a) Cheng, M.-C.; Lin, C.-H.; Khoo, K.-H.; Wu, S.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 686. (b) Cheng, M.-C.; Lin, C.-H.; Wang, H.-Y.; Lin, H.-R.; Wu, S.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 772.