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Inter- and intramolecular alcohol additions to *exo*-glycals

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Abstract—Various *exo*-glycals were explored for the glycosidic bond formation and synthesis of spiroacetals in a stereoselective manner. The former reaction was an intermolecular alcohol addition to give the *S* new stereogenic center, resulting from the nucleophilic attack from the bottom face of the sugar ring. The latter one was carried out by the hydroboration of a sugar diene, followed by a subsequent acid workup.

endo-Glycals (1,2-unsaturated sugars) have been well recognized as versatile building blocks in the preparation of numerous biomolecules. For example, the glycal assembly method, developed by Danishefsky et al., has offered a novel and efficient strategy to synthesize Lewis and blood group determinants, gangliosides, and tumor-associated antigens.[1–7] *endo*-Glycals are also chiral precursors for biologically interesting compounds such as staurosporine[8] and brevetoxin B,[9] as well as substrates for a variety of chemical transformations including azidonitration[10,11] and Michael addition to 2-nitrogalactal.[12–14] Therefore, it is reasonable that *exo*-glycals can be widely utilized with the same great potential as *endo*-glycals.

1-*exo*-Methylene sugars, the simplest members in the *exo*-glycal family, have been used as valuable glycosidase inhibitors,[15] and applied for the synthesis of *C*-glycosides.[16] However, the reactions of *exo*-glycals have not been investigated in detail, which is attributed to no universal procedures of preparation. The reported syntheses of substituted or specially functionalized *exo*-glycals usually require more laborious efforts, including Keck reaction of glycosyl dihalides,[17] Wittig olefination of sugar lactones,[18] Ramburg-Bäcklund rearrangement of *S*-glycosides,[19,20] and [2,3]-Wittig sigmatropic rearrangement.[21] We recently presented a general method to synthesize *exo*-glycals by a nucleophilic addition of fully protected sugar lactones and the subsequent dehydration.[22,23] The method is applicable to the *gluco*-, *galacto*-, and *manno*-type precursors, and stereoselective to give exclusively the (*Z*)-isomers of *exo*-glycals.[23] Herein we demonstrate inter- and intramolecular addition reactions of *exo*-glycals leading to a new stereocenter at the anomeric position. To build up the chemistry with high stereoselectivity is indeed a synthetic challenge, the importance of which can be appreciated by the example as follows. Schmidt's group recently reported a novel and potent galactosyltransferase inhibitor based on the design of disubstrate analogue.[24] The synthesis took more than six reaction steps from fully protected galactonolactone to construct two tethers extending from the anomeric center.[24]

exo-Glycals were first explored for glycosidic bond formation. Sugar diene **1** was subjected to the addition of allyl alcohol in the presence of BF_3–OEt_2 to give a single product **2** in 51% yield (entry a of Table 1). On the basis of NOESY analysis, compound **2** was determined to have a *C*-substituent on the β-position and an *O*-allyl group on the α-position.[25] The reactivity was greatly improved as the ethylene substituent was replaced with carboxyethyl ester (entry b). Table 1 also demonstrated the Michael addition reactions to conjugated esters **3**–**5** to generate products **6**–**14**, respectively. The reaction yields varied in different nucleophiles (e.g. entries b–f). Apparently the steric hindrance played the role here. When different types of *exo*-glycals were investigated (e.g. entries b, g and i), the significant difference in reactivity was observed. The *exo*-glycal of *manno*-type was more reactive than those of *gluco*- and *galacto*-types.

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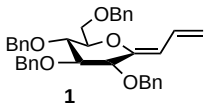
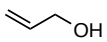
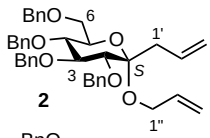
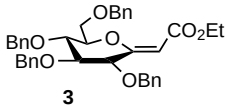
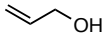
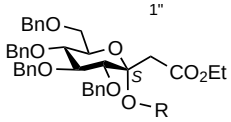
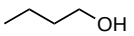
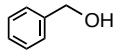
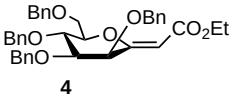
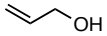
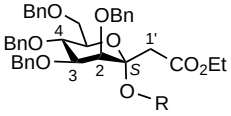
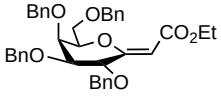
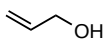
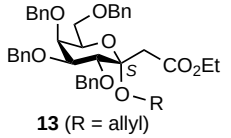
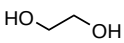
Table 1.

entry	substrate	nucleophile[b]	time	product	yield
a	 **1**		24 h	 **2**	51%
b	 **3**		12 h	 **6** (R = allyl)	92%
c	**3**		24 h	**7** (R = ethyl)	89%
d	**3**		16 h	**8** (R = 1-butyl)	93%
e	**3**		24 h	**9** (R = benzyl)	78%
f	**3**		24 h	**10** (R = 2-propyl)	53%
g	 **4**		6 h	 **11** (R = allyl)	98%
h	**4**		10 h	**12** (R = ethyl)	91%
i	 **5**		12 h	 **13** (R = allyl)	95%
j	**5**		16 h	**14** (R = CH_2CH_2OH)	99%

[a] Reaction conditions: all the reactions were carried out at 25 °C in CH_2Cl_2 in the presence of $BF_3{\cdot}OEt_2$ (5 eq) and 4 Å molecular seives.
[b] 10 equivalents of nucleophiles were added.

In addition, all the reactions led to the same stereochemical outcome; i.e. the *S*-configuration was obtained at the anomeric center of all the products. The stereochemistry was consistent with a nucleophilic attack from the bottom face of the sugar ring. All the product structures were supported by DEPT[26] and NOESY spectra in addition to other spectroscopic properties. For instance, the NOESY spectra of ester **11** indicated the cross peaks between H1′ (δ 3.22) and H2 (δ 4.33); the ones between H1″ (δ 4.10)[27] and H5 (δ 3.66). The data thus verify the *O*-allyl group located at the α-position. It is of interest that the spatial correlation always exists between H-1″ and H-5 among all the glycoside products, consistent with that between H-1′ and H-2.

Furthermore, the addition reactions to *exo*-glycals were carried out intramolecularly by a built-in alcohol. In our previous work the hydroboration of *exo*-glycosyl diene **15** resulted in the formation of isomeric spiroacetals **16** under an acidic workup condition, as shown in Fig. 1.[22a] The result was realized due to the selective functionalization of the terminal olefin and a subsequent acid-catalyzed cyclization.[22a] Further studies on various types of sugar dienes **17**–**21** (Fig. 1) including *gluco*-, *galacto*-, *manno*-, and *fuco*-type precursors revealed several interesting features. Some of the glycosyl spiroacetals can be obtained in a stereoselective manner. The hydroboration of dienes **17**–**19**, quenched by oxidation with H_2O_2 and camphor sulfonic acid (CSA), gave spiroacetals **22**–**24** as a single isomer, respectively. On the other hand, when dienes **20** and **21** were individually subjected to the same conditions, only moderate selectivity was observed and pairs of separable isomers were obtained in ratios of 3:1 (**25**/**26**) and 8:1 (**27**/**28**), respectively. A mixture of **25** and **26** (3/1) were deprotected using TBAF and benzylated to give the known compounds **29** and **30** in the ratio of 3/1.[28] Upon treatment with trifluoroacetic acid (TFA), only the former product **29** was left as the thermodynamically favored isomer. The result was in accordance with the anomeric effect. Likewise, fully benzylated spiroacetals **31** and **32** (as a mixture of 8/1) can be derived from the mixture of **27** and **28** (8/1). Compound **32**

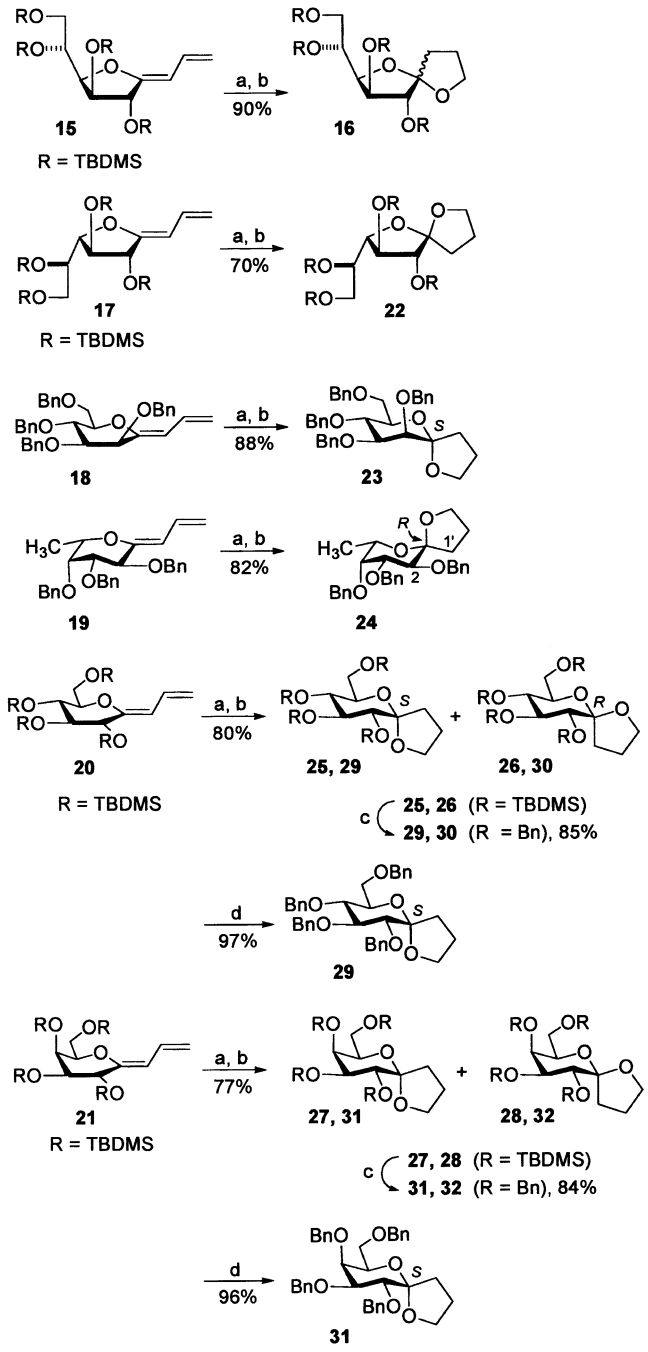


Figure 1. *Reagents and conditions*: (a) BH_3–THF; (b) H_2O_2, CSA; (c) (i) TBAF; (ii) NaH, BnBr; (d) TFA.

completely converted to the other more stable isomer **31** under the condition of TFA.

The new stereogenic center of the spiro sugars was diagnosed by comparison with the reported NMR spectral data (e.g. compounds **29** and **30**)[28] or NOESY studies. For instance, the NOESY spectra of spiroacetal **24** indicated the cross peaks between H1′ (δ 1.95) and H2 (δ 4.03), which thus supported *R*-configuration at C1 position.[29] The stereochemical configurations assigned for spiro sugars **23**, **24**, **29** and **31** were also favored by the anomeric effect.

During the formation of these spiro sugars, a homoallyl alcohol has been suggested to exist after the selective hydration of the terminal olefin,[22a] which was followed by the acid-catalyzed cyclization. According to Baldwin's rule for the five-membered ring closure, however, 5-*endo*-trigonal annulation (Fig. 2) is not favored. An oxocarbenium ion was thus proposed to be the plausible intermediate to qualify for the stereochemical requirement (5-*exo*-trigonal annulation) of Baldwin's ring forming processes.

Interestingly, when 2 equiv. of borane were used in the hydroboration of diene **17**, a *C*-glycosyl diol **33** was produced (Fig. 3). Further derivatization with *p*-bromobenzoyl chloride gave compound **34** as a crystalline product, suitable for single crystal X-ray analysis as shown in the ORTEP drawing in Fig. 3.[30] Thus the new stereogenic centers were corroborated to exhibit the (1*R*, 1′*R*) chirality. The result can be rationalized that the steric hindrance owing to the C2 silyl group forced the *syn* addition of borane to occur in the top face of the sugar ring. As a consequence, it is possible to prepare *C*-glycosides by the hydroboration of *exo*-glycals with high stereoselectivity.

In conclusion, *exo*-glycals were applied for the stereoselective alcohol additions to afford unusual glycosides with both *O*- and *C*-glycosidic linkages, as well as glycosyl spiroacetals. In addition to simple alcohols, we are currently utilizing sugars as nucleophiles to generate disaccharides or oligosaccharides, which will be reported in due course. Also it is of interest to investigate how various different factors affect the reactivity of *exo*-glycals, such as Lewis acid and substituted functionality.

Supplementary material available: ^1H and ^{13}C NMR spectra of compounds **2**, **6**–**14**, **22**–**25**, **28**–**34** and NOESY spectra of compounds **2**, **6**, **11**, **12**, **24** to indicate the correlation of H1′ and H2 in space were all included.

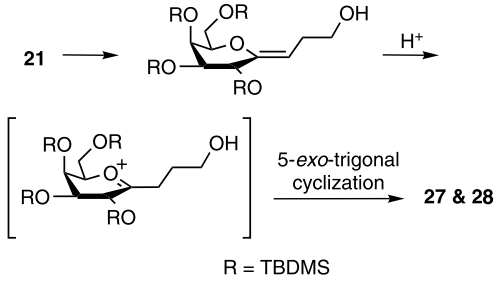


Figure 2.

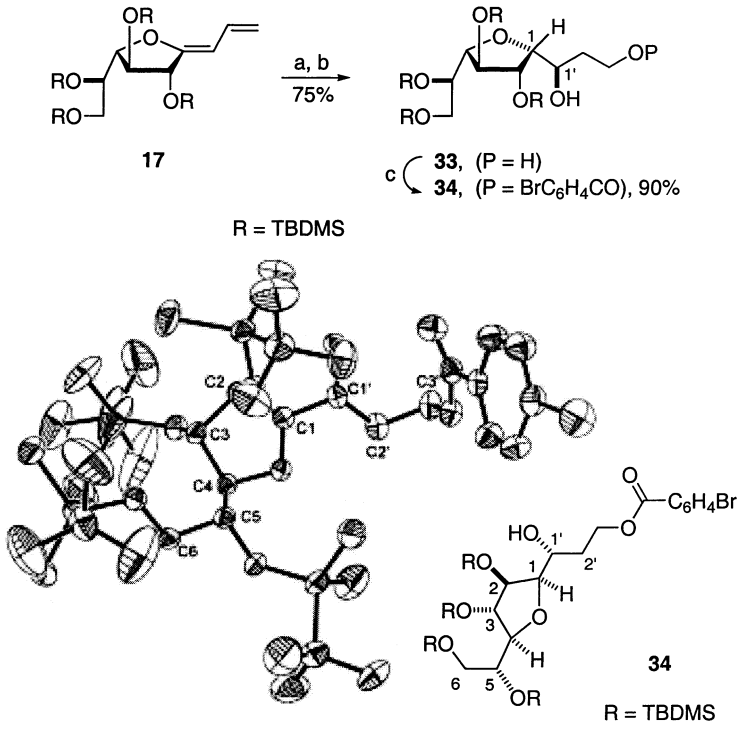


Figure 3. *Reagents and conditions*: (a) BH_3–THF (2 equiv.); (b) H_2O_2, NaOH; (c) *p*-bromobenzoyl chloride, pyridine.

Acknowledgements

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References

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. Seeberger, P. H.; Beebe, X.; Sukenick, G. D.; Pochapsky, S.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 491.
4. Zheng, C.; Seeberger, P. H.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 786.
5. Zheng, C.; Seeberger, P. H.; Danishefsky, S. J. *J. Org. Chem.* **1998**, *63*, 1126.
6. Seeberger, P. H.; Eckhardt, M.; Gutteridge, C. E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10064.
7. Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1318.
8. (a) Link, J. T.; Gallant, M.; Huber, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 3782; (b) Link, J. T.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 552; (c) Link, J. T.; Raghavan, S.; Gallant, M.; Danishefsky, S. J.; Ballas, M. *J. Am. Chem. Soc.* **1995**, *117*, 552.
9. Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K.; Somers, P. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1359.
10. Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1997**, *57*, 1244.
11. Paulson, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155.
12. Winterfeld, G. A.; Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 2654.
13. Winterfeld, G. A.; Ito, Y.; Ogawa, T.; Schmidt, R. R. *Eur. J. Org. Chem.* **1999**, 1167.
14. Das, J.; Schmidt, R. R. *Eur. J. Org. Chem.* **1998**, 1609.
15. (a) Hehre, E. J.; Brewer, C. F.; Uchiyama, T.; Schlesselmann, P.; Lehmann, J. *Biochemistry* **1980**, *19*, 3557; (b) Dettinger, H.-M.; Kurz, G.; Lehmann, J. *Carbohydr. Res.* **1979**, *74*, 301; (c) Fritz, H.; Lehmann, J.; Schlesselmann, P. *Carbohydr. Res.* **1983**, *113*, 71; (d) Brewer, C. F.; Hehre, E. J.; Lehmann, J.; Weiser, W. *Liebigs Ann.* **1984**, 1078; (e) Vasella, A.; Witzig, C.; Waldraff, C.; Uhlmann, P.; Briner, K.; Bernet, B.; Panza, L.; Husi, R. *Helv. Chim. Acta* **1993**, *76*, 2847.
16. (a) Smoliakova, I. P. *Curr. Org. Chem.* **2000**, *4*, 589; (b) Belica, P. S.; Franck, R. W. *Tetrahedron Lett.* **1998**, *39*, 8225; (c) Lay, L.; Nicotra, F.; Panza, L.; Russo, G.; Caneva, E. *J. Org. Chem.* **1992**, *57*, 1304.
17. (a) Praly, J.-P.; Chen, G.-R.; Gola, J.; Hetzer, G.; Raphoz, C. *Tetrahedron Lett.* **1997**, *38*, 8185; (b) Praly, J.-P.; Kharraf, Z. E.; Descotes, G. *Carbohydr. Res.* **1992**, *232*, 117; (c) Praly, J.-P.; Chen, G.-R.; Gola, J.; Hetzer, G. *Eur. J. Org. Chem.* **2000**, 2831.
18. (a) Xie, J.; Molina, A.; Czernecki, S. *J. Carbohydr. Chem.* **1999**, *18*, 481; (b) Molina, A.; Czernecki, S.; Xie, J. *Tetrahedron Lett.* **1998**, *39*, 7507.
19. (a) Alcaraz, M.-L.; Griffin, F. K.; Paterson, D. E.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 8183; (b) Griffin, F. K.; Murphy, P. V.; Paterson, D. E.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 8179; (c) For a detailed

review, see: Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.* **1999**, 217.
20. (a) Belica, P. S.; Franck, R. W. *Tetrahedron Lett.* **1998**, *39*, 8225; (b) Pasetto, P.; Chen, X.; Drain, C. M.; Franck, R. W. *Chem. Commun.* **2001**, 81; (c) Yang, G.; Franck, R. W.; Bittman, R.; Samadden, P.; Arthur, G. *Org. Lett.* **2001**, *3*, 197.
21. Lay, L.; Meldal, M.; Nicotra, F.; Panza, L.; Russo, G. *J. Chem. Soc., Chem. Commun.* **1997**, 1469.
22. (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.
23. Yang, W.-B.; Yang, Y.-Y.; Gu, Y.-F.; Wang, S.-H.; Chang, C.-C.; Lin, C.-H. *J. Org. Chem.* **2002**, *67*, 3773.
24. Waldscheck, B.; Streiff, M.; Notz, W.; Kinzy, W.; Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 4007.
25. The NOESY spectra of glycoside **2** indicated the spatial correlation between H1′ (δ 2.63) and H2 (δ 3.51), which thus verified the *C*-substituent located at the β-position.
26. The DEPT spectra of ester **11**, for example, indicated C1 (δ 101.2) to be a quartenary carbon.
27. C1″ is defined as the carbon next to the glycosidic oxygen.
28. Martin, A.; Salazar, J. A.; Suarez, E. *J. Org. Chem.* **1996**, *61*, 3999.
29. The NOESY and NOE experiments have been used for the characterization of similar molecules, see (a) Schweizer, F.; Inazu, T. *Org. Lett.* **2001**, *3*, 4115; (b) Wardrop, D. J.; Zhang, W., Fritz, J. *Org. Lett.* **2002**, *4*, 489.
30. Crystallographic data of **34** have been deposited with the Cambridge Crystallographic Data Centre as the deposition number CCDC 173784. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).