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Synthesis of Novel Fused Ring *C*-Glycosides

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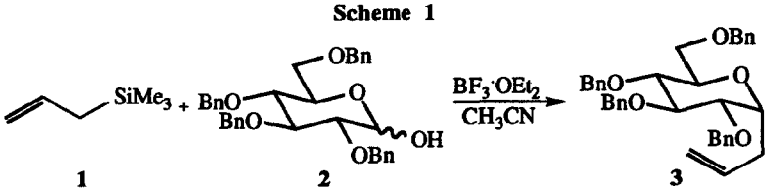
Abstract: The Lewis acid mediated addition of olefins to *O*-benzyl protected sugars is studied. The results show the formation of *C*-glycosides with α selectivity and a propensity to cyclize with loss of a benzyl group.

The formation of allyl *C*-glycosides is well established. For example, in the synthesis of palytoxin,[2] Kishi, *et al.*, utilized the reaction of allyl trimethylsilane, **1**, with 2,3,4,6-tetra-*O*-benzyl-D-glucose, **2**, to give the α-allyl-*C*-glycoside, **3**, in an anomeric ratio of 10:1. This type of reaction was reported by a number of researchers.[3]

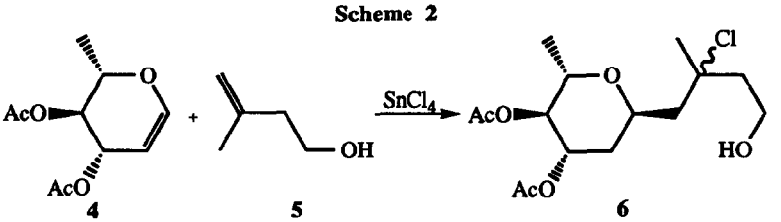
Scheme 1



1 **2** **3**

The reactions of olefins with glycals are also well documented sources of *C*-glycosides. For example, Herscovici, *et al.*, treated diacetyl L-rhamnal, **4**, with 3-methyl-3-buten-1-ol, **5**, to obtain the *C*-glycoside, **6**.[4] As similarly stated above, related reactions have found utility in many publications.[5]

Scheme 2



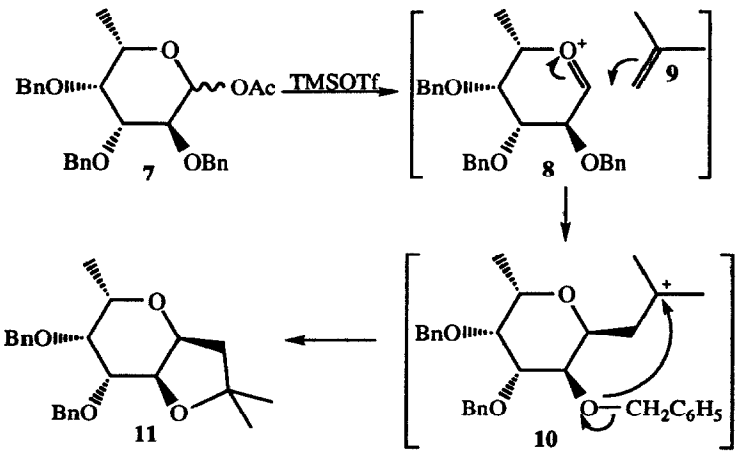
4 **5** **6**

While these examples illustrate precedence for the reaction of pyranose lactols with activated olefins and the reaction of pyranose glycals with unactivated olefins, there appears to be little or no precedence for the reaction of pyranose lactols, or derivatives thereof, with unactivated olefins.[6] We now report that 1-*O*-acetyl-benzyl protected pyranose sugars form *C*-glycosides with unactivated olefins in the presence of Lewis acids.

As shown in Scheme 3, the reaction of 1-*O*-acetyl-2,3,4-tri-*O*-benzyl-L-fucose, **7**, with isobutylene, **9**, and an excess of trimethylsilyl triflate gave the fused ring *C*-glycoside, **11**.[7] The reaction proceeded in >70%

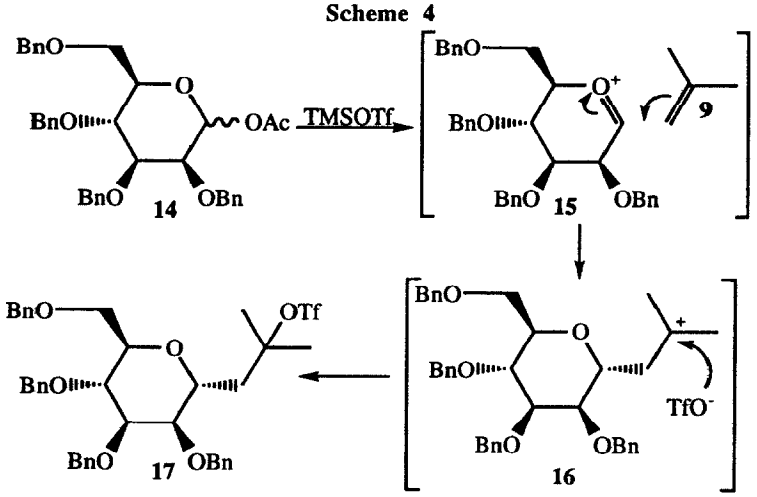
yield in both methylene chloride and acetonitrile. Additionally, $BF_3{\cdot}OEt_2$ could also be used. The proposed mechanism involves initial elimination of the acetate to form the oxonium ion, **8**. This species then undergoes a Prins-type[8] reaction with the olefin to give the tertiary carbocation, **10**. Spontaneous cyclization with loss of a benzyl cation gives the product.

Scheme 3



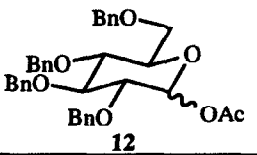
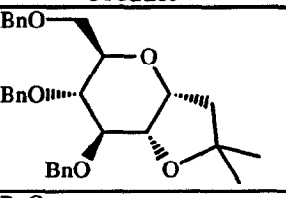
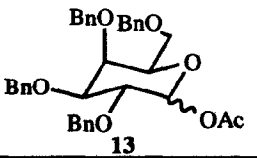
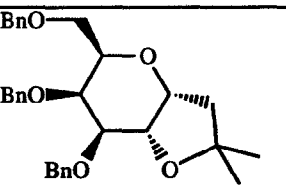
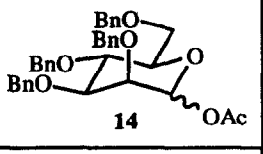
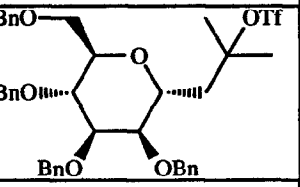
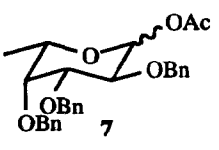
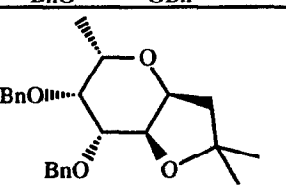
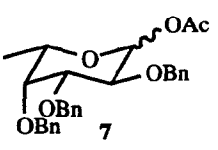
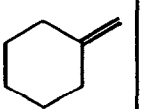
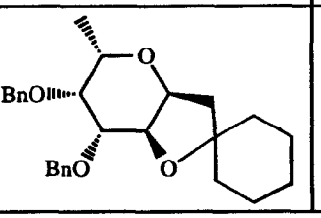
Exploring the generality of this reaction, we studied 1-*O*-acetyl-tetra-*O*-benzyl-D-glucose, **12**, 1-*O*-acetyl-tetra-*O*-benzyl-D-galactose, **13**, and 1-*O*-acetyl-tetra-*O*-benzyl-D-mannose, **14**. In all three cases, $BF_3{\cdot}OEt_2$ was found to be too weak a Lewis acid to effect this reaction. However, the reactions of these compounds with trimethylsilyl triflate and isobutylene are summarized in Table 1. An additional example with L-fucose and methylene cyclohexane is also included therein. In all cases, the fused ring products were formed in yields ranging from 70-80% and were easily purified by silica gel chromatography.

Scheme 4



When comparing the data presented in Table 1, the anomalous results observed in the D-mannose case (Entry C) can be explained as shown in Scheme 4. The initial α-*C*-glycosidation gives the tertiary carbocation, **16**. This preference places the newly formed bond *trans* to the 2-benzyloxy group. The high strain associated with a 6-5 *trans*-fused ring system disfavors attack by the oxygen of the neighboring group allowing the triflate anion to add to the tertiary carbocation giving **17** (yield unoptimized). The fact that the major isolated product was compound **17** lends support to the premise that the initial *C*-glycosidation is non-reversible and stereoselective. If any of the β anomer had formed, irreversible cyclization would be expected in the usual fashion as exemplified in the case of other pyranoses. Furthermore, if the glycosidation was an equilibrium process, we would expect that the bicyclic system would become the major product.

Table 1

Entry	Sugar	Olefin	Lewis Acid	Product	Yield
A	 **12**		TMSOTf		74%
B	 **13**		TMSOTf		76%
C	 **14**		TMSOTf		21%
D	 **7**		TMSOTf or BF_3·OEt_2		71%
E	 **7**		$SnCl_4$		78%

In a typical experiment, 1-*O*-acetyl-2,3,4-tri-*O*-benzyl-L-fucose (**7**, 10.24 g, 21.51 mmoles) was dissolved in methylene chloride (100 mL) and cooled to -10° C under argon utilizing an ice-salt bath.[9]

Isobutylene (50 mL) was condensed at -78° C and poured into the above solution. $BF_3{\cdot}OEt_2$ was added[10] and the reaction was maintained at -10° C for 30 minutes and quenched with saturated aqueous sodium bicarbonate solution (40 mL). After warming to room temperature over 1 hour, the layers were separated and the aqueous phase was washed with methylene chloride (50 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated to dryness. Purification of the residue on silica gel (15% ethyl acetate/hexane) gave the desired product (**11**, 5.84 g, 71%) as a colorless oil.[11]

In conclusion, we have demonstrated the feasibility of utilizing *C*-glycoside technology to form highly functionalized *cis*-fused tetrahydrofuran-tetrahydropyran ring systems in high yields. The structures present in nature containing this type of subunit include the halichrondrins,[12] the herbicidins,[13] and octosyl acid.[14] The synthetic approaches utilized to target these classes of compounds generally utilize aldol reactions and related chemistry. Two other methods for the formation of the structures contained herein have been described. The first, reported by Cabaret, *et al.*, involves the oxidative cyclization of α-*C*-allyl glycosides.[15] The second, reported by De Mesmaeker, *et al.*, involves a radical cyclization from 2-*O*-allyl selenoglycosides.[16] It is our hope that our new and generally applicable method for the formation of *cis*-fused tetrahydrofuran-tetrahydropyran ring systems will find utility within the general realm of synthetic organic chemistry.

References and Notes

1. Current address: Sugen, Inc. 515 Galveston Dr. Redwood City, CA 94063.
2. Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.
3. (a) Sorgi, K. L.; Kozikowski, A. P. *Tetrahedron Lett.* **1982**, *23*, 2281. (b) Danishefsky, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3803. (c) Hosomi, A.; Sakata, Y.; Sakurai, H. *Carbohydr. Res.* **1987**, *171*, 223. (d) Bennek, J. A.; Gray, G. R. *J. Org. Chem.* **1987**, *52*, 892. (e) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 223.
4. (a) Herscovici, J.; Delatre, S.; Antonakis, K. *J. Org. Chem.* **1987**, *52*, 5691. (b) Herscovici, J.; Muleka, K.; Lotfi, B.; Antonakis, K. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1995.
5. (a) Wincott, F. E.; Danishefsky, S.; Schulte, G. *Tetrahedron Lett.* **1987**, *28*, 4951. (b) Ichikawa, Y.; Isobe, M.; Goto, T. *Tetrahedron* **1987**, *43*, 4749. (c) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K.; Sommers, P. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1359. (d) Panek, J. S.; Sparks, M. A. *J. Org. Chem.* **1989**, *54*, 2034.
6. Examples illustrating the reaction of furanose sugars with unactivated olefins as well as 2-*O*-benzyl (and related) protecting groups have been reported: (a) Cupps, T. L.; Wise, D. S.; Townsend, L. B. *Carbohydr. Res.* **1983**, *115*, 59. (b) Martin, O. R.; Rao, P.; Hendricks, A. V.; Mahnken, R. E. *Carbohydr. Res.* **1990**, *202*, 49.
7. This reaction was consistently unsuccessful with tetra-*O*-acetyl-L-fucose under all solvent and Lewis acid conditions discussed herein.
8. Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, *10*, 661.
9. Reactions attempted at -78° C did not proceed. Furthermore, no reaction was observed until the temperature rose to -30° C. The optimal results were observed at -10° C.
10. Use of TMSOTf (1.5 equivalents) was similarly effective and produced comparable yields.
11. ^{1}H NMR data for **11**: (300 MHz, $CDCl_3$) δ 1.23(s, 3H, CH_3), 1.28(d, 3H, CH_3), 1.34(s, 3H, CH_3), 1.76-1.82(dd, 1H, ABX), 1.91-1.98(dd, 1H, ABX), 3.75-3.82(m, 2H, CH + CH), 3.99-4.08(dq, 1H, CH), 4.15-4.19(dd, 1H, CH), 4.47-4.52(q, 1H, CH), 4.56-4.84(m, 4H, benzyl), 7.25-7.4(m, 10H, aromatic).
12. Cooper, A. J.; Salomon, R. G. Tetrahedron Lett. 1990, 31, 3813.
13. (a) Newcombe, N. J.; Mahon, M. F.; Molloy, K. C.; Alker, D.; Gallagher, T. *J. Am. Chem. Soc.* **1993**, *115*, 6430. (b) Terahara, A.; Haneishi, T.; Arai, M.; Hata, T. *J. Antibiot.* **1982**, *35*, 1711. (c) Yoshikawa, H.; Takiguchi, Y.; Terao, M. *J. Antibiot.* **1983**, *36*, 30.
14. Kozaki, S.; Sakanaka, O.; Yasuda, T.; Shimizu, T.; Ogawa, S.; Suami, T. *J. Org. Chem.* **1988**, *53*, 281.
15. Cabaret, D.; Wakselman, M. *Carbohydr. Res.* **1989**, *189*, 341.
16. De Mesmaeker, A.; Waldner, A.; Hoffman, P.; Hug, P.; Winkler, T. *Synlett* **1992**, 285.

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