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Is Donor−Acceptor Hydrogen Bonding Necessary for 4,6-*O*-Benzylidene-directed β-Mannopyranosylation? Stereoselective Synthesis of β-*C*-Mannopyranosides and α-*C*-Glucopyranosides

David Crich* and Indrajeet Sharma

Department of Chemistry, Wayne State University, 5101 Cass Avenue, Detroit, Michigan 48202, and Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607

dcrich@chem.wayne.edu

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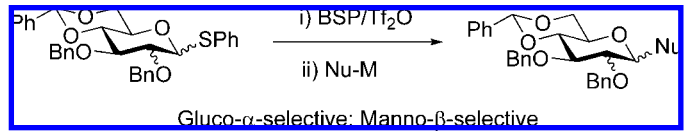
ABSTRACT



2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-thiohexopyranosides, on activation with 1-benzenesulfinyl piperidine and triflic anhydride, react with allyl silanes and stannanes, and with silyl enolethers to give *C*-glycosides. In the mannose series the β-isomers are formed selectively whereas the glucose series provides the α-anomers. This selectivity pattern parallels that of *O*-glycoside formation and eliminates the need to consider donor−acceptor hydrogen bonding in the formation of the *O*-glycosides.

4,6-*O*-Benzylidene protected mannopyranosyl triflates carrying ether-type blocking groups on O2 and O3 are highly β-selective in their reactions with alcohols.[1,2] This selectivity is independent of the nature of the triflate precursor, thioglycoside or sulfoxide, and extends to other classes of glycosyl donor including the imidates,[3] the 2-hydroxycarbonylbenzyl glycosides,[4] and the phosphites.[5] The selectivity, however, is highly dependent on the presence of the benzylidene acetal or related group, as the corresponding tetra-*O*-benzyl or alkyl donors are unselective under comparable conditions.[1] In terms of reaction mechanism, the covalent triflate[6] is understood to serve as a resevoir for a transient contact ion pair (CIP) and, thereafter, for a solvent separated ion pair (SSIP). The CIP, in which the triflate shields the α-face of the oxacarbenium ion, is β-selective whereas the SSIP is α-selective in agreement with the dictates of the anomeric effect (Scheme 1).[7] As established by Bols,[8] the benzylidene effect is due to the locking of the C5−C6 bond in the most electron-withdrawing trans-gauche conformation, which destabilizes the oxacarbenium ion and limits the concentration of the undesired, α-selective SSIP.[9]

(1) (a) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321–8348. (b) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015–9020. (c) Crich, D.; Lim, L. B. L. *Org. React.* **2004**, *64*, 115–251.

(2) For a review on cyclic protecting groups in glycoside synthesis see: Litjens, R. E. J. N.; van den Bos, J. L.; Codée, J. D. C.; Overkleeft, H. S.; van der Marel, G. *Carbohydr. Res.* **2007**, *342*, 419–429.

(3) (a) Weingart, R.; Schmidt, R. R. *Tetrahedron Lett.* **2000**, *41*, 8753–8758. (b) Tanaka, S.-i.; Takashima, M.; Tokimoto, H.; Fujimoto, Y.; Tanaka, K.; Fukase, K. *Synlett* **2005**, *232*, 5–2328.

(4) Kim, K. S.; Kim, J. H.; Lee, Y. J.; Lee, Y. J.; Park, J. *J. Am. Chem. Soc.* **2001**, *123*, 8477–8481.

(5) Tsuda, T.; Sato, S.; Nakamura, S.; Sato, S. *Heterocycles* **2003**, *59*, 509–515.

(6) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217–11223.

(7) Crich, D.; Chandrsekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386–5387.

(8) Jensen, H. H.; Nordstrom, M.; Bols, M. *J. Am. Chem. Soc.* **2004**, *123*, 9205–9213.

(9) The possibility that the benzylidene effect also contains a torsional component exists: Andrews, C. W.; Rodebaugh, R.; Fraser-Reid, B. *J. Org. Chem.* **1996**, *61*, 5280–5289.

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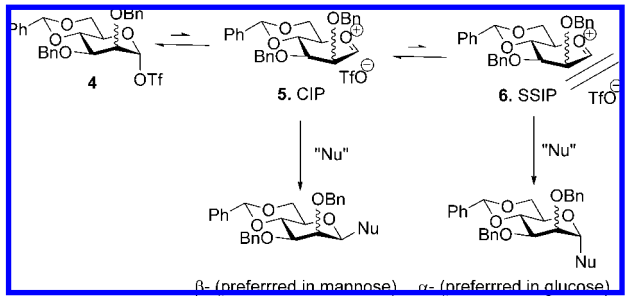
Scheme 1. General Glycosylation Mechanism



In stark contrast the corresponding 4,6-*O*-benzylidene glucosyl donors are α-selective.[10] With the help of a series of 2- or 3-deoxy and the corresponding deoxy fluoro gluco and mannosyl donors, we have rationalized the glucose/mannose stereoselectivity shift on the basis of the differing O2−C2−C3−O3 torsional interactions as the covalent triflates collapse to the ion pairs.[11] In mannose, this torsion angle is compressed as the oxacarbenium ion is formed, whereas in glucose it is relaxed. Effectively, the formation of the glucosyl oxacarbenium ion is less endothermic than that of its mannosyl counterpart leading to a higher concentration of ion pairs in glucose than in mannose.[12]

A potential alternative explanation for the change in selectivity between the glucose and mannose series invokes hydrogen bonding between the OH group of the incoming nucleophilic alcohol and O2 of the donor as the major influence on reaction stereoselectivity, at least for the case of the benzylidene acetal protected donors.[13,14] As we now describe, to address this issue we have investigated the reaction of glucosyl and mannosyl triflates with C-nucleophiles, for which the possibility of hydrogen bonding does not exist.

Thioglycosides **4**−**6** (Figure 1) were synthesized as previously described[15] and converted in dichloromethane at

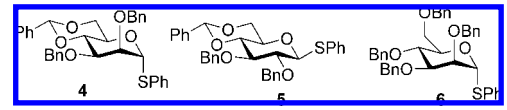


Figure 1. Thioglycosides Employed.

−60 °C with the combination of 1-benzenesulfinyl piperidine (BSP, Figure 2)[1b] and trifluoromethanesulfonic anhydride,

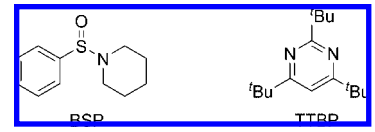


Figure 2. Coupling Reagents.

in the presence of the hindered base 2,4,6-tri-*tert*-butylpyrimidine (TTBP, Figure 2),[16] to the corresponding glycosyl triflates. The nucleophile was then added and the reaction mixture was stirred for a further 2 h at −60 °C, before it was quenched at that temperature, leading to the results presented in Table 1.

It is immediately apparent from the results presented in Table 1 that the carbon nucleophiles follow the well-established pattern of the alcohols, with the 4,6-*O*-benzylidene protected mannosyl donors being *β*-selective, their gluco counterparts α-selective, and the tetrabenzyl mannosyl donor relatively unselective, ergo, there is no requirement for hydrogen bonding to direct these systems.

Comparison of Table 1, entries 1 and 2 reveals that, not unexpectedly, the more reactive allylstannane gives better *β*-selectivity than the allylsilane in reactions with the benzylidene protected mannosyl triflate. In the gluco-series (Table 1, entries 7 and 8) complete α-selectivity is observed regardless of the nature of the allylmetal employed. With the trimethylsilyl enolethers as nucleophiles excellent *β*-selectivity was again observed for the formation of benzylidene protected mannosyl *C*-glycosides (Table 1, entries, 3,4, and 5), whereas the opposite selectivity was observed for glucose (Table 1, entry 9). Interestingly, with the pinacolone silyl enolether a minor amount of an α-*O*-glycosyl enolether **8b** was observed as byproduct in coupling to the mannosyl donor **4** (Table 1, entry 3). With the corresponding glucosyl donor **5**, the α-enolether was formed in greater yield than the correspoding *C*-glycoside (Table 1, entry 9).[17] With trimethylsiloxycyclohexene as nucleophile the major product

(10) (a) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926–4930. (b) Bousquet, E.; Khitri, M.; Lay, L.; Nicotra, F.; Panza, L.; Russo, G. *Carbohydr. Res.* **1998**, *311*, 171–181.

(11) (a) Crich, D.; Vinogradova, O. *J. Org. Chem.* **2006**, *71*, 8473–8480. (b) Crich, D.; Li, L. *J. Org. Chem.* **2007**, *72*, 1681–1690.

(12) As discussed previously,[11a,b] this rationale is based on the computed conformations of the 4,6-*O*-benzylidene-protected gluco- and mannopyranosyl oxacarbenium ions as provided by Whitfield and co-workers: Nukada, T.; Bérces, A.; Whitfield, D. M. *Carbohydr. Res.* **2002**, *337*, 765–774.

(13) Hydrogen bonding between the acceptor OH and O3, but not O2, of the benzylidene protected mannosyl donor has been invoked previously on the basis of computations as one of several factors possibily affecting stereoselectivity in these glycosylations. Likewise, computational work has also raised the possibility of hydrogen bonding between the incoming acceptor and the departing triflate, in an S_Ni-like manner as a possible rationale for the α-selective glycosylations: (a) Reference 12. (b) Nukada, T.; Bérces, A.; Wang, L.; Zgierski, M. Z.; Whitfield, D. M. *Carbohydr. Res.* **2005**, *340*, 841–852. (c) Ionescu, A. R.; Whitfield, D. M.; Zgierski, M. Z.; Nukada, T. *Carbohydr. Res.* **2006**, *341*, 2912–2920. (d) Whitfield, D. M.; Nukada, T. *Carbohydr. Res.* **2007**, *342*, 1291–1304.

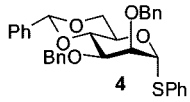
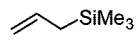
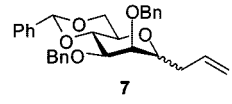
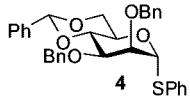
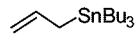
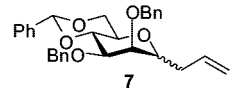
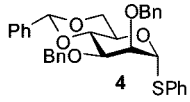
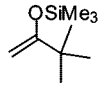
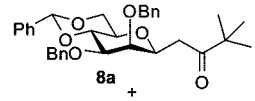
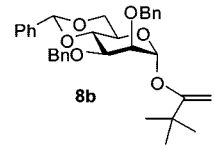
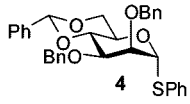
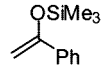
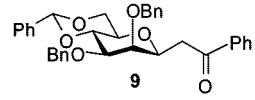
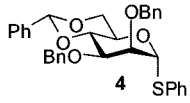
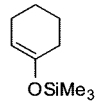
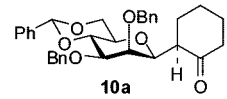
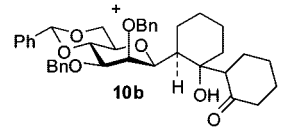
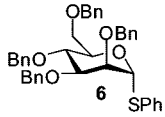
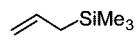
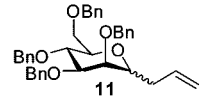
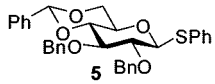
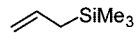
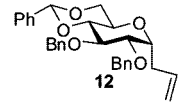
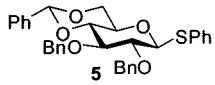
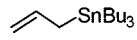
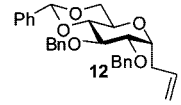
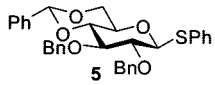
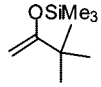
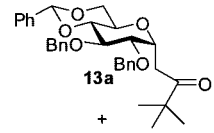
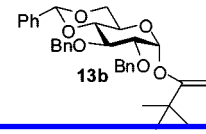
(14) For previous discussions of the potential effects of donor−acceptor hydrogen bonding in glycosylation reactions see: Bérces, A.; Whitfield, D. M.; Nukada, T.; do Santos, I.; Obuchoskwa, A.; Krepinsky, J. J. *Can. J. Chem.* **2004**, *82*, 1157–1171.

(15) (a) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321–8348. (b) Dubois, E.; Beau, J. M. *Carbohydr. Res.* **1992**, *228*, 103–120.

(16) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323–326.

(17) Previous syntheses and applications of glycosyl enolethers, or vinyl glycosides: (a) Chenault, H. K.; Castro, A.; Chafin, L. F.; Yang, Y. *J. Org. Chem.* **1996**, *61*, 5024–5031. (b) Boons, G.-J.; Heskamp, B.; Hout, F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2845–2847. (c) Boons, G.-J.; Isles, S. *J. Org. Chem.* **1996**, *61*, 4262–4271. (d) Yuan, J.; Lindner, K.; Frauenrath, H. *J. Org. Chem.* **2006**, *71*, 5457–5467. (e) Wang, P.; Haldar, P.; Wang, Y.; Hu, H. *J. Org. Chem.* **2007**, *72*, 5870–5873.

Table 1. Formation of *C*-Glycosides

entry	donor	acceptor	coupled product	isolated yield[a]	α: β ratio[b,c]
1	 **4**		 **7**	58%	1:5
2	 **4**		 **7**	61%	1:8
3	 **4**		 **8a** +  **8b**	63% (7:1, **8a**:**8b**)	**8a** β only **8b**, α only
4	 **4**		 **9**	80%	β only
5	 **4**		 **10a** +  **10b**	51% (2:1, **10a**:**10b**)	**10a**, β only[d] **10b**, β only[d]
6	 **6**		 **11**	70%	2:1
7	 **5**		 **12**	54%	α only
8	 **5**		 **12**	52%	α only
9	 **5**		 **13a** +  **13b**	**13a**, 22% **13b**, 33%	**13a**, α only **13b**, α only

[a] Isolated yields after column chromatography. [b] Ratio was determined by ^{1}H NMR of crude reaction mixtures. [c] Anomeric stereochemistry was assigned on the basis of NOESY measurements. [d] See Supporting Information for the assignment of stereochemistry α to the ketone in **10a** and **10b**.

10a was accompanied by the formation of a double adduct **10b** arising from a subsequent condensation step.

Importantly, the reaction of the tetra-*O*-benzyl thiomannoside **6** with allyl trimethylsilane afforded *C*-glycoside **11** as a mixture of anomers favoring the α-anomer, thereby revealing the importance of the benzylidene acetal in the control of stereochemistry (Table 1, entry 6). Lucero and Woerpel have discussed the preferential formation of α-*C*-

mannopyranosides from tetra-*O*-benzyl mannopyranosyl acetate and allyl trimethylsilane with activation by trimethylsilyl trifluoromethanesulfonate in terms of a Curtin-Hammett kinetic scheme in which reaction takes place preferentially on the less populated $^4H_3$ conformer of the intermediate oxacarbenium ion that is in equilibrium with the more stable $^3H_4$ conformer.[18] While the result obtained with the tetra-*O*-benzyl system **6** (Table 1, entry 6) could be interpreted as consisent with the Woerpel model, the β-selective reactions (Table 1, entries 1−5) from the 4,6-*O*-benzylidene mannosyl donor, for which the intermediate cation is locked in the $^4H_3$ or a closely related conformer clearly require another explanation. Consistent with our explanation for the selective formation of β-*O*-mannosides (Scheme 1) we suggest that the explanation lies in the role of the counterion, with glycosylation occurring via the CIP in the benzylidene protected mannose series.

In conclusion, the benzylidene acetal effect extends beyond the formation of *O*-glycosides to that of *C*-glycosides. The stereoselective formation of β-*C*-mannosides and α-*C*-glucosides by this chemistry strongly suggests that hydrogen bonding between the incoming acceptor and O2 of the donor, or indeed any other donor oxygen, or the departing triflate anion, does not exert a strong influence on the formation of the equivalent *O*-glycosides. The benzylidene acetal-controlled one step stereoselective formation of β-*C*-mannosides is an attractive alternative to existing methods.[19,20]

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Supporting Information Available: Full experimental details and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Lucero, C. G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 2641–2647.

(19) (a) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Oxford, 1995. (b) Postema, M. H. D., Ed. *C-Glycoside Synthesis*; CRC: Boca Raton, 1995. (c) Beau, J.-M.; Gallagher, T. *Top. Curr. Chem.* **1997**, *187*, 1–54. (d) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55–83.

(20) For the analogous C-glycoside formation in the absence of the benzylidene acetal see the accompanying paper: McGarvey, G. J.; Leclair, C. A.; Schmidtmann, B. A. *Org. Lett.* **2008**, *10*, 4727–4730.