

Approximate ${}^{\circ}H_5$ ring conformation of 2,3-*O*-carbonate protected α - and β -L-rhamnopyranosides as confirmed by X-ray crystallography

David Crich,* A. U. Vinod, John Picione, and Donald J. Wink

Department of Chemistry, University of Illinois at Chicago, Chicago, IL 60607-7061, USA

E-mail: Dcrich@uic.edu

Dedicated to Eusebio Juaristi on his 55th birthday in recognition of his many contributions to the anomeric effect

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Abstract

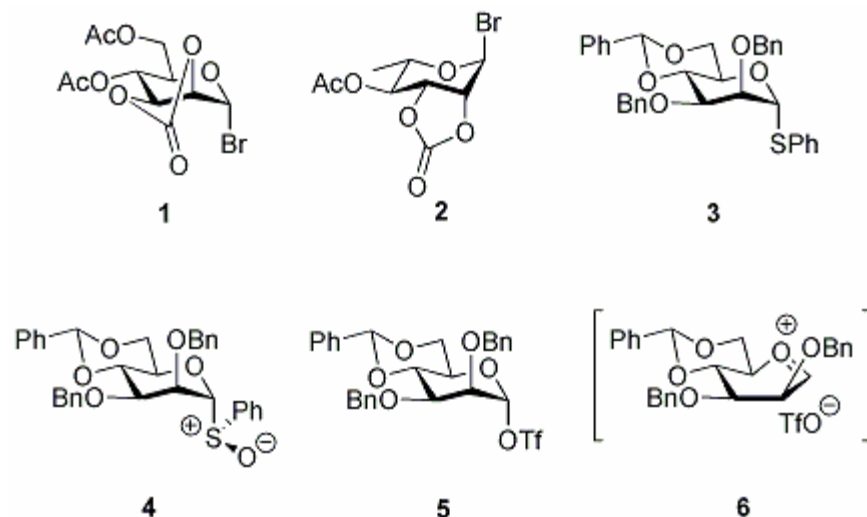
2,3-*O*-Carbonate protected rhamnopyranosides with both the α - and β -anomeric configuration are shown crystallographically to have ring conformations that differ significantly from the chair and which approach the ${}^{\circ}H_5$ half-chair. This distortion, which is greatest in the α -anomer, provides a basis for the α -selectivity of 2,3-*O*-carbonate protected manno- and rhamnopyranosyl donors as well as the conformationally related 2,3-*O*-alkylidene derivatives, in homogeneous solution phase glycosylation reactions.

Keywords: Glycosylation, rhamnopyranose, mannopyranose, carbonate ester, conformation

Introduction

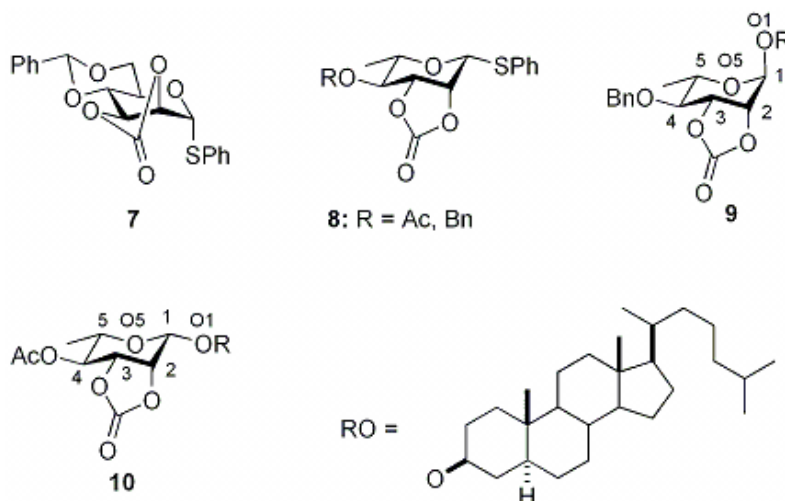
The stereocontrolled synthesis of the β -manno- and rhamnopyranosides has long been recognized as a significant challenge in carbohydrate chemistry.¹⁻⁷ The first direct⁸ solutions to this problem, variants on the venerable Koenigs Knorr reaction, employed the α -mannosyl⁹ and rhamnosyl¹⁰ bromides **1** and **2** carrying the 2,3-*O*-carbonate protecting group. This cyclic protecting group is both strongly electron-withdrawing and stereoelectronically incapable of neighboring group participation. More recently, we have introduced a method for direct β -mannopyranoside formation in which a 4,6-*O*-benzylidene protected thiomannoside **3**, bearing ether-type protecting groups on O-2 and O-3, serves as donor after brief activation with 1-benzenesulfinyl piperidine (BSP) and trifluoromethanesulfonic anhydride at low temperature in dichloromethane.^{11,12} This chemistry is a refinement on our initial solution to the problem when we employed the corresponding mannosyl sulfoxide **4** with activation by trifluoromethanesulfonic anhydride.^{12,13} With both classes of donor, **3** or **4**, the activation

protocol leads to the formation of an α -glycosyl triflate **5**,¹⁴ which is transformed to the β -glycoside on addition of the alcohol via attack on the exposed β -face of a transient oxacarbenium ion within the confines of a contact ion pair **6**.¹⁵ The 4,6-*O*-benzylidene acetal, or related group, is critical to the success of this stereoselective protocol and functions by destabilization of the transient oxacarbenium ion.^{14,16,17} Here, we present X-ray crystallographic structures of 2,3-*O*-carbonate protected steroidal α - and β -rhamnopyranosides and discuss the reactivity of these molecules in terms of their pyranose ring conformations.



Results and Discussion

Seeking to improve the selectivity of our protocol further we considered the juxtaposition of the 2,3-*O*-carbonate group and the 4,6-*O*-benzylidene acetal as in donor **7**. In view of the β -“directing” effect of these two individual groups we were surprised to find that **7** was an extremely α -selective mannosyl donor when activated with benzenesulfonyl triflate and triflic anhydride,^{13,18} a precursor to the present BSP/Tf₂O system, at low temperature in dichloromethane before addition of an acceptor.¹⁹ More recently, we found the 2,3-*O*-carbonate protected thiorhamnosides **8** to be α -selective when activated by our standard protocols.²⁰ Moreover, the 2,3-*O*-carbonate protected rhamnosyl bromides were also α -selective when activated with a soluble silver salt (AgOTf), but β -selective when activated with an insoluble silver salt (Ag₂CO₃).²⁰ We concluded that 2,3-*O*-carbonate protected manno- and rhamnopyranosyl donors are generally α -selective when employed in homogeneous coupling reactions and only show β -selectivity when employed at a heterogeneous surface. We hypothesized that the general α -selectivity of these donors is a function of the conformation imposed on the pyranoside ring by the *cis*-fused cyclic carbonate on the basis of NMR measurements.²⁰



The two steroidal glycosides **9** and **10** were prepared as previously described²⁰ and were examined crystallographically leading to the structures presented in Figures 1 and 2. It is immediately obvious from simple inspection of Figures 1 and 2 that both **9** and **10** exhibit considerable flattening of the pyranose ring due to the presence of the carbonate group and approach the ${}^{\circ}H_5$ conformation postulated by Kunz²¹ and ourselves^{19,20} on the basis of NMR measurements. The intra-ring torsion angles presented in Table 1 put this on a more quantitative basis with significant reduction below the 60° torsion angles of an ideal chair conformation. Both the α - (**9**) and the β -glycosides (**10**) show the same type of distortion from the chair conformation, but the extent is somewhat greater in the case of the α -anomer. This flattening of the ring influences the magnitude of the anomeric ${}^1J_{C,H}$ coupling constant,²²⁻²⁵ normally the most useful parameter for assignment of anomeric configuration in the manno- and rhamnopyranosides, rendering it unreliable in this case. On the other hand the twist in the pyranose ring increases the difference between the ${}^3J_{(H1,H2)}$ scalar coupling constants making this the parameter of choice for assignment of configuration, as we have discussed previously.^{19, 20} The same pattern of ${}^3J_{(H1,H2)}$ scalar coupling constants occurs in the 2,3-*O*-alkylidene rhamnopyranosides, indicating a similar conformation,^{26, 27} whose thioglycosides are α -selective in homogeneous couplings, but whose glycosyl bromides are β -selective in heterogenous silver-promoted glycosylations.²⁸

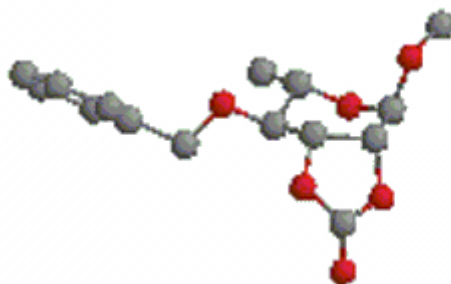


Figure 1. Partial X-ray crystal structure of **9** showing the pyranose ring conformation.

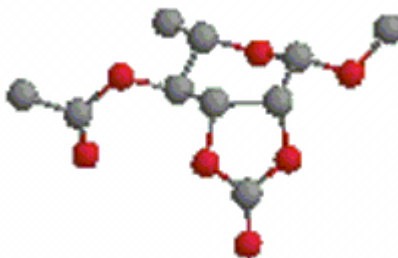


Figure 2. Partial X-ray crystal structure of **10** showing the pyranose ring conformation.

Table 1. Key structural data for **9** and **10**

	9	10
configuration	α	β
glycosidic torsion angle φ ($^\circ$)	50.96	-33.49
C1-O1 (\AA)	1.3975	1.3835
O5-C1 (\AA)	1.3895	1.4115
C1,C2,C3,C4 ($^\circ$)	25.22	33.16
O2,C2,C3,O3 ($^\circ$)	25.49	30.42
C5,O5,C1,C2 ($^\circ$)	50.7	58.7
H2,C2,C3,H3 ($^\circ$)	25.62	32.60
H1,C1,C2,H2 ($^\circ$)	85.13	-42.68
$^3J_{(H1,H2)}$ (Hz)	0	3.0
$^1J_{(C1,H1)}$ (Hz)	169.1	166.5

In conclusion, the conformations of rhamnopyranosides **9** and **10**, as determined crystallographically, are shown to exhibit very considerable distortion from the chair toward the $^{\circ}H_5$ half-chair. This affords support to our earlier hypothesis in which the high α -selectivity of the 2,3-*O*-carbonate protected manno- and rhamnopyranosides **7** and **8** is a function of the donor conformation in which much of the energetic penalty normally incurred on going from the chair form donor to the sofa form oxacarbenium was already been paid.

Supplementary Information

X-Ray crystallographic CIF files have been deposited with the Cambridge Crystallographic Database.

Acknowledgements

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References and Footnotes

1. Barresi, F.; Hindsgaul, O. In *Modern Methods in Carbohydrate Synthesis*; Khan, S. H.; O'Neill, R. A. Eds; Harwood Academic Publishers: Amsterdam, 1996; pp 251.
2. Gridley, J. J.; Osborn, H. M. I. *J. Chem. Soc., Perkin Trans 1* **2000**, 1471.
3. Demchenko, A. V. *Synlett* **2003**, 1225.
4. Pozsgay, V. In *Carbohydrates in Chemistry and Biology*, Ernst, B.; Hart, G. W.; Sinaÿ, P. Eds; Wiley-VCH: Weinheim, 2000; p 319.
5. Ito, Y.; Ohnishi, Y. In *Glycoscience: Chemistry and Chemical Biology*, Fraser-Reid, B.; Kuniaki, T.; Thiem, J. Eds; Springer-Verlag: Berlin, 2001; Vol. 2, p 1589.
6. Crich, D. In *Glycochemistry: Principles, Synthesis, and Applications*, Wang, P. G.; Bertozzi, C. R. Eds; Dekker: New York, 2001; p 53.
7. Crich, D. *J. Carbohydr. Chem.* **2002**, *21*, 663.
8. We distinguish direct solutions in which the β -manno- or rhamnopyranosides are formed in a single intermolecular step from a mannosyl or rhamnosyl donor and an acceptor alcohol from indirect solutions requiring either initial tethering of the acceptor to the donor or the correction of stereochemistry at either C1 or C2 following glycosidic bond formation.
9. Gorin, P. A. J.; Perlin, A. S. *Can. J. Chem.* **1961**, *39*, 2474.
10. Backinowsky, L. V.; Balan, N. F.; Shashkov, A. S.; Kochetkov, N. K. *Carbohydr. Res.* **1980**, *84*, 225.
11. Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015.
12. Crich, D.; Lim, L. B. L. *Org. React.* **2004**, *64*, 115.
13. Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321.
14. Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217.
15. Crich, D.; Chandrasekera, N. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 5386.
16. Jensen, H. H.; Nordstrom, M.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205.
17. Andrews, C. W.; Rodebaugh, R.; Fraser-Reid, B. *J. Org. Chem.* **1996**, *61*, 5280.
18. Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435.
19. Crich, D.; Cai, W.; Dai, Z. *J. Org. Chem.* **2000**, *65*, 1291.
20. Crich, D.; Vinod, A. U.; Picione, J. *J. Org. Chem.* **2003**, *68*, 8453.
21. Guenther, W.; Kunz, H. *Carbohydr. Res.* **1992**, *228*, 217.
22. Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293.
23. Tvaroska, I.; Taravel, F. R. *Adv. Carbohydr. Chem. Biochem.* **1995**, *51*, 15.
24. Duus, J. O.; Gotfredsen, C. H.; Bock, K. *Chem. Rev.* **2000**, *100*, 4589.

25. For the most recent interpretation of the underlying causes of this effect see Cuevas, G.; Martínez-Mayorga, K.; Fernández-Alonso, M. D. C.; Jiménez-Barbero, J.; Perrin, C. L.; Juaristi, E.; López-Mora, N. *Angew. Chem. Int. Ed.* **2005**, *44*, 2360.
26. Crich, D.; Li, H. *J. Org. Chem.* **2002**, *67*, 4640.
27. Anisuzzaman, A. K. M.; Whistler, R. L. *Carbohydr. Res.* **1977**, *55*, 205.
28. Iversen, T.; Bundle, D. R. *Carbohydr. Res.* **1980**, *84*, C13.