Pergamon

Tetrahedron Letters, Vol. 35, No. 42, pp. 7743-7746, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01665-8

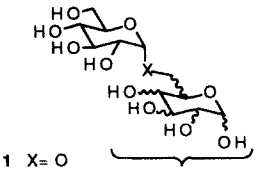
Strategies for the Synthesis of C-Disaccharides Containing D and L Sugars

Robert W. Armstrong* and Daniel P. Sutherlin

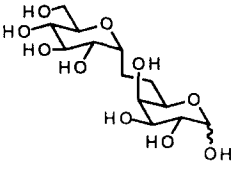
Contribution from the Department of Chemistry and Biochemistry,
University of California at Los Angeles,
Los Angeles, CA 90024

Abstract: The osmylation of C-1 homologated diene ester monosaccharides readily affords C-disaccharides of diverse but predictable stereochemistry. As an example, D-glu-α(1,6)-D-gal (**3**), D-glu-α(1,6)-L-gal (**4**), D-glu-α(1,6)-D-ido (**10**), and D-glu-α(1,6)-L-ido (**11**) were synthesized from a single precursor.

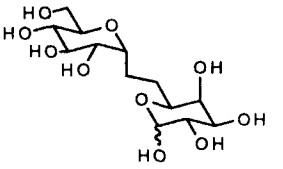
In an effort to identify carbohydrates as lead structures in a protein-binding screening program, we sought to synthesize all possible stereoisomers of an individual sugar unit in a disaccharide or higher order oligomer. In parallel to peptide combinatorial libraries,[1] we envisioned keeping the stereochemistry of a single sugar(s) in the oligomer constant (i.e. D-glucose in disaccharide **1**) while varying the structure of the second sugar to include all D and L hexose diastereomers. Hexose C-disaccharides (**2**) in which the bridging anomeric oxygen has been replaced by carbon were targeted since this substitution provides resistance to chemical and enzymatic deglycosylation. These properties are potentially relevant to in vivo applications.[2] Previously, chemical[3] and/or chemienzymatic[4] synthesis of disaccharides represented by structures **1** and **2** has been described for selected disaccharides via the condensation of preformed sugars. This general approach is limited by the need for selective blocking/deblocking stratagies specific to each sugar, the high cost of less common sugars,[5] and the inability of some sugars to be substrates for specific enzymatic couplings. The de novo synthesis of carbohydrates has led to the generation of numerous natural and unnatural monosaccharides[6] and should circumvent these limitations when incorporated into an oligosaccharide synthesis.



1 X= O
2 X= CH_2 32 diastereomers



3 D-Glu-α(1,6)-D-Gal

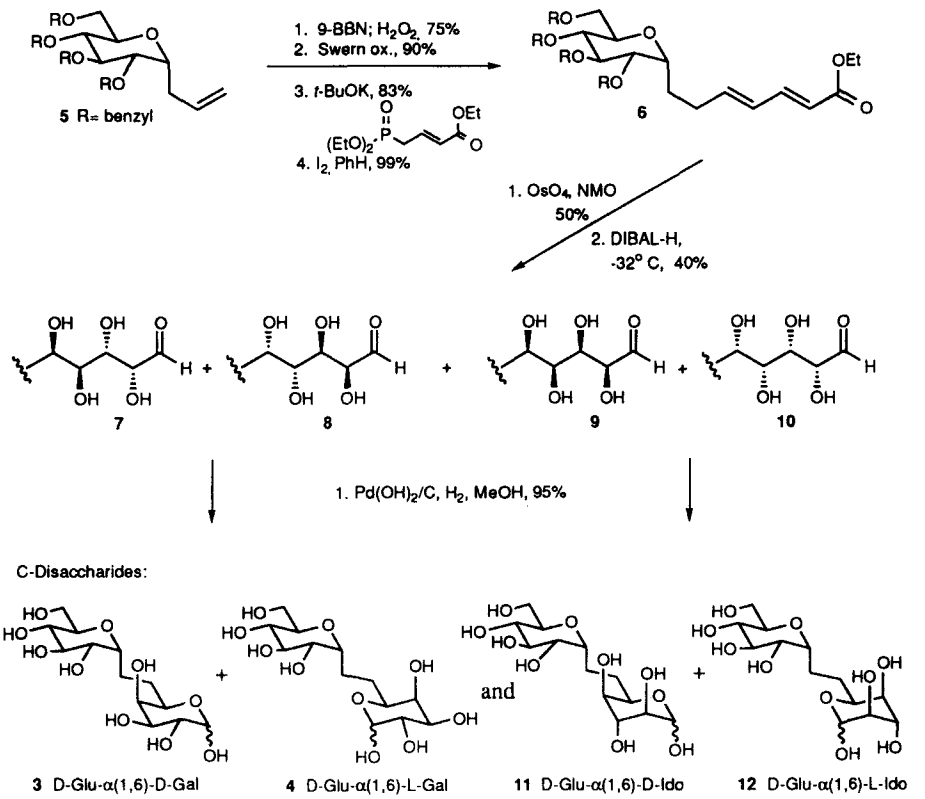


4 D-Glu-α(1,6)-L-Gal

In this paper we describe the synthesis of several D-glucose-α(1,6)-hexose C-disaccharides starting from C-1 homologated monosaccharides containing a fixed sugar. The second carbohydrate is then generated via a de novo synthesis.[7] This route is applicable to the complete hexose-(1,6)-hexose library. Illustrative of this strategy is the rapid synthesis of C-disaccharide **3** and the hybrid D/L C-disaccharide **4**.

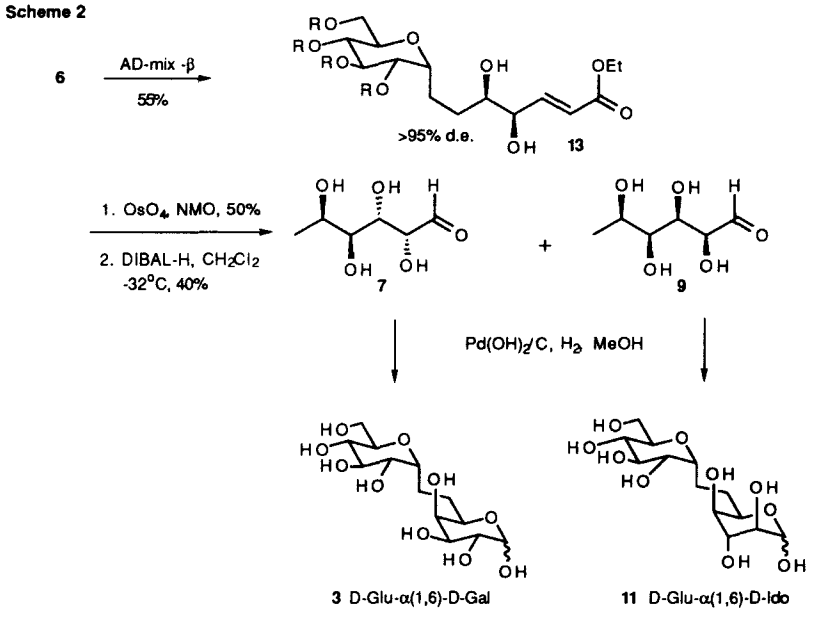
Readily available C-monosaccharide **5**[8] was homologated to diene ester **6** and subjected to osmylation[9] followed by reduction to afford a 5:1 mixture (**7/8:9/10**) of lactols which were readily separable by chromatography. Following a deprotection of an equimolar mixture of **7** and **8**, **3** and the D/L hybrid C-disaccharide D-glucose-α(1,6)-L-galactose **4** were obtained. The structure of the newly formed sugar pyranose in disaccharides **3** and **4** was unequivocally assigned by ^{1}H NMR decoupling experiments and comparison to an authentic sample of D-galactose.[10] The chemical shift, multiplicity and ratio of the C-1 anomeric hydrogen in both reducing sugars in **3** and **4** are nearly identical to their monosaccharide analogs.[11] The D/D and D/L derivatives **11** and **12** of glucose-α(1,6)-idose were also obtained as a near equimolar mixture after deprotection of **9** and **10**. Comparison of the anomeric hydrogens in this more complicated spectra (2:2:1:1 mixture of furanose and pyranose α and β anomers) with the monosaccharide D-idose provides similar diagnostic data.[12]

Scheme 1



In order to generate single stereoisomers of the C-disaccharides for detailed structure assignment, **6** was subjected to the Sharpless asymmetric dihydroxylation (Scheme 2).[13] Reduction of the lactols followed by separation and debenzylation afforded the all D-sugar C-disaccharides D-glucose-α(1,6)-D-galactose **3** and D-glucose-α(1,6)-D-idose **11** as anomeric mixtures.

Scheme 2



The process outlined above provides a route to glucose-α(1,6)-hexoses without the use of blocking groups on the newly created sugars and allows for generation of the D and L-sugar derivatives with equal synthetic effort. Based on the predicted ground-state conformations, the D/L hybrids should provide a different spacial relationship of functionality compared to their D/D analogs and thus provides a newly accessible ligand to probe as a possible drug candidate.[14] These D/D and D/L analogs would also be prohibitively expensive to synthesize via a traditional condensation strategy using the monosaccharide precursors. Of the thirty-two possible diastereomers of **2**, eight were generated from **6**. The remaining diastereomers could be generated from the other geometrical isomers of **6**. The synthesis of these substrates on solid support are efforts underway in our laboratories.

Acknowledgment.

We thank the Sloan Foundation for financial support of this work.

REFERENCES AND NOTES

1. Geysen, H. M.; Meloen, R. H.; Barteling, S. J., *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 3998; Houghten, R. A., *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 5131; Schnorrenberg, G.; Gehardt, H., *Tetrahedron* **1989**, *45*, 7759; Geysen, H. M.; Mason, T.J., *BioMed. Chem. Lett.* **1993**, *3*, 397; Houghten, R. A.; Pinilla, C.; Blondelle, S. E.; Appel, J. R.; Dooley, C. T.; Cuervo, J. H., *Nature*, **1991**, *354*, 84.

2. For a comprehensive review of C-glycoside chemistry, see: Postema, M. H. D., *Tetrahedron* **1992**, *48*, 8545.

3. Udodong U. E.; Madsen R.; Roberts C.; Fraser-Reid B., *J. Am. Chem.Soc.* **1993**, *115*, 7886; Randolph J. T.; Danishefsky S. J., *J. Am. Chem.Soc.*, **1993**, *115*, 8473; Liu K. K. C.; Danishefsky S. J., *J. Am. Chem.Soc.* **1993**, *115*, 4933; Danishefsky S. J; Mcclure K. F.; Randolph J. T.; Ruggeri R. B., *Science* **1993** , *260*, 1307; Kim S. H.; Augeri D.; Yang D.; Kahne D., *J. Am. Chem.Soc.* **1994**, *116*, 1766.

4. Wang P.; Shen G. J.; Wang Y. F.; Ichikawa Y., *J. Org. Chem.* **1992** , *57*, 4343.

5. Prices for D and L idose average $ 1000 per gram and L galactose $ 500 per gram from commercial sources.

6. A de novo strategy for the synthesis of higher sugars (7-11 carbon) has recently appeared: Marshall, J. A.; Beaudoin, S.; Lewinski, K., *J. Org. Chem.* **1993**, *58*, 5876.

7. A tandem asymmetric dihydroxylation and enzyme-catalyzed aldol reaction for the generation of monosoaccharides has recently been described: Henderson, I.; Sharpless, K.B.; Wong, C., *J. Am. Chem. Soc.* **1994**, *116*, 558.

8. Hosomi, A.; Sakata, Y.; Sakurai, H., *Tetrahedron Lett.* **1984**, *25*, 2383.

9. Relative induction in the osmylation of allylic diols, alcohols and silyl ethers has been reported as moderate to high: Cha, J.K.; Christ, W. J.; Kishi, Y., *Tetrahedron Lett.* **1983**, *24*, 3947; Saito, S.; Morikawa, Y.; Moriwake, T. J., *J. Org. Chem.* **1990**, *55*, 5424; Park, C.Y.; Kim, B. M.; Sharpless, K. B., *Tetrahedron Lett.* **1991**, *32*, 1003; Morikawa, K.; Sharpless, K. B.; *Tetrahedron Lett.* **1993**, *34*, 5575.

10. Complete analytical data for all compounds was obtained.

11.

D-Gal:	5.07 (J = 4.6 Hz, 0.4 H, H^1 α)
	4.39 (J = 9.8 Hz, 0.6 H, H^1 ß);
D-Glu D-Gal:	5.03 (J = 4.8 Hz, 0.4 H, H^1 α)
	4.36 (J = 9.8 Hz, 0.6 H, H^1 ß);
D-Glu D-Gal/	5.03 (J = 4.8 Hz, 0.4 H, H^1 α)
D-Glu L-Gal	4.36 (J = 9.8 Hz, 0.6 H, H^1 ß);
	5.04 (J = 4.8,Hz, 0.4 H, H^1 α)
	4.38 (J = 9.8,Hz, 0.6 H, H^1 ß).

12. Snyder, J.R.; Serianni, A.S., *J. Org. Chem.* **1986**, *51*, 2694.

13. Wang, Z. M.; Sharpless, K. B., *Tetrahedron Lett.* **1993**, *34*, 8225; Morikawa, K.; Sharpless, K.B.,*Tetrahedron Lett.* **1993**, *35*, 5575; Crispino, G. A.; Ho P. T.; Sharpless, K. B., *Science* **1993**, *259*, 64; Keinan, E.; Sinha, S. C.; Sinhabagchi, A.; Wang, Z. M.,*Tetrahedron Lett.* **1992**, *33*, 6411.

14. Houk, K.N.; Eksteriowicz, J.E.; Wu, Y.; Fuglesang, C.D.; Mitchell, D.B., *J. Am. Chem. Soc.* **1993**, *115*, 4170.

(*Received in USA* 7 *July* 1994; *accepted* 26 *August* 1994)