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SYNTHESIS OF A HIGHER CARBON SUGAR *VIA* DIRECTED ALDOL CONDENSATION

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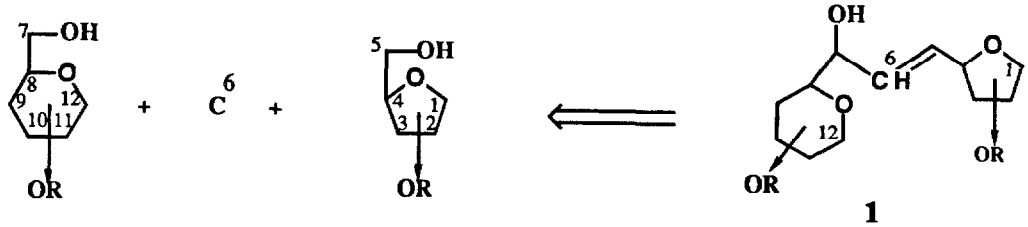
Abstract: *3-O-Benzyl-5-deoxy-1,2-O-isopropylidene-α-D-xylo-hexadialdo-1,4-furanose (**2**) upon treatment with LiN(TMS)$_2$ at -50° furnished the enolate which reacted with methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside-6-ulose (**5**) to afford two erythro aldols **3** and **4** in 6:1 ratio and 43% yield. **5R;6R** Configuration was assigned to the main aldol on the basis of the ^{1}H-n.m.r. spectra of appropriate derivatives of **3**.*

Higher carbon sugars (those containing 10 or more carbon atoms) although not common in nature, are important components of some antibiotics such as hikizimycin[2] or tunicamycin.[3] They also can serve as chiral synthons for the preparation of macrolide antibiotics e.g. erythromycin[4] or streptovaricin.[5] The synthesis of higher sugars, has gained considerable attention in the past few years.[6]

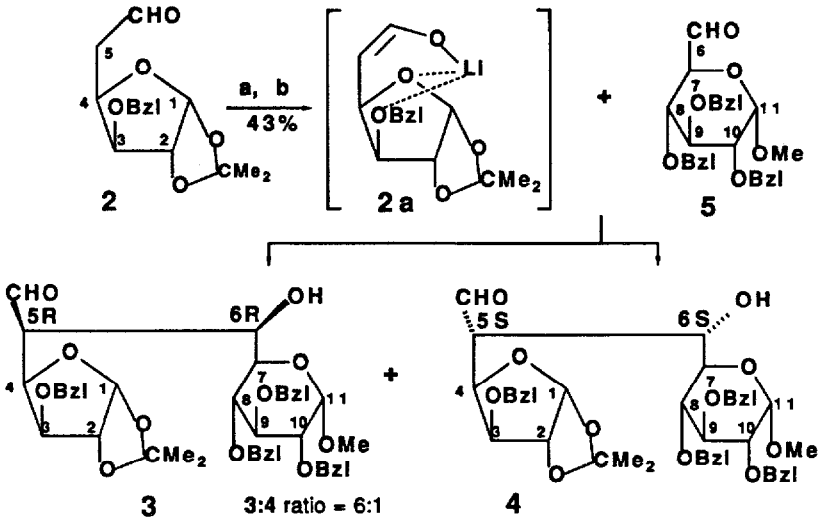
Recently we have shown that allylic alcohols **1**, convenient precursors of higher sugars,[7] could be prepared by coupling of two monosaccharide sub-units *via* an additional carbon atom (Scheme 1).[8]



1

Scheme 1. Preparation of higher sugar allylic alcohols from monosaccharide sub-units

In this paper a more convenient approach to higher sugars *via* a direct coupling of two monosaccharide subunits (without an additional carbon atom) is presented. The aldol condensation route leading to higher monosaccharides is shown in Scheme 2. Aldehyde **2**[9] was treated with bis(trimethylsilyl)lithium amide in dry THF under argon atmosphere for 30

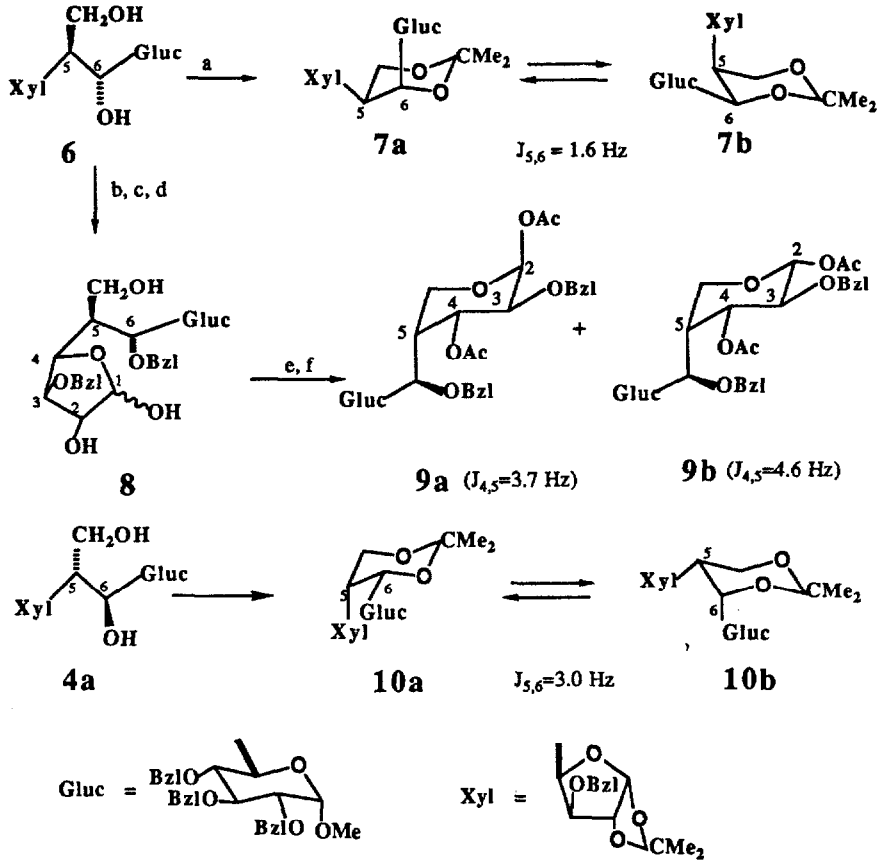


Scheme 2. a. 1.1 equiv. of $LiN(TMS)_2$, THF, -50°, 30 min. b. **5**, -50 to -30°, 1 h

minutes at ca. -50°. The enolate formed smoothly and no β-elimination products were seen. The possibility of C4 epimerization *via* elimination and readdition of the ring oxygen was ruled out by quenching the enolate with aqueous ammonium chloride, whereupon **2** was recovered in 85% yield. Addition of aldehyde **5**[10] to the enolate resulted in formation of two aldols: **3** and **4** in 6:1 ratio and 43% overall yield.[11]

The relative configurations of both aldols were expected to be *erythro* , in keeping with ample precedents.[13] However, these assignments were confirmed, as shown in Scheme 3. The main product **3** was reduced with DIBAL-H, and the conformation of the resulting diol **6** was fixed by the formation of the acetonide **7**. The small coupling constant between H-5 and H-6 ($J_{5,6}$=1.6 Hz) was clearly consistent with the *erythro* configuration.[13] The minor product **4** was converted into **10**, which showed a coupling constant ($J_{5,6}$=3.0 Hz), also consistent with the *erythro* configuration.

In order to assign the relative configuration between the C-4 and C-5 centers, compound **3** was differentially protected, and hydrolysis led to the furanose **8**. After periodate cleavage, lactol formation occurred and acetylation led to **9a** and **9b**. The small coupling constants between H-4 and H-5 ($J_{4,5}$=3.7 for **9a** and 4.6 Hz for **9b**) confirms the *cis* arrangement[15] of the two substituents at centers C-4 and C-5. Since the configuration of C-4 is known, we were able to assign the **5R; 6R** configuration to the main aldol **3** and consequently the **5S; 6S**



Scheme 3. a. Me_2CO, $Me_2C(OMe)_2$, CSA (cat), 6 h r.t. ; b. TrCl /Py / DMAP, CH_2Cl_2, reflux, 6 h ; c.BzlBr / NaH / DMF, 2 h ; d. 6N HCl / THF - 2:3, r.t. , 2 h ; e. $NaIO_4$; f. Ac_2O / Py / DMAP

configuration to the minor isomer **4**. This result indicated also that the attack of **5** occurs from the less hindered side of the enolate **2a** (from" behind the ring").

The reaction presented here, although proceeds with moderate yield, can be a method of choice in the stereoselective preparation of higher carbon sugars. The higher homologue of aldehyde **5** and the lower homologue of **2** also underwent aldol addition, but the product underwent ready dehydration and was therefore less interesting as a synthon for higher carbon sugars. Its chemistry will be described in the full paper.

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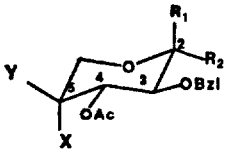
REFERENCES AND NOTES

1. Permanent address: Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44, Warsaw, Poland.
2. Uchida, K.; Ichikawa, T.; Schimauchi, Y.; Ishikura, T.; Ozaki, A. *J. Antibiot.*, **1971**, *24*, 259.
3. Takatsuki, A.; Arima, K.; Tamura, G., *J. Antibiot.*, **1971**, *24*, 215.
4. Sviridov, A. F.; Ermolenko, M. S.; Yashunsky, D. V.; Borodkin, V. S.; Kochetkov, N. K., *Tetrahedron Lett.*, **1987**, *28*, 3835, 3839.
5. Fraser-Reid, B.; Magdzinski, L.; Molino, B. F.; Mootoo, D. R., *J. Org. Chem.*, **1987**, *52*, 4495, 4505; Mootoo, D. R.; Fraser-Reid, B., *J. Org. Chem.*, **1987**, *52*, 4511.
6. See for example: (a) Danishefsky, S. J.; De Ninno, M. P., *Angew. Chem., Int. Ed., Engl.*, **1987**, *26*, 15; (b) Secrist, III, J. A.; Wu, S.-R, *J. Org. Chem.*, **1979**, *44*, 1434; (c) Suami, T.; Sasai, H.; Matsuno, K., *Chem. Lett.*, **1985**, 819; (d) Jarosz, S.; Mootoo, D.; Fraser-Reid, B., *Carbohydr. Res.*, **1986**, *147*, 59; (e) Babired, S. A.; Wang, Y.; Kishi, Y., *J. Org. Chem.*, **1987**, *52*, 1370; (f) Brimacombe J. S.; Kabir A. K. M. S., *Carbohydr. Res.*, **1988**, *179*, 21, and references cited therein; (g) Dawson, I. M.; Johnson, T.; Paton, R. M.; Rennie, R. A. C., *J. Chem. Soc., Chem. Comm.*, **1988**, 1339.
7. Jarosz S.; *Carbohydr. Res.*, **1988**, *183*, 209, 217.
8. Jarosz, S., *Tetrahedron Lett.*, **1988**, *29*, 1193; Jarosz, S., *Carbohydr. Res.*, **1987**, *166*, 211; Jarosz, S., *Carbohydr. Res.*, **1988**, *183*, 201; Jarosz, S., *Bull. Polish Acad. Chem.*, **1987**, *35*, 161.
9. Compound **2** (Tronchet, J. M. J.; Bonefant, A.-P., *Helvetica Chim. Acta.*, **1980**, *66*, 1644) was prepared from known 3-O-benzyl-1,2-O-isopropylidene-α-D-xylopentadialdo-1,4-furanose[14] by reaction with 1.5 eq. of Ph_3P=CH-OMe at 0° (75%), followed by hydrolysis of the resulting enol ethers with PPTs in refluxing acetone-water (99:1) for 1 h (64%).
10. Hashimoto, H.; Asano, K.; Fujii, F.; Yoshimura, I., *Carbohydr. Res.*, **1982**, *104*, 87.
11. The purity of **2** is essential to get the reproducible results in the aldol condensation. Low yield of aldols was probably due to the retro-aldol reaction caused by silica gel during column chromatography. Although t.l.c. showed complete conversion of the starting materials, we isolated significant amounts of **2** and **5** from the column. When the post-reaction mixture was reduced with DIBAL-H before separation of aldols the yield of products (diols **6** and **4a**) was slightly higher (50%; the ratio of **6**:**4a** was also 6:1).
12. Mukaiyama, T., *Organic Reactions*, **1982**, *28*, 203; Heathcock, C., *Asymmetric Synthesis*, Ed., Morrison, J. D., Academic Press: New York; Vol. 3, chapter 2 (1983); Evans, D. A., *Asymmetric Synthesis*, Ed., Morrison, J. D., Academic Press: New York; Vol. 3, chapter 1.
13. Lipshutz B.; Barton, J. C., *J. Org. Chem.*, **1988**, *53*, 4495.
14. Wolfrom M. L.; Hanessian, S., *J. Org. Chem.*, **1962**, *27*, 1800.
15. The ^{1}H-n.m.r. data for **9a** δ: 6.44 ($J_{2,3}$=3.5 Hz, H-2), 5.34 ($J_{3,4}$=6.3, $J_{4,5}$=3.7 Hz, H4) and **9b** δ: 5.46 ($J_{2,3}$=7.3 Hz, H-2), 5.19 ($J_{3,4}$=7.8, $J_{4,5}$=4.6 Hz, H-2) compared with the data for **11** and **12** (prepared from 3,5-di-O-benzyl-1,2-O-isopropylidene-α-D-gluco- and β-L-idofuranoses respectively) pointed clearly at the *cis* arrangement of substituents connected with C-4 and C-5 as in **11**.



11 (X=OBzl, Y=H)
12 (X=H, Y=OBzl)

11a. R_1 = OAc R_2 = H
H-2 δ=6.37 $J_{2,3}$=3.7 Hz
H-4 δ=5.29 $J_{3,4}$=10.2 Hz $J_{4,5}$=3.0 Hz

11b. R_1 = H R_2 = OAc
H-2 δ=5.75 $J_{2,3}$=5.2 Hz
H-4 δ=5.20 $J_{3,4}$=7.6 Hz $J_{4,5}$=3.2 Hz

12a. R_1 = OAc R_2 = H
H-2 δ=6.24 $J_{2,3}$=3.5 Hz
H-4 δ=5.22 $J_{3,4}$=9.0 Hz $J_{4,5}$=6.6 Hz

12b. R_1 = H R_2 = OAc
H-2 δ=5.58 $J_{2,3}$=7.8 Hz
H-4 δ=5.04 $J_{3,4}$=9.3 Hz $J_{4,5}$=8.2 Hz

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