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# Synthesis of *C*-Disaccharides from *C*-Formyl Glycosides

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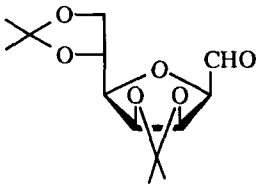
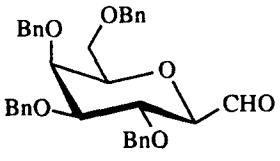
***Abstract:*** The coupling between *C*-formyl 2,3:5,6-di-*O*-isopropylidene-D-mannofuranoside (**1**) and 2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside (**2**) with the protected galactose 6-phosphorane **3** leads to the corresponding olefins which upon hydrogenolysis give β (1 →6')-linked *C*-disaccharides **6** and **8** in 56 and 72% yield, respectively. Copyright © 1996 Elsevier Science Ltd

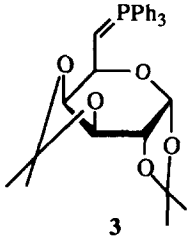
Isosteric *C*-disaccharides are non-natural analogs of disaccharides in which the ether linkage holding the two sugar moieties has been replaced by a carbon-carbon bond.[1] The increasing attention which is currently addressed to this class of *C*-glycosides[2] stems from their potential as inhibitors of glycosidases since they are conformationally similar to their natural counterparts[3,4] but cannot be chemically or biochemically hydrolyzed. The recent method of preparation of *C*-formyl glycofuranosides and pyranosides through the thiazole-based formylation of sugars lactones developed in our laboratory,[5] provides new opportunities for the synthesis of *C*-disaccharides through the various reactions of the formyl group. The appeal of this approach stems from various considerations including the availability of various *C*-formyl glycosides with different hydroxyl protecting groups and the stereochemistry at the anomeric carbon already in place. We report below the model syntheses of two β(1→6')-linked *C*-disaccharides by Wittig olefination of *C*-furanosyl and *C*-pyranosyl aldehydes **1** and **2** with the protected galactose 6-phosphorane **3**. The use of **1** and **2** in this exploratory study was opportunistically determined by their ease of preparation. Similarly, the partner phosphorane **3** was selected among other known sugar phosphoranes because of its configurational stability at C5 and the easy and multigram scale preparation[6] of the precursor phosphonium salt **4**.




**1**



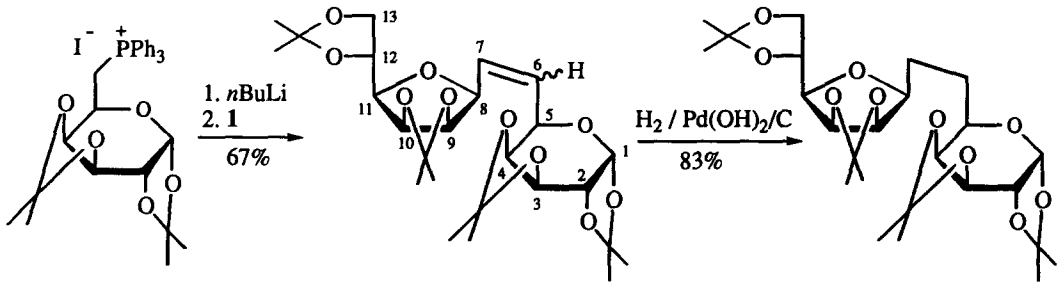

**2**




**3**

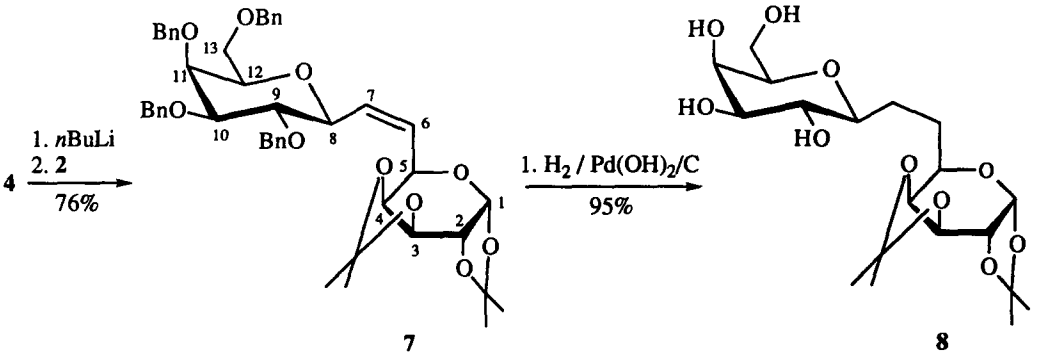
The red-colored ylide **3** was simply generated by adding *n*BuLi (1 equiv) to the phosphonium salt **4** in 2:1 THF-HMPA at -30°C in the presence of activated 4Å powdered molecular sieves with *n*BuLi (1 equiv). Then, freshly prepared[7] β-D-mannofuranosyl aldehyde **1** (1.1 equiv.) was added at the same temperature and the solution was slowly (3 h) allowed to warm up to room temperature. Work-up and purification gave the

olefin **5** (67%) as a mixture of *Z* and *E* isomers in a 7:3 ratio. Confirmation that the β-D-manno configuration was retained during the Wittig reaction was obtained by NOE experiments on the individual isomers which were isolated by preparative TLC (ethyl acetate-cyclohexane 1:3).[8] Similarly, the expected conservation of the α-D-galacto configuration in the other sugar moiety[6] was supported by consistent H4-H5 coupling constant ($J_{4,5}$ 2.0 Hz). Furthermore, all the other coupling constants of the galactose moiety were maintained. Having linked the two sugar moieties by a carbon-carbon bond without affecting the nearby stereogenic centers, the rest of the synthesis was straightforward. The disubstituted sugar olefin **5** (*E*:*Z* mixture) in ethyl acetate-ethanol (1:1) was reduced by hydrogenation over $Pd(OH)_2$ on carbon at 3 atm for 1.5 h. After standard work up and flash chromatography over silica gel (ethyl acetate-cyclohexane 1:4), the fully protected β(1→6')-linked *C*-disaccharide **6** was isolated in 83% yield.[9]



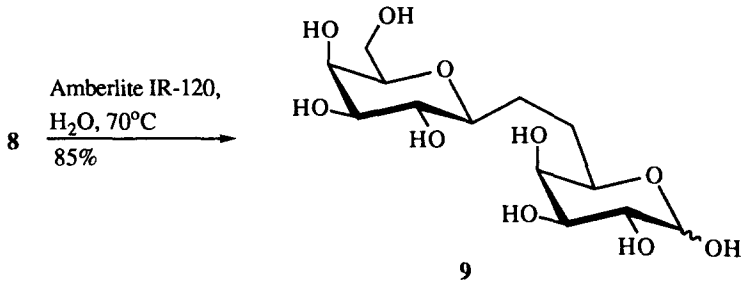

**4** **5** (*Z* : *E*, 7:3) **6**

The coupling between the phosphorane **3** and the β-D-galactopyranosyl aldehyde **2** was carried out using the above-mentioned conditions. In this case the olefination turned out to be stereoselective since the $^1H$ NMR analysis of the crude reaction mixture showed the presence of the *Z* alkene **7** as a single isomer. Flash chromatography over silica gel (ethyl acetate-cyclohexane 1:4) afforded pure **7** (76%) and 2-3% of the *C*-formyl glycal arising from base-induced β-elimination of the benzyloxy group at the C2 of **2**.[10] The configurational integrity of both sugar moieties present in **7** was again confirmed through NMR analysis ($J_{4,5}$ 2.0 Hz, $J_{8,9}$ 9.0 Hz).[9] The reduction of the olefin **7** by the same Pd-catalyzed hydrogenation described above was accompanied by the removal of all *O*-benzyl protective groups, thus leading to the partially protected β(1→6')-linked *C*-disaccharide **8** in almost quantitative yield.[9]




**7** **8**

In conclusion, a method for the synthesis of *C*-disaccharides has been presented that utilizes a Wittig olefination between readily available *C*-glycosyl aldehydes and a sugar phosphorane. This method appears to be by far more efficient in terms of chemical yields, number of steps, and types of manipulations than the method involving a nitro aldol condensation.[11] The single compound β-D-*C*-Gal-(1→6')-α-D-Glc-OMe that has been prepared was obtained in only 5% overall yield from the aldehyde **2**. Several problems associated with the troublesome conversion of the nitro aldol product into the olefin and the inertness to hydrogenation of the latter were responsable for the above low yield.[12] On the other hand, just for the sake of a comparison, removal of the two isopropylidene groups of **8** by treatment with Amberlite IR-120[1b,13] gave free β-D-*C*-Gal-(1→6')-D-Gal disaccharide **9** in 85% yield.[14] Hence the overall yield of **9** from **2** was 61% unoptimized.




**8** → **9**

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## References and Notes

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7. Aldehydes **1** and **2** were liberated from the corresponding thiazole precursor as described (ref. 5) and purified by rapid chromatography over a short column of silica gel (ethyl acetate-cyclohexane 2:1 for aldehyde **1** and ethyl acetate-cyclohexane 1:1 for aldehyde **2**). These compounds form hydrates.

8. Both compounds showed a NOE between H-8 and H-11 upon irradiation of H-11. Compound **Z-5** showed: $[\alpha]_D^{20}$ = -32.0° (*c* 0.2, $CHCl_3$), M+Na 521, $^1H$ NMR ($C_6D_6$): δ 3.38 (dd, 1H, H-11, $J_{11,12}$ 8.0 Hz, $J_{11,10}$ 3.5 Hz), 4.37 (ddd, 1H, H-8, $J_{8,7}$ 6.5 Hz, $J_{8,9}$ 4.0 Hz, $J_{8,6}$ 1.0 Hz), 5.98 (ddd, 1H, H-7, $J_{7,6}$ 12.0 Hz, $J_{7,5}$ 1.0 Hz ), 6.06 (ddd, 1H, H-6, $J_{6,7}$ 12.0 Hz, $J_{6,5}$ 6.4 Hz). Compound ***E*-5** showed: $[\alpha]_D^{20}$ = -36.0° (*c* 0.2, $CHCl_3$), M+Na 521, $^1H$ NMR ($C_6D_6$): δ 3.31 (dd, 1H, H–11, $J_{11,12}$ 7.0 Hz, $J_{11,10}$ 3.5 Hz), 3.60 (dd, 1H, H-8, $J_{8,7}$ 6.0 Hz, $J_{8,9}$ 4.0 Hz), 6.24 (c, 2H, H-6, H-7, $J_{6,7}$ 15.3 Hz, $J_{6,5}$ 5.7 Hz).
9. Consistent $^1H$ and $^{13}C$ NMR spectra were obtained for all compounds. Characteristic data were : **6**, $[\alpha]_D^{20}$ = -42.8° (*c* 0.6, $CHCl_3$), M+Na 523; **7**, $[\alpha]_D^{20}$ = -4.9° (*c* 0.4, $CHCl_3$), M+Na 801, $^1H$ NMR ($CDCl_3$): δ 4.02 (dd, 1H, H-8, $J_{8,7}$ 7.5 Hz, $J_{8,9}$ 9.0 Hz), 5.66 (dd, 1H, H-7, $J_{7,6}$ 11.5 Hz, $J_{7,8}$ 7.5 Hz), 5.74 (dd, 1H, H-6, $J_{6,5}$ 8.0 Hz); **8**, $[\alpha]_D^{20}$ = -37.5° (*c* 1.2, $CHCl_3$), M+Na 443.
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12. The unoptimized low yield was justified by an unusual and extraordinary event: closure of the laboratory! (see ref. 11).
13. Removal of the isopropylidene groups with 80% acetic acid at reflux temperature for 1/2 h gave **9** as a mixture of furanose and pyranose forms in 87% yield.
14. Compound **9** was a mixture of α and β anomers showing the following data: M+Na 363, $[\alpha]_D^{20}$ +39.1° (*c* 0.9, $CH_3OH$), $^1H$ NMR ($CD_3OD$): δ 4.40 (d, 1H, H-1β, $J_{1,2}$ 7.5 Hz), 5.10 (d, 1H, H-1α, $J_{1,2}$ 3.5 Hz), $^{13}C$ NMR ($CD_3OD$): δ 28.0, 29.2 (C-6, C-7), 94.1 (C-1α), 98.6 (C-1β).

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