

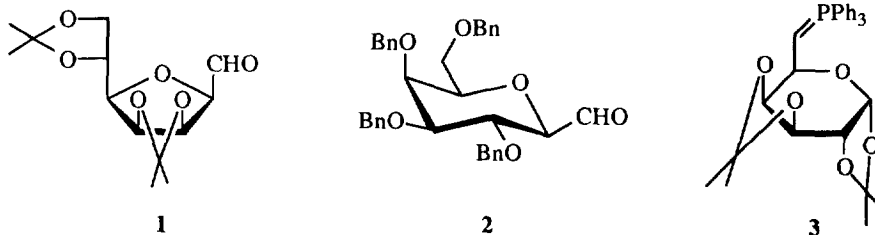
## Synthesis of *C*-Disaccharides from *C*-Formyl Glycosides

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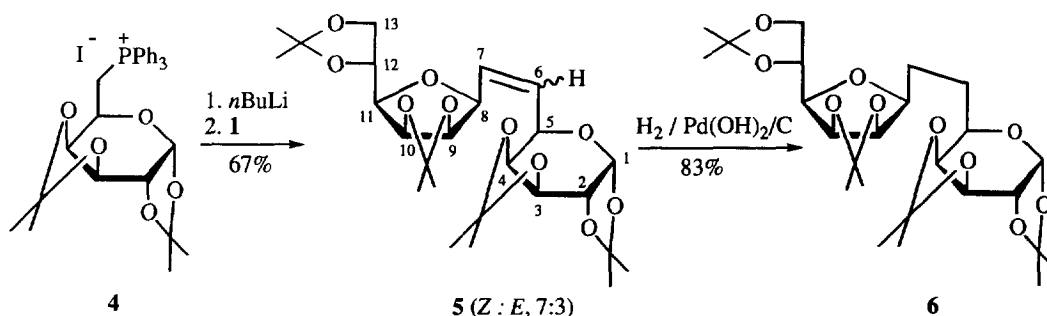
**Abstract:** The coupling between *C*-formyl 2,3:5,6-di-*O*-isopropylidene-D-mannofuranoside (**1**) and 2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside (**2**) with the protected galactose 6-phosphorane **3** leads to the corresponding olefins which upon hydrogenolysis give  $\beta$  (1  $\rightarrow$ 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are non-natural analogs of disaccharides in which the ether linkage holding the two sugar moieties has been replaced by a carbon-carbon bond.<sup>1</sup> The increasing attention which is currently addressed to this class of *C*-glycosides<sup>2</sup> stems from their potential as inhibitors of glycosidases since they are conformationally similar to their natural counterparts<sup>3,4</sup> 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,<sup>5</sup> 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  $\beta$ (1  $\rightarrow$ 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<sup>6</sup> of the precursor phosphonium salt **4**.

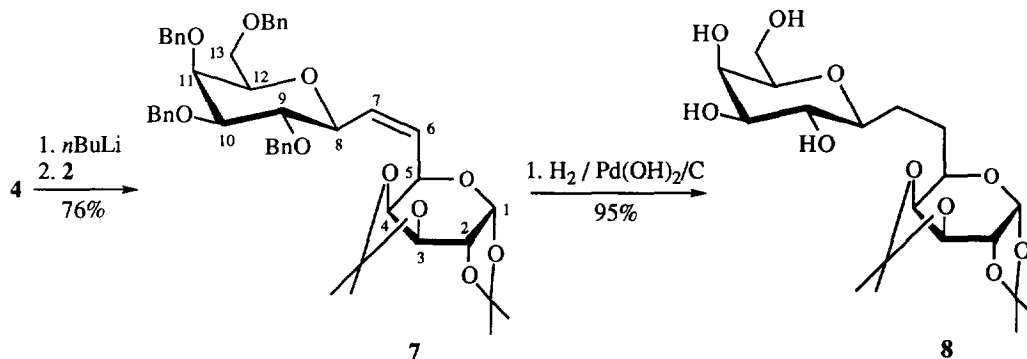


The red-colored ylide **3** was simply generated by adding *n*BuLi (1 equiv) to the phosphonium salt **4** in 2:1 THF-HMPA at -30°C in the presence of activated 4Å powdered molecular sieves with *n*BuLi (1 equiv). Then, freshly prepared<sup>7</sup>  $\beta$ -D-mannofuranosyl aldehyde **1** (1.1 equiv.) 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

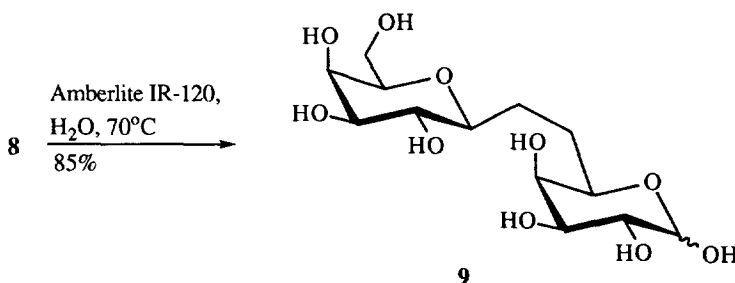
olefin **5** (67%) as a mixture of *Z* and *E* isomers in a 7:3 ratio. Confirmation that the  $\beta$ -D-manno configuration was retained during the Wittig reaction was obtained by NOE experiments on the individual isomers which were isolated by preparative TLC (ethyl acetate-cyclohexane 1:3).<sup>8</sup> Similarly, the expected conservation of the  $\alpha$ -D-galacto configuration in the other sugar moiety<sup>6</sup> 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)<sub>2</sub> 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  $\beta(1 \rightarrow 6')$ -linked *C*-disaccharide **6** was isolated in 83% yield.<sup>9</sup>



The coupling between the phosphorane **3** and the  $\beta$ -D-galactopyranosyl aldehyde **2** was carried out using the above-mentioned conditions. In this case the olefination turned out to be stereoselective since the <sup>1</sup>H 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  $\beta$ -elimination of the benzyloxy group at the C2 of **2**.<sup>10</sup> 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).<sup>9</sup> 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  $\beta(1 \rightarrow 6')$ -linked *C*-disaccharide **8** in almost quantitative yield.<sup>9</sup>



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.<sup>11</sup> The single compound  $\beta$ -D-C-Gal-(1 $\rightarrow$ 6')- $\alpha$ -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 responsible for the above low yield.<sup>12</sup> 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<sup>1b</sup>,<sup>13</sup> gave free  $\beta$ -D-C-Gal-(1 $\rightarrow$ 6')-D-Gal disaccharide **9** in 85% yield.<sup>14</sup> Hence the overall yield of **9** from **2** was 61% unoptimized.



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## References and Notes

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- 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:  $[\alpha]_{\text{D}}^{20} = -32.0^{\circ}$  (*c* 0.2, CHCl<sub>3</sub>), M+Na 521, <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>): δ 3.38 (dd, 1H, H-11, *J*<sub>11,12</sub> 8.0 Hz, *J*<sub>11,10</sub> 3.5 Hz), 4.37 (ddd, 1H, H-8, *J*<sub>8,7</sub> 6.5 Hz, *J*<sub>8,9</sub> 4.0 Hz, *J*<sub>8,6</sub> 1.0 Hz), 5.98 (ddd, 1H, H-7, *J*<sub>7,6</sub> 12.0 Hz, *J*<sub>7,5</sub> 1.0 Hz), 6.06 (ddd, 1H, H-6, *J*<sub>6,7</sub> 12.0 Hz, *J*<sub>6,5</sub> 6.4 Hz). Compound **E-5** showed:  $[\alpha]_{\text{D}}^{20} = -36.0^{\circ}$  (*c* 0.2, CHCl<sub>3</sub>), M+Na 521, <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>): δ 3.31 (dd, 1H, H-11, *J*<sub>11,12</sub> 7.0 Hz, *J*<sub>11,10</sub> 3.5 Hz), 3.60 (dd, 1H, H-8, *J*<sub>8,7</sub> 6.0 Hz, *J*<sub>8,9</sub> 4.0 Hz), 6.24 (c, 2H, H-6, H-7, *J*<sub>6,7</sub> 15.3 Hz, *J*<sub>6,5</sub> 5.7 Hz).
9. Consistent <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained for all compounds. Characteristic data were : **6**,  $[\alpha]_{\text{D}}^{20} = -42.8^{\circ}$  (*c* 0.6, CHCl<sub>3</sub>), M+Na 523; **7**,  $[\alpha]_{\text{D}}^{20} = -4.9^{\circ}$  (*c* 0.4, CHCl<sub>3</sub>), M+Na 801, <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.02 (dd, 1H, H-8, *J*<sub>8,7</sub> 7.5 Hz, *J*<sub>8,9</sub> 9.0 Hz), 5.66 (dd, 1H, H-7, *J*<sub>7,6</sub> 11.5 Hz, *J*<sub>7,8</sub> 7.5 Hz), 5.74 (dd, 1H, H-6, *J*<sub>6,5</sub> 8.0 Hz); **8**,  $[\alpha]_{\text{D}}^{20} = -37.5^{\circ}$  (*c* 1.2, CHCl<sub>3</sub>), M+Na 443.
10. Dondoni, A.; Scherrmann, M.-C., *Tetrahedron Lett.*, **1993**, *34*, 7319.
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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,  $[\alpha]_{\text{D}}^{20} +39.1^{\circ}$  (*c* 0.9, CH<sub>3</sub>OH), <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 4.40 (d, 1H, H-1β, *J*<sub>1,2</sub> 7.5 Hz), 5.10 (d, 1H, H-1α, *J*<sub>1,2</sub> 3.5 Hz), <sup>13</sup>C NMR (CD<sub>3</sub>OD): δ 28.0, 29.2 (C-6, C-7), 94.1 (C-1α), 98.6 (C-1β).

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