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Short, Stereoselective Syntheses of *C*(1→3)-linked Disaccharides

Yao-Hua Zhu and Pierre Vogel*

Section de Chimie de l'Université de Lausanne, BCH,
CH-1015 Lausanne-Dorigny, Switzerland

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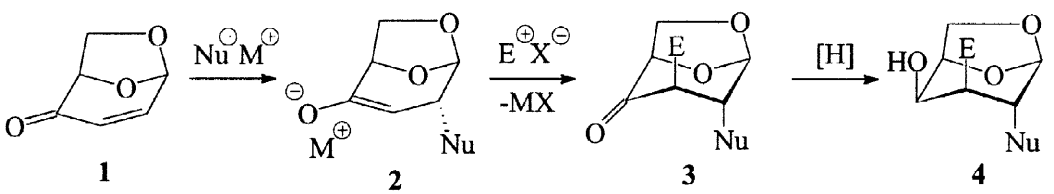
Abstract: Nucleophilic additions to D-isolevoglucosenone are face selective and generate the corresponding enolates which react with 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose to give aldol adducts. These can be reduced stereoselectively into *C*(1→3) glycosides of 1,6-anhydro-D-*galacto*-pyranose.

The interaction between cell surface carbohydrates and their protein receptors is implicated in several important biological events.[1] Carbohydrate mimics are potentially useful tools to study cellular interactions and may represent leads for drug discovery.[2] In particular, *C*-linked disaccharides[3] offer the advantage of being resistant to acidic and enzymatic hydrolysis. They are therefore potential inhibitors of glycosidases and may represent non-hydrolysable epitopes. Since the first synthesis of a β-(1→6)-*C*-disaccharide by Rouzaud and Sinaÿ[4] in 1983, several approaches to *C*-disaccharides have been proposed.[3,5] They are invariably multiple-step syntheses which do not always offer the necessary versatility for wide molecular diversity.[6] Hence, there is still a need for shorter and more convergent synthetic schemes. We report our latest efforts toward this goal which feature the conjugate additions of nucleophiles to isolevoglucosenone (**1**) followed by electrophilic quenching of the intermediate enolate **2** and reduction of the ketone **3** (*Scheme 1*).



1 **2** **3** **4**

Scheme 1

Recently, Witczak and coworkers[7] used levoglucosenone (1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyran-2-ulose) to generate *C*-disaccharides through Michael addition of (β-D-*gluco*-pyranosyl) nitromethane. This provided β-*C*(1→4)glucopyranosides of 3-deoxy-D-glucose. Isolevoglucosenone (**1**) is readily derived from D-glucose in four synthetic steps.[8] Enone **1** is known to add nucleophiles[8,9] and radicals[10] exclusively on its less hindered face (*syn* with respect to the oxa bridge). Oshima and co-workers[11] have shown that conjugate addition of Me_2AlSPh to simple enones, followed by reaction of the aluminum enolates with aldehydes allow the preparation of the corresponding aldols in one-pot procedures. When a 1:1 mixture of **1**

*e-mail: pierre.vogel@ico.unil.ch; fax: +41 21 692 39 75

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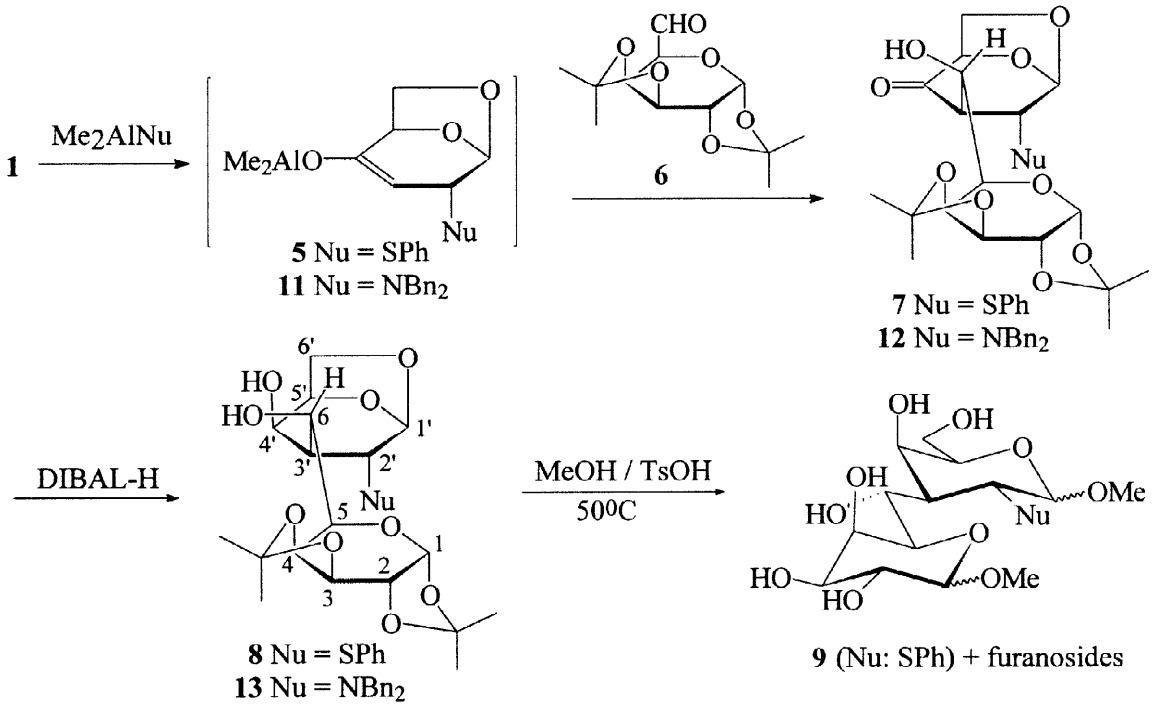
and Me_2AlSPh was allowed to react at -78°C in CH_2Cl_2, the corresponding aluminum enolate **5** was formed (*Scheme 2*). One equivalent of aldehyde **6** (derived in two steps from D-galactose[12]) was then added and allowed to react for 3h at -78°C. A solution of DIBAL-H in CH_2Cl_2 was then added dropwise and the reaction mixture was stirred at 20°C for 1h. This afforded the semi-protected *C*-disaccharide **8** which was isolated in 60% yield after flash chromatographic purification on silica gel. No other stereoisomeric product was isolated. Furthermore, the ^{1}H-NMR spectrum of the crude reaction mixture did not reveal other stereomeric *C*-disaccharide. Acidic methanolysis (MeOH, TsOH, 50°C, 5h) led to a mixture of unprotected methyl pyranosides **9** and the corresponding methyl furanosides.



Scheme 2

This result demonstrates that the doubly convergent approach depicted in *Scheme 1* is not only feasible but is also highly stereoselective, the "aglycone" part of the *C*-glycoside having the configuration of D-galactose. The relative configuration of aldol **7** and of its reduction product **8**[13] was established by ^{1}H-NMR (400 MHz, COSY, NOESY) of the acetonide **10**, obtained on treatment of **8** with a 3:1 mixture of acetone and 2,2-dimethoxypropane in the presence of TsOH and Drierite at 20°C. A coupling constant ^3J(H-3', H-6) = 9.1 Hz proves the *trans* relationship between these two protons. Strong NOE's observed between proton pairs H-2'/H-6 and H-6/H-6' confirm the *galacto* relative configuration of C(2',3',4',5'). These results demonstrate that the face *anti* with respect to the oxa bridge of enolate **5** is preferred for the cross-aldolisation, probably for steric reasons, the *exo* face being hindered by the substituent at C(2). The high diastereoselectivity of the cross-aldolisation can be interpreted in terms of the Zimmerman-Traxler model shown in *Figure 1* (closed transition state, control by steric factors).[14]

Replacing Me_2AlSPh by Me_2AlNBn_2[15] allowed one to generate the corresponding *C*-glycoside of protected D-galactosamine **13** which was characterized as its diacetate[16]. The configuration was established by ^{1}H-NMR (400 MHz, COSY, NOESY) of its acetonide **14,** prepared by the same way as acetonide **10.** Boat

conformation of the tetrahydropyran ring in the aglycone part results in a ^3J(H-2', H-3') = 10.0 Hz and NOE's between proton pairs H-2'/H-6 (strong), H-6/H-6'(weak), H-Me_a/H-5, H-Me_a/H-4', H-Me_b/H-2' and H-Me_b/H-6. Using Me_2AlOBn[17] failed to produce the expected *C*-disaccharide with a 2-*O*-benzyl D-galactose. An alternative procedure had to be developed.

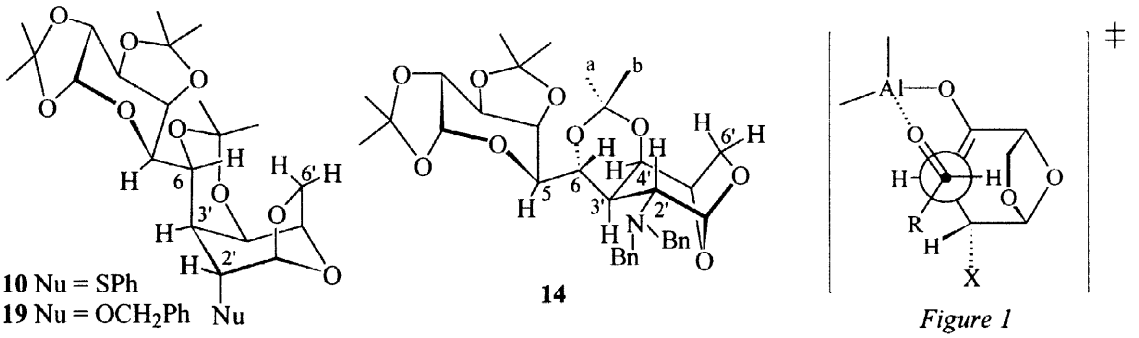
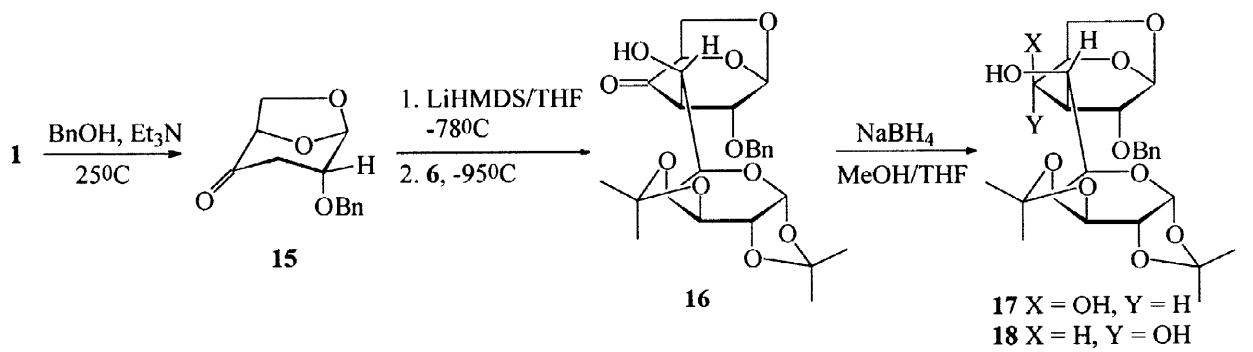


Figure 1

Conjugate addition of LiOBn or NaOBn to **1** at -50°C produced the desired adduct **15** in low yield, the major product arising from the Michael addition of the resulting enolate to the starting enone. In the presence of Et_3N, however, benzyl alcohol (as solvent) added to **1** at 20°C and afforded **15** in 90% yield. As expected, the reaction was highly stereoselective. The lithium enolate of **15** obtained on treatment with one equivalent of $(Me_3Si)_2NLi$ at -78°C (THF) did not eliminate lithium benzylate and could be reacted with all kinds of aldehydes, including **6**.[18] When the cross-aldolisation was carried out at -95°C, with **6**, a single aldol **16** was obtained in 79% yield. Its reduction with $NaBH_4$ (MeOH/THF, 0°C) was less stereoselective than reduction **7**→**8**, and gave a 5:1 mixture of **17**[19] and **18**. The major diol **17** has the configuration of D-galactose for its aglycone moiety as established by ^{1}H-NMR (^{3}J(H-3', H-6) = 10.3 Hz, NOE's between proton pairs H-2'/H-6 and H-6/H-6') of its acetonide **19,** which was obtained on treating **17** (readily separated from **18** by flash chromatography on silica gel) with acetone/2,2-dimethoxypropane/TsOH/Drierite (25°C).



Our aldols should allow one to introduce fluoro or amino substituents at the methylene linker. Inversion at C-4' in our *C*-disaccharides should generate the corresponding D-glucose derivatives. Work is underway in our laboratory in order to evaluate the versatility of this new method of synthesis of *C*-disaccharides and analogues.

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19. Data for **17**: mp: 155-156°C; $[\alpha]^{25}_D$ = -27 (*c* 0.65, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): 7.43-7.29 (*m*, 5H), 5.56 (*d*, *J* = 5.1, H-1), 5.47 (*s*, H-1'), 4.72 and 4.53 (2*d*, *J* = 11.8), 4.67-4.58 (*m*, 3H), 4.42 (*dd*, *J* = 7.9, 1.8, H-4), 4.35 (*dd*, *J* = 5.1, 2.4, H-2), 4.34 (*d*, *J* = 7.6, H_a-6'), 4.25 (*dd*, *J* = 8.5, 4.5, H-6), 3.98 (*dd*, *J* = 8.5, 1.8, H-5), 3.53 (*d*, *J* = 8.2, H-2'), 3.46 (*dd*, *J* = 7.3, 4.5, H_b-6'), 2.18 (*m*, H-3'), 1.54, 1.49, 1.37, 1.34 (4*s*, Me × 4); ^{13}C-NMR (100.61 MHz, $CDCl_3$): 137.9, 128.5, 127.9, 109.5, 108.7, 102.0, 96.5, 77.1, 73.9, 71.6, 71.0, 70.8, 70.4, 70.1, 67.6, 65.3, 61.9, 38.7, 26.0, 25.9, 24.9, 24.6.