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Synthesis of Spiro Carbon linked disaccharides: *de novo* Synthesis from Furan by Chirality Transfer from Sugar Derived Templates#

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Abstract: An enantioselective synthesis of spiro carbon linked disaccharides, using furan as a masked sugar moiety with chirality induced from 'diacetone glucose' has been developed.

Keywords: C-glycosides; 2-furyl lithium; chirality transfer; bio-active carbohydrates; spiro carbon linked disaccharides.

The importance of carbohydrates for asymmetric synthesis is well recognized[1] and our increased awareness of the role played by carbohydrates in biological processes has focussed much attention on the synthesis of bio-active carbohydrates[2]. This has resulted in interest in the synthesis of glycosyl mimics such as C-glycosides, C-saccharides[3], aza-sugars[4] etc. Notwithstanding these advances, no attempt has been made to synthesize spiro-C-disaccharides in which the sugars are attached through a 'spiro' carbon atom. Due to the rigidity of the 'spiro' system, it should hold the hydroxy substituents in a precisely defined fashion and hence should have potential for specific interactions. Our continued interest in the use of carbohydrate derived chiral templates for the synthesis of various bio-active compounds as well as glycosyl mimics[5,6,7], prompted us to examine the synthesis of the 'spiro carbon linked disaccharides' **1** and **2**.

In the present study, addition of 2-furyl lithium[8] to the enantiopure ketone template, 1,2:5,6-di-O-isopropylidene-α-D-glucofuranos-3-ulose **3**[9,10], obtained from diacetone glucose, and further transformation was identified in offering a direct access to the

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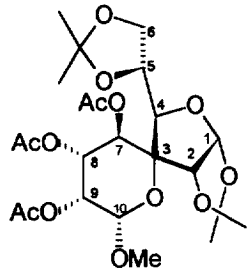
disaccharides **1** and **2**, where a new sugar unit has been constructed from the furan moiety with chirality induced from the sugar template.



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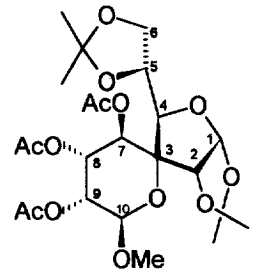

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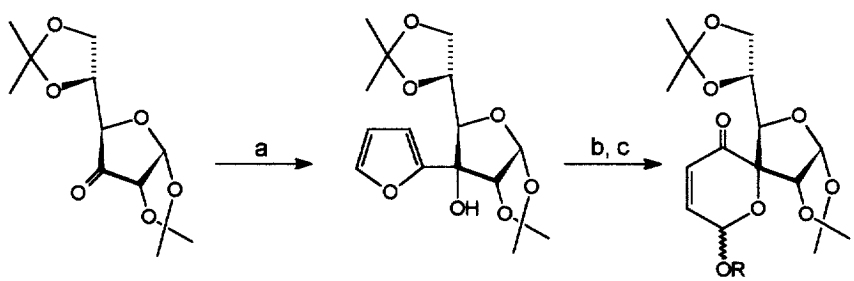
Accordingly, addition of 2-furyl lithium to the known ketone **3**[9] (Scheme 1) afforded the 3-C-furanyl-D-allose derivative **4**[1][11] in 75% yield, $[\alpha]_D$ +21.6 (*c* 0.72, $CHCl_3$), where the stereochemical outcome is the consequence of the steric hindrance of the 1,2-O-isopropylidene group on the α-face. Oxidative ring opening[12] of the furan **4** with NBS in aq. THF gave the lactols **5**, which on reaction with Ag_2O-MeI, were subsequently converted into an inseparable mixture of the α,β-methyl pyranosides **6** in 80% overall yield from **4**.

Scheme 1



3 **4** **5** R = H **6** R = Me

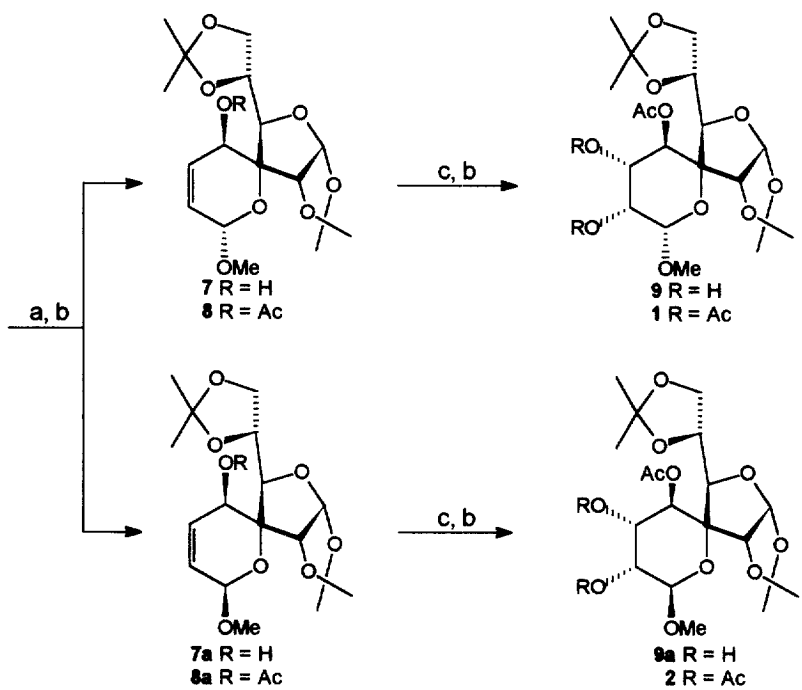
Reagents: a) furan, n-BuLi, THF, -78 °C; b) NBS, aq. THF (3:2), -5 °C; c) Ag_2O-MeI, CH_2Cl_2

Stereoselective reduction of **6** (Scheme 2) under Luche's reaction conditions[13] using $CeCl_3$-$NaBH_4$ in MeOH afforded an anomeric mixture of the allylic alcohols **7** and **7a** (3:3.5) in 75% yield with complete facial selectivity[14]. This mixture was easily separated chromatographically into the α and β-methyl glycosides **7** $[\alpha]_D$ +63.9 (*c* 1.1, $CHCl_3$) and **7a**, m.p. 143°C, $[\alpha]_D$ +59.1 (*c* 0.61, $CHCl_3$) respectively. The ^1H NMR spectra of **7** and **7a** indicated H-7 as a double-doublet at δ 4.65 ($J_{7,8}$ 7.0, $J_{7,OH}$ 8.5 Hz), while H-10 resonated at δ 4.95 (d, $J_{9,10}$ 3.0 Hz) and δ 5.32 (br.s) respectively.

1. All new compounds gave satisfactory spectral analysis.

Alcohols **7** and **7a** were acetylated using Ac_2O-pyridine to give the acetates **8** (81%) and **8a** (87%), in whose ^1H NMR, H-7 resonated as a doublet at δ 4.75 ($J_{7,8}$ 7.0 Hz) in both the isomers. The acetates **8** and **8a** were submitted to catalytic osmylation[15,16] using OsO_4-NMO in acetone-water (3:1) to afford the diols **9** and **9a** with diastereofacial control, *anti* relative to the -OAc group. However it is pertinent to mention that the α-anomer **8** underwent osmylation

Scheme 2



Reagents: a) $CeCl_3$-$NaBH_4$,MeOH; b) Ac_2O-pyridine; c) OsO_4-NMO, acetone-water (3:1)

at a very slow rate with only 15% conversion even after 5 days with the majority of the starting material recovered. On the contrary, **8a** gave the diol **9a** in 87% yield in 16 hrs. The diols **9** and **9a** were acetylated (Ac_2O-pyridine) to furnish the spiro furano-3-C-5-pyranosides **1** (74%) and **2** (77%) respectively, whose structures were established by ^1H NMR and other spectral data.[2] In the ^1H NMR spectrum of **1**, H-10 resonated at δ 5.09 (d, $J_{9,10}$ 3.0 Hz) and δ 5.1 (d, $J_{9,10}$ 9.1 Hz)

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2. Spectral data of selected compounds - **1**: $[\alpha]_D$ –8.0 (*c* 0.25, $CHCl_3$); ^1H-NMR (200 MHz, $CDCl_3$, TMS): δ 1.25, 1.35, 1.45, 1.6 (4s, 12H), 2.02, 2.12, 2.18 (3s, 9H, OAc), 3.55 (s, 3H, OMe), 3.8-3.95 (m, 2H, H-6,6'), 4.15 (d, 1H, $J_{4,5}$ 4.5 Hz, H-4), 4.36-4.48 (m, 1H, $J_{4,5}$ 4.5 Hz, H-5), 4.5 (d, 1H, $J_{1,2}$ 4.05 Hz, H-2), 4.85 (d, 1H, $J_{7,8}$ 1.9 Hz, H-7), 5.02 (d, 1H, $J_{9,10}$ 3.7 Hz, H-10), 5.09 (dd, 1H, $J_{8,9}$ 5.3, $J_{9,10}$ 3.7 Hz, H-9), 5.4 (dd, 1H, $J_{7,8}$ 1.9, $J_{8,9}$ 5.3 Hz, H-8), 5.75 (d, 1H, $J_{1,2}$ 4.05 Hz, H-1); FABMS: 519 (M^++1), 503 (M-15); **2**: m.p. 117-119°C; $[\alpha]_D$ +27.9 (*c* 0.91, $CHCl_3$); ^1H-NMR (200 MHz, $CDCl_3$, TMS): δ 1.38, 1.49, 1.62 (3s, 1x6H, 2x3H), 2.10, 2.12, 2.19 (3s, 9H, OAc), 3.55 (s, 3H, OMe), 3.8-4.2 (m, 2H, H-6,6'), 4.2 (d, 1H, $J_{4,5}$ 4.5 Hz, H-4), 4.59-4.7 (m, 1H, $J_{4,5}$ 4.5 Hz, H-5), 4.8 (d, 1H, $J_{1,2}$ 4.5 Hz, H-2), 4.86 (d, 1H, $J_{7,8}$ 5.4 Hz, H-7), 5.1 (d, 1H, $J_{9,10}$ 9.1 Hz, H-10), 5.16 (dd, 1H, $J_{8,9}$ 4.5, $J_{9,10}$ 9.1 Hz, H-9), 5.48 (dd, 1H, $J_{7,8}$ 5.4, $J_{8,9}$ 4.5 Hz, H-8), 5.61 (d, 1H, $J_{1,2}$ 4.5 Hz, H-1); ^{13}C-NMR (50 MHz, $CDCl_3$ TMS): δ 20.7 (2C), 25.5, 26.4, 26.7 (2C), 29.6, 56.6, 65.8, 66.9, 68.8, 69.2, 73.5, 82.2, 82.8, 98.1, 102.9, 108.8, 112.9 (2C), 168.9, 169.6 (2C); FABMS: 519(M^++1), 503 (M-15); HRMS (FAB) calcd for $C_{22}H_{31}O_{13}$ (M-15) 503.176467. Found 503.176270.

for **2**; clear indications of the axial-equatorial and diaxial relationship between H-9 and H-10 in **1** and **2** respectively. In NOESY experiments (400 MHz) conducted on both anomers **1** and **2**, H-7 did not show any NOE with H-2, H-4 and H-5. Irradiation of H-2 in compound **1** did show NOE's with H-8 and H-9 while in compound **2** only H-9 showed an NOE on irradiation of H-2. The NOE studies on H-2 indicates that H-8 and H-9 are in proximity to H-2 through space while H-7 is not. Thus the NOESY experiments suggests the structures assigned to **1** and **2**.

Thus, in conclusion, a simple, efficient and enantioselective synthesis of the spiro carbon linked disaccharides **1** and **2** has been achieved starting from the chiral ketone **3** and furan. The salient features of this approach are a) the stereochemical outcome of the spiro junction being defined by the 1,2-O-isopropylidene group, b) the chirality being translated from the sugar synthon and c) the diol stereochemistry arising from the *anti* facial attack relative to the -OAc group.

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