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Carbon - Carbon Linked Disaccharides by *de novo* Construction from Furanyl Sugar Templates

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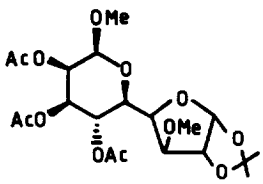
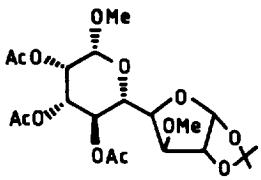
Abstract: The furanylated sugar units on *de novo* construction of a sugar moiety by oxidative unmasking of furan and introduction of three contiguous oxygenated carbon centers led to the incorporation of D and L-sugar units at the C-4 position of the furanoside, thereby leading to the synthesis of C(4) - C(5) linked disaccharides.

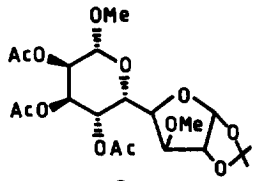
Bio-active carbohydrates[1] play a vital role in several life processes. The fundamental structural unit, the O-glycosidic linkage[2], that is present in such compounds essentially is very labile to metabolic processes. To evaluate and study the pharmacological properties of these systems, there is an urge for the synthesis of pseudosugars having a glycosyl linkage with increased metabolic stability, where the O-glycosyl linkage is replaced by a C-C linkage[3] leading to C-glycosides[4]. Research in this direction has resulted in the development of C-disaccharides[5] along with other types of C-linked disaccharides with[6] or without[7] spacers between two sugar moieties. Herein, we describe our protocol for the synthesis of C(4) - C(5) linked (L) and (D)-disaccharides **1**, **2** and **3** from 'diacetone glucose' (DAG).



1



2



3

In the present protocol a reiterative C5+C4 homologation strategy was adopted for the collection of required carbon skeleton, where the chirality is dictated by the C-5 sugar aldehyde unit while *de novo* construction of the additional sugar unit was achieved from the 'masked sugar' synthon, the C-4 furan moiety.

Accordingly, known[8] aldehyde **4**, on four carbon homologation (scheme 1) utilizing 2-furyl lithium[9] as reagent (n-BuLi, THF,-78°C) gave a mixture of diastereoisomers[10] **5** and **5a** (1.8:1) in 60% yield. However, this mixture was successfully converted into the major diastereomer **5** in 4:1ratio by a two-step synthetic sequence viz. a) oxidation of mixture of **5** under Swern oxidation conditions and b) subsequent reduction of the ketone

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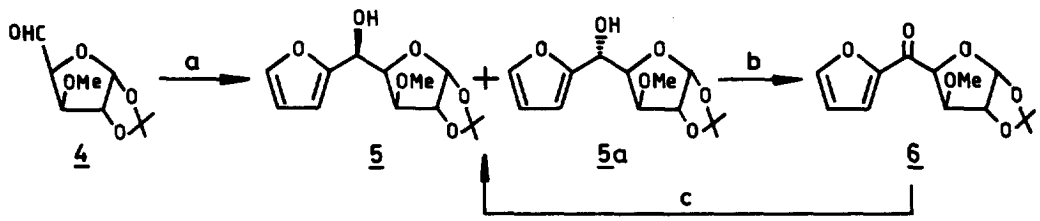
6 with $NaBH_4$ under the steric approach control.

Scheme-1

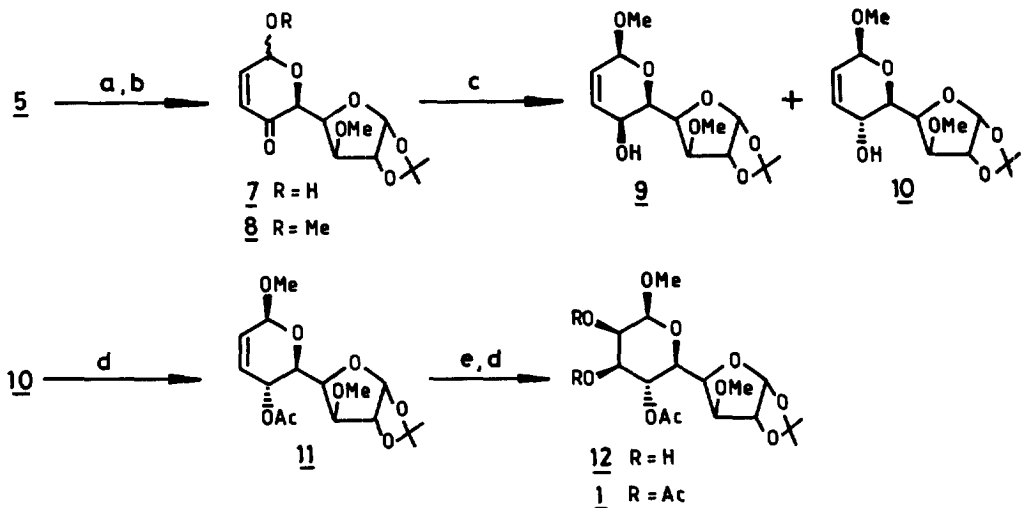


a)Furyl lithium,THF, -78°C; b) $(COCl_2)$, DMSO, Et_3N, CH_2Cl_2; c) $NaBH_4$, MeOH

Synthesis of C(4)-C(5) linked (L)-disaccharide

Having obtained the required carbon frame work with D-gluco configuration in **5**, next it was aimed at the transformation of the furan unit into a sugar moiety. Accordingly, carbinol **5** on oxidative [11]unmasking of the furan with Br_2-pyridine in acetone-water system resulted in the formation of lactol **7** (scheme 2), which was subsequently

Scheme-2



a) Br_2-Pyridine, aq. Acetone; b) Ag_2O, MeI; c) $NaBH_4$, MeOH; d) Ac_2O, Pyridine; e) OsO_4, NMO, t-BuOH-THF

converted into the corresponding α , β-methyl pyranosides **8** (Ag_2O, MeI; 1.4:1 ratio) as an inseparable mixture. The thus obtained enone **8** is now set for the further installation of the remaining additional 3 contiguously oxygenated carbon atoms as described below.

Thus, $NaBH_4$ reduction (scheme 2) of the enone **8** and chromatographic purification (SiO_2, 17:3 pet.ether-EtOAc) afforded the two β-glycosides **9** (minor) and **10** (major) in 3:5 ratio, while the α-anomers were not separable. **9** $[\alpha]_D$ -24.6°(c 1.25, $CHCl_3$; **10** $[\alpha]_D$ -75.8°, (c 1.0 $CHCl_3$). The major isomer **10** was subjected to acetylation (Ac_2O, pyridine) to give **11**, which on subsequent anti selective[12] *cis*-dihydroxylation (OsO_4, NMO, t-BuOH-THF) of the

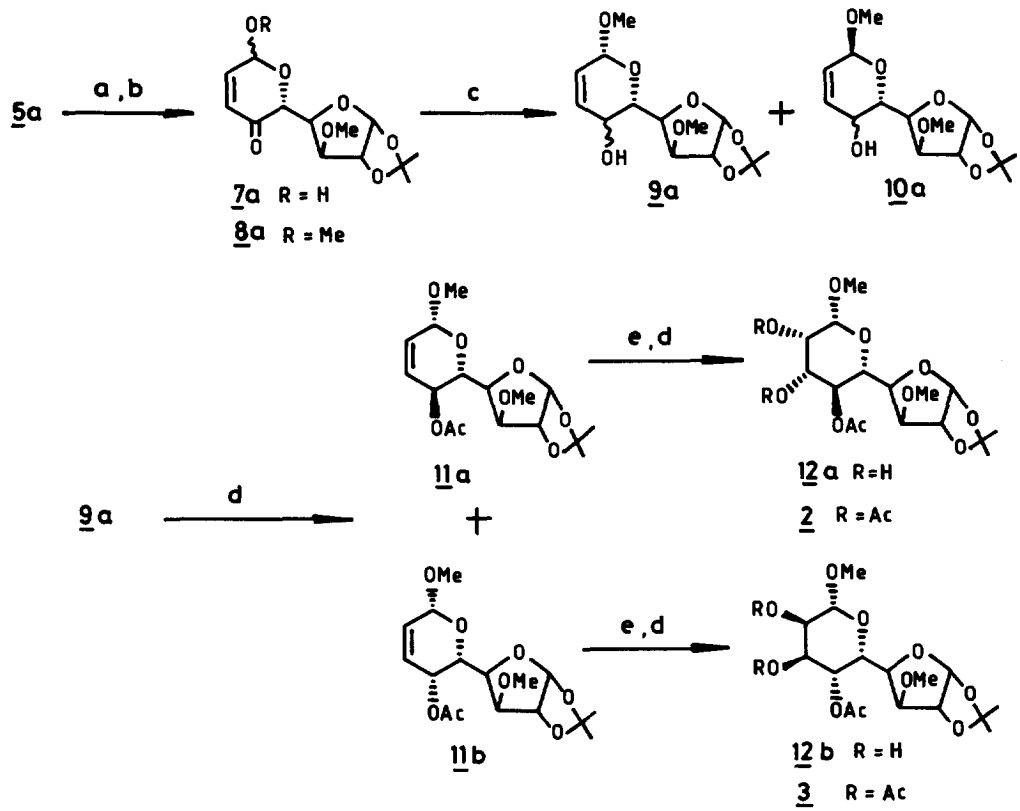
double bond gave the diol **12** (95%), [α]$_D$ -31.7°, (c 0.98, $CHCl_3$). Finally acetylation of diol **12** with Ac_2O-pyridine gave the tri-O-acetate **1**, [α]$_D$-26.25°,(c 0.8, $CHCl_3$), whose ^1H and ^{13}C-NMR data indicated the assigned structure. Thus, the furan moiety installed at the C-5 center of gluco -furanoside was successfully converted into a sugar moiety thereby leading to the synthesis of C(4)-C(5) linked (L)-saccharide**1**.

Synthesis of C(4)-C(5) linked (D)-disaccharides

Similarly, functional group transformations have been performed on the minor L isomer **5a** leading to **2,** the antipode of **1,** and **3**.

Accordingly, the L-isomer **5a** was unmasked to lactol **7a** (scheme 3),which was subsequently converted into a mixture of methyl glycosides **8a**. Reduction of the enone **8a** with $NaBH_4$ and chromatographic separation gave **9a**

Scheme-3



a) Br_2-Pyridine, aq. Acetone; b) Ag_2O, MeI; c) $NaBH_4$, MeOH; d) Ac_2O, Pyridine; e) OsO_4, NMO, t-BuOH-THF

(major) and **10a** (minor) in 2:1 ratio. However, from the ^1H-NMR of **9a** it was found to be a mixture of two compounds. Acetylation of **9a** and chromatographic purification (SiO_2, 4:1 pet.ether-EtOAc) afforded **11a** (major) and **11b** (minor) in : ratio with optical rotation values of [α]$_D$+54.9°(c 1.02, $CHCl_3$ and -75.7°(c 0.95, $CHCl_3$)

respectively. Subsequently *cis*-hydroxylation of **11a** and **11b** afforded the diols **12a** (90%) and **12b** (92%), which on acetylation furnished the respective tri-O-acetates **2**, $[\alpha]_D$ +31.0°, (c 0.98, $CHCl_3$) and **3**, $[\alpha]_D$ -15.8°, (c 1.1, $CHCl_3$).

Thus, the above transformations on **5** and **5a** respectively led to the diastereospecific installation of the L-manno, D-manno and D-gulo pyranoside moieties at the C-4 carbon center of D-furanoside moiety, leading to the synthesis of carbon-carbon linked disaccharides **1**, **2** and **3** respectively.

In conclusion, a concise strategy has been developed utilizing the furan moiety as masked sugar synthon on aldehydo sugar, thereby leading to the D and L antipodes of C(4)-C(5) linked furano-pyranosides. This flexible method is adoptable for the synthesis of several unnatural saccharides linked both to the furano- as well as pyranosides very effectively. Adoption of this method for the synthesis of C-linked inositol saccharides is in progress.

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10. All new compounds gave satisfactory spectral analysis. ^{1}H-NMR data of selected compounds (200MHZ, $CDCl_3$, TMS, δ in ppm, J in Hz): **5** - $[\alpha]_D$ -46.2° (c1.0, $CHCl_3$); 7.38(s,1H,H-9), 6.32 (s,2H,H-7,8), 5.97(d,1H,$J_{1,2}$4.54,H-1), 4.95(d,1H,$J_{4,5}$6.8,H-5), 4.52(d,1H,H-2), 4.35(dd,1H,H-4), 3.85(d,1H,$J_{3,4}$4.54,H-3), 3.45(s,3H,OMe), 1.48, 1.30(2s,6H); **5a** - $[\alpha]_D$ -23.0° (c1.0, $CHCl_3$); 7.38(s,1H,H-9), 6.32(s,2H,H-7,8), 5.9(d,1H,$J_{1,2}$ 4.09,H-1), 4.95(d,1H,$J_{4,5}$ 9.0,H-5), 4.5(d,1H,H- 2),4.4(dd,1H,H-4), 3.48(d,1H, $J_{3,4}$ 4.09,H-3), 3.26(s,3H,OMe), 1.49, 1.3(s,6H); **11** - $[\alpha]_D$ -82.0° (c 0.9, $CHCl_3$); 5.9-5.8(m,3H,H-1,7,8), 5.5(d,1H,$J_{5,6}$ 9.0,H-6), 4.81(s,1H,H-9), 4.5(d,1H,$J_{1,2}$4.4,H-2), 4.25-4.0(m,2H,H4,5), 3.8(br.s,1H,H-3), 3.4(2s,6H,OMe), 2.0(s,3H,OAc), 1.48,1.3(2s,6H); **11a** - $[\alpha]_D$ +54.9°(c 0 .95, $CHCl_3$); 5.95-5.72(m,3H,H-1,7,8), 5.4(d,1H, $J_{5,6}$ 8.0, H-6), 4.88(br.s,1H,H-9), 4.62(m,1H,H-2),4.35(t,1H,H-5), 4.15(dd,1H,$J_{3,4}$4.0,$J_{4,5}$10.0,H-4), 3.85(d,1H,H-3), 3.48(s,3H,OMe), 2.08(s,3H,OAc), 1.5,1.38(2s,6H).
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