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Stereoselective synthesis of 4-*C*-methyl-2,3,5-tri-*O*-benzyl-D-ribofuranose and 4-*C*-methyl-2,3,5-tri-*O*-benzyl-L-lyxofuranose

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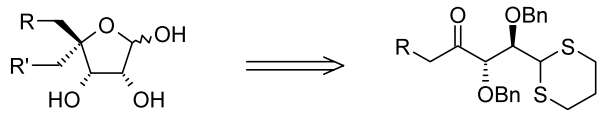
Abstract—Sugar intermediates 4-*C*-methyl-2,3,5-tri-*O*-benzyl-D-ribofuranose (**8b**) and 4-*C*-methyl-2,3,5-tri-*O*-benzyl-L-lyxofuranose (**8a**) were synthesized by addition of alkylithium reagents to pentanones **3a**,**b**. The nucleophilic additions proceeded with good stereoselectivity and good yields to give the titled compounds in four steps from perbenzylated methyl D-ribofuranoside and methyl 5′-deoxy-D-ribofuranoside.

Sugar-modified nucleosides and nucleotides have long been used against a wide variety of diseases. Drugs such as AZT, 2′,3′-dideoxy nucleosides and 2′,3′-didehydro-dideoxy nucleosides are in used to treat HIV,[1] arabino-nucleosides such as fludarabine and cytarabine are used to treat various leukemias,[1b,2] whereas the antisense oligonucleotide field uses modified sugar nucleosides to design RNA/DNA probes.[3]

Tubercidin analogs with potent adenosine kinase (AK) inhibition were shown to have anti-epileptic and anti-inflammatory activities.[4] However, such nucleosides present limitations as therapeutic agents because of toxicities arising from potential 5′-*O*-phosphorylation and subsequent incorporation into the nucleotide pools resulting in toxic side effects.[5] Accordingly, our efforts focused on designing nucleosides that would not be phosphorylated. Since efficient phosphorylation is dependent on sugar conformation and possibly substitutions near the 5′-hydroxyl, we hypothesized that introduction of a methyl group at the C4′-position of nucleosides would cause subtle changes in the orientation of the 5′-hydroxyl group and thereby prevent phosphorylation while maintaining enzyme inhibition. To synthesize such nucleosides, suitably protected 4-*C*-methyl-D-ribose and 4-*C*-methyl-L-lyxose were needed as key intermediates.

Although many syntheses of 4-*C*-modified sugars have been published,[6] in all but Johnson's synthesis,[6d] the C4-substituent was introduced via the aldol-Cannizaro reaction of the corresponding C5-aldehyde with formaldehyde.[7] While this procedure is very useful for the synthesis of bis-(4-hydroxymethyl)-sugar analogs, low selectivity is generally observed when attempting to deoxygenate only one of the C4-hydroxymethyls.[6e,f] In contrast, Johnson's synthesis is highly stereoselective and allows for introduction of a large array of substituents at the C4 position.[6d] However, this procedure involves multiple steps and was judged unsuitable for the synthesis of the current targets. Herein we describe an alternative stereoselective synthesis of 4-*C*-methyl-D-ribose (**1**) and 4-*C*-methyl-L-lyxose (**2**).

Upon retro-synthetic analysis of the target compounds, the introduction of the C4-methyl group was envisioned to proceed via the nucleophilic addition of a methyl equivalent to pentanone **3a** (Scheme 1). Such addition could proceed through one of the three chelated transition states as shown in Figure 1 (Cram's model, **T1**–**3**) or through a non-chelated transition state (Felkin–Ahn's model, **T4**).[8]



1, R=OH; R'=H
2, R=H; R'=OH

3a, R=OBn
3b, R=H

Scheme 1.

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Based on the transition states in Figure 1, the incoming nucleophile would be expected to add to the *re*-face of ketone **3a** in transition state **T2** whereas, in transition state **T3**, the carbanion would add to the *si*-face giving rise to the opposite stereochemistry at the 4-carbon. On the other hand, no selectivity would be expected from transition state **T1** since the 5-carbon is achiral. Due to the uncertainties associated with the stereochemical outcome of a nucleophilic addition to ketone **3a** via a chelated transition state, we hypothesized that the non-chelated addition of a carbanion proceeding through transition state **T4**, where the stereochemical outcome is only dictated by the chirality of the 3-carbon through steric and electronic factors, should give rise to products with predictable stereochemistry.[9]

Our hypothesis was first tested on ketone **3a**.[10] Addition of methyl lithium to a THF solution of ketone **3a** at −78°C produced a mixture of two products (Scheme 2) in a 12/1 ratio, as evidenced by integration of the methyl resonances at 1.25 ppm (major) and 1.13 ppm (minor) in the ^{1}H NMR spectrum of the crude reaction mixture. Both products were isolated by column chromatography and were tentatively assigned structure **7a**[11] (major, 69%) and **7b**[11] (minor, 8%).

To further test the hypothesis, benzyloxymethyl lithium[12] was added under similar reaction conditions to ketone **3b**[10] (Scheme 2). Once again, the reaction mixture gave two products in a 7.5:1 ratio, which were isolated by column chromatography. As predicted in this case, the ^{1}H NMR spectrum of the major isomer matched with that of the minor isomer **7b**[11] from the previous reaction, whereas the spectrum of the minor isomer matched that of isomer **7a**,[11] indicating that the addition took place with the same facial selectivity.

Unambiguous stereochemical assignments were made by first removing the dithiane protecting group[13] and derivatizing both benzylated furanoses **8a**,**b**[11] into methyl furanosides **10a**,**b** (Scheme 3). Initial attempts to remove the benzyl protecting groups via hydrogenolysis resulted in significant decomposition. However this problem was overcome by protecting the anomeric hydroxyls of furanoses **8a**,**b** as acetates prior to hydrogenolysis. Further treatment of the triol intermediates **9a**,**b** with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid in CH_2Cl_2 resulted in not only the formation of the 2,3-isopropylidene, but also exchanged the anomeric acetate to produce methyl furanosides **10a**,**b**.[11] Direct comparison of the ^{1}H and

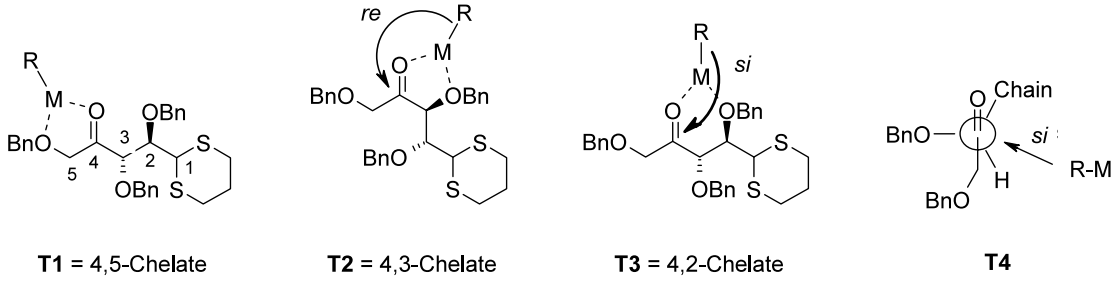
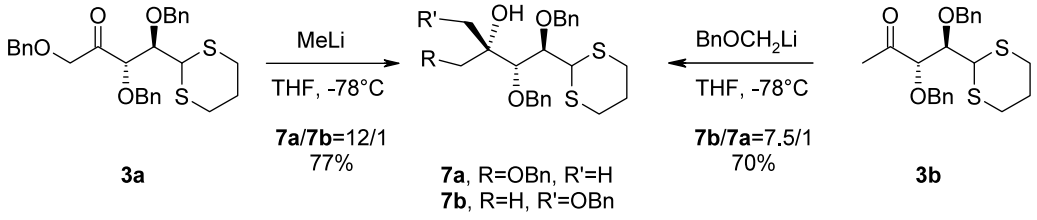
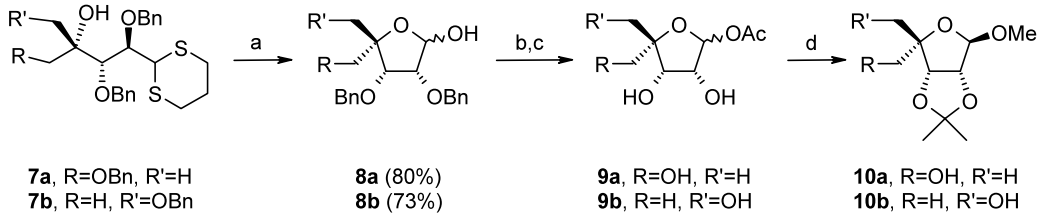


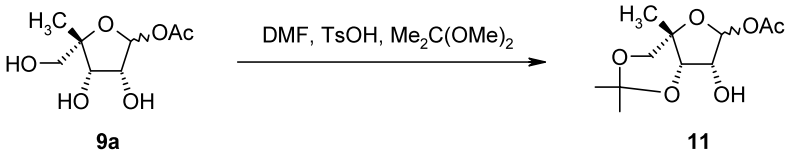
Figure 1.



Scheme 2.



Scheme 3. *Reagents and conditions*: (a) $CaCO_3$, MeI, ACN/H_2O/THF (2/9/2), reflux; (b) Ac_2O, pyridine, DMAP; (c) $Pd(OH)_2$/C, 1 atm H_2, EtOAc/AcOH (5/1); (d) CH_2Cl_2, *p*-TsOH, $Me_2C(OMe)_2$.



9a **11**

Scheme 4.

^{13}C NMR spectra for both isopropylidene-protected methyl furanosides with the spectrum of compound **10b**, synthesized independently as an intermediate in the total synthesis of *S*-(4′-methyladenosyl)-L-homocysteine,[6d] confirmed the original assignment of the stereochemistry of the 4-carbon. Further evidence confirming the structures of **10a** and **10b** came from the solvent effect studies conducted during the protection of the 2- and 3-hydroxyls of intermediates **9a**,**b**. It was noticed that in DMF, triol **9a** (Scheme 4) gave a new product, which was assigned structure **11** based on ^{1}H NMR studies, whereas **9b** gave **10b**, confirming the *lyxo*-configuration for intermediate **9a**.

In conclusion, this work demonstrates the generality and the good stereoselectivity of the non-chelation controlled addition of alkyllithium reagents to ketones **3a**,**b** for the stereoselective synthesis of 4-*C*-substituted sugar analogs.

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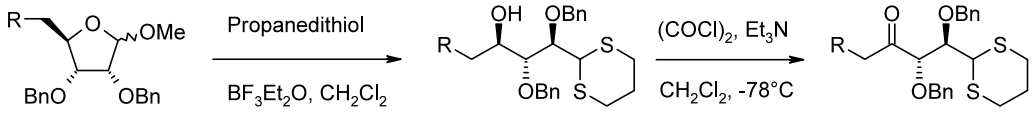
10. Ketone **3a** was synthesized from methyl 2,3,5-tri-*O*-benzyl-D-ribofuranoside (**4a**, Barker, R.; Fletcher, H. G., Jr. *J. Org. Chem.* **1961**, *26*, 4605) in the following two-step sequence. Ketone **3b** was synthesized in a similar fashion from methyl 5-deoxy-2,3-di-*O*-benzyl-D-ribofuranoside (**4b**, Chen, X.; Schneller, S. W. *J. Med. Chem.* **1993**, *36*, 3727–3730).



4a, R=OBn
4b, R=H

5a (94%)
5b (92%)

3a (88%)
3b (80%)

11. Selected data for compound **7a**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.45–7.20 (m, 15H), 5.46 (d, $J=10.1$ Hz, 1H), 4.90–4.37 (m, 7H), 4.12 (dd, $J=7.1$, 1.8 Hz, 1H), 3.75 (d, $J=7.1$ Hz, 1H), 3.53 (s, 1H), 3.50 (d, $J=8.6$ Hz, 1H), 3.41 (d, $J=8.6$ Hz, 1H), 2.90–2.40 (m, 4H), 2.15–1.80 (m, 2H), 1.25 (s, 3H). Compound **7b**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.50–7.20 (m, 15H), 5.18 (d, $J=10.5$ Hz, 1H), 4.86–4.48 (m, 6H), 3.97 (s, 2H), 3.65 (br s, 1H), 3.55 (d, $J=9.9$ Hz, 1H), 3.30 (d, $J=9.9$ Hz, 1H), 2.90–2.55 (m, 4H), 2.20–1.80 (m, 2H), 1.13 (s, 3H). Compound **8a**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.45–7.15 (m, 15H), 5.48–5.42 (m, 0.5H), 5.28 (dd, $J=11.2$, 4 Hz, 0.5H), 4.88–4.32 (m, 6H), 4.10 (t, $J=4$ Hz, 0.5H), 4.02 (d, $J=5.1$ Hz, 0.5H), 3.97 (dd, $J=7.1$, 2 Hz, 0.5H), 3.90–3.74 (m, 1.5H), 3.64 (d, $J=10.2$ Hz, 1H), 3.46 (d, $J=9.1$ Hz, 0.5H), 3.75 (d, $J=3$ Hz, 0.5H), 1.48 (s, 1.5H), 1.28 (s, 1.5H). Compound **8b**: ^{1}H NMR ($CDCl_3$) δ 7.40–7.10 (m, 15H), 5.28–5.22 (m, 0.3H), 5.16 (br d, $J=7$ Hz, 0.7H), 4.80–4.28 (m, 6H), 4.24 (d, $J=5$ Hz, 0.7H), 4.16–4.00 (m, 0.3H), 3.96 (d, $J=5$ Hz, 0.3H), 3.81 (d, $J=5$ Hz, 0.7H), 3.57 (br d, $J=7$ Hz, 0.7H), 3.33 (d, $J=10$ Hz, 0.7H), 3.22 (s, 0.6H), 3.17 (d, $J=10$ Hz, 0.7H), 1.33 (s, 0.9H), 1.29 (s, 2.1H). Compound **10a**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.95 (s, 1H), 4.69 (d, $J=6$ Hz, 1H), 4.52 (d, $J=6$ Hz, 1H), 3.75–3.65 (m, 2H), 3.32 (s, 3H), 2.45 (m, 1H), 1.48 (s, 3H), 1.31 (s, 3H), 1.3 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 112.8, 108.9, 86.7, 86.5, 85.6, 67.0, 54.7, 26.2, 24.6, 23.5. Compound **10b**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.90 (s, 1H), 4.68 (d, $J=6$ Hz, 1H), 4.64 (d, $J=6$ Hz, 1H), 3.67 (dd, $J=11$, 2.9 Hz, 1H), 3.55 (dd, $J=12.1$, 2.9 Hz, 1H), 3.45 (t, $J=11$ Hz, 1H), 3.42 (s, 3H), 1.48 (s, 3H), 1.32 (s, 3H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 112.2, 109.7, 90.6, 87.3, 82.9, 69.4, 55.7, 26.5, 24.9, 18.2.

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