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First synthesis of 4a-carba-β-D-galactofuranose

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Abstract—The synthesis of 4a-carba-β-D-galactofuranose is described starting from diacetone glucose. The key ring-closure step was carried out by metathesis to form a cyclopentene. Catalytic hydrogenation of the C=C double bond gave the *galacto* configured saturated carbahexofuranose with excellent diastereoselectivity.

Galactose is an unusual sugar in that, while in its pyranose form, it is widespread in the oligo- and polysaccharides of mammals and lower organisms alike; in its furanose form, it is common in bacteria but unknown in mammals. An interesting example is *Mycobacterium tuberculosis*, the bacterium responsible for causing tuberculosis, whose cell wall polysaccharide, arabinogalactan, contains a polymeric region built up of galactofuranose Gal*f*β(1→5)Gal*f*β(1→6) repeating units.[1] Various molecules containing a structural unit mimicking the galactofuranose monosaccharide have been synthesised, including iminosugars,[2] thiosugars[3] and C-glycosides (Fig. 1).[4] The ability of some of these compounds to inhibit bacterial enzymes, i.e., UDP Gal mutase and potentially galactofuranosyl transferase (GlfT),[5] that are responsible for the biosynthesis of this cell wall glycan makes galactofuranose mimics interesting biological targets with potential therapeutic value. Carbasugars, in which the ring oxygen is replaced by a methylene group, can also act as glycomimetics.[6] Syntheses of some carbahexofuranoses[7] and carbapentofuranoses[8] have been reported, but carbagalactofuranose **1** has not been synthesised before, despite the biological importance of its natural analogue. We report its synthesis in this Letter for the first time.

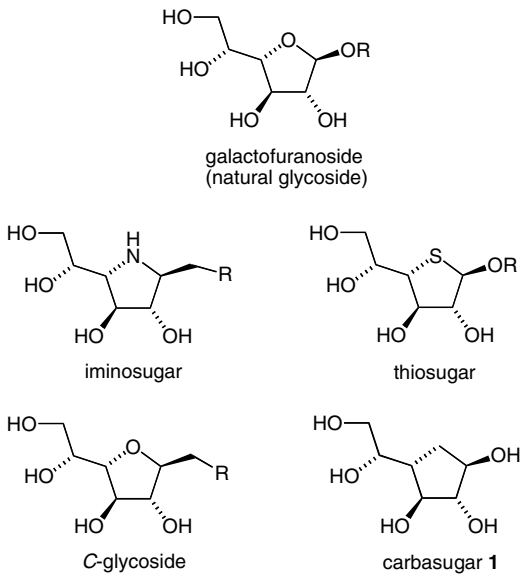

Figure 1. Galactofuranose and some analogues.

We planned to start the synthesis of **1** from a hemiacetal of the same ring size as the desired product, a furanose hemiacetal in this case, and to use ring-closing metathesis to form the carbocyclic ring.[9,10] As the C-4 stereochemistry is lost during the synthesis, it is possible to use the C-4 epimer of galactose, glucose, which is easily persuaded to adopt a furanose structure as its diacetonide derivative **2**. To avoid the potential problem of selective protection of an allylic alcohol in the presence of another secondary alcohol,[10] we opted to use hemiacetal **3** as a key synthetic intermediate, so that the product of Grignard addition **4** would contain a 1,2-diol that could be selectively protected leaving OH-4[11] as the only free hydroxyl group.[12]

Keywords: Carbasugars; Galactofuranose; Glycomimetics; Ring-closing metathesis.
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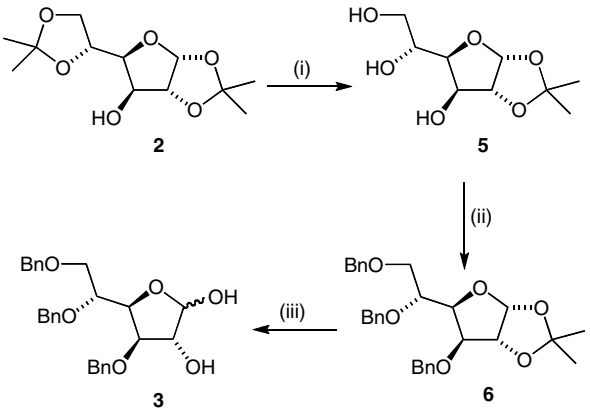


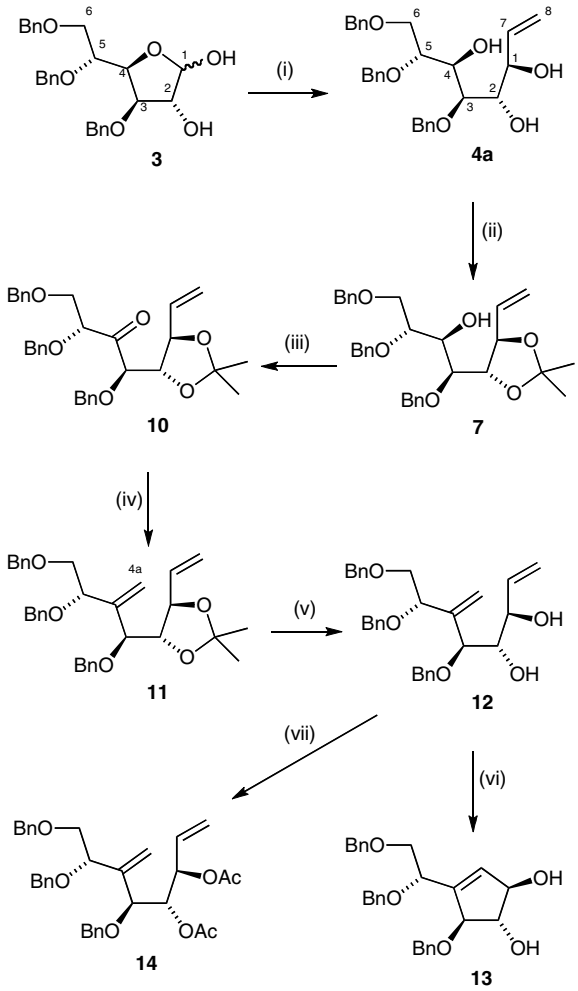
Scheme 1. Reagents and conditions: (i) AcOH, H_2O, 91%; (ii) BnBr, NaH, DMF; (iii) AcOH, H_2O, HCl, 80 °C, 67% over two steps.

Hemiacetal **3** is available by a published route from diacetone glucose **2** (Scheme 1): selective deprotection of the primary acetonide, perbenzylation of the resulting triol **5**, and then hydrolysis of the remaining acetonide gave hemiacetal **3**.[13]

Treatment of hemiacetal **3** with vinylmagnesium bromide in THF gave triols **4a**,**b** as a 6:1 mixture of C-1 epimers (as measured by ^{1}H NMR spectroscopy) that was separable by column chromatography (Scheme 2). The stereoselectivity of this reaction was dramatically improved to ca. 20:1 by using vinylmagnesium chloride, also in THF (for assignment of the stereochemistry of the major product **4a**, see below). Treatment of the major diastereomer **4a** with 2,2-dimethoxypropane using camphorsulfonic acid as catalyst gave 1,2-acetonide **7** as the major product in 33% isolated yield. Two further products, **8** and **9**, were also formed (ratio **7**:**8**:**9**, 10:5:2) and were assigned the seven- and six-membered ring structures, respectively, on the basis of ^{13}C NMR signals.[14] Regioselectivity for the desired 5-membered ring compound **7** could be increased by running the reaction under kinetic control:[12] treatment of triol **4a** with 2-methoxypropene and pyridinium tosylate in DCM for 15 min gave the 5-membered ring compound **7** in 94% yield as essentially the only regioisomer (as seen by crude NMR).

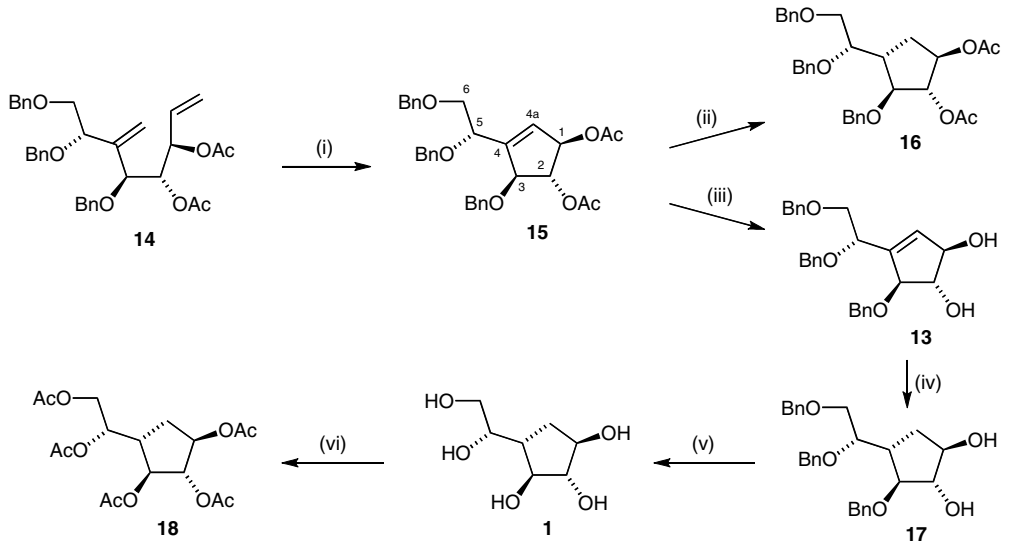
The free alcohol in **7** was oxidised under Swern conditions to give ketone **10**, which was then treated with a phosphonium ylid to give the methylenated product **11**, the best yields being obtained at low temperature. The acetonide protection was removed from diene **11** by acidic hydrolysis to give diol **12**. This was then treated with Grubbs' 2nd generation catalyst, but the ring-closed product **13** was only formed in low yield (24%), along with various unidentified by-products. Changing the solvent to dichloromethane or running the reaction under microwave irradiation did not help.

Thus, we protected diol **12** as its diacetate **14**, which in contrast underwent smooth ring-closure to give cyclopentene **15** (Scheme 3). Reduction of the C=C double bond in **15** was attempted by catalytic hydrogenation,

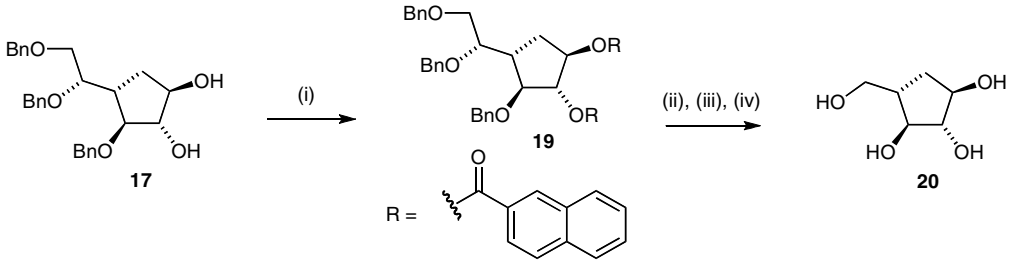


Scheme 2. Reagents and conditions: (i) Vinylmagnesium chloride (4 equiv), THF, 0 °C–rt, 17 h, 87% (**4a**:**4b**, ca. 20:1); (ii) 2-methoxypropene (2.8 equiv), PPTS (0.1 equiv), DCM, rt, 15 min, 94%; (iii) DMSO (2 equiv), oxalyl chloride (2 equiv), DCM −60 °C; then Et_3N (5 equiv), rt, 80%; (iv) Ph_3PMeBr (5 equiv), ^{t}BuOK (4.7 equiv), toluene, 80 °C, then **11**, −78 °C, 49%; (v) AcOH, H_2O, HCl (1 M) (7:4:1), 80 °C, 2 h, 84%; (vi) Grubbs' 2nd generation catalyst (0.1 equiv), toluene, 60 °C, 24 h, 24%; (vii) pyridine, Ac_2O (1:1), rt, 2 h, quant.

with Et_3N present to ensure the integrity of the benzyl ether protecting groups during the reaction.[15] A single diastereoisomer of the saturated cyclopentane **16** was isolated in 49% yield; much of the remaining mass balance could be accounted for by the formation of a product in which one acetate group had been lost. The configuration at C-4 of the reduced product **16** was assigned later (see below). We therefore decided to attempt reduction of the 1,2-deprotected compound **13**, which was formed from **15** by Zemplen deacetylation. Reduction of diol **13** was thus attempted under the same reaction conditions as for **15**, and the saturated carbasugar **17** was formed as the major product in 75% yield, as a single diastereomer. That the stereoselectivity in the reduction of **15** and **13** was of the same sense was demonstrated by acetylation of **17** to give **16** (Ac_2O, pyridine (1:1), rt, 3 h, 72%). The carbafuranose **17** was deprotected by hydrogenolysis over palladium on charcoal to



Scheme 3. Reagents and conditions: (i) Grubbs' 2nd generation catalyst (0.02 equiv × 4), toluene, 60 °C, 24 h, 89%; (ii) H_2, Pd(C), Et_3N (5 equiv), EtOAc, rt, 1.5 h, 49%; (iii) NaOMe, MeOH, rt, 90 min, 93%; (iv) H_2, Pd(C), Et_3N (4 equiv), EtOAc, rt, 1.5 h, 75%; (v) H_2, Pd(C), EtOAc, EtOH (1:1), rt, 1.5 h, quant.; (vi) Ac_2O, pyridine (1:1), rt, 15 h, 69%.



Scheme 4. Reagents and conditions: (i) 2-Naphthoyl chloride (4 equiv), DMAP, pyridine, 50 °C, 4 h, 76%; (ii) H_2, Pd(C), EtOAc, 7 d; (iii) $NaIO_4$, H_2O, 0 °C, 1 h; (iv) $NaBH_4$, H_2O, rt, 18 h, (iv) NaOMe, MeOH, rt, 2 h, 47% from **19**.

give the free carbasugar **1**.[16] We also prepared peracetate **18** by treatment of **1** with Ac_2O and pyridine.[17]

Our final problem was the assignment of the stereochemistry at C-1 and C-4 of the final product **1**. To determine this, we decided to degrade our compound into a known carbapentofuranose by cleavage of the C-5–C-6 bond.[7] First, OH-1 and OH-2 in **17** were protected as their 2-naphthoate esters (Scheme 4). The fully protected compound **19** was then subjected to catalytic hydrogenation conditions to remove the benzyl ethers from C-3, C-5 and C-6, followed by treatment with sodium periodate to oxidatively cleave the C-5–C-6 bond and work up with sodium borohydride to reduce the C-5 aldehyde and then treatment with sodium methoxide to cleave the C-1 and C-2 ester protection. This sequence gave a carbapentofuranose **20** in 47% yield that was unambiguously identified as 4a-carba-α-L-arabinofuranose by comparison of the ^1H and ^{13}C NMR spectra with those of known compounds.[18] Thus, the starting material **17** and its derivatives **16**, **18**, and **1** can be assigned the β-D-*galacto* stereochemistry.

We have synthesised 4a-carba-β-D-galactofuranose for the first time. Key steps in the synthesis were stereoselective Grignard opening of a hemiacetal, use of a 1,2-diol to ensure regioselectivity in alcohol protection, ring-closing metathesis to form the carbasugar, and stereoselective reduction of a C=C double bond to give the *galacto* configured compound.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.138.

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11. Numbering of carbohydrates **2**, **3**, **5** and **6** and carbasugars **1**, **13** and **15**–**21** is according to the carbohydrate convention. Polyhydroxylated open chain derivatives **4**, **7**–**12** and **14** are, for simplicity, numbered using the same numbering scheme as shown in Scheme 2.
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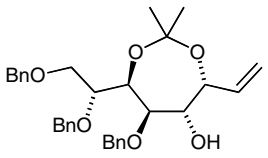
14. The acetonide ring sizes were assigned based on the chemical shifts for the acetonide carbons, as described in Ref. 12. Relevant data for **7** (5-membered ring): 27.1, 27.1 ($2\times$q, C(CH_3)$_2$), 109.3 (s, $C(CH_3)_2$); **8** (7-membered ring): 24.4, 25.2 ($2\times$q, C(CH_3)$_2$), 101.5 (s, $C(CH_3)_2$); **9** (6-membered ring): 19.4, 29.7 ($2\times$q, C(CH_3)$_2$), 99.7 (s, $C(CH_3)_2$)



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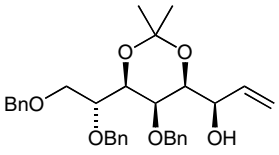

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15. Sajiki, H.; Hirota, K. *Tetrahedron* **1998**, *54*, 13981–13996.
16. *Characterisation data for 4a-carba-*β-D-*galactofuranose* **1**: $[\alpha]_D^{25}$ −15.6 (*c*, 1.0 in CH_3OH); δ_H (400 MHz, CD_3OD) 1.67 (1H, m, H-4a), 1.96–2.05 (2H, m, H-4, H-4a′), 3.51 (1H, dd, $J_{5,6}$ 7.8 Hz, $J_{6,6'}$ 11.7 Hz, H-6), 3.62 (1H, dd, $J_{5,6'}$ 4.2 Hz, $J_{6,6'}$ 11.7 Hz, H-6′), 3.71–3.79 (3H, m, H-2, H-3, H-5), 3.90 (1H, m, H-1); δ_C (100.6 MHz, CD_3OD) 30.5 (t, C-4a), 45.1 (d, C-4), 66.4 (t, C-6), 73.5, 78.4, 85.5 ($3\times$d, C-2, C-3, C-5), 75.5 (d, C-1); HRMS calcd for $C_7H_{14}O_5Na$ (MNa^+) 201.0733. Found 201.0728.
17. *Characterisation data for 1,2,3,5,6-penta-O-acetyl-4a-carba-*β-D-*galactofuranose* **18**: δ_H (400 MHz, $CDCl_3$) 1.90 (1H, ddd, $J_{1,4a}$ 2.4 Hz, $J_{4,4a}$ 8.6 Hz, $J_{4a,4a'}$ 14.5 Hz, H-4a), 2.05, 2.06, 2.06, 2.07, 2.10 (15H, $5\times$s, $5\times CH_3$), 2.17 (1H, m, H-4a′), 2.54 (1H, ddat, *J* 4.6 Hz, *J* 8.6 Hz, *J* 11.2 Hz, H-4), 4.01 (1H, dd, $J_{5,6}$ 6.5 Hz, $J_{6,6'}$ 11.9 Hz, H-6), 4.21 (1H, dd, $J_{5,6'}$ 4.2 Hz, $J_{6,6'}$ 11.9 Hz, H-6′), 5.02 (1H, m, H-3), 5.04 (1H, m, H-1), 5.17 (1H, m, H-5), 5.20 (1H, m, H-2); δ_C (100.6 MHz, $CDCl_3$) 20.9, 21.0, 21.0, 21.0, 21.2 ($5\times$q, $5\times CH_3$), 29.5 (t, C-4a), 41.8 (d, C-4), 64.0 (t, C-6), 69.4 (d, C-5), 75.3 (d, C-1), 76.6 (d, C-3), 81.1 (d, C-2), 170.3, 170.5, 170.7 ($3\times$s, $5\times C{=}O$); IR (film) 1743 (s, O$C{=}$O) cm^{-1}; HRMS calcd for $C_{17}H_{24}O_{10}Na$ (MNa^+) 411.1262. Found 411.1251 ('at' refers to apparent triplet).
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