Hydroformylation of cyclopentenes, novel strategy for total synthesis of carba-D-fructofuranose

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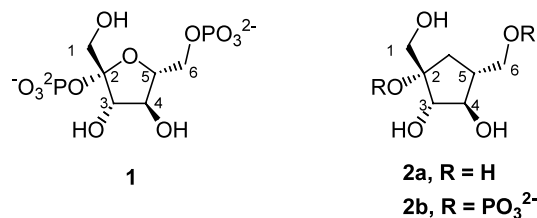[d]*Physiologisch-chemisches Institut der Universitat, Hoppe-Seyler-Strasse 4, D-72076 Tubingen, Germany*

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Abstract—Carba-D-fructofuranose (**2a**) was synthesized in 3 steps from cyclopentene **3**. Compound **3** was prepared in 90% yield from commercially available 2,3,5-tri-*O*-benzyl-D-arabinose. The C-5 hydroxylmethyl unit was incorporated into **3** via hydroformylation using Wilkinson's catalyst. Reduction and hydrogenation afforded carba-D-fructofuranose (**2a**). © 2002 Published by Elsevier Science Ltd.

Carba-sugars are analogues of monosaccharides that contain a methylene (CH_2) group as substitution for the ring oxygen of the acetal moiety. As components of antiviral carbocyclic nucleosides and as substrates for glycosyl transferases,[1–3] these pseudo-sugars have been shown to enhance metabolic stability and potential clinical utility. Carba-D-fructofuranose (**2a**) is a carba-sugar that, if phosphorylated (**2b**), mimics fructose 2,6-bisphophate in polarity and shape, and thus may act as a stable modulator of iPFK-2 activity with potentially useful therapeutic effects on cancer cell metabolism (Fig. 1). We recently identified an inducible isozyme of 6-phosphofructo-2-kinase (iPFK-2; EC 2.7.1.105) that functions to produce fructose 2,6-bisphosphate (F2,6BP) **1**, a powerful allosteric activator of glycolysis.[4] Transformed cells constitutively express iPFK-2 and sustain the high glycolytic flux that supports de novo nucleic acid synthesis during the sustained cellular proliferation typical of cancer. We postulated that structure–activity analysis of fructose analogues might provide a pharmacophore for inhibition of the stimulatory effects of F2,6BP on tumor cell.[5]
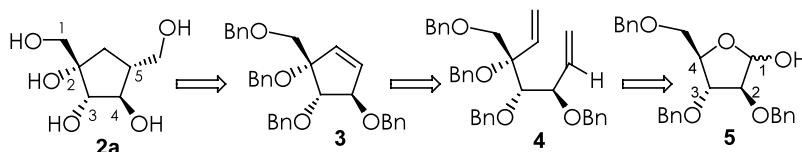
Wilcox and Gaudino initially demonstrated a 12-step total synthesis of carba-D-fructofuranose (**2a**) in 16% yield employing a free radical cyclization.[6] Recently, we employed a unique variation of the olefin metathesis and synthesized **2a** in 11 steps with an overall yield of 43%.[7] In the present report, we refine our improved synthetic route to **2a** via hydroformylation of a polyfunctionalized cyclopentene.
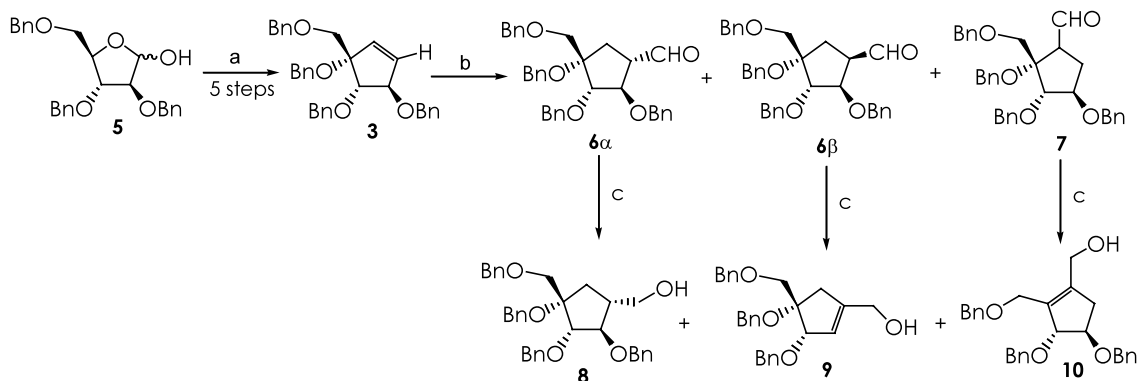
Although hydroformylation of simple and partially functionalized substrates has been well characterized, hydroformylation of highly functionalized substrates, such as polyhydroxy cyclopentenes, has not been demonstrated.[8] Our previously synthesized cyclopentene **3** (Scheme 1) is an attractive starting point because it possesses all the required functionality except a hydroxymethyl group at the C-5 position and can be prepared in five steps in 90% overall yield.[9] Aone-carbon extension can be derived via hydroformylation followed by reduction to furnish a hydroxymethyl group. We reasoned that steric hindrance around C-2 would limit hydroformylation at C-6 in favor of C-5.

Figure 1. Structures of fructose 2,6-bisphosphate and carbafructofuranose.

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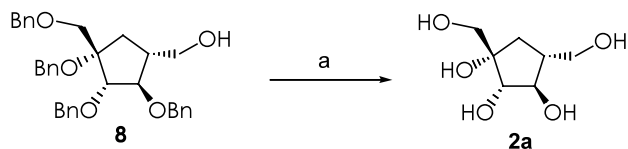**Scheme 1.** Retrosynthetic route to carba-D-fructofuranose.

Scheme 2. Synthesis of substrates **6**, **7**. (a) Five steps, 90%; (b) Wilkinson's catalyst, CO, H$_2$, 80°C, 24 h, quant.; (c) NaBH$_4$, MeOH, 100%.

The hydroformylation reaction employed Wilkinson's catalyst [(Ph$_3$P)$_3$RhCl], a mixture of carbon monoxide (40 bar) and hydrogen (40 bar) at 80°C for 24 h.[10] Under these reaction conditions the functionalized cyclopentene **3** was converted quantitatively to the corresponding aldehyde (Scheme 2). The catalytically active species for the carbonylation reaction, [(Ph$_3$P)$_3$Rh(CO)H], is postulated to be formed as an intermediate complex in situ.[11] Attempts to carry out the reaction using Co$_2$(CO)$_8$ as catalyst were unsuccessful.[12]

The inseparable mixture of aldehydes **6** and **7** was reduced using NaBH$_4$ in MeOH.[13] Reductants were separated by flash column chromatography (10–40% ethyl acetate:petroleum ether) to afford the alcohols **8**–**10**. Compounds **6α** and **6β** were converted, respectively, into **8** and **9**. The anti-parallel orientation of the β benzyloxy substituent in compound **6β** with the respect to the carbonyl α proton favors the elimination reaction, as shown in Scheme 2. Finally, compound **8** was hydrogenated to form carba-D-fructofuranose **2a** (Scheme 3).[7]

This is the first demonstration of the formylation of a highly oxygenated cyclopentene. With this strategy **2a** was synthesized in eight steps with a yield of 32%. Importantly, this approach facilitates the potential for

selective phosphorylation of **2a** at C-2/C-6, since C-2 was generated and protected in our initial cyclopentene synthesis and C-6 was generated after cyclopentene construction. We are currently examining chiral catalysts that could direct the hydroformylation regio- and stereoselectively. Furthermore, we intend to investigate the extent to which **2a** might modulate the production of F2,6BP and its potential effects on glucose metabolism, cellular transformation and proliferation.

Acknowledgements

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Scheme 3. Hydrogenation of compound **8**. (a) Pd/H$_2$, EtOH, 98%.

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10. **2,3,4-Tris-benzyloxy-4-benzyloxymethyl-cyclopentanecarbaldehyde 6** and **2,3,4-tris-benzyloxy-2-benzyloxymethyl-cyclopentanecarbaldehyde 7**. A solution containing the chlorotris(triphenylphosphine)rhodium(I) (0.05 g, 0.05 mmol), toluene (70 mL) and the olefin **4a** (0.50 g, 1 mmol) were placed in a 300 mL mechanically-stirred steel autoclave (equipped with a gas entrainment impeller) which was then charged with carbon monoxide (40 bar) and hydrogen (40 bar). The reaction mixture was stirred at 80°C for 24 h. Remaining gases then were vented off and the solvent was evaporated and subjected to flash column chromatography to furnish quantitatively the crude mixture of inseparable aldehydes **6/7** (0.52 g): $R_f = 0.35$ (10% EtOAc:PE). The aldehyde mixture was subjected directly to reduction as described in Ref. 13.

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13. **Compounds 8–10**. NaBH$_4$ (11 mg, 0.28 mmol) was added to a solution of the aldehydes **6/7** (75 mg, 0.14 mmol) in MeOH (5 mL) at 0°C. The solution was then allowed to warm up and after 20 min TLC (25% EtOAc:PE) showed complete disappearance of the starting material. The solution was then cooled to 0°C and quenched by addition of 10% methanolic HCl, to pH 7. The mixture was filtered through a bed of Celite and the filtrate concentrated under reduced pressure. Flash column chromatography (10–40% ethyl acetate:petroleum ether) of the residue afforded three compounds. **(2,3,4-Tris-benzyloxy-4-benzyloxymethyl-cyclopentyl)-methanol 8** (28 mg, 37%): $R_f = 0.63$ (25% EtOAc:PE); ^{1}H NMR (CDCl$_3$, 270 MHz) δ 1.77 ($J = 11.4$, 17.6 Hz, H$_{5'}$), 2.05 (m, 1H), 2.10 (dd, $J = 8.9$, 17.6 Hz, H$_{5'}$), 3.64 (m, 4H), 4.01 (d, $J = 6.7$ Hz, H$_3$), 4.10 (dd, $J = 2.2$, 6.7 Hz, H$_4$), 4.52 (ABq, $J = 13.1$ Hz, $\Delta\delta = 0.06$ ppm, 2H), 4.64 (ABq, $J = 9.9$ Hz, $\Delta\delta = 0.06$ ppm, 2H), 4.73 (ABq, $J = 11.4$ Hz, $\Delta\delta = 0.16$ ppm, 2H), 4.74 (ABq, $J = 11.5$ Hz, $\Delta\delta = 0.07$ ppm, 2H), 7.3 (m, 20H). ^{13}C NMR (CDCl$_3$, 67.5 MHz) δ 32.8, 41.9, 65.6, 66.6, 71.8, 72.6, 73.1, 73.5, 82.7, 86.2, 86.9, 127.3–128.7 (several signals), 138.1, 138.5, 138.7, 139.4. LR (ES) m/z [M+Na$^+$] 561 (base peak), 413, 355. **(3,4-Bis-benzyloxy-4-benzyloxymethyl-cyclopent-1-enyl)-methanol 9** (13 mg, 21%): $R_f = 0.38$ (25% EtOAc:PE); ^{1}H NMR (CDCl$_3$, 270 MHz) δ 2.56 (ABq, $J = 16.8$ Hz, $\Delta\delta = 0.20$ ppm, CH$_2$), 3.56 (ABq, $J = 9.9$ Hz, $\Delta\delta = 0.08$ ppm, CH$_2$–OBn), 4.15 (ABq, $J = 14.6$ Hz, $\Delta\delta = 0.07$ ppm, CH$_2$–OH), 4.47 (s, H$_3$), 4.56 (m, 2H), 4.59 (ABq, $J = 10.6$ Hz, $\Delta\delta = 0.12$ ppm, 2H), 4.70 (ABq, $J = 13.2$ Hz, $\Delta\delta = 0.05$ ppm, 2H), 5.74 (d, $J = 1.5$ Hz, H$_4$), 7.3 (m, 15H). ^{13}C NMR (CDCl$_3$, 67.5 MHz) δ 38.7, 62.0, 67.6, 72.2, 73.5, 73.7, 78.5, 79.0, 83.7, 85.0, 124.3, 126.8–128.5 (several signals), 138.4, 139.0, 139.9, 146.2. LR (ES) m/z [M+Na$^+$] 453 (base peak), 305, 181. **(3,4-Bis-benzyloxy-2-benzyloxymethyl-cyclopent-1-enyl)-methanol 10** (25 mg, 42%): $R_f = 0.32$ (25% EtOAc:PE); ^{1}H NMR (CDCl$_3$, 270 MHz) δ 2.42 (dd, $J = 3.5$, 16.6 Hz, H$_4$), 2.83 (dd, $J = 7.0$, 16.6 Hz, H$_4$), 4.14 (m, 5H), 4.6 (m, 7H), 7.3 (m, 15H). ^{13}C NMR (CDCl$_3$, 67.5 MHz) δ 39.2, 60.2, 64.1, 71.4, 71.7, 72.7, 83.1, 90.4, 127.0, 129.5 (several signals), 133.2, 137.8, 138.2, 138.5, 142.1. LR (ES) m/z [M+Na$^+$] 453 (base peak), 305, 149.1.