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Total Synthesis of Carba-D-fructofuranose via a Novel Metathesis Reaction

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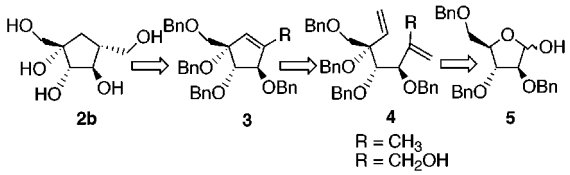
ABSTRACT



Carba-D-fructofuranose 2b was synthesized in 11 steps (45%), from 2,3,5-tri-*O*-benzyl-D-arabinofuranose 5 using a ring closing metathesis. Schrock's catalyst was employed on the unique substituted diene synthon 4 to furnish the pentahydroxlated cyclopentene 3. Hydrogenation afforded 2b.

We recently were involved in the identification of an inducible isoform of phosphofructokinase-2 (PFK-2, EC 2.7.1.105) that is specifically induced by inflammation stimuli or oncogenic transformation[1] and suggested that fructose analogues might serve as useful pharmacophores for inhibiting cell activation and cancer cell growth.[2] Fructose 2,6-bisphospate **1** (Figure 1) is formed by phosphorylation of fructose-6-phosphate, a key substrate in the glycolysis pathway, in a reaction catalyzed by PFK-2.[3] Fructose-2,6-bisphosphate is a powerful allosteric regulator of glycolysis via its potent stimulatory effect on phosphofructokinase-1 (EC 2.7.1.11) activity and its inhibitory effect on fructose-1,6-bisphosphatase (EC 3.1.3.11). Unlike phosphorylated fructose, carba-D-fructofuranose **2a** (Figure 1) cannot be metabolized and therefore can be shuttled repeatedly through cycles of kinase and phosphatase activity. The first and only synthetic approach to **2**, by Wilcox and Guadino,[4] was via a free radical ring closure.

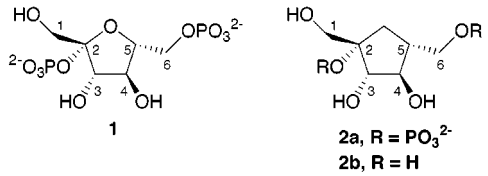


Figure 1.

We have previously reported[5] that highly functionalized cyclopentene compounds may be prepared via a ring closing metathesis (RCM) employing Schrock's or Grubb's catalyst.[6] Thus cyclopentene **3**, a potential precursor to the target **2b**, may be obtained from RCM of diene **4**, which could arise

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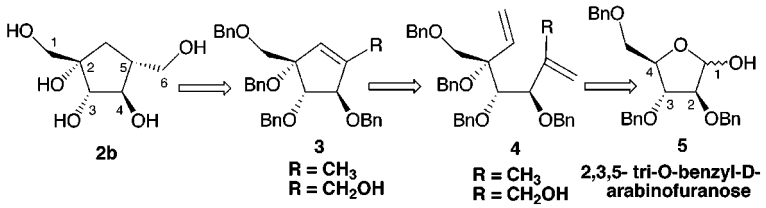
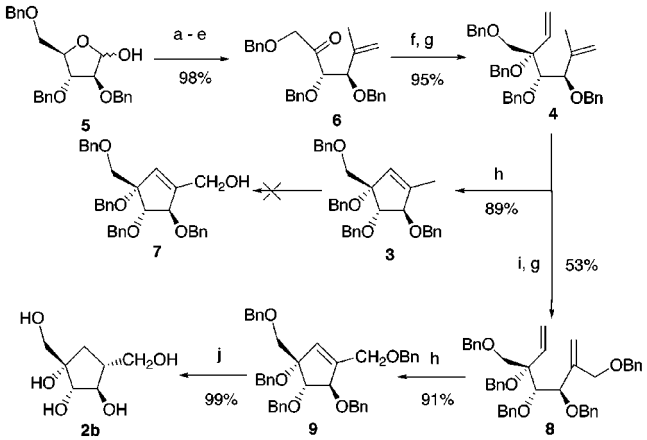
Scheme 1



from a D-arabinose precursor. 2,3,5-Tri-*O*-benzyl-D-arabinose[7] **5** is an appropiate starting material since the two stereogenic centers at C_2/C_3 match C_3/C_4 of carba-D-fructofuranose. Our strategy also facillitates the selective phosphorylation of C_2/C_6 to resemble the target **2a**, thus differentiating between the conserved protected hydroxyl and the generated ones (Scheme 1).

Oxidation of commercially available 2,3,5-tri-*O*-benzyl-D-arabinofuranose[7] **5** employing NaOCl and TEMPO gave the lactone. Addition of MeMgBr (2 equiv) to the lactone followed by selective acylation of the resulting diol at the secondary alcohol provided the tertiary alcohol which was subjected to elimination via the chloride ($SOCl_2$, pyridine). In situ removal of the acetate provided the secondary alcohol, which was treated under Swern oxidation conditions to provide ketone **6** in 98% overall yield from **5**. Addition of vinylmagnesium bromide afforded a single tertiary alcohol which was subsequentially protected as benzyl ether **4** (Scheme 2).

Scheme 2



(a) [O], TEMPO, NaOCl; (b) MeMgBr/THF; (c) Ac_2O, DMAP, EtOAc; (d) $SOCl_2$, Pyr, then NaOMe; (e) DMSO, $(COCl)_2$, Et_3N; (f) Vinylmagnesiumbromide, THF; (g) BnBr, DMF, NaH; (h) Schrock's catalyst,hexane, reflux; (i) SeO_2, TBHP, CH_2Cl_2; (j) Pd/H_2, EtOH.

Compound **4** was identical to the sample obtained from an alternative synthesis using 1,2:3,5-di-*O*-isopropylidene-α-D-apiose[8] **10**, a carbohydrate precursor, where the stereochemistry of the tertiary carbon is conserved (Scheme 3). Hydrolysis, selective protection of the tertiary center as the benzyl ether, and oxidation of the primary center followed by a Wittig reaction gave **11**. Hydrolysis followed by isopropenylmagnesium bromide addition gave a single diene isomer, which was subsequently protected to give **4**.

Treatment of **4** under standard RCM conditions that were sucessful in our previous studies with nonsubstituted diene precursors failed. These conditions led to quantitative recovery of the starting material.[5,6] The cyclization was then attempted under conditions reported by Furstner and Langemann.[9] Addition of the diene to a solution of Schrock's catalyst (0.05 M) in hexane followed by refluxing for 12 h gave methyl cyclopentene **3** in 89% yield. Compound **3** was now primed for elaboration to the allylic alcohol. There have been several reports[10] using SeO_2 for the oxidation of allylic methylcyclopentenes and methylcyclohexenes. However, treatment of polyhydroxylated methylcyclopentene **3** under these conditions gave only decomposition products. We next turned our attention to oxidation of the methyl unit before the cyclization. We were concerned that the allylic benzyloxy groups would be problematic since there have been no reported examples of RCM on such substrates. Thus, diene **4** was treated with SeO_2 and TBHP in CH_2Cl_2 and stirred for 12 h to yield the allylic alcohol which was subsequently protected as benzyl ether **8**. Addition of compound **8** to a solution of Schrock's catalyst and refluxing the mixture for 18 h led to the desired product **9**, in 91% yield. Finally, hydrogenation of **9** provided carba-D-fructofuranose **2b**. The diastereofacial selectivity observed from the hydrogenation of the alkene could arise from intramolecular complexation of the Pd/H_2 complex with the C_1/C_4 benzyloxy groups, resulting in *syn* attack of H_2 (Scheme 2).[11]

The ^1H and ^{13}C NMR data[12] of **2b** were identical to the

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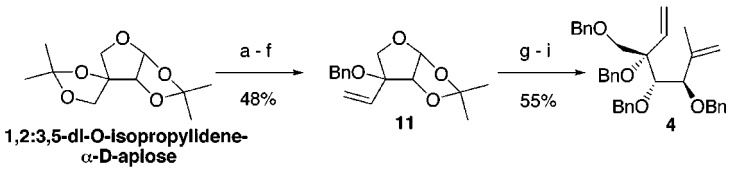
Scheme 3



(a) AcOH:H_2O, 50:50; (b) MPMCl/NaH; (c) BnBr/NaH; (d) DDQ, CH_2Cl_2; (e) DMSO, $(COCl)_2$, Et_3N; (f)PPH_3CH_2Br, nBuLi, THF; (g) TfOH/H_2O; (h) isopropenylmagnesiumbromide (i) BnBr/NaH.

data published by Wilcox and Guadino.[4] Additionally, a NOE study of **2b** confirmed the stereochemistry at C_5. A 2% NOE between H_3/H_5 (Figure 2) indicates the *syn* arrangement.

Biological investigation of the effects of this phosphocarba-D-fructofuranose on the purified PFK-2 enzyme are presently under investigation. Overall, this synthesis demonstrates the enormous potential of the RCM methodology on diene systems of polyhydroxylated carbon chains. A practical and straightforward route to carbafructofuranose **2b** from 2,3,5-tri-*O*-benzyl-D-arabinofuranose (11 steps, unoptimized yield 45%) was devised. By comparison, the Wilcox synthesis of **2b** involved 12 steps with a yield of 18%.

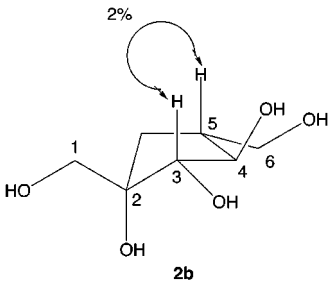


Figure 2.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for key compounds **3**, **4**, **6**, **8**, **9**, **2b**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See Supporting Information.