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1-Deoxy-D-xylulose: Synthesis Based on Molybdate-Catalyzed Rearrangement of a Branched-Chain Aldotetrose

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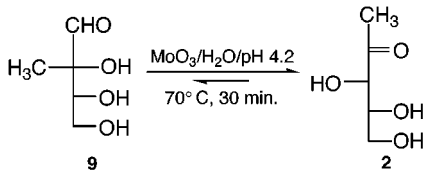
ABSTRACT



1-Deoxy-D-xylulose has been prepared in seven steps and ~21% overall yield from 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone. The key reaction involves transformation of a branched-chain aldotetrose to the 1-deoxy-2-ketopentose catalyzed by molybdic acid. Other branched-chain aldotetroses containing bulkier substituents at C2 also engage in the conversion, suggesting routes to protected 2-ketoses and α-ketoacids/esters. This synthetic route mimics reactions of the non-mevalonate isoprenoid pathway in plants and bacteria.

In most eukaryotic organisms and archaebacteria, the mevalonate pathway is responsible for the biosynthesis of isoprenoid compounds wherein acetyl CoA serves as the metabolic precursor. Recent studies, however, suggest that 1-deoxy-D-xylulose 5-phosphate **1** serves as a precursor in the biosynthesis of isoprenoids in bacteria, green algae, and plants, as well as in the biosynthesis of vitamins B_6 and B_1.[1−5] Interest in elucidating these new pathways has stimulated recent reports on the preparation of 1-deoxy-D-xylulose **2** and its 5-phosphate **1**.[6−11] Here we describe a chemical route to **2** (Scheme 1) involving a unique carbon skeleton rearrangement that mimics one of the putative metabolic reactions of these pathways.

Earlier work had demonstrated a unique C2-epimerization reaction of aldoses catalyzed by molybdate in which C1 and C2 are transposed stereospecifically, thereby leading to facile interconversion of [1-^{13}C]aldoses with their [2-^{13}C]C2-epimers.[12] Using ^{13}C and ^{2}H isotopes as structural probes, a reaction mechanism was proposed that implicated dimolybdate−acyclic aldose complexes as productive species in the reaction. Subsequent NMR[13] and crystallographic[14] studies of molybdate complexed with acyclic alditols confirmed the structure of this species. It was observed recently that the

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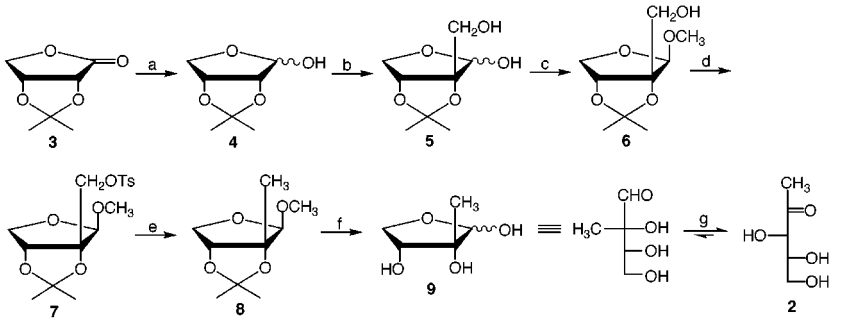
Scheme 1[a]



[a] (a) $NaBH_4$, pH 4−7, 0−5 °C, 90 min; (b) CH_2O/CH_3OH, K_2CO_3, 80−85 °C, 48 h; (c) MeOH/acetone, HCl/ether, 40 °C, 72 h; (d) TsCl/pyridine, 0−25 °C, 12 h; (e) LAH/$CHCl_3$/ether, 30 °C, 20 h; (f) Dowex 50 (H^+), 80 °C, 60 min; (g) MoO_3/H_2O/pH 4.2, 70 °C, 30 min.

aldehydic proton of an acyclic aldose could be replaced by a CH_2OH group, thereby promoting interconversion between a C2 branched-chain aldose and a 2-ketose.[15] It thus became evident that the synthesis of **2** might be effected through a similar transformation.

To explore this possibility, 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone **3** (commercially available from Aldrich) was reduced with $NaBH_4$ in H_2O to give the reducing sugar **4** in 85% yield and **4** was alkylated with CH_2O under mildly basic conditions to give the protected branched-chain aldotetrose **5** in 65% yield. Methyl glycosidation of **5** gave the β-furanoside **6** in 65% yield, and tosylation followed by reduction with LAH and deprotection gave 2-*C*-(methyl)-D-erythrose **9**[16] in 23% overall yield from **3** (Scheme 1, Figure 1). The key transformation of **9** into the desired 1-deoxy-

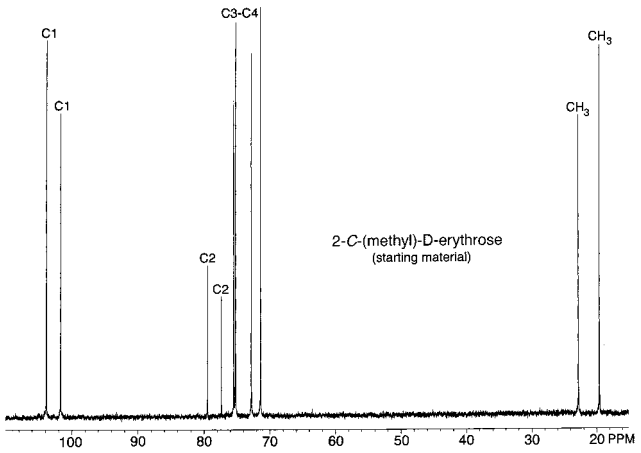


Figure 1. The $^{13}C\{^1H\}$ NMR spectrum (75 MHz) of the starting branched-chain aldotetrose, 2-*C*-(methyl)-D-erythrose **9**, showing the presence of α- and β-furanose forms. Signal assignments are indicated; specific chemical shift values are given in ref 16.

2-ketopentose **2** is catalyzed by molybdic acid in aqueous solution at 70 °C and pH 4.2 and yields an equilibrium mixture containing ~95% **2** and ~5% **9** and no other NMR-detectable byproducts. Purification of this mixture was achieved by chromatography on Dowex 50WX8-400 ion-exchange resin in the Ca^{2+} form[17] (**2** elutes first, followed by **9**[18]) (Figure 2). This route could be shortened appreciably

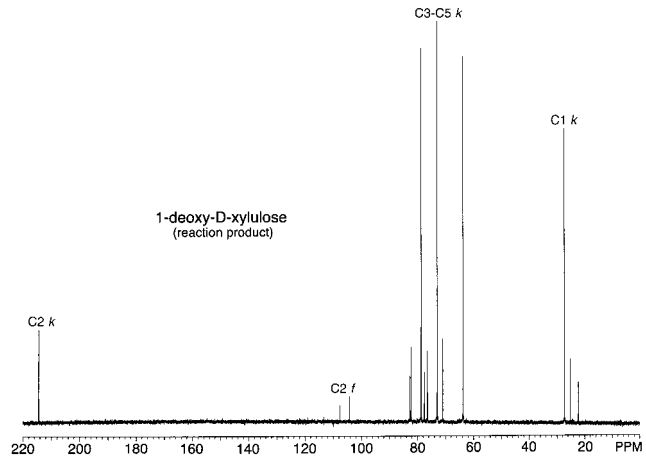


Figure 2. The $^{13}C\{^1H\}$ NMR spectrum (75 MHz) of the product ketose, 1-deoxy-D-xylulose **2**, after purification, showing the presence of α- and β-furanoses and acyclic *keto* forms. The acyclic *keto* form predominates (signal assignments shown). Specific chemical shift values are given in ref 18.

if **9** could be prepared via direct methylation of an appropriate precursor rather than through the traditional but cumbersome protection/deprotection strategy applied here.

The remarkable transformation of **9** into **2** is believed to involve the formation of dimolybdate complexes **I** and **II**

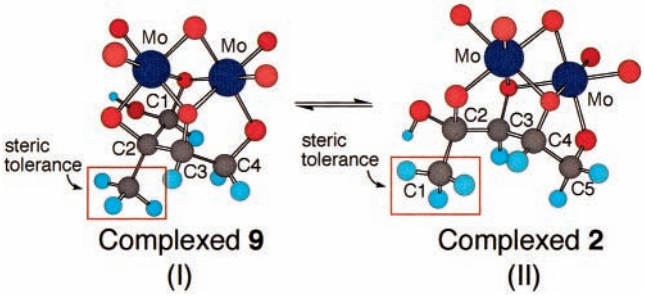
(15) Hricoviniova-Bilikova, Z.; Hricovini, M.; Petrusova, M.; Serianni, A. S.; Petrus, L. *Carbohydr. Res.* **1999**, *319*, 38−46.

(16) The $^{13}C\{^1H\}$NMR spectrum of **9** in $H_2O/^2H_2O$ solvent showed the presence of α- and β-furanoses in nearly equal abundance (Figure 1) and having the following chemical shifts (in ppm relative to δC1 of α-D-mannopyranose (95.2 ppm)): C1 (103.9, 101.7); C2 (79.5, 77.4); C3, C4 (75.5, 75.2, 72.8, 71.4); CH_3 (22.8, 19.5).

(17) Angyal, S. J.; Bethell, G. S.; Beveridge, R. *Carbohydr. Res.* **1979**, *73*, 9−18.

having structures shown in Scheme 2. Similar complexes were originally proposed in molybdate-catalyzed C2-epimer-

Scheme 2



ization of aldoses in which C1 and C2 are transposed via C2−C3 bond cleavage,[12] and more recently in the molybdate-catalyzed conversion of 2-*C*-(hydroxymethyl)aldopentoses to 2-ketohexoses.[15] An inspection of these proposed complexes reveals that the aldehydic hydrogen in aldose−dimolybdate complexes can be replaced by CH_3 without introducing unfavorable steric crowding in this region of the complexes (see Scheme 2), thus explaining the facile interconversion of **9** and **2** via analogous C2−C3 bond cleavage and transposition.

As observed previously,[12] the stereochemistry of the reaction is controlled by the structures of **I** and **II**, but the underlying driving force governing C−C bond cleavage remains elusive. A putative transition state (Figure 3) for

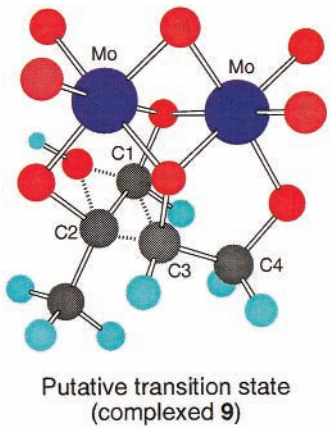
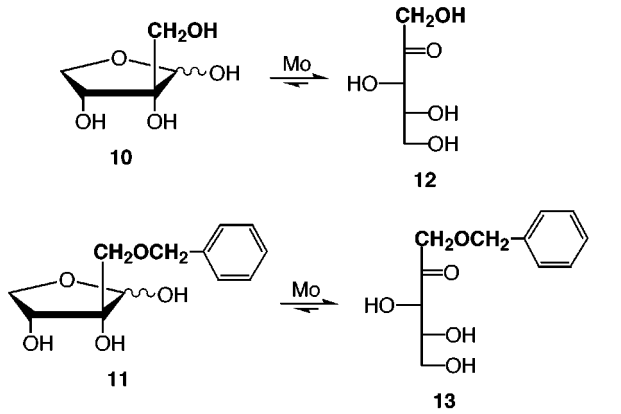


Figure 3.

the reaction starting from complexed **9** (see Scheme 2) involves partial breaking of the C1−O1 and C2−C3 bonds and partial formation of C2−O1 and C1−C3 bonds. The dimolybdate bridge controls the stereochemistry at C1 and C3, which become the chiral C3 and C4 atoms in the product **2**. The original C2 of **9** becomes the C2 carbonyl of **2** in its hydrated (gem-diol) state. Diol formation at C2 may be facilitated by attack of OH^- or water during the reaction instead of internal transfer of O1 as shown in Figure 3. In the present case, the thermodynamic equilibrium favors the 2-ketopentose despite its preferred acyclic form,[19] rather than the cyclic branched-chain aldotetrose.

We examined the ability of the proposed dimolybdate complexes to accommodate alkyl groups other than CH_3 at C2 of **9**. The CH_2OH and CH_2OBn substituents in **10** and **11**, respectively, were accepted, yielding D-xylulose **12** and 1-*O*-benzyl-D-xylulose **13**, respectively (Scheme 3). In both

Scheme 3



cases, the equilibria highly favored the 2-ketopentoses. The observed reactivity of **11** suggests a high tolerance of relatively large functional groups at C2 of the aldotetrose core. While COOH(R) substituents were not investigated, these reactions are expected to yield α-ketoacid(ester) products, thus potentially providing a convenient route to these biologically important compounds.

The route shown in Scheme 1 can be adapted for selective or multiple ^{13}C-labeling of **2** at sites in addition to C1. ^{13}C-Labeled D-erythrono-1,4-lactones are obtained from the oxidation of labeled D-erythroses, which are available in various ^{13}C-isotopomeric forms.[20−22] Thus, for example, [2,5-$^{13}C_2$]-**2** is prepared from D-[2,4-$^{13}C_2$]erythrose **14**, which is obtained via glycol scission[21,22] from D-[4,6-$^{13}C_2$]glucose **15** as shown in Scheme 4.

The uniqueness of the epimerization reaction described herein assumes further significance when the close correspondence is noted between the Mo-catalyzed interconversion of **9** and **2** and the proposed metabolism of **1** via the

(18) The $^{13}C\{^1H\}$ NMR spectrum of purified **2** in $H_2O/^2H_2O$ solvent showed the presence of α- and *β*-furanose and acyclic *keto* forms, with the latter considerably more abundant than the former (Figure 2). The following chemical shifts (in ppm relative to *δ*C1 of α-mannopyranose (95.2 ppm)) were observed for the *keto* (*k*) and furanose (*f*) forms: C2*k* (214.5); C2*f* (107.6, 104.2); C3, C4, C5 (82.7*f*, 82.3*f*, 78.7*k*, 77.6*f*, 76.5*f*, 73.0*k*, 71.0*f*, 63.7*k*); C1 (27.3*k*, 25.2*f*, 22.3*f*).

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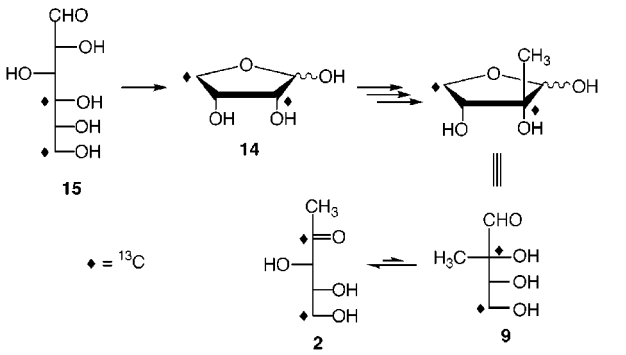
Scheme 4



non-mevalonate isoprenoid pathway. It has been suggested that **1** is converted in vivo to 2-*C*-(methyl)-D-erythritol 4P via tandem pinacol rearrangement/reduction during its metabolism.[1−5] The molybdate-catalyzed rearrangement described herein mimics this biological transformation. In the metabolic pathway, no evidence exists implicating the involvement of molybdenum in the pinacol rearrangement. However, the ease with which Mo-catalyzed epimerization occurs may hint at a heretofore unrecognized role for molybdenum in other biological epimerizations via a mechanism similar to that shown in Scheme 2. This is an intriguing possibility that remains to be explored.

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Supporting Information Available: Experimental procedures and characterization data for compounds **2**, **8**−**11**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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