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A New and Concise Synthesis of 3-Deoxy-D-*arabino*-2-heptulopyranosonic Acid (DAH) and Derivatives through the Radical Chemistry of Barton Esters

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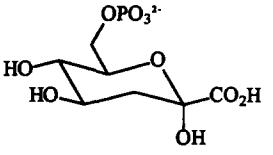
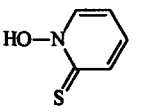
Abstract: Barton ester-based radical chemistry was applied in the synthesis of 3-deoxy-D-*arabino*-2-heptulopyranosonic acid (**DAH**) from commercial D-ribonolactone. The radical reaction with olefin **2**, followed by aqueous work-up, provided the seven-carbon sugar compounds **5** and **6** (3:1) in 60% yield. Removal of the isopropylidene groups from **5** and hydrolysis of the ethyl ester yielded the **DAH** barium salt quantitatively.

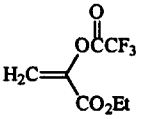
3-Deoxy-D-*arabino*-2-heptulopyranosonic acid 7-phosphate (**DAHP**) is known as the first seven-carbon intermediate of the shikimate pathway.[1] The latter is employed by plants and microorganisms to furnish aromatic amino acids and other important compounds such as folic acid and quinones, *inter alia*.[2] **DAHP** is formed by the condensation of D-erythrose-4-phosphate and phosphoenolpyruvate in a reaction catalyzed by **DAHP** synthase. Due to the putative inhibiting abilities of **DAHP** analogues towards dehydroquinate synthase,[3] enzymatic[4] and chemical[5] syntheses of precursor **DAH** have become increasingly important in the discovery of potential herbicides.[6] Most of the chemical syntheses reported thus far have started from D-arabinose derivatives, taking advantage of the three desired stereogenic centers embedded in the starting material. We have shown that the acyl derivatives of *N*-hydroxy-2-thiopyridone (**1**) (Barton esters) are excellent sources of disciplined radicals.[7] We have successfully applied these thiohydroxamates to the syntheses of α-keto acids using ethyl 2-(trifluoroacetoxy)acrylate (**2**) as a radical trap.[8] We, and others, have also demonstrated that carbon-carbon bond formation through radical reactions is an important tool in synthetic carbohydrate chemistry.[9] In this communication, we report a new approach to **DAH** and its derivatives.



DAHP

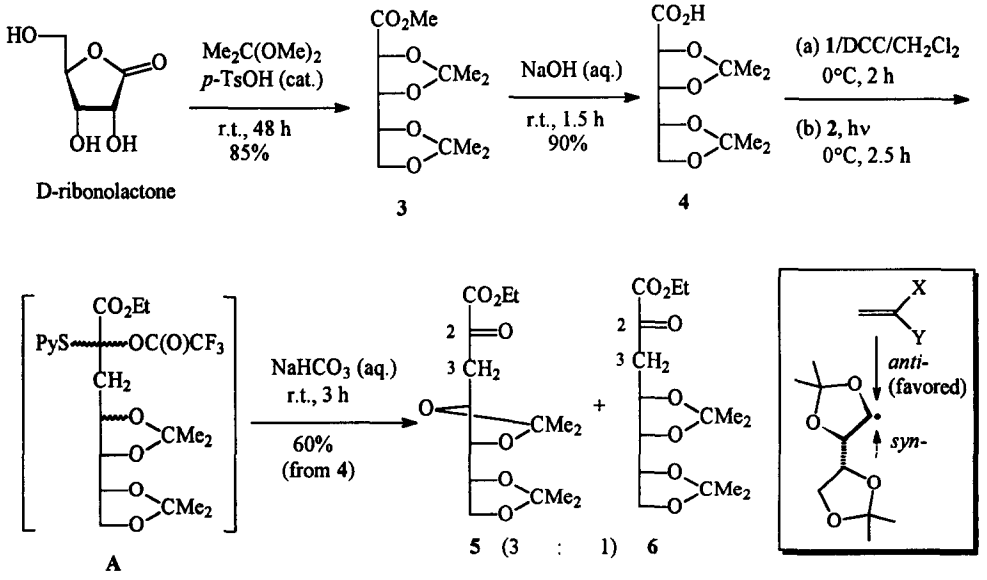


1



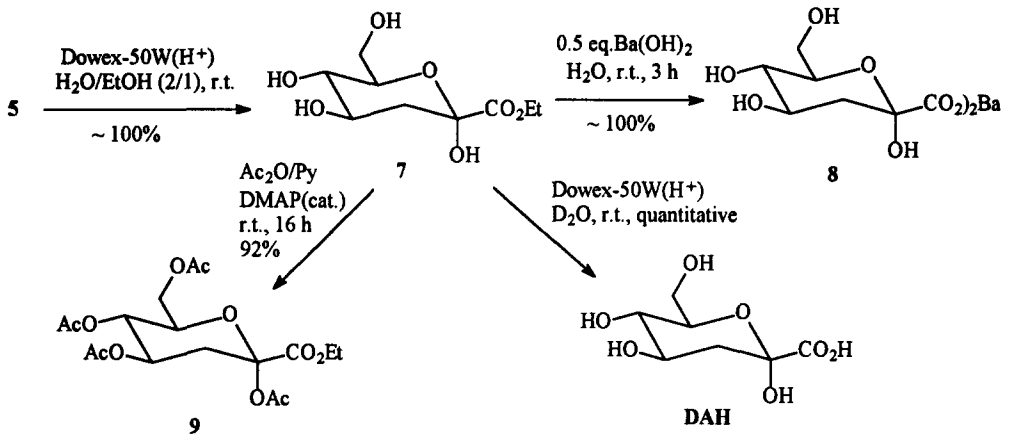
2

D-Ribonolactone was transformed to methyl 2,3:4,5-di-*O*-isopropylidene-D-ribonate (**3**) in 85% yield using the conventional procedure (Scheme 1).[10] The by-product of this reaction, 2,3-*O*-isopropylidene-D-ribonolactone (9%), was also readily transformed to **3** under similar conditions. 2,3:4,5-Di-*O*-isopropylidene-D-ribonic acid (**4**) was obtained in 90% yield from hydrolysis of the methyl ester by aqueous sodium hydroxide at room temperature.[11] The acid **4** was coupled to **1** by the 1,3-dicyclohexylcarbodiimide (DCC) method to form the Barton ester. The latter, upon photolysis with a 150W tungsten lamp at 0°C and in the presence of olefin **2**, afforded the expected thiopyridyl adduct (**A**).[12] This intermediate was hydrolyzed by aqueous sodium bicarbonate to give ethyl 4,5:6,7-di-*O*-isopropylidene-3-deoxy-D-*arabino*-2-heptulosonate (**5**, 45%) and the 4-epimer (**6**, 15%). As expected, the desired compound **5** was the major product since the olefin approached the substituted five-membered cyclic carbon radical from the *anti*-face as a result of steric hindrance at the *syn*-face.[13] The ^{1}H and ^{13}C-NMR spectra showed that compounds **5** and **6** exist exclusively in the α-keto form in $CDCl_3$ (two C=O groups of **6** at 160.4 and 191.0 ppm in ^{13}C-NMR) and not in the tautomeric 2-enol form.[14]



Scheme 1

Treatment of intermediate **5** with Dowex-50W(H^+) resin in ethanol and water gave ethyl 3-deoxy-D-*arabino*-2-heptulopyranosonate (**7**) in quantitative yield (Scheme 2).[15] The latter was hydrolyzed with a stoichiometric amount of barium hydroxide in water to give the corresponding **DAH** barium salt (**8**) quantitatively. Physical and spectroscopic data were in full agreement with those reported in the literature.[5a] When the **DAH** ethyl ester **7** was treated with acetic anhydride, pyridine, and a catalytic amount of 4-dimethylaminopyridine (DMAP), the **DAH** ethyl ester 2,4,5,7-tetra-*O*-acetate (**9**) was obtained in 92% yield.[16] The spectroscopic data and optical rotation conformed to those of the methyl ester congener.[4b]



Scheme 2

When **DAH** ethyl ester **7** in D_2O was treated with Dowex-50W(H^+) resin, the formation of free **DAH** and the release of ethanol were readily followed by ^1H and ^{13}C-NMR. A single isomer, presumably the α-pyran form as deduced from the signal at 94.7 ppm (C-2) in the ^{13}C-NMR spectrum,[17] was observed. These studies proved the conformational stability of **DAH** in D_2O.

In conclusion, the biologically important sugar **DAH** was readily synthesized utilizing a radical carbon-carbon bond formation reaction. The mild reaction conditions should find application in other related carbohydrate syntheses.

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14. **5**: The procedure used to synthesize this compound is as given in Reference 12, $C_{15}H_{24}O_7$ requires C 56.95, H 7.65; found C 57.06, H 7.60. $[\alpha]_D^{28}$ +26.0 (c = 1.02, $CHCl_3$); IR (neat): (C=O) 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.32 (s, 3H), 1.37 (s, 6H), 1.39 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 3.18 (dd, *J* = 16.8, 7.6 Hz, 1H), 3.25 (dd, *J* = 16.8, 4.6 Hz, 1H), 3.60 (t, *J* = 8.1 Hz, 1H), 3.90-4.18 (m, 3H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.43 (td, *J* = 7.8, 4.4 Hz, 1H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): 14.0, 25.1, 26.6, 26.8, 27.0, 42.8, 62.5, 67.8, 75.6, 76.8, 80.7, 109.7, 109.8, 160.7, 191.3 ppm; HRMS (FAB): 317.1600, $C_{15}H_{24}O_7$ (MH^+) requires 317.1600.
15. **7**: $[\alpha]_D^{26}$ +37.0 (c = 0.62, H_2O); IR (neat): (OH) 3405, (C=O) 1734 cm^{-1}; ^{1}H-NMR (D_2O, 300 MHz): 1.34 (t, *J* = 7.1 Hz, 3H), 1.88 (dd, *J* = 12.9, 7.1 Hz, 1H), 2.31 (dd, *J* = 13.2, 5.1 Hz, 1H), 3.40-3.54 (m, 4H), 4.32 (q, *J* = 7.1 Hz, 2H) ppm; ^{13}C-NMR (D_2O, 75 MHz): 14.1, 39.4, 61.5, 64.4, 69.3, 71.5, 74.9, 96.0, 171.9 ppm; HRMS (FAB): 259.0804, $C_9H_{16}O_7$ (MNa^+) requires 259.0794.
16. **9**: $[\alpha]_D^{26}$ +59.0 (c = 0.85, $CHCl_3$); IR (neat): (C=O) 1744 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.29 (t, *J* = 7.2 Hz, 3H), 2.04 (s, 3H), 2.05 (s, 3H), 2.08 (s, 3H), 2.09 (dd, *J* = 13.6, 11.4 Hz, 1H), 2.17 (s, 3H), 2.66 (dd, *J* = 13.6, 5.2 Hz, 1H), 4.02-4.14 (m, 2H), 4.26 (qd, *J* = 7.2, 1.8 Hz, 2H), 4.35 (dd, *J* = 12.4, 4.2 Hz, 1H), 5.13 (t, *J* = 9.8 Hz, 1H), 5.25-5.35 (m, 1H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): 13.9, 20.64, 20.74, 20.77, 20.84, 35.5, 61.7, 62.5, 68.3, 68.4, 71.5, 97.4, 98.6, 165.7, 168.3, 169.6, 170.1, 170.7 ppm; HRMS (FAB): 427.1224, $C_{17}H_{24}O_{11}$ (MNa^+) requires 427.1216.
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