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Synthesis of an Analog of Natural 3-Deoxyheptulosonic Acids on the Basis of Methyl 3-Chloro-3-deoxy-4,6:5,7-di-*O*-ethylidene-*L*-*xylo*-hept-2-ulosonate

V. I. Kornilov†, Z. I. Glebova, and T. P. Sudareva

Institute of Physical and Organic Chemistry, Rostov State University, Rostov-on-Don, Russia

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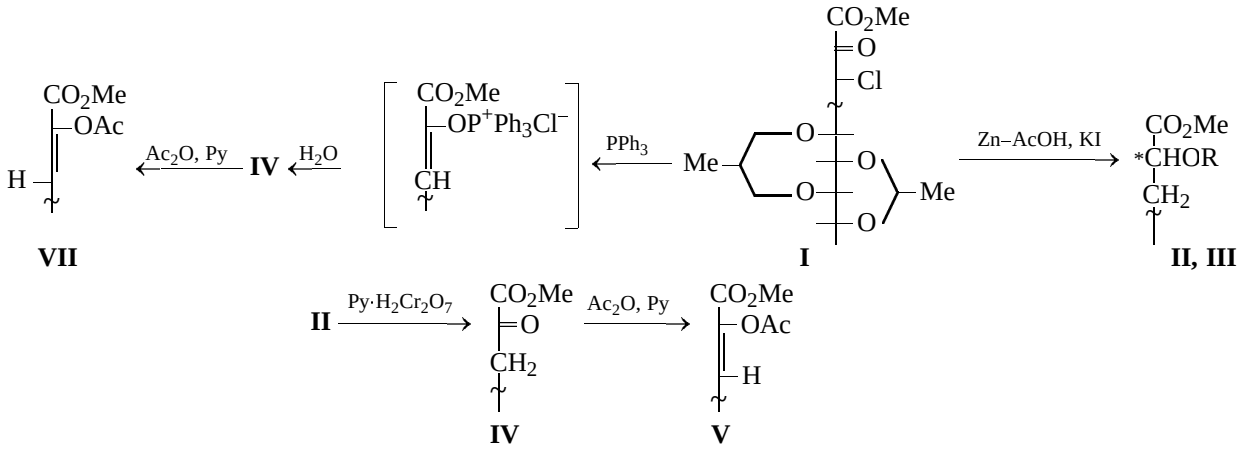
Abstract—The *L*-*xylo* analog of natural 3-deoxyheptulosonic acids can be synthesized by reductive dehalogenation of methyl 3-chloro-3-deoxy-4,6:5,7-di-*O*-ethylidene-*L*-*xylo*-hept-2-ulosonate. The direct oxidation with zinc dust involves the keto group and gives a mixture of epimeric 2-hydroxymethyl heptanoates which were characterized as acetates and oxidized with pyridinium dichromate into 3-deoxyheptulosonate. The indirect reduction involves formation, under the action of triphenylphosphine, of an enol phosphonium salt and its hydrolytic cleavage.

According to [1–3], our developed chloroglycidate synthesis of biologically important 3-deoxy-2-ketaldonic acids and their analogs is based on the epoxide → ketone conversion. Opening of the oxirane ring in the chloroglycidic ester under the action of magnesium iodide yields pyruvic acid derivatives via reduction of the intermediate 3-iodopyruvate with sodium bisulfite.

Here we present a synthetic approach to an analog of natural 3-deoxyheptulosonic acids, in which the oxirane ring is cleaved in another way [1], under the action of lithium perchlorate [1], to form 3-chloropyruvate **I**.

Pyruvate **I** can be converted into pyruvate **IV** either via direct reductive dehalogenation or via intermediate formation of enol phosphonium salt **VI** and its subsequent hydrolysis as shown in Scheme 1.

Scheme 1.



R = H (**II**), Ac (**III**).

The key intermediate, methyl 3-chloro-3-deoxy-4,6:5,7-di-*O*-ethylidene-*L*-*xylo*-hept-2-ulosonate (**I**), was prepared from the corresponding chloroepoxide under the action of lithium perchlorate under conditions of phase-transfer catalysis [1].

For direct reduction of the chlorine atoms we

† Deceased.

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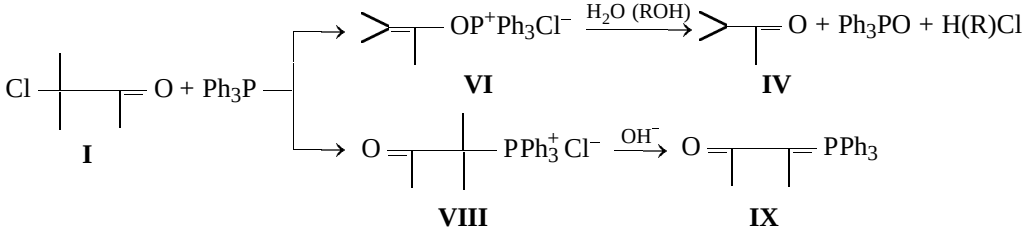
used the method of synthesis of steroid methyl ketones from chloromethyl derivatives [4]. The reaction occurs in glacial acetic acid under the action of zinc dust in the presence of potassium iodide under stirring (6 h, 25°C) in a good yield (78%). The product was assigned structure **II**, which implies that the reaction occurs unselectively and involves the keto group which is probably activated here by the neighboring ester function.

The IR spectrum of the isolated mixture of methyl heptonate **II** epimers displays absorption bands at 3500 (OH) and 1720 cm^{-1} (CO_2Me). The ^1H NMR spectrum shows a broad threeproton multiplet at 2.0–2.8 ppm (CH_2, OH) and two singlets at 3.65 and 3.75 ppm (CO_2CH_3), which suggests that we deal here with epimers with respect to the new asymmetric center at C^2. Further evidence for the suggested structure is provided by the spectral characteristics of acetyl derivative **III** of compound **II**. The IR spectrum of compound **III** no longer shows OH absorption, and the carbonyl absorption band is shifted to 1750 cm^{-1} (CO_2Me, OAc). The ^1H NMR spectrum contains two singlets at 2.0 and 2.1 ppm from three OAc protons, a broad two-proton CH_2 multiplet (2.2–3.0 ppm), and two multiplets (5.15 and 5.40 ppm) from the proton at the C^2 atom attached to the AcO group.

Methyl heptonate **II** was oxidized into desired pyruvate **IV** with pyridinium dichromate in dichloromethane in the presence of 4 Å molecular sieves (25°C, 36 h) in 52% yield (after chromatographic purification) by the procedure in [5]. Compound **IV** and its enol acetate **V** have IR spectra typical of such compounds, ν, cm^{-1}: 3400 (OH) and 1730 [$C(O)CO_2Me$] for pyruvate **IV** and 1767 (OAc), 1740 (CO_2Me), and 1670 (C=C) for enol acetate **V**. In the ^1H NMR spectrum, pyruvate **IV** appears as a keto ester (our previous studies showed that the keto–enol equilibrium in such esters is strongly shifted to the keto form), viz., the CH_2 group appears as two multiplets at 3.2 and 3.5 ppm. Enol acetate **V** gives a threeproton singlet (2.2 ppm) from the AcO group and a vinyl proton doublet (6.65 ppm, $^3J_{HH}$ 8 Hz).

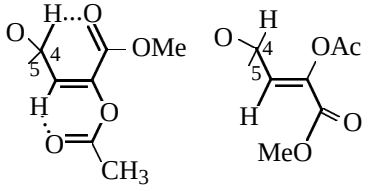
Indirect reductive dehalogenation of compound **I** can be accomplished via its reaction with triphenylphosphine. It is known [6] that the Hlg–C–C=O system contains reaction centers of two types, readily available for nucleophilic attack, with P(III) nucleophiles inclusive. Thus, the reaction of triphenylphosphine with α-halocarbonyl compounds can yield both enol and keto phosphonium salts **VI** and **VIII**, respectively.



Enol phosphonium ions **VI** are readily cleaved by protic solvents to form reduction products **IV**. By contrast, C-phosphonium salts **VIII** are stable under these conditions but convert into phosphorane **IX** under the action of bases. The fact that the ratio of the P–O and P–C products is solvent dependent has been noted in [7, 8]. Thus, the reaction in 1,2-dimethoxyethane results in exclusive formation of enol phosphonium salt **VI** and, finally, in reductive halogenation of the chloro ketone. In benzene, acetonitrile, or nitromethane, reduction and substitution products are formed in comparable amounts [7]. The reaction in acetone yields a single product, C-phosphonium salt **VIII** whose treatment with aqueous sodium bicarbonate gives phosphorane **IX**.

The reaction of 3-chloropyruvate **I** with triphenylphosphine in various conditions (1,2-dimethoxyethane, acetonitrile, 14 days, 25°C or acetone in the presence of sodium bromide, 3 h under reflux) unexpectedly gave a single product **IV** whose spectral characteristics are identical to those of the above-described product of direct reduction of compound **I**. Consequently, in this case the reaction results in exclusive formation of enol phosphonium salt **VI** and its protolytic cleavage product **IV**. However, the crystalline enol acetate **VII** (mp 205°C) formed by acetylation of pyruvate **IV** in standard conditions slightly differed in spectral characteristics from the syrupy enol acetate **V**. In the IR spectrum of compound **VII**, there is a smaller gap between the CO_2Me and OAc frequencies

(1747 and 1760 cm^{-1}, respectively, against 1740 and 1767 cm^{-1} for compound **V**). In the ^1H NMR spectrum of the crystalline compound **VII**, the vinyl (6.1 ppm) and allyl proton signals (4.1 ppm) are shifted upfield telative to the respective signals of enol acetate **V** (6.65 and 4.45 ppm). These findings suggest that the crystalline enol acetate **VII** is a *Z* isomer and the syrupy enol acetate **V**, an *E* isomer. The latter is more susceptible to H bonding which shifts downfield the signals of both H-bonded protons.



E-**V** *Z*-**VII**

EXPERIMENTAL

The IR spectra were taken on a Specord IR-75 instrument in thin films. The ^1H NMR spectra were obtained on a Bruker DPX-250 instrument in $CDCl_3$, internal reference tetramethylsilane. The ^1H NMR spectra were measured at the North Caucasus Center for Collective Use, Russian Foundation for Basic Research.

Methyl 3-deoxy-4,6:5,7-di-*O*-ethylidene-*L*-*xylo*-*D*-*galacto*(*D*-*talo*)heptonate (II). Zinc dust, 3.2 g, was added over the course of 6 h to a stirred solution of 0.5 g of chloropyruvate **I** and 0.64 g of KI in 10 ml of glacial acetic acid at room temperature. The reaction mixture was diluted with 20 ml of water, the solution was decanted and treated with chloroform, and the precipitate was washed with chloroform. The combined chloroform extracts were washed with 5% aqueous Na_2CO_3 to neutral washings and then with water, and dried with $CaCl_2$. The solvent was removed, and the residue was subjected to column chlromatography on Silochrom C-80, eluent chloroform (R_f 0.25), yield 0.35 g (78%), syrup. IR spectrum, ν, cm^{-1}: 3500 (OH), 1720 (CO_2Me). ^1H NMR spectrum, δ, ppm: 1.35 m (6H, CH*Me*), 2.0–2.8 m (3H, CH_2, OH), 3.45–4.40 m (9H, OMe, $HC^{2,4-7}$), 4.7 m (2H, C*H*Me). Found, %: C 52.52; H 7.62. $C_{12}H_{20}O_7$. Calculated, %: C 52.17; H 7.25.

Methyl 2-*O*-acetyl-3-deoxy-4,6:5,7-di-*O*-ethylidene-*L*-*glycero*-*D*-*galacto*(*D*-*talo*)heptonate (III) was prepared by treatment of 0.3 g of 2-hydroxy ester **II** with a mixture of 2 ml of Ac_2O and 1 ml of pyridine at room temperature for 12 h. The solvent was removed, and the residue was subjected to column chlromatography on Silochrom C-80, eluent chloroform (R_f 0.3), yield 0.22 g (63%), syrup; R_f 0.45 (Al_2O_3, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1750 (OAc). ^1H NMR spectrum, δ, ppm: 1.35 m (6H, CH*Me*), 2.0, 2.1 two s (3H, OCOMe), 2.2–3.0 m (2H, CH_2), 3.4–4.1 m (8H, OMe, HC^{4-7}), 4.7 m (2H, C*H*Me), 5.15, 5.40 two m (1H, HC^2). Found, %: C 53.15; H 7.32. $C_{14}H_{22}O_8$. Calculated, %: C 52.83; H 6.92.

Methyl 3-deoxy-4,6:5,7-di-*O*-ethylidene-*L*-*xylo*-hept-2-ulosonate (IV). *a*. A mixture of 0.5 g 2-hydroxy ester **II**, 1.45 g of pyridinium dichromate, and 1 g of powdered 4 Å molecular sieves in 10 ml of dichloromethane was stirred at room temperature for 36 h (control by TLC). The solution was decanted, the precipitate was thoroughly washed with dichloromethane, the reaction product was extracted from the aqueous solution with dichloromethane, and the extract was dried with $CaCl_2$. The solvent was removed, and the residue was subjected to column chlromatography on Silochrom C-80, eluent chloroform (R_f 0.3), yield 0.26 g (52%), syrup. IR spectrum, ν, cm^{-1}: 3400 (OH), 1730 (CO). ^1H NMR spectrum, δ, ppm: 1.35 m (6H, CH*Me*), 3.20–3.55 m (3H, CH_2, HC^7), 3.8–4.2 m (7H, OMe, HC^{4-7}), 4.65, 4.75 two q (2H, C*H*Me). Found, %: C 52.65; H 7.04. $C_{12}H_{18}O_7$. Calculated, %: C 52.55; H 6.57.

Enol acetate V derived from keto ester IV was prepared by treatment of the latter (0.2 g) with a mixture of 1 ml of acetic anhydride and 0.5 ml of dry pyridine for 12 h. The solvent was removed, and the residue was subjected to column chromatography on alumina (R_f 0.6, eluent chloroform), yield 0.13 g (56%), syrup. IR spectrum, ν, cm^{-1}: 1767 (OAc), 1740 (CO_2Me), 1670 (C=C). ^1H NMR spectrum, ν, ppm: 1.35 m (6H, CH*Me*), 2.2 s (3H, OCOMe), 3.50–4.15 m (7H, OMe, HC^{5-7}), 4.45 d (1H, HC^4, *J* 8 Hz), 4.65, 4.80 two q (2H, C*H*Me), 6.65 d (1H, =CH, *J* 8 Hz). Found, %: C 53.35; H 6.51. $C_{14}H_{20}O_8$. Calculated, %: C 53.16; H 6.33.

b. A mixture of 0.31 g of chloropyruvate **I**, 0.26 g of triphenylphosphine, and 0.1 g of sodium bromide in 10 ml of acetone was heated under reflux for 3 h. The reaction mixture was diluted by half with water, the reaction product was extracted with chloroform (3×10 ml), and the extract was dried with $CaCl_2$. The solvent was removed, and the residue was subjected to column chromatography on Silochrom C-80. Unchanged reactants were eluted with benzene and the reaction product, with chloroform (R_f 0.3); the last fraction contained Ph_3PO. The yield of pyruvate **IV** was 0.2 g (73%), syrup. The ^1H NMR and IR spectra of the sample were identical to those of the sample obtained by procedure *a*.

Methyl 2-*O*-acetyl-3-deoxy-4,6:5,7-di-*O*-ethylidene-*L*-*xylo*-2-heptenate (VII) was prepared by acetylation in standard conditions of pyruvate **IV** obtained by procedure *b*. Yield 65% (after chromatographic purification, mp 205°C (from chloroform–hexane). IR spectrum, ν, cm^{-1}: 1760 (OAc), 1747 (CO_2Me). ^1H NMR spectrum, ν, ppm: 1.25, 1.35 two d (6H, CH*Me*, *J* 5 Hz), 2.15 s (3H, OCOMe), 3.5–4.1 m (8H, OMe, HC^{4-7}), 4.65 q (2H, C*H*Me), 6.1 d (1H, =CH, *J* 8 Hz). Found, %: C 52.85; H 6.57. $C_{14}H_{20}O_8$. Calculated, %: C 53.16; H 6.33.

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