Acetylation of 2-*C*-Benzyl-L-*lyxo*-3-hexulosono-1,4-lactone

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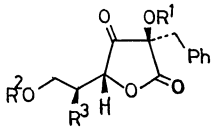
Synopsis. Acetylation of 2-*C*-benzyl-L-ascorbic acid afforded an unexpected enone, 2,6-di-*O*-acetyl-2-*C*-benzyl-5-deoxy-D-*glycero*-hex-4-en-3-ulosono-1,4-lactone (**3**) of the open form, along with 2,3,5-tri-*O*-acetyl-2-*C*-benzyl-L-*lyxo*-3-hexulosono-1,4-lactone (**4**) of the closed form.

Acetates have been used frequently for the protection[1,2] of alcoholic hydroxyl group of sugars. Riggs and Stevens[3,4] reported that treatment of piptosidin with acetic anhydride–pyridine at room temperature for 4 days gave diacetylpiptosidin corresponding to the closed form as a single product. As a part of our synthetic work on delesserine,[5–7] this report describes the formation of the open form enone (**3**).

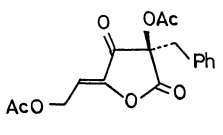
Treatment of 2-*C*-benzyl-L-*lyxo*-3-hexulosono-1,4-lactone (**2**)[8] with acetic anhydride–sulfuric acid at 0 °C or acetic anhydride–pyridine at 0 °C afforded, after chromatographic separation, diacetate **3** (42%, 43%) and triacetate (**4**) (29%, 45%), respectively.

The structure of **3** was determined on the basis of the IR, MS, and ^{1}H NMR and ^{13}C NMR spectra. The mass spectrum gave a molecular ion peak at 332. The IR absorptions at ν_{max} 1830 and 1680 cm^{-1} and the ^{13}C NMR signals at δ 189.6 (s, C-3; $^3J_{C\text{-}3,H\text{-}5}$=4.4 Hz), 170.3 (s, C-1), 144.7 (s, C-4) and 108.2 (d, C-5) suggest the presence of an α,β-unsaturated keto lactone with *Z* configuration. In addition, the presence of the keto lactone moiety was deduced from IR ν_{max} 1810 and 1770 cm^{-1} and from ^{13}C NMR δ 170.6 (s, C-1) and 204.7 (s, C-3) of the compound (**5**) derived from **3** on hydrogenation. On the basis of these spectral results, the structure of this compound was determined to be **3**, which bears the enone structure resulting from trans elimination of acetic acid at the C-5 position of the open form.



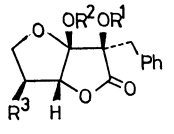
open form

(1) R^1=R^2=H, R^3=OH
(5) R^1=R^2=Ac, R^3=H



(3)

(2) R^1=R^2=H, R^3=OH
(4) R^1=R^2=Ac, R^3=OAc
(6) R^1=R^3=H, R^2=CH_3
(7) R^1=H, R^2=CH_3, R^3=OH
(8) R^1=H, R^2=CH_3, R^3=OC(S)SCH_3



closed form

Acid or base treatment[9] of **4** did not change it. Triacetate **4** is, therefore, not a precursor for producing **3**. It is supposed that the starting material exists in two forms as an equilibrium mixture (**1**⇄**2**) in solution and the closed form **2** gives **4**, while the open form **1** gives **3**. No trace of **1** was , however, found by ^{13}C NMR measurement in various solvents between −30 and 50 °C.

Hydrogenation of **3** over 10% palladiun-on-carbon catalyst gave **5** as a sole product, which, on treatment with 3% methanolic hydrogen chloride, was converted into methyl glycoside (**6**). Compound **6** was identified by comparing its spectral data (TLC, IR, ^{1}H NMR and ^{13}C NMR) with those of a sample derived from **2** via the following sequence of reactions: methyl glycosidation of **2**, *S*-methyl dithiocarbonate formation[10] from **7** and deoxygenation[11] of **8** with tributylstannane. The stereochemistry at C-4 in **5** was confirmed to have the *R* configuration.

In acetylation of piptosidin[3] diacetylpiptosidin of the closed form was obtained as a single product, while the acetylation of 2-*C*-benzyl-L-ascorbic acid afforded the open form compound **3** accompanied with elimination, along with the closed form compound **4**.

Experimental

General Methods. Melting points were determined on a micro hot-stage and are uncorrected. Column chromatography was performed with silica gel (Merck No. 7734; 63—200 μm). Optical rotations were determined with a Jasco Model DIP-4 polarimeter. Elemental analyses were performed with a Perkin-Elmer Model 240 elemental analyzer. IR spectra were taken on a JASCO A-102 IR spectrophotometer and were calibrated against the 1600 cm^{-1} band of polystyrene. Proton and carbon magnetic resonance spectra were recorded with a JEOL FX-100 spectrometer. Chemical shifts are given on the δ scale and spin coupling in Hz. Unless otherwise stated, NMR spectra were measured at 25 °C in chloroform-*d*, with tetramethylsilane (δ 0.00) as the internal standard. The assigments were confirmed by ^{1}H–^{1}H and ^{1}H–^{13}C spin-decoupling experiments. Mass spectra were recorded with a JEOL D-300 mass spectrometer.

2-*C*-benzyl-L-*lyxo*-3-hexulosono-1,4-lactone **2** and it's methyl glycoside **7**, methyl 2-*C*-benzyl-L-*lyxo*-3-hexulosidono-1,4-lactone, were prepared according to the procedure described by Jackson and Jones.[8]

Compound 2; mp 155—156 °C [lit,[8] mp 156—156.5 °C]; $[\alpha]_D^{10}$+6° (*c* 1.0 in MeOH) [lit,[8] $[\alpha]_D^{23}$+7±1° (*c* 1.0 in MeOH)]; ^{13}C NMR (in DMSO-d_6) δ=40.7, 74.1 (d, C-5), 74.1 (t, C-6), 79.3 (s, C-2), 86.9 (d, C-4), 107.2 (s, C-3), 126.7, 127.7, 130.6, 134.9, and 175.1 (s, C-1); (in pyridine-d_5) δ=42.4, 75.6 (d, C-5), 75.6 (t, C-6), 81.1 (s, C-2), 88.3 (d, C-4), 109.0 (s, C-3), 127.3, 128.4, 131.7, 135.9, and 176.9 (s, C-1); (in D_2O) δ=41.0, 74.1 (d, C-5), 75.6 (t, C-6), 80.5 (s, C-2), 87.2 (d, C-4), 108.0 (s, C-3), 128.3, 129.1, 131.4, 134.2, and 177.5 (s, C-1).

Compound 7; mp 138—139 °C [lit,[8] mp 139—140 °C]; $[\alpha]_D^{10}$ +11.1° (*c* 1.5 in MeOH) [lit,[8] $[\alpha]_D^{23}$+12±1° (*c* 1.0 in MeOH)]

^{13}C NMR ($CDCl_3$) δ=40.0, 51.3, 74.4 (d, C-5), 76.2 (t, C-6), 80.4 (s, C-2), 86.0 (d, C-4), 109.3 (s, C-3), 127.6, 128.4, 130.7, 132.9, and 175.0 (s, C-1).

Acetylation of 2. (a) With Acetic Anhydride-Sulfuric Acid: To a stirred suspension of hemiacetal **2** (3.0 g) in acetic anhydride (21 ml) at 0 °C was added 2 drops of concentrated sulfuric acid. After stirring for 30 min at 0 °C, the mixture was poured into ice-water and extracted with ether. The extract was washed with water and dried over sodium sulfate. Upon removal of solvent, the residue was chromatographed (2:1 hexane–ethyl acetate) to give syrupy 2,6-di-*O*-acetyl-2-*C*-benzyl-5-deoxy-D-*glycero*-hex-4-en-3-ulosono-1,4-lactone **3** (1.58 g, 42%); $[\alpha]_D^{27}$+39.0° (*c* 1.3 in MeOH); IR (neat) 1830, 1765 sh, 1740 and 1680 cm^{-1}; ^{1}H NMR δ=2.03 (s, OAc), 2.18 (s, OAc), 3.30 (s, benzyl), 4.55 (q, *J*=6.6 Hz, H-6), 4.57 (q, *J*=12.5 Hz, H-6′), 5.74 (t, H-5), and 7.15—7.32 (m, arom); ^{13}C NMR δ=19.1, 20.5, 39.0, 57.4 (t, C-6), 75.8 (s, C-2), 108.2 (d, C-5), 128.3, 128.8, 129.2, 130.3, 144.7 (s, C-4), 170.2, 170.3 (s, C-1), and 189.6 (s, C-3; $^3J_{C\text{-}5,H\text{-}3}$=4.4 Hz); MS: *m/z* 332 (M^+), 272 (M−CH_3COOH), 230; Found: C, 61.86; H, 5.14%. Calcd for $C_{17}H_{16}O_7$; C, 61.44; H, 4.85%; and crystalline 2,3,5-tri-*O*-acetyl-2-*C*-benzyl-L-*lyxo*-3-hexulosono-1,4-lactone **4** (1.27 g, 29%); mp 115—116 °C; $[\alpha]_D^{27}$+29.1° (*c* 1.0 in MeOH); IR (Nujol) 1810, 1750 sh and 1740 cm^{-1}; ^{1}H NMR δ=2.08 (s, OAc), 2.12 (s, OAc), 2.17 (s, OAc), 3.27 (q, *J*=14.2 Hz, benzyl), 4.10 (dd, *J*=4.9 Hz, *J*=9.5 Hz, H-6), 4.43 (dd, *J*=2.4 Hz, H-6), 4.47 (d, *J*=2.0 Hz, H-4), 5.33 (dddd, H-5), and 7.27 (s, arom); ^{13}C NMR δ=20.3, 20.5, 21.4, 39.5, 76.0 (t, C-6), 77.8 (d, C-5), 81.0 (s, C-2), 87.4 (d, C-4), 109.5 (s, C-3), 127.5, 128.2, 130.7, 132.6, 168.4, 169.1, 169.6 (s, C-1), and 169.8; MS: *m/z* 332 (M−CH_3COOH), 272 (M−2CH_3COOH), 213. Found: C, 58.26; H, 5.13%. Calcd for $C_{19}H_{20}O_9$: C, 58.16; H, 5.14%.

(b) With acetic anhydride-pyridine: A mixture of **2** (3.0 g) and acetic anhydride (30 ml) in pyridine (50 ml) was stirred for 12 h at 0 °C. After removal of the pyridine and acetic anhydride in vacuo at room temperature, the residue was chromatographed to give **3** (1.6 g, 43%) and **4** (2.0 g, 45%).

2,6-Di-*O*-acetyl-2-*C*-benzyl-5-deoxy-D-*erythro*-3-hexulosono-1,4-lactone 5. Hydrogenolysis of the enone **3** (0.61 g) over 10% Pd–C (200 mg) in methanol (20 ml) for 15 h afforded syrupy **5** (0.59 g, 98%): $[\alpha]_D^{30}$+28.9° (*c* 1.4 in MeOH); IR (neat) 1810, 1770 and 1735 cm^{-1}; ^{1}H NMR δ=1.97 (s, OAc), 2.17 (s, OAc), 2.00—2.25 (m, H-5), 3.31 (q, *J*=13.0 Hz, benzyl), 3.58 (dd, *J*=4.9 Hz, *J*=8.5 Hz, H-4), 3.90—4.30 (m, H-6), and 7.17—7.38 (m, arom); ^{13}C NMR, δ=19.1, 20.5, 30.2 (t, C-5), 39.3, 59.7 (t, C-6), 76.2 (s, C-2), 80.7 (d, C-4), 128.5, 129.1, 129.5, 130.1, 170.1, 170.6 (s, C-1), and 204.7 (s, C-3); MS: *m/z* 274 (M−CH_3COOH), 214 (M−2CH_3COOH).

Methyl 2-*C*-benzyl-5-deoxy-D-*erythro*-3-hexulosidono-1,4-lactone 6. The keto lactone **5** (550 mg) was dissolved in 3% methanolic hydrogen chloride (20 ml; prepared from 20 ml of dry methanol and 1 ml of acetyl chloride), and the solution was boiled for 6 h. The acid was neutralized by addition of solid sodium carbonate, and the solution was concentrated and extracted with dichloromethane. The combined extracts were dried over sodium sulfate and evaporated to give methyl glycoside **6** (390 mg, 90%): TLC (R_f 0.38; 2:1 hexane–acetone) $[\alpha]_D^{30}$−1.6° (*c* 1.0 in MeOH); IR (neat) 3450 and 1790 cm^{-1}; ^{1}H NMR δ=2.12—2.31 (m, H-5), 3.14 (s, benzyl), 3.52 (s, OCH_3), 3.99 (dd, *J*=2.0 Hz, *J*=4.2 Hz, H-4), 4.02—4.19 (m, H-6), and 7.29 (s, arom); ^{13}C NMR δ=30.2 (t, C-5), 39.7, 50.5, 68.1 (t, C-6), 80.0 (s, C-2), 81.7 (d, C-4), 109.2 (s, C-3), 127.0, 127.7, 130.3, 133.1, and 174.9 (s, C-1); MS: *m/z* 264 (M^+).

Methyl 2-*C*-benzyl-5-*O*-[(methylthio)thiocarbonyl]-L-*lyxo*-3-hexulosidono-1,4-lactone 8. Methyl glycoside **7** (2.8 g), sodium hydride (50% dispersion in oil, 1.92 g) and imidazole (20 mg) were stirred for 2 h in tetrahydrofuran (40 ml). Carbon disulfide (3.6 ml) was added, and the stirring continued (1 h). Methyl iodide (0.93 ml) was added and the stirring again continued (15 min). The mixture was processed conventionally (dichloromethane extraction), and the product chromatographed, giving crystalline **8** (2.5 g, 68%); mp 137—138°; $[\alpha]_D^{28}$+72.5° (*c* 1.3 in MeOH); IR (Nujol) 3550 and 1810 cm^{-1}; ^{1}H NMR δ=2.55 (s, SCH_3), 3.14 (s, benzyl), 3.58 (s, OCH_3), 4.06 (dd, *J*=4.2 Hz, *J*=10.7 Hz, H-6), 4.23 (s, H-4), 4.58 (dd, *J*=6.6 Hz, H-6), 5.76 (dd, H-5), and 7.29 (s, arom); ^{13}C NMR δ=19.5 (SCH_3), 40.0, 51.1 (OCH_3), 73.2 (t, C-6), 80.1 (s, C-2), 83.1 (d, C-5), 83.9 (d, C-4), 109.2 (s, C-3), 127.6, 128.3, 130.6, 132.7, 174.1 (s, C-1), and 214.4 (C=S). Found: C, 51.91; H, 4.91%. Calcd for $C_{16}H_{18}S_2O_6$: 51.88; H, 4.90%.

Deoxygenation of 8. The dithiocarbonate **8** (840 mg) in dry toluene (25 ml) was added dropwise to a solution of tributylstannane (873 mg) in refluxing toluene (15 ml), and the refluxing continued overnight. The solvent was removed by evaporation and the oily residue purified by chromatography, giving the 5-deoxy compound **6** (520 mg, 87%): TLC (R_f 0.38, 2:1 hexane–acetone); $[\alpha]_D^{30}$−1.9° (*c* 1.0 in MeOH). IR, ^{1}H NMR and ^{13}C NMR spectral data agreed with those of a sample derived from **3**.

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9) Acid or base treatment of **4**: Starting material was recovered from the treatment with (A) acetic anhydride and 2 drops of concentrated sulfuric acid at 0° for 30 min; (B) silica gel in chloroform at room temperature for 24 h; (C) pyridine at room temperature for 24 h; (D) pyridine and acetic anhydride for 12 h.

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