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Note

Synthesis of fused lactone nucleosides *via* stereoselective Wittig olefination of hexopyranosyl keto-nucleosides

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Unsaturated keto-nucleosides[1] are versatile intermediates in the preparation of unsaturated and branched-chain nucleosides[2,3], and the L and D forms are highly cytotoxic towards KB cells[4] and L1210 leukemia[5]. The Michael reaction of various nucleoside enones (**1**) with thiols has been demonstrated[6] and it has been shown that the most potent cytostatic nucleosides reduced considerably the SH level in the membrane surface of cells.

During the last decade, there has been interest in the chemical reactivity of enone-type sesquiterpene antitumour compounds[7], which can also undergo conjugate addition with thiols. The active part of these molecules is considered to be the α,β-unsaturated ester or lactone function and, in investigating nucleoside analogues, we have synthesised α,β-unsaturated esters by Wittig olefination of keto-nucleosides. The reaction was stereoselective and the product could be used in a facile synthesis of fused lactone nucleosides.

The key intermediate 1-(2,6-dideoxy-2-*C*-ethoxycarbonylmethylene-3,4-*O*-isopropylidene-β-L-*lyxo*-hexopyranosyl)thymine (**7**) was synthesised as follows. Condensation[8] of 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine[9] (**2**) with 1,2,3,4-tetra-*O*-acetyl-6-deoxy-L-galactopyranose yielded the tri-*O*-acetyl-β-L-nucleoside derivative **3**, which was deacetylated to give 1-(6-deoxy-β-L-galactopyranosyl)-thymine (**4**). Acetalation of **4** with 2,2-dimethoxypropane afforded the 3,4-*O*-isopropylidene derivative **5**, oxidation[10] of which gave the keto-nucleoside derivative **6**.

Wittig olefination of **6**, using the Buddrus one-pot procedure[11] (PPh_3, $BrCH_2COOEt$, and propylene oxide), afforded the nucleoside derivative **7** as a unique isomer (60% after chromatography). The ^{1}H-n.m.r. data for **7** indicated the presence of the unsaturated ester function. Furthermore, H-3′ (d) was deshielded by the ester group, which established[12] that the ethoxycarbonyl group and C-3′ are *cis*.

Treatment[13] of **7** with ethanol–trifluoroacetic acid gave 70% of the un-

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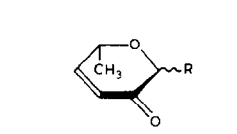
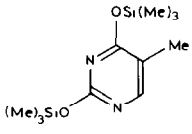


1 R = purine or pyrimidine



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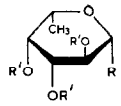
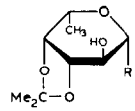


3 R′ = Ac
4 R′ = H



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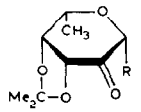

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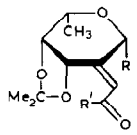
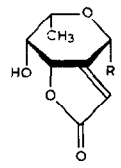


7 R′ = OEt



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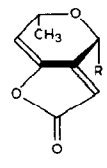

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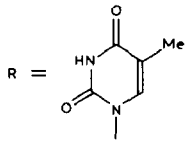

saturated lactone **8**. The ^{1}H-n.m.r. spectrum of **8** reflected the loss of the ethyl group, and i.r. absorption at 1760 cm^{-1} (characteristic of an unsaturated γ-lactone) indicated the occurrence of lactonisation. This view was confirmed by the mass spectrum which contained a peak at *m/z* 294 of high intensity for M^+, and peaks of *m/z* 169 and 126 for the nitrogen heterocycle and fused lactone-carbohydrate fragments formed by cleavage of the nucleoside bond.

Treatment of the lactone **8** with acetic anhydride and pyridine in the presence of 2,4 dimethylaminopyridine gave 60% of the enol-lactone **9**. The downfield position of the signals for H-4′ and H-5′ in the ^{1}H-n.m.r. spectrum of **9** showed that the desired elimination had occurred. In addition, the singlet at 6.9 p.p.m. and the marked λ_{max} at 266 nm indicated the butadienolide structure.

EXPERIMENTAL

Melting points were determined on a Reichert microstage-block and are uncorrected. ^{1}H-N.m.r. spectra (60 MHz, internal Me_4Si) were recorded with a Varian T60 instrument. I.r. spectra were recorded with a Perkin–Elmer 137 spectrophotometer and u.v. spectra with a Varian 635 spectrophotometer. Microanalysis and mass spectrometry were performed by the Laboratoire Central de Microanalyse du CNRS Vernaison. T.l.c. was performed on Silica Gel F_{254} (Merck) with detection by u.v. light and spraying with anisaldehyde or 20% sulfuric acid. Flash chromatography was performed on Silica Gel 60 (Merck) (0.04–0.063 mm).

Methanol, acetone (3 Å), and dichloromethane (4 Å) were dried with molecular sieves and used without further purification. Solvents were evaporated under reduced pressure at room temperature.

1-(2,3,4-Tri-O-acetyl-6-deoxy-β-L-galactopyranosyl)thymine (**3**). — Thymine (15 g, 119 mmol) was suspended in acetonitrile (600 mL) and hexamethyldisilazane (50.21 mL, 237 mmol). Saccharin (0.102 g, 0.56 mmol) was added, the mixture was boiled under reflux with the exclusion of moisture for 2 h and then concentrated, and the residual 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine (**2**) was used without further purification.

A solution of 1,2,3,4-tetra-*O*-acetyl-6-deoxy-L-galactopyranose[14] (39 g, 119 mmol) in acetonitrile (600 mL) was added to **2**. Stannic chloride (14.28 mL, 119 mmol) was added and the yellow solution was boiled under reflux for 2 h. Most of the acetonitrile was then evaporated and, to a solution of the residue in dichloromethane (600 mL), solid sodium hydrogencarbonate was added portionwise in the presence of water (100 mL) until CO_2 evolution ceased. The organic phase was washed twice with water, dried (Na_2SO_4), and concentrated to give **3** (35.52 g, 75%), m.p. 130–133° (from ethanol), $[\alpha]_D^{20}$ −10° (*c* 0.1, methanol), R_F 0.78 (ethyl acetate); λ_{max}^{MeOH} 261 nm (ε 10,945); ν_{max}^{KBr} 1733, 1695, and 1664 cm^{-1}. ^{1}H-N.m.r. data (acetone-d_6): δ 7.3 (s, 1 H, H-6), 5.9 (m, 1 H, H-1′), 5.3 (m, 3 H, H-2′,3′,4′), 4.4 (q, 3 H, *J* 6.5 Hz, H-5′), 2.2, 2.1 and 1.9 (3 s, 9 H, 3 AcO), 1.9 (s, 3 H, Me thymine), 1.3 (d, 3 H, *J* 6.5 Hz, H-6′,6′,6′).

Anal. Calc. for $C_{17}H_{22}N_2O_9$: C, 51.25; H, 5.52; N, 7.03; O, 36.18. Found: C, 51.05; H, 5.80; N, 7.05; O, 36.10.

1-(6-Deoxy-β-L-galactopyranosyl)thymine (**4**). — A mixture of **3** (20 g, 50 mmol) and methanol in 0.08M sodium methoxide (250 mL, 20 mmol) was stirred for 1 h, then neutralised with Amberlite IR-120 (H^+) resin, and concentrated. The residue was crystallised from ethanol to give **4** (10.84 g, 80%), m.p. 240–241°, $[\alpha]_D^{20}$ −25° (*c* 0.1, water), R_F 0.31 (methanol–ethyl acetate, 15:85); $\lambda_{max}^{H_2O}$ 265 nm (ε 8704); ν_{max}^{KBr} 3600, 1700, and 1680 cm^{-1}. ^{1}H-N.m.r. data (CD_3CO_2D): δ 7.6 (s, 1 H, H-6), 6.3 (d, 1 H, *J* 9 Hz, H-1′), 4.7 (dd, 1 H, *J* 9 Hz, H-2′), 4.4–3.8 (m, 3 H, H-3′,4′,5′), 1.7 (s, 3 H, Me thymine), 1.5 (d, 1 H, *J* 6 Hz, H-6′,6′,6′).

Anal. Calc. for $C_{11}H_{16}N_2O_6$: C, 48.53; H, 5.86; N, 10.29. Found: C, 48.54; H, 5.75; N, 10.3.

1-(6-Deoxy-3,4-O-isopropylidene-β-L-galactopyranosyl)thymine (**5**). — A mixture of 2,2-dimethoxypropane (96.5 mL, 750 mmol), 18M sulfuric acid (0.05 mL, 0.9 mmol), **4** (13.6 g, 50 mmol), and *N,N*-dimethylformamide (150 mL) was stirred for 1 h at room temperature, then neutralised with M sodium hydroxide, and concentrated at 0.01 mmHg. Crystallisation of the residue from water gave **5** (12.45 g, 70%), m.p. 130–132°, $[\alpha]_D^{20}$ −105° (*c* 0.1, methanol), R_F 0.56 (ethyl acetate); λ_{max}^{MeOH} 264 nm (ε 13,166); ν_{max}^{KBr} 3571, 1724, and 1661 cm^{-1}. ^{1}H-N.m.r. data (CD_3CO_2D): δ 7.6 (s, 1 H, H-6), 5.7 (d, 1 H, *J* 9 Hz, H-1′), 4.5–3.8 (m, 4 H, H-2′,3′,4′,5′), 2.1 (s, 3 H, Me thymine), 1.7–1.3 (m, 9 H, H-6′,6′,6′ and CMe_2).

Anal. Calc. for $C_{14}H_{20}N_2O_6 \cdot H_2O$: C, 50.90; H, 6.66; N, 8.48. Found: C, 51.23; H, 6.75; N, 8.54.

*1-(6-Deoxy-3,4-*O*-isopropylidene-β-*L*-lyxo-hexopyranosylulose)thymine* (**6**). — A mixture of molecular sieves (3 Å, 18.75 g), pyridinium dichromate (17.4 g, 37 mmol), **5** (6 g, 19.2 mmol), and dichloromethane (100 mL) was stirred at room temperature for 4.5 h. The black mixture was then diluted with ether (300 mL), filtered through a pad of silica gel, and concentrated. Crystallisation of the residue from ether yielded **6** (4.17 g, 70%), m.p. 188–190°, $[\alpha]_D^{20}$ −45° (*c* 0.1, methanol), R_F 0.68 (methanol–ethyl acetate, 15:85); λ_{max}^{MeOH} 265 nm (ε 12,568); ν_{max}^{KBr} 1740 cm^{-1}. ^{1}H-N.m.r. data (CD_3CO_2D): δ 7.2 (s, 1 H, H-6), 6.4 (s, 1 H, H-1′), 5 (d, 1 H, *J* 6 Hz, H-3′), 4.8–4.5 (m, 2 H, H-4′,5′), 2.1 (s, 3 H, Me thymine), 1.7–1.3 (m, 9 H, H-6′,6′,6′ and CMe_2).

Anal. Calc. for $C_{14}H_{19}N_2O_6 \cdot 0.5\ H_2O$: C, 52.60; H, 5.95; N, 8.77. Found: C, 52.86; H, 6.18; N, 8.47.

*1-(2,6-Dideoxy-2-*C*-ethoxycarbonylmethylene-3,4-*O*-isopropylidene-β-*L*-lyxo-hexopyranosyl)thymine* (**7**). — To a solution of triphenylphosphine (6 g, 22.8 mmol), ethyl bromoacetate (2.23 g, 13.35 mmol), and **6** (3.1 g, 10 mmol) in dry dichloromethane (50 mL) at −20° was added ethylene or propylene oxide (10 mL), and the mixture was stored overnight at room temperature. The product, isolated as a foam (2.28 g, 60%) after flash chromatography (ethyl acetate–pentane, 1:3), had $[\alpha]_D^{20}$ −70° (*c* 0.1, methanol), R_F 0.84 (ethyl acetate); λ_{max}^{MeOH} 263 nm (ε 9196); ν_{max}^{KBr} 1700 cm^{-1}. ^{1}H-N.m.r. data (C_6D_6): δ 7.83 (s, 1 H, H-6), 6.66 (d, 1 H, *J* 1.5 Hz, C*H*COOEt), 6.46 (d, 1 H, *J* 1.5 Hz, H-1′), 6.21 (d, 1 H, *J* 7.5 Hz, H-3′), 3.93 (q, 2 H, *J* 7 Hz, OCH_2), 3.65 (dd, 1 H, *J* 7.5 and 2 Hz, H-4′), 2.91 (dq, 1 H, *J* 2 and 7 Hz, H-5′), 1.75 (s, 3 H, Me thymine), 1.41 and 1.33 (2 s, each 3 H, CMe_2), 1.12 (d, 3 H, *J* 7 Hz, H-6′,6′,6′), 0.93 (t, 3 H, *J* 7 Hz, OCH_2CH_3).

Anal. Calc. for $C_{18}H_{24}N_2O_7 \cdot 0.5\ H_2O$: C, 56.84; H, 6.31; N, 7.36; O, 29.47. Found: C, 56.09; H, 6.30; N, 7.36; O, 31.25.

*1-(2-*C*-Carboxymethylene-2,6-dideoxy-β-*L*-lyxo-hexopyranosyl 2²,3-lactone)-thymine* (**8**). — A solution of **7** (1.95, 5 mmol) in trifluoroacetic acid and ethanol (9:1, 40 mL) was stored for 5 min at room temperature and then concentrated. Crystallisation of the residue from ethanol gave **8** (2.1 g, 70%), m.p. 167–170°, $[\alpha]_D^{20}$ −55° (*c* 0.1, methanol), R_F 0.64 (ethyl acetate); λ_{max}^{MeOH} 263 nm (ε 9877); ν_{max}^{KBr} 3350, 1760, 1709, 1667, and 1630 cm^{-1}. Mass spectrum: *m/z* 294, 277, 169, 151, 126. ^{1}H-N.m.r. data (pyridine-d_5): δ 7.58 (s, 1 H, H-6), 6.93 (s, 1 H, CHCO), 6.45 (d, 1 H, *J* 2 Hz, H-1′), 5.51 (dd, 1 H, *J* 3 and 2 Hz, H-3′), 4.36 (d, 1 H, *J* 3 Hz, H-4′), 4.23 (q, 1 H, *J* 6.5 Hz, H-5′), 1.81 (s, 3 H, Me thymine), 1.51 (d, 3 H, *J* 6.5 Hz, H-6′,6′,6′).

Anal. Calc. for $C_{13}H_{14}N_2O_6 \cdot CH_3OH$: C, 51.53; H, 5.52; N, 8.58. Found: C, 51.83; H, 5.12; N, 8.71.

*1-(2-*C*-Carboxymethylene-2,4,6-trideoxy-β-*L*-glycero-hex-3-enopyranosyl 2²,3-lactone)thymine* (**9**). — A solution of **8** (1.7 g, 5 mmol) in dichloromethane (10 mL) was treated with acetic anhydride (1.02 g, 10 mmol) and pyridine (0.790 g, 10 mmol) in the presence of a catalytic amount of 2,4-dimethylaminopyridine. After 2 h, the solvent was removed and the residue was crystallised from ethanol to give **9**

(0.825 g, 60%), m.p. 167–168°, $[\alpha]_D^{20}$ +125° (*c* 0.1, methanol), R_F 0.72 (ethyl acetate); λ_{max}^{MeOH} 265 nm (ε 21,390); ν_{max}^{KBr} 2933, 1786, 1709, 1681, and 1664 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 7.09 (s, 1 H, H-6), 6.9 (s, 1 H, CHCO), 6.09 (b s, 1 H, H-1′), 5.93 (d, 1 H, *J* 1.5 Hz, H-4′), 4.83 (q, 1 H, *J* 1.5 and 7 Hz, H-5′), 1.93 (s, 3 H, Me thymine), 1.5 (d, 1 H, *J* 7 Hz, H-6′,6′,6′).

Anal. Calc. for $C_{13}H_{12}N_2O_5 \cdot 0.5\ H_2O$: C, 54.72; H, 4.56; N, 9.82. Found: C, 55.47; H, 4.57; N, 9.61.

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