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Note

α,β-Unsaturated-7,3-lactone-nucleosides *via* an intramolecular Wittig reaction: a short route to nucleosides related to goniothalenol

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Goniothalenol, isolated from the stem bark of *Goniothalamus giganteus*, has been shown by n.m.r. and X ray analysis to have the fused tetrahydrofurano-2-pyrone structure[1] **1**, not reported previously in natural compounds, and is of interest because of its activity against various lines of cancer cells[1].

Because nucleosides containing *α,β*-unsaturated carbonyl groups have antitumor activity[2], we were prompted to undertake a synthesis of nucleosides related to goniothalenol and now describe here a short synthesis of thymine nucleosides.

The retrosynthetic analysis of **1** indicated L-glucose to be the starting point but, for practical reasons, the initial synthesis study was carried out on D-glucose.

1,2:5,6-Di-*O*-isopropylidene-D-glucose (**2**) was converted into the 3-bromoacetate **3**. Reaction of **3** with periodic acid in the presence of formic acid resulted in hydrolysis of the 5,6-acetal group, then glycol cleavage to give the aldehyde **4**. Attempted cyclisation of **4** in basic medium via the corresponding phosphoranylidene failed, giving mostly elimination products, but reaction of **4** with triphenylphosphine and propylene oxide[3] gave the expected unsaturated lactone **5**. The n.m.r. spectrum of **5** contained signals at 6.96 and 6.23 p.p.m. (*J* 9.8 Hz) for the olefinic protons, which accords with the proposed structure. Acetolysis of the 1,2-*O*-isopropylidene group in **5** gave the corresponding diacetate **6**, Vorbrüggen condensation[4] of which with bis-(trimethylsilyl)thymine gave the nucleoside derivative **7**. The ^{1}H-n.m.r. data for the pyrone ring corresponded closely to the values reported for goniothalenol[1]. However, care must be taken when the configurations in furanoid systems are assigned on the basis of coupling constant data[5,6]. The stereochemistry at the anomeric centre of **7** was therefore determined by n.O.e. difference spectroscopy and the results are shown in Fig. 1; the enhancements of the signals related to H-1′,H-4′ and H-2′, H-6 are consistent with a *β*-D configuration. Attempts at deacetylation of **7** with methanolic 0.1M sodium methoxide gave mainly the addition product **8**. However, treatment of **7** with tetrahydrofuran–aqueous ammonia gave the expected deacetylated nucleoside **9**, the ^{1}H-n.m.r. data of which confirmed the presence of the unsaturated lactone.

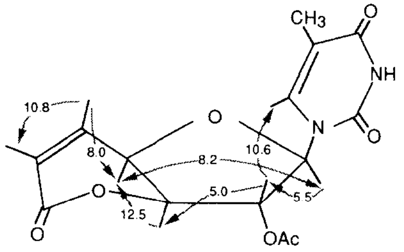
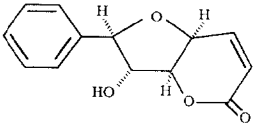


Fig. 1. Enhancements (%) obtained by n.O.e. difference spectroscopy for **7**



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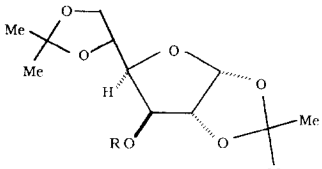
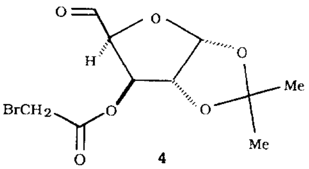


2 R = H

3 R = CO-CH2 Br



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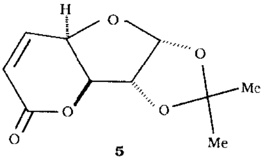

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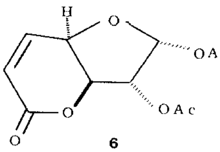

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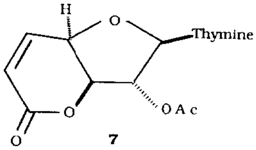

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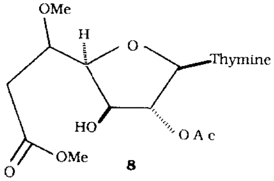

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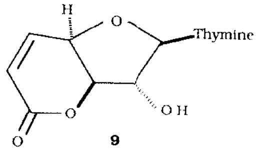

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EXPERIMENTAL

General. — Optical rotations were measured with a Roussel Quick polarimeter I.r. spectra were recorded with a Perkin–Elmer 137 instrument, and ^{1}H-n.m.r. spectra ($CDCl_3$, internal Me_4Si) with a Bruker MSL 300 spectrometer. Reactions were monitored by t.l.c. on silica gel (Merck, 5735), with detection by u.v. light (254 nm) or by charring with sulphuric acid. Flash column chromatography was carried out on Chromagel 60 Å (S.D.S., 200.17) at 10 p.s.i. Solvents for chromatography were dichloromethane–acetone *A*, 99:1; *B*, 85:15.

*3-O-Bromoacetyl-1,2:5,6-di-O-isopropylidene-α-*D*-glucofuranose* (**3**). — To a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**; 12 g, 46 mmol) in dry dichloromethane (100 mL) were added pyridine (5.5 mL, 1.5 equiv.) and 4-dimethylaminopyridine (0.056 g, 0.01 equiv.), and the solution was cooled under nitrogen to 0°. Bromoacetyl bromide (5 mL, 1.25 equiv.) was added dropwise, the mixture was left for

30 min at 0°, water (1 mL) was added, and, after 15 min, the mixture was diluted with ether (200 mL), washed with water (2 × 20 mL) and brine, dried ($MgSO_4$), and filtered through a short column of silica. Concentration of the eluate gave **3**, isolated as a colorless syrup (17 g, 97%), $[\alpha]_D$ −22.5° (*c* 0.1, methanol; R_F 0.6 (solvent *A*). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.90 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.31 (d, 1 H, $J_{3,4}$ 2.63 Hz, H-3), 4.52 (d, 1 H, $J_{1,2}$ 3.67, H-2), 4.26–4.21 (m, 2 H, H-4,5), 4.12 and 4.02 (2 m, 2 H, H-6), 3.87 (s, 2 H, CH_2), 1.52, 1.41, and 1.32 (3 s, 12 H, 4 CH_3).

Anal. Calc. for $C_{14}H_{21}BrO_7 \cdot 0.5H_2O$: C, 43.07; H, 5.64. Found: C, 42.98; H, 5.51.

*3-*O*-Bromoacetyl-1,2-*O*-isopropylidene-α-*D-xylo*-pentodialdose* (**4**). — To a solution of **3** (15 g, 39 mmol) in ether–methanol (90:10, 150 mL) at 0° were added formic acid (75 mL) and periodic acid (13.5 g, 1.5 equiv.). The solution was stirred for 5 min at 0° and for 40 min at ambient temperature, then concentrated (40° max.), and a solution of the residue in ethyl acetate (200 mL) was washed with water (2 × 10 mL), aqueous sodium hydrogen carbonate (2 × 10 mL), and aqueous sodium thiosulfate (5 mL), dried ($MgSO_4$), and concentrated to give **4** (11 g, 90%), $[\alpha]_D$ −15° (*c* 0.1, methanol); R_F 0.2 (solvent *A*). ^{1}H-N.m.r. data ($CDCl_3$): δ 9.66 (s, 1 H, H-5), 6.09 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.53 (dd, 1 H, J 3.1 Hz, H-4), 4.72 (d, 1 H, $J_{3,4}$ 3.5 Hz, H-3), 4.59 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-2), 3.77 (s, 2 H, CH_2), 1.52 and 1.35 (2 s, 6 H, 2 CH_3).

Anal. Calc. for $C_{10}H_{13}BrO_6$: C, 38.83; H, 4.20. Found: C, 39.01; H, 4.7.

*5,6-Dideoxy-1,2-*O*-isopropylidene-α-*D-xylo*-hept-5-enofuranurono-7,3-lactone* (**5**). — To a solution of **4** (10 g, 32 mmol) in dichloromethane (240 mL) at 0° were added propylene oxide (30 mL) and triphenylphosphine (17 g, 2 equiv.). The mixture was left at room temperature for 20 h, then concentrated, diluted with ethyl acetate (200 mL), washed with water (2 × 20 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (hexane–ethyl acetate, 92:8, then 85:15) of the residue gave **5** (1.5 g, 22%), $[\alpha]_D$ +12.5° (*c* 0.1, methanol); R_F 0.5 (solvent *A*). ^{1}H-N.m.r. data ($CDCl_3$): δ 6.96 (dd, 1 H, $J_{5,6}$ 9.88, $J_{4,5}$ 5.94 Hz, H-5), 6.23 (d, 1 H, $J_{5,6}$ 9.73 Hz, H-6), 6.01 (d, 1 H, $J_{1,2}$ 3.55 Hz, H-1), 4.81 (m, 2 H, H-2,3), 4.62 (dd, 1 H, $J_{3,4}$ 3.17, $J_{4,5}$ 5.67 Hz, H-4), 1.52 and 1.35 (2 s, 6 H, 2 CH_3).

Anal. Calc. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.66. Found: C, 56.44; H, 5.81.

*1,2-Di-*O*-acetyl-5,6-dideoxy-α-*D-xylo*-hept-5-enofuranurono-7,3-lactone* (**6**). — To a solution of **5** (0.6 g, 2.8 mmol) in acetic anhydride (20 mL) was added sulfuric acid (0.63 mL). The mixture was heated at 60° for 30 min, then diluted with ethyl acetate (40 mL), washed with water (2 × 5 mL) and aqueous sodium hydrogen carbonate (5 mL), dried ($MgSO_4$), and concentrated to give **6** (0.63 g, 87%), $[\alpha]_D$ −75° (*c* 0.1, methanol); R_F 0.25 (solvent *A*). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.04 (dd, 1 H, $J_{5,6}$ 10, $J_{4,5}$ 6.1 Hz, H-5), 6.90 (d, 1 H, $J_{1,2}$ 2.1 Hz, H-1), 6.23 (d, 1 H, $J_{5,6}$ 9.8 Hz, H-6), 5.57 (dd, 1 H, $J_{3,4}$ 2.7, $J_{2,3}$ 8.2 Hz, H-3), 5.35 (dd, 1 H, $J_{3,4}$ 2.4, $J_{4,5}$ 5.5 Hz, H-4), 4.72 (dd, 1 H, $J_{1,2}$ 2.8, $J_{2,3}$ 8.3 Hz, H-2), 2.18 and 2.11 (2 s, 6 H, 2 CH_3).

Anal. Calc. for $C_{11}H_{12}O_7$: C, 51.57; H, 4.72. Found: C, 51.60; H, 4.83.

*1-(2-*O*-Acetyl-5,6-dideoxy-β-*D-xylo*-hept-5-enofuranosylurono-7,3-lactone)-thymine* (**7**). — To a solution of **6** (0.1 g, 0.4 mmol) in dry acetonitrile (5 mL) were added thymine (0.05 g, 1 equiv.), hexamethyldisilazane (0.066 mL, 0.8 equiv.), chlorotrimethylsilane (0.04 mL, 0.8 equiv.), and stannic chloride (0.056 mL, 1.2 equiv.). After stirring for 30 min at 120°, the mixture was concentrated, diluted with ethyl acetate (20 mL), neutralized with aqueous sodium hydrogen carbonate, washed with water, dried ($MgSO_4$), and concentrated. Column chromatography (solvent *B*) of the residue gave **7**, isolated as a white powder (0.075 g, 60%), m.p. 95°, $[\alpha]_D$ $-116°$ (*c* 0.1, methanol; R_F 0.2 (solvent *B*); λ_{max} 265 nm (ε 13 500). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.5 (s, 1 H, NH), 7.0 (m, 2 H, H-6,5'), 6.36 (d, 1 H, $J_{5',6'}$ 9.8 Hz, H-6'), 6.17 (d, 1 H, $J_{1',2'}$ 3 Hz, H-1'), 5.36 (d, 1 H, H-2'), 4.96 (d, 1 H, $J_{3',4'}$ 3.5 Hz, H-3'), 4.61 (dd, 1 H, $J_{4',5'}$ 5.5 Hz, H-4'), 2.16 (s, 3 H, CH_3), 1.91 (s, 3 H, CH_3).

Anal. Calc. for $C_{14}H_{14}N_2O_7$: C, 52.18; H, 4.38. Found: C, 52.60; H, 4.72.

1-(Methyl-2-O-acetyl-6-deoxy-5-O-methylheptofuranosyluronate)thymine (**8**). — To a solution of **7** (0.1 g, 0.3 mmol) in methanol (0.9 mL) was added methanolic M sodium methoxide (0.1 mL). After 15 min, the solution was neutralized with Amberlite IR-120 (H^+) resin, filtered, and concentrated. The major product **8**, isolated (24 mg, 20%) after chromatography (ethyl acetate), had $[\alpha]_D$ $-80°$ (*c* 0.1, methanol); R_F 0.25 (ethyl acetate). ^{1}H-N.m.r. data (CD_3COOD): δ 7.04 (d, 1 H, *J* 1.3 Hz, H-6), 5.77 (d, 1 H, $J_{1',2'}$ 3.5 Hz, H-1'), 4.65 (dd, 1 H, $J_{2',3'}$ 1.5 Hz, H-2'), 4.42 (dd, 1 H, $J_{3',4'}$ 3.6 Hz, H-3'), 4.38 (t, 1 H, $J_{3',4'}$ 3.7 Hz, H-4'), 3.79 (m, 1 H, H-5'), 3.35 and 2.89 (2 s, 6 H, 2 OCH_3), 2.76 and 2.57 (2 AB, 2 H, CH_2), 2.52 (s, 3 H, OAc), 1.75 (d, 3 H, *J* 1.3 Hz, CH_3).

Anal. Calc. for $C_{16}H_{22}N_2O_9$: C, 49.74; H, 5.70. Found: C, 50.14; H, 5.73.

*1-(5,6-Dideoxy-β-*D-xylo*-hept-5-enofuranosylurono-7,3-lactone)thymine* (**9**). — Tetrahydrofuran (5 mL) was saturated with ammonium hydroxide in a separatory funnel and decanted. Nucleoside **7** (0.1 g, 0.3 mmol) was dissolved in this solution. After 30 min, the solution was concentrated, and the residue was dissolved in methanol and chromatographed (t.l.c.; 20 × 20 cm, 1.5 mm; ethyl acetate) to give **9** isolated as a hygroscopic powder (54 mg, 65%), $[\alpha]_D$ $-130°$ (*c* 0.1, methanol); R_F 0.36 (ethyl acetate). ^{1}H-N.m.r. data (CD_3COOD): δ 7.77 (s, 1 H, H-6), 6.36 (dd, 1 H, $J_{4',5'}$ 6.5 $J_{5',6'}$ 11.7 Hz, H-5'), 6.14 (d, 1 H, $J_{5',6'}$ 11.9 Hz, H-6') 5.96 (s, 1 H, H-1'), 5.65 (m, 1 H, H-4'), 5.17 (s, 1 H, H-2'), 4.55 (d, 1 H, $J_{3',4'}$ 3.15 Hz, H-3'), 1.9 (s, 3 H, CH_3).

Anal. Calc. for $C_{12}H_{12}N_2O_6 \cdot 3.3H_2O$: C, 42.43; H, 5.48. Found: C, 42.49; H, 5.36.

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