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Synthesis of 2′,3′-dideoxy-2′,3′-α-methanocytidine*

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ABSTRACT

A six-stage synthesis of 2′,3′-dideoxy-2′,3′-α-methanocytidine (**3**) from (5*S*)-5-benzoyloxymethyl-(5*H*)-furan-2-one (**5**) is described. The key step involved the stereoselective formation of (1*R*,4*S*,5*S*)-4-benzoyloxymethyl-3-oxabicyclo[3.1.0]hexan-2-one (**7**) *via* 1,3-dipolar cycloaddition of diazomethane to **5** followed by photoinduced elimination of nitrogen. Reduction of **7** to the corresponding lactol followed by acetylation yielded primarily 1-*O*-acetyl-5-*O*-benzoyl-2,3-dideoxy-β-D-ribofuranose (**8**). Reaction of **8** with 2,4-bis(trimethylsilyl)cytosine and $EtAlCl_2$ followed by deprotection and chromatography gave **3**, which exhibited only weak activity against the human immunodeficiency virus (HIV).

INTRODUCTION

Several nucleoside analogues have been evaluated for the treatment of AIDS[1] of which 3′-α-azido-3′-deoxythymidine (AZT, **1**) and 2′,3′-dideoxycytidine[2] (**2**) show the most promise. When this work was commenced, no 2′,3′-dideoxy-2′,3′-methanonucleosides had been prepared, and the cytidine analogue **3** seemed to be an appropriate target for synthesis and biological evaluation. We had already reported[3] a novel, high-yielding synthesis of (5*S*)-5-hydroxymethyl-(5*H*)-furan-2-one (**4**), and this was an appealing starting material for a synthesis of **3** and other 2′,3′-dideoxy-2′,3′-methanonucleoside analogues.

RESULTS AND DISCUSSION

The butenolide **4** was converted easily into its benzoic ester **5**, which reacted with diazomethane to yield mainly the pyrazoline **6**. On u.v. irradiation of **6** in benzene–acetonitrile (1:1), nitrogen was eliminated, and the 2,3-α-methano derivative **7** was obtained (overall yield of 83%). A 400-MHz n.m.r. spectrum of **2** revealed ~5% of an olefinic contaminant (3-exo-methylene product?) which could not be removed by chromatography, but there was no evidence for the presence of the alternative 2,3-β-methano stereoisomer. In particular, n.O.e. studies demonstrated no interaction of H-6,6 and the benzoyloxy-methylene hydrogens, but a significant interaction between one H-6 and H-4.

* Dedicated to Professor Leslie Hough in the year of his 65th birthday.
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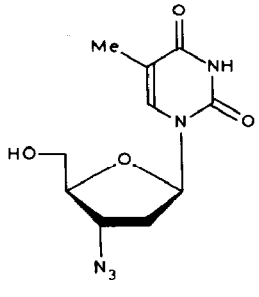
Reduction of this mixture was accomplished with disiamylborane[4], and subsequent acetylation provided one pure acetate (**8**) after chromatography (overall yield, ~65%). The anomeric proton of **8** gave a singlet at δ 6.0.

Finally, reaction of **8** with 2,4-bis(trimethylsilyl)cytosine in dichloromethane, with slow addition of an equivalent of ethylaluminium dichloride ($EtAlCl_2$), yielded a ~1:1 mixture (37%) of the 5′-*O*-benzoylnucleoside analogues **9** and **10**. This mixture could not be resolved by chromatography, and it was treated with methanolic ammonia to provide the desired product **3** and the α anomer **11**, in essentially quantitative yield, which were isolated by chromatography. In the 400-MHz n.m.r. spectra of **3** and **11**, the most significant differences involved the resonances of methano hydrogens (δ 0.43 and 0.58 for the α anomer, and δ 0.31 and 0.91 for the β anomer), and for H-1′ (δ 6.07, d, J 2.8 Hz, for the α anomer, and δ 5.83, s, for the β anomer). In addition, there was a significant n.O.e. enhancement between H-1′ and H-2′,3′ for the α anomer, but no enhancement for the β anomer.

Following the completion of this work, an alternative synthesis of **3** was reported[5], and the n.m.r. data and $[\alpha]_D$ value are identical to those now recorded (no data for **11** were given[5]).

Preliminary biological evaluation of **3** showed that it exhibited only weak activity against HIV. The route described above should allow easy access to other 2′,3′-



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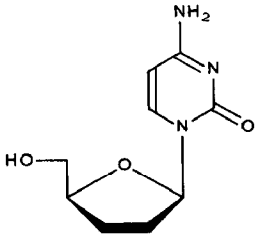

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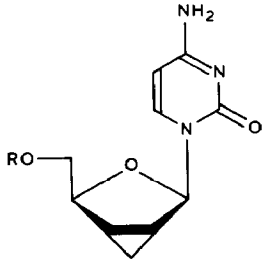

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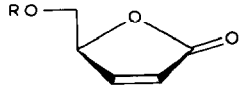
9 R = Bz



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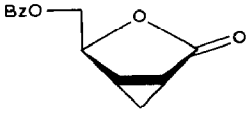

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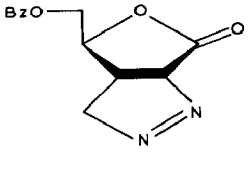

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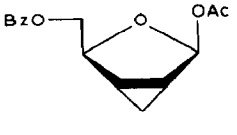

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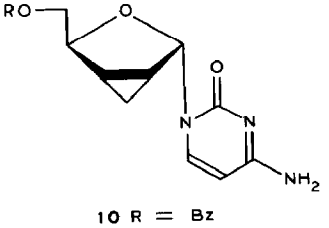

10 R = Bz
11 R = H

methano-nucleosides. In addition, the key intermediate **7** is functionalised appropriately for conversion into a range of cyclopropane-containing amino acids, which are of considerable contemporary interest[6], and we are working towards this goal.

EXPERIMENTAL

I.r. spectra were recorded for solutions in CH_2Cl_2 with a Perkin–Elmer 157 spectrophotometer. N.m.r. spectra (internal Me_4Si) were recorded with a Perkin–Elmer R34 (220 MHz) or Bruker WM400 (400 MHz) instrument (University of Warwick). Flash chromatography was performed using Merck silica gel (250–400 mesh); solvents were distilled from calcium hydride when required anhydrous; light petroleum refers to the fraction b.p. 40–60°.

(5S)-5-Benzoyloxymethyl-(5H)-furan-2-one (**5**). — To a solution of **4** (1.29 g, 11.3 mmol) in dry pyridine (30 mL) under nitrogen at 0° was added dropwise a solution of benzoyl chloride (1.0 equiv.) in CH_2Cl_2 (15 mL). The mixture was stirred for 1 h, the solvent was removed *in vacuo*, and a solution of the residue in chloroform (75 mL) was washed with saturated aqueous $NaHCO_3$ (3 × 25 mL), saturated aqueous $NaHSO_4$ (2 × 25 mL), and water (2 × 25 mL), dried ($MgSO_4$), and concentrated to dryness. The white crystalline solid (2.1 g, 85%) was recrystallised from ether to give **5**, m.p. 94.5°, $[\alpha]_D$ −125.5° (*c* 2.4, chloroform), R_F 0.37 (ether); ν_{max}^{KBr} 1770 (C=O, lactone), 1715 (C=O, ester), 1605 (C=C), 1590 (C=C, aryl) cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$, 220 MHz): δ 4.54 (d, 2 H, J_{gem} 4 Hz, CH_2OCO), 5.3 (m, 1 H, H-5), 6.15 (dd, 1 H, $J_{3,4}$ 6.5, $J_{3,5}$ 2 Hz, H-3), 7.3–8.0 (m, 6 H, ArH and H-4).

Anal. Calc. for $C_{12}H_{10}O_4$ (218.21): C, 66.05; H, 4.61. Found: C, 66.11; H, 4.54.

(1R,4S,5S)-4-Benzoyloxymethyl-3-oxa-7,8-diazabicyclo[3.3.0]oct-7-en-2-one (**6**). — A solution of **5** (1.67 g, 7.6 mmol) in the minimum amount of chloroform was treated with CH_2N_2 (~1.5 g) in ether (~120 mL) at 0° overnight (18 h). Filtration and evaporation *in vacuo* of the solvent yielded **6** as a white crystalline solid (1.76 g, 88%), m.p. 103°, R_F 0.22 (light petroleum–ethyl acetate, 4:1), 0.52 (light petroleum–ethyl acetate, 1:1); ν_{max}^{Nujol} 1770 (C=O, lactone), 1715 (C=O, ester), 1600 (C=C, aryl) cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$, 220 MHz); δ 2.96 (m, 1 H, H-5), 4.44 (m, 1 H, H-4), 4.54 (m, 2 H, CH_2OCO), 4.95 (m, 2 H, CH_2N), 5.70 (m, 1 H, H-1), 7.42–8.03 (m, 5 H, Ph).

Anal. Calc. for $C_{13}H_{12}N_2O_4$ (260.37): C, 59.99; H, 4.64; N, 10.76. Found: C, 59.96; H, 4.61; N, 10.64.

(1R,4S,5S)-4-Benzoyloxymethyl-3-oxabicyclo[3.1.0]hexan-2-one (**7**). — A 2% solution of **6** (1.6 g, 6.3 mmol) in dry 1:1 benzene–acetonitrile containing benzophenone (0.5 equiv.) as a photosensitiser was irradiated in a Pyrex apparatus (medium-pressure mercury lamp) for 2 h, then concentrated *in vacuo*. Flash chromatography (ether–ethyl acetate, 9:1) of the resulting yellow oil yielded **7**, isolated as a colourless oil (1.4 g, 94%), R_F 0.46 (ether–ethyl acetate, 9:1); ν_{max}^{Nujol} 1780 (C=O, lactone), 1710 (C=O, ester), and 1600 cm^{-1}. ^{1}H-N.m.r. data (220 MHz, $CDCl_3$): δ 0.93 (m, 1 H, *J* 3.3 and 4.7 Hz, H-6), 1.27 (m, 1 H, *J* 5.0 and 8.3 Hz, H-6), 2.14 (m, 1 H, H-5), 2.20 (m, 1 H, H-1), 4.45 (dd, 1 H, *J* 12.1 and 3.6 Hz, CH_2O), 4.59 (dd, 1 H, *J* 12.1 and 3.9 Hz, CH_2O), 4.66 (m, 1 H, H-4), 7.41–7.59 and 7.94–8.01 (2 m, 5 H, Ph).

Anal. Calc. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.20. Found: C, 67.27; H, 4.98.

1-O-Acetyl-5-O-benzoyl-2,3-dideoxy-2,3-methano-β-D-ribofuranose (**8**). — A 0.5M solution of disiamylborane in tetrahydrofuran (35 mL) was prepared by the slow addition of 2M 2-methyl-2-butene in tetrahydrofuran (17.5 mL) to M BH_3–tetrahydrofuran complex in tetrahydrofuran (17.5 mL) at −10° under nitrogen, and stirring was continued for 2 h at 0°. The lactone **7** (1.0 g, 4.3 mmol) was added in small portions and the mixture was stirred overnight at room temperature. Water was added slowly, the mixture was boiled under reflux for 30 min, then cooled to 0°, and aqueous 27% H_2O_2 (2 mL) was added dropwise, followed by adjustment of pH to 8–9 by addition of 2M NaOH. The mixture was concentrated under reduced pressure, the residue was extracted with chloroform, and the extract was dried (Na_2SO_4) and concentrated.

The resulting oily mixture was not purified further, but was dissolved in chloroform (15 mL) and stirred with acetic anhydride (2 mL), pyridine (3 mL), and 4-dimethylaminopyridine (10 mg) for 3 days. T.l.c. (light petroleum–ether, 1:4) showed transformation of the faster-running product into a slightly faster-running one. The mixture was concentrated under reduced pressure and the oily residue was subjected to flash chromatography (ether–light petroleum, 1:1 then 4:1) to afford acetate **8** (450 mg, 67% allowing for the **7** recovered), isolated as a white oil, and **7** (400 mg). Compound **8** had R_F 0.62 (ether–light petroleum, 4:1). ^{1}H-N.m.r. data (60 MHz, $CDCl_3$): δ 0.25 (t, 1 H, J 5 Hz, H-6), 0.8 (m, 1 H, H-6), 1.6–1.9 (m, 2 H, H-2,3), 1.9 (s, 3 H, COOMe), 4.3 (m, 3 H, H-4,5,5), 6.0 (s, 1 H, H-1), 7.3–8.1 (m, 5 H, Ph).

2',3'-Dideoxy-2',3'-methanocytidines (**3** and **11**). — To a solution of cytosine (280 mg, 2.5 mmol) in dry hexamethyldisilazane (2 mL) under nitrogen was added ammonium sulphate (10 mg). The mixture was boiled under reflux for 1 h, then allowed to cool to room temperature. The excess of hexamethyldisilazane was evaporated and the residue was dried by distillation of toluene therefrom. The resulting white solid was stored under vacuum.

A solution of **8** (650 mg, 2.5 mmol) in dry dichloromethane (8 mL) was added to the above bis(trimethylsilyl)cytidine derivative under nitrogen. A 1.8M solution of $EtAlCl_2$ in toluene (1.3 mL) was added dropwise to the mixture during 30 min and the temperature was maintained at 25°. The mixture was then stirred for a further 40 min at room temperature (a brown colour developed). T.l.c. (chloroform–2-propanol, 9:1) showed the rapid disappearance of **8**. The mixture was stirred with dichloromethane and saturated aqueous sodium hydrogencarbonate for 10 min at 0°, then filtered through Celite, and the organic layer was dried (Na_2SO_4) and concentrated. Flash chromatography (8–20% 2-propanol in $CHCl_3$) of the resulting oil yielded a semi-solid ~1:1 αβ-mixture (300 mg, 37%). A solution of this mixture in saturated methanolic ammonia (30 mL) was stirred for 24 h at room temperature, then the solvent was removed under reduced pressure. Flash chromatography (MeOH–$CHCl_3$, 1:3) of the resulting semi-solid gave the α anomer (30 mg) and an αβ-mixture (165 mg). This mixture was recrystallised from methanol–ether to afford (n.m.r. data) a solid 3:1 mixture of the β (**3**) and α anomer (**11**). Further flash chromatography of this enriched mixture afforded pure **3** (9 mg).

2′,3′-Dideoxy-2′,3′-α-methano-β-cytidine (**3**) had $[\alpha]_D^{20}$ −37° (*c* 0.16, methanol); lit[5]. $[\alpha]_D$ −36°. ^{1}H-N.m.r. data [400 MHz, $(CD_3)_2SO$]: δ 0.31 (dt, 1 H, *J* 4.3 and 4.1 Hz, H-6′), 0.91 (dt, 1 H, *J* 4.6 and 8.2 Hz, H-6′), 1.87 (m, 2 H, H-2′,3′), 3.40 (m, 2 H, H-5′,5′), 3.91 (t, 1 H, 5.8 Hz, H-4′), 4.97 (m, 1 H, OH), 5.70 (d, 1 H, *J* 7.4 Hz, H-5), 5.83 (s, 1 H, H-1′), 7.10 (bs, 1 H, NH), 7.16 (bs, 1 H, NH), 7.83 (d, 1 H, *J* 7.4 Hz, H-6).

Anal. Calc. for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82: Found: C, 53.87; H, 5.80; N, 18.75.

2′,3′-Dideoxy-2′,3′-α-methano-α-cytidine (**11**) had $[\alpha]_D^{20}$ −90° (*c* 0.3, methanol). ^{1}H-N.m.r. data [400 MHz, $(CD_3)_2SO$]: δ 0.43 (dt, 1 H, *J* 4.3 and 8.6 Hz, H-6′), 0.58 (dt, 1 H, *J* 5.1 and 7.8 Hz, H-6′). 1.67 (dt, 1 H *J* 3.3 and 7.4 Hz, H-3′), 2.00 (m, 1 H, H-4′), 3.46 (m, 1 H, H-5′,5′), 4.07 (t, 1 H, *J* 4.7 Hz, H-4′), 4.87 (m, 1 H, OH), 5.66 (d, 1 H, *J* 7.4 Hz, H-5), 6.07 (d, 1 H, *J* 2.8 Hz, H-1′), 7.03 (bs, 1 H, NH), 7.12 (bs, 1 H, NH), 7.59 (d, 1 H, *J* 7.4 Hz, H-6).

Anal. Found: C, 53.74; H, 5.90; N, 18.90.

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