Short Communication

Synthesis of a Phosphonomethyl Analogue of 3′-Deoxy-3′-fluorothymidine

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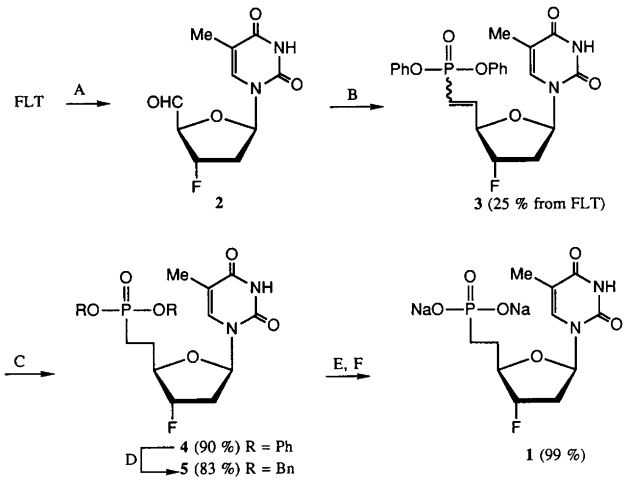
In a search for more potent therapeutic agents directed towards AIDS, 1-(2′,3′,5′,6′-tetradeoxy-3′-fluoro-6′-phosphono-β-D-*erythro*-hexofuranosyl)thymine (**1**) has been synthesized via a Wittig-type reaction between the 5′-aldehydo analogue of 1-(2′,3′-dideoxy-3′-fluoro-β-D-*erythro*-pentofuranosyl)thymine (FLT)[1,2] (**2**) and diphenyl triphenylphosphoranylidenemethyl phosphonate. FLT is a potent inhibitor of HIV *in vitro* and is currently undergoing clinical trials. FLT is phosphorylated by cellular kinases in three steps to give the triphosphate, FLT-TP, which is believed to be responsible for the anti-HIV activity of FLT. In the first phosphorylation step, the monophosphate FLT-MP is formed. In the present work a structural analogue ofg FLT-MP **1** has been synthesized as a potential anti-HIV agent.



Scheme 1. Reagents: A. DCC, pyridine, CF_3COOH, DMSO; B, diphenyl triphenylphosphoranylidenemethyl phosphonate; C, H_2/Pd–C; D, BnONa; E, H_2/Pd–C; F, NaOH/H_2O, lyophilisation.

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Results and discussion

In the synthesis (Scheme 1) of the isosteric phosphonic acid derivative of FLT-MP (**1**), FLT was oxidized in a Pfitzner–Moffatt reaction[3] using dicyclohexyl carbodiimide, pyridine, trifluoroacetic acid and dimethyl sulfoxide to give the 5′-aldehydo analogue of FLT (**2**). After filtration of the mixture, the aldehyde was reacted directly with diphenyl triphenylphosphoranylidenemethyl phosphonate[4,5] to give the Wittig product **3** in 25 % yield from FLT. Hydrogenation of the olefin with palladium on activated carbon in ethanol gave **4** in 90 % yield. Transesterification of **4** with sodium benzyloxide gave the dibenzyl ester **5** in 83 % yield. Hydrogenolysis of **5** using palladium on activated carbon in ethanol gave **1** in a quantitative yield.

Compound **1** showed no inhibition of HIV in an H9 cell system. A structurally related compound, 5′-*O*-(phosphonomethyl)-3′-deoxy-3′-fluorothymidine, has been reported as having a weak anti-HIV activity in a MT-4 cell system.[6]

Experimental

General methods. Evaporations were performed under diminished pressure (1–2 kPa) at a bath temperature not exceeding 40 °C. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. NMR spectra were recorded at 25 °C, with a Jeol GSX-270 instrument. Chemical shifts are given in ppm downfield from tetramethylsilane. NMR spectra for all compounds were in accordance with the postulated structures. Thin layer chromatography was carried out using precoated silica gel plates (F250 Merck) and the spots were visualized by UV light and/or charring with 8 % aqueous sulfuric acid. All reactions were monitored by TLC. Column chromatography was performed on silica gel 60 (0.04–0.063 mm Merck). The loadings were in the range 1/25–1/100. Organic phases were dried over anhydrous magnesium sulfate. The yields given below are for purified products.

*1-(2′,3′,5′,6′-Tetradeoxy-3′-fluoro-6′-diphenoxyphosphoryl-β-D-*erythro*-hex-5′-enofuranosyl)thymine* (**3**). To a stirred

solution of 1-(2′,3′-dideoxy-3′-fluoro-β-D-*erythro*-pentofuranosyl)thymine[1,2] (1.00 g, 4.10 mmol), dicyclohexyl carbodiimide (1.27 g, 6.15 mmol) and pyridine (0.17 ml, 2.05 mmol) in DMSO (9 ml) was added trifluoroacetic acid (79 µl, 0.455 mmol) at room temperature. After 19 h, the mixture was filtered and diphenyl triphenylphosphoranylidenemethyl phosphonate[4,5] (3.65 g, 7.17 mmol) was added. After 24 h, the mixture was poured into water (100 ml) and extracted with chloroform (3 × 30 ml). The organic layer was dried and concentrated. Column chromatography (ethyl acetate) yielded **3** (500 mg, 25 %) as a brown glass: ^{1}H NMR ($CDCl_3$) δ 2.0–2.7 (m, H-2′), 4.7 (dt, H-4′), 5.1 (dd, H-3′), 6.3 (m, H-1′ and H-6′), 6.9–7.4 (2 m, 2 Ph, H-5′ and H-6), 8.5 (br NH); ^{13}C NMR ($CDCl_3$) δ 11.2 (CH_3), 35.1 (d, C-2′, $J_{F,2'}$ 22 Hz), 82.9 (q, C-4′), 85.2 (C-1′), 93.5 (d, C-5′), 110.8 (C-5), 114.3, 119.7 (C-6′), 119.6–129.0 (Ph), 135.2 (C-6), 149.1 (C-2), 163.8 (C-4).

*1-(2′,3′,5′,6′-Tetradeoxy-3′-fluoro-6′-diphenoxyphosphoryl-β-D-*erythro-*hexofuranosyl)thymine* (**4**). A solution of compound **3** (0.20 g, 0.42 mmol) in ethanol (20 ml) containing 10 % palladium on activated carbon (60 mg) as the catalyst was hydrogenated for 6 h at atmospheric pressure. Removal of the catalyst by filtration and evaporation of the solvent yielded chromatographically homogeneous **4** (180 mg, 90 %) as a clear glass: $[\alpha]_D^{20}$ +17.3° (*c* 0.7, $CHCl_3$): ^{1}H NMR ($CDCl_3$) δ 1.8 (CH_3), 2.0–2.7 (m, H-6′, H-5′ and H-2′), 4.2 (d, H-4′), 5.1 (d, H-3′), 6.2 (d, H-1′), 7.1–7.4 (m, Ph and H-6).

*1-(6′-Dibenzyloxyphosphoryl-2′,3′,5′,6′-tetradeoxy-3′-fluoro-β-D-*erythro-*hexofuranosyl)thymine* (**5**). To a stirred solution of sodium hydride (70 mg, 3 mmol) in dry diethyl ether (4 ml) at room temperature was added benzyl alcohol (4.5 ml). After the evolution of hydrogen had stopped the ether was removed by evaporation. The resulting mixture was added dropwise to a stirred solution of **4** in benzyl alcohol (6 ml) at room temperature. After 3 h, TLC indicated that the reaction had gone to completion. The reaction mixture was subjected to column chromatography and eluted with diethyl ether (100 ml), diethyl ether–ethyl acetate (100 ml 1:1), ethyl acetate (200 ml), and ethyl acetate–methanol (200 ml 9:1) to yield **5** as a clear glass (159 mg, 83 %): $[\alpha]_D^{20}$ +16.3° (*c* 1.0, $CHCl_3$): ^{1}H NMR ($CDCl_3$) δ 1.7–2.1 (m, H-6′, H-5′ and CH_3), 2.6 (m, H-2′), 4.0 (d, H-4′), 4.8 (dd, H-3′), 4.9–5.1 (m, benzyl), 6.2 (m, H-1′), 7.0–7.3 (t, Ph and H-6), 8.4 (NH); ^{13}C NMR ($CDCl_3$) δ 11.6 (CH_3), 20.2 (C-6′, $J_{6'P}$ = 143 Hz), 25.1 (C-5′), 36.2 (C-2′, $J_{2'F}$ = 22 Hz), 66.4 (benzyl), 82.2 (q, C-4′, $J_{4'F}$ = 24 Hz, $J_{4'P}$ = 16 Hz), 92.3 (C-3′, $J_{3'F}$ = 18 Hz), 110.6 (C-5), 127.0 and 127.6 (Ph), 133.8 (C-6), 135.1 (Ph), 149.4 (C-2), 162.9 (C-4). Found: C 58.37; H 5.63; N 5.30. Calc. for $C_{25}H_{28}FN_2O_6P$: C 59.75; H 5.62; N 5.57.

*1-(2′,3′,5′,6′-Tetradeoxy-3′-fluoro-6′-phosphono-β-D-*erythro-*hexofuranosyl)thymine disodium salt* (**1**). A solution of compound **5** (0.111 g, 0.22 mmol) in ethanol (8 ml) containing 10 % palladium on activated carbon (40 mg) as the catalyst was hydrogenated for 3.5 h at atmospheric pressure. Removal of the catalyst by filtration and evaporation of solvent yielded **1** (74 mg, 99 %) as a clear glass. Water was added and the mixture was made basic by addition of 1 M sodium hydroxide. Purification of 10 % of the residue on a P2 column yielded **1** (7 mg, 94 %): $[\alpha]_D^{20}$ +4.0° (*c* 0.5, H_2O): ^{1}H NMR (D_2O) δ 1.6–1.9 (m, H-6′, H-5′ and CH_3), 2.5 (H-2′), 4.2 (H-4′), 5.2 (dd, H-5′), 6.3 (q, H-1′), 7.5 (H-6); ^{13}C NMR (CD_3OD) δ 12.8 (CH_3), 25.6 (C-6′), 28.2 (C-5′), 86.5 (C-4′, C-1′), 97.2 (C-5′), 112.6 (C-5), 136.8 (C-6), 152.1 (C-2), 166.3 (C-4). Anal. $C_{11}H_{14}FN_2Na_2O_6 \cdot H_2O$: C, H.

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