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Synthesis of 1,2-unsaturated pyranosylphosphonate nucleosides from 3,4,6-tri-*O*-acetyl-D-glycal

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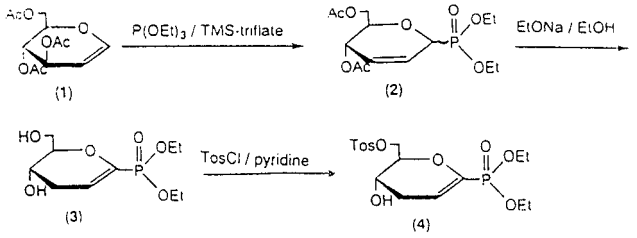
Ferrier rearrangement of 3,4,6-tri-*O*-acetyl-D-glucal (**1**) in the presence of triethylphosphite afforded the 2,3-unsaturated pyranose **2**. Deacetylation and simultaneous migration of the double bond to 1,2-position in the sugar moiety was achieved by stirring in sodium ethoxide. Tosylation with one equivalent of tosyl chloride afforded **4**. Nucleophile displacement of the tosylate of **4** with nucleobase in the presence of NaH/DMF followed by deprotection gave the desired 1,2-unsaturated pyranosylphosphonates **7a–c**.

1. Introduction

In the field of antiviral nucleoside synthesis a great deal of attention has been devoted to modifications of the sugar residue. Various nucleoside derivatives having double bonds between C-2 and C-3 of the sugar portions are known to have antibiotic activity [1, 2]. In HIV therapy, the main interest of unsaturated compounds has been focused on furanosyl nucleoside [3], whereas the interest in pyranosyl analogues has been stimulated by blasticiden S being a 2-enopyranosylcytosine with antibiotic and antitumoral activity [4]. A series of novel 1,2-unsaturated pyranosylphosphonates on which the purine or pyrimidine base was substituted at the 6-position have been prepared and evaluated as anti-HIV agents. The present paper deals with the synthesis of new 1,2-unsaturated pyranosylphosphonates which are cyclic nucleotide analogous of 9-[2-(phosphonylmethoxy)ethyl]adenine (PMEA) [5] and 1-[3-hydroxy-2-(phosphonomethoxy)propyl]adenine (HPMPA) [6].

Scheme 1



2. Investigations, results and discussion

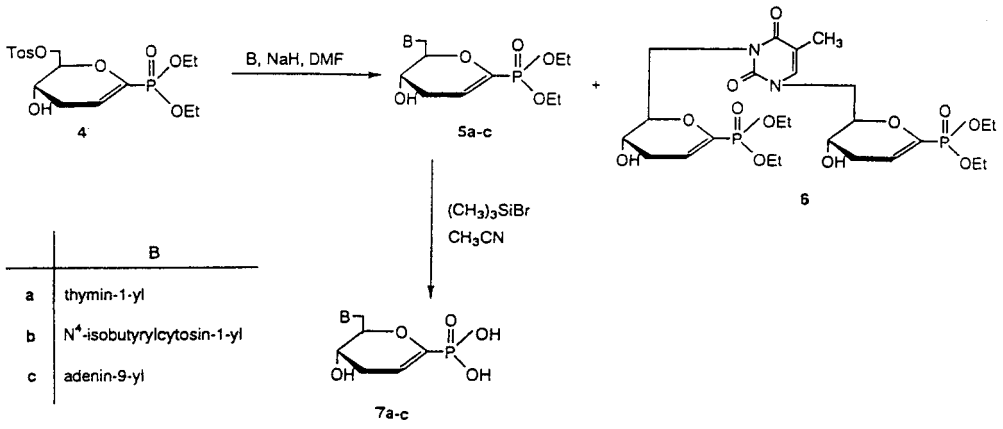
The conversion of 3,4,6-tri-*O*-acetyl-D-glycal (**1**) to diethyl 4,5-di-*O*-acetyl-2,3-dideoxyhex-1-enoyranosylphosphonate (**2**) via a Ferrier rearrangement has been described in the literature [7, 8]. Reaction of commercially available **1** with triethyl phosphite in the presence of trimethylsilyl trifluoromethanesulfonate (TMS-triflate) afforded the 2,3-unsaturated pyranose (**2**) in 92% yield as an approximately equal mixture of anomeres. Deacetylation of **2** with sodium ethoxide under simultaneous migration of the double bond in the sugar to the 1,2-position to give **3** in 79% yield. Subsequent selective tosylation of the primary hydroxy group of compound **3** affording diethyl 6-*O*-(*p*-toluenesulfonyl)-2,3-dideoxy-D-*erythro*-1-enopyranosyl-phosphonate (**4**) in 59.3% yield (Scheme 1).

Nucleophile displacement of the tosylate [9] of **4** with nucleobase/NaH in DMF afforded **5a–c** in 56% yield along with the 1,3-bis-alkylated nucleoside **6** in 34% yield. The phosphonate ester **5a–c** were cleaved with bromotrimethylsilane in the presence of lutidine and afforded the enopyranosylphosphoric acids **7a–c** after chromatographic purification (Scheme 2).

3. Experimental

NMR spectra were recorded on a Bruker 250 FT NMR spectrometer, TMS as internal standard. MS were recorded on a Varian Mat 311 A spectrometer. FAB MS were recorded on a Kratos MS-50 spectrometer. The silica gel (0.040–0.63 mm) used for CC was purchased from Merck. Analytical TLC was performed on precoated TLC sheets (Merck silica gel 60 F_{254} 0.2 mm). Results of elemental analyses were in an acceptable range.

Scheme 2



3.1. Diethyl 4,6-di-O-acetyl-2,3-dideoxy-α,β-D-erythro-hex-2-enopyranosylphosphonate (2)

3,4,6-Tri-*O*-acetyl-D-glycal (**1**, 2.72 g, 10 mmol) was dissolved in dry CH_2Cl_2 (40 ml), cooled to 0 °C. Freshly distilled $P(OE)_3$ (1.8 ml, 12 mmol) was added at 0 °C. TMS-triflate (1.4 ml, 11.6 mmol) was added dropwise under N_2 and the mixture was stirred at RT. After 5 h, analytical TLC showed disappearance of the starting glycal **1**. The reaction mixture was quenched with H_2O (2 ml) and diluted with EtOH (500 ml). The organic layer was washed with a cold saturated aqueous $NaHCO_3$ solution (200 ml), and cold saturated aqueous NaCl solution (200 ml), and dried over $MgSO_4$. The solvent was removed in vacuo and used in the next step without further purification. Yield: 3.23 g (92%); δ_H 2.07 ($\underline{CH_3}CO$), 3.68 (H-4), 4.20 (2 H-6), 4.64 (H-5), 5.21 (H-1), 5.91 (H-3), 6.03 (H-2); δ_C 72.41 (m, C-1), 124.80 (m, C-3), 126.67 (m, C-2), 170.05 (m, $CH_3\underline{CO}$); m/z (FAB) 351 ($M + H^+$)
$C_{14}H_{23}O_3P$\momega

3.2. Diethyl 2,3-dideoxy-D-erythro-hex-1-enopyranosylphonate (3)

Into the abs. EtOH (100 ml) solution, compound **2** (3.5 g, 10 mmol), and EtONa (50 ml, prepared from 0.4 g Na in 50 ml abs. EtOH) were added dropwise at 0 °C. The reaction mixture was stirred at room temperature. After 16 h, analytical TLC showed disappearance of the starting material. The mixture was neutralized with NH_4Cl, and the solvent was removed in vacuo. The residue was purified by chromatography on silica gel with CH_2Cl_2/MeOH (95.5, v/v) to obtain the title compound **3**; yield: 2.1 g (79%); δ_H 2.39 (H-3), 3.59 (H-4), 3.85 (2 H-6), 4.12 (H-5), 5.67 (H-2); δ_C 16.11 (d, J = 6.28 Hz, CH_3), 29.72 (d, J = 13.18 Hz, C-3), 61.48 (C-6), 62.75 (d, J = 1.26 Hz, C-4), 63.00 (d, J = 5.65 Hz, $\underline{CH_2}$), 80.47 (d, J = 27.63 Hz, C-5), 113.17 (d, J = 23.86 Hz, C-2); m/z (FAB) 267 ($M + H^+$).
$C_{10}H_{19}O_6P$

3.3. Diethyl 2,3-dideoxy-6-O-p-toluenesulfonyl-D-erythro-hex-1-enopyranosylphosphonate (4)

A stirred solution of compound **3** (2.66 g, 10 mmol) in dry pyridine (150 ml) was cooled to 0 °C and *p*-toluenesulphonyl chloride (1.9 g, 10 mmol) was added portionwise during 1 h. The reaction mixture was left overnight at 0 °C and for additional 24 h at RT. The pyridne was removed in vacuo and the residue purified by chromatography on silica gel with CH_2Cl_2/MeOH (95 : 5, v/v) to obtain the title compound **4**; yield: 2.91 g (59.3%). δ_H, 1.30 ($\underline{CH_3}CH_2O-$), 2.12 (H-3), 2.52 (CH_3-tosyl), 3.7 (H-4), 3.8 (2 H-6), 4.15 ($CH_3\underline{CH_2}O$), 4.40 (H-5), 5.79 (H-2), 7.33, 781 (2d, tosyl); δ_C, 29.83 (d, J = 13.18 Hz, C-3), 26.05 (d, J = 1.2 Hz, C-4), 68.19 (C-6), 77.42 (d, J = 8.79 Hz, C-5), 113.89 (d, J = 10.18 Hz, C-2), 143.73 (d, J = 172.07, C-1), 127.33–144.83 (tosyl); m/z (FAB) 421 ($M + H^+$).
$C_{17}H_{25}O_8PS$

3.4. Diethyl 2,3-dideoxy-6-(thymin-1-yl)-D-erythro-hex-1-enopyranosylphosphonate (5a) and the corresponding 1,3-bis-phophonate 6

A mixture of thymine (0.32 g, 2.5 mmol) and 50% oil-immersed sodium hydride (NaH 200 mg, 1.10 mmol) in dry DMF was stirred at 90 °C for 1 h under N_2 and cooled to RT. A solution of compound **4** (1.05 g, 2.5 mmol) in dry DMF (10 ml) was added dropwise during 1 h and the reaction mixture was stirred at 90 °C for 18 h. Analytical TLC (5% MeOH in CH_2Cl_2) showed two main products and some unchanged thymine. The mixture was neutralized with acetic acid, evaporated in vacuo, extracted with hot $CHCl_3$ and purified by chromatography on silica gel with CH_2Cl_2/MeOH (95-90 : 5-a0, v/v) to give the pure compounds **5a** and **6**.
5a: Yield: 0.535 g (58%); δ_H 1.90 (CH_3-thymine), 2.25 (H-3), 3.73 (H-5), 4.55 (H-4), 4.63 (H-6), 5.80 (H-2), 7.20 (H-6), 9.79 (NH); δ_C 28.92 (d, J = 13.18 Hz, C-3), 47.24 (C-4), 62.02 (C-6), 78.87 (d, J = 8.16 Hz, C-5), 111.12 (C-5), 114.49 (d, J = 23.86 Hz, C-2), 142.011 (C-6), 141.25 (d, J = 146.32 Hz, C-1), 152.90 (C-2), 164.10 (C-4); ^{31}P NMR δ 9.25; m/z (FAB) 375 ($M + H^+$).
$C_{15}H_{23}N_2O_2P$
6a: Yield: 0.32 g (34%) δ_H, 2.20 (H-3), 2.55 (H-4), 3.65 (H-6), 4.49 (H-5), 5.85 (H-2), 7.28 (H-6), δ_C 2.08 (CH_3-thymine), 29.30 (m, C-3), 41.0 (C-4), 49.48 (C-6), 79.26 (m, C-5), 109.32 (d, J = 23.86 Hz, C-2), 140.41 (C-6), 144.05 (m, C-1); m/z (FAB) 623 ($M + H^+$).
$C_{22}H_{40}N_2O_{12}P_2$

3.5. Diethyl 2,3-dideoxy-6-(N^4-isobutrylcytosin-1-yl)-D-erythro-hex-1-enopyranosylphosphonate (5b)

The same procedure as described for preparation of **5a** was used. Amounts used: N^4-isobutyrylcytosin (366 mg, 2 mmol), NaH (100 mg), anh. DMF (30 ml), compound **4** (420 mg, 1.0 mmol) in anh. DMF (20 ml). Reaction time: 18 h at 90 °C. After purification on silica gel CH_2Cl_2/MeOH (95-90 : 2-10; v/v) the title compound **5b** was obtained; yield 0.221 g (53%). δ_H 2.28 (H-3), 2.75 [$(CH_3)_2\underline{CH}$], 3.50 (H-4), 3.92 (H-6), 7.5 (H-5), 7.75 (H-6), 8.30 (H-5), 8.62 (H-2), 9.33 (NH); δ_C 28.51 (d, J = 27.63 Hz, C-3), 36.80 (C-4), 78.70 (d, J = 11.93 Hz, C-5), 150.67 (C-4), 141.42 (d, J = 192.78 Hz, C-1), 157.89 (C-5), 162.97 (C-6), 179.20 (C-2); ^{31}P NMR δ 9.22; m/z (FAB) 430 ($M + H^+$).
$C_{18}H_{28}N_3O_7P$

3.6. Diethyl 6-(adenin-9-yl)-2,3-dideoxy-D-erythro-hex-1-enopyrranosylphosphonate (5c)

The same procedure as described for the preparation **5a** was used. Amounts used: Adenin (165 mg, 1.25 mmol), NaH (100 mg), anh. DMF (20 ml), compound **4** (0.5 g, 1.35 mmol) in anh. DMF (10 ml). Reaction time: 18 h at 90 °C. After purification on silica gel CH_2Cl_2/MrOH (95-90 : 2-10; v/v) the title compound **5c** was obtained; yield 0.269 g (56%). δ_H 1.30 ($\underline{CH_3}CH_2O$), 2.25 (2 H-3), 3.15 (H-4), 4.01 ($CH_3\underline{CH_2}O$), 4.38 (H-6), 4.75 (H-5), 5.73 (H-2), 6.52 (NH), 7.85 (H-2), 8.30 (H-8); δ_C 29.12 (d, J = 13.19 Hz, C-3), 43.34 (C-4), 62.11 (d, J = 41.45 Hz, C-5), 62.55 (d, J = 4.40 Hz, C-6), 114.40 (d, J = 23.21 Hz, C-2), 141.85 (C-8), 146.28 (C-4), 152.75 (C-2); 155.90 (C-6); ^{31}P NMR δ 9.15; m/z (FAB) 384 ($M + H^+$).
$C_{15}H_{22}N_5O_5P$

3.7. 2,3-Dideoxy-6-(thymin-1-yl)-D-erythro-hex-1-enopyranosylphosphonic acid (7a)

A stirred solution of compound **5a** 100 mg in dry CH_3CN 10 ml was cooled to 0 °C and bromotrimethylsilane (0.75 ml, 5.8 mm) was added under N_2. The solvent was removed in vacuo, H_2O (5 ml) and pyridine (5 ml) were added to the residue and the mixture was stirred at RT for 1 h. The solvent was removed in vacuo and the crude pyridinnium salt was isolated and purified by ion exchange chromatography using Dewax to obtain the title compound **7a**; yield 0.073 g (86%). δ_H 1.72 (CH_3-thymine), 2.10 (H-3), 2.85 (H-4), 4.59 (H-6), 4.78 (H-5), 5.59 (H-2), 7.55 (H-6); δ_C 27.27 (d, J = 12.56 Hz, C-3), 76.63 (d, J = 57.78 Hz, C-5), 108.28 (d, J = 5.65 Hz, C-2), 110.43 (C-5), 143.30 (C-6), 150.72 (d, J = 22.60 Hz, C-1), 153.46 (C-2), 166.95 (C-4).
$C_{11}H_{15}N_2O_7P$

3.8. 2,3-Dideoxy-6-(N^4-isobutyrylcytosin-1-yl)-D-erythro-hex-1-enopyranosylphosphonic acid (7b)

The same procedure as described for preparation of **7a** was used. Amounts used: Compound **5b** (104 mg, 0.25 mmol) in 10 ml dry CH_2ClCH_2Cl, bromotrimethylsilane (1 ml, 7.7 mmol). Reaction time: 18 h at RT. H_2O and pyridine (4 ml, 2 ml). Reaction time: 1 h at RT. After Dewax ion exchange chromatography, the title compound **7b** was obtained; yield: 0.503 g (54%).
$C_{14}H_{20}N_3O_7P$

3.9. 6-(Adenin-9-yl)-2,3-dideoxy-D-erythro-hex-1-enopyranosylphosphonic acid (7c)

The same procedure as described for the preparation **7a** was used. Amounts used: Compound **5c** (200 mg, 0.5 mmol) in 10 ml dry CH_2ClCH_2Cl, bromotrimethylsilane (1 ml, 7.7 mmol). Reaction time: 18 h at RT. H_2O and pyridine (4 ml,. 3 ml). Reaction time: 1 h at RT. After Dewax ion exchange chromatography, the title compound **7c** was obtained: yield: 0.161 g (95%).
$C_{11}H_{14}N_5O_5P$

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