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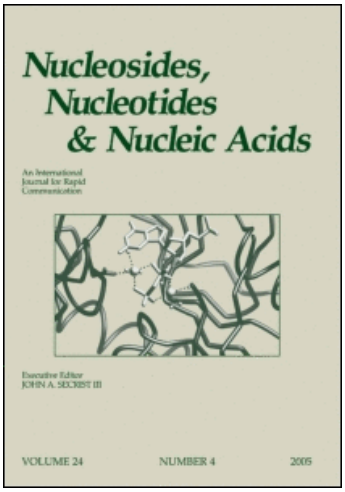

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The Bis-Trityl Route to (S)-HPMPA

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THE BIS-TRITYL ROUTE TO (S)-HPMPA

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Abstract. (S)-HPMPA, (S)-9-(3-hydroxy-2-phosphonyl)methoxypropyl)-adenine 1, a broad spectrum adenine nucleotide antiviral, was prepared from (S)-DHPA 2. Protection of (S)-DHPA 2 as its' N,O-di-trityl derivative 3 followed by regioselective 2'-O-alkylation with p-toluene-sulfonyloxymethyldiethylphosphonate yielded bis-trityl-protected diethyl-(S)-HPMPA 4. De-protection and ester cleavage gave (S)-HPMPA 1.

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(S)-HPMPA, (S)-9-(3-hydroxy-2-phosphonylmethoxy)propyladenine 1, is a novel phosphonate antiviral recently reported by De Clercq[2] and Holy.[3,4] (S)-HPMPA was found to be active against TK$^-$ herpesviruses, cytomegalovirus (CMV), and other DNA viruses.[2]

Recently, we communicated a convenient synthesis of this material.[5] In this note, we provide a full account of this synthetic route with experimental details.

The synthesis of 1 proceeds from (S)-DHPA ((S)-9-(2,3-dihydroxy)propyladenine 2).[6] Regioselective 2'-O-phosphonylation is accomplished simply by the use of the trityl protecting group.[7] (S)-DHPA 2 was heated at 80°C with 2.2 equivalents of chlorotri-phenylmethane in DMF. The reaction was judged complete in 12 hours (TLC), and the solution was then cooled, treated with methanol, filtered and concentrated in vacuo, and the crude bis-trityl-(S)-DHPA 3 was purified by chromatography over silica gel.[8]

The sodium salt of 3 (NaH/THF) alkylated smoothly with p-toluene-sulfonyloxymethyldiethylphosphonate[9] to furnish fully protected phosphonate 4, isolated in 90% yield.[10] The identity of 4 was unequivocally established by examination of the 360 MHz proton NMR spectra of 3 and 4. In addition, the ^{13}C NMR spectrum of 4 showed a

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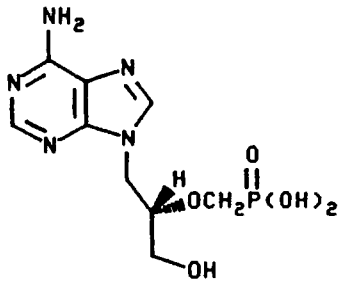

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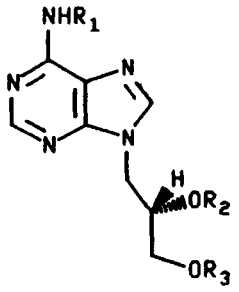

a ⌐ 2 : R_1, R_2, R_3 = H
  └→ 3 : R_1, R_3 = C(Phenyl)$_3$, R_2 = H
b ⌐
  └→ 4 : R_1, R_3 = C(Phenyl)$_3$, R_2 = $CH_2P(O)(OEt)_2$
c ⌐
  └→ 5 : R_1, R_3 = H, R_2 = $CH_2P(O)(OEt)_2$
d ⌐
  └→ 1

a: (Phenyl)$_3$CCl, DMF, NEt_3, 80C; b: NaH, THF, $TsOCH_2P(O)(OEt)_2$; c: AcOH, H_2O, 80C; d: bromotrimethylsilane, DMF.

through-bond coupling between C-2' and the phosphonate phosphorous of 4 Hz, indicating that 2'-O-alkylation had occurred.

The trityl groups were removed from 4 with 80% aqueous acetic acid (80°C, 1/2 h) to give diethyl-ester 5. The purification of 5 was effected by removal of the crystalline tritanol by-product by filtration, removal of the acetic acid and water by co-evaporation with ethanol and toluene, and recrystallization of the crude solid diethyl ester from ethanol/toluene to yield highly pure 5 in 89% yield. Crystalline (S)-HPMPA 1 was obtained directly by treatment of 5 with TMS-bromide[11] in DMF, evaporation to dryness, and crystallization of the residue from water and acetone. The (S)-HPMPA obtained could be recrystallized from aqueous ethanol thus obviating the need for chromatographic purification.[12]

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EXPERIMENTAL

Melting points were determined on an Electrothermal capillary apparatus and are uncorrected. TLC was performed on silica gel 60 F-254 plates purchased from E. Merck Co., and column chromatography was performed on flash silica gel (240-400 mesh, Baker). Elemental analyses were performed by the Analytical Research Department, Bristol-Myers, Wallingford. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 360 NMR spectrometer for protons at 360MHz and carbon-13 at 90MHz; chemical shifts are reported in parts per million. Tetrahydrofuran (THF) was distilled from sodium and benzophenone under nitrogen; N,N-dimethylformamide (DMF) was distilled from P_2O_5 under vacuum; HPLC grade acetone and bromotrimethylsilane were used as received.

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$\underline{N}^6$,3'-$\underline{O}$-Bis-(triphenyl)methyl-(S)-9-(2,3-dihydroxy)propyladenine (3)

A suspension of (S)-DHPA[6] (2, (S)-9-(2,3-dihydroxypropyl)adenine, 27.50 g, 0.131 mol) in dry dimethylformamide (200 mL) was treated with chlorotriphenylmethane (80.70 g, 0.289 mol) and triethylamine (92 mL, 0.655 mol), and the resulting mixture was heated at 80°C for 12 h. The dark orange solution was then cooled, filtered, and the filtrate concentrated at 70°C and 5mm Hg. The orange residue remaining was partitioned between ethyl acetate and water, and the combined ethyl acetate layers were dried over magnesium sulfate, and concentrated under reduced pressure. The oil remaining was chromatographed over SiO_2 eluting with 1:1 ethyl acetate/hexanes to yield 56.4 g (65%) of dityrityl-$\underline{S}$-DHPA (3) as a crisp orange foam. An analytical sample was obtained from CCL_4/hexane as a white solid: mp. 230-231°C; ^{1}H NMR ($CDCl_3$) δ7.39(s, 1H), 7.66(s, 1H), 7.27(m, complex, 30H), 7.08(brs, 1H), 4.41(d, B part, ABX, J=12Hz, 1H), 4.32(dd, A part, ABX, J=6, 12Hz, 1H), 4.15(m, 1H), 3.26(dd, J=6, 8Hz, 1H), 2.94(dd, J=8, 12Hz, 1H), 1.29(brs, 1H). Anal. ($C_{46}H_{39}N_5O_2$) C, H, N.

$\underline{N}^6$,3'-$\underline{O}$-Bis-(triphenyl)methyl-(S)-9-(3-hydroxy-2-(diethyl)-phosphonylmethoxy)propyladenine (4)

A solution of $\underline{N}^6$,3'-$\underline{O}$-bis-(triphenyl)methyl-(S)-9-(2,3-dihydroxy)-propyladenine (3, 9.12 g, 0.0137 mol) in dry THF (30 mL) was treated,

under argon, with sodium hydride (0.6 g, 0.0150 mol, 60% by weight dispersion in oil). The resulting yellowish-grey suspension was stirred for 15 minutes, then p-toluenesulfonyloxymethyldiethylphosphonate[10] (4.0 g, 0.0137 mol) dissolved in dry tetrahydrofuran (10 mL) was added. The resulting mixture was stirred for 14 h at room temperature under argon, at which time TLC analysis of the mixture indicated that the reaction was complete. Brine was then added, and the mixture extracted with ethyl acetate. The combined ethyl acetate layers were dried over magnesium sulfate, and concentrated under reduced pressure to yield 10.3 g (90%) of phosphonate (4) as a colorless foam. An analytical sample was obtained by chromatography over silica gel, eluting with ethyl acetate, and slow crystallization of the material obtained from ethyl acetate/hexane to yield a white solid: mp. 88-89°C; ^{1}H NMR ($CDCl_3$) δ7.97(s, 1H), 7.82(s, 1H), 7.28 (m, complex, 30H), 6.90(s, 1H), 4.38(dd, B part, ABX, J=3, 11Hz, 1H), 4.30(dd, A part, ABX, J=6, 11Hz, 1H), 3.94(3 overlapping m, complex, 6H), 3.62(dd, J=9, 11Hz, 1H), 3.16(dd, B part, ABq, J=3, 9Hz, 1H), 3.13(dd, A part, ABq, J=3, 9Hz, 1H), 1.25(t, J=6Hz, 3H), 1.17(t, J=6Hz, 3H); ^{13}C NMR($CDCl_3$) δ151.83, 148.90, 144.92, 143.28, 140.91, 128.86, 128.42, 127.75, 127.62, 127.07, 126.65, 120.33, 87.04, 79.49(d, C-2', $J_{C-O-C-P}$=4Hz), 71.21, 64.95-63.12(d, J_{C-P}=164Hz), 62.57, 62.22(d, J_{C-O-P}=4Hz), 44.55, 16.27. Anal. ($C_{51}H_{50}N_5O_5P$) C, H, N.

(S)-9-(3-hydroxy-2-(diethylphosphonyl)methoxy)propyladenine (5)

A solution of N^6,3'-O-bis-(triphenyl)methyl-(S)-9-(3-hydroxy-2-(diethylphosphonyl)methoxy)propyladenine (4, 2.00 g, 0.00236 mol) in 80% aqueous acetic acid (50 mL) was heated on a steam bath. After 1/2 h, TLC analysis indicated the reaction was complete. The solution was cooled to room temperature, and allowed to stand for 12 h. The crystalline tritanol that had formed was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was dried by co-evaporation with 4 successive volumes of absolute ethanol under reduced pressure, and finally with 2 volumes of toluene similarly. The solid remaining was recrystallized from ethanol/toluene to yield 0.754 g (89%) of diethyl-S-HPMPA (5) as a colorless crystalline solid: mp. 154-156°C; ^{1}H NMR($CDCl_3$) δ8.35(s, 1H), 7.90(s,1H), 5.80(brs, 2H), 4.80(dd, J=3, 8Hz, 1H), 4.42(m, 1H), 4.15(m, complex, 4H), 3.85(d,

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J=6Hz, 2H), 3.56(m, 2H), 3.40(m, complex, 2H), 1.25(2 overlapping t, 6H); ^{13}C NMR(DMSO-d_6) δ155.42, 152.27, 149.68, 118.68, 80.35 and 80.24(C-2', $J_{C-O-C-P}$=10Hz), 63.60(d, J_{C-P}=166.5Hz), 62.03(d, J_{C-O-P}=4.5Hz), 61.92(d, J_{C-O-P}=8.1Hz), 59.66, 43.19, 15.83. Anal. ($C_{13}H_{22}N_5O_5P$) C, H, N.

(S)-9-(3-Hydroxy-2-phosphonyl-methoxy)propyl adenine ((S)-HPMPA) (1)

A solution of diethyl-(S)-HPMPA (5, 1.00 g, 0.00278 mol) in dry DMF (10 mL) was treated under nitrogen with bromotrimethylsilane (4.0 mL, 0.0278 mol). After the resulting light yellow mixture had been allowed to stand for 3 hours at room temperature, the volatiles were removed at 60°C and 5mm. The residue remaining was dissolved in water (5 mL) and acetone (5 mL) by alternatively adding small quantities of each until complete dissolution had occurred. Acetone was then added until the solution turned cloudy (ca. 50 mL). The solution was then stored at -20°C for one hour. The solid that had formed was collected, washed with acetone and recrystallized from aqueous ethanol to yield 0.872 g (100%) of (S)-HPMPA (1) as a white solid: mp. 255-257°C. A second recrystallization from aqueous ethanol provided an analytical sample which proved to be a hemi-hydrate; ^1H NMR(DMSO-d_6) δ8.12(s, 1H), 8.10(s, 1H), 7.20(brs, 2H), 4.39(dd, B part, ABX, J=3, 12Hz, 1H), 4.17(dd, A part, ABX, J=6, 12Hz, 1H), 3.75(m, 5 lines, 1H), 3.60(m, complex, 2H), 3.38(m, complex, 2H), 3.30(brs, 3H); ^{13}C NMR(D_2O) δ156.07, 153.09, 149.64, 144.08, 118.66, 80.78(d, $J_{C-O-C-P}$= 11.25Hz), 69.01 and 67.97(d, J_{C-P}=153Hz), 61.15, 44.60; MS(FAB) m/z 304(M+H), 277, 241, 219, 185(P); UV(H_2O, pH7) λ_{max}260 (ε=14,191), UV(H_2O, pH2) λ_{max}260(ε= 17,702), UV(H_2O, pH12) λ_{max}262 (ε=11,170). Anal. ($C_9H_{14}H_5O_5P \cdot 1/2\ H_2O$) C, H, N.

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12. The (S)-HPMPA obtained was identical (^1H, ^{13}C) to a sample of 1 kindly provided us by Professor Antonin Holy.

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