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A CONVENIENT SYNTHESIS OF S-HPMPA

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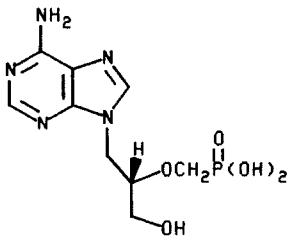
Summary. S-HPMPA, (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine **1**, a broad spectrum adenine nucleotide antiviral, has been synthesized in 4 steps from S-DHPA **2** (36% overall yield from adenine).

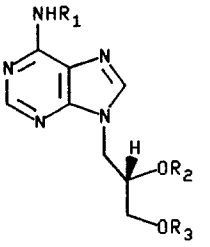
S-HPMPA, (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine **1**, is a broad spectrum nucleotide antiviral recently described by De Clercq.[1] While the synthesis of this compound was reported by Holy,[2] we needed a synthesis of **1** not requiring the separation of isomers or ion-exchange chromatography/de-salting, procedures deemed impractical on a large scale. The starting material for the synthesis was (S)-DHPA,[3] (S)-9-(2',3'-dihydroxypropyl)adenine **2**, prepared from adenine.[3] This compound was heated with 2.2 eq. of trityl chloride in DMF/NEt_3 to give a 65% yield of bis-N,O-dityrityl-(S)-DHPA **3**. The sodium salt of **3** (NaH/DMF) alkylated readily with (toluenesulfonyloxy)methyl-diethylphosphonate[4] to give phosphonate **4** in 90% yield after chromatography. Alkylation proceeded on oxygen as determined by examination of the 360 MHz proton spectra of **3** and **4**, in which all resonances and couplings were well resolved and unambiguously assigned.[5] Trityl group removal (80% aqueous acetic acid, 80C, 1/2 h) gave diethyl-S-HPMPA **5**[5] in 85% yield after chromatography. Treatment of **5** in DMF with TMS-bromide[6] was followed by evaporation to dryness, and the remaining residue was dissolved in H_2O/acetone. Further addition of acetone and subsequent storage at -20C gave a quantitative yield of crystalline (S)-HPMPA **1**. The structure of **1** was unequivocally established by 360 MHz proton NMR.[5]

This convenient alternative synthesis of S-HPMPA **1** involves 6 steps, proceeds in 36% overall yield from adenine, and provides distinct ad-

Scheme I



1



2 : R_1, R_2, R_3 = H

3 : R_2 = H; R_1, R_3 = -C(phenyl)$_3$

4 : R_2 = $-CH_2P(O)(OEt)_2$;
R_1, R_3 = -C(phenyl)$_3$

5 : R_2 = $-CH_2P(O)(OEt)_2$; R_1, R_3 = H

vantages: it does not require isomer separations, ion-exchange chromatography or de-salting isolation procedures, and it provides ready access to **1** on a large scale.

References

1. DeClercq, E.; Holy, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P. **Nature 1986**, 323, 464.
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3. Holy, A. **Collect. Czech. Chem. Comm. 1975**, 40, 187; Holy, A. **Ibid 1978**, 43, 3103.
4. Holy, A.; Rosenberg, I. **Collect. Czech. Chem. Comm. 1982**, 47, 3447; Kluge, A.F. **Org. Syn. 1985**, 64, 80-84.
5. Compounds 3-5 all gave satisfactory analytical data (^{1}H NMR, ^{13}C, etc.) including elemental analyses. Complete experimental details will be given in a full paper.
6. McKenna, C.E.; Schmidhauser, J. **J.C.S. Chem. Comm. 1979**, 739; see also **reference 4**.

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