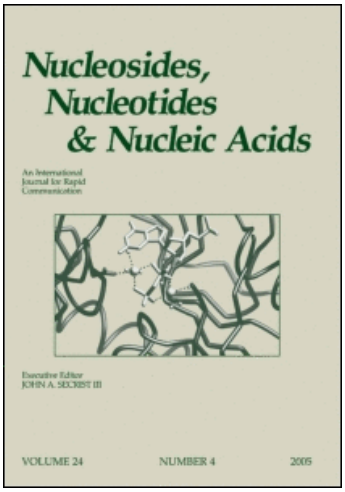

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PHOSPHONATE ISOSTERES OF 2',3'-DIDEHYDRO-2,3-DIDEOXYNUCLEOSIDE MONOPHOSPHATES: SYNTHESIS AND ANTI-HIV ACTIVITY

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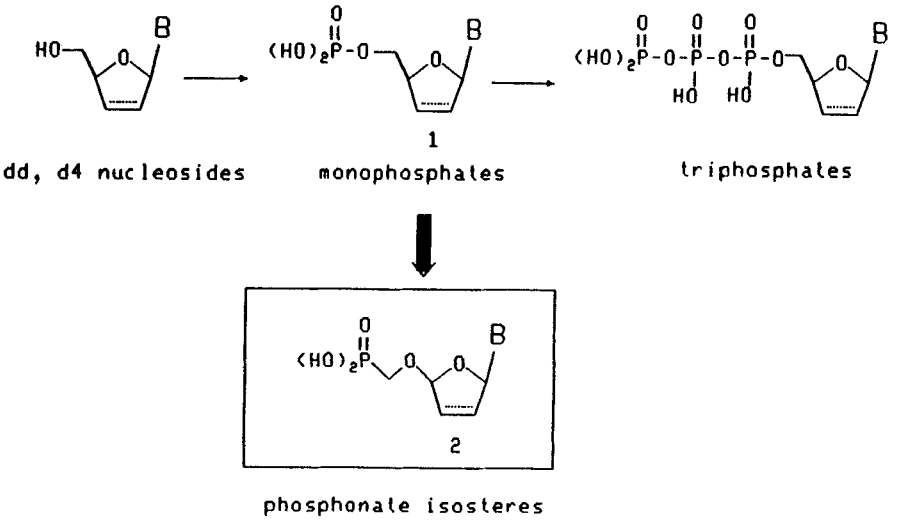
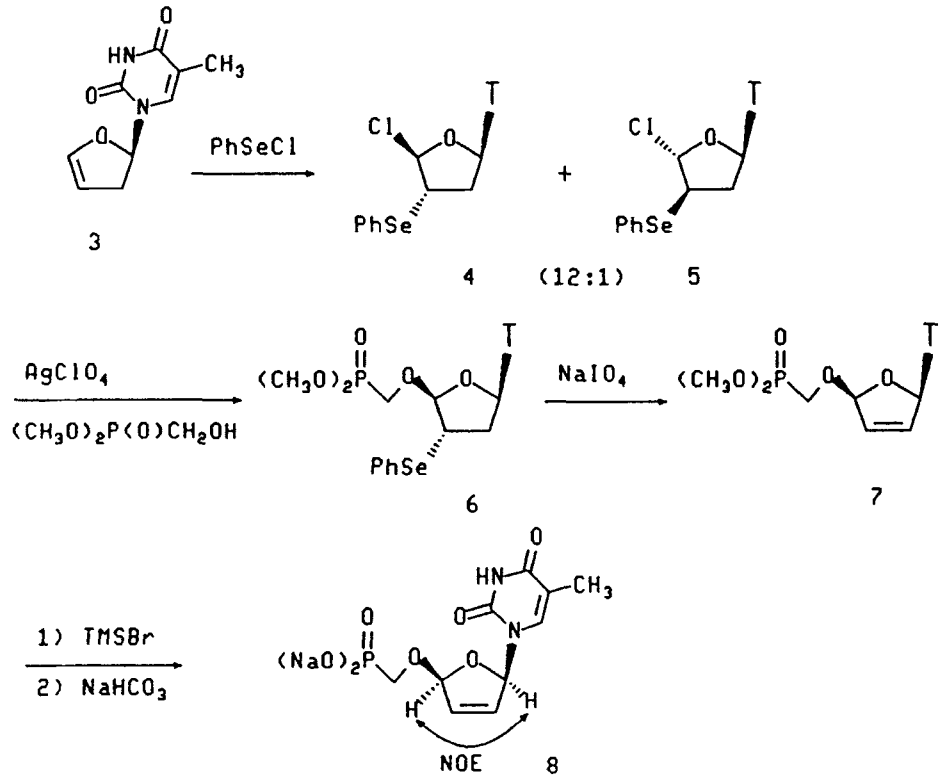
Abstract: Phosphonate analogues of d4T and d4A monophosphates have been synthesized using stereocontrolled addition of dimethyl hydroxymethylphosphonate to furanoid glycals. The new phosphonates exhibited a potent activity against HIV.

A number of 2',3'-dideoxy (dd) and 2',3'-didehydro-2',3'-dideoxy (d4) nucleosides have been shown to inhibit in vitro HIV-induced cytopathogenicity. Several of these compounds, such as ddI[1], ddC[2] and d4T[3] are currently in clinical trial. These compounds, as their 5'-triphosphates, inhibit HIV reverse transcriptase by competing with the natural substrate at the same binding site on the enzyme[4]. One logical



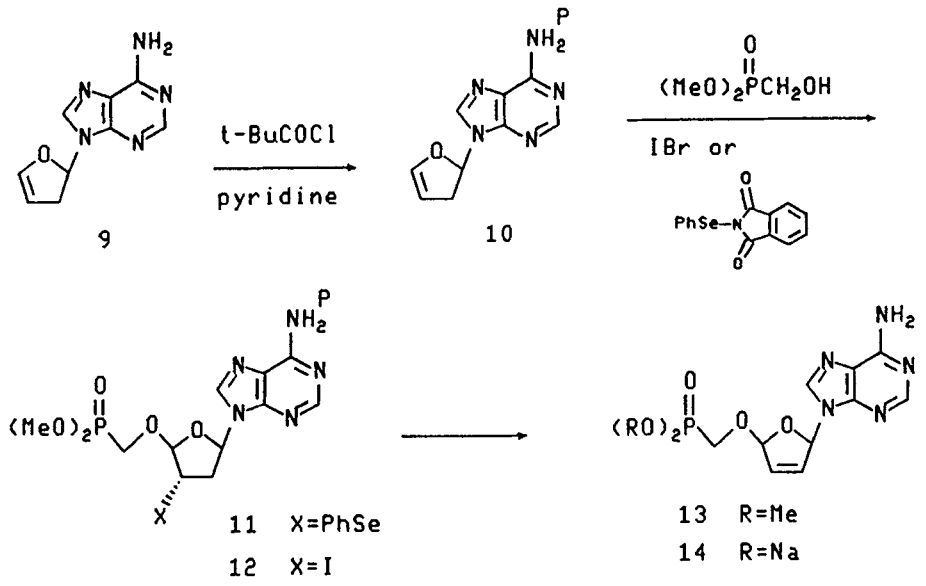
Scheme I



Scheme II

approach to the discovery of new and potent HIV inhibitors involves the design of phosphonate analogues where the phosphate moiety is changed to isosteric and isoelectronic phosphonates. Those enzymatically and chemically stable phosphonate analogues, which mimic the nucleoside monophosphates, bypass the initial enzymatic phosphorylation and could potentially be more effective antiviral agents against HIV. Taking into account that the phosphonomethoxy functionality (P-C-O) would be the closest chemical equivalent of the phosphonooxymethyl (P-O-C) of the phosphate, the new phosphonates 2 have emerged as the most promising isosteres of the monophosphates 1 (Scheme I).

The synthesis of 8, the phosphonate isostere of d4T monophosphate was carried out as shown in Scheme II. When the glycal 3[5] was reacted with phenylselenyl chloride at -70°C, a 12:1 mixture of 4 and 5 was



Scheme III

obtained in high yield. Treatment of this mixture with silver perchlorate in the presence of dimethyl hydroxymethylphosphonate[6] afforded the phosphonate 6 in 41% overall yield. Assignment of the relative stereochemistry in 6 was based on mechanistic considerations. The phosphonate 6 was transformed into the d4T phosphonate analogue 8 by the sequence (1) oxidation with sodium periodate in methanol to generate the olefin 7, and (2) removal of the phosphonate ester by treatment with bromotrimethylsilane in DMF followed by neutralization with sodium bicarbonate in overall 52% yield. The cis configuration in 8 is consistent with the NOE enhancement for the 5-H proton upon irradiation of the 2-H.

The chemistry now developed was next applied to the purine series. For this purpose, the glycal 9[5] was prepared from 2'-deoxyadenosine by the procedure analogous to that described for synthesis of the glycal 3. As illustrated in Scheme III, the (dimethylphosphono)methoxy functionality was directly introduced to the glycal 10 with the aid of N-

Table I. Antiretroviral and Anticellular Activities of the Cyclic Phosphonates in Tissue Culture

		ID_{50} (μM)	
Virus or Cell	8	14	d4T
R-MuLV[a]	0.6	0.003	2.5
HIV-1[b]	12.0	1.5	1.2
MT-4 cells[c]	>600	>600	>600

a) Rauscher-murine Leukemia virus: The R-MuLV in vitro assay was performed according to the published procedure, Rowe: et al. Virology 1970, 42 1136.

b) Fifty percent effective dose required to protect 50% of the HIV-1 infected MT-4 cells against cytopathcity following a 5-day incubation period in the presence of the compound.

c) Fifty percent cytotoxic dose.

(phenylseleno)phthalimide or iodine bromide to give 11 (65%) or 12 (95%) in a regiospecific and a highly stereoselective manner. Oxidative elimination of the phenylselenyl group in 11 or base (DBU) promoted elimination of hydrogen iodide in 12 gave rise to the olefin 13 in high yield. The deblocking of protecting groups in 13 in a similar manner described for conversion of 7 to 8 produced 14, which is a phosphonate isostere of d4A monophosphate.

The phosphonate analogues 8 and 14 prepared in this study were evaluated for their inhibitory effect on the replication of retroviruses, including Rauscher-murine leukemia virus (R-MuLV) and human immunodeficiency virus-1 (HIV-1). As seen in Table I, both 8 and 14 exerted very potent inhibition of HIV-induced cytopathogenicity in MT04 cells comparable to that of d4T without any sign of cytotoxicity up to 600 μM. Furthermore, compound 14 was superior to d4T in inhibiting R-MuLV at 3 orders magnitude low concentration, indicating that the murine model might be useful to evaluate 14 for its in vivo efficacy against the retrovirus. The finding obtained here for 8 and 14 suggests that these compounds are worthy of further biological evaluation for their potential as anti-HIV drugs.

REFERENCES

1) Yarchoan, R.; Mitsuya, H.; Thomas, R. V.; Pluda, J. M.; Hartman, N. R.; Perno, C.-F.; Marczyk, K. S.; Allain, J.-P.; Johns, D. G.; Broder, S. Science 1989, 245, 412.

2) Mitsuya, H.; Broder, S. Proc. Natl. Acad. Sci. U.S.A. 1986, 83, 1911.

3) (a) Lin, T. S.; Schinazi, R. F.; Prusoff, W. H. Biochem. Pharmacol. 1987, 36, 2713. (b) Mansuri, M. M.; Starrett, J. E.; Ghazzouli, I.; Hitchcock, M. J. M.; Sterzycki, R. Z.; Brankovan, V.; Lin T. S.; August, E. M.; Prusoff, W. H.; Sommadossi, J.-P.; Martin, J. C. J. Med. Chem. 1989, 32, 461.

4) De Clercq, E. J. Antimicrob. Chemother. Suppl. A 1989, 23, 35.

5) Zemlicka, J; Gasser, R.; Friesler, J. V.; Horwitz, J. P. J. Am. Chem. Soc. 1972, 94, 3213.

6) Phillion, D. P.; Andrew, S. S. Tetrahedron Lett. 1986, 27, 1477.