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SYNTHESIS AND HIV ACTIVITY OF PHOSPHONATE ISOSTERES OF D4T MONOPHOSPHATE

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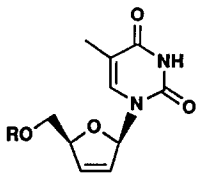
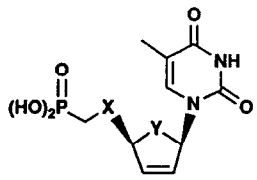
ABSTRACT: Two new phosphonate isosteres of d4T monophosphate have been prepared and tested against HIV.

2',3'-Didehydro-2',3'-dideoxythymidine (d4T, **1**) is an HIV reverse transcriptase (RT) inhibitor that is currently under investigation in human subjects for the treatment of AIDS.[2] Like many other nucleoside analogues, d4T does not directly exert antiviral activity, but rather is a prodrug of active phosphorylated metabolites which are formed by the action of various kinases in cells. Ultimately, the triphosphate of d4T is responsible for antiviral activity by acting as an inhibitor of HIV RT.[3] As part of a program to mimic nucleoside monophosphates, we have prepared the chemically and enzymatically stable phosphonate analogue **3** as an isostere of d4T monophosphate **2**.[4] The new cyclic phosphonate **3** has exhibited potent HIV activity (IC_{50} = 1.3 μM) without signs of cellular toxicity up to 600 μM in MT-4 cells.[4] For further studies on the structure-activity relationships (SAR) in this class of compounds, we have undertaken the synthesis of the related carba analogues **4** and **5**.



1 R = H

2 R = $P(O)(OH)_2$



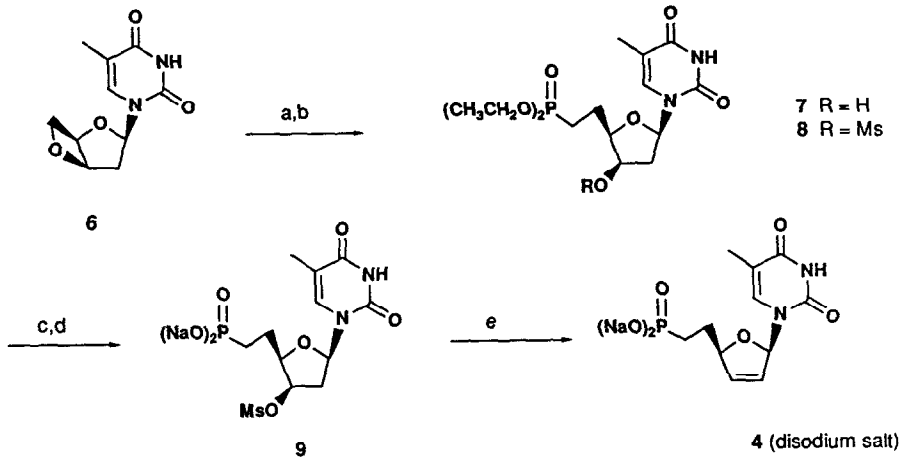
3 X = Y = O
4 X = CH_2, Y = O
5 X = O, Y = CH_2

As shown in Scheme I, the synthesis of **4** commenced with the phosphonate intermediate **7** which was obtained by the ring opening of oxetane **6** with the lithium anion of diethyl methylphosphonate according to the procedure of Tanaka and his co-workers.[5] Mesylation of **7** and deblocking of the phosphonate ester in **8** with trimethylsilylbromide in DMF followed by neutralization of the reaction mixture with sodium bicarbonate gave rise to phosphonic acid sodium salt **9**. This early removal of the phosphonate ester was crucial, because once the C_3-C_4 double bond of the furan ring was introduced, the resulting molecule was too acid labile for deblocking of the phosphonate ester. Elimination of the methanesulfonyl group in **9** with 1N NaOH at reflux provided **4** as a disodium salt.

The carbocyclic phosphonate derivative **5** was synthesized as outlined in Scheme II. The (+)-enantiomer of **5** was prepared since this isomer has the same configuration as naturally-occuring thymidine. Reaction of (+)-(1R, 4S)-cis-1-acetoxy-4-hydroxycyclopent-2-ene[6] with methoxyethoxymethyl chloride in the presence of diisopropylethylamine furnished ether **11**. Treatment of **11** with dimethylboronbromide then gave an intermediate bromomethyl ether which was used without isolation in an Arbuzov reaction with triethyl phosphite. The resulting phosphonate **12** was obtained in 76% yield. Introduction of the thymine base was accomplished using a palladium-mediated coupling[7] of allylic acetate **12** with the sodium salt of 4-O-methylthymine. This reaction proceeds with high regio- and stereoselectivity to give cyclopentene **13** in which the 4-O-methylthymine group is introduced cis and in a 1,4-relationship to the phosphonomethoxy group. Acidic hydrolysis of the 4-O-methylthymine moiety followed by cleavage of the phosphonate esters with trimethylsilyl bromide in DMF afforded the target phosphonic acid **5**.

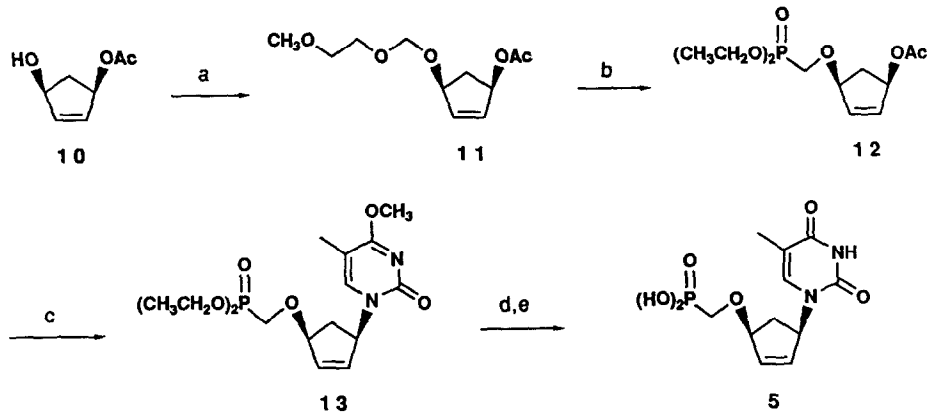
Of three phosphonate isosteres **3**, **4**, and **5** of d4T monophosphate (**2**), only **3** exhibited potent antiviral activity against HIV comparable to **1** (Table I). The lack of antiviral activity found for **4** is consistent with our earlier observation that the β oxygen atom from the phosphorous atom in the acyclic chain plays a critical role for antiherpesvirus and antiretrovirus activity.[8] Lack of HIV activity observed for carba analogues **4** and **5** may be due to the inability of cellular or virally-induced kinases to catalyse their conversions to the mono- and diphosphate forms. Alternatively, the respective diphosphates, if formed, may be poor inhibitors of HIV reverse transcriptase.

Scheme I



(a) $LiCH_2P(O)(OCH_2CH_3)_2$, $BF_3{\cdot}Et_2O$, THF, 23°C (75%); (b) CH_3SO_2Cl, $(CH_3CH_2)_3N$, CH_2Cl_2 (92%); (c) $(CH_3)_3SiBr$, DMF, 23°C; (d) aqueous $NaHCO_3$ (70%); (e) 1N NaOH, reflux (87%).

Scheme II



(a)$CH_3OCH_2CH_2OCH_2Cl$, (i-Pr)$_2$NEt, CH_2Cl_2, 0°C, (93%); (b) $(CH_3)_2BBr$, CH_2Cl_2, -78°C, then $(CH_3CH_2O)_3P$, -78°C to 23°C (76%); (c) 4-O-methylthymine, NaH, DMF, 23°C, then PPh_3, 12, and $Pd(PPh_3)_4$, 55°C (58%); (d) HCl, aqueous EtOH, 23°C (74%); (e) $(CH_3)_3SiBr$, DMF, 23°C (98%).

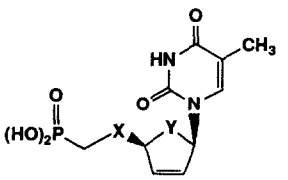


Table I

	IC_{50} (μM)[a]
1 (d4T)	1.2
3 X = Y = O	1.3
4 X = CH_2, Y = O	> 1000
5 X = O, Y = CH_2	> 1000

a: Concentration needed to inhibit HIV replication by 50% in MT-4 cells.

References and Notes

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9. All new compounds were fully characterized by the ir and ^{1}H NMR spectra, and gave satisfactory elementary analysis.