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SYNTHESIS AND ANTIVIRAL ACTIVITY OF ALKYLPHOSPHONIC ACID DERIVATIVES OF OXETANOCIN-A

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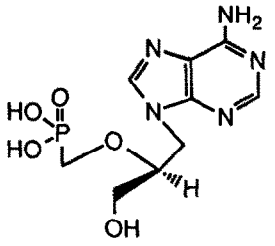
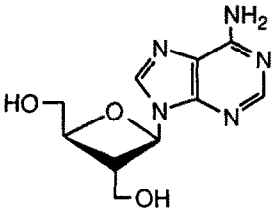
Abstract: A series of phosphonoalkyl derivatives of antiviral antibiotics oxetanocin-A **2** were synthesized and tested in vitro for anti-HSV-1, HSV-2, and anti-HIV-1 activity.

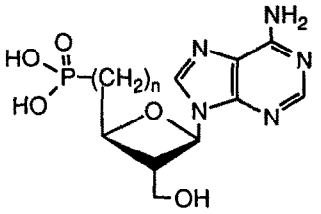
Interest has recently been growing in the discovery of new nucleoside compounds with potential antiretroviral activity, due to the significant medical problem associated with the treatment of the acquired immunodeficiency syndrome (AIDS). Since the discovery of the broad spectrum anti-DNA virus activity of (*S*)-HPMPA **1** by De Clercq and co-workers,[1] phosphonylated nucleoside analogs have attracted considerable interest. In continuation of our studies on the preparation and antiviral evaluation of the derivatives of unusual antiviral antibiotics oxetanocin-A **2**,[2] we set ourselves the target of preparing phosphonates of the type **3**. In this report the synthesis and antiviral activity of a series of alkylphosphonic acid derivatives **10**, **14**, **15**, and **22** are described.



1 (*S*)-HPMPA

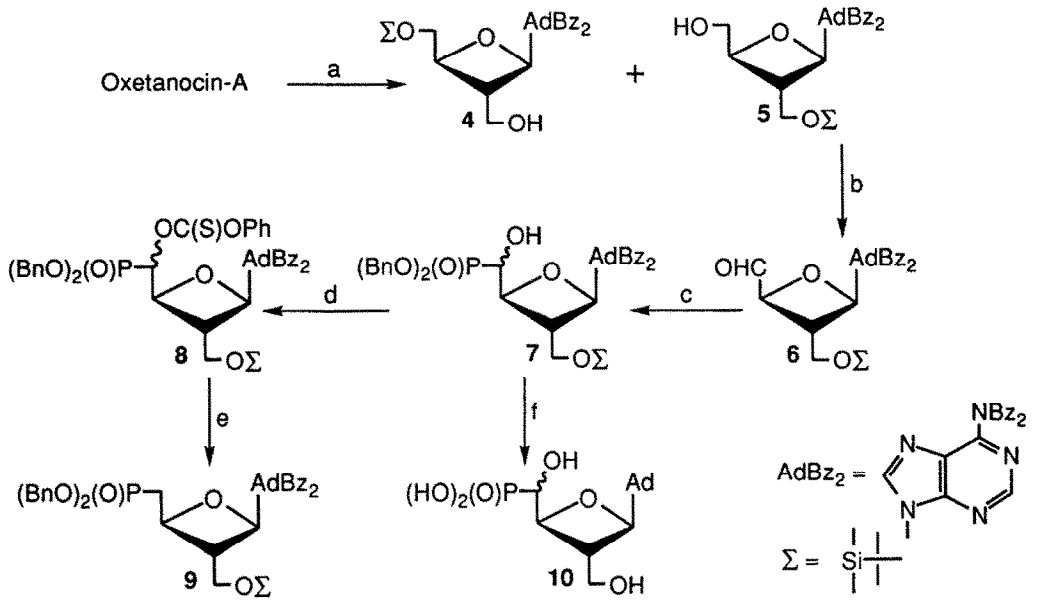


2 Oxetanocin-A



3 n = 1, 2, 3

As shown in Scheme 1, the common aldehyde intermediate **6** was prepared from oxetanocin-A **2** by a three-step process (1. TBDMSiCl→BzCl, 2.nBuNF, 3. Swern oxidation).[3] Treatment of **6** with dibenzyl phosphite under the basic NaH conditions in THF provided the phosphonate-alcohol **7** as a diastereoisomeric mixture in the ratio of ca. 5:1. No attempt was made to separate each isomer of **7** which was then subjected to a next step. The free secondary hydroxyl of **7** was deoxygenated in two steps using the procedure proposed by Barton.[4] Thus, reaction of **7** with phenyl chlorothionoformate mediated with NaH as a base gave the thionocarbonate **8**, which was then reduced to **9**. Unfortunately, several attempts of deprotection of **9** underwent extensive decomposition, producing only adenine (and/or N-benzoyladenine).[5,6] However, effective removal of the protecting groups of **7** was accomplished by sequential treatment with nBu_4NF, 35 % NH_4OH, and catalytic hydrogenation, providing the target compound **10** (**Scheme 1**).

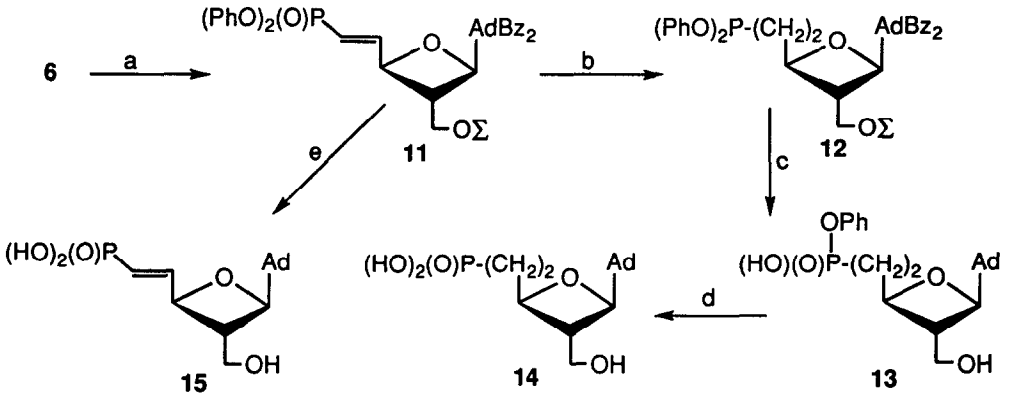


Scheme 1. *Reagents and Conditions*: (a) 1: 3.3 eq.TBDMSiCl, pyridine, rt, 17 hr, then 5 eq. BzCl, 0 °C→ rt, 4 hr, 98 %. 2: 0.6 eq.nBu_4NF, THF, 0 °C, 15min, 78 %, **4**/**5** = 1/10. (b) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C→ -30 °C, 1 hr, then Et_3N, 20 min, 98 %. (c) $(BnO)_2(O)PH$, NaH, THF, -30 °C, 1 hr, 65 %. (d) PhOC(S)Cl, NaH, THF, -30 °C, 20 min, 72 %. (e) nBu_3SnH, AIBN, benzene, refluxing temp., 45 min, 46 %. (f) 1: nBu_4NF, THF, rt, 14 hr. 2: 35% NH_4OH, MeOH, rt, 4 hr. 3: H_2, 10% Pd/C, 70% MeOH, rt, 10 min, 22 % in 3 steps.

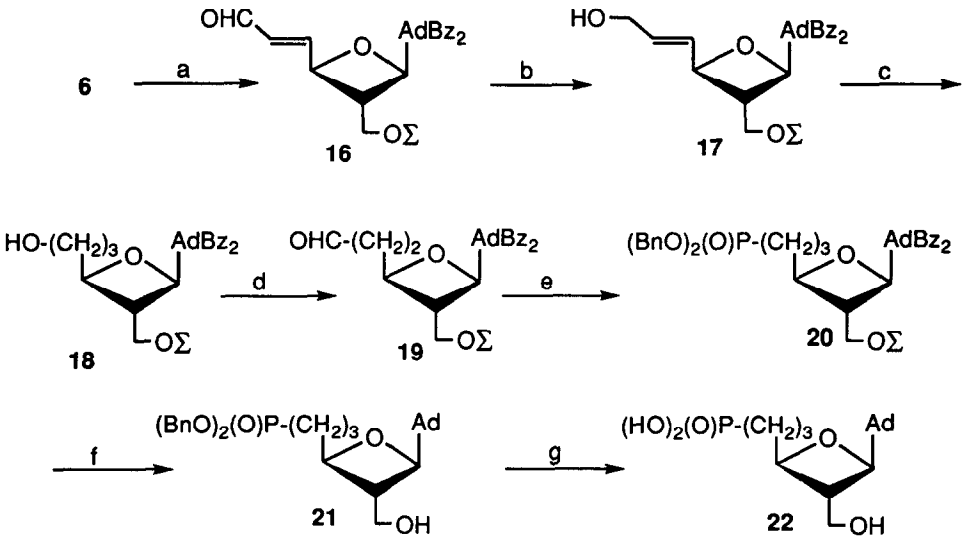
In order to obtain the phophonate **14**, **6** was reacted with diphenyl (triphenylphosphoranylidenemethyl) phosphonate [7] in benzene to give exclusively the (*E*)-phosphonate **11**. Catalytic hydrogenation of **11** followed by hydrolysis with 1N sodium hydroxide in dioxane/water gave the monophenyl ester **13**. Removal of the second phenyl group was achieved enzymatically with *Crotalus atrox* phosphodiesterase I [8] to give the target compound **14**. Synthesis of the 4', 5'-double bond analog **15** was directly accomplished by deblocking compound **11** with 2N sodium hydroxide in dioxane/water in low yield (10 % yield) (**Scheme 2**).

To obtain the phosphonate **22**, **6** was reacted with formylmethylenetriphenylphosphorane in benzene to give the (*E*)-aldehyde **16**. Compound **16** was readily converted to the aldehyde **19** by a three-step process (1. $NaBH_4$, 2. Catalytic hydrogenation, 3. Swern oxidation). Addition reaction of dibenzyl phosphite to **19** mediated with NaH and *in situ* phenoxythionocarbonylation of the intermediate, followed by deoxygenation under the same reaction conditions tried for compound **8** provided the phosphonate **20**. Finally, removal of the protecting groups of **20** was accomplished by sequential treatment with nBu_4NF, 35 % NH_4OH, and catalytic hydrogenation, giving the target compound **22** (**Scheme 3**).

Biological Activity: Evaluation of compounds **10**, **14**, **15**, and **22** [11] against HSV-1 and HSV-2 in Vero cells by a plaque reduction assay at concentrations up to 10 μg/ml, and HIV-1 in MT-4 cells by an indirect immunofluorescence assay at concentrations up to 100 μg/ml revealed these compounds to be devoid of antiviral activity and cytotoxicity.



Scheme 2. *Reagents and Conditions*: (a) Ph_3P=CHP(O)$(OPh)_2$, benzene, rt, 19 hr, 96 %. (b) H_2, 10% Pd/C, MeOH, rt, 7hr, 59 %. (c) 1N aq.NaOH, dioxane, rt, 13 hr, 72 %. (d) *C. atrox* phosphodiesterase I, Tris HCl buffer, 37 °C, 12 hr, 59 %. (e) 2N aq.NaOH, dioxane, rt, 2 hr, 10 %.



Scheme 3. *Reagents snd Conditions*: (a) Ph_3P=CHCHO, benzene, rt, 2.5 hr, 87 %. (b) $NaBH_4$, MeOH, -10 °C, 10 min, 69 %. (c) H_2, 10% Pd/C, EtOAc, rt, 20 hr, 58 %. (d) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C→ -40 °C, 30 min, then Et_3N, 20 min, 92 %. (e) 1: $(BnO)_2$(O)PH, NaH, THF, 0 °C, 1 hr, then PhOC(S)Cl, 0 °C, 10 min. 2: nBu_3SnH, AIBN, benzene, refluxing temp., 10 hr, 36 % in 3 steps. (f) 1: nBu_4NF, THF, 0 °C, 2.5 hr, 67 %. 2: 35% NH_4OH, MeOH, rt, 24 hr, 30 %. (g) H_2, 10 % Pd/C, MeOH, rt, 10 min, 85 %.

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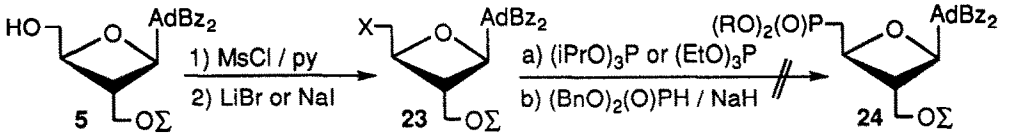
3. Initial attempts to synthesize the phosphonate **24** from **23** by an Arbuzof reaction with triethylphosphite and triisopropylphosphite [9] or by substitution reaction with the anion of dibenzyl phosphite (Michaelis-Becker reaction [10]) were unsuccessful (Scheme 4), the oxetane ring proving to be unstable to the elevated reaction temperatures and the increased amount of NaH.[5]

Scheme 4



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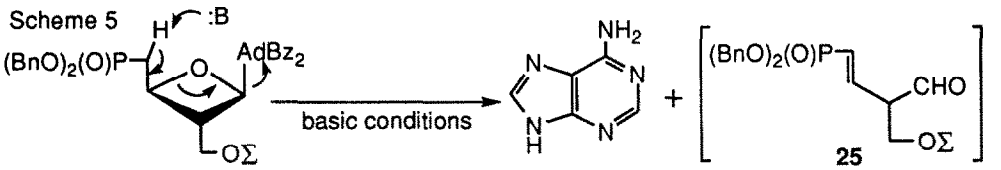
5. A possible mechanism for the release of the nucleic base adenine is given (Scheme 5): Under basic conditions required for deprotection, abstraction of a hydrogen atom from the active methylene adjacent to phosphonate group caused the breakdown of the fragile oxetane ring to afford adenine compound, but formation of **25** was not observed.

Scheme 5



Similar degradation reactions have been found in several publications.[12]

6. De-esterification of **9** with trimethylsilyl bromide failed because of the instability of the oxetane ring against Lewis acids.[13]
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11. All new compounds were finally purified using Sephadex DEAE-A25 and C_{18} reverse-phase silica gel (Cosmosil 75C_{18}-OPN®) chromatography, and a desalting apparatus (Micro-Acilyzer®), and gave satisfactory analytical and spectroscopic characteristics.
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