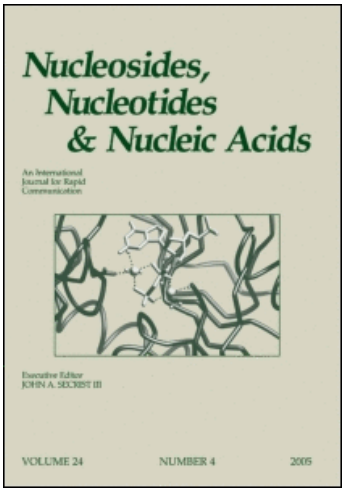

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SYNTHESIS OF β-HYDROXYPHOSPHONATE AND 1,2-DIHYDROXY ACYCLIC NUCLEOSIDE ANALOGS VIA 1,3-DIPOLAR CYCLOADDITION STRATEGY

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□ *A convenient synthetic approach toward nucleoside analogs where β-hydroxyphosphonate- or 1,2-dihydroxy units are connected to the nucleic acid base through a triazole spacer is discussed.*

Keywords Nucleoside analogs; triazole spacer; acyclic nucleoside phosphonates

INTRODUCTION

Synthesis of nucleoside analogs with biomimetically modified "sugar" or the "base" moieties is an area of tremendous interest due to their potential to target pathogens such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and cytomegalovirus (CMV).[1,2] Therapeutic effects from such molecules arise due to their interaction with targets like DNA polymerase, reverse transcriptase, or thymidine kinase. Nucleoside analogs with varying degrees of conformational flexibilities are known; important prototypes among these include: acyclic nucleoside phosphonates (ANPs) where the purine base is attached to the phosphonate unit via an acyclic linker,[1] analogs in which saturated,[3] unsaturated,[4,5] or fused[6] carbon rings replace the furanose moiety, those with spirocyclic restriction of furanose ring,[7] and the locked nucleoside analogs, which restricts the furanose ring to adopt either N-type or S-type puckering through appropriate intramolecular bridging.[8–10] ANPs, the structurally simplest among these, have emerged as one of the most important class with promising antiviral and cytostatic activities. Of these, 9-[2-(phosphonomethoxy)ethyl]adenine

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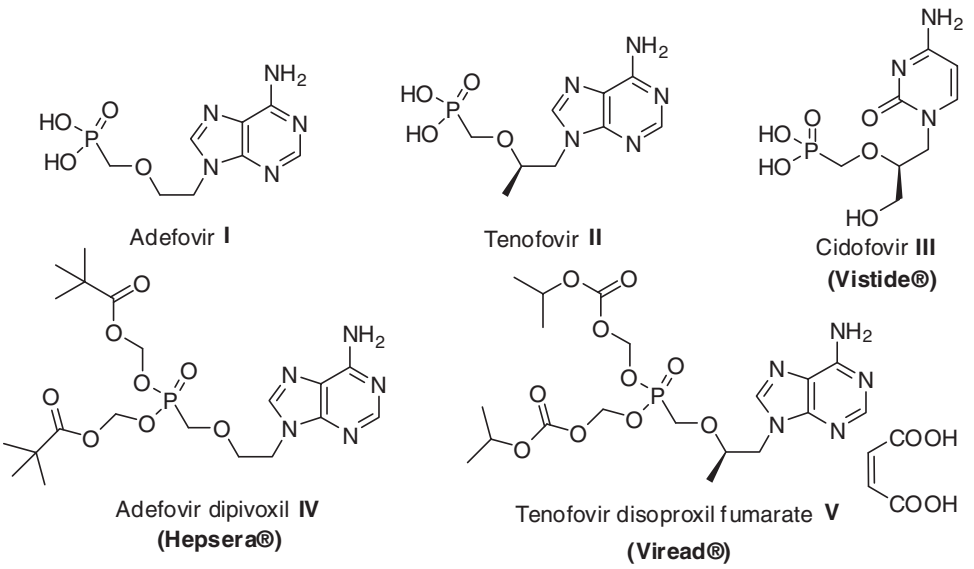


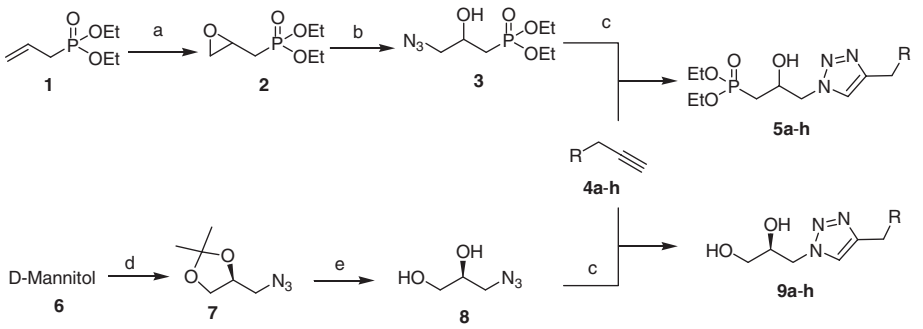
FIGURE 1 Examples of therapeutically important acyclic nucleoside analogs; Vistide, Hepsera, and Viread are marketed by Gilead Sciences, Inc., Foster City, CA, USA.

(PMEA, Adefovir) shows activity against DNA and retrovirus,[11] and its prodrug known as adefovir dipivoxil has been approved for hepatitis B treatment (Figure 1).[12]

Small modification in the linker region led to the development of tenofovir, and its prodrug, tenofovir disoproxil fumarate (Viread) is a useful anti-HIV agent.[13,14] Another clinically useful compound from this series is Cidofovir, which contains a hydroxymethyl group at 2-position of 2-(phosphonomethoxy)ethyl]cytosine.[15] A plethora of information on structure-activity relationships in ANPs is currently available[16,17] and there is still significant research interest in identifying new skeletons with correct balance of potency and selectivity. In this article, we report the synthesis and crystallographic structural details of a class of nucleoside analogs in which the terminal β-hydroxyphosphonate- or 1,2-dihydroxy groups and the nucleic acid bases are linked through a triazole spacer in place of the sugar ring.

RESULTS AND DISCUSSION

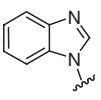
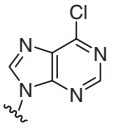
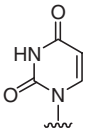
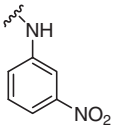
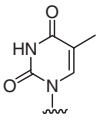
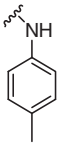
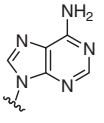
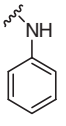
The synthesis of 1,2,3-triazole-based nucleoside analogs presented here commenced with the preparation of the azide component **3** by opening the epoxide ring in **2**.[18,19] This on Cu(I) catalyzed dipolar cycloaddition with N-propargylated benzimidazole (**4a**), pyrimidines (**4b**,**c**), purines (**4d**,**e**), and arylamines (**4f–h**) led to the formation of adducts **5a–h** in 62–98% yields (Scheme 1, Table 1).[20–22] Due to the lack of stereo-control during the epoxidation step, analogs **5a–h** were obtained as a mixture of enantiomers.

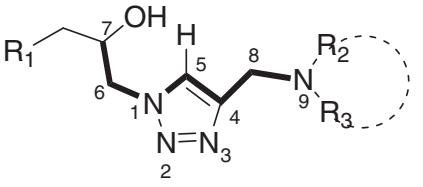


SCHEME 1 Synthesis of 1,2,3-triazole-based nucleoside analogs; R groups in **4a–h** correspond to the substituents (R) shown in Table 1. Reagents and conditions: (a) mCPBA, CH_2Cl_2, 0°C, 45%; (b) NaN_3, NH_4Cl, MeOH-H_2O (4:1), 80°C, 6 h, 89%; (c) $CuSO_4$ (5 mol%), Na-ascorbate (20 mol%), Ethanol-H_2O (2:1), rt; (d) (i) $ZnCl_2$, acetone, 18hrs, 35%; (ii) $NaIO_4$, $NaHCO_3$, CH_2Cl_2, 1hr; (iii) $NaBH_4$, ethanol, 0°C (59%, two steps); (iv) MsCl, Et_3N, 0°C, 2hrs, quantitative; (v) NaN_3, DMF, 90°C, 73%; (e) 20% TFA-CH_2Cl_2, 80%.

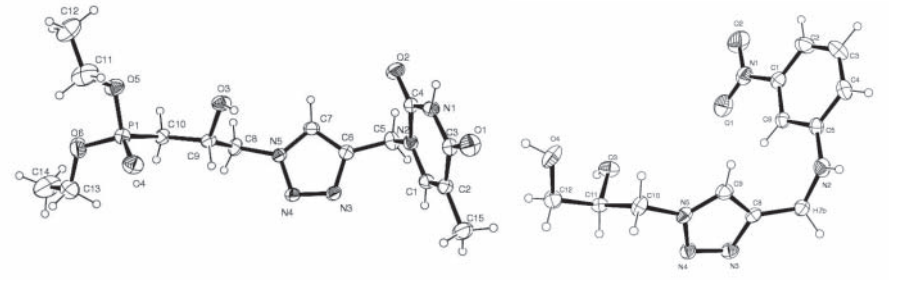
In order to prepare optically pure hydroxylated analogs, we redesigned the reaction sequence by including (D)-mannitol-derived isopropylidene-azide (**7**)[23] in the cycloaddition step to generate another series of nucleoside analogs **9a–h** in 67–92% yields.

TABLE 1 β-hydroxyphosphonate- and 1,2-dihydroxy nucleoside analogs prepared via dipolar cycloaddition strategy

R	Compounds	Reaction time (h)	% Yield	R	Compounds	Reaction time (h)	% Yield
	**5a**	26	62		**5e**	9	76
	9a	8	67		**9e**	6	73
	**5b**	9	78		**5f**	28	78
	9b	18	67		**9f**	27	92
	**5c**	30	98		**5g**	18	67
	9c	16	71		**9g**	12	83
	**5d**	10	81		**5h**	24	68
	9d	18	64		**9h**	10	81



Bond parameter	5c	9f
C7-N9 (A°)	6.32	6.581
C5-**N1-C6**-C7 (torsion)	–95.57	130.29
C5-**C4-C8**-N9 (torsion)	107.24	–3.60



5c **9f**

FIGURE 2 X-ray crystallographic structures and relevant details of compounds **5c** and **9f**.

Crystals suitable for x-ray diffraction studies were obtained by slow evaporation of a solution of compound **5c** in methanol. This belonged to the triclinic form under the space group P-1 with Z = 2. In the solid state, the molecule adopted a conformation with C7-N9 distance of 6.32 A°. The dihedral angles of −95.57° and 107.24°, respectively, across C5-**N1-C6**-C7 and C5-**C4-C8**-N9 bonds led to a syn-orientation of the thymine and phosphonate groups with respect to the central triazole ring as shown in Figure 2.

Although the dihydroxy-analogs from nucleic acid bases (**9a–e**) did not give crystals suitable for diffraction studies, we were successful in getting crystals of the nitro-derivative **9f** by slow evaporation of its chloroform solution. Molecules in this case, crystallized in rhombohedral form under the space group R3, had Z = 2. The C7-N9 distance in this case was 6.581 A°, a value very close to that observed in **5c**. The dihedral angles across C5-**N1-C6**-C7 and C5-**C4-C8**-N9 bonds were however notably different from that in **5c** (130.29° and −3.60°, respectively), which shows the greater conformational flexibility of the terminal moieties with respect to the triazole ring.

There have been a number of reports on the biological activities of phosphonate-based nucleoside analogs which carry chemically and enzymaticaly stable P-C linkage instead of P-O.[24,25] Herein, we have demonstrated a useful approach that can give such compounds in minimum number of reaction steps. Dipolar cycloaddition approach, particularly

that involving an azide and alkyne for preparing therapeutically important chemical entities is well documented in literature and has benefited the area of nucleoside analogs as well.[26] Lazrek et al., has previously adopted this method to prepare acyclic nucleoside analogs by reacting 4-azidobutyl acetate and 2-(azidomethoxy)ethyl acetate with propargylated nucleo-bases.[27,28] In the present work, we have explored the possibility of connecting β-hydroxyphosphonate and 1,2-dihydroxy units to the nucleic acid bases through the "click" protocol. X-ray diffraction studies involving crystals of **5c** and **9f** (CCDC numbers 749638 and 750866, respectively) have given useful information on the preferred orientations of terminal hydroxyl- or hydroxyphosphonate units and the nucleic acid bases with respect to the triazole ring. Biological activities of these phosphonates (as phosphonic acids)[17] and diols will be evaluated and reported in due course.

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