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Synthesis of C-4′Truncated Phosphonated Carbocyclic 2′-Oxa-3′-azanucleosides as Antiviral Agents

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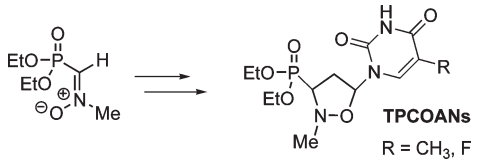

A new template of C-4′-truncated phosphonated nucleosides (TPCOANs) has been obtained in good yields according to two different routes which exploit the reactivity of a phosphonated nitrone. The one-step procedure based on the 1,3-dipolar cycloaddition of a phosphonated nitrone with vinyl nucleobases leads to the unnatural α-nucleosides as the main adducts. On the other hand, the target β-anomers have been obtained in high yield by a two-step procedure based on the 1,3-dipolar cycloaddition of a phosphonated nitrone with vinyl acetate followed by nucleosidation reaction. The reactivity of the phosphonated nitrone has been investigated trough quantum mechanical DFT calculations at the B3LYP/D95+(d,p) theory level. Preliminary biological assays show that β-anomers of TPCOANs are able to inhibit the reverse trancriptase of different retroviruses at concentrations in the nanomolar range, with a potency comparable with that of tenofovir.

Introduction

The introduction in chemotherapy of the phosphonated nucleosides cidofovir, tenofovir, and adefovir represents a turning point in the fight against viral infections.[1] Before their discovery, the collection of nucleoside analogues was limited to anti-HIV and anti-herpes agents.[2] The acyclic phosphonated nucleosides have been shown to be novel selective broad-spectrum anti-DNA virus agents, acquiring a prominent therapeutic position: (i) cidofovir[3] in the treatment of papilloma, herpes, adeno, and pox virus, (ii) adefovir[4] in the treatment of hepatitis B virus (HBV) infections, and (iii) tenofovir[5] in the treatment of retrovirus infections. New templates of both acyclic and cyclic phosphonated nucleosides have been intensively investigated in order to discover new lead compounds for extending the current spectrum of antiviral activity, avoiding some unwanted side effects.[6]

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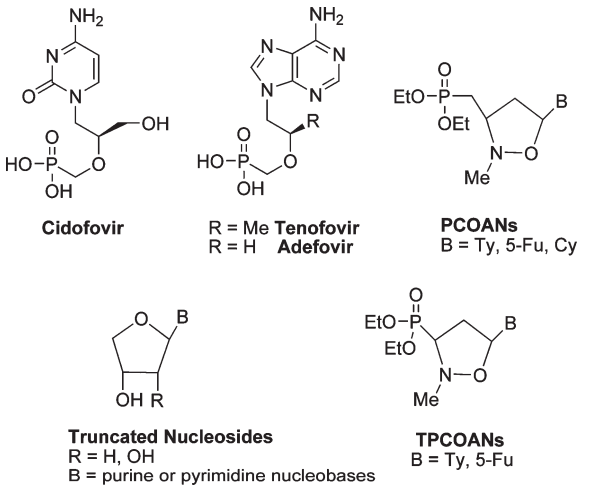

FIGURE 1. Phosphonated nucleosides and general structure of truncated nucleosides.

A phosphonated nucleoside is essentially a monophosphate nucleoside analogue where the monophosphate group is replaced by a phosphonic or alkylphosphonic acid residue, metabolically and chemically more stable.[7] The presence of a 5′-phosphonate group allows the reaction to overcome the first, inefficient, and often rate-limiting step of monophosphorylation in the conversion to 5′-triphosphate nucleotides.[8]

Recently, we have reported the synthesis of a new class of phosphonated nucleosides, the phosphonated carbocyclic 2′-oxa-3′-azanucleosides (PCOANs), which have been shown to be potent inhibitors of the reverse transcriptase of different retroviruses and have been proposed for ensuring a long last control of HTLV-1, an oncogen retrovirus associated with adult T-cell leukemia/lymphoma.[9] In our ongoing program, aimed to the discovery of new polymerase inhibitors, our interest was focused on the class of the truncated phosphonated carbocyclic 2′-oxa-3′-aza nucleosides (TPCOANs), where the phosphonate group is directly linked to the C-4′ position of the sugar moiety (Figure1).

Generally, truncated nucleosides, lacking of the C-4′ hydroxymethyl group, have been designed as anticancer agents[10] or as ligands of adenosine receptors,[11] while the antiviral activity is unexpected since they cannot turn into their triphosphate form, the substrate of the polymerase in the nucleic acid synthesis. The insertion of a phosphonic moiety allows the construction of compounds in which the first monophosphate group, mimed by the phosphonate moiety, is already present in the structure: thus, the biological antiviral effects could depend on the length of the chain linking the nucleic acid base to the phosphorus atom and, imperatively, from the presence in the chain of an heteroatom able to coordinate metal ions.[12] These considerations suggest that truncated phosphonated carbocyclic 2′-oxa-3′-aza nucleosides (TPCOANs) can be regarded as new potential antiviral agents, since the nitrogen atom in the isoxazolidine ring could be involved in metal ion coordination, with a role similar to that of ethereal oxygen present in the adefovir.

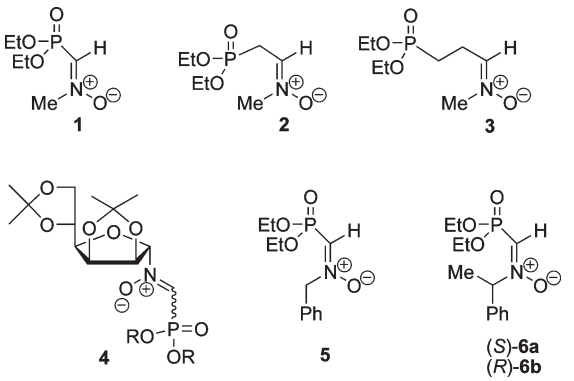

FIGURE 2. Known *C*-phosphonated nitrones.

Our target compounds, TPCOANs, were prepared by exploiting the 1,3-dipolar cycloaddition of the phosphonated nitrone **1**, following two different approaches:[13] the one-step procedure, which employs vinyl nucleobases as dipolarophiles, and the two-step procedure, where the cycloaddition with vinyl acetate is followed by Vorbrüggen nucleosidation. From these studies an outstanding reactivity of dipole **1** with respect to the other *C*-phosphonated nitrones **2** and **3** emerged (Figure 2).[7,9a,9b]

In this paper, we report the synthesis of the second generation of PCOANs, the TPCOANs, their preliminary biological evaluation, and the mechanistic considerations for the rationalization of the different reactivity of dipoles **1**−**3** in the 1,3-cycloaddition process.

Results and Discussion

1. One-Step Synthesis of TPCOANs. Truncated phosphonated carbocyclic 2′-oxa-3′-aza nucleosides **8a**,**b** and **9a**,**b** were synthesized by 1,3-dipolar cycloaddition of nitrone **1**, prepared from the commercially available diethyl hydroxymethyl phosphonate, as previously described.[14]

A study of the optimal experimental conditions in the one-step procedure, using equimolar amounts of nitrone **1** and the respective dipolarophile **7**, was carried out by employing dipolarophiles **7a** and **7b** under conventional heating or microwave irradiation (Scheme 1, Table 1, entries 1−4).

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SCHEME 1. One-Step Procedure

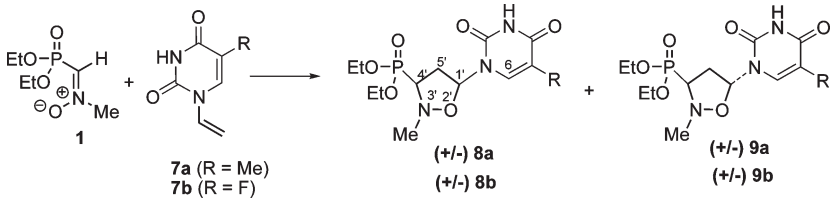

TABLE 1. Different Reaction Conditions for the One-Step Procedure

entry[a]	dipolarophile	conditions	**9**/**8** ratio	yield[b] (%)
1	**7a**	EtOH, reflux, 12 h	5:1	30
2	**7a**	CH_3CN, MW, 90 °C, 5 h, 100W	5:1	70
3	**7b**	EtOH, reflux, 12 h	5:1	35
4	**7b**	CH_3CN, MW, 90 °C, 5 h, 100W	5:1	73

[a]Molar ratio **7a**,**b**/**1** = 1:1. [b]Total yields, calculated by the conversion of vinyl nucleobases.

The reaction of nitrone **1** in refluxing ethanol proceeded slowly in moderate yield (entry 1). After switching to microwave irradiation, at 100 W for 5 h at 90 °C, an acceleration of the reaction time together with an increased yield was observed (entry 2). In both experiments, a 5:1 mixture of α- and β-anomers was obtained and the unreacted vinyl base was easily recovered. Compounds **8a** and **9a** were separated by flash chromatography, and the relative configurations were assigned on the basis of 2D NOE measurements.

The ^{1}H NMR spectrum of the major product **9a** shows the diagnostic resonances of H1′ at 6.07 ppm (dd), H4′ at 3.25 ppm (bm), H5′α at 2.60 ppm (dddd), H5′β at 3.00 ppm (bm), and H6 at 7.25 ppm (q). In the 2D NOE NMR spectrum of the isoxazolidine **9a**, positive signals were noticed between protons in the following pairs: H4′−H5′α and H1′−H5′β. These observations prove the *cis* relationship for H1′ and H5′β as well as H4′ and H5′α and thus allow for assigning the *trans* configuration between the diethoxyphosphoryl and thymine substituents in **9a**. The ^{1}H NMR spectrum of the minor isomer **8a** shows a different set of signals in comparison to **9a**. In particular, the H1′ proton resonates at 6.23 ppm (dd), H4′at 3.01 ppm (ddd), H5′β at 2.70 ppm (dddd), H5′α at 3.20 ppm (dddd), and the H6 appears as a quartet at 7.75 ppm. The positive NOE signals were observed within H1′−H5′α and H4′−H1′ pairs of protons and fully support the *cis* configuration of the substituents at C1′ (thymine) and C4′ (diethoxyphosphoryl) in the β-isomer **8a**.

Since values of all vicinal coupling constants were successfully extracted from the ^{1}H and ^{13}C NMR spectra of **8a** and **9a**, detailed conformational analyses of the isoxazolidines **8a** and **9a** were accomplished. On the basis of the vicinal couplings found for **8a** [J(C1′−C−C−P) = 10.6 Hz, J(H−C4′−C5′−Hβ) = 9.6 Hz, J(H−C4′−C5′−Hα) = 9.0 Hz, J(P−C4′−C5′−Hβ) = 17.1 Hz, J(P−C4′−C5′−Hα) = 4.8 Hz, J(H−C1′−C5′−Hα) = 7.8 Hz, J(H−C1′−C5′−Hβ) = 3.6 Hz], it was concluded that the isoxazolidine ring exists in an $E_{1'}$ conformation in which the thymine residue occupies the equatorial position while the diethoxyphosphoryl group is located pseudoequatorially (Figure 3). On the other hand, from vicinal couplings found for **9a** [J(C1′−C−C−P) = 10.2 Hz, J(H−C4′−C5′−Hβ) = 9.6 Hz, J(H−C4′−C5′−Hα) = 8.0 Hz, J(P−C4′−C5′−Hβ) = 16.8 Hz, J(P−C4′−C5′−Hα) = 6.8 Hz, J(H−C1′−C5′−Hα) = 3.9 Hz, J(H−C1′−C5′−Hβ) = 7.7 Hz], an $E_{4'}$ conformation is assigned for the isoxazolidine ring. In this conformation the diethoxyphosphoryl group occupies the equatorial position, whereas thymine substituent is pseudoaxialy oriented (Figure 3). Such disposition of the thymine group in the major isomer **9a** is a result of the additional stabilization by the anomeric effect.

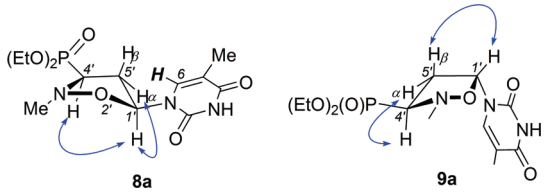

FIGURE 3. Preferred conformations of **8a** and **9a** together with 2D NOESY correlations.

Furthermore, a significant downfield shift of the H6 signal noticed in **8a** (δ ^{1}H = 7.75 ppm) as compared to the signal of the same proton in **9a** (δ ^{1}H = 7.25 ppm) may be attributed to the deshielding effect of the P═O group. This effect, higher in TPCOANs (0.5 ppm), is lower in the superior homologous where the difference in chemical shift is, respectively, 0.43 and 0.26 ppm for the phosphonated nucleosides containing a methylene or two extra methylene moieties, respectively.[9b,15] This observation additionally supports the *cis*-relationship of the substituents at C1′ (thymine) and C4′ (diethoxyphosphoryl) positions of the isoxazolidine ring in the minor isomer **8a**.

The synthetic methodology was also applied to the synthesis of the 5-fluorouracil derivatives **8b** and **9b**, by using the vinyl base **7b** as dipolarophile (Scheme 1 and Table 1, entries 3 and 4). Analogously to the cycloaddition with **7a**, the best results were obtained by microwave irradiation conditions, affording a 5:1 mixture of α and β anomers in 73% yield.

2. Mechanistic Consideration. *C*-Phosphonated nitrones have been poorly investigated as dipoles in the 1,3-dipolar cycloadditions, and to the best of our knowledge, only seven examples of *N*-substituted *C*-phosphonated nitrones (Figure 2) have been reported. Nitrone **4** is the first reported phosphonated nitrone;[16] recently, nitrones **2** and **3** have been exploited as substrates for the synthesis of antiviral agents[9a,b,15] while

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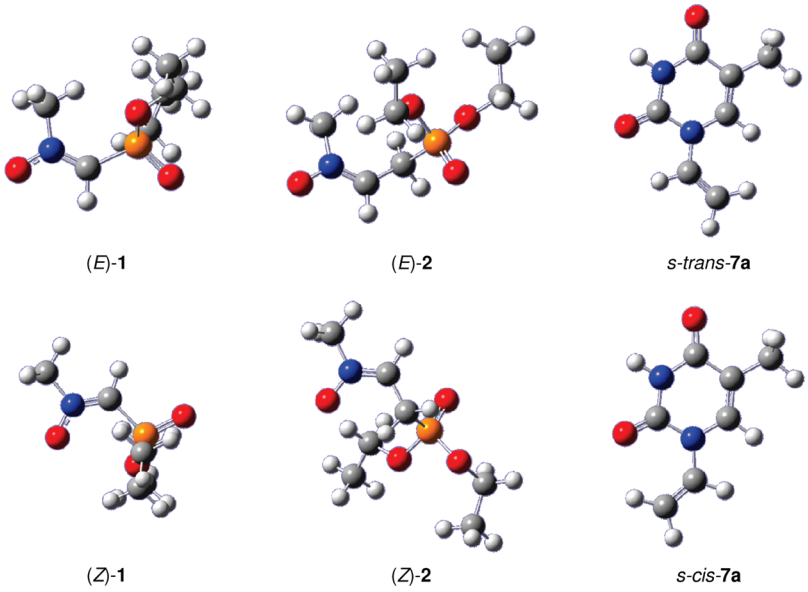

FIGURE 4. Acetonitrile B3LYP/D95+(d,p)-optimized structures of the reactants.

nitrones **5** and **6** appeared to be useful intermediates in the syntheses of phosphonate analogues of various amino acids.[17]

During our study on the 1,3-dipolar cycloaddition we observed a different reactivity of *C*-phosphonated nitrones **1**−**3**. In particular, nitrone **1** easily reacts with various electron-rich or electron-poor dipolarophiles,[18] including vinyl nucleobases. The cycloaddition reactions of nitrones **2** and **3** with vinyl acetate proceed in moderate to excellent yields (90% for nitrone **2** and 50−65% for nitrone **3**),[9b,16] but no reaction was observed when vinyl nucleobases were used under conventional heating or microwave irradiation. In all cases, the electron-rich carbon of the olefin tends to attack the nitrone carbon atom, leading to C_5 regioisomers.

For a rationalization of the experimental results, quantum mechanical calculations have been carried out at DFT level of theory[19] in both the gas phase and solvent.

We have also analyzed the cycloaddition reactions using the global indexes, as defined in the context of DFT,[20] which are useful tools to understand the reactivity of molecules in their ground states (see the Supporting Information). So, the chemical potential μ, the chemical hardness η, and the global electrophilicity power ω were calculated according to the previous reported formulas.[21] Nitrone **3**, being electronically similar to nitrone **2**, was not considered in the calculations.

The calculated energies for nitrones **1** and **2**, in both *E* and *Z* configurations, and for the vinyl thymine **7**, in both s-*trans* and s-*cis* configurations (Figure 4), are reported in Table 2.

TABLE 2. B3LYP/D95+(d,p) Free Energies *G* (Hartrees) and Relative Free Energies ΔG (kcal/mol) for Nitrones 1 and 2 and Vinyl Thymine 7a

	gas phase		acetonitrile	
	G	ΔG	*G*	ΔG
(*E*)-**1**	−934.022697	0.00	−934.028700	0.00
(*Z*)-**1**	−934.021654	0.65	−934.028590	0.07
(*E*)-**2**	−973.321370	5.28	−973.331032	3.03
(*Z*)-**2**	−973.329793	0.00	−973.335858	0.00
s-trans-**7a**	−531.529636	0.00	−531.535100	0.00
s-cis-**7a**	−531.526152	2.19	−531.531921	1.99

Relative energies shown in Table 2 indicate that the energy difference among *E* and *Z* isomers of nitrone **1** is small in the gas phase and practically zero in acetonitrile, suggesting the instauration of a rapid equilibrium in the polar solvent; on the contrary, for nitrone **2** the energy difference is quite significant in both the gas phase and acetonitrile in favor of the *Z*-isomer that should be the only one present in solution. The same considerations are valid for vinyl thymine: the *s-trans* isomer is clearly predominant in solution.

The values of μ, η, and ω for the starting compounds **1**, **2**, and **7a** are listed in Table 3, besides the ΔN_{max} values, that are the maximum amount of electronic charge that the electrophile system may accept.[20a] The electronic chemical potential of vinyl thymine **7a** is lower than that of nitrone **1** so indicating that a net charge transfer will take place from **7a** to **1**; i.e., a $HOMO_{dipolarophile}-LUMO_{dipole}$ interaction occurs. Conversely, in the case of nitrone **2**, the μ value is lower than that of vinyl thymine **7a** and the charge transfer will take place from **2** to **7a**, indicating a $HOMO_{dipole}-LUMO_{dipolarophile}$ interaction. The same trend is observed considering the electrophilicity power values, which measure the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment; this is because the electrophilicity index encompasses both the propensity of the electrophile to acquire an additional electronic charge driven by μ^2 and the resistance of the system to exchange electronic charge with the environment described by η simultaneously. Thus, nitrone **1** possesses

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TABLE 3. HOMO, LUMO, and Global Properties[a] for Nitrones 1 and 2 and Vinyl Thymine 7a Calculated at the B3LYP/D95+(d,p) Level in Acetonitrile

	HOMO	LUMO	μ	η	ω	ΔN_{max}
(*E*)-**1**	−0.26172	−0.08215	−0.17194	0.17957	2.24	0.96
(*Z*)-**1**	−0.26256	−0.07955	−0.17106	0.18301	2.18	0.93
(*E*)-**2**	−0.23626	−0.05458	−0.14542	0.18168	1.58	0.80
(*Z*)-**2**	−0.24161	−0.04900	−0.14531	0.19261	1.49	0.75
s-trans-**7a**	−0.24513	−0.07110	−0.15812	0.17403	1.95	0.91
s-cis-**7a**	−0.24319	−0.06228	−0.15274	0.18091	1.75	0.84

[a]HOMO, LUMO, electronic chemical potential μ, and chemical hardness η values are in au; electrophilicity power ω values are in e*V*.

a high electrophilicity value, and according to the absolute scale of electrophilicity based on the ω index,[22] it can be classified as a strong electrophile (ω = 2.24 eV); on the other hand, nitrone **2** is only a moderate electrophile ($\omega \sim 1.54$ eV). The *s-trans* vinyl thymine **7a** results as a strong electrophile (ω = 1.95 eV) with the electrophilic value between those of nitrones **1** and **2**; compound **7a** then behaves as nucleophile with respect to nitrone **1** and as electrophile with respect to nitrone **2**. Moreover, the electrophilicity differences between **7a** and nitrones **1** and **2** ($\Delta\omega$ = 0.29 and 0.37 eV, respectively) indicate a lower polar character for these cycloadditions, and their values are characteristic of nonpolar pericyclic reactions.[23]

Knowing that the C5-regioisomers are the only product for this type of reactions,[9b,16] we also studied diastereoselectivities for the reaction of nitrone **1** with vinyl thymine **7a**. For each transition state, the most stable conformation of vinyl thymine has been chosen. Both *E* and *Z* configurations of nitrone **1** have been evaluated. The stability of the reactants was evaluated, and the most stable conformations were chosen for performing the study and employed for locating the corresponding transition states.

The relative free and electronic energies, in both the gas phase and acetonitrile, with respect to reactants for the transition structures located for the reaction between nitrones **1** and vinyl thymine **7a** are collected in Table 4. The same table reports the values for charge transfer, i.e., the charge transferred between the two reactants at the TSs geometry, in terms of the residual charge on the nitrone; these charges have been calculated by natural population analysis (NPA).[24] For nitrone **2**, which does not react with dipolarophile **7a**, we have considered only the *E-exo*-TS, the more stable of all TSs, to perform a comparison.

For nitrone **1**, the analysis of relative electronic (ΔE) shows that, both in gas-phase and acetonitrile, the *exo* approach is the preferred one with the *Z-exo*-TS, which leads to compound α-**9a**, more stable than that *E-exo*-TS, which leads to compound β-**8a**. Considering the free energies (ΔG), although the *exo* approach remains the lowest in energy, the introduction of entropy inverts the stability of *Z*- and *E*-TS and the energetic gap between these two TSs (Figure 5) further increases in acetonitrile solvent; this gap in

TABLE 4. B3LYP/D95+** Relative Electronic Energies ΔE (kcal/mol), Relative Free Energies ΔG (kcal/mol), and Charge Transfer (au) in Terms of the Residual Charge of the Nitrone Fragment in the Transition State for the Reaction of Nitrones 1 and 2 with Vinyl Thymine 7a

	gas phase		acetonitrile		
	ΔE^a	ΔG^a	ΔE^a	ΔG^a	NPA q_{CT} (e)
E-exo-TS	15.09	28.40	16.76	30.29	−0.07
E-endo-TS	18.15	32.00	20.33	34.59	−0.05
Z-exo-TS	14.26	28.44	16.51	30.95	−0.07
Z-endo-TS	16.68	31.16	19.66	33.92	−0.06
E-exo-TS-**2**			14.36	32.30	−0.03

[a]Referenced to (*E*)-**1** or (*Z*)-**2** + *s-trans*-**7a** (see Table 2 for *G* values).

free activation energies, in acetonitrile, equal to 0.66 kcal/mol, inserted in the Boltzman's equation gives a calculated **9a**:**8a** ratio of 3:1 that is in good agreement with the experimental one.

It is noteworthy that the activation's free energies for the cycloaddition of nitrone **1** with vinyl thymine **7a** are in the range of 30.29−30.95 kcal/mol, that is, almost 2−6 kcal/mol highest than that of analogous cycloadditions of electron-poor nitrones, e.g., *C*-methoxycarbonyl-*N*-methyl nitrone, with methyl acrylate or vinyl acetate,[21b] and this implies the necessity of more drastic conditions of reaction. The most stable TS for cycloaddition of nitrone **2** has a more high $\Delta G^{\ddagger}$, and this accounts for the lack of cycloaddition reaction due to the instability of the substrate **7a** at more elevate temperatures.

Taking into account NPA charges, the negative values are indicative of an electron flow from the HOMO of the vinyl thymine to the LUMO of both nitrones **1** and **2**. Whereas this value is in agreement with the lower absolute value of the electronic chemical potential of vinyl thymine (μ = −0.15812) with respect to nitrone **1** (μ = −0.17194), in the case of reaction with nitrone **2** the NPA charge transfer at TS shows an inversion of electron demand respect to that evidenced by global parameters. Because the NPA charge transfer at TSs level is more reliable than any value calculated on the ground state of the reagents, in this latter case the reaction takes place as $HOMO_{dipolarophile}-LUMO_{dipole}$ interplay; despite this, the interaction is unfavored by 15.9 kcal/mol respect to the $HOMO_{dipole}-LUMO_{dipolarophile}$. It probably occurs owing to a better orbital coefficient superposition. Again, this result is in agreement with more drastic experimental conditions and with the failure of the reaction.

3. Two-Step Synthesis of TPCOANs. In order to obtain as major products the β-anomers **8a**,**b**, the biologically interesting compounds,[25] a two-step procedure was investigated. The 1:9 mixture of cycloadducts **10** and **11**, obtained from the nitrone **1** and vinyl acetate as previously described,[18] was subjected to nucleosidation reaction with silylated nucleobases (Scheme 2).

Nucleosidation of **10** and **11** with silylated thymine or 5-fluorouracil, in the presence of 0.4 equiv of TMSOTf as catalyst in dry acetonitrile at room temperature, proceeded with a low stereoselectivity to give the α- and β-anomers in a 2:3 ratio. When the reaction was carried out at higher temperature, the β-anomers were obtained as almost exclusive compounds in 70% yield for **8a** and 75% for **8b**. The β/α ratio of β- and α-nucleosides does not change when the

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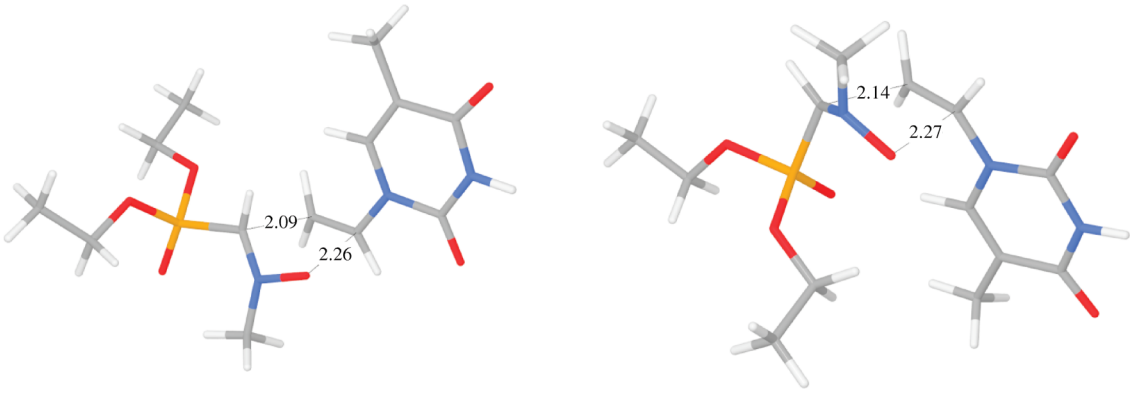
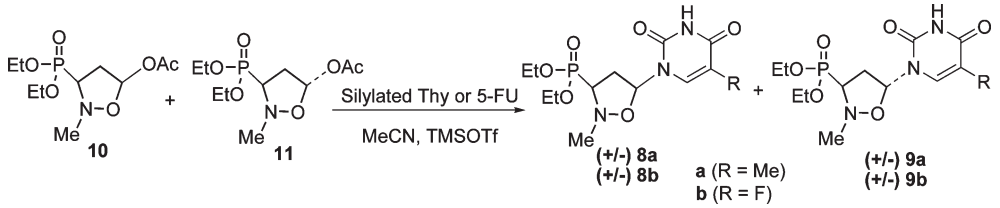


FIGURE 5. Optimized geometries at the B3LYP/D95+(d,p) level, in acetonitrile, for the most stable transition structures leading to compounds **9a** and **8a**. Distances of forming bonds are given in angstroms.

SCHEME 2. Two-Step Procedure



nucleosidation reaction was performed starting from the pure *trans*- or *cis*-isoxazolidine. These results show that the coupling reaction of isoxazolidines with silylated bases occurs with low selectivity with respect to the anomeric center. As previously reported,[26] this is due to the formation of an intermediate oxonium ion and an equilibration of the products is possible under the reaction conditions. The nucleosidation reaction can proceed under kinetic or thermodynamic control, but in our case, **8a** appears to be the thermodynamically controlled compound. To confirm this hypothesis, compound **9a**, which was obtained as a major cycloadduct in the one step procedure (vide supra), was heated with the silylated thymine in the presence of TMSOTf in acetonitrile at 70 °C for 12 h to produce the β-isomer **8a** as a single product.

4. Biological Results. For testing the potential activity of TPCOANs against human retroviruses, we determined their ability to inhibit the reverse transcriptase activity of different retroviruses by means of a cell-free assay, recently described by us,[9a−c] after incubation with a crude extract from 1×10^6 PMMCs (human peripheral blood mononuclear cells) which serve as enzyme supplier for phosphorylation processes. Zidovudine (AZT), a well-known nucleoside, and tenofovir, a phosphonated nucleoside actually used in antiviral chemotherapy, were utilized in the assay as internal positive controls. The obtained preliminary results show that compounds **8a** and **8b** completely inhibit the reverse transcriptase activity of Avian Moloney Virus (AMV) and Human Immunodeficiency Virus (HIV), at 1 ± 0.1 nM, at a level comparable with that of tenofovir (1 nM) and 10-fold lower than AZT (10 nM). The α-anomers **9a** and **9b** are completely inactive at the higher concentration tested (1000 nM). Moreover, the citotoxicity, evaluated by MTS assay,[25] indicates for **8a**,**b** and **9a**,**b** a very low toxicity ($CC_{50} > 500\ \mu$M) in comparison with AZT (CC_{50} 12.14 μM).

The obtained results, in agreement with our previous data on similar derivatives,[9a−c] indicate that diethyl esters of *N,O*-phosphonated nucleosides seem to be a good delivery system. Probably, by action of nonspecific cellular esterases, they release the two ethanol unities, not toxic for the cell, leading to the free phosphonic acid which can be subsequently phosphorylated by cellular kinases. In the cell free assay, the cellular lysate is a source of enzymes which cleave the estereal unit and promote the phosphorylation step.

The exact mechanism by which this class of compounds exert RT inhibition has not been addressed, but it seems plausible that they act as chain terminators as indicated by several evidence. In fact, the α-anomers are completely inactive and only the β-anomers, analogues of natural nucleosides are active. Moreover, compounds **8a**,**b** are active on RT assay only after incubation with a crude extract from PBMCs and are completely inactive without this pretreatment. These data suggest that our compounds are not allosteric inhibitors and that they act at the active site of the enzyme.

Biological assays in order to understand if the TPCOANs possess the necessary requirements to efficiently inhibit the transmission of human retroviruses, by specific cellular assays, are actually in progress.

5. Conclusion. TPCOANs have been synthesized in good yields by 1,3-dipolar cycloaddition methodology, according to two different routes which exploit the reactivity of phosphonated nitrone **1**. The obtained results show that the two-step procedure gives in high yield the desired β-anomers, while the unnatural α-nucleosides represent the main adduct in the one-step methodology.

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The different reactivity of phosphonated nitrones **1**−**3** in the 1,3-dipolar cycloaddition has been rationalized through quantum mechanical DFT calculations.

Preliminary biological assays show that the β-anomers of TPCOANs are able to inhibit the reverse transcriptase of different retroviruses at concentrations in the nanomolar range, with a potency comparable with Tenofovir. TPCOANs represent a new template of cyclic phosphonated nucleosides which deserve further investigations as lead compounds for extending the current spectrum of antiviral activity of the acyclic phosphonated nucleosides, avoiding some unwanted side effects.

Experimental Section

General Procedures for the Preparation of Truncated Phosphonated Carbocyclic 2′-Oxa-3′-aza Nucleosides 8 and 9. One-Step Procedure. A solution of nitrone **1** (200 mg, 1.02 mmol) in dry acetonitrile (20 mL) and vinyl nucleobases[27] **7a** (156 mg, 1.02 mmol) or **7b** (160 mg, 1.02 mmol) was put in a sealed tube and irradiated under microwave conditions at 100 W, 90 °C, for 5 h. The removal of the solvent in vacuo afforded a crude material which, after MPLC purification by using as eluent a mixture of $CHCl_3$/MeOH 99:1, gives the nucleosides **8** and **9**.

Two-Step Procedure. A suspension of thymine (252 mg, 2 mmol) or 5-fluorouracil (260 mg, 2 mmol) in dry acetonitrile (30 mL) was treated with bis(trimethylsilyl)acetamide (1,5 mL, 6 mmol) and left under stirring until the solution was clear. A solution of a mixture of isozaxolidines **10** and **11** (282 mg, 1 mmol) in dry acetonitrile (10 mL) and trimethylsilyl triflate (72 μL, 0.4 mmol) was then added, and the reaction mixture was heated at 70 °C for 5 h. After being cooled at 0 °C, the solution was carefully neutralized by addition of aqueous 5% sodium bicarbonate and then concentrated in vacuo. After addition of dichloromethane (20 mL), the organic phase was separated, washed with water (2 × 10 mL), dried over sodium sulfate, filtered, and evaporated to dryness. The ^{1}H NMR spectrum of the crude reaction mixture shows the presence of β-anomers as nearly exclusive adducts, while the α-anomers are present only in traces. The residue was purified by MPLC on a silica gel column using as eluent a mixture of $CHCl_3$/MeOH 99:1 to afford **8a** with a 70% yield and **8b** in 75% yield.

Diethyl [(1′*SR*,4′*SR*)-1′-[5-Methyl-2,4-dioxo-3,4-dihydropyrimid-1(2*H*)-yl]-3′-methyl-2′-oxa-3′-azacyclopent-4′-yl]phosphonate 8a: sticky foam (243 mg, 70% yield by the two-step procedure; 40 mg, 12% yield by the one-step procedure); ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.08 (s, NH, 1H), 7.75 (br q, *J* = 0.7 Hz, C*H*═, 1H), 6.23 (dd, *J* = 7.5 and 3.3 Hz, H-C1′, 1H), 4.23−4.10 (m, 4H), 3.20 (dddd, *J* = 13.8, 9.0, 7.5, and 4.8 Hz, Hα-C5′, 1H), 3.01 (ddd, *J* = 9.6, 9.0, and 2.7 Hz, H-C4′, 1H), 2.97 (s, 3H), 2.70 (dddd, *J* = 17.1, 13.8, 9.6, and 3.3 Hz, Hβ-C5′, 1H), 1.95 (d, *J* = 0.7 Hz, 3H), 1.34 (t, *J* = 7.0 Hz, 3H), 1.32 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 164.2 (C4), 150.9 (C2), 136.6 (C6), 110.8 (C5), 82.3 (d, *J* = 10.6 Hz, C1′), 64.2 (d, *J* = 167.3 Hz, C4′), 63.6 (d, *J* = 7.0 Hz), 63.0 (d, *J* = 7.0 Hz), 46.2 (CH_3N), 41.5 (d, *J* = 3.5 Hz, C5′), 16.8 (d, *J* = 5.2 Hz), 16.7 (d, *J* = 5.3 Hz), 13.0 (*C*H_3-CH═); ^{31}P NMR (121.5 MHz, $CDCl_3$, δ) 21.44; HRMS-EI (*m*/*z*) $[M]^+$ calcd for $C_{13}H_{22}N_3O_6P$ 347.1246, found 347.1242.

Diethyl [(1′*SR*,4′*RS*)-1′-[5-Methyl-2,4-dioxo-3,4-dihydropyrimid-1(2*H*)-yl]-3′-methyl-2′-oxa-3′-azacyclopent-4′-yl]phosphonate 9a: sticky foam (200 mg, 58% yield by the one-step procedure); ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.97 (s, NH, 1H), 7.27 (q, *J* = 0.95 Hz, C*H*═, 1H), 6.07 (dd, *J* = 7.7, 3.9 Hz, H-C1′, 1H), 4.27−4.22 (m, 2H), 4.22−4.15 (m, 2H), 3.30−3.25 (very br m, H-C4′, 1H), 3.10−3.00 (br m, Hβ-C5′, 1H), 3.05 (s, 3H), 2.60 (dddd, *J* = 13.6, 8.0, 6.8, 3.9 Hz, Hα-C5′, 1H), 1.96 (d, *J* = 0.95 Hz, 3H), 1.39 (t, *J* = 7.0 Hz, 3H), 1.37 (t, *J* = 7.0 Hz, 3H); ^{1}H NMR (700 MHz, C_6D_6) δ 10.17 (s, 1H, NH), 6.67 (s, 1H, C*H*═), 5.97 (br s, 1H, H−C1′), 4.10−4.00 (m, 2H), 4.00−3.80 (m, 2H), 3.17 (very br t, 1H, H-C4′), 2.87 (dddd, *J* = 16.8, 13.6, 9.6, 7.7 Hz, 1H, Hβ-C5′), 2.96 (s, 3H), 2.39 (dddd, *J* = 13.6, 8.0, 6.8, 3.9 Hz, 1H, Hα-C5′), 1.70 (s, 3H), 1.06 (t, *J* = 7.0 Hz, 3H), 1.03 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 163.5 (C4), 150.1 (C2), 135.3 (C6), 111.3 (C5), 83.2 (d, *J* = 10.2 Hz, C1′), 63.1 (d, *J* = 164.7 Hz, C4′), 62.6 (d, *J* = 7.3 Hz), 62.6 (d, *J* = 7.3 Hz), 38.7 (CH_3N), 29.7 (C5′), 16.52 (d, *J* = 5.6 Hz), 16.50 (d, *J* = 6.3 Hz), 12.6 (*C*H_3-CH═); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 20.73; HRMS-EI (*m*/*z*) $[M]^+$ calcd for $C_{13}H_{22}N_3O_6P$ 347.1246, found 347.1244.

Diethyl [(1′*SR*,4′*SR*)-1′-[5-Fluoro-2,4-dioxo-3,4-dihydropyrimid-1(2*H*)-yl]-3′-methyl-2′-oxa-3′-azacyclopent-4′-yl]phosphonate 8b: sticky foam (263 mg, 75% yield by the two-step procedure; 43 g, 13% yield by the one step procedure); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.01 (d, *J* = 6.5 Hz, 1H), 6.21 (d, *J* = 5.5 Hz, 1H), 4.30−4.15 (m, 4H), 3.22 (ddd, *J* = 13.5, 9.5, and 5.5 Hz, 1H), 3.03 (td, *J* = 9.5 and 2.5 Hz, 1H), 2.95 (s, 3H), 2.69 (ddd, *J* = 17.0, 9.5, and 2.5 Hz, 1H), 1.35 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0 (d, *J* = 26.4 Hz), 149.2, 140.2 (d, *J* = 234.8 Hz), 124.7 (d, *J* = 34.4 Hz), 82.4 (d, *J* = 8.8 Hz), 63.42 (d, *J* = 6.2 Hz), 63.40 (d, *J* = 165.3 Hz), 62.7 (d, *J* = 6.9 Hz), 45.6, 41.0, 16.35, 16.34; HRMS-EI (*m*/*z*) $[M]^+$ calcd for $C_{12}H_{19}FN_3O_6P$ 351.0996, found 351.0999.

Diethyl [(1′*SR*,4′*RS*)-1′-[5-Fluoro-2,4-dioxo-3,4-dihydropyrimid-1(2*H*)-yl]-3′-methyl-2′-oxa-3′-azacyclopent-4′-yl]phosphonate 9b: sticky foam (213 mg, 60% yield by the one-step procedure); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 10.0 (bs, 1H), 7.29 (d, *J* = 9.5 Hz, 1H), 6.60 (dd, *J* = 7.0 Hz, 1H), 4.32− 4.15 (m, 4H), 3.94 (m, 1H), 3.0 (s, 3H), 2.95 (m, 1H), 2.40 (m, 1H), 1.35 (m, 6H); ^{13}C NMR (125 MHz $CDCl_3$ δ) 157.2 (d, *J* = 26.5 Hz), 149.3, 139.9 (d, *J* = 234.9 Hz), 123.6 (d, *J* = 34.1 Hz), 80.9 (d, *J* = 13.1 Hz), 63.4 (d, *J* = 163.8 Hz), 63.3 (d, *J* = 6.3 Hz), 62.7 (d, *J* = 6.3 Hz), 45.5, 35.5, 16.33, 16.30; HRMS-EI (*m*/*z*) $[M]^+$ calcd for $C_{12}H_{19}FN_3O_6P$ 351.0996, found 351.0998.

Reverse Transcriptase Inhibition Assay. The new synthesized compounds **8a**,**b** and **9a**,**b** and the control compounds AZT and tenofovir were activated through preincubation with a crude extract prepared from phytohemagglutinin- and IL-2-stimulated PBMCs from healthy donors negative for HIV and hepatitis B and C viruses. For preparation of the crude extract, 1×10^6 PBMCs, previously stimulated with phytohemagglutinin (2 μg/mL) and IL-2 (20 U/mL) for 72 h in RPMI medium plus 20% FBS, were rinsed three times in cold phosphate-buffered saline and then solubilized in lysis buffer on ice and centrifuged at 10000*g*. Lysed extracts were incubated with the compounds at different concentrations for 15 min on ice and subsequently for 45 min at 30 °C. After incubation, the crude extract−compound mixture was inactivated for 5 min at 95 °C. The reverse transcriptase (RT) inhibition assay was performed by using an RT assay kit (Roche), and the procedure for assaying RT inhibition was performed as described in the kit protocol. Briefly, the reaction mixture consists of template/primer complex, 2′-deoxy-nucleotide-5′-triphosphates (dNTPs) and RT enzyme in the lysis buffer with or without inhibitors. After 1 h of incubation at 37 °C, the reaction mixture was transferred to a streptavidine-coated microtiter plate (MTP). The biotin-labeled dNTPs that are incorporated in the template due to activity of RT were bound to streptavidine. The unbound dNTPs were washed using wash buffer, and anti-digoxigenin peroxidase (DIG-POD) was added in MTP. The DIG-labeled dNTPs incorporated in the template was bound to anti-DIG-POD antibody. The unbound anti-DIG-POD was washed, and the peroxide substrate (ABST) was added to the MTP. A colored reaction product was produced during the cleavage of the substrate catalyzed by a peroxide enzyme.

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The absorbance of the sample was determined at OD 405 nM using microtiter plate ELISA reader. The resulting color intensity is directly proportional to the actual RT activity. The percentage inhibitory activity of RT inhibitors was calculated by comparing to a sample that does not contain an inhibitor. The percentage inhibition was calculated by formula: % inhibition $= 100 - [(\text{OD 405 nm with inhibitor}/\text{OD 405 nm without inhibitor}) \times 100]$. Data represent mean values for three separate experiments, and the variation among triplicate samples was less than 10%. Compounds **8ab** completely inhibit (100% inhibition rate) the RT activity at 1 ± 0.1 nM. No inhibition of reverse transcriptase activity was observed at the higher concentration tested (1000 nM) for compounds **9ab**.

Determination of Cytotoxycity of the Compounds. The cytotoxicity of the compounds on cells MOLT-3 was evaluated by MTS assay. Inhibition of cell metabolic activity revealed by reduction of the oxidative burst was detected through formazan product formation using a commercial colorimetric kit (MTS [3,4-(5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium salt], Cell Titer 96 Aqueous One Solution; Promega). The assay was performed by seeding 1×10^4 MOLT-3 cells in 100 μL in the presence or absence of the different compounds at different concentrations ranging from 1 μM to 1 mM in RPMI medium supplemented with 5% FBS. A 20-μL portion of Cell Titer 96 Aqueous One Solution reagent was added directly to culture wells at the end of the culture period and incubated for 1−4 h, and then absorbance was read at 490 nm. Each condition was analyzed in triplicate.

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Supporting Information Available: General information and for all new compounds **8a**,**b** and **9a**,**b**; proton and carbon spectra; supplementary phosphorus NMR and 2D NOESY spectra for compounds **9a** and **9b**. Tables of computational Cartesian coordinates, energies, and TS frequencies. This material is available free of charge via the Internet at http://pubs.acs.org.