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Modified nucleosides. A general and diastereoselective approach to *N,O*-psiconucleosides

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Abstract—An efficient reaction route towards the new class of *N,O*-psiconucleosides has been designed, based on the 1,3-dipolar cycloaddition of *C*-[(*tert*-butyldiphenylsilyl)oxy]methyl-*N*-methyl nitrone with ethyl 2-acetyloxyacrylate, followed by nucleosidation. The process has been successfully applied to all pyrimidine and purine nucleobases.

1. Introduction

Modified nucleosides have received great attention over the last decade largely due to their apparent promise as antiviral and antitumor agents.[1] In this context, a great deal of interest has been recently devoted towards the synthesis of systems in which the furanose moiety is replaced by alternative carbo- or heterocyclic rings. Since these compounds are analogs of natural compounds, they utilize the biochemical machinery of the host cells and act at the catalytic site of HIV reverse transcriptase by terminating DNA synthesis.[2]

In this context, relevant importance assume *N,O*-modified nucleosides, and considerable progress has been made since the pioneering work of Tronchet and coll.[3]

Our efforts in these area have been devoted towards the development of new synthetic schemes for the construction of a series of *N,O*-modified nucleosides, some of which have shown promising anti-AIDS activity in vitro.[4] The synthetic strategy we privileged moves from the potentialities offered by 1,3-dipolar cycloaddition processes for the synthesis of stereochemically defined heterocyclic systems.

In a previous paper,[5] we have reported the first synthetic approach towards the till now unreported class of *N,O*-psiconucleosides in which the heterocyclic ring is branched at the anomeric position: by this route *N,O*-psiconucleosides **1**, carrying a hydroxymethyl group at the anomeric position and at C_4 have become accessible. The synthetic scheme develops in only three steps: cycloaddition of a *C*-alkoxycarbonylnitrone with enol esters, nucleosidation with silylated bases and finally reduction of ester groups with $NaBH_4$ to give α-and β-nucleosides. When performed under thermodynamic control conditions, the reaction leads exclusively to the corresponding β-nucleosides, in the case of pyrimidine derivatives, and to α-nucleosides in the case of purine derivatives[6] (Fig. 1).

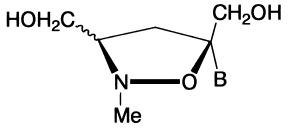

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Figure 1.

The designed reaction route appears to be versatile and of general application but suffers from a serious limitation in the difficult reduction of ester groups. In the present paper we report a successful implementation of the synthetic strategy achieved by the use of the novel nitrone **2**, containing a protected alcoholic group in α with respect to the nitrone functionality: in this way different functionalizations at $C_{3'}$ and $C_{5'}$ could be achieved. The approach has been successfully extended to all purine and pyrimidine nucleobases.

2. Results and discussion

The synthetic scheme is based on the 1,3-dipolar cycloaddition of *C*-α-silyloxymethyl-*N*-methyl nitrone **2** with ethyl 2-acetyloxyacrilate **3**, followed by nucleosidation performed with silylated purine and pyrimidine bases.

Nitrone **2** has been prepared in good yields starting from mannitol; thus, D-mannitol **4** (1 mmol) has been reacted

Keywords: psiconucleosides; modified nucleosides; 1,3-dipolar cycloaddition; PM3 calculation.

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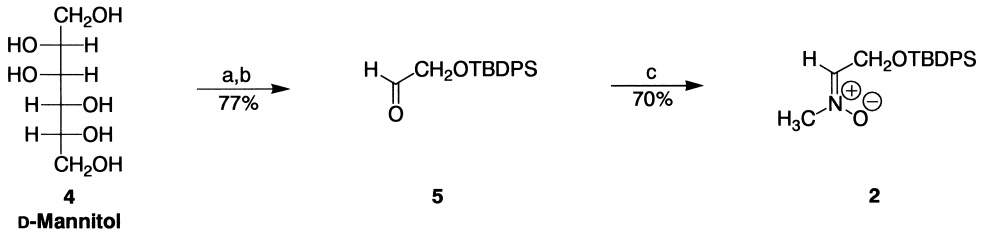
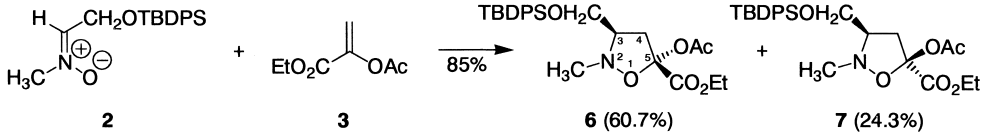


Scheme 1. (a) t-Butyldiphenylsilylchloride (TBDPSCI), imidazole, DMF; (b) $Pb(AcO)_4$, benzene; (c) CH_3NHOH, CH_2Cl_2.



Scheme 2.

with *t*-butyl-diphenylsilylchloride (2 mmol) in the presence of imidazole (4.4 mmol) in anhydrous DMF to give the 1,6-di-*O*-*tert*-butyldiphenylsilyl-D-mannitol. The subsequent treatment with lead tetracetate in benzene afforded aldehyde **5** which has been reacted with *N*-methyl hydroxylamine in toluene, in the presence of triethylamine, to give, after column chromatography separation (chloroform/methanol 98:2 as eluant), the expected nitrone **2** (70% global yield starting from mannitol) (Scheme 1).

The cycloaddition reaction between **2** and the enol acetate **3**, in anhydrous ether at room temperature for 24 h, has been found to proceed with a moderate stereoselectivity, affording a mixture of epimeric isoxazolidines **6** and **7** in a relative ratio 2.5:1 (global yield 85%) (Scheme 2). The crude mixture was purified by flash chromatography (cyclohexane/diethyl ether 9:1 as eluant) followed by HPLC and two cycloadducts **6** and **7** were obtained in pure form.

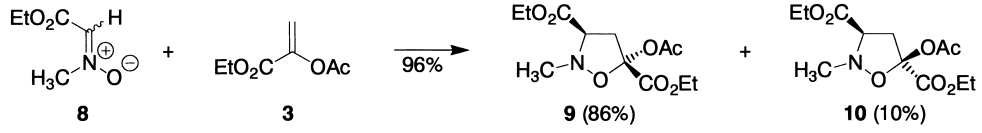
The structure of the obtained adducts has been assigned on the basis of ^{1}H NMR data and confirmed by NOE experiments. Thus, the main product **6** shows the resonance of H_3 as a multiplet at 3.08 ppm, while H_4 protons give rise to two doublets of doublets centered at 2.36 and 3.08 ppm; the methylene group of the substituent at C_3 resonates as two doublets of doublets at 3.74 and 3.75 ppm. In compound **7**, H_3 resonates at 3.26 ppm, while H_4 protons collapse to a multiplet at 2.69 ppm; the CH_2OR group at C_3 gives rise to resonances centered at 3.70 and 3.79 ppm. The stereochemistry of the adducts was readily deduced by means of NOE measurements. Thus, for compound **6**, irradiation of H_{4a} (dd, 2.36 ppm) produced strong enhancements for the CH_2OR group (dd, 3.74 and 3.75 ppm; 11%) and H_{4b} (dd, 3.08 ppm; 20%); conversely, when the resonance at 3.08 (H_3 and H_{4b}) was irradiated, a positive NOE effect was observed for H_{4a} and the methyl group of the acetyl moiety at C_5 (d, 2.07 ppm). These data support a *cis* relationship between H_{4b}, H_3 and the acetyl group at C_5 and between the CH_2OR group at C_3 and the CO_2Et group at C_5.

As a consequence, the configuration of compound **7** can be assigned as the alternative one showing the group at C_3 and the acetyl moiety at C_5 in a *cis* relationship.

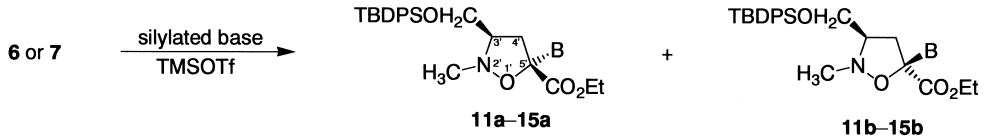
The stereochemical outcome obtained in the cycloaddition process can be explained by considering that nitrone **2** has been shown by ^{1}H NMR and NOE data to be the expected *Z*-isomer: thus, the major product **6** could be formed by the *Z*-nitrone reacting in an *endo* mode, according to the results reported for similar α-alkoxyalkylnitrones.[7] PM3 calculations afford a theoretical support to experimental data: the *Z-endo* transition state leading to **6** is about 0.52 kcal mol^{-1} more stable than *Z-exo* transition state leading to *Z* stereoisomer **7**. This value is in satisfactory agreement with the observed *E*/*Z* ratio.

In the previously reported cycloaddition reaction of *C*-alkoxycarbonyl-*N*-methyl nitrone **8** with the same dipolarophile **3**, a better diastereoselectivity had been previously obtained: in this case, isoxazolidines **9** and **10** are obtained in a relative ratio 8.6:1 (Scheme 3). The different results can be rationalized taking into account that nitrone **8** exists as a 4:1 mixture of *E* and *Z* stereoisomers with the more reactive *E*-isomer predominating:[8] thus, as confirmed by PM3 calculations, compounds **9** and **10** originate from the *E* form through an *exo* transition state.

Two cycloadducts were independently coupled with all the silylated nucleobases, according to the Vorbrüggen glycosylation methodology. The condensation with silylated thymine, *N*-acetylcytosine, 5-fluorouracil, adenine and 2-*N*-acetyl-6-*O*-diphenylcarbamylguanine, has been



Scheme 3.



	B	α/β Ratio	Combined yield (%)
11	Thymine	1:2.1	60
12	*N*-Acetylcytosine	1:0	70
13	5-Fluorouracil	1:9	80
14	Adenine	3:1	55
15	2-*N*-Acetyl-6-*O*-diphenylcarbamylguanine	1:1	60

Scheme 4.

performed in acetonitrile, at 50°C, in the presence of 0.4 equiv. of TMSOTf as catalyst: a mixture of α-and β-nucleoside **11**–**15** has been obtained. (Scheme 4). Pure anomers were isolated by flash chromatography and the relative configuration was assigned on the basis of ^{1}H NMR and NOE experiments. In particular, for β-compounds **11b** and **13b**, irradiation of $H_{4'a}$ (the upfield resonance of methylene protons at $C_{4'}$) increased the proton signal of $H_{4'b}$ and the vinylic proton in the base moiety at C_6; conversely, when $H_{4'b}$ was irradiated, a positive NOE effect is detected for $H_{4'a}$ and $H_{3'}$. These data unambiguously point to a β-configuration indicating that $H_{3'}$ and the pyrimidine base at $C_{5'}$ are in a *trans* relationship. Furthermore, the α-configuration for anomers **11a**–**13a** is supported by the strong NOE observed for H_6 when irradiating $H_{3'}$.

The stereochemistry of purine derivatives **14** and **15** is also derived from NOE measurements. In fact, diagnostic NOE effects have been detected by irradiation of the methyl group on the isoxazolidine nitrogen atom: the assignment of the α-configuration to anomers **14a** and **15a** receives support from the enhancements observed for $H_{3'}$, H_9 and the downfield resonance of methylene protons at $C_{4'}$. Consequently the β-configuration may be confidently assigned to **14b** and **15b**, where the irradiation of *N*-CH_3 induced a positive NOE effect on the upfield resonance of methylene protons at $C_{4'}$ and on the methylene protons of CH_2OSi– group.

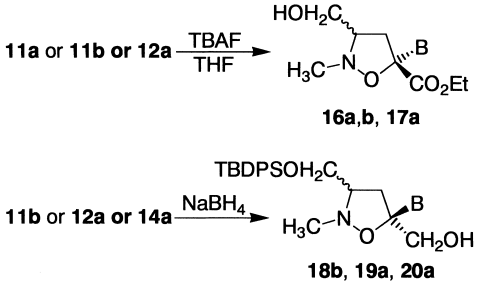
The ratio between α-and β-nucleosides did not change if the nucleosidation reaction was performed starting from the crude mixture of isoxazolidines without any preventive separation. These results show that the coupling reaction of isoxazolidines with silylated bases occurs without selectivity with respect to the anomeric center. As previously reported, this is due to the formation of an intermediate oxonium ion, which would not be expected to have any significant facial bias since the substituents at C_3 and C_4 are not in a close proximity to induce any steric effect upon the incoming group at C_5.[6]

The obtained anomeric distribution depends on the attacking nucleobase. When pyrimidine nucleobases were used, the β-anomers clearly predominate with thymine and 5-fluorouracil, while, in the case of *N*-acetylcytosine, the α-nucleoside was the exclusive product. By contrast, with purine bases, both anomers are obtained in significative amounts. Evidently, the attack on the intermediate oxonium ion from either α-or β-side is possible, and hence the product distribution is sensitive to structural changes of the reactants.[9]

PM3 data gave a rationalization to the experimental results (Table 1).

The anomeric ratio is insensitive to the adopted experimental conditions. In fact, silylated thymine, chosen as model compound, was coupled with the mixture of isoxazolidines **6** and **7** at different temperatures and using different amounts of catalyst: no difference was observed in the product distribution.

Finally, the synthetic scheme has been completed by removal of the protecting group and reduction of the estereal function at $C_{5'}$. Thus, **11a**,**b** and **12a**, as selected models, furnished $C_{5'}$-branched nucleosides **16a**,**b** and **17a** by treatment with TBAF in THF. The reduction with $NaBH_4$ of **11b**, **12a** and **14a** led to the target psiconucleosides **18b**, **19a** and



	B
11, 16, 18	Thymine
12, 17, 19	*N*-Acetylcytosine
14, 20	Adenine

Scheme 5.

Table 1. PM3 calculated heat formation for compounds **12**–**16**

Psiconucleoside	ΔH_f[a] α-Anomer	ΔH_f β-Anomer	Calculated α/β ratio
11	−261.49	−261.69	1:1.4
12	−241.57	−240.25	9.3:1
13	−292.51	−292.70	1:1.3
14	132.51	−131.18	9.4:1
15	−183.85	−183.41	2:1

[a] kcal mol^{-1}.

20a, with a yield of 70% after column chromatography purification on neutral alumina (Scheme 5).

3. Conclusion

In summary, we have designed an efficient reaction route towards the new class of *N*,*O*-psiconucleosides. The process has been easily extended to all pyrimidine and purine derivatives. The enantioselective synthesis of these compounds is actually in progress as well as their clinical evaluation.

4. Experimental

4.1. General

Melting points were measured on a Kofler apparatus and are uncorrected. Elemental analyses were performed with a Perkin–Elmer elemental analyzer. ^{1}H NMR spectra were measured on a 500 MHz Varian Unity Inova instrument in $CDCl_3$ as solvent. Chemical shifts are in ppm (δ) from TMS as internal standard. NOE difference spectra were obtained by subtracting alternatively right-off-resonance free induction decays (FIDS) from right-on-resonance-induced FIDS. Merck silica gel 60H was used for preparative short-column chromatography. Preparative HPLC was performed with a microsorb silica DYNAMAX-100 Å (21×250 mm) column.

4.1.1. Preparation of *Z*-nitrone 2. To a suspension of **4** (2.00 g, 11 mmol) and imidazole (3.30 g, 44 mol) in dry DMF (50 mL) at 0°C, a solution of *tert*-butyldiphenylsilylchloride (5.8 mL, 22 mmol) in dry DMF (15 mL) was added dropwise. The reaction mixture was stirred at 0°C for 1 h and then at 25°C for 24 h. At the end of this time the clear solution was extracted with dichloromethane/water; the combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to afford 1,6-di-*O*-*tert*-butyldiphenylsilyloxy-D-mannitol as a colorless oil. Lead tetraacetate (14.60 g, 33 mmol) was then added to a stirred solution of the above protected mannitol (7.25 g, 11 mmol) in benzene (100 mL). The reaction mixture was stirred at room temperature for 3 h and then filtered. The filtrate was evaporated under reduced pressure to afford an oil, identified as diphenyl-*tert*-butylsilyloxyacetaldehyde **5**;[10] δ_H (500 MHz, $CDCl_3$) 1.47 (s, 9H), 4.26 (s, 2H), 7.37–7.50 (m, 6H); 7.77 (d, 4H, *J*=7.5 Hz), 9.78 (s, 1H, CHO).

To a solution of crude aldehyde **5** in toluene, *N*-methyl hydroxylamine hydrochloride (1.80 g, 22 mmol) and triethylamine (3 mL, 22 mmol) were added and the mixture was maintained under stirring for 3 h at 25°C. After filtration, the solvent was evaporated at reduced pressure and the residue was subjected to silica gel column chromatography (chloroform/methanol 98:2) to give (*Z*)-*C*-[(*tert*-butyldiphenylsilyl)oxy]methyl-*N*-methyl nitrone **2** (3.34 g, 70%) as a colorless oil, δ_H (500 MHz, $CDCl_3$) 1.1 (s, 9H), 3.60 (s, 3H, *N*-CH_3), 4.65 (d, 2H, *J*=4.0 Hz), 6.86 (t, 1H, *J*=4.0 Hz), 7.31–7.40 (m, 6H); 7.68 (d,4H, *J*=7.0 Hz); δ_C (125 MHz, $CDCl_3$) 19.06, 26.75, 51.78, 60.58, 127.83, 129.93, 132.69, 135.46, 141.02. IR (neat) 3264, 3071, 3049, 2958, 2931, 2857, 1619, 1589, 1472, 1428, 1391, 1361, 1113, 998, 823 cm^{-1}. Exact mass calculated for $C_{19}H_{25}NO_2Si$: 327.1654. Found: 327.1649.

4.1.2. Preparation of isoxazolidines 6 and 7. A solution of nitrone **2** (3.80 g, 17.5 mmol) ethyl 2-acetyloxyacrilate **3** (2.85 g, 18 mmol) in dry ether (100 mL) was stirred at room temperature for 24 h. The reaction mixture was evaporated and the residue purified by flash chromatography (cyclohexane/ethyl ether 8:2) to afford a mixture of isoxazolidines **6** and **7** (85% global yield), that were further separated by HPLC (*n*-hexane/2-propanol 96:4). The first eluted product was ethyl (3*RS*,5*SR*)-5-(acetyloxy)-3-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2-methylisoxazolidine-5-carboxylate **6** (t_R 11.0 min, 60.7%) as a colorless oil; δ_H (500 MHz, $CDCl_3$) 1.05 (s, 9H), 1.28 (t, 3H, *J*=7.5 Hz), 2.07 (s, 3H), 2.36 (dd, 1H, H_{4a}, *J*=8.5, 13.0 Hz), 2.93 (s, 3H, *N*-CH_3), 3.08 (m, 2H, H_3 and H_{4b}), 3.74 (dd, 1H, $H_{3'a}$, *J*=4.5, 10.1 Hz), 3.75 (dd, 1H, $H_{3'b}$, *J*=7.5, 10.1 Hz), 4.25 (q, 2H, *J*=7.5 Hz), 7.4–7.6 (m, 6H), 7.65 (d, 4H, *J*=8.0 Hz); δ_C (125 MHz, $CDCl_3$) 13.20, 13.90, 26.72, 29.60, 44.00, 44.60, 62.50, 63.75, 69.75, 103.50, 127.81, 129.90, 135.59, 140.00, 156.40, 163.00. IR (neat) 3072, 3050, 2959, 2931, 2858, 1756, 1746, 1589, 1428, 1370, 1142, 1097, 1013, 824, 752 cm^{-1}. Exact mass calculated for $C_{26}H_{35}NO_6Si$: 485.2233. Found: 485.2232.

The second eluted product was ethyl (3*RS*,5*RS*)-5-(acetyloxy)-3-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2-methylisoxazolidine-5-carboxylate **7** (t_R 11.9 min, 24.3%) as a colorless oil; δ_H (500 MHz, $CDCl_3$) 1.05 (s, 9H), 1.27 (t, 3H, *J*=7.0 Hz), 2.12 (s, 3H), 2.65 (dd, 1H, H_{4a}, *J*=9.5, 13.0 Hz), 2.70 (dd, 1H, H_{4b}, *J*=9.5, 13.0 Hz), 2.93 (s, 3H, *N*-CH_3), 3.26 (m, 1H, $H_{3'}$), 3.70 (dd, 1H, $H_{3'a}$, *J*=5.5, 10.5 Hz), 3.79 (dd, 1H, $H_{3'b}$, *J*=4.5, 10.5 Hz), 4.24 (q, 2H, *J*=7.0 Hz), 7.26–7.43 (m, 6H), 7.65 (d, 4H, *J*=8.0 Hz); δ_C (125 MHz, $CDCl_3$) 13.90, 19.16, 21.12, 26.76, 43.13, 44.50, 62.40, 63.50, 69.75, 103.45, 127.78, 129.85, 135.54, 135.99, 139.41, 156.35, 162.50. IR (neat) 3071, 3051, 2959, 2927, 2855, 1754, 1741, 1463, 1428, 1370, 1261, 1112, 1014, 824, 750 cm^{-1}. Exact mass calculated for $C_{26}H_{35}NO_6Si$: 485.2233. Found: 485.2233.

4.2. Preparation of *N*,*O*-psiconucleosides 12–16—general procedure

A suspension of bases (2.0 mmol) in dry acetonitrile (70 mL) was treated with bis(trimethylsilyl)acetamide (0.61 g, 3.0 mmol) and stirred at room temperature until a clear solution was obtained (0.5–6 h). A solution of isoxazolidine **6** or **7** (0.55 g, 1.0 mmol) in dry acetonitrile (5 mL) and TMSOTf (0.056 g, 0.25 mmol) were then added and the resulting mixture was stirred at 45–50°C for 6 h. After this time, the mixture was neutralized by addition of aqueous 5% sodium bicarbonate, and then concentrated in vacuo. The aqueous layer was extracted with ethyl acetate (5×10 mL) and the combined organic layers were dried over sodium sulfate, filtered, and evaporated to dryness. The residue was purified by flash chromatography (cyclohexane/ethyl acetate 1:1 or chloroform/methanol 95:5) to give compound **12**–**15**.

4.2.1. Reaction of isoxazolidine 6 or 7 with thymine. First eluted product was (3′*RS*,5′*RS*)-1-[3′-({[*tert*-butyl-

(diphenyl)silyl]oxy}methyl)-5′-ethoxycarbonyl-2′-methyl-1′,2′-isoxazolidin-5′-yl]thymine **11b** (40.65%) as a sticky oil; δ_H (500 MHz, $CDCl_3$) 1.02 (s, 9H), 1.25 (t, 3H, J=7.1 Hz), 1.95 (d, 3H, J=1.3 Hz), 2.37 (dd, 1H, $H_{4'a}$, J=9.7, 13.9 Hz), 2.91 (s, 3H, N-CH_3), 3.10 (dddd, 1H, $H_{3'}$, J=4.0, 5.9, 7.7, 9.7 Hz), 3.59 (dd, 1H, $H_{4'b}$, J=7.7, 13.9 Hz), 3.65 (dd, 1H, $H_{3''a}$, J=5.9, 11.2 Hz), 3.75 (dd, 1H, $H_{3''b}$, J=4.0, 11.2 Hz), 4.21 (dq, 1H, J=7.1, 13.1 Hz), 4.25 (dq, 1H, J=7.1, 13.1 Hz), 7.40–7.54 (m, 6H), 7.55 (q, 1H, H_6, J=1.3 Hz), 7.64 (d, 4H, J=8.0 Hz), 8.86 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 12.70, 13.83, 19.08, 26.65, 44.75, 45.30, 62.99, 63.07, 70.27, 92.80, 109.17, 127.77, 129.87, 129.93, 132.62, 134.93, 135.46, 135.51, 150.38, 165.25, 164.30. IR (neat) 3204, 3101, 2983, 2927, 2854, 1760, 1698, 1659, 1469, 1294, 1192, 1020, 863, 799 cm^{-1}. Exact mass calculated for $C_{29}H_{37}N_3O_6Si$: 551.2451. Found: 551.2453.

Second eluted compound was (3′*RS*,5′*SR*)-1-[3′-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-5′-ethoxycarbonyl-2′-methyl-1′,2′-isoxazolidin-5′-yl]thymine **11a** (19.35%) as a sticky oil; δ_H (500 MHz, $CDCl_3$) 1.05 (s, 9H), 1.20 (t, 3H, J=7.1 Hz), 1.97 (d, 3H, J=1.3 Hz), 2.75 (dd, 1H, $H_{4'a}$, J=6.7, 14.1 Hz), 2.95 (s, 3H, N-CH_3), 2.98 (m, 1H, $H_{3'}$), 3.33 (dd, 1H, $H_{4'b}$, J=7.7, 14.1 Hz), 3.73 (m, 1H, $H_{3''a}$), 3.91 (m, 1H, $H_{3''b}$), 4.17 (dq, 1H, J=7.1, 10.8 Hz), 4.20 (dq, 1H, J=7.1, 10.8 Hz), 7.37–7.45 (m, 6H), 7.61 (q, 1H, H_6, J=1.3 Hz), 7.64 (d, 4H, J=8.0 Hz), 8.84 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 12.74, 13.78, 19.08, 26.73, 29.65, 36.44, 42.89, 62.97, 70.01, 93.24, 109.43, 127.79, 129.86, 129.81, 132.80, 134.93, 135.47, 135.51, 150.25, 164.07, 165.65. IR (neat) 3210, 3090, 2987, 2937, 2850, 1763, 1700, 1655, 1460, 1299, 1191, 1020, 865, 800 cm^{-1}. Exact mass calculated for $C_{29}H_{37}N_3O_6Si$: 551.2451. Found: 551.2449.

4.2.2. Reaction of isoxazolidine 6 or 7 with 4-*N*-acetylcytosine. (3′*RS*,5′*SR*)-1-[3′-({[*ter*-Butyl(diphenyl)silyl]-oxy}methyl)-5′-etoxycarbonyl-2′-methyl-1′,2′-isoxazolidin-5′-yl]4-*N*-acetylcytosine **12a** (70%), white solid: mp 62–65°C; δ_H (500 MHz, $CDCl_3$) 0.99 (s, 9H), 1.20 (t, 3H, J=7.1 Hz), 2.23 (s, 3H), 2.28 (dd, 1H, $H_{4'a}$, J=9.9, 14.1 Hz), 2.91 (s, 3H, N-CH_3), 3.12 (dddd, 1H, $H_{3'}$ J=3.5, 6.6, 7.9, 9.9 Hz), 3.60 (dd, 1H, $H_{3''a}$, J=6.6, 11.2 Hz), 3.64 (dd, 1H, $H_{3''b}$, J=3.5, 11.2 Hz), 3.70 (dd, 1H, $H_{4'b}$, J=7.9, 14.1 Hz), 4.18 (dq, 1H, J=7.1, 13.2 Hz), 4.20 (dq, 1H, J=7.1, 13.2 Hz), 7.30–7.40 (m, 10H); 7.46 (d, 1H, H_5, J=7.7 Hz), 8.12 (d, 1H, H_6, J=7.7 Hz), 10.37 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 13.76, 19.06, 24.69, 26.67, 44.26, 45.30, 62.86, 63.20, 70.27, 93.54, 95.99, 127.60, 127.76, 127.78, 129.83, 129.90, 132.57, 132.73, 134.77, 135.42, 135.46, 143.93, 155.13, 163.56, 164.83, 171.16. IR (KBr) 3441, 3130, 3050, 2983, 1781, 1700, 1612, 1503, 1464, 1314, 1219, 1092, 813, 781 cm^{-1}. Exact mass calculated for $C_{30}H_{38}N_4O_6Si$: 578.2560. Found: 578.2558.

4.2.3. Reaction of isoxazolidine 6 or 7 with 5-fluorouracil. First eluted product was (3′*RS*,5′*RS*)-1-[3′-({[*tert*-butyl-(diphenyl)silyl]oxy}methyl)-5′-ethoxycarbonyl-2′-methyl-1′,2′-isoxazolidin-5′-yl]5-fluorouridine **13b** (72%) as a white solid: mp 136–139°C; δ_H (500 MHz, $CDCl_3$) 1.03 (s, 9H), 1.26 (t, 3H, J=7.2 Hz), 2.41 (dd, 1H, $H_{4'a}$, J=9.5, 14.1 Hz), 2.90 (s, 3H, N-CH_3), 3.12 (dddd, 1H, H_3', J=4.0, 6.0, 7.9, 9.5 Hz), 3.57 (dd, 1H, $H_{4'b}$, J=7.9, 14.1 Hz), 3.65 (dd, 1H, $H_{3''a}$, J=6.0, 11.2 Hz), 3.68 (dd, 1H, $H_{3''b}$, J=4.0, 11.2 Hz), 4.23 (dq, 1H, J=7.2, 10.8 Hz), 4.27 (dq, 1H, J=7.2, 10.8 Hz), 7.35–7.45 (m, 6H), 7.63 (d, 4H, J=8.0 Hz), 7.79 (d, 1H, H_6, J=6.4 Hz), 8.01 (d, 1H, NH, J=4.0 Hz); δ_C (125 MHz, $CDCl_3$) 13.83, 19.11, 26.70, 44.53, 45.24, 63.06, 63.29, 70.16, 93.01, 123.98, 127.83, 129.95, 130.00, 132.56, 135.46, 135.50, 135.54, 138.36, 141.49, 157.04, 157.40, 164.63. IR (KBr) 3440, 3208, 3103, 2981, 2930, 2859, 1759, 1699, 1663, 1471, 1302, 1185, 1010, 850, 750 cm^{-1}. Exact mass calculated for $C_{28}H_{34}FN_3O_6Si$: 555.2201. Found: 555.2200.

Second eluted compound was (3′*RS*,5′*SR*)-1-[3′-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-5′-ethoxycarbonyl-2′-methyl-1′,2′-isoxazolidin-5′-yl]5-fluorouridine **13a** (8%) as a white solid: mp 145–148; δ_H (500 MHz, $CDCl_3$) 1.05 (s, 9H), 1.24 (t, 3H, J=7.0 Hz), 2.78 (dd, 1H, $H_{4'a}$, J=7.5, 14.7 Hz), 2.82 (m, 1H, $H_{3'}$), 2.98 (s, 3H, N-CH_3), 3.29 (dd, 1H, $H_{4'b}$, J=7.2, 14.7 Hz), 3.74 (m, 1H, $H_{3''a}$,), 3.89 (m, 1H, $H_{3''b}$), 4.25 (dq, 1H, J=7.0, 11.1 Hz), 4.29 (dq, 1H, J=7.0, 11.1 Hz), 7.35–7.45 (m, 6H), 7.65 (d, 4H, J=8.0 Hz), 7.80 (d, 1H, H_6, J=6.4 Hz), 8.85 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 13.84, 19.05, 25.68, 43.90, 44.10, 63.06, 63.29, 68.05, 93.20, 123.00, 127.83, 129.95, 130.00, 135.46, 135.50, 135.54, 141.49, 157.04, 157.40, 164.63. IR (KBr) 3430, 3200, 3080, 2990, 2945, 2863, 1761, 1707, 1650, 1310, 1200, 1020, 860, 800 cm^{-1}. Exact mass calculated for $C_{28}H_{34}FN_3O_6Si$: 555.2201. Found: 555.2204.

4.2.4. Reaction of isoxazolidine 6 or 7 with adenine. First eluted product was (3′*SR*,5′)-1-[3′-({[*tert*-butyl(diphenyl)-silyl]oxy}methyl)-5′-ethoxycarbonyl-2′-methyl-1′,2′-isoxazolidin-5′-yl]adenine **14a** (45%) as a sticky oil; δ_H (500 MHz, $CDCl_3$) 1.02 (s, 9H), 1.17 (t, 3H, J=7.2 Hz), 2.95 (s, 3H, N-CH_3), 3.18 (m, 2H, $H_{4'a}$ and $H_{3'}$), 3.81 (m, 3H, $H_{4'b}$ and $H_{3''}$), 4.17 (q, 2H, J=7.2 Hz), 5.85 (bs, 2H, NH_2), 7.35–7.45 (m, 6H), 7.60 (d, 4H, J=8.0 Hz), 8.16 (s, 1H, H_3), 8.28 (s, 1H, H_9); δ_C (125 MHz, $CDCl_3$) 13.76, 19.07, 26.56, 41.55, 45.45, 63.19, 63.75, 68.36, 92.43, 120.37, 127.73, 129.83, 123.70, 132.80, 135.39, 135.46, 135.51, 149.22, 152.81, 155.68, 166.26. IR (neat) 3303, 3153, 3072, 2959, 2929, 2857, 1757, 1674, 1604, 1470, 1205, 1112, 824, 799 cm^{-1}. Exact mass calculated for $C_{29}H_{36}N_6O_4Si$: 560.2567. Found: 560.2566.

Second eluted compound was (3′*RS*,5′*RS*)-1-[3′-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-5′-ethoxycarbonyl-2′-methyl-1′,2′-isoxazolidin-5′-yl]adenine **14b** (15%) as a sticky oil; δ_H (500 MHz, $CDCl_3$) 1.04 (s, 9H), 1.26 (t, 3H, J=7.2 Hz), 2.98 (s, 3H, N-CH_3), 3.00 (dd, 1H, $H_{4'a}$, J=5.7, 13.2 Hz), 3.13 (m, 1H, $H_{3'}$), 3.47 (dd, 1H, $H_{4'b}$, J=9.6, 13.2 Hz), 3.83 (m, 2H, $H_{3''}$), 4.11 (dq, 1H, J=7.2, 11.3 Hz), 4.17 (dq, 1H, J=7.2, 11.3 Hz), 5.81 (bs, 2H, NH_2), 7.35–7.45 (m, 6H), 7.70 (d, 4H, J=8.0 Hz), 8.17 (s, 1H, H_3), 8.27 (s, 1H, H_9); δ_C (125 MHz, $CDCl_3$) 13.80, 19.15, 26.61, 41.60, 44.50, 63.25, 63.27, 70.38, 92.42, 120.37, 127.73, 129.83, 123.70, 132.80, 135.39, 135.46, 135.51, 149.22, 152.81, 155.40, 166.05. IR (neat) 3300, 3155, 3070, 2961, 2933, 2855, 1759, 1670, 1609, 1475, 1198, 1110, 830, 800 cm^{-1}. Exact mass calculated for $C_{29}H_{36}N_6O_4Si$: 560.2567. Found: 560.2565.

4.2.5. Reaction of isoxazolidine 6 or 7 with 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanine. First eluted product was (3′*RS*,5′*SR*)-1-[3′-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-5′-ethoxycarbonyl-2′-methyl-1′,2′-isoxazolidin-5′-yl]2-*N*-acetyl-6-*O*-diphenylcarbamylguanine **15a** (30%) as a white solid: mp 130–133°C; δ_H (500 MHz, $CDCl_3$) 0.95 (s, 9H), 1.16 (t, 3H, *J*=7.1 Hz), 2.49 (s, 3H), 2.80 (dd, 1H, $H_{4'a}$, *J*=9.0, 13.7 Hz), 2.96 (s, 3H, *N*-CH_3), 3.21 (m, 1H, $H_{3'}$), 3.50 (dd, 1H, $H_{4'b}$, *J*=8.1, 13.7 Hz), 3.62 (m, 2H, $H_{3''}$), 4.15 (dq, 1H, *J*=7.1, 11.2 Hz), 4.21 (dq, 1H, *J*=7.1, 11.2 Hz), 7.24–7.71 (m, 20H), 7.90 (bs, 1H, NH), 8.26 (s, 1H, H_8); δ_C (125 MHz, $CDCl_3$) 13.83, 19.01, 25.12, 26.59, 43.45, 45.33, 63.40, 68.13, 70.30, 91.99, 121.42, 127.79, 129.17, 129.94, 132.51, 132.61, 135.38, 135.47, 141.72, 144.28, 150.29, 151.76, 153.85, 155.97, 165.28, 171.22. IR (KBr) 3300, 3071, 3043, 2960, 2927, 2855, 1752, 1700, 1619, 1588, 1492, 1290, 1186, 1112, 701 cm^{-1}. Exact mass calculated for $C_{44}H_{47}N_7O_7Si$: 813.3306. Found: 813.3304.

Second eluted compound was (3′*RS*,5′*RS*)-1-[3′-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-5′-ethoxycarbonyl-2′-methyl-1′,2′-isoxazolidin-5′-yl]2-*N*-acetyl-6-*O*-diphenylcarbamylguanine **15b** (30%) as a white solid: mp 125–127°C; δ_H (500 MHz, $CDCl_3$) 1.04 (s, 9H), 1.16 (t, 3H, *J*=7.0 Hz), 2.49 (s, 3H), 2.97 (s, 3H, *N*-CH_3), 3.12 (m, 1H, $H_{3'}$), 3.22 (dd, 1H, $H_{4'a}$, *J*=9.7, 3.4 Hz), 3.51 (m, 1H, $H_{4'b}$), 3.78 (dd, 1H, $H_{3''a}$, *J*=4.4, 10.8 Hz), 3.85 (dd, 1H, $H_{3''a}$, *J*=7.0, 10.8 Hz), 4.14 (dq, 1H, *J*=7.0, 11.2 Hz), 4.19 (dq, 1H, *J*=7.0, 11.2 Hz), 7.25–7.70 (m, 20H), 7.98 (bs, 1H, NH), 8.29 (s, 1H, H_8); δ_C (125 MHz, $CDCl_3$) 13.83, 19.09, 25.13, 26.72, 38.68, 41.46, 63.42, 68.11, 68.23, 92.54, 121.64, 126.94, 127.81, 129.20, 129.93, 132.60, 132.70, 135.47, 135.52, 141.65, 145.02, 150.32, 151.93, 153.71, 156.29, 165.74, 170.94. IR (KBr) 3300, 3070, 3050, 2970, 2930, 2850, 1750, 1705, 1620, 1590, 1490, 1290, 1185, 1117, 700 cm^{-1}. Exact mass calculated for $C_{44}H_{47}N_7O_7Si$: 813.3306. Found: 813.3307.

4.3. Preparation of *N*,*O*-$C_{5'}$-branched nucleosides 16a,b and 17a—general procedure

To a solution of nucleosides **11a**,**b** and **12a** (1 mmol) in dry THF (20 mL), TBAF (1.05 mL, 1.1 mmol, 1 M solution in THF) was added, and the mixture was stirred at room temperature for 1.5 h. At the end of this time, the solvent was removed and the residue was subjected to silica gel column chromatography (chloroform/methanol 95:5).

4.3.1. Reaction of 11a with TBAF. (3′*RS*,5′*SR*)-1-[5′-Ethoxycarbonyl-3′-hydroxymethyl-2′-methyl-1′,2′-isoxazolidin-5′-yl]thymine **16a** (80%), sticky oil; δ_H (500 MHz, $CDCl_3$) 1.26 (t, 3H, *J*=7.2 Hz), 1.97 (d, 3H, *J*=1.3 Hz), 1.98 (m, 1H, $H_{4'a}$), 2.92 (m, 1H, $H_{3'}$), 2.95 (s, 3H, *N*-CH_3), 3.49 (dd, 1H, $H_{4'b}$, *J*=5.1, 14.4 Hz), 3.71 (m, 1H, $H_{3''a}$), 3.84 (m, 1H, $H_{3''b}$), 4.22 (dq, 1H, *J*=7.2, 10.8 Hz), 4.26 (dq, 1H, *J*=7.2, 10.8 Hz), 7.61 (q, 1H, H_6, *J*=1.3 Hz), 8.65 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 12.73, 14.10, 44.32, 44.80, 61.16, 63.27, 71.10, 92.90, 109.64, 135.01, 150.32, 163.91, 165.97. IR (neat) 3440, 3210, 3090, 2987, 2937, 2850, 1763, 1700, 1655, 1460, 1299, 1191, 1020, 865, 800 cm^{-1}. Exact mass calculated for $C_{13}H_{19}N_3O_6$: 313.1273. Found: 313.1271.

4.3.2. Reaction of 11b with TBAF. (3′*RS*,5′*RS*)-1-[5′-Ethoxycarbonyl-3′-hydroxymethyl-2′-methyl-1′,2′-isoxazolidin-5′-yl]thymine **16b** (85%), sticky oil; δ_H (500 MHz, $CDCl_3$) 1.25 (t, 3H, *J*=7.2 Hz), 1.93 (d, 3H, *J*=1.1 Hz), 2.57 (dd, 1H, $H_{4'a}$, *J*=9.5, 13.9 Hz), 2.92 (s, 3H, *N*-CH_3), 3.12 (dddd, 1H, $H_{3'}$, *J*=3.6, 5.1, 7.5, 9.5 Hz), 3.65 (dd, 1H, $H_{4'b}$, *J*=7.5, 13.9 Hz), 3.66 (dd, 1H, $H_{3''a}$, *J*=5.1, 12.0 Hz), 3.75 (dd, 1H, $H_{3''b}$, *J*=3.6, 12.0 Hz), 4.21 (q, 2H, *J*=7.2 Hz), 7.61 (q, 1H, H_6, *J*=1.1 Hz), 9.90 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 12.50, 12.57, 44.31, 44.74, 60.57, 62.63, 70.18, 92.87, 109.21, 134.92, 150.61, 164.53, 165.34. IR (neat) 3443, 3200, 2980, 2947, 2850, 1760, 1695, 1660, 1470, 1295, 1190, 1020, 865, 750 cm^{-1}. Exact mass calculated for $C_{13}H_{19}N_3O_6$: 313.1273. Found: 313.1272.

4.3.3. Reaction of 12a with TBAF. (3′*RS*,5′*SR*)-1-[5′-Ethoxycarbonyl-3′-hydroxymethyl-2′-methyl-1′,2′-isoxazolidin-5′-yl]-*N*-acetylcytosine **17a** (86%), sticky oil; δ_H (500 MHz, $CDCl_3$) 1.21 (t, 3H, *J*=7.1 Hz), 2.21 (s, 3H), 2.61 (dd, 1H, $H_{4'a}$, *J*=9.5, 14.1 Hz), 2.90 (s, 3H, *N*-CH_3), 3.09 (dddd, 1H, $H_{3'}$, *J*=3.4, 4.5, 7.9, 9.5 Hz), 3.62 (dd, 1H, $H_{3''a}$, *J*=4.5, 12.1 Hz), 3.69 (dd, 1H, $H_{3''b}$, *J*=3.4, 12.1 Hz), 3.74 (dd, 1H, $H_{4'b}$), 4.12 (q, 2H, *J*=7.1 Hz), 7.45 (d, 1H, H_5, *J*=7.5 Hz), 8.12 (d, 1H, H_6, *J*=7.5 Hz), 9.99 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 13.76, 24.73, 43.69, 44.65, 60.27, 65.54, 70.38, 93.74, 96.05, 115.99, 143.79, 149.66, 155.52, 163.21, 170.96. IR (neat) 3418, 3341, 3230, 3071, 2958, 2929, 2856, 1717, 1700, 1655, 1603, 1488, 1275, 1112, 1068, 823, 795 cm^{-1}. Exact mass calculated for $C_{14}H_{20}N_4O_6$: 340.1383. Found: 340.1384.

4.4. Preparation of *N*,*O*-psiconucleosides 18b, 19a and 20a—general procedure

To a solution of nucleosides **11b**, **12a** and **14a** (1 mmol) in methanol (20 mL), at 0°C, $NaBH_4$ (0.060 g, 1.5 mmol) was added and the mixture was stirred for 3 h. At the end of this time, the solvent was removed and the residue was subjected to column chromatography on neutral alumina (chloroform/methanol 95:5).

4.4.1. Reaction of 11b with $NABH_4$. Already reported.[5]

4.4.2. Reaction of 12a with $NaBH_4$. (3′*RS*,5′*SR*)-1-[3′-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-5′-hydroxymethyl-2′-methyl-1′,2′-isoxazolidin-5′-yl]-*N*-acetylcytosine **19a** (80%), sticky oil; δ_H (500 MHz, $CDCl_3$) 1.10 (s, 9H), 2.09 (s, 3H), 2.40 (dd, 1H, $H_{4'a}$, *J*=9.3, 13.5 Hz), 2.59 (dd, 1H, $H_{4'b}$, *J*=7.5, 13.5 Hz), 2.80 (s, 3H, *N*-CH_3), 3.81 (m, 1H, $H_{3'}$), 3.50 (m, 2H, $H_{3''}$), 3.52–3.60 (bs, 2H, NH and OH), 3.68 (d, 1H, $H_{5''a}$, *J*=11.8 Hz), 4.15 (d, 1H, $H_{5''b}$, *J*=11.8 Hz), 5.60 (d, 1H, H_5 or H_6 *J*=6.9 Hz), 7.30–7.40 (m, 10H), 7.70 (d, 1H, H_5 or H_6 *J*=6.9 Hz); δ_C (125 MHz, $CDCl_3$) 19.03, 26.70, 42.17, 45.30, 64.29, 64.40, 70.06, 93.60, 96.65, 127.70, 127.63, 129.74, 132.80, 132.91, 135.43, 135.49, 142.15, 156.29, 165.83. IR (neat) 3440, 3200, 3030, 3015, 2980, 2950, 1698, 1665, 1475, 1100, 1010, 850, 750 cm^{-1}. Exact mass calculated for $C_{28}H_{36}N_4O_5Si$: 536.2455. Found: 536.2458.

4.4.3. Reaction of 14a with $NaBH_4$. (3′*RS*,5′*SR*)-1-[3′-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-5′-hydroxymethyl-2′-methyl-1′,2′-isoxazolidin-5′-yl]adenine **20a** (65%), sticky

oil; δ_H (500 MHz, $CDCl_3$) 1.03 (s, 9H), 2.68 (dd, 1H, $H_{4'a}$, J=8.1, 12.3 Hz), 2.96 (s, 3H, N-CH_3), 3.02 (m, 2H, $H_{4'b}$ and $H_{3'}$), 3.62 (m, 2H, $H_{3''}$), 4.10 (d, 1H, $H_{5''a}$, J=12.1 Hz), 4.19 (d, 1H, $H_{5''b}$, J=12.1 Hz), 5.12 (bs, 1H, OH), 6.06 (bs, 2H, NH_2), 6.60 (d, 4H, J=7.5 Hz), 7.25–7.35 (m, 6H), 8.16 (s, 1H, H_9), 8.23 (s, 1H, H_3); δ_C (125 MHz, $CDCl_3$), 18.23, 26.60, 42.27, 45.16, 63.63, 65.60, 70.17, 95.37, 120.10, 127.63, 129.48, 129.79, 129.83, 132.70, 132.79, 134.82, 135.42, 135.49, 148.35, 152.0, 155.24. IR (neat) 3420–3340, 3220, 3060, 3030, 2960, 2925, 1705, 1645, 1600, 1480, 1105, 1050, 850, 790 cm^{-1}. Exact mass calculated for $C_{27}H_{34}N_6O_3Si$: 518.2461. Found: 518.2459.

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References

1. (a) Kuritzkes, D. *HIV Clinical Management*, Vol. 13; Medscape Inc, Hillsboro, 1999. (b) Schinazi, R. F.; Mead, J. R.; Feorino, P. M. *AIDS RES. Hum. Retroviruses* **1992**, *8*, 963–970. (c) Bonnet, P.; Robins, R. K. *J. Med. Chem.* **1995**, *36*, 635–641. (d) Chiacchio, U.; Iannazzo, D.; Rescifina, A.; Romeo, G. *J. Org. Chem.* **1999**, *64*, 28–36. (e) Caputo, R.; Guaragna, A.; Palumbo, G.; Pedatella, S. *Eur. J. Org. Chem.* **1999**, 1455–1458.
2. Tan, X.; Boudinot, F. D.; Chu, C. K.; Egron, D.; Perigaud, C.; Gosselin, G.; Imbach, G. L. *Antiviral Chem. Chemoth.* **2000**, *11*, 203–212.
3. (a) Tronchet, J. M. J.; Iznaden, M.; Barlat-Rey, F.; Dhimane, H.; Ricca, A.; Balzarini, J.; De Clercq, E. *Eur. J. Med. Chem. Chim. Ther.* **1992**, *27*, 555–560. (b) Tronchet, J. M. J.; Iznaden, M.; Barbalat-Rey, F.; Komaromi, I.; Dolatshahi, N.; Bernardinelli, G. *Nucleosides Nucleotides* **1995**, *14*, 1737–1758.
4. (a) Chiacchio, U.; Gumina, G.; Rescifina, A.; Romeo, R.; Uccella, N.; Piperno, A.; Romeo, G. *Tetrahedron* **1996**, *52*, 8889–8898. (b) Chiacchio, U.; Corsaro, A.; Gumina, G.; Iannazzo, D.; Rescifina, A.; Piperno, A.; Romeo, G.; Romeo, R. *J. Org. Chem.* **1999**, *64*, 9321–9327. (c) Chiacchio, U.; Corsaro, A.; Rescifina, A.; Romeo, G. *Tetrahedron: Asymmetry* **2000**, *11*, 2045–2048. (d) Gi, H. J.; Xiang, Y.; Schinazi, R. F.; Zhao, K. *J. Org. Chem.* **1997**, *62*, 88–92. (e) Tronchet, J. M. J.; Zsely, M.; Brenas, L.; Lassout, O.; Grand, E.; Seuret, P.; Grigorov, M.; Rivara-Minten, E.; Geoffroy, M. *Nucleosides Nucleotides* **1999**, *18*, 1077–1078. (f) Leggio, A.; Liguori, A.; Procopio, A.; Siciliano, C.; Sindona, G. *Tetrahedron Lett.* **1996**, *37*, 1277–1280. (g) Leggio, A.; Liguori, A.; Procopio, A.; Sindona, G. *Nucleosides Nucleotides* **1997**, *16*, 1515–1518.
5. Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Rescifina, A.; Piperno, A.; Romeo, R.; Romeo, G. *Tetrahedron Lett.* **2001**, 1777–1780.
6. Chiacchio, U.; Corsaro, A.; Pistarà, V.; Rescifina, A.; Iannazzo, D.; Piperno, A.; Romeo, G.; Romeo, R.; Grassi, G. *Eur. J. Org. Chem.*, submitted for publication.
7. Herrera, R.; Nagarajan, A.; Morales, M. A.; Méndez, F.; Jiménez-Vázquez, H. A. L.; Zepeda, G.; Tamariz, J. *J. Org. Chem.* **2001**, *66*, 1252–1263.
8. (a) DeShong, P.; Dicken, C. M.; Staib, R. R.; Freyer, A. J.; Weireb, S. M. *J. Org. Chem.* **1982**, *47*, 4397–4403. (b) Kametani, T.; Chu, S.-D.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1593–1598.
9. Wilson, L. J.; Hager, M. W.; El Katten, Y. A.; Liotta, D. C. *Synthesis* **1995**, 1465–1479.
10. Jenn, T.; Heissler, D. *Tetrahedron* **1998**, *54*, 107–118.