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Modified Dideoxynucleosides: Synthesis of 2'-*N*-Alkyl-3'-Hydroxyalkyl-1',2'-Isoxazolidinyl Thymidine and 5-Fluorouridine Derivatives

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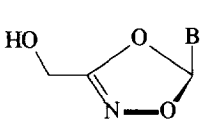
Abstract: Isoxazolidine nucleosides bearing an hydroxyl group at C_3, have been prepared in only three steps, with overall high yields. The synthetic approach is based on the 1,3-dipolar cycloaddition of 3-carboxyalkyl- or acylnitrones to vinyl acetate, followed by condensation with silylated thymine or 5-fluorouracil and $NaBH_4$ reduction. Copyright © 1996 Elsevier Science Ltd

In recent years, a considerable interest has been devoted towards the chemistry and biochemistry of nucleoside analogs in which the sugar moiety has been modified.[1,2] Several of these compounds exhibit anticancer[3] and broad-spectrum antiviral[4] activity in addition to their antibiotic properties.[5] Recent reports, in fact, have indicated that nucleosides with a 3'-spiro unit[6,7] possess anti-HIV-1 activity[7] and that 3'-deoxy-3'-*N*-hydroxyaminonucleoside derivatives have been tested to be moderately active against HIV-1.[8,9]

Following the discovery of AZT, DDC, DDI and D_4T as anti-HIV drugs, and the currently undergoing clinical trials on lavimudine (3TC)[10] and its 5-fluoroderivative (FTC),[11] the preparation of modified dideoxynucleosides has become a very active research area and new synthetic methods have been designed and developed for the synthesis of hetero- and dihetero-substituted nucleosides.

In the context of compounds containing nitrogen as the second heteroatom, nucleosides containing an unsaturated *N,O* sugar moiety **1**[12] and isoxazolidine nucleosides with *N*-alkyl **2**[13] or hydroxymethyl groups **3**[12] have been reported. The latter compounds appear particularly interesting since the presence of the hydroxyl group is necessary for phosphorylation to serve as chain terminators of DNA synthesis or to interfere with DNA systems in the infected cells.



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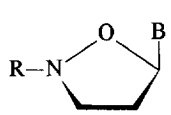

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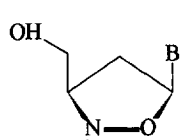


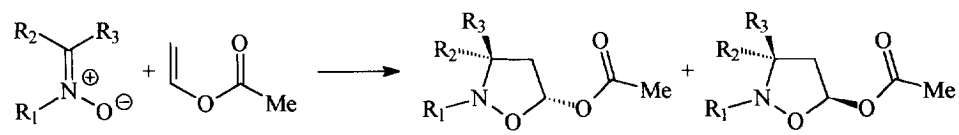
3

As part of our ongoing interest in the exploitation of 1,3-dipolar cycloaddition for the synthesis of suitably functionalized molecules,[14] we report in this paper a new strategy for the development of a facile entry to *N,O*-nucleosides **3** according to pericyclic reaction of substituted nitrones with vinyl acetate.[15] The designed reaction scheme develops in only 3 steps with an overall high yield and allows for the insertion of different functionalizable groups on the *C*-nucleoside system.

RESULTS AND DISCUSSION

Nitrones **4-7** have been reacted with vinyl acetate in the absence of solvent, using a 1:10 relative ratio of dipole to dipolarophile, until t.l.c. showed the disappearance of the starting nitrone. As reported in table 1, the investigated reaction was found to be regiospecific to afford a mixture of epimeric 5-substituted isoxazolidines **8-15** (81-92% yields) as exclusive adducts.

Table 1. Reaction of Nitrones **4-7** with Vinyl acetate.



4-7 **8-11** **12-15**

Nitrone	R_1	R_2	R_3	Yield %[a]	Epimeric ratio *cis/trans*
4[b]	Me	CO_2Et	Me	90	**8**:**12** (1:1)
5[b]	$PhCH_2$	CO_2Et	CH_3–$(CH_2)_4$–	81	**9**:**13** (1:1)
6[b]	$PhCH_2$	CO_2Et	H	87	**10**:**14** (1:4)[d]
7[c]	$PhCH_2$	PhCO	H	92	**11**:**15** (1:3)

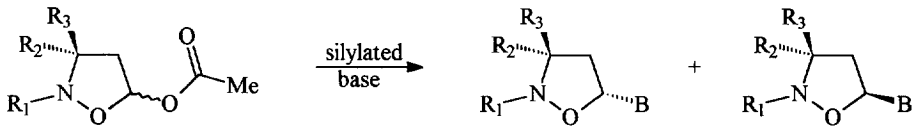
[a]Total yield. [b]Reaction at 70 °C in sealed tube. [c]Reaction at room temperature. [d]Unseparable mixture.

The molecular structure of the reaction products was assigned on the basis of analytical and spectroscopic data. The regiochemistry of the cycloaddition process was readily deduced from the ^{1}H NMR data. In each case, there was one proton signal at 6.60-6.24 δ which corresponded to the H_5 proton; the alternative regioisomers are not reported to show a resonance at this chemical value.

As expected,[15] the reaction of *C*-disubstituted nitrones **4** and **5** resulted in the observation of a poor stereoselectivity leading to the formation of a nearly equimolar mixture of epimeric isoxazolidines **8**, **12** and **9**, **13** respectively; on the contrary, nitrones **6** and **7** showed a good stereoselectivity with the *trans* isomers **14** and **15** as the major products. The relative configurational assignments of compounds **8-15** were attributed by NOE experiments.[16]

Isoxazolidines **8-15**, as epimeric mixtures, were coupled with silylated thymine or 5-fluorouracil, in CH_2Cl_2 at 0° C, in the presence of $SnCl_4$ as catalyst: nucleosidation proceeded with a moderate stereoselectivity in good yields to give **16-19** (α) and **20-23** (β) in a 60:40 ratio respectively, as determined by ^{1}H NMR of the crude reaction mixture (Table 2). Compounds **18**, **22** and **19**, **23** have also been separated by silica gel flash-chromatography ($CHCl_3$-MeOH, 95:5).

Table 2. Reaction of Isoxazolidines **8-15** with Silylated Thymine or 5-Fluorouracil.



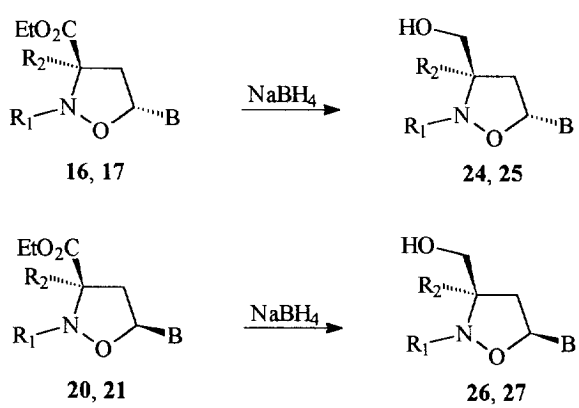
8-15 **16-19** (α) **20-23** (β)

Isoxazolidine	R_1	R_2	R_3	B	Yield %[a]	Nucleoside
8, 12	Me	Me	CO_2Et	Thymine	91	**16, 20**
9, 13	$PhCH_2$	CH_3–$(CH_2)_4$–	CO_2Et	5-Fluorouracil	89	**17, 21**
10, 14	$PhCH_2$	H	CO_2Et	5-Fluorouracil	82	**18, 22**[b]
11, 15	$PhCH_2$	H	PhCO	Thymine	90	**19, 23**[b]

[a]Yield of α + β mixture. [b]Separated by silica gel flash-chromatography.

The stereochemical assignments to the obtained nucleosides has been performed by NOEDS spectroscopy. The positive NOE effect observed for $H_{3'}$, in compounds **22** and **23**, on irradiating $H_{5'}$, is clearly indicative of their *cis* relationship. On the contrary, in compounds **18** and **19** no NOE effect has been detected between $H_{3'}$ and $H_{5'}$: irradiation of $H_{5'}$ gives rise only to enhancement of H_6 signal in thymine or 5-fluorouracil moiety and of the downfield resonance corresponding to methylene protons at $C_{4'}$. Analogously, in the crude reaction mixture, the stereochemical attribution to compound **16** has been performed by the positive NOE measured for the methyl group at $C_{3'}$ upon irradiation of H_6 of the thymine moiety.

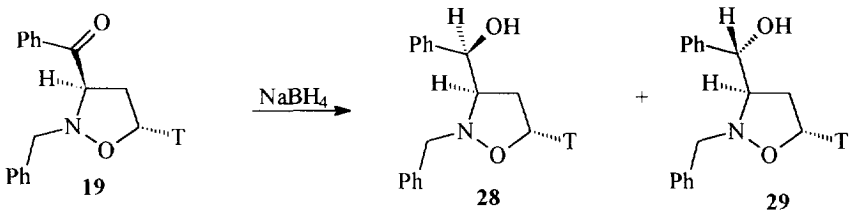
Our initial goal, directed towards the design of a new synthetic approach to suitably substituted *N,O* nucleosides containing a carbinolic group at $C_{3'}$ has been then reached by $NaBH_4$ reduction. Treatment of the epimeric mixtures of **16, 20** and **17, 21** with $NaBH_4$ in a 1:2 ratio (dioxane/water 1:1), at room temperature, afforded, in high yields, nucleosides **24, 25** and **26, 27** respectively.



16, 17 **24, 25**

20, 21 **26, 27**

Similar reduction of compound **19** afforded, after chromatographic separation, the expected pair of diastereoisomers **28, 29** (95% yield; 2:1 ratio).



The configurations of 3'-hydoxyalkyl-nucleosides **24-27** were assigned on the basis of NOEDS experiments: irradiation of $H_{5'}$, in compound **24** and **25**, induces a positive NOE effect on the carbinolic protons at $C_{3'}$, so suggesting that these protons are topologically close together. In contrast, in compounds **26**, **27**, the NOE effect was observed between $H_{5'}$ and the methyl or methylene group at $C_{3'}$, respectively.

The configuration of the new stereocentres in compounds **28**, **29**, as *R* and *S* respectively, was tentatively assigned on the basis of PM3 calculations which show that **28** is about 1.02 Kcal mol^{-1} more stable than **29**.

In conclusion, the use of a [2+3] cycloaddition methodology constitutes a general and quite easy synthetic entry to variously substituted *N-O* diheterocyclic nucleosides, bearing an hydroxymethyl group at $C_{3'}$, potentially apt to biophosphorylation, with overall high yields. The obtained results show that the outlined three step sequence, starting from suitable nitrones, is an excellent alternative to the previously reported approach, and is extensible to other base-modified analogs.

Exploitations of the scope and potential of this synthetic scheme, in the aim of the preparation of optically active *N,O*-nucleosides, are also in progress.

EXPERIMENTAL

Mp were measured on a Kofler apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer elemental analyzer. Infrared spectra were recorded on a Perkin-Elmer 377 instrument. ^{1}H Nmr spectra were measured on a Bruker WP 200 SY 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. Nitrones **4-7** have been prepared according to a procedure already reported in literature.[17]

Reaction of nitrones 4-7 with vinyl acetate.

General procedure. 1.5 mmol of nitrone was stirred with 10 ml of vinyl acetate, until tlc showed the disappearance of the starting nitrone (24 h). The reaction mixture was evaporated under reduced pressure and the residue was subjected to flash-chromatography on silica gel column with cyclohexane-ethyl acetate 9:1 as eluent.

*Reaction of C-carboxyethyl-C-methyl-N-methylnitrone **4** with vinyl acetate*. First elution gave *trans* (*3SR, 5SR*)-2,3-dimethyl-3-carboxyethyl-5-acetoxyisoxazolidine **12**, 45% yield. Colorless oil. ^{1}H NMR: δ ($CDCl_3$) 1.27 (t, 3H, J = 7.2 Hz), 1.41 (s, 3H, $H_{3'}$), 2.06 (s, 3H, CH_3CO), 2.19 (dd, 1H, H_{4a}, J = 13.7 and 3.3 Hz), 2.65 (s, 3H, NCH_3), 3.17 (dd, 1H, H_{4b}, J = 13.7 and 6.5 Hz), 4.18 (q, 2H, J = 7.2 Hz), 6.26 (dd, 1H, H_5, J = 6.5 and 3.3 Hz). ^{13}C NMR: δ ($CDCl_3$) 14.18, 19.37, 21.20, 38.99, 46.17, 61.79, 70.13, 95.20, 170.49, 171.28. Ms: m/e

231(M^+), 186, 172, 158, 127, 113, 99. (Found: C, 51.90; H, 7.43; N, 6.10%. Calc. for $C_{10}H_{17}NO_5$: C, 51.92; H, 7.41; N, 6.06%). Further elution gave *cis* (*3SR, 5RS*)-2,3-dimethyl-3-carboxyethyl-5-acetoxyisoxazolidine **8**, 45% yield. Colorless oil; ^{1}H NMR: δ ($CDCl_3$) 1.28 (t, 3H, *J* = 7.2 Hz), 1.35 (s, 3H, $H_{3'}$), 2.07 (s, 3H, CH_3CO), 2.56 (dd, 1H, H_{4a}, *J* = 14.4 and 6.3 Hz), 2.73 (s, 3H, NCH_3), 2.95 (dd, 1H, H_{4b}, *J* = 14.4 and 3.0 Hz), 4.21 (q, 2H, *J* = 7.2 Hz), 6.23 (dd, 1H, H_5, *J* = 6.3 and 3.0 Hz). ^{13}C NMR: δ ($CDCl_3$) 14.00, 16.84, 21.23, 38.60, 47.06, 61.66, 69.14, 94.38, 170.64, 171.31. Ms: m/e 231(M^+), 186, 172, 158, 127, 113, 99. (Found: C, 51.89; H, 7.39; N, 6.08%. Calc. for $C_{10}H_{17}NO_5$: C, 51.92; H, 7.41; N, 6.06%).

Reaction of C-carboxyethyl-C-pentyl-N-benzylnitrone ***5*** *with vinyl acetate*. First elution gave *trans* (*3SR, 5SR*)-2-benzyl-3-carboxyethyl-3-penthyl-5-acetoxyisoxazolidine **13**, 40.5% yield. Sticky oil; ν_{max} (neat) 2970, 2940, 2880, 1710, 1525, 1130, 1030, 705 cm^{-1}. ^{1}H NMR: δ ($CDCl_3$) 0.89 (t, 3H, *J* = 6.4 Hz), 1.26-1.43 (m, 6H, aliphatic protons), 1.34 (t, 3H, *J* = 7.1 Hz), 1.62 (dt, 1H, $H_{3'a}$, *J* = 14.9 and 6.4 Hz), 1.87-2.12 (m, 1H, $H_{3'b}$) 2.04 (s, 3H, CH_3CO), 2.24 (dd, 1H, H_{4a}, *J* = 13.3 and 3.5 Hz), 3.26 (dd, 1H, H_{4b}, *J* = 13.3 and 6.6 Hz), 3.74 (d, 1H, $H_{2'a}$, *J* = 15.0 Hz), 4.15 (d, 1H, $H_{2'b}$, *J* = 15.0 Hz), 4.27 (q, 2H, *J* = 7.1 Hz), 6.30 (dd, 1H, H_5, *J* = 6.6 and 3.5 Hz), 7.24-7.40 (m, 5H, aromatic protons).^{13}C NMR: δ ($CDCl_3$) 13.85, 14.34, 21.22, 22.27, 24.92, 32.01, 33.70, 44.41, 55.59, 61.22, 73.93, 95.32, 126.97, 128.08, 128.15, 137.71, 170.50, 170.66. Ms: m/e 363(M^+), 348, 334, 320, 312, 306, 292, 290, 272, 91, 77. (Found: C, 66.04; H, 8.09; N, 3.84%. Calc. for $C_{20}H_{29}NO_5$: C, 66.08; H, 8.05; N, 3.86%). Further elution gave *cis* (*3SR, 5RS*)-2-benzyl-3-carboxyethyl-3-penthyl-5-acetoxyisoxazolidine **9**, 40.5% yield. Sticky oil; ν_{max} (neat) 2970, 2940, 2880, 1710, 1525, 1130, 1030, 705 cm^{-1}. ^{1}H NMR: δ ($CDCl_3$) 0.90 (t, 3H, *J* = 6.3 Hz), 1.17-1.37 (m, 6H, aliphatic protons), 1.28 (t, 3H, *J* = 7.1 Hz), 1.77 (dt, 1H, $H_{3'a}$, *J* = 13.7 and 6.3 Hz), 1.99 (dt, 1H, $H_{3'b}$, *J* = 13.7 and 6.3 Hz), 2.04 (s, 3H, CH_3CO), 2.70 (dd, 1H, H_{4a}, *J* = 14.2 and 6.6 Hz), 3.02 (dd, 1H, H_{4b}, *J* = 14.2 and 2.8 Hz), 4.00 (d, 1H, $H_{2'a}$, *J* = 14.3 Hz), 4.20 (dq, 2H, *J* = 7.1 and 2.7 Hz), 4.31 (d, 1H, $H_{2'b}$, *J* = 14.3 Hz), 6.25 (dd, 1H, H_5, *J* = 6.6 and 2.8 Hz), 7.22-7.41 (m, 5H, aromatic protons).^{13}C NMR: δ ($CDCl_3$) 13.89, 14.09, 21.23, 22.36, 24.33, 32.03, 32.26, 42.86, 56.11, 61.49, 73.35, 95.69, 126.70, 128.17, 128.35, 137.88, 170.41, 170.49. Ms: m/e 363(M^+), 348, 334, 320, 312, 306, 292, 290, 272, 91, 77. (Found: C, 66.03; H, 8.06; N, 3.87%. Calc. for $C_{20}H_{29}NO_5$: C, 66.08; H, 8.05; N, 3.86%).

Reaction of C-carboxyethyl-N-benzylnitrone ***6*** *with vinyl acetate*. First fractions gave an unseparable mixture of *cis* (*3SR, 5RS*)-2-benzyl-3-carboxyethyl-5-acetoxyisoxazolidine **10** and *trans* (*3SR, 5SR*)-2-benzyl-3-carboxyethyl-5-acetoxyisoxazolidine **14**, 87% yield (epimeric mixture). Colorless oil; ν_{max} (neat) 2960, 2920, 2850, 1745, 1465, 1375 cm^{-1}. ^{1}H NMR (major isomer): δ ($CDCl_3$) 1.21 (t, 3H, *J* = 7.2 Hz), 2.07 (s, 3H, CH_3CO), 2.61 (ddd, 1H, H_{4a}, *J* = 13.3, 7.3 and 1.2 Hz), 2.88 (ddd, 1H, H_{4b}, *J* = 13.3, 8.2 and 5.0 Hz), 3.88 (dd, 1H, H_3, *J* = 8.2 and 7.3 Hz), 4.11 (q, 2H, *J* = 7.2 Hz), 4.15 (d, 1H, $H_{2'a}$, *J* = 13.0 Hz), 4.33 (d, 1H, $H_{2'b}$, *J* = 13.0 Hz), 6.41 (dd, 1H, H_5, *J* = 5.0 and 1.2 Hz), 7.27-7.39 (m, 5H, aromatic protons).^{13}C NMR (major isomer): δ ($CDCl_3$) 13.86, 21.16, 39.44, 61.42, 64.16, 64.39, 96.81, 127.57, 128.18, 129.30, 135.71, 169.64, 169.66. Ms: m/e 293(M^+), 234, 220, 202, 91, 77.

Reaction of C-benzoyl-N-benzylnitrone 7 with vinyl acetate. First fractions gave *cis* (*3SR, 5RS*)-2-benzyl-3-benzoyl-5-acetoxyisoxazolidine **11**, 23% yield. White solid, mp 140 °C; ν_{max} (KBr) 1740, 1680, 1445, 1250, 1215 cm^{-1}. ^{1}H NMR: δ ($CDCl_3$) 2.07 (s, 3H, CH_3CO), 2.69 (ddd, 1H, H_{4a}, *J* = 14.0, 8.1 and 2.1 Hz), 2.98 (ddd, 1H, H_{4b}, *J* = 14.0, 9.3 and 6.4 Hz), 4.07 (dd, 1H, H_3, *J* = 9.3 and 8.1 Hz), 4.15 (s, 2H, NCH_2), 6.40 (dd, 1H, H_5, *J* = 6.4 and 2.1 Hz) 7.23-8.10 (m, 10H, aromatic protons). ^{13}C NMR: δ ($CDCl_3$) 21.24, 36.65, 61.39, 69.95,

95.17, 127.72, 128.23, 128.43, 128.82, 129.64, 130.10, 133.11, 133.46, 134.95, 135.19, 170.39, 195.03; ms: m/e 325 (M^+), 234, 220, 105, 91, 77. (Found: C, 70.12; H, 5.90; N, 4.33%. Calc. for $C_{19}H_{19}NO_4$: C, 70.13; H, 5.89; N, 4.31%). Second fractions gave *trans* (*3SR, 5SR*)-2-benzyl-3-benzoyl-5-acetoxyisoxazolidine **15**, 69% yield. White solid, mp 135 °C; ν_{max} (KBr) 1745, 1680, 1450, 1240, 1220 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.14 (s, 3H, CH_3CO), 2.70 (ddd, 1H, H_{4a}, J = 13.5, 7.2 and 2.6 Hz), 3.27 (ddd, 1H, H_{4b}, J = 13.5, 6.3 and 4.5 Hz), 4.16 (d, 1H, $H_{2'a}$, J = 12.3 Hz), 4.30 (d, 1H, $H_{2'b}$, J = 12.3 Hz), 4.77 (dd, 1H, H_3, J = 7.2 and 4.5 Hz), 6.58 (dd, 1H, H_5, J = 6.3 and 2.6 Hz) 7.26-7.61 (m, 10H, aromatic protons). ^{13}C NMR: δ ($CDCl_3$) 21.40, 36.70, 64.10, 66.70, 99.05, 128.12, 128.33, 128.64, 129.02, 129.96, 133.27, 134.78, 135.77, 168.49, 195.08. Ms: m/e 325 (M^+), 266, 105, 91, 77. (Found: C, 70.13; H, 5.91; N, 4.32%. Calc. for $C_{19}H_{19}NO_4$: C, 70.13; H, 5.89; N, 4.31%).

Reaction of isoxazolidines 8-15 with silylated thymine and 5-fluorouracil.

General procedure. To a stirred mixture of thymine or 5-fluorouracil (1.5 mmol) and isoxazolidine **8-15** in epimeric mixtures (1.5 mmol) in anhydrous CH_2Cl_2 was added *N,O*-Bis(trimethylsilyl)acetamide (3.5 mmol). After 3 h of stirring at room temperature, the clear solution was cooled to 0 °C and $SnCl_4$ (0.3 mmol) was added. The mixture was then warmed to room temperature, left to stir overnight and, finally, poured slowly into a mixture of cold saturated aqueous $NaHCO_3$ (5 ml) and $CHCl_3$ (10 ml). The resulting emulsion was separated by filtration through Celite, the aqueous layer was extracted further with ethyl acetate (3 x 10 ml), and the combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was then subjected to flash-chromatography on silica gel column with chloroform-methanol 95:5 as eluent.

*Reaction of isoxazolidines **8** and **12** with silylated thymine*. First fraction gave an unseparable mixture of *cis* (*3'SR, 5'RS*)-2',3'-dimethyl-3'-carboxyethyl-1',2'-isoxazolidinyl-α-thymidine **20** and *trans* (*3'SR, 5'SR*)-2',3'-dimethyl-3'-carboxyethyl-1',2'-isoxazolidinyl-β-thymidine **16**, 91% yield. White solid, mp 175-180 °C. Cis isomer: ^1H NMR: δ ($CDCl_3$) 1.23-1.26 (t, 3H, J = 6.2 Hz), 1.34 (s, 3H, $H_{3''}$), 1.89 (s, 3H, CH_3), 2.66 (s, 3H, N-CH_3), 2.70 (dd, 1H, $H_{4'}$, J = 14.1 and 7.8 Hz), 2.80 (dd, 1H, $H_{4'}$, J = 14.1 and 4.8 Hz), 4.18 (m, 2H), 6.16 (m, 1H, $H_{5'}$), 7.50 (s, 1H, H_6), 9.10 (bs, 1H, NH). *Trans* isomer: ^1H NMR: δ ($CDCl_3$) 1.23-1.26 (t, 3H, J = 6.2 Hz), 1.35 (s, 3H, $H_{3''}$), 1.88 (s, 3H, CH_3), 2.03 (dd, 1H, $H_{4'}$, J = 13.5 and 4.8 Hz), 2.62 (s, 3H, N-CH_3), 3.32 (dd, 1H, $H_{4'}$, J = 13.5 and 7.2 Hz), 4.18 (m, 2H), 6.16 (m, 1H, $H_{5'}$), 7.69 (s, 1H, H_6), 9.10 (bs, 1H, NH). ^{13}C nmr (epimeric mixture): δ ($CDCl_3$) 13.52, 13.78, 18.81, 21.39, 37.91, 37.97, 47.00, 47.68, 60.94, 61.49, 69.22, 69.79, 81.22, 81.75, 110.23, 110.42, 135.41, 136.28, 150.53, 150.72, 164.54, 164.61, 169.90, 170.81. Ms: m/e 297(M^+), 224, 179, 166, 121. (Found: C, 52.52; H, 6.43; N, 14.15%. Calc. for $C_{13}H_{19}N_3O_5$: C, 52.50; H, 6.44; N, 14.14%).

*Reaction of isoxazolidines **9** and **13** with silylated 5-fluorouracil*. First elutions gave an unseparable mixture of *trans* (*3'SR, 5'SR*)-2'-benzyl-3'-carboxyethyl-3'-penthyl-1',2'-isoxazolidinyl-α-5-fluorouridine **17**, 53% yield and *cis* (*3'SR, 5'RS*)-2'-benzyl-3'-carboxyethyl-3'-penthyl-1',2'-isoxazolidinyl-β-5-fluorouridine **21**, 36% yield. Colorless sticky oil; ν_{max} (neat) 3190, 3070, 2960, 2930, 2870, 1735, 1715, 1660, 1465, 1395, 1260, 1195, 740, 695 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 0.91 (t, 3H, J = 6.2 Hz), 0.93 (t, 3H, J = 6.2), 1.30-1.42 (m, 18 H), 1.52-1.87 (m, 2H), 1.94-2.16 (m, 2H), 2.96 (m, 2H), 3.57 (dd, 1H, $H_{4'}$, J = 14.3 and 6.2 Hz), 3.64 (d, 1H, $H_{2'}$, J = 14.3 Hz), 3.96 (d, 1H, $H_{2'}$, J = 14.0 Hz), 4.18-4.40 (m, 7H, $H_{2'}$ and aliphatic protons), 6.01 (m, 2H, $H_{5'}$), 7.23-7.39 (m, 11H, H_6 and aromatic protons), 7.62 (d, 1H, H_6, J = 6.5 Hz), 9.44 (bs, 2H, NH).^{13}C NMR: δ ($CDCl_3$) 13.88, 14.16, 14.18, 14.42, 22.37, 24.42, 24.44, 24.84, 30.64, 31.96, 32.09, 33.75, 44.44, 46.60, 55.52, 56.13, 61.58, 61.95, 72.84, 73.59, 82.47, 83.16, 123.69, 124.40, 124.57, 125.27, 127.78, 128.00,

128.56, 128.79, 136.77, 137.00, 137.83, 142.54, 148.79, 149.05, 156.60, 157.12, 169.79, 170.32. Ms: m/e 414(M^+), 399, 385, 371, 357, 343, 341, 323, 286, 250, 91, 77. (Found: C, 63.75; H, 6.83; N, 10.40%. Calc. for $C_{22}H_{28}N_3O_5$: C, 63.74; H, 6.81; N, 10.41%).

*Reaction of isoxazolidines **10** and **14** with silylated 5-fluorouracil.* First fractions gave *trans* (*3'SR, 5'SR*) 2'-benzyl-3'-carboxyethyl-1',2'-isoxazolidinyl-α-5-fluorouridine **18**, 49% yield. Sticky oil; ν_{max} (KBr) 3180, 3060, 3000, 1740, 1720, 1700, 1660, 1470, 1400, 1260, 1200, 1110, 1050, 750, 695 cm^{-1}. ^1H NMR (main isomer): δ (DMSO-d_6) 1.17 (t, 3H, J = 7.0 Hz), 2.59 (ddd, 1H, $H_{4'a}$, J = 13.2, 7.1 and 1.1 Hz), 3.21 (ddd, 1H, $H_{4'b}$, J = 13.2, 9.4 and 6.3 Hz), 3.77 (dd, 1H, $H_{3'}$, J = 9.4 and 7.1 Hz), 4.01 (d, 1H, $H_{2''a}$, J = 13.8 Hz), 4.07 (q, 2H, J = 7.0 Hz), 4.20 (d, 1H, $H_{2''b}$, J = 13.8 Hz), 6.18 (dd, 1H, $H_{5'}$, J = 6.3 and 1.1 Hz), 7.29-7.36 (m, 5H, aromatic protons), 7.97 (d, 1H, H_6, J = 7.3), 11.88 (d, 1H, NH, J = 5.3).^{13}C NMR (main isomer): δ (DMSO-d_6) 13.79, 60.86, 61.24, 65.68, 79.27, 82.63, 124.58, 125.28, 127.54, 128.26, 128.84, 136.28, 141.82, 149.09, 169.64. Ms: m/e 344(M^+), 271, 253, 216, 180, 91, 77. (Found: C, 59.27; H, 5.30; N, 12.20%. Calc. for $C_{17}H_{18}N_3O_5$: C, 59.28; H, 5.27; N, 12.21%). Further elution gave *cis* (*3'SR, 5'RS*)-2'-benzyl-3'-carboxyethyl-1',2'-isoxazolidinyl-β-5-fluorouridine **22**, 33% yield. Sticky oil; ν_{max} (KBr) 3170, 3060, 3000, 1740, 1715, 1700, 1660, 1470, 1400, 1260, 1200, 1110, 1050, 745, 700 cm^{-1}. ^1H nmr: (minor isomer) δ (DMSO-d_6) 1.22 (t, 3H, J = 7.0 Hz), 2.63 (ddd, 1H, $H_{4'a}$, J = 13.0, 6.9 and 3.1 Hz), 2.89 (ddd, 1H, $H_{4'b}$, J = 13.0, 8.7 and 6.5 Hz), 3.78 (dd, 1H, $H_{3'}$, J = 8.7 and 6.9 Hz), 4.02 (d, 1H, $H_{2''a}$, J = 13.5 Hz), 4.09 (q, 2H, J = 7.0 Hz), 4.18 (d, 1H, $H_{2''b}$, J = 13.5 Hz), 6.03 (dd, 1H, $H_{5'}$, J = 6.5 and 3.1 Hz), 7.28-7.38 (m, 5H, aromatic protons), 7.86 (d, 1H, H_6, J = 7.2), 11.80 (d, 1H, NH, J = 5.3).^{13}C NMR (minor isomer): δ (DMSO-d_6) 13.95, 60.48, 61.35, 65.52, 79.05, 82.95, 124.21, 124.99, 127.67, 128.34, 128.91, 136.21, 141.80, 149.13, 169.71. Ms: m/e 344(M^+), 271, 253, 216, 180, 91, 77. (Found: C, 59.29; H, 5.29; N, 12.22%. Calc. for $C_{17}H_{18}N_3O_5$: C, 59.28; H, 5.27; N, 12.21%).

*Reaction of isoxazolidines **11** and **15** with silylated thymine.* First fractions gave *trans* (*3'SR, 5'SR*)-2'-benzyl-3'-benzoyl-1',2'-isoxazolidinyl-α-thymidine **19**, 54% yield. White solid, mp 190-192 °C; ν_{max} (KBr) 1670, 1450, 1370, 1270, 1110, 960 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.76 (s, 3H), 2.52 (ddd, 1H, $H_{4'a}$, J = 14.0, 11.4 and 3.6 Hz), 3.25 (ddd, 1H, $H_{4'b}$, J = 14.0, 8.1 and 4.0 Hz), 3.94 (d, 1H, $H_{2''a}$, J = 13.5 Hz), 4.18 (d, 1H, $H_{2''b}$, J = 13.5 Hz), 4.54 (dd, 1H, $H_{3'}$, J = 11.4 and 8.1 Hz), 6.19 (dd, 1H, $H_{5'}$, J = 4.0 and 3.6 Hz) 7.23-7.77 (m, 10H, aromatic protons), 7.53 (s, 1H, H_6), 11.01 (s, 1H, NH). ^{13}C NMR: δ ($CDCl_3$) 12.08, 42.08, 60.79, 67.84, 82.21, 109.30, 127.31, 127.89, 127.97, 128.22, 128.61, 128.73, 133.33, 135.48, 135.67, 150.37, 163.80, 194.91. Ms: m/e 391(M^+), 300, 286, 266, 105, 91, 77. (Found: C, 67.51; H, 5.40; N, 10.75%. Calc. for $C_{22}H_{21}N_3O_4$: C, 67.49; H, 5.41; N, 10.74%). Further elution gave *cis* (*3'SR, 5'RS*)-2'-benzyl-3'-benzoyl-1',2'-isoxazolidinyl-β-thymidine **23**, 36% yield. White solid, mp 195-196 °C; ν_{max} (KBr) 1680, 1445, 1360, 1280, 1105, 950 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.74 (s, 3H), 2.72 (m, 1H, $H_{4'a}$), 3.09 (m, 1H, $H_{4'b}$), 4.06 (s, 2H, NCH_2), 5.03 (m, 1H, $H_{3'}$), 6.18 (m, 1H, $H_{5'}$) 7.25-7.87 (m, 10H, aromatic protons), 7.50 (s, 1H, H_6), 11.05 (s, 1H, NH). ^{13}C NMR: δ ($CDCl_3$) 22.05, 40.58, 61.25, 68.30, 83.10, 110.09, 127.85, 128.27, 128.33, 128.46, 128.66, 129.09, 129.21, 133.86, 135.27, 135.69, 174.63, 195.07. Ms: m/e 391(M^+), 300, 286, 266, 105, 91, 77. (Found: C, 67.50; H, 5.39; N, 10.73%. Calc. for $C_{22}H_{21}N_3O_4$: C, 67.49; H, 5.41; N, 10.74%).

Reduction of nucleosides 16, 17, 19-21 with sodium borohydride.

General procedure. To a stirred mixture of nucleoside **16, 17, 19-21** (2.3 mmol) in dioxane/H_2O 1:1 (10 ml) was added $NaBH_4$ (11.5 mmol) at room temperature, until tlc showed the disappearance of the starting compound (5-36 h). The reaction mixture was then extracted with ethyl acetate (5 x 10 ml) and the combined

organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was then subjected to flash-chromatography on silica gel column with chloroform-methanol 95:5 as eluent.

*Reaction of nucleosides **16** and **20** with $NaBH_4$.* First eluted product was *cis* (*3'SR, 5'RS*)-2',3'-dimethyl-3'-hydroxymethyl-1',2'-β-thymidine **24**, 48% yield. White solid; mp 178-180 °C; ν_{max} (KBr) 3480 (broad),1680, 1450, 1270, 1060, 890 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.04 (s, 3H, $H_{3''}$), 1.18 (s, 1H, OH), 1.86 (s, 3H, CH_3), 2.54 (d, 2H, $H_{4'}$, J = 6.3 Hz), 2.58 (s, 3H, NCH_3), 3.46 (s, 2H), 6.04 (dd, 1H, $H_{5'}$, J = 6.3 and 6.3 Hz), 7.58 (s, 1H, H_6), 9.27 (bs, 1H, NH). ^{13}C NMR: δ ($CDCl_3$) 12.67, 15.42, 37.00, 46.34, 64.66, 66.92, 81.97, 110.48, 135.92, 150.57, 164.18. Ms: m/e 255(M^+), 237, 210, 130, 112, 85. (Found: C, 51.75; H, 6.72; N, 16.44%. Calc. for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46%). Further eluted product was *trans* (*3'SR, 5'SR*)-2',3'-dimethyl-3'-hydroxymethyl-1',2'-α-thymidine **26**, 34% yield. White solid; mp 180-185 °C; ν_{max} (KBr) 3470 (broad), 1680, 1455, 1260, 1065, 880 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.14 (s, 3H, $H_{3''}$), 1.18 (s, 1H, OH), 1.89 (s, 3H, CH_3), 2.25 (dd, 1H, $H_{4'a}$, J = 14.1 and 5.0 Hz), 2.69 (s, 3H, NCH_3), 2.99 (dd, 1H, $H_{4'b}$, J = 14.1 and 7.5 Hz), 3.45 (s, 2H), 6.04 (dd, 1H, $H_{5'}$, J = 7.5 and 5.0 Hz), 7.55 (s, 1H, H_6), 8.67 (bs, 1H, NH). ^{13}C NMR: δ ($CDCl_3$) 12.69, 15.38, 36.96, 46.31, 64.57, 66.51, 81.93, 110.47, 135.71, 150.32, 163.79. Ms: m/e 255(M^+), 237, 210, 130, 112, 85. (Found: C, 51.77; H, 6.69; N, 16.45%. Calc. for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46%).

*Reaction of nucleosides **17** and **21** with $NaBH_4$.* First eluted product was *cis* (*3'SR, 5'RS*)-2'-benzyl-3'-hydroxymethyl-3'-penthyl-1',2'-α-5-fluorouridine **25**, 47% yield. white solid; mp 176-178 °C; ν_{max} (KBr) 3520, 3170, 3070, 2960, 2930, 2860, 1710, 1660, 1470, 1400, 1265, 1085, 725, 590 cm^{-1}. ^1H NMR: δ (DMSO-d_6) 0.90 (t, 3H, J = 6.0), 1.33 (m, 6H), 1.61 (m, 2H, $H_{3'''a}$ and $H_{3'''b}$), 2.20 (dd, 1H, $H_{4'a}$, J = 13.9 and 3.4 Hz), 2.73 (dd, 1H, $H_{4'b}$, J = 13.9 and 7.8 Hz), 3.57 (dd, 1H, $H_{3''a}$, J = 11.6 Hz), 3.63 (d, 1H, $H_{3''b}$, J = 11.6 Hz), 3.78 (d, 1H, $H_{2''a}$, J = 14.7 Hz), 4.25 (d, 1H, $H_{2''b}$, J = 14.7 Hz), 5.93 (dd, 1H, $H_{5'}$, J = 7.8 and 3.4 Hz), 7.24-7.40 (m, 5H, aromatic protons), 7.91 (d, 1H, NH, J = 7.3 Hz). ^{13}C NMR: δ (DMSO-d_6) 13.53, 22.03, 23.84, 28.10, 32.21, 42.21, 54.24, 63.04, 68.90, 81.48, 124.77, 125.47, 126.92, 127.74, 128.01, 128.27, 137.08, 138.72, 141.63, 148.96, 156.70, 157.22. Ms: m/e 372(M^+), 357, 354, 343, 329, 315, 244, 224, 153, 91, 77. (Found: C, 64.45; H, 7.05; N, 11.27%. Calc. for $C_{20}H_{26}N_3O_4$: C, 64.48; H, 7.04; N, 11.29%). Further elution gave *trans* (*3'SR, 5'SR*)-2'-benzyl-3'-hydroxymethyl-3'-penthyl-1',2'-β-5-fluorouridine **27**, 29% yield. colorless sticky oil; ν_{max} (neat) 3470, 3190, 3070, 2960, 2930, 2870, 1715, 1685, 1470, 1400, 1065, 725, 695 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 0.90 (t, 3H, J = 6.1), 1.33 (m, 7H), 1.51 (m, 1H, $H_{3'''a}$), 1.78 (dt, 1H, $H_{3'''b}$, J = 8.9 and 7.2 Hz), 2.22 (dd, 1H, $H_{4'a}$, J = 14.1 and 3.7 Hz), 2.88 (dd, 1H, $H_{4'b}$, J = 14.1 and 7.5 Hz), 3.77 (d, 1H, $H_{3''a}$, J = 11.7 Hz), 3.89 (d, 1H, $H_{3''b}$, J = 11.7 Hz), 3.95 (d, 1H, $H_{2''a}$, J = 14.3 Hz), 4.17 (d, 1H, $H_{2''b}$, J = 14.3 Hz), 5.88 (dd, 1H, $H_{5'}$, J = 7.5 and 3.7 Hz), 7.26-7.39 (m, 6H, H_6 and aromatic protons). ^{13}C NMR: δ ($CDCl_3$) 13.97, 22.46, 24.24, 29.68, 32.31, 45.95, 54.74, 63.26, 69.03, 82.90, 124.28, 124.98, 127.80, 128.62, 137.58, 137.81, 142.50, 149.05, 156.94, 157.48. Ms: m/e 372(M^+), 357, 354, 343, 329, 315, 244, 224, 153, 91, 77. (Found: C, 64.46; H, 7.03; N, 11.30%. Calc. for $C_{20}H_{26}N_3O_4$: C, 64.48; H, 7.04; N, 11.29%).

*Reaction of nucleoside **19** with $NaBH_4$.* First eluted product was *trans* (*3'SR, 3''R, 5'SR*)-2'benzyl-3'-phenylmethanol-1',2'-isoxazolidinyl-α-thymidine **28**, 60% yield. White solid; mp 180-183 °C; ν_{max} (KBr) 3500, 1690, 1480, 1260, 1230, 1060, 900 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.52 (s, 3H), 2.06 (ddd, 1H, $H_{4'a}$, J = 13.7, 8.2 and 3.3 Hz), 2.37 (d, 1H, OH, J = 2.7 Hz), 2.62 (ddd, 1H, $H_{4'b}$, J = 13.7, 8.2 and 7.3 Hz), 3.36 (ddd, 1H, $H_{3'}$, J = 8.2, 8.2 and 7.3), 3.86 (d, 1H, $H_{2''a}$, J = 14.1 Hz), 4.52 (d, 1H, $H_{2''b}$, J = 14.1 Hz), 4.69 (dd, 1H, $H_{3''}$, J = 7.3 and 2.7 Hz), 5.79 (dd, 1H, $H_{5'}$, J = 7.3 and 3.3 Hz), 7.15 (s, 1H, H_6), 7.21-7.36 (m, 10 H, aromatic protons),

8.23 (bs, 1H, NH). ^{13}C nmr: δ ($CDCl_3$) 22.49, 29.68, 41.54, 62.58, 69.60, 75.47, 83.17, 109.69, 126.76, 127.67, 128.45, 128.60, 128.78, 129.00, 135.86, 137.16, 140.90, 150.21, 164.04. Ms: m/e 393(M^+), 375, 302, 284, 268, 207, 91, 77. (Found: C, 67.13; H, 5.91; N, 10.70%. Calc. for $C_{22}H_{23}N_3O_4$: C, 67.16; H, 5.89; N, 10.68%). Further elution gave *trans* (*3'SR, 3''S, 5'SR*)-2'benzyl-3'-phenylmethanol-1',2'-isoxazolidinyl-α-thymidine **29**, 30% yield. White solid; mp 188-190 °C; ν_{max} (KBr) 3400, 1685, 1470, 1260, 1235, 1060, 910 cm^{-1}. ^{1}H NMR: δ ($CDCl_3$) 1.66 (s, 3H), 2.02 (m, 1H, $H_{4'a}$, J = 13.5, 8.1 and 2.2 Hz), 2.43-2.48 (ddd, 1H, $H_{4'b}$, J = 13.5, 7.3 and 6.6 Hz), 3.86 (ddd, 1H, $H_{3'}$, J = 8.1, 7.3 and 3.6 Hz), 3.92 (d, 1H, $H_{2''a}$, J = 14.0 Hz), 4.52 (d, 1H, $H_{2''b}$, J = 14.0 Hz), 4.75 (d, 1H, $H_{3''}$, J = 3.6 Hz), 5.83 (dd, 1H, $H_{5'}$, J = 6.6 and 2.2 Hz), 6.90 (s, 1H, H_6), 7.20-7.30 (m, 10 H, aromatic protons), 8.51 (bs, 1H, NH). ^{13}C NMR: δ ($CDCl_3$) 22.42, 29.43, 38.25, 61.18, 70.30, 71.60, 84.51, 110.41, 128.32 ,128.36, 128.43, 128.53, 128.64, 128.82, 128.87, 129.24, 136.20, 139.90, 150.53, 164.49. Ms: m/e 393(M^+), 375, 302, 284, 268, 207, 91, 77. (Found: C, 67.18; H, 5.87; N, 10.71%. Calc. for $C_{22}H_{23}N_3O_4$: C, 67.16; H, 5.89; N, 10.68%).

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