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TETRAHEDRON: *ASYMMETRY*

Diastereo- and enantioselective synthesis of *N,O*-nucleosides

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Abstract—The diastereo- and enantioselective synthesis of α- and β-3′-hydroxymethyl-*N,O*-nucleosides is described, based on the 1,3-dipolar cycloaddition of a *N*-glycosyl nitrone. Two approaches have been evaluated: the one-step procedure, which uses vinyl nucleobases, showed a better stereoselectivity towards β-nucleosides.

1. Introduction

The improved knowledge of the HIV virus and its replication mechanism have suggested in recent years the synthesis of new molecules able to block the viral replication.[1] These compounds originate from chemical modifications of the nucleic acid fragments at the level of the sugar moiety and/or the heterocyclic base. In this context, the design of novel 'ribose' rings has resulted in the discovery of effective biological agents; promising results have been obtained from a new generation of nucleoside analogues where the ribose moiety has been replaced by either carbo- or heterocyclic rings.[2–4]

The synthesis of isoxazolidinyl nucleosides **1**, unsubstituted on the nitrogen atom and in racemic form, has been recently reported:[5] ADT **1** shows interesting antiviral and anti-AIDS activity (Fig. 1).

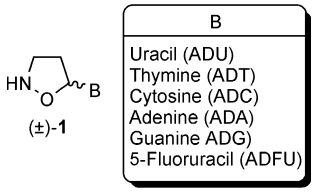

Figure 1. Isoxazolidinyl nucleosides.

The asymmetric version has also been investigated through the use of chiral dipoles:[6,7] In this way, ADU, ADT, ADC, ADA and ADFU have been synthesized in enantiomerically pure form. (–)-ADFU shows promising biological properties: in particular it appears as a good inductor of apoptosis on lymphoid and monocytoid cells, acting as a strong potentiator of Fas-induced cell death.[7]

Herein we report a successful extension of the methodology towards the enantioselective synthesis of 3-hydroxymethyl derivatives of ADT, ADU, ADFU: the presence in the molecule of the hydroxymethyl group should promote the biological phosphorylation of the compounds and hence their biological activity.[8]

2. Results and discussion

N-Glycosylnitrones[9] have been exploited as versatile building blocks in the preparation of the target modified nucleosides: the chiral auxiliary is easily introduced before the cycloaddition process and removed subsequently to give *N,O*-nucleosides unsubstituted on the nitrogen atom.

Thus, the reaction of (4*S*,5*R*)-5-[(1*R*)-2[[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy]-1-hydroxyethyl]-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde oxime **2**, with ethyl glyoxylate and vinyl acetate, in $CHCl_3$ at

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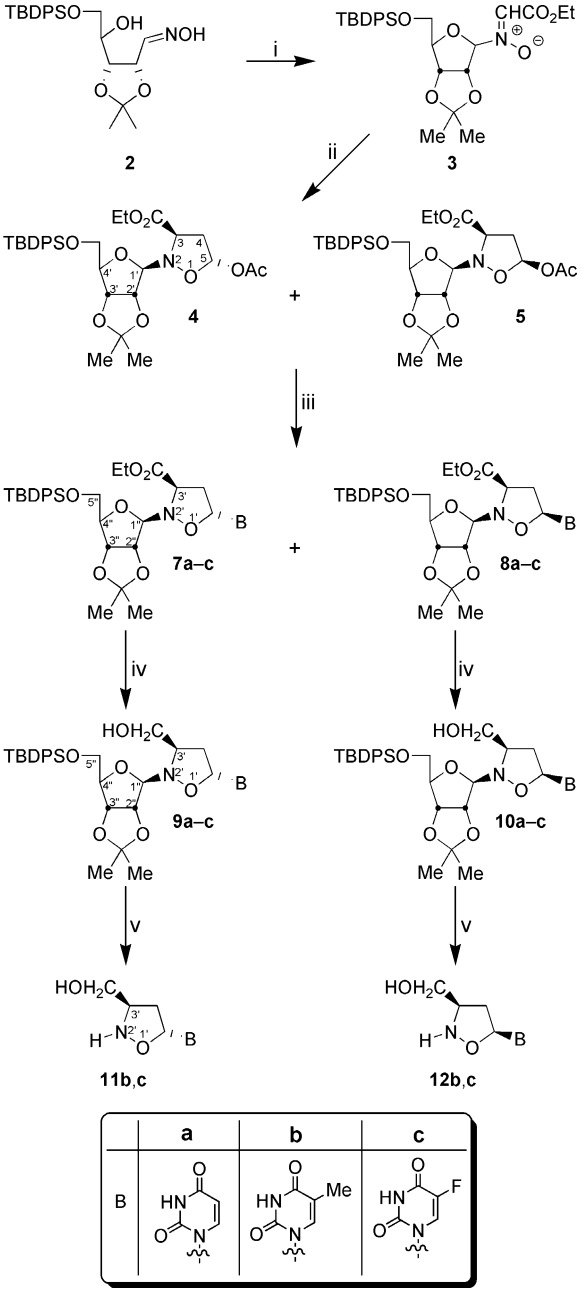
reflux at 60°C for 14 h gives, as previously reported,[10] a mixture of two homochiral isoxazolidines **4** and **5**, epimeric at C_5, in a relative ratio *trans*/*cis* 1:1 (Scheme 1).

The two cycloadducts were independently converted in the (3*R*)-2-(5′-*O*-*tert*-butyldiphenylsilyl-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-3-ethoxycarbonylisoxazolidin-5-one[10] through hydrolysis with K_2CO_3, followed by oxidation with potassium permanganate. This result indicates that isoxazolidines **4** and **5** are epimeric at C_5, while they possess the same stereochemistry at C_3 and $C_{1'}$.



Scheme 1. *Reagents and conditions*: (i) Ethyl glyoxylate; (ii) vinyl acetate, 70°C; (iii) BSA, nucleobases, Me_3SiOTf in refluxed MeCN for 1 h, or $SnCl_4$, at 0°C for 2 h, and then overnight at rt; (iv) $NaBH_4$, dioxane:water 1:1, rt, 5 h; (v) 1.5% HCl in EtOH, rt, 3 h.

Thus, the cycloaddition reaction proceeds with a complete diastereofacial selectivity by involving, according to PM3 calculations,[11] the attack of dipolarophile on the *re*-face of nitrone in an *E*-*exo* and *E*-*endo* transition-state: in fact, an energy difference of 2.5 kcal/mol is observed in favor of the *re*-face attack with respect to the *si*-face one. This behaviour is also in accord with ab initio DFT calculations on *C*-methoxycarbonyl nitrone with vinyl acetate.[12] On these basis, the absolute configuration of the cycloadducts **4** and **5** can be tentatively assigned as (3*R*,5*R*) and (3*R*,5*S*) respectively.

The mixture of epimeric isoxazolidines **4** and **5** was then reacted with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and uracil **6a**, or thymine **6b**, in acetonitrile in the presence of TMSOTf or with 5-fluorouracil **6c** in CH_2Cl_2 at 0°C, in the presence of one equivalent of $SnCl_4$, to afford, with moderate stereoselectivity and good yields, the expected α- and β-nucleosides **7a**–**c** and **8a**–**c**, respectively (ratio 2.2:1), in enantiomerically pure form.

The structures of the obtained compounds were assessed on the basis of analytical and spectroscopic data (see Section 3). The ^1H NMR spectra of compounds **7a**–**c** showed the diagnostic resonances of $H_{5'}$ as dd, in the range 6.23–6.24 ppm, while $H_{3'}$ protons appear as dd, at 4.16–4.17 ppm; the methylene group at $C_{4'}$ resonate as ddd at 2.40–2.41 and 2.99–2.99. For compounds **8a**–**c**, $H_{5'}$ protons resonate as dd at 5.94–6.43, while $H_{3'}$ appear as dd at 4.05–4.12 ppm. Noteworthy, in **8a**–**c** $H_{5'}$ protons show a long-range coupling with $H_{3'}$, thus indicating a *cis* topological arrangement.

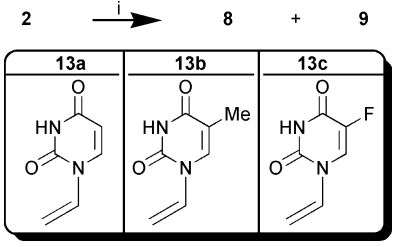
The stereochemical assignments have been performed on the basis of NOE and T-Roesy measurements. Irradiation of the $H_{5'}$ signal in **8a**–**c** (*cis*) induces a positive NOE effect on the upfield resonance of methylene protons at $C_{4'}$; in turn, irradiation of this proton gives rise to enhancement of the $H_{3'}$ resonance, thus indicating that these protons are in a *cis* arrangement. As confirmation, T-Roesy experiments reveal an intense NOE effect between $H_{5'}$, $H_{4'b}$ and $H_{3'}$.

Conversely, nucleosides **7a**–**c** (*trans*) shows a NOE correlation between $H_{5'}$ and the upfield resonance at $C_{4'}$, but only a negligible NOE effect between this last resonance and $H_{3'}$.

The reduction of the ester function was performed by treatment with $NaBH_4$ in dioxane/H_2O 1:1 to give 3′-hydroxymethyl derivatives **9a**–**c** and **10a**–**c**. Finally, the synthetic scheme was completed by removal of the sugar moiety, which was easily achieved by treatment with 1.5% aqueous HCl, to afford the target nucleosides **11** (α) and **12** (β), in enantiomerically pure form, with a satisfactory global yield starting from nitrone **3**. However, all the attempts to obtain uracil derivatives **11a** and **12a** failed.

A valuable improvement in the synthetic strategy has been exploited through the use of vinylated nucleobases, as dipolarophiles, to afford modified isoxazolidinyl nucleosides **7** and **8** in one step.

Thus, ribosyl oxyme **2** was reacted with ethyl glyoxylate and vinyl bases **13a**–**c** in $CHCl_3$ at 60°C for 12 h to afford nucleosides **7** and **8** in a 1:1.4 ratio (global yield 48%). In this case the reaction pathway appears to be different from the one presented in the above procedure, based on the Vorbrüggen nucleosidation; in fact, β-nucleosides **8a**,**c** are the major adducts. No attack of dipole to the double bond of nucleobases has been observed (Scheme 2).



Scheme 2. *Reagents and conditions*: (i) Ethyl glyoxylate, vinyl bases **13a**–**c**, 60°C, $CHCl_3$, 12 h.

The cycloaddition reaction shows, besides a complete diastereofacial selectivity, a moderate *cis*/*trans* diastereoselectivity, which can be rationalized by assuming that the *E*-*endo* attack of the dipolarophile on the *re*-face of the nitrone is the preferred reaction pathway, because of secondary orbital interactions exerted by the pyrimidine ring of nucleobases.

In conclusion, the enantioselective synthesis of α- and β-3′-hydroxymethyl-*N*,*O*-nucleosides has been described. Two different approaches have been evaluated: the two-step procedure, based on the 1,3-dipolar cycloaddition of the chiral nitrone **3** with vinyl acetate, followed by Vorbrüggen nucleosidation, leads to better yields with respect to the one-step approach based on the cycloaddition reaction, performed with vinyl nucleobase. In this latter case, however, the procedure shows an improved stereoselectivity towards the formation of β adducts.

The designed methodologies appear versatile and extendable to the synthesis of all *N*,*O*-nucleosides containing different purine and pyrimidine bases. Tests on the biological activity of the synthesized compounds are in progress.

3. Experimental

Melting points were determined with a Kofler apparatus and are uncorrected. Elemental analyses were performed with a Perkin–Elmer elemental analyzer. IR spectra were recorded on a Perkin–Elmer Paragon 500 FT-IR Spectrometer using potassium bromide discs. NMR spectra were recorded on a Varian instrument at 200 or 500 MHz (^{1}H) and at 50 or 125 MHz (^{13}C) using deuteriochloroform or deuterated methanol as solvent; chemical shifts are given in ppm from TMS as internal standard. Thin-layer chromatographic separations were performed on Merck silica gel 60-F_{254} precoated aluminium plates. Preparative separations were made by flash column chromatography using Merck silica gel 0.063–0.200 mm and 0.035–0.070 mm, respectively, with chloroform-methanol mixtures as eluent. HPLC purifications were made with a preparative column (Microsorb Dynamax 100Å, 21.4×250 mm). The purity of all homochiral compounds has been tested with a Nucleosil Chiral-2, 4×250 mm column with mixtures of *n*-hexane-2-propanol as eluent.

The identification of samples from different experiments was secured by mixed mps and superimposable IR spectra.

3.1. Starting materials

Ethyl glyoxylate, thymine, uracil, fluorouracil, and D-ribose were purchased from Aldrich Co. Isoxazolidines **4** and **5**,[10] and vinyl bases **13**[13] were prepared as already reported. All solvents were dried according to standard procedures.

3.2. Method A. General procedure for reactions between bases 6a,b and isoxazolidines 4 and 5

A suspension of bases **6a**–**c** (0.618 mmol) in dry acetonitrile (3 mL) was treated with *N*,*O*-bis(trimethylsilyl)acetamide (2.54 mmol) and refluxed for 15 min; to the clear solution obtained was added a solution of isoxazolidine **4** and **5** (0.517 mmol) in dry acetonitrile (3 mL) and then trimethylsilyltriflate (0.78 mmol) dropwise; the reaction mixture was refluxed for 1 h. After being cooled to 0°C, the solution was neutralized by careful addition of aqueous 5% sodium bicarbonate, and then it was concentrated in vacuo. To the crude was added dichloromethane (8 mL), and the organic phase was separated, washed with water (2×10 mL), dried over sodium sulfate, filtered, and evaporated to dryness. The residue was purified by radial chromatography (cyclohexane/ethyl acetate 3:2) and then by HPLC with a linear gradient of 2-propanol (6–10%, 0–10 min, flow 3.5 mL/min) in *n*-hexane.

3.2.1. 1-[(3*R*,5*R*)-2-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-ethoxycarbonyl-1,2-isoxazolidin-5-yl]-1*H*-pyrimidine-2,4-dione 7a. Yield 20%; HPLC: t_R 20.5 min. Oil; $[\alpha]_D^{25}=+15.3$ (*c* 2.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.06 (s, 9H), 1.19 (t, 3H, $J=7.5$ Hz), 1.34 (s, 3H), 1.52 (s, 3H), 2. 40 (ddd, 1H, $J=6.5$, 7.4, 14.0 Hz, $H_{4'a}$), 2.99 (ddd, 1H, $J=2.0$, 7.0, 13.0 Hz, $H_{4'b}$), 3.74 (dd, 1H, $J=6.0$, 11.0 Hz, $H_{5''a}$), 3.76 (dd, 1H, $J=5.0$, 11.5 Hz, $H_{5''b}$), 4.09 (dq, 1H, $J=7.5$, 15.5 Hz), 4.10 (dq, 1H, $J=7.5$, 15.5 Hz), 4.16 (dd, 1H, $J=2.0$, 8.0 Hz, $H_{3'}$), 4.22 (ddd, 1H, $J=2.5$, 5.0, 6 Hz, $H_{4''}$), 4.65 (dd, 1H, $J=3,0$ e 6,5 Hz, $H_{2''}$), 4.71 (dd, 1H, $J=2.5$, 6.5 Hz, $H_{3''}$), 4.98 (d, 1H, $J=3.0$ Hz, $H_{1''}$), 5.66

(d, 1H, $J=8.0$ Hz, H_5), 6.24 (dd, 1H, $J=6.5$, 7.0 Hz, $H_{5'}$), 7.37–7.43 (m, 6H), 7.60–7.43 (m, 5H), 8.93 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 13.9, 19.2, 25.3, 26.8, 27.1, 38.5, 61.5, 61.8, 63.7, 80.8, 82.8, 85.4, 98.9, 102.7, 113.6, 127.8, 129.9, 129,9, 132.8, 132.9, 135.5, 135.5, 139.6, 150.1, 163.1, 169.6. Anal. calcd for $C_{34}H_{43}N_3O_9Si$: C, 61.33; H, 6.51; N, 6.31%. Found: C, 61.31; H, 6.50; N, 6.32%.

3.2.2. 1-[(3*R*,5*S*)-2-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-ethoxycarbonyl-1,2-isoxazolidin-5-yl]-1*H*-pyrimidine-2,4-dione 8a. Yield 44%; HPLC: t_R 18.4 min. Amorphous solid; $[\alpha]_D^{25}=-55.0$ (c 1.50, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.07 (s, 9H), 1.27 (t, 3H, $J=7.1$ Hz), 1.33 (s, 3H), 1.53 (s, 3H), 2.53 (ddd, 1H, $J=3.1$, 6.2, 13.9 Hz, $H_{4'a}$), 2.87 (ddd, 1H, $J=7.7$, 9.7, 13.9 Hz, $H_{4'b}$), 3.72 (dd, 1H, $J=6.0$, 13.0 Hz, $H_{5''a}$), 3.74 (dd, 1H, $J=6.0$, 13.0 Hz, $H_{5''b}$), 4.05 (dd, 1H, $J=6.2$, 9.7 Hz, $H_{3'}$), 4.19 (dq, 2H, $J=7.1$, 10.5 Hz), 4.24 (dq, 1H, $J=3.5$ and 6.0 Hz, $H_{4''}$), 4.51 (dd, 1H, $J=3.5$, 6.2 Hz, $H_{3''}$), 4.77 (dd, 1H, $J=2.0$, 6.2 Hz, $H_{2''}$), 5.02 (dd, 1H, $J=1.1$, 2.0 Hz, $H_{1''}$), 5.71 (d, 1H, $J=8.1$ Hz, H_5), 5.94 (ddd, 1H, $J=1.1$, 3.1, 7.7 Hz, $H_{5'}$), 7.37–7.45 (m, 6H), 7.69–7.70 (m, 4H), 7.80 (d, 1H, $J=8.1$ Hz, H_6), 8.45 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.1, 19.3, 25.4, 26.8, 27.2, 39.8, 60.4, 62.1, 64.4, 81.0, 82.7, 83.7, 86.6, 97.6, 102.2, 113.4, 127.7, 129.8, 129.9, 133.2, 135.6, 135.6, 140.4, 150.1, 162.9 169.3. Anal. calcd for $C_{34}H_{43}N_3O_9Si$: C, 61.33; H, 6.51; N, 6.31%. Found: C, 61.35; H, 6.52; N, 6.33%.

3.2.3. 1-[(3*R*,5*R*)-2-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-ethoxycarbonyl-1,2-isoxazolidin-5-yl]-5-methyl-1*H*-pyrimidine-2,4(1*H*,3*H*)-dione 7b. Yield 58%; HPLC: t_R 13.5 min. White solid: mp 53–56°C from EtOAc; $[\alpha]_D^{25}=-36.2$ (c 1.08; $CHCl_3$). Anal. calcd for $C_{35}H_{45}N_3O_9Si$: C, 61.84; H, 6.67; N, 6.18%. Found: C, 61.81; H, 6.69; N, 6.14%. All spectroscopic data are identical to the reported ones.[10]

3.2.4. 1-[(3*R*,5*S*)-2-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-ethoxycarbonyl-1,2-isoxazolidin-5-yl]-5-methyl-1*H*-pyrimidine-2,4(1*H*,3*H*)-dione 8b. Yield 23%; HPLC: t_R 11.5 min. White solid: mp 51–55°C from EtOAc; $[\alpha]_D^{25}=+5.6$ (c 1.22; $CHCl_3$). Anal. calcd for $C_{35}H_{45}N_3O_9Si$: C, 61.84; H, 6.67; N, 6.18%. Found: C, 61.89; H, 6.65; N, 6.21%. All spectroscopic data are identical to the reported ones.[10]

3.3. Method B. General procedure for reactions between base 6c and isoxazolidines 4 and 5

To a stirred mixture of 5-fluorouracil **6c** (1.5 mmol), and isoxazolidines **4** and **5** as epimeric mixtures in anhydrous CH_2Cl_2 was added *N*,*O*-bis(trimethylsilyl)acetamide (3.5 mmol). After 2 h of stirring at room temperature, the clear solution was cooled at 0°C and $SnCl_4$ was added. The mixture was 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 (3×10 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by radial chromatography (cyclohexane/ethyl acetate 3:2) and then by HPLC with a linear gradient of 2-propanol (6–10%, 0–10 min, flow 3.5 mL/min) in *n*-hexane.

3.3.1. 5-Fluoro-1-[(3*R*,5*R*)-2-(5-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropyliden-β-D-ribofuranosyl)-3-ethoxycarbonyl-1,2-isoxazolidin-5-yl]-1*H*-pyrimidine-2,4-dione 7c. Yield 38.2%; HPLC: t_R 16.8 min. White solid: mp 52–56°C from EtOAc; $[\alpha]_D^{25}=-31.2$ (c 0.08; $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.00 (s, 9H), 1.13 (t, 3H, $J=7.1$ Hz), 1.28 (s, 3H), 1.46 (s, 3H), 2.30 (ddd, 1H, $J=6.7$, 7.0 and 13.6 Hz, $H_{4'a}$), 2.90 (ddd, 1H, $J=1.8$, 7.1 and 13.6 Hz, $H_{4'b}$), 3.70 (dd, 1H, $J=4.4$ and 11.3 Hz, $H_{5''a}$), 3.74 (dd, 1H, $J=5.4$ and 11.3 Hz, $H_{5''b}$), 4.05 (dq, 1H, $J=7.1$ and 14.8 Hz), 4.07 (dq, 1H, $J=7.1$ and 14.8 Hz), 4.11 (dd, 1H, $J=1.8$ and 7.0 Hz, $H_{3'}$), 4.16 (ddd, 1H, $J=2.6$, 4.4 and 5.4 Hz, $H_{4''}$), 4.56 (dd, 1H, $J=3.3$ and 6.2 Hz, $H_{2''}$), 4.64 (dd, 1H, $J=2.6$ and 6.2 Hz, $H_{3''}$), 4.95 (d, 1H, $J=3.3$ Hz, $H_{1''}$), 6.19 (dd, 1H, $J=6.7$ and 7.1 Hz, $H_{5'}$), 7.30–7.56 (m, 10H), 7.76 (d, 1H, $J=6.2$ Hz, H_6), 8.78 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 13.9, 19.2, 25.3, 26.9, 27.1, 38.4, 61.2, 61.9, 63.7, 80.5, 82.7, 85.2, 85.9, 99.1, 113.9, 124.0 (d, $J=33.8$ Hz), 127.8, 127.8, 129.9, 130.0, 132.8, 132.9, 135.5, 135.6, 140.6 (d, $J=232.7$ Hz), 155.9 (d, $J=27.5$ Hz), 169.5. Anal. calcd for $C_{34}H_{42}FN_3O_9Si$: C, 59.72; H, 6.19; N, 6.15%. Found: C, 59.91; H, 6.17; N, 6.14%.

3.3.2. 5-Fluoro-1-[(3*R*,5*S*)-2-(5-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropyliden-β-D-ribofuranosyl)-3-ethoxycarbonyl-1,2-isoxazolidin-5-yl]-1*H*-pyrimidine-2,4-dione 8c. Yield 31.8%; HPLC: t_R 19.6 min. White solid: mp 51–55°C from EtOAc; $[\alpha]_D^{25}=-6.8$ (c 0.22; $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.99 (s, 9H), 1.04 (t, 3H, $J=7.2$ Hz), 1.28 (s, 3H), 1.45 (s, 3H), 2.52 (ddd, 1H, $J=3.3$, 3.4, 14.0 Hz, $H_{4'a}$), 2.82 (ddd, 1H, $J=7.7$, 9.9, 14.0 Hz, $H_{4'b}$), 3.65 (dd, 1H, $J=4.0$, 11.2 Hz, $H_{5''a}$), 3.73 (dd, 1H, $J=6.4$, 11.2 Hz, $H_{5''b}$), 3.90 (dq, 1H, $J=7.2$, 10.8 Hz), 3.97 (dq, 1H, $J=7.2$, 10.8 Hz), 4.04 (ddd, 1H, $J=1.5$, 3.3, 9.9 Hz, $H_{3'}$), 4.16 (ddd, 1H, $J=2.3$, 4.0, 6.4 Hz, $H_{4''}$), 4.61 (dd, 1H, $J=2.9$, 6.4 Hz, $H_{2''}$), 4.69 (d, 1H, $J=2.9$ Hz, $H_{1''}$), 4.70 (dd, 1H, $J=2.3$, 6.4 Hz, $H_{3''}$), 6.29 (dd, 1H, $J=1.5$, 3.4, 7.7 Hz, $H_{5'}$), 7.30–7.63 (m, 10H), 7.91 (d, 1H, $J=6.2$ Hz, H_6), 9.30 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 13.9, 19.2, 25.2, 26.8, 38.1, 60.6, 62.0, 63.7, 81.0, 82.6, 85.2, 85.6, 100.3, 113.5, 124.9 (d, $J=35.1$ Hz), 127.9, 127.9, 130.0, 132.8, 132.9, 135.4, 135.5, 140.3 (d, $J=239.7$ Hz), 156.7 (d, $J=27.1$ Hz), 170.8. Anal. calcd for $C_{34}H_{42}FN_3O_9Si$: C, 59.72; H, 6.19; N, 6.15%. Found: C, 59.63; H, 6.21; N, 6.13%.

3.4. General procedure for reactions between vinyl-bases 13a–c and Vasella-type nitrone 3

A suspension containing one of the vinyl bases **13a–c** (1 equiv.), ribosyl hydroxylamine **2** (1 equiv.) and ethyl glyoxylate (1 equiv.) in chloroform (ca. 10 mL)

was heated in a sealed vessel at 60°C under stirring, until the ribosyl hydroxylamine was consumed (8 h); after this time, to the reaction mixture were added 0.5 equiv. of the ribosyl hydroxylamine and of formaldehyde and was left to react for additional 4 h. Removal of the solvent in vacuo affords a crude material which was purified by flash chromatography to give a mixture of homochiral isoxazolidines **7a**–**c** and **8a**–**c** (1.5:1, 40% global yield), which was purified by radial chromatography (cyclohexane/ethyl acetate 3:2) and then by HPLC with a linear gradient of 2-propanol (6–10%, 0–10 min, flow 3.5 mL/min) in *n*-hexane, shows physical and spectral data listed above.

3.5. General procedure for reduction of nucleosides 7, 8

To a stirred solution of **7a**–**c**, **8a**–**c** (1.0 mmol) in a 1:1 methanol/dioxane mixture (50 mL), was added at 0°C $NaBH_4$ (6 mmol) and the obtained mixture was stirred for 5 h. At the end of this time the solvent was removed and the residue was extracted with ethyl acetate (3×5 mL); the collected organic phases, dried over sodium sulphate, gave after evaporation of the solvent at reduced pressure a yellow oil, which was purified by flash chromatography (chloroform/methanol 85:15).

3.5.1. 1-[(3*R*,5*R*)-2-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-hydroxymethyl-1,2-isoxazolidin-5-yl]-1*H*-pyrimidine-2,4-dione 9a.

Yield 86%; amorphous solid; $[\alpha]_D^{25}=-59.6$ (*c* 0.86; $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.01 (s, 9H), 1.24 (s, 3H), 1.43 (s, 3H), 2.21 (ddd, 1H, $J=5.6$, 7.8, 13.4 Hz, $H_{4'a}$), 2.65 (ddd, 1H, $J=3.1$, 7.6, 13.4 Hz, $H_{4'b}$), 3.56 (bs, 1H, OH), 3.59 (dd, 1H, $J=6.7$, 12.4 Hz, $H_{3'a}$), 3.61 (dd, 1H, $J=3.4$, 12.4 Hz, $H_{3'b}$), 3.64 (dddd, 1H, $J=3.1$, 3.4, 6.7, 7.8 Hz, $H_{3'}$), 3.81 (dd, 1H, $J=4.5$, 10.9 Hz, $H_{5''a}$), 3.84 (dd, 1H, $J=5.9$, 10.9 Hz, $H_{5''b}$), 4.45 (ddd, 1H, $J=2.7$, 4.5, 5.9 Hz, $H_{4''}$), 4.51 (dd, 1H, $J=2.7$, 5.9 Hz, $H_{3''}$), 4.68 (dd, 1H, $J=3.1$, 5.9 Hz, $H_{2''}$), 5.25 (d, 1H, $J=3.4$ Hz, $H_{1''}$), 5.89 (d, 1H, $J=8.2$ Hz, H_5), 6.33 (dd, 1H, $J=5.6$, 7.6 Hz, $H_{5'}$), 7.32–7.51 (m, 6H), 7.54 (d, 1H, $J=8.2$ Hz, H_6), 7.63–7.66 (m, 4H), 9.04 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 12.6, 19.4, 25.0, 27.0, 27.2, 38.5, 62.7, 63.1, 64.1, 80.1, 83.4, 84.1, 85.5, 98.5, 103.5, 113.9, 127.8, 127.6, 130.0, 130.2, 132.7, 132.8, 135.5, 135.6, 135.7, 150.2, 164.0. Anal. calcd for $C_{32}H_{41}N_3O_8Si$: C, 61.62; H, 6.63; N, 6.74%. Found: C, 61.67; H, 6.61; N, 6.79%.

3.5.2. 1-[(3*R*,5*S*)-2-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-hydroxymethyl-1,2-isoxazolidin-5-yl]-1*H*-pyrimidine-2,4-dione 10a.

Yield 75%; amorphous solid; $[\alpha]_D^{25}=+12.8$ (*c* 1.08; $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.99 (s, 9H), 1.21 (s, 3H), 1.41 (s, 3H), 2.11 (ddd, 1H, $J=5.6$, 7.4, 13.5 Hz, $H_{4'a}$), 2.79 (ddd, 1H, $J=5.9$, 8.1, 13.5 Hz, $H_{4'b}$), 3.44 (dddd, 1H, $J=6.3$, 7.1, 8.1, 8.7 Hz, $H_{3'}$), 3.52 (dd, 1H, $J=8.7$, 11.9 Hz, $H_{3'b}$), 3.57 (dd, 1H, $J=5.1$, 11.1 Hz, $H_{5''a}$), 3.62 (bs, 1H, OH), 3.74 (dd, 1H, $J=6.4$, 11.9 Hz, $H_{3'a}$), 3.80 (dd, 1H, $J=2.7$, 11.1 Hz, $H_{5''b}$), 4.27 (ddd, 1H, $J=2.0$, 2.7, 6.4 Hz, $H_{4''}$), 4.57 (dd, 1H, $J=2.0$, 6.4 Hz, $H_{3''}$), 4.70 (dd, 1H, $J=2.7$, 6.4 Hz, $H_{2''}$), 4.95 (d, 1H, $J=2.7$ Hz, $H_{1''}$), 5.86 (d, 1H, $J=8.0$ Hz, H_5), 6.42 (dd, 1H, $J=5.6$, 8.1 Hz, $H_{5'}$), 7.33–7.41 (m, 6H), 7.50 (d, 1H, $J=8.0$ Hz, H_6), 7.58–7.68 (m, 4H), 9.04 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 12.5, 19.3, 25.4, 26.6, 27.3, 38.2, 62.6, 63.9, 63.9, 80.7, 83.3, 84.4, 85.5, 98.1, 101.2, 113.6, 127.77, 127.84, 131.1, 131.8, 132.8, 133.0, 135.5, 135.6, 150.2, 163.4. Anal. calcd for $C_{32}H_{41}N_3O_8Si$: C, 61.62; H, 6.63; N, 6.74%. Found: C, 61.69; H, 6.62; N, 6.77%.

3.5.3. 1-[(3*R*,5*R*)-2-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-hydroxymethyl-1,2-isoxazolidin-5-yl]-5-methyl-1*H*-pyrimidine-2,4-dione 9b.

Yield 93%; white foam; $[\alpha]_D^{25}=-42.9$ (*c* 0.35; $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.07 (s, 9H), 1.33 (s, 3H), 1.53 (s, 3H), 1.90 (d, 3H, $J=1.1$ Hz), 2.41 (ddd, 1H, $J=5.8$, 8.0, 13.6 Hz, $H_{4'a}$), 2.56 (ddd, 1H, $J=2.9$, 7.7, 13.6 Hz, $H_{4'b}$), 3.24 (bs, 1H, OH), 3.57 (dd, 1H, $J=6.9$, 12.1 Hz, $H_{3'a}$), 3.62 (dd, 1H, $J=3.3$, 12.1 Hz, $H_{3'b}$), 3.68 (dddd, 1H, $J=2.9$, 3.3, 6.9, 8.0 Hz, $H_{3'}$), 3.75 (dd, 1H, $J=4.7$, 11.3 Hz, $H_{5''a}$), 3.81 (dd, 1H, $J=6.2$, 11.3 Hz, $H_{5''b}$), 4.25 (ddd, 1H, $J=2.5$, 4.7, 6.2 Hz, $H_{4''}$), 4.55 (dd, 1H, $J=2.5$, 6.2 Hz, $H_{3''}$), 4.71 (dd, 1H, $J=2.9$, 6.2 Hz, $H_{2''}$), 5.05 (d, 1H, $J=2.9$ Hz, $H_{1''}$), 6.23 (dd, 1H, $J=5.8$, 7.7 Hz, $H_{5'}$), 7.36–7.46 (m, 6H), 7.54 (q, 1H, $J=1.1$ Hz, H_6), 7.63–7.66 (m, 4H), 9.04 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 12.6, 19.2, 25.2, 26.8, 27.1, 38.1, 62.7, 63.0, 64.1, 80.5, 83.1, 83.9, 85.7, 98.5, 111.2, 113.5, 127.8, 127.8, 129.9, 130.0, 132.7, 132.9, 135.3, 135.5, 135.6, 150.4, 163.6. Anal. calcd for $C_{34}H_{45}N_3O_7Si$: C, 64.23; H, 7.13; N, 6.61%. Found: C, 64.47; H, 7.16; N, 6.59%.

3.5.4. 1-[(3*R*,5*S*)-2-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-hydroxymethyl-1,2-isoxazolidin-5-yl]-5-methyl-1*H*-pyrimidine-2,4-dione 10b.

Yield 72%; white solid: mp 54–58°C; $[\alpha]_D^{25}=+5.1$ (*c* 0.31; $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.09 (s, 9H), 1.31 (s, 3H), 1.51 (s, 3H), 1.69 (bs, 1H, OH), 1.87 (d, 3H, $J=1.3$ Hz), 2.19 (ddd, 1H, $J=5.3$, 6.9, 13.7 Hz, $H_{4'a}$), 2.86 (ddd, 1H, $J=7.9$, 8.8, 13.7 Hz, $H_{4'b}$), 3.49 (dddd, 1H, $J=6.2$, 6.9, 8.1, 8.8 Hz, $H_{3'}$), 3.56 (dd, 1H, $J=5.3$, 12.0 Hz, $H_{5''a}$), 3.79 (dd, 1H, $J=6.2$, 11.3 Hz, $H_{3'a}$), 3.80 (dd, 1H, $J=8.1$, 11.3 Hz, $H_{3'b}$), 3.81 (dd, 1H, $J=2.9$, 12.0 Hz, $H_{5''b}$), 4.25 (ddd, 1H, $J=2.1$, 2.9, 5.3 Hz, $H_{4''}$), 4.58 (dd, 1H, $J=2.1$, 6.4 Hz, $H_{3''}$), 4.74 (dd, 1H, $J=2.9$, 6.4 Hz, $H_{2''}$), 4.80 (d, 1H, $J=2.9$ Hz, $H_{1''}$), 6.37 (dd, 1H, $J=5.3$, 7.9 Hz, $H_{5'}$), 7.39–7.46 (m, 6H), 7.60 (q, 1H, $J=1.3$ Hz, H_6), 7.64–7.66 (m, 4H), 8.60 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 12.7, 19.2, 25.2, 26.8, 26.9, 29.6, 38.2, 62.9, 63.8, 64.5, 80.8, 82.7, 83.5, 85.9, 101.4, 111.1, 113.5, 127.9, 128.0, 130.0, 130.1, 132.6, 132.9, 135.5, 135.6, 150.3, 163.4. Anal. calcd for $C_{34}H_{45}N_3O_7Si$: C, 64.23; H, 7.13; N, 6.61%. Found: C, 64.37; H, 7.12; N, 6.58%.

3.5.5. 5-Fluoro-1-[(3*R*,5*R*)-2-(5-*O*-*tert*-butyldiphenilsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-hydroxymethyl-1,2-isoxazolidin-5-yl]pyrimidine-2,4(1*H*,3*H*)-dione 9c.

Yield 81%; white solid: mp 53–55°C from EtOAc; $[\alpha]_D^{25}=-40.8$ (*c* 0.30; $CHCl_3$). ^1H NMR ($CDCl_3$,

500 MHz) δ: 0.99 (s, 9H), 1.26 (s, 3H), 1.47 (s, 3H), 2.34 (ddd, 1H, J=5.8, 7.9, 13.8 Hz, $H_{4'a}$), 2.53 (ddd, 1H, J=2.5, 7.5, 13.8 Hz, $H_{4'b}$), 3.05 (bs, 1H, OH), 3.47 (dd, 1H, J=6.8, 12.2 Hz, $H_{3'a}$), 3.57 (dd, 1H, J=3.1, 12.2 Hz, $H_{3'b}$), 3.63 (dddd, 1H, J=2.5, 3.1, 5.8, 6.8 Hz, $H_{3'}$), 3.70 (dd, 1H, J=4.2, 11.1 Hz, $H_{5''a}$), 3.74 (dd, 1H, J=5.9, 11.1 Hz, $H_{5''b}$), 4.18 (ddd, 1H, J=2.7, 4.2, 5.9 Hz, $H_{4''}$), 4.46 (dd, 1H, J=2.7, 6.4 Hz, $H_{3''}$), 4.58 (dd, 1H, J=3.3, 6.4 Hz, $H_{2''}$), 5.04 (d, 1H, J=3.3 Hz, $H_{1''}$), 6.14 (dd, 1H, J=7.5, 7.9 Hz, $H_{5'}$), 7.32–7.61 (m, 10H), 7.80 (d, 1H, J=6.2 Hz, H_6), 8.76 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 25.3, 26.8, 27.2, 29.7, 38.5, 62.4, 62.8, 64.0, 80.1, 84.3, 85.4, 98.3, 113.8, 124.1 (d, J=34.2 Hz), 127.8, 127.9, 129.9, 130.0, 132.7, 133.0, 135.5, 135.6, 141.1 (d, J=237.4 Hz), 150.3, 157.0 (d, J=27.9 Hz). Anal. calcd for $C_{32}H_{40}FN_3O_8Si$: C, 59.89; H, 6.28; N, 6.55%. Found: C, 60.08; H, 6.25; N, 6.58%.

3.5.6. 5-Fluoro-1-[(3*R*,5*S*)-2-(5-*O*-*tert*-butyldiphenilsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-hydroxymethyl-1,2-isoxazolidin-5-yl]pyrimidine-2,4(1*H*,3*H*)-dione 10c. Yield 56%; amorphous solid; $[\alpha]_D^{25}$=+15.0 (c 0.27; $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.01 (s, 9H), 1.24 (s, 3H), 1.44 (s, 3H), 2.19 (ddd, 1H, J=4.2, 7.3, 14.0 Hz, $H_{4'a}$), 2.85 (ddd, 1H, J=7.7, 8.0, 14.0 Hz, $H_{4'b}$), 2.97 (bs, 1H, OH), 3.28 (dddd, 1H, J=2.6, 4.6, 7.3, 8.0 Hz, $H_{3'}$), 3.49 (dd, 1H, J=4.6, 12.0 Hz, $H_{3'a}$), 3.68 (dd, 1H, J=4.9, 11.3 Hz, $H_{5''a}$), 3.70 (dd, 1H, J=6.2, 11.3 Hz, $H_{5''b}$), 3.79 (dd, 1H, J=2.6, 12.0 Hz, $H_{3'b}$), 4.19 (ddd, 1H, J=1.8, 4.9, 6.2 Hz, $H_{4''}$), 4.49 (dd, 1H, J=1.8, 5.3 Hz, $H_{3''}$), 4.67 (d, 1H, J=1.8 Hz, $H_{1''}$), 4.68 (dd, 1H, J=1.8, 5.3 Hz, $H_{2''}$), 6.22 (dd, 1H, J=4.2, 7.7 Hz, $H_{5'}$), 7.31–7.59 (m, 10H), 7.93 (d, 1H, J=6.1 Hz, H_6), 9.22 (d, 1H, J=4.4 Hz, NH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 19.2, 25.1, 26.81, 26.85, 29.7, 38.6, 62.1, 64.5, 64.6, 80.9, 82.8, 83.4, 86.2, 101.7, 113.5, 124.7 (d, J=34.7 Hz), 127.87, 127.95, 130.09, 130.11, 132.5, 132.7, 135.4, 135.5, 140.0 (d, J=236.2 Hz), 149.0, 156.8 (d, J=26.9 Hz). Anal. calcd for $C_{32}H_{40}FN_3O_8Si$: C, 59.89; H, 6.28; N, 6.55%. Found: C, 60.13; H, 6.26; N, 6.53%.

3.6. General procedure for hydrolysis of homochiral isoxazolidines 9b,c and 10b,c

Isoxazolidines **9b**,**c** and **10b**,**c** were dissolved in a 1.5% HCl solution in EtOH (ca. 2.5 mL), and the reaction mixture was stirred at room temperature for 3 h. The solution was brought to pH 10 by adding aqueous 10% sodium carbonate and extracted with dichloromethane (2×10 mL). The organic phase, dried over sodium sulfate, was filtered and evaporated to dryness. The residue was purified by radial chromatography (chloroform/methanol 9:1) to furnish homochiral *N*,*O*-nucleosides **11b**,**c** and **12b**,**c**.

3.6.1. 1-[(3*R*,5*R*)-3-(Hydroxymethyl)isoxazolidin-5-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione 11b. Yield 73%; HPLC: t_R 20.0 min. colourless oil; $[\alpha]_D^{25}$=−102.4 (c 0.12; H_2O). ^{1}H NMR (D_2O, 500 MHz) δ: 1.92 (d, 3H, J=0.9 Hz), 2.58 (ddd, 1H, J=4.9, 7.9, 13.9 Hz, $H_{4'a}$), 2.71 (ddd, 1H, J=3.6, 7.7, 13.9 Hz, $H_{4'b}$), 3.65 (d, 2H, J=6.0 Hz, $H_{3''}$), 3.85 (ddd, 1H, J=4.9, 6.0, 7.7 Hz, $H_{3'}$), 6.13 (dd, 1H, J=3.6, 7.9 Hz, $H_{5'}$), 7.55 (q, 1H, J=0.9 Hz, H_6). ^{13}C NMR (D_2O, 125 MHz) δ: 11.5, 36.5, 60.6, 61.5, 81.3, 111.0, 138.9, 151.9, 166.8. Anal. calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.76; N, 18.49%. Found: C, 47.42; H, 5.74; N, 18.56%.

3.6.2. 1-[(3*R*,5*S*)-3-(Hydroxymethyl)isoxazolidin-5-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione 12b. Yield 77%; HPLC: t_R 22.2 min. colourless oil; $[\alpha]_D^{25}$=+108.3 (c 0.06; H_2O). ^{1}H NMR (D_2O, 500 MHz) δ: 1.92 (d, 3H, J=1.3 Hz), 2.35 (ddd, 1H, J=6.2, 8.2, 13.7 Hz, $H_{4'a}$), 2.87 (ddd, 1H, J=7.7, 7.8, 13.7 Hz, $H_{4'b}$), 3.72 (dddd, 1H, J=4.4, 6.1, 7.7, 8.2 Hz, $H_{3'}$), 3.78 (dd, 1H, J=6.1, 11.9 Hz, $H_{3''a}$), 3.84 (dd, 1H, J=4.4, 11.9 Hz, $H_{3''b}$), 6.12 (dd, 1H, J=6.2, 7.8 Hz, $H_{5'}$), 7.63 (q, 1H, J=1.3 Hz, H_6). ^{13}C NMR (D_2O, 125 MHz) δ: 13.9, 38.3, 62.5, 63.9, 86.1, 113.5, 141.1, 150.7, 162.2. Anal. calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.76; N, 18.49%. Found: C, 47.44; H, 5.79; N, 18.44%.

3.6.3. 5-Fluoro-1-[(3*R*,5*R*)-3-(hydroxymethyl)isoxazolidin-5-yl]pyrimidine-2,4(1*H*,3*H*)-dione 11c. Yield 75%; colourless oil; $[\alpha]_D^{25}$=−89.7 (c 0.15; H_2O). ^{1}H NMR (D_2O, 500 MHz) δ: 2.61 (ddd, 1H, J=5.3, 7.4, 14.3 Hz, $H_{4'a}$), 2.71 (ddd, 1H, J=3.4, 7.6, 14.3 Hz, $H_{4'b}$), 3.66 (d, 2H, J=5.9 Hz, $H_{3''}$), 3.83 (ddt, 1H, J=5.3, 5.9, 7.6 Hz, $H_{3'}$), 6.14 (dd, 1H, J=3.4, 7.4 Hz, $H_{5'}$), 7.95 (d, 1H, J=6.4 Hz, H_6). ^{13}C NMR (D_2O, 125 MHz) δ: 39.2, 62.6, 63.6, 91.9, 129.34 (d, J=34.0 Hz), 142.9 (d, J=231.9 Hz), 152.7, 158.3 (d, J=26.7 Hz). Anal. calcd for $C_8H_{10}FN_3O_4$: C, 41.56; H, 4.36; N, 18.18%. Found: C, 41.51; H, 4.34; N, 18.19%.

3.6.4. 5-Fluoro-1-[(3*R*,5*S*)-3-(hydroxymethyl)isoxazolidin-5-yl]pyrimidine-2,4(1*H*,3*H*)-dione 12c. Yield 78%; white solid: mp 133–134°C from EtOH; $[\alpha]_D^{25}$=+57.9 (c 0.16; H_2O). ^{1}H NMR (D_2O, 500 MHz) δ: 2.33 (dd, 1H, J=6.0, 14.1 Hz, $H_{4'a}$), 2.91 (ddd, 1H, J=7.2, 7.5, 14.1 Hz, $H_{4'b}$), 3.66–3.83 (m, 3H, $H_{3'}$ and $H_{3''}$), 6.11 (dd, 1H, J=6.0, 7.2 Hz, $H_{5'}$), 8.02 (d, 1H, J=6.4 Hz, H_6). ^{13}C NMR (D_2O, 125 MHz) δ: 36.5, 61.3, 63.9, 89.8, 127.4 (d, J=34.1 Hz), 141.1 (d, J=230.6 Hz), 150.5, 158.6 (d, J=27.1 Hz). Anal. calcd for $C_8H_{10}FN_3O_4$: C, 41.56; H, 4.36; N, 18.18%. Found: C, 41.43; H, 4.35; N, 18.19%.

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