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Enantioselective synthesis of *N,O*-psiconucleosides

Ugo Chiacchio,[a,*] Luisa Borrello,[a] Daniela Iannazzo,[b] Pedro Merino,[c,*] Anna Piperno,[b] Antonio Rescifina,[a] Barbara Richichi[b] and Giovanni Romeo[b,*]

[a]*Dipartimento di Scienze Chimiche, Università di Catania, Viale Andrea Doria 6, Catania 95125, Italy*
[b]*Dipartimento Farmaco-Chimico, Università di Messina, Viale SS. Annunziata, Messina 98168, Italy*
[c]*Departamento de Quimica Organica, Facultad de Ciencias, ICMA, Universidad de Zaragoza, Zaragoza E-50009, Spain*

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Abstract—The first enantioselective synthesis of β-D and β-L *N,O*-psiconucleosides is reported. The synthetic approach is based on the asymmetric 1,3-dipolar cycloaddition of the *C*-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-*N*-methyl nitrone with ethyl 2-acetyloxyacrylate followed by Vorbrüggen nucleosidation, and removal of the chiral auxiliary. Stereochemical assignments are supported by a DFT theoretical study of the cycloaddition reaction.

1. Introduction

There is increasing interest in the synthesis of nucleoside analogues and their incorporation into DNA sequences for the search of new antiviral agents and for the study of ligand DNA and protein–DNA interactions.[1,2] A variety of nucleoside derivatives has been prepared through the deletion or change in the nature of the functional groups present on the heterocyclic bases or their sugar moieties.[3] Such modified nucleosides allow the synthesis of oligonucleotides in which a single functional group at a preselected position has been deleted or otherwise altered.[4]

Natural psicofuranosyl nucleosides, bearing a CH_2OH group at the anomeric carbon atom, have been reported to possess promising biological activities.[5] Typical examples are represented by Angustmycins A and C, which show interesting antimicrobial and antiviral properties,[5c,d] and by Hydantocydin, which exhibits herbicidal activity,[5e] able to regulate plant growth (Fig. 1).

As part of our continuing efforts to develop novel strategies for preparing new heterocyclic nucleosides[6] (i.e. nucleoside analogues in which the furanose unit has been replaced by different heterocyclic rings), we have recently been interested in the synthesis of *N,O*-psiconucleosides **1**,[7] a new class of nucleoside analogues, in which the sugar unit has been changed into an isoxazolidine system. In this context we have reported a general and easy approach towards all purine or pyrimidine derivatives, based on cycloaddition reaction of suitable nitrones (Scheme 1).

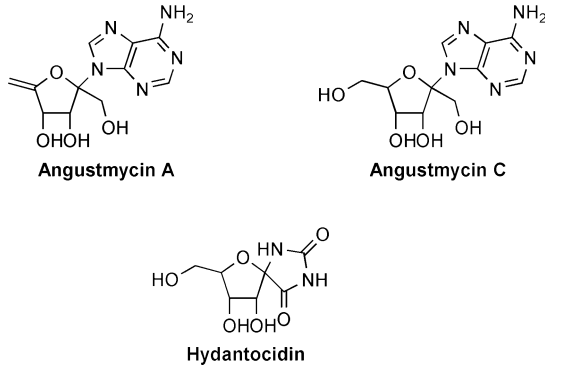
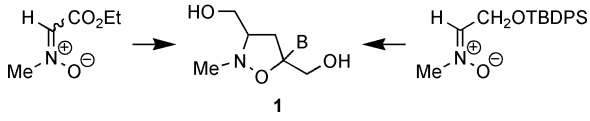


Figure 1. Modified nucleosides.



Scheme 1.

* Corresponding authors. Tel.: +39-095-7385014; fax: +39-06-233230624; e-mail: uchiacchio@dipchi.unict.it

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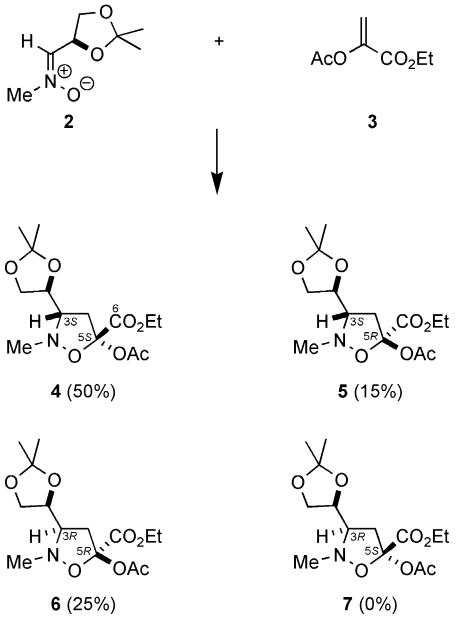
In connection with our recent reports on the use of chiral nitrones for the synthesis of biologically interesting nitrogenated compounds, we have here devised a synthetic route towards enantiomerically pure *N*,*O*-nucleosides of type **1**, via the 1,3-dipolar cycloaddition of a nitrone bearing a stereogenic centre at the α carbon atom. This paper describes the first stereoselective synthesis of *N*,*O*-psiconucleosides based on the asymmetric cycloaddition of nitrone **2** (MIGN).

2. Results and discussion

The nitrone **2** has been prepared from 2,3-*O*-isopropylidene-D-glyceraldehyde as described by one of us.[8] The cycloaddition of **2** with ethyl 2-acetyloxyacrylate **3**, in dry ether at room temperature for 24 h, affords a mixture of three isoxazolidines **4**–**6** with a 90% global yield. The reaction proceeds with a good control of *cis*/*trans* diastereoselectivity (**4**+**6**:**5** ratio = 5:1) and a moderate *anti*/*syn* diastereofacial selectivity (**4**+**5**:**6** ratio = 2.6:1) (Scheme 2).



Scheme 2.

The assignment of *cis*/*trans* configurations[9] to the individual diastereoisomers appears to be not reliable on the basis of (^{1}H–^{1}H) NOEDS experiments; however, a heteronuclear Overhauser effect has been successfully measured, for compounds **4** and **6**, between C_6 and H_3 of the isoxazolidine ring by a classical one-dimensional (^{1}H–^{13}C) HOESY sequence,[10] so confirming the *cis* stereochemistry for these derivatives.

The determination of the diastereofacial induction, i.e. the configuration of the side chain, containing the dioxolane ring, with respect to the isoxazolidine ring, proved troublesome. In fact, all attempts to obtain useful information by variable temperature NMR measurements and NOE experiments failed, due to the complexity of ^{1}H NMR spectra.

On the basis of these considerations, we have assumed the configurations as indicated in Scheme 2, according to a theoretical study of the cycloaddition reaction.

Even though these assignments cannot be considered unambiguous, the suggested asymmetric induction is in complete agreement with previous experiments reported by other authors. In all reported cycloadditions between a chiral α-alkoxy nitrone bearing a rigid system in α-position, the attack of the dipolarophile took place on the *Si* face, leading to an *anti* configuration. Such a stereochemical behaviour of the reaction has been observed with vinyltrimethylsilane,[11] vinyl acetate,[12] styrene,[13] vinylphosphine oxides,[14] methyl crotonate,[15] methyl acrylate[16] and vinyl carbonate[17] among others. The same sense of stereoselection has been observed in cycloadditions with nitrile oxides and it can be considered general for α-alkoxy nitrones.[18] Moreover, we have demonstrated in our laboratories that, when not chelated or complexed with Lewis acids, nitrone **2** reacts with both vinyl acetate[8] and methyl acrylate[19] in a conformation where the nitrone functionality is oriented outside the dioxolane ring (Fig. 2).

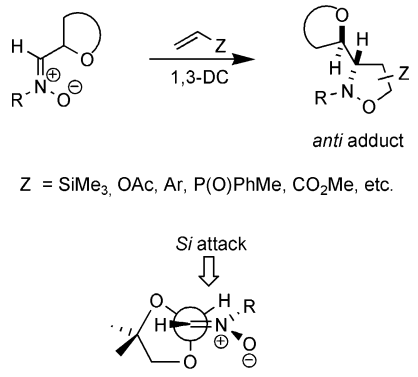


Figure 2. Stereochemical induction in 1,3-dipolar cycloadditions of α-alkoxy nitrones.

Dipolarophiles then attack the *Si* face, probably due both to unfavourable interactions between the incoming alkene and the axially oriented dioxolane methylene and favourable electrostatic interactions with the O_α dioxolane oxygen. Since this hypothesis is supported by DFT calculations[8,19,20] and in order to confirm the same trend of reactivity with **3** as dipolarophile, we carried out a DFT theoretical study of the reaction.[21] The results are summarized in Table 1 and the TSs illustrated in Figure 3.

The most favoured approach corresponds to the attack of the dipolarophile through an *exo* approach by the *Si* face of the nitrone.[22] The activation energy value for the corresponding transition state TS1 is 24.69 kcal/mol. From the analysis of the rest of activation energies, a mixture of products can be expected. These results are in agreement with the experimental observations, since the energy of TS1 is only 1.1 kcal/mol higher than that of TS3, thus justifying the preferential, but not exclusive, formation of **4**.

Table 1. Total electronic energies (E),[a] relative electronic energies,[b] free energies and relative free energies[b] of reactants, transition states and products for cycloadditions of nitrone **2** with alkene **3**

Structure	E (Hartrees)	ΔE (kcal/mol)	G (Hartrees)	ΔG (kcal/mol)
Nitrone **2**	−554.696533		−554.746502	
Alkene **3**	−534.191359		−534.241332	
TS1 *exo-Si*	−1088.871131	41.87	−1088.948494	24.69
TS2 *endo-Si*	−1088.867791	43.97	−1088.945078	26.83
TS3 *exo-Re*	−1088.868999	43.21	−1088.946684	25.82
TS4 *endo-Re*	−1088.866282	44.92	−1088.943693	27.70
(3*S*,5*S*)-**4**[c]	−1088.929078	−25.84	−1089.004803	−10.65
(3*S*,5*R*)-**5**[d]	−1088.928887	−25.72	−1089.004116	−10.22
(3*R*,5*R*)-**6**[e]	−1088.930007	−26.43	−1089.005598	−11.15
(3*R*,5*S*)-**7**[f]	−1088.928899	−25.73	−1089.004123	−10.22

[a] Including ZPVE corrections.
[b] Relative to nitrone+dipolarophile.
[c] From TS *exo-Si*.
[d] From TS *endo-Si*.
[e] From TS *exo-Re*.
[f] From TS *endo-Re*.

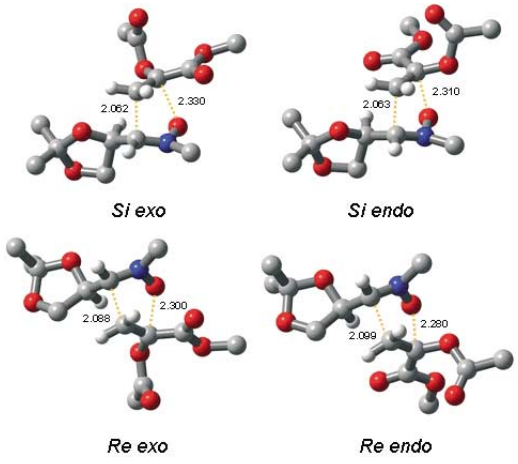


Figure 3. Optimized (B3LYP/6-31G(d) transition structures (bond lengths in Å) for cycloaddition of nitrone **2** and alkene **3**.

Thus, it can be assumed that the three different type of dipolarophiles, vinyl acetate (electron-rich),[8,20] methyl acrylate (electron-poor)[19,20] and ethyl 2-acetyloxyacrylate **3** (push–pull) react following the same stereochemical trend. Indeed, the diastereofacial induction only depends on the chiral nitrone and theoretical calculations demonstrate that the orientation in the transition state is practically identical for the cycloaddition with the three dipolarophiles. In terms of forming bonds, dipolarophile **3** shows an intermediate position to vinyl acetate and methyl acrylate, as it can be anticipated from its electronic nature.

Subsequent coupling of separated cycloadducts **4**–**6** with silylated thymine **8**, *N*-acetyl cytosine **9** and 5-fluorouracil **10** (Fig. 4), performed at 70°C, afforded, as expected,[7] the exclusive β-anomers **11** and **12** (*anti* β and *syn* β (Scheme 3). The stereochemical assignments have been performed by T-ROESY experiments. Thus, H_6 shows a diagnostic ROE effect on $H_{4''}$, so confirming that the dioxolane ring and the nucleobase possess a *cis* topological arrangement.

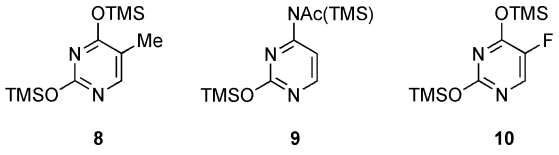
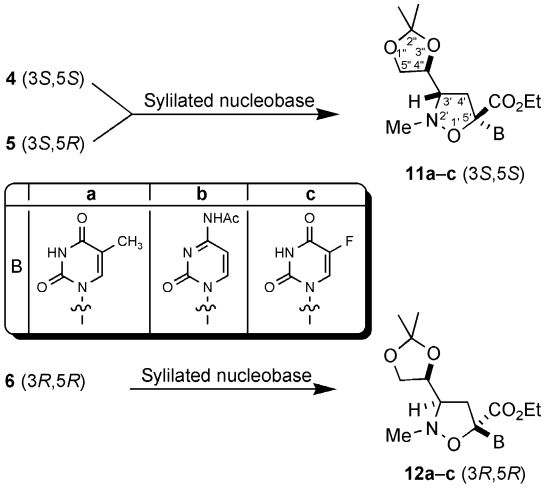
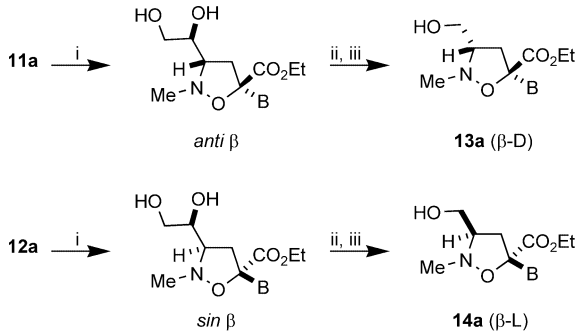


Figure 4. Sylilated nucleobases.



Scheme 3.

Deprotection of the separated stereoisomers was performed on **11a** and **12a**, selected as model compounds, by using catalytic *p*-TsOH in MeOH (Scheme 4). The resulting 1,2-diols were treated sequentially with sodium periodate and sodium borohydride.[8] Purification by column chromatography on silica gel led to the isolation of β-D- and β-L-nucleosides **13a** and **14a**.



Scheme 4. *Reagents and conditions*: (i) *p*-TsOH, MeOH, reflux; (ii) $NaIO_4$, MeOH–H_2O, 0°C; (iii) $NaBH_4$, MeOH, 0°C.

3. Conclusions

The enantioselective synthesis of β-D- and β-L-psiconucleosides has been performed by the use of the chiral nitrone **2**. The assumption of the diastereofacial induction has been carried out by DFT theoretical study of the reaction.

The approach is general and easily applicable to the synthesis of compounds containing all the different nucleobases.

Biological evaluations are actually in progress and will be reported in due course.

4. Experimental

All reactions were monitored by TLC on silica gel 60 F254; the position of the spots were detected with 254 nm UV light or by spraying with one of the following staining systems: 50% methanolic sulfuric acid, 5% ethanolic fosfomolibdic acid and iodine. Preparative column chromatography was performed on columns of silica gel (60–240 mesh) and with solvents that were distilled prior to use. Preparative centrifugally accelerated radial thin-layer chromatography (PCAR-TLC) was performed with a Chromatotron® Model 7924 T (Harrison Research, Palo Alto, CA, USA); the rotors (1 or 2 mm layer thickness) were coated with silica gel Merck grade type 7749, TLC grade, with binder and fluorescence indicator (Aldrich 34,644-6) and the eluting solvents were delivered by the pump at a flow rate of 0.5–1.5 mL min^{-1}. Melting points were uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity instrument in $CDCl_3$ at 55°C. Chemical shifts are reported in ppm (δ) relative to $CHCl_3$ ($\delta = 7.26$) in $CDCl_3$. Optical rotations were taken at 25°C on a Perkin–Elmer 241 polarimeter. Elemental analysis were performed on a Perkin Elmer 240B microanalyzer.

The NOE difference spectra were obtained by subtracting alternatively right off-resonance free induction decays (FIDS) from right-on-resonance-induced FIDS. All reactions involving air-sensitive agents were conducted under nitrogen atmosphere. All reagents were purchased from commercial suppliers and were used without further purification.

4.1. Synthesis of isoxazolidines 4–6

A solution of (*Z*)-*C*-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-*N*-methyl nitrone[8] **2** (3.00 g, 18.8 mmol) and ethyl 2-acetyloxyacrylate **3** (3.70 g, 23.4 mmol) in dry ether (100 mL) was stirred at room temperature for 24 h. The reaction solvent was evaporated and the residue was purified by silica gel flash chromatography (chloroform/methanol, 99:1).

4.1.1. Ethyl (3*S*,5*S*)-5-(acetyloxy)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methylisoxazolidine-5-carboxylate 4. (3.60 g, 50%). Light yellow oil; $[\alpha]_D^{25} = -9.7$ (*c* 0.36, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.29 (t, $J = 7.1$ Hz, 3H, ester CH_3), 1.35 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.12 (s, 3H, acetylic CH_3), 2.75 (dd, $J = 5.4$ and 13.3 Hz, 1H, H_{4a}), 2.84 (s, 3H, *N*-CH_3), 3.05 (ddd, $J = 5.4$, 6.0 and 8.0 Hz, 1H, H_3), 3.09 (dd, $J = 8.0$ and 13.3 Hz, 1H, H_{4b}), 3.78 (dd, $J = 6.0$ and 8.4 Hz, 1H, $H_{5'a}$), 4.11 (dd, $J = 6.2$ and 8.4 Hz, 1H, $H_{5'b}$), 4.21 (dt, $J = 6.0$ and 6.2 Hz, 1H, $H_{4'}$), 4.25 (dq, $J = 7.1$ and 10.8 Hz, 1H, ester CH_2), 4.28 (dq, $J = 7.1$ and 10.8 Hz, 1H, ester CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 20.9, 25.1, 26.5, 41.5, 45.7, 62.5, 67.2, 69.0, 74.3, 103.5, 109.6, 166.3, 170.0. Anal. calcd for $C_{14}H_{23}NO_7$: C, 52.99; H, 7.31; N, 4.41%. Found: C, 53.06; H, 7.32; N, 4.40%. HRMS calcd for $C_{14}H_{23}NO_7$: 317.1474. Found: 317.1471.

4.1.2. Ethyl (3*S*,5*R*)-5-(acetyloxy)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methylisoxazolidine-5-carboxylate 5. (1.08 g, 15%). Light yellow oil; $[\alpha]_D^{25} = +11.7$ (*c* 0.13, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.29 (t, $J = 7.1$ Hz, 3H, ester CH_3), 1.34 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.12 (s, 3H, acetylic CH_3), 2.28 (dd, $J = 9.5$ and 13.7 Hz, 1H, H_{4a}), 2.92 (ddd, $J = 7.8$, 7.9 and 9.5 Hz, 1H, H_3), 2.93 (s, 3H, *N*-CH_3), 3.11 (dd, $J = 7.9$ and 13.7 Hz, 1H, H_{4b}), 3.69 (dd, $J = 6.8$ and 8.4 Hz, 1H, $H_{5'a}$), 4.03 (dd, $J = 6.4$ and 8.4 Hz, 1H, $H_{5'b}$), 4.15 (ddd, $J = 6.4$, 6.8 and 7.8 Hz, 1H, $H_{4'}$), 4.24 (dq, $J = 7.1$ and 10.8 Hz, 1H, ester CH_2), 4.27 (dq, $J = 7.1$ and 10.8 Hz, 1H, ester CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 20.9, 25.3, 26.6, 43.7, 45.5, 62.6, 66.8, 70.5, 76.2, 102.6, 110.2, 165.7, 170.3. Anal. Calcd for $C_{14}H_{23}NO_7$: C, 52.99; H, 7.31; N, 4.41%. Found: C, 53.05; H, 7.33; N, 4.39%. HRMS calcd for $C_{14}H_{23}NO_7$: 317.1474. Found: 317.1472.

4.1.3. Ethyl (3*R*,5*R*)-5-(acetyloxy)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methylisoxazolidine-5-carboxylate 6. (1.80 g, 25%). Light yellow oil; $[\alpha]_D^{25} = +7.3$ (*c* 0.12, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.30 (t, $J = 7.1$ Hz, 3H, ester CH_3), 1.31 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.13 (s, 3H, acetylic CH_3), 2.66 (dd, $J = 2.1$ and 13.5 Hz, 1H, H_{4a}), 2.90 (s, 3H, *N*-CH_3), 2.91 (dd, $J = 6.3$ and 13.5 Hz, 1H, H_{4b}), 3.21 (ddd, $J = 2.1$, 6.3 and 6.5 Hz, 1H, H_3), 3.69 (dd, $J = 6.2$ and 8.4 Hz, 1H, $H_{5'a}$), 4.07 (dd, $J = 2.2$ and 8.4 Hz, 1H, $H_{5'b}$), 4.16 (ddd, $J = 2.2$, 6.2 and 6.5 Hz, 1H, $H_{4'}$), 4.24 (dq, $J = 7.1$ and 10.8 Hz, 1H, ester CH_2), 4.28 (dq, $J = 7.1$ and 10.8 Hz,

1H, ester CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 21.1, 26.7, 26.8, 42.0, 47.6, 62.6, 67.6, 68.9, 75.7, 103.8, 110.0, 166.0, 169.0. Anal. calcd for $C_{14}H_{23}NO_7$: C, 52.99; H, 7.31; N, 4.41%. Found: C, 52.85; H, 7.28; N, 4.42%. HRMS calcd for $C_{14}H_{23}NO_7$: 317.1474. Found: 317.1477.

4.2. Synthesis of 3-dioxolanyl-*N*,*O*-psiconucleosides 11a–c and 12a–c

A solution of isoxazolidine **4**–**6** (1.0 mmol) in dry acetonitrile (5 mL) and TMSOTf (0.056 g, 0.25 mmol) was added to a stirred solution of **8**–**10** (2.0 mmol, obtained by standard procedures) in dry acetonitrile (70 mL). The resulting mixture was stirred at 70°C for 6 h. After this period the solution was neutralized by addition of aqueous 5% sodium bicarbonate, and then concentrated in vacuum. 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 with chloroform/methanol (98:2) and then by HPLC with a mixed linear gradient of 2-propanol (0–12%, 0–18 min) in *n*-hexane, followed by isocratic elution (12%, 18–28 min). Reaction of **4** and **5** give rise to compounds **11** while reaction of **6** lead to compounds **12**.

4.2.1. Ethyl (3*S*,5*S*)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)isoxazolidine-5-carboxylate 11a. (241.5 mg, 63%); HPLC: t_R 17.2 min. Sticky foam; $[\alpha]_D^{25}=-4.5$ (*c* 0.56, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.26 (t, $J=7.3$ Hz, 3H, ester CH_3), 1.33 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.97 (d, $J=1.1$ Hz, 3H, thymine CH_3), 2.23 (dd, $J=9.9$ and 14.0 Hz, 1H, $H_{4'a}$), 2.99 (s, 3H, *N*-CH_3), 3.01 (ddd, $J=3.0$, 7.7 and 9.9 Hz, 1H, $H_{3'}$), 3.60 (dd, $J=7.7$ and 14.0 Hz, 1H, $H_{4'b}$), 3.66 (dd, $J=5.5$ and 7.0 Hz, 1H, $H_{5''a}$), 4.01 (ddd, $J=3.0$, 5.5 and 6.2 Hz, 1H, $H_{4''}$), 4.03 (dd, $J=6.2$ and 7.0 Hz, 1H, $H_{5''b}$), 4.22 (dq, $J=7.3$ and 10.7 Hz, 1H, ester CH_2), 4.26 (dq, $J=7.3$ and 10.7 Hz, 1H, ester CH_2), 7.54 (q, $J=1.1$ Hz, 1H, H_6), 8.97 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.7, 13.8, 25.4, 26.6, 45.1, 45.6, 63.2, 67.0, 71.3, 76.6, 92.6, 109.4, 110.3, 134.7, 150.4, 164.3, 165.0. Anal. Calcd for $C_{17}H_{25}N_3O_7$: C, 53.26; H, 6.57; N, 10.96%. Found: C, 53.10; H, 6.55; N, 10.99%. HRMS calcd for $C_{17}H_{25}N_3O_7$: 383.1692. Found: 383.1690.

4.2.2. Ethyl (3*R*,5*R*)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)isoxazolidine-5-carboxylate 12a. (230.0 mg, 60%); HPLC: t_R 21.3 min. Sticky foam; $[\alpha]_D^{25}=-7.7$ (*c* 0.58, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.18 (t, $J=7.3$ Hz, 3H, ester CH_3), 1.25 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.89 (d, $J=1.1$ Hz, 3H, thymine CH_3), 2.55 (dd, $J=8.8$ and 14.3 Hz, 1H, $H_{4'a}$), 2.83 (s, 3H, *N*-CH_3), 3.06 (ddd, $J=3.6$, 7.7 and 8.8 Hz, 1H, $H_{3'}$), 3.61 (dd, $J=7.7$ and 14.3 Hz, 1H, $H_{4'b}$), 3.65 (dd, $J=6.9$ and 8.2 Hz, 1H, $H_{5''a}$), 3.99 (dd, $J=6.6$ and 8.2 Hz, 1H, $H_{5''b}$), 4.09 (ddd, $J=3.6$, 6.6 and 6.9 Hz, 1H, $H_{4''}$), 4.15 (dq, $J=7.3$ and 10.7 Hz, 1H, ester CH_2), 4.19 (dq, $J=7.3$ and 10.7 Hz, 1H, ester CH_2), 7.53 (q, $J=1.1$ Hz, 1H, H_6), 9.71 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.6, 13.7, 24.7, 25.9, 43.1, 45.0, 63.0, 66.2, 69.5, 73.3, 93.1, 109.6, 109.7, 134.7, 150.5, 164.7, 165.3. Anal. calcd for $C_{17}H_{25}N_3O_7$: C, 53.26; H, 6.57; N, 10.96%. Found: C, 53.34; H, 6.55; N, 10.94%. HRMS calcd for $C_{17}H_{25}N_3O_7$: 383.1692. Found: 383.1689.

4.2.3. Ethyl (3*S*,5*S*)-5-[4-(acetylamino)-2-oxopyrimidin-1(2*H*)-yl]-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methylisoxazolidine-5-carboxylate 11b. (225.7 mg, 55%); R_f (hexane:isopropanol, 80:20) = 0.3. Sticky foam; $[\alpha]_D^{25}=+18.3$ (*c* 1.20, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.15 (t, $J=7.1$ Hz, 3H, ester CH_3), 1.22 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 2.11 (dd, $J=9.8$ and 14.2 Hz, 1H, $H_{4'a}$), 2.19 (s, 3H, $COCH_3$), 2.47 (dd, $J=9.0$ and 14.2 Hz, 1H, $H_{4'b}$), 2.84 (s, 3H, *N*-CH_3), 3.09 (ddd, $J=3.6$, 9.0 and 9.8 Hz, 1H, $H_{3'}$), 3.55–3.77 (m, 2H, $H_{4''}$ and $H_{5''a}$), 3.82–3.98 (m, 1H, $H_{5''b}$), 4.13 (q, $J=7.1$, 2H, ester CH_2), 7.43 (d, $J=7.6$ Hz, 1H, H_5), 8.08 (d, $J=7.6$ Hz, 1H, H_6), 10.43 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.7, 24.7, 24.8, 25.9, 42.6, 45.1, 62.9, 66.1, 69.5, 73.5, 93.7, 96.2, 109.7, 143.8, 155.2, 163.6, 164.8, 171.2. Anal. calcd for $C_{18}H_{26}N_4O_7$: C, 52.68; H, 6.39; N, 13.65%. Found: C, 52.73; H, 6.39; N, 13.63%. HRMS calcd for $C_{18}H_{26}N_4O_7$: 410.1801. Found: 410.1798.

4.2.4. Ethyl (3*R*,5*R*)-5-[4-(acetylamino)-2-oxopyrimidin-1(2*H*)-yl]-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methylisoxazolidine-5-carboxylate 12b. (213.4 mg, 52%); R_f (hexane:isopropanol, 80:20) = 0.33. Sticky foam; $[\alpha]_D^{25}=+12.5$ (*c* 0.12, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, $J=7.1$ Hz, 3H, ester CH_3), 1.31 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.18 (dd, $J=8.8$ and 14.1 Hz, 1H, $H_{4'a}$), 2.20 (s, 3H, $COCH_3$), 2.99 (s, 3H, *N*-CH_3), 2.97–3.04 (m, 1H, $H_{3'}$), 3.63–3.78 (m, 2H, $H_{4'b}$ and $H_{5''a}$), 3.91–3.99 (m, 2H, $H_{4''}$ and $H_{5''b}$), 4.23 (q, $J=7.1$, 2H, ester CH_2), 7.46 (d, $J=7.2$ Hz, 1H, H_5), 8.13 (d, $J=7.2$ Hz, 1H, H_6), 9.03 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.8, 24.9, 25.5, 26.6, 42.3, 44.5, 63.1, 67.0, 71.3, 76.6, 93.5, 95.7, 110.3, 144.0, 155.3, 163.5, 164.6, 170.1. Anal. calcd for $C_{18}H_{26}N_4O_7$: C, 52.68; H, 6.39; N, 13.65%. Found: C, 52.47; H, 6.39; N, 13.66%. HRMS calcd for $C_{18}H_{26}N_4O_7$: 410.1801. Found: 410.1804.

4.2.5. Ethyl (3*S*,5*S*)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methylisoxazolidine-5-carboxylate 11c. (244.0 mg, 63%); HPLC: t_R 19.3 min. Sticky foam; $[\alpha]_D^{25}=+6.4$ (*c* 0.31, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.27 (t, $J=7.1$ Hz, 3H, ester CH_3), 1.33 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.28 (dd, $J=9.8$ and 13.9 Hz, 1H, $H_{4'a}$), 2.99 (s, 3H, *N*-CH_3), 3.00 (ddd, $J=3.3$, 7.9 and 9.8 Hz, 1H, $H_{3'}$), 3.59 (dd, $J=7.9$ and 13.9 Hz, 1H, $H_{4'b}$), 3.66 (dd, $J=5.5$ and 10.9 Hz, 1H, $H_{5''a}$), 4.02 (ddd, $J=3.3$, 5.5 and 6.2 Hz, 1H, $H_{4''}$), 4.03 (dd, $J=6.6$ and 10.9 Hz, 1H, $H_{5''b}$), 4.24 (dq, $J=7.1$ and 10.8 Hz, 1H, ester CH_2), 4.27 (dq, $J=7.1$ and 10.8 Hz, 1H, ester CH_2), 7.78 (d, $J=6.2$ Hz, 1H, H_6), 9.78 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8,

25.4, 26.5, 44.8, 45.4, 63.4, 66.9, 69.3, 71.1, 92.8, 110.4, 123.8 ($J=35.1$ Hz), 140.0 ($J=235.1$ Hz), 148.9, 157.1 ($J=26.1$ Hz), 164.4. Anal. calcd for $C_{16}H_{22}FN_3O_7$: C, 49.61; H, 5.72; N, 10.85%. Found: C, 49.72; H, 5.71; N, 10.86%. HRMS calcd for $C_{16}H_{22}FN_3O_7$: 387.1442. Found: 387.1445.

4.2.6. Ethyl (3*R*,5*R*)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methylisoxazolidine-5-carboxylate 12c. (255.9 mg, 66%); HPLC: t_R 21.2 min. Sticky foam; $[\alpha]_D^{25}=+6.5$ (*c* 0.85, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.27 (t, $J=7.1$ Hz, 3H, ester CH_3), 1.33 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 2.67 (dd, $J=8.6$ and 14.1 Hz, 1H, $H_{4'a}$), 2.90 (s, 3H, *N*-CH_3), 3.14 (ddd, $J=3.8$, 8.2 and 8.6 Hz, 1H, $H_{3'}$), 3.66 (dd, $J=8.2$ and 14.1 Hz, 1H, $H_{4'b}$), 3.70 (dd, $J=7.0$ and 8.1 Hz, 1H, $H_{5''a}$), 4.07 (dd, $J=6.8$ and 8.1 Hz, 1H, $H_{5''b}$), 4.15 (ddd, $J=3.8$, 6.8 and 7.0 Hz, 1H, $H_{4''}$), 4.24 (dq, $J=7.1$ and 10.7 Hz, 1H, ester CH_2), 4.27 (dq, $J=7.1$ and 10.7 Hz, 1H, ester CH_2), 7.81 (d, $J=6.2$ Hz, 1H, H_6), 9.55 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 24.8, 26.0, 42.9, 45.0, 63.4, 66.3, 69.6, 73.4, 93.1, 109.9, 124.0 ($J=35.2$ Hz), 139.9 ($J=235.1$ Hz), 148.9, 157.2 ($J=26.1$ Hz), 164.6. Anal. calcd for $C_{16}H_{22}FN_3O_7$: C, 49.61; H, 5.72; N, 10.85%. Found: C, 49.67; H, 5.74; N, 10.81%. HRMS calcd for $C_{16}H_{22}FN_3O_7$: 387.1442. Found: 387.1443.

4.3. Synthesis of *N*,*O*-psiconucleosides 15a and 16a

To a solution of **11a** or **12a** (1.0 mmol) in methanol (60 mL) was added *p*-TosOH (43 mg, 0.25 mmol) and the resulting solution was heated under reflux temperature for 4 h. The reaction mixture was cooled at room temperature and neutralized with Amberlite IRA-400. The mixture was filtered and the filtrate evaporated under reduced pressure. The crude diol **13a** or **14a** was taken up into a 1:1 mixture of MeOH:H_2O (30 mL), cooled at 0°C and treated with $NaIO_4$ (214 mg, 1 mmol). The resulting suspension was stirred at 0°C for 1 h and then filtered. The filtrate was maintained at 0°C and treated with solid $NaBH_4$ (117 mg, 3.0 mmol). The mixture was stirred at 0°C for an additional hour, at which time it was concentrated under reduced pressure. The residue was purified by PCAR–TLC to give pure **15a** or **16a** as a foam.

4.3.1. Ethyl (3*S*,5*S*)-3-(hydroxymethyl)-2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)isoxazolidine-5-carboxylate 15a. (213.0 mg, 68%). Sticky foam; $[\alpha]_D^{25}=+13.1$ (*c* 0.96, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.25 (t, $J=7.2$ Hz, 3H, ester CH_3), 1.93 (d, $J=1.1$ Hz, 3H, thymine CH_3), 2.61 (dd, $J=9.5$ and 14.0 Hz, 1H, $H_{4'a}$), 2.92 (bs, 1H, OH), 2.94 (s, 3H, *N*-CH_3), 3.11 (ddd, $J=4.8$, 7.7 and 9.5 Hz, 1H, $H_{3'}$), 3.64 (dd, $J=7.7$ and 14.0 Hz, 1H, $H_{4'b}$), 3.65 (dd, $J=4.8$ and 12.1 Hz, 1H, $H_{3''a}$), 3.74 (d, $J=12.1$ Hz, 1H, $H_{3''b}$), 4.22 (dq, $J=7.2$ and 11.4 Hz, 1H, ester CH_2), 4.25 (dq, $J=7.2$ and 11.4 Hz, 1H, ester CH_2), 7.58 (q, $J=1.1$ Hz, 1H, H_6), 9.46 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.6, 13.8, 44.2, 44.7, 60.4, 63.1, 70.1, 92.9, 109.3, 134.9, 150.6, 164.6, 165.4. Anal. Calcd for $C_{13}H_{19}N_3O_6$: C, 49.84; H, 6.11; N, 13.41%. Found: C, 49.65; H, 6.09; N, 13.43%. HRMS calcd for $C_{13}H_{19}N_3O_6$: 313.1274. Found: 313.1270.

4.3.2. Ethyl (3*R*,5*R*)-3-(hydroxymethyl)-2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)isoxazolidine-5-carboxylate 16a. (203.6 mg, 65%). Sticky foam; $[\alpha]_D^{25}=-12.8$ (*c* 0.85, $CHCl_3$). ^1H and ^{13}C NMR spectroscopic data are identical to **15a**. Anal. calcd for $C_{13}H_{19}N_3O_6$: C, 49.84; H, 6.11; N, 13.41%. Found: C, 50.03; H, 6.12; N, 13.36%. HRMS calcd for $C_{13}H_{19}N_3O_6$: 313.1274. Found: 313.1271.

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