A Stereoselective Approach to Isoxazolidinyl Nucleosides

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A stereoselective approach towards isoxazolidinyl nucleosides has been designed. The 1,3-dipolar cycloaddition of a *C*-chiral nitrone with purine and pyrimidine nucleobases produces thymidine and adenine *N*,*O*-nucleosides, in enantiomerically pure forms.

Introduction

The synthesis of nucleosides has recently received a considerable amount of attention thanks to the search for compounds with antiviral and anticancer activity.[1] In this context, new classes of modified nucleoside analogues have been developed and the design of novel "ribose" rings has resulted in the discovery of effective biologically active agents.[2] In particular, promising results have been obtained from a new generation of nucleoside analogues in which the ribose moiety has been replaced by alternative heterocyclic rings.[3]

The insertion of a second heteroatom into the furanosyl ring has resulted in the preparation of dioxolane-T (**1**) and 3TC (**2**), containing dioxolane or oxathiolane rings, respectively:[4,5] These compounds have shown excellent antiviral (HIV and HBV) activities with no significant drug resistance after one year of clinical trials when used in combination with AZT[6] (Figure 1).

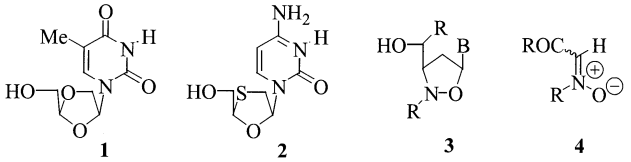

Figure 1. Modified nucleosides and carbonylnitrones

The nucleosides **3**, containing isoxazolidine moieties, have also been reported to possess promising therapeutic utility in the development of anti-AIDS agents. Consequently, after the first report on the synthesis of *N*,*O*-nucleosides,[7] a series of synthetic efforts were devoted towards the preparation of suitably substituted compounds.[8,9]

We have previously designed a new synthetic route towards nucleosides **3**, bearing pyrimidine bases, in racemic form.[10] That scheme involved 1,3-dipolar cycloaddition between *C*-substituted carbonylnitrones **4** and vinyl acetate, followed by nucleosidation of the obtained 5-acetyloxyisoxazolidines with persilylated nucleobases.[11]

The asymmetric version of this reaction route has also been investigated with the aid of chiral dipoles: The presence of a chiral auxiliary on the nitrogen atom offers a powerful measure of stereochemical control over the cycloaddition process, thus providing a good means of access to *N*,*O*-nucleosides, unsubstituted at the nitrogen atom, in enantiomerically pure form.[12,13]

We have also exploited the presence of a chiral center in the position α to the nitrone functionality: The use of *C*-[(1*R*,2*S*,5*R*)-menthoxycarbonyl] *N*-methyl nitrone allows diastereoselective synthetic access to homochiral isoxazolidinyl nucleosides.[12] In the same context, Merino's group has recently reported the 1,3-dipolar cycloaddition reaction between a *C*-chiral nitrone, elaborated from D-glyceraldehyde, and vinylthymine to form homochiral *N*,*O*-thymidines.[14]

Since we have previously achieved the synthesis of a series of vinyl nucleobases,[15] we realized that it should be possible to design a general and simple stereoselective approach to the different types of *N*,*O*-nucleosides **3**. In this paper we report a successful implementation of the 1,3-dipolar cycloaddition methodology: The presence of a chiral center in the substituent at the position α to the nitrone group and the use of vinyl nucleobases open an easy and one-pot reaction pathway towards purine and pyrimidine *N*,*O*-nucleosides.

Results and Discussion

The strategy of the approach is based on the stereoselective construction of the isoxazolidine ring through the 1,3-dipolar cycloaddition between the chiral nitrone **6** and vinyl nucleobases. Thus, the transesterification of **5** with (1*S*)-*endo*-(−)-borneol, performed in the presence of catalytic amounts of $TiCl_4$ and molecular sieves, gave the enantiomerically pure nitrone **6** as a 3:1 mixture of (*E*) and (*Z*) forms. A subsequent 1,3-dipolar cycloaddition reaction between **6**

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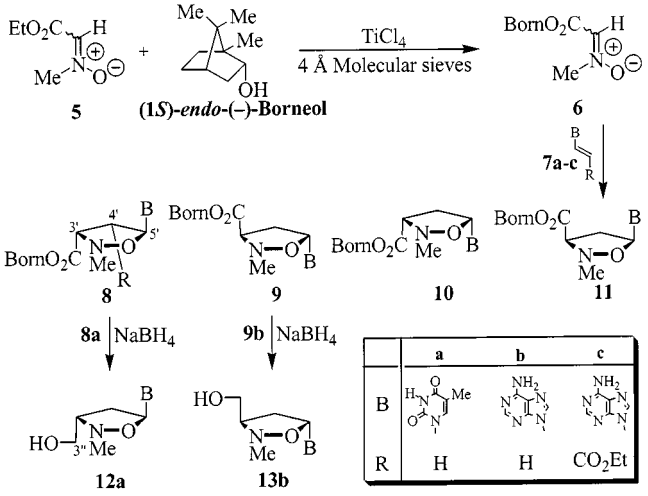
and vinylthymine (**7a**) afforded three stereoisomeric compounds (90% overall yield): two of them, **8a** and **9a**, with a $C^{3'}-C^{5'}$ *trans* configuration (α anomers) (relative ratio 9.7:1), and one, **10a**, with a $C^{3'}-C^{5'}$ *cis* configuration (β-anomer) (*trans*/*cis* ratio 6.1:1). HPLC allowed the separation of **8a** and **10a**, in enantiomerically pure form (Scheme 1, Table 1).



Scheme 1

Table 1. 1,3-Dipolar cycloadditions between nitrone **6** and vinyl nucleobases **7**

	Product ratio[a]				
	8	**9**	**10**	**11**	Yield [%][b]
a	78	8	14	0	90
b	0	91	0	9	88
c	100	0	0	0	84

[a] Measured by integration of the corresponding signals in the ^{1}H NMR spectra. – [b] Isolated yield of mixture of isomers.

The structure of the obtained adducts has been confirmed by ^{1}H NMR experiments. Thus, **8a**, the main compound, shows the $H^{5'}$ resonance as a doublet of doublets at δ = 6.27, while proton $H^{3'}$ appears as a doublet of doublets at δ = 3.92. Protons $H^{4'}$ give rise to two doublets of doublets of doublets centered at δ = 3.14 and 2.53; the thymine moiety proton at C^6 resonates at δ = 7.45. The analogous resonances in **10a** appear at δ = 6.27 (doublet of doublets), 3.41 (doublet of doublets), 3.20 (doublet of doublet of doublets) and 2.65 (doublet of doublet of doublets), and δ = 7.81 (quadruplet).

Stereochemical assignments were established by ^{1}H NOEDS. While, in compound **10a**, diagnostic enhancements were observed between $H^{3'}$, the more downfield $C^{4'}$ methylene proton resonance, and $H^{5'}$, thus indicating a *cis* relationship between these protons, no such effects were detectable in the α-anomeric counterpart. In addition, the NOE between $H^{3'}$ and H^6 in compound **8a** clearly indicates a *syn* relationship between these protons.

The complete regioselectivity of the cycloaddition process and the preference for the *exo* approach (producing *trans* adducts) is comparable with the results reported in the literature for similar reactions and with our own previous data concerning cycloaddition reactions of *C*-(alkoxycarbonyl) nitrones.[10]

The reaction shows a satisfactory control over *cis*/*trans* diastereoselectivity and a good level of asymmetric induction. Nitrone **6** exists as a mixture of (*E*)/(*Z*) isomers, with the more reactive (*E*) isomer predominating (3:1). The cycloaddition reaction proceeds with nearly complete diastereofacial selectivity: The major cycloadduct **8a** arises from the reaction of the (*E*)-nitrone through an *exo* TS. This assumption is supported by PM3 calculations,[16] which show that the *E*-*Exo* TS (addition of vinylthymine to the *Si* face of nitrone), resulting in the L stereoisomer **8a**, (3′*S*,5′*S*), is 1.37 kcal/mol more stable than (*E*)-*exo* attack to the *Re* face, which results in the D stereoisomer **9a**, (3′*R*,5′*R*) (Figure 2, Table 2). This value is in agreement with the experimentally observed **8a**/**9a** ratio.

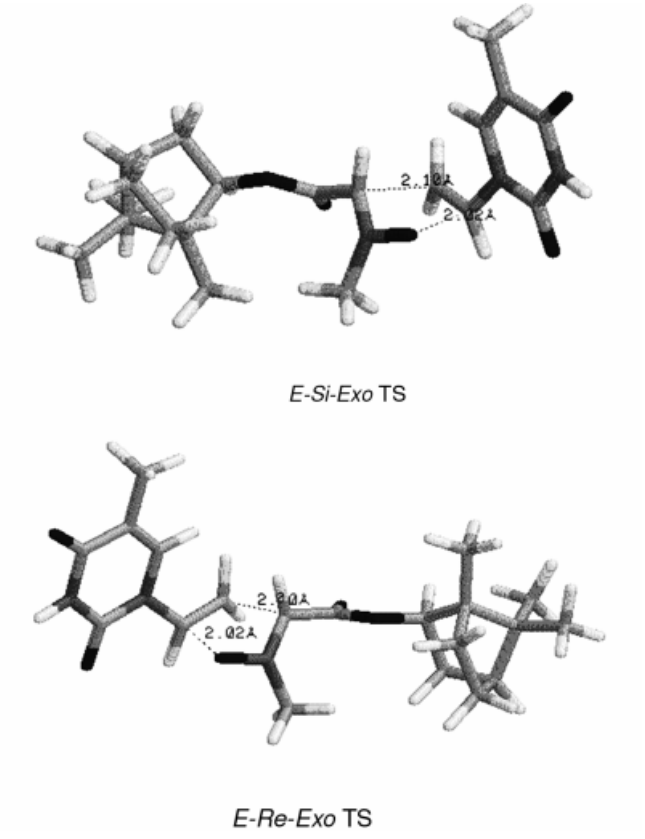


Figure 2. Transition-state structures for 1,3-dipolar cycloaddition of **6** and **9a**

Furthermore, the calculated TS energies for *exo* ($TS_{Si\text{-}exo}$) and *endo* ($TS_{Si\text{-}endo}$) approaches indicate that the reaction should result in the experimentally observed *cis*/*trans* mixture of cycloadducts. For *cis* isomers, the lowest calculated

Table 2. PM3 calculations for 1,3-dipolar cycloadditions between nitrone **6** and vinyl nucleobases **7**

Isoxazolidine	Transition state	PM3 [kcal/mol]	Calculated yield [%]	Observed yield [%]
8a	*E-Si-Exo*	−106.72712	74.5	70.2
9a	*E-Re-Exo*	−105.35320	10.3	7.2
10a	*E-Si-Endo*	−105.55256	13.5	12.6
11a	*E-Re-Endo*	−104.12838	1.7	0
8b	*E-Si-Exo*	24.82731	25.5	0
9b	*E-Re-Exo*	24.21918	62.2	80.0
10b	*E-Si-Endo*	26.14781	3.5	0
11b	*E-Re-Endo*	25.57342	8.5	8.0
8c	*E-Si-Exo*	−64.04305	65.5	84.0
9c	*E-Re-Exo*	−63.36122	24.1	0
10c	*E-Si-Endo*	−62.59035	7.7	0
11c	*E-Re-Endo*	−61.83660	2.7	0

TS energy is for the *endo* approach of vinylthymine to the *Si* face of the dipole, thus predicting the preferential formation of the (3′*S*,5′*R*) isomer (**10a**) [the TS for *Si-endo* attack is 1.42 kcal/mol more stable than the TS for *Re-endo* attack resulting in the (3′*R*,5′*S*) isomer (**11a**)]. Accordingly, compound **11a** was not detected in the NMR spectrum of the crude reaction mixture, allowing for the limits of the NMR technique.

Finally, the reduction of **8a** with $NaBH_4$ generated the target isoxazolidine nucleoside **12a** in good overall yield and in an enantiomerically pure form:[17] $[\alpha]_D^{25} = -18.5$ (c = 0.14, $CHCl_3$).

The generality of this synthetic approach was tested with a purine nucleobase, by treatment of **6** with vinyladenine (**7b**). The ^{1}H NMR spectrum of the crude reaction mixture showed the formation of two adducts **9b** and **11b** in a relative ratio 10:1 (total yield 88%), together with traces of a further product that was not isolable. The crude mixture was purified by a combination of flash and preparative radial chromatography.

Nucleoside **9b** possesses a $C^{3'}$,$C^{5'}$-*trans* configuration, while **11b** is characterized by a $C^{3'}$,$C^{5'}$-*cis* configuration (Scheme 1). The stereochemistry of the obtained adducts was determined on the basis of NOE measurements. For *trans* compound **9b**, irradiation of proton $H^{3'}$ at δ = 4.09 only induced a strong enhancement of $H^{4'a}$ (δ = 3.17), while irradiation of $H^{5'}$ (δ = 6.41) produced enhancement of $H^{4'b}$ (δ = 3.24) and H^8 (δ = 8.05), thus confirming a *trans* topological arrangement between the $H^{3'}$ and $H^{5'}$ protons. For *cis* compound **11b**, irradiation of $H^{4'b}$ (δ = 3.30) resulted in a positive NOE effect on both $H^{3'}$ (δ = 3.48) and $H^{5'}$ (δ = 6.52), together with a large enhancement of $H^{4'a}$ (δ = 3.00).

Notably, the methyl group signal at δ = 2.93 in *trans* isomer **9b** resonates as a quadruplet (J = 3.0 Hz): This is the result of the occurrence of a through-space interaction[18] between the *N*-methyl group and the methyl group at $C^{1''}$ in the bornyl moiety, as confirmed by selective long-range decoupling experiments. The observed coupling is explainable on the basis of conformational restriction due to the presence of the bulky bornyl group.

Also in this case, the cycloaddition process shows a good control of *cis*/*trans* diastereoselectivity, and a nearly complete level of asymmetric induction. The absolute configuration of the obtained products cannot confidently be assigned on the basis of semiempirical calculations. In fact, PM3 data do not provide theoretical support for the experimental results, indicating the formation of three adducts, two *trans* and one *cis*, in a relative ratio 62.2:25.5:8.5.

We tentatively assume that the *trans* compounds **9b** might arise from a *Re-Exo* TS and possesses the stereochemistry indicated in Figure 1 (3′*R*,5′*R*), which is 0.6 kcal/mol more stable than the unobtained diastereomer **8b** (3′*S*,5′*S*). On the same basis, *cis* isomer **11b** could be assigned the configuration (3′*R*,5′*S*) as the product of an *E-Re-Endo* TS (Table 2).

Treatment of **9b** with $NaBH_4$ (THF, reflux) afforded the nucleoside **13b** in an enantiomerically pure state, with $[\alpha]_D^{25} = -41.3$ (c = 0.23, H_2O). Chiral HPLC indicated the presence of a single compound, thus confirming the complete enantioselectivity of the reaction process considered.

As a further exploitation of the potential offered by the described procedure, we investigated the 1,3-dipolar cycloaddition between **6** and ethyl 3-(9-adenyl)acrylate (**7c**), prepared in 86% yield by a modification of the reported procedure.[19] The reaction (dipole/dipolarophile ratio 10:1, anhydrous THF, 70 °C, 48 h) displayed complete regioselectivity and stereoselectivity, exclusively affording a single *trans* cycloadduct **8c** in 84% yield.

The regiochemistry of **8c** was determined by ^{1}H NMR measurements. In particular, proton $H^{5'}$ resonates as a doublet at δ = 6.63: This value is diagnostic of an acetal proton. Proton $H^{3'}$ gives rise to a doublet at δ = 4.96, while $H^{4'}$ (doublet of doublets) resonates at δ = 4.35. Furthermore, the resonances of H^3 and H^8 appear as singlets, at δ = 8.32 and 7.97, respectively.

The cycloaddition process permits the simultaneous introduction of three new chiral centers in the final adduct in a highly stereoselective fashion: Only one out of eight possible stereoisomers was obtained, as confirmed by HPLC analysis. The stereochemical assignment was performed by NOEDS spectroscopy. The stereochemical information present in the dipolarophile moiety is completely retained in the obtained cycloadduct and the relative stereochemistry at $C^{4'}-C^{5'}$ in the isoxazolidine ring produced is predetermined by the alkene geometry. Furthermore, the positive

NOE observed for $H^{4'}$ and H^{8} when irradiating $H^{3'}$ is clearly indicative of their *cis* relationship. Analogously, irradiation of H^{8} induces an enhancement on the $H^{3'}$ and $H^{4'}$ resonances.

As for the cycloaddition process performed with the nucleobase **7c**, transition state calculations for this reaction, at PM3 semiempirical level, do not correctly predict the observed diastereoselectivity, indicating the formation of two *trans* adducts in a relative ratio of 3:1: The main product, possessing the (3′*S*,4′*S*,5′*S*) configuration, originates from an *E-Si-Exo* TS, which is 0.68 kcal/mol more stable than the *E-Re-Exo* TS producing the (3′*R*,4′*R*,5′*R*) stereoisomer. According to these considerations, the obtained compound can tentatively be assigned the absolute stereochemistry reported in Scheme 1.

Conclusion

In conclusion, an easy means of access to 4′-azanucleosides in an enantiomerically pure form has been established. In particular, the designed scheme demonstrates interesting versatility in the possibility of synthesizing nucleosides with three chiral centers in a single and enantioselective step, in a manner controlled by the nature of the substitution pattern present in the starting compounds.

Experimental Section

Melting points are uncorrected. − NMR spectra were recorded at 500 MHz (^{1}H) and at 125 MHz (^{13}C) and are reported in ppm downfield from TMS. − Thin layer chromatography was performed on Merck 60 F_{254} coated plates. Silica gel chromatography was performed with Macherey−Nagel 60 M (0.040−0.063 mm) silica gel. Preparative radial chromatography was performed with a glass rotor coated with Merck 60 PF_{254} silica gel (1−4 mm layer). − All reactions involving air-sensitive agents were conducted under nitrogen. All reagents were purchased from Aldrich or Acros Chimica and were used without further purification. Solvents for chromatography were distilled at atmospheric pressure prior to use and dried using standard procedures. HPLC purifications were performed with a semipreparative column (Partisil-10 Magnum 9, 9.4 × 250 mm). The purity of all homochiral compounds was tested with a Phenomenex CHIREX (S), using 0.01 M ammonium acetate in methanol as eluent.

***C*-{[(1*S*)-*endo*-Bornyl]oxycarbonyl} *N*-Methyl Nitrone (6):** $TiCl_4$ (0.1 M solution in 1,2-dichloroethane, 10 mL, 1.0 mmol) and (1*S*)-*endo*-(−)-borneol (2.77 g, 18.0 mmol) were added successively to a stirred suspension of molecular sieves (4 Å, 20.00 g) and nitrone **5** (1.57 g, 12 mmol) in dry 1,2-dichloroethane (300 mL) at room temperature under nitrogen. After stirring for 24 h, a small amount of water and Celite were added to the mixture, and the mixture was filtered through a pad of Celite. The filtrate was diluted with water, extracted with dichloromethane, dried with sodium sulfate, and concentrated in vacuo. The residue, purified by column flash chromatography on silica gel (cyclohexane/ethyl acetate, 3:7), gave an (*E*)/(*Z*) mixture (3:1) of nitrone **6** (2.73 g, 95%) as a light yellow oil. − $[\alpha]_D^{25}$ = −44.7 (*c* = 0.98, $CHCl_3$). − ^{1}H NMR [$CDCl_3$, 500 MHz, (*E*) isomer]: δ = 0.85 (s, 3 H), 0.89 (s, 3 H), 0.93 (s, 3 H), 1.03 (m, 1 H), 1.19 (m, 1 H), 1.38 (m, 1 H), 1.73 (m, 1 H), 1.79 (m, 1 H), 1.91 (m, 1 H), 2.40 (m, 1 H), 4.18 (s, 3 H, *N*-Me), 4.97 (m, 1 H), 7.28 (s, 1 H). − ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.5, 18.8, 19.6, 27.00, 27.9, 36.7, 44.8, 47.9, 48.9, 52.0, 81.4, 127.9, 161.4. − $C_{13}H_{21}NO_3$ (239.3): calcd. C 65.25, H 8.84, N 5.85; found C 65.07, H 8.86, N 5.86.

(3′*S*,5′*S*)- and (3′*S*,5′*R*)-1-(3′-{[(1*S*)-*endo*-Bornyl]oxycarbonyl}-2′-methyl-1′,2′-isoxazolidin-5′-yl)thymine (8a and 10a): A solution of nitrone **6** (2.68 g, 11.2 mmol) and vinyl nucleobase **7a** (1.87 g, 12.3 mmol) in dry benzene (40 mL) was heated at 70 °C, in a sealed tube, for 24 h. The reaction mixture was concentrated and the residue was purified by flash chromatography (cyclohexane/ethyl acetate, 1:1) and then by HPLC with a linear gradient of 2-propanol (5%, 0−10 min, 5−10% 10−20 min, flow 3.5 mL/min) in *n*-hexane. The first eluted product was compound **10a**. − t_R = 15.3 min, 12.6% yield; white solid, m.p. 110−112 °C. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (s, 3 H), 0.89 (s, 3 H), 0.92 (s, 3 H), 0.96 (m, 1 H), 1.21 (m, 1 H), 1.29 (m, 1 H), 1.72 (m, 1 H), 1.77 (m, 1 H), 1.83 (m, 1 H), 1.95 (d, 3 H, *J* = 1.0 Hz), 2.40 (m, 1 H), 2.65 (ddd, 1 H, *J* = 2.5, 8.5 and 13.5 Hz, $H^{4'a}$), 2.88 (s, 3 H, *N*-Me), 3.20 (ddd, 1 H, *J* = 7.5, 9.0 and 13.5 Hz, $H^{4'b}$), 3.41 (dd, 1 H, *J* = 8.5 and 9.0 Hz, $H^{3'}$), 4.97 (m, 1 H), 6.27 (dd, 1 H, *J* = 2.5 and 7.5 Hz, $H^{5'}$), 7.81 (q, 1 H, *J* = 1.0 Hz, H^6), 8.14 (br. s, 1 H, NH). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.7, 13.6, 18.8, 19.6, 27.1, 28.0, 29.7, 31.9, 36.8, 44.7, 69.4, 81.7, 82.4, 106.8, 136.4, 148.2, 163.68, 169.9. − $C_{20}H_{29}N_3O_5$ (391.4): calcd. C 61.36, H 7.47, N 10.73; found C 61.23, H 7.45, N 10.74. − The second eluted fraction was compound **8a**. − t_R = 18.7 min, 70.2% yield; white solid, m.p. 111−113 °C; $[\alpha]_D^{25}$ = − 18.5 (*c* = 0.16; $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (d, 3 H, *J* = 2.9 Hz), 0.89 (s, 3 H), 0.92 (s, 3 H), 1.01 (m, 1 H), 1.21 (m, 1 H), 1.25 (m, 1 H), 1.72 (m, 1 H), 1.79 (m, 1 H), 1.90 (m, 1 H), 1.96 (d, 3 H, *J* = 1.0 Hz), 2.42 (m, 1 H), 2.53 (ddd, 1 H, *J* = 0.8, 5.2 and 13.0 Hz, $H^{4'a}$), 2.87 (d, 3 H, *J* = 2.9 Hz, *N*-Me), 3.14 (ddd, 1 H, *J* = 3.3, 4.2 and 13.0 Hz, $H^{4'b}$), 3.92 (dd, 1 H, *J* = 3.3 and 5.2 Hz, $H^{3'}$), 4.98 (m, 1 H), 6.27 (dd, 1 H, *J* = 0.8 and 4.2 Hz, $H^{5'}$), 7.45 (q, 1 H, *J* = 1.0 Hz, H^6), 8.64 (br. s, 1 H, NH). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.7, 13.7, 18.8, 19.6, 27.2, 28.0, 29.7, 36.9, 40.7, 44.8, 47.8, 66.7, 81.7, 83.4, 111.0, 135.6, 150.7, 163.7, 169.0. − $C_{20}H_{29}N_3O_5$ (391.4): calcd. C 61.36, H 7.47, N 10.73; found C 61.21, H 7.46, N 10.75.

(3′*R*,5′*R*)- and (3′*R*,5′*S*)-9-(3′-{[(1*S*)-*endo*-Bornyl]oxycarbonyl}-2′-methyl-1′,2′-isoxazolidin-5′-yl)adenine (9b and 11b): Nitrone **6** (14.36 g, 60.0 mmol) was added in three portions over a 24 h period to a solution of vinyl nucleobase **7b** (0.97 g, 6.0 mmol) in dry benzene (40 mL), and the mixture was heated at 70 °C for 48 h. After concentration at reduced pressure, the residue was purified by flash chromatography (chloroform/methanol, 95:5) and then by radial chromatography (chloroform/methanol, 98:2). The first eluted fraction gave compound **11b**. − 8% yield; white solid, m.p. 173−175 °C; $[\alpha]_D^{25}$ = −80.9 (*c* = 0.07; $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (s, 3 H), 0.89 (s, 3 H), 0.92 (s, 3 H), 0.99 (m, 1 H), 1.23 (m, 1 H), 1.35 (m, 1 H), 1.72 (m, 1 H), 1.76 (m, 1 H), 1.85 (m, 1 H), 2.42 (m, 1 H), 2.90 (s, 3 H, *N*-Me), 3.00 (ddd, 1 H, *J* = 2.5, 7.8 and 13.9 Hz, $H^{4'a}$), 3.30 (ddd, 1 H, *J* = 8.0, 9.5 and 13.9 Hz, $H^{4'b}$), 3.48 (dd, 1 H, *J* = 7.8 and 9.5 Hz, $H^{3'}$), 5.02 (m, 1 H), 5.68 (br. s, 2 H, NH_2), 6.52 (dd, 1 H, *J* = 2.5 and 8.0 Hz, $H^{5'}$), 8.35 (s, 1 H, H^3), 8.43 (s, 1 H, H^8). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.6, 18.8, 19.6, 27.1, 28.0, 36.9, 41.0, 44.6, 44.8, 48.0, 49.0, 69.2, 80.1, 81.9, 124.1, 143.9, 153.0, 155.3, 156.9, 173.4. − $C_{20}H_{28}N_6O_3$ (400.4): calcd. C 59.98, H 7.05, N 20.99; found C 61.18, H 7.04, N 20.95. − The second eluted fraction gave compound **9b**. − 80% yield; white solid, m.p. 174−178 °C; $[\alpha]_D^{25}$ =

−17.2 (*c* = 0.11; $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (q, 3 H, *J* = 3.0 Hz), 0.90 (s, 3 H), 0.93 (s, 3 H), 1.04 (m, 1 H), 1.26 (m, 1 H), 1.37 (m, 1 H), 1.73 (m, 1 H), 1.79 (m, 1 H), 1.93 (m, 1 H), 2.43 (m, 1 H), 2.93 (q, 3 H, *J* = 3.0 Hz, *N*-Me), 3.17 (ddd, 1 H, *J* = 0.4, 6.5 and 13.5 Hz, H$^{4'a}$), 3.24 (ddd, 1 H, *J* = 1.5, 6.5 and 13.5 Hz, H$^{4'b}$), 4.09 (t, 1 H, *J* = 6.5 Hz, H$^{3'}$), 5.00 (m, 1 H), 5.74 (br. s, 2 H, NH_2), 6.41 (dd, 1 H, *J* = 0.4 and 1.5 Hz, H$^{5'}$), 8.05 (s, 1 H, H^8), 8.37 (s, 1 H, H^3). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.6, 18.8, 19.6, 27.2, 28.0, 36.8, 39.4, 44.74, 44.76, 47.8, 48.9, 67.2, 81.6, 82.2, 119.8, 149.4, 153.1, 154.2, 155.6, 169.3. − $C_{20}H_{28}N_6O_3$ (400.4): calcd. C 59.98, H 7.05, N 20.99; found C 61.17, H 7.07, N 20.93.

(3′*S*,4′*S*,5′*S*)-9-(3′-{[(1*S*)-*endo*-Bornyl]oxycarbonyl}-4′-ethoxycarbonyl-2′-methyl-1′,2′-isoxazolidin-5′-yl)adenine (8c): Nitrone **6** (14.36 g, 60.0 mmol) was added in three portion over a 24 h period to a solution of vinyl nucleobase **7c** (1.40 g, 6.0 mmol) in dry THF (40 mL), and the mixture was heated at reflux temperature for 48 h. After concentration at reduced pressure, the residue was purified by flash chromatography (chloroform/methanol, 95:5) and then by radial chromatography (chloroform/methanol, 98:2). − 84% yield; sticky oil; $[\alpha]_D^{25}$ = + 15.4 (*c* = 0.94; $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (s, 3 H), 0.85 (s, 3 H), 1.01 (m, 1 H), 1.16 (s, 3 H), 1.17 (t, 3 H, *J* = 7.1 Hz), 1.31 (m, 2 H), 1.65 (m, 1 H), 1.67 (m, 1 H), 1.83 (m, 1 H), 2.35 (m, 1 H), 2.84 (s, 3 H, *N*-Me), 4.15 (q, 2 H, *J* = 7.1 Hz), 4.35 (dd, 1 H, *J* = 0.8, and 4.5 Hz, H$^{4'}$), 4.91 (m, 1 H), 4.96 (d, 1 H, *J* = 4.5 Hz, H$^{3'}$), 5.98 (br. s, 2 H, NH_2), 6.63 (d, 1 H, *J* = 0.8 Hz, H$^{5'}$), 7.97 (s, 1 H, H^8), 8.32 (s, 1 H, H_3). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.5, 13.9, 18.8, 19.7, 27.2, 27.2, 28.01, 28.06, 36.5, 36.8, 46.9, 61.9, 69.9, 77.3, 82.0, 102.6, 120.2, 149.6, 153.0, 153.2, 155.5, 167.8, 167.9. − $C_{23}H_{32}N_6O_5$ (472.5): calcd. C 58.46, H 6.83, N 17.78; found C 58.35, H 6.85, N 17.74.

General Procedure for Preparation of Isoxazolidinyl Nucleosides 12a and 13b: Sodium borohydride (25.90 mg, 0.675 mmol) was added to a solution of compound **8a** or **9b** (0.15 mmol) in a 1:1 dioxane/water mixture (2.8 mL), and the mixture was vigorously stirred for 12 h. After this period, the reaction mixture was cooled to 0 °C and successively extracted with ethyl acetate (3 × 5 mL). The collected organic phases, dried with sodium sulfate, gave after solvent evaporation a light yellow solid, which was purified by flash chromatography (chloroform/methanol, 85:15).

(3′*S*,5′*S*)-1-[3′-(Hydroxymethyl)-2′-methyl-1′,2′-isoxazolidin-5′-yl]thymine (12a): 62% yield; white solid, m.p. 141−145 °C; $[\alpha]_D^{25}$ = − 18.5 (*c* = 0.14; $CHCl_3$). − ^{1}H NMR (500 MHz, CD_3CN): δ = 1.85 (d, 3 H, *J* = 1.2 Hz), 2.25 (br. s, 1 H, H), 2.35 (ddd, 1 H, *J* = 4.6, 7.7 and 13.7 Hz, H$^{4'a}$), 2.51 (ddd, 1 H, *J* = 3.5, 7.9 and 13.7 Hz, H$^{4'b}$), 2.78 (s, 3 H, *N*-Me), 3.57 (dddd, 1 H, *J* = 3.5, 4.0, 4.5 and 7.7 Hz, H$^{3'}$), 3.59 (dd, 1 H, *J* = 4.0 and 12.1 Hz, H$^{3''a}$), 3.60 (dd, 1 H, *J* = 4.5 and 12.1 Hz, H$^{3''b}$), 6.04 (dd, 1 H, *J* = 4.6 and 7.9 Hz, H$^{5'}$), 7.41 (q, 1 H, *J* = 1.2 Hz, H_6), 9.08 (br. s, 1 H, NH). − ^{13}C NMR (125 MHz, $CDCl_3$/CD_3OD 9:1): δ = 12.2, 29.4, 34.1, 60.6, 67.3, 82.9, 111.0, 135.6, 150.5, 164.3. − $C_{10}H_{15}N_3O_4$ (241.2): calcd. C 49.79, H 6.27, N 17.42; found C 49.98, H 6.25, N 17.48.

(3′*R*,5′*R*)-9-[3′-(Hydroxymethyl)-2′-methyl-1′,2′-isoxazolidin-5′-yl)adenine (13b): 51% yield; white solid, m.p. 203−204 °C with decomposition; $[\alpha]_D^{25}$ = − 41.3 (*c* = 0.23; H_2O). − ^{1}H NMR (500 MHz, D_2O): δ = 2.64 (ddd, 1 H, *J* = 0.3, 8.1 and 13.7 Hz, H$^{4'a}$), 2.65 (s, 3 H, *N*-Me), 2.91 (ddd, 1 H, *J* = 0.2, 7.5 and 13.7 Hz, H$^{4'b}$), 3.34 (dddd, 1 H, *J* = 0.2, 4.7, 6.0 and 8.1 Hz, H$^{3'}$), 3.58 (dd, 1 H, *J* = 6.0 and 12.2 Hz, H$^{3''a}$), 3.63 (dd, 1 H, *J* = 4.7 and 12.2 Hz, H$^{3''b}$), 6.12 (dd, 1 H, *J* = 0.3 and 7.5 Hz, H$^{5'}$), 7.99 (s, 1 H, H^8), 8.16 (s, 1 H, H^3). − ^{13}C NMR (125 MHz, D_2O): δ = 36.6, 43.1, 61.1, 67.8, 82.8, 118.7, 148.5, 150.3, 152.6, 155.4. − $C_{10}H_{14}N_6O_2$ (250.2): calcd. C 47.99, H 5.64, N 33.58; found C 48.13, H 5.62, N 33.51.

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