Chemistry of Heterocyclic Compounds, Vol. 43, No. 1, 2007

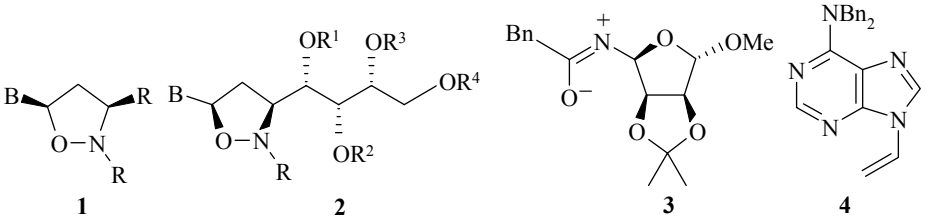
DIASTEREOSELECTIVE SYNTHESIS OF SOME CARBOCYCLIC 2'-OXA-3'-AZA-NUCLEOSIDES

E. Hýrošová[1], L. Fišera[1], R. M.-A. Jame[1], N. Prónayová[2], M. Medvecký[1], and M. Koóš[3]

Two strategies for the synthesis of isoxazolidinyl nucleosides as potential antiviral agents are reported: a one-step approach based on 1,3-dipolar cycloaddition of D-lyxosyl nitrone with N,N-dibenzyl-9-vinyl adenine, and a two-step methodology based on the Vorbrüggen nucleosidation of the 5-acetoxy-isoxazolidine. The chiral D-lyxosyl nitrone undergoes regioselective 1,3-dipolar cycloadditions with N,N-dibenzyl-9-vinyl adenine and vinyl acetate giving 5-substituted isoxazolidines as a mixture of four diastereoisomers in good yields. The condensation of 5-acetoxyisoxazolidine with silylated uracil, thymine, and N-acetylcytosine proceeded with moderate to good stereoselectivity with the formation of the expected isoxazolidinyl β- and α-nucleosides.

Keywords: chiral, dipolar cycloadditions, isoxazolidines, modified nucleosides, nitrones.

Many nucleoside analogues have been synthesized with the modification of the base, sugar, and phosphane regions. In particular, nucleoside analogues, in which the furanose ring was replaced by different carbon or heterocyclic systems, have attracted a special interest by virtue of their biological action as antiviral and/or anti-cancer agents [1]. Among them uracil, thymine, cytosine, and adenine nucleosides **1** possessing an isoxazolidinyl moiety (carbocyclic-2'-oxo-3'-azanucleosides) are emerging as an interesting class of dideoxynucleo-side analogues with potential pharmacological activity [1]. Two strategies can be used for the synthesis of modified isoxazolidinyl nucleosides. In particular, a one-step approach based on 1,3-dipolar cycloaddition of nitrones with vinyl nucleobases and a two-step methodology based on the Vorbrüggen nucleosidation of the 5-acetoxyisoxazolidines [2-9].



1 **2** **3** **4**

B = nucleoside base

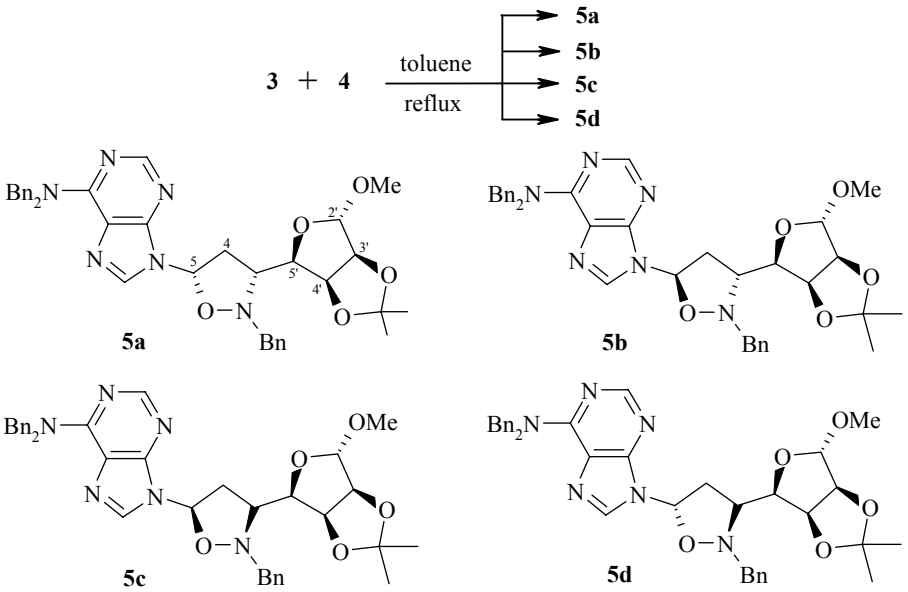
* Dedicated to Prof. Dr. E. Lukevics on the occasion of his 70th birthday

[1]Institute of Organic Chemistry, Catalysis and Petrochemistry, Slovak University of Technology, 81237 Bratislava, Slovak Republic; e-mail: lubor.fisera@stuba.sk, [2]Institute of Analytical Chemistry, Slovak University of Technology, 81237 Bratislava, Slovak Republic, [3]Institute of Chemistry, Slovak Academy of Sciences, 84538 Bratislava, Slovak Republic. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 01, pp. 14-21, Januvary, 2007. Original article submitted September 12, 2006.

The use of C-chiral nitrones allows a diastereoselective synthetic access to homochiral isoxazolidinyl nucleosides **2** [8]. With our continuing efforts to utilize chiral 1,3-dipolar cycloadditions [10-15], we are now extending the 1,3-dipolar cycloaddition approach to synthesize novel 4'-aza-2',3'-dideoxyfuranosyl nucleosides by the reaction of readily available chiral sugar derived D-lyxosyl nitrone **3** with N,N-dibenzyl-9-vinyl adenine **4** as well as by 1,3-dipolar cycloadditions of nitrone **3** to vinyl acetate with the subsequent transformation of the formed 5-acetoxyisoxazolidines.

Our strategy for the preparation of isoxazolidinyl nucleosides is based on the stereoselective construction of the isoxazolidine ring through the 1,3-dipolar cycloaddition between chiral nitrone **3** that was easily prepared from the corresponding aldehyde following the described procedure [16] and vinyl nucleobases. Merino and coworkers have described the cycloaddition of this nitrone **3** with methyl acrylate [17].

Scheme 1

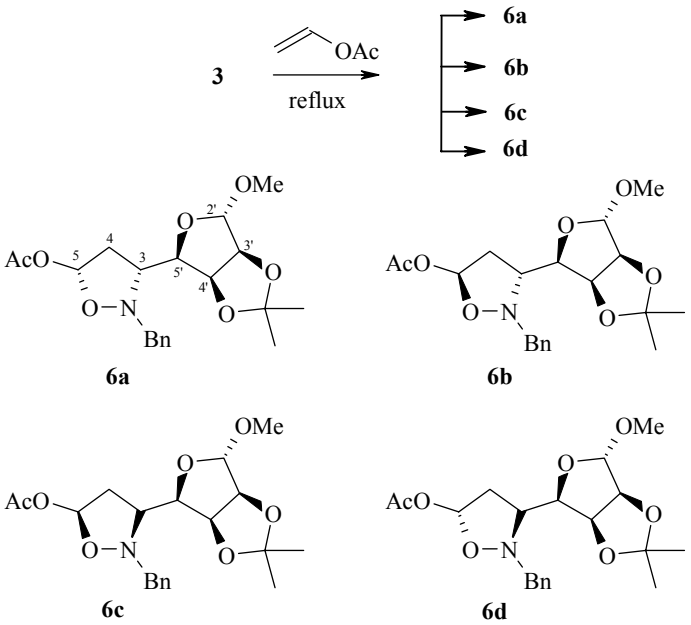


5a : **5b** : **5c** : **5d** = 39 : 27 : 19 : 15; *anti : syn* = 66 : 34, *cis : trans* 58 : 42

It was found that chiral nitrone **3** reacted with vinyl adenine **4** to give a mixture of all possible 3,5-disubstituted isoxazolidines **5a**–**d** in 98% yield. Two of them, **5b** and **5d**, are with a C-3/C-5 *trans* configuration (α-anomers) and two, **5a** and **5c**, with a C-3/C-5 *cis* configuration (β-anomers). Purification by flash chromatography allowed separation of all diastereoisomers **5a-d** in an enantiomerically pure form (Scheme 1). Whereas the regioselectivity of the reaction was very high (the corresponding 3,4-regioisomers were not detected) both *cis/trans* selectivity and the diastereofacial induction (*Re/Si* ratio 66 : 34) were rather low. The complete regioselectivity of the cycloaddition and the preference for the *exo* approach (producing *cis* adducts) is comparable with the results reported in the literature [2-7] as well with our own previous data for isoxazolidines **2** prepared by nitrone cycloadditions with vinyl uracil [8]. The relative configuration of all adducts **5a-d** could be elucidated by NOE and NOESY experiments. For instance, the NOE spectra of adduct **5b** established a *trans* relationship deduced from the spatial proximity of H-5 with H-4a, and of H-4b with H-3. NOESY experiments confirmed the spatial proximity between H-3 and H-5 in the major *cis* adduct **5a**. The relative configuration at C-3 and C-5' for nucleosides **5a-d** has been tentatively assigned in Scheme 1, according to our own previous data concerning chiral nitrone cycloadditions with vinyl uracil [8].

We have recently reported the 1,3-dipolar cycloaddition of the chiral nitrones prepared from D-xylose with vinyl acetate [18]. Since we used the soprepared adducts for the synthesis of isoxazolidinyl nucleosides by the Vorbrüggen nucleosidation with silylated nucleobases, we would like to compare these two procedures. Therefore, the cycloaddition of the chiral nitrone **3** with vinyl acetate was investigated next. Cycloaddition of chiral nitrone **3** with vinyl acetate (Scheme 2) afforded a mixture of four diastereoisomers **6a-d** and proceeded as compared to the cycloaddition with vinyl adenine **4** with better selectivity in favor of major isomer **6a** (*cis/trans* ratio 65 : 35, *Re/Si* ratio 68 : 32).

Scheme 2

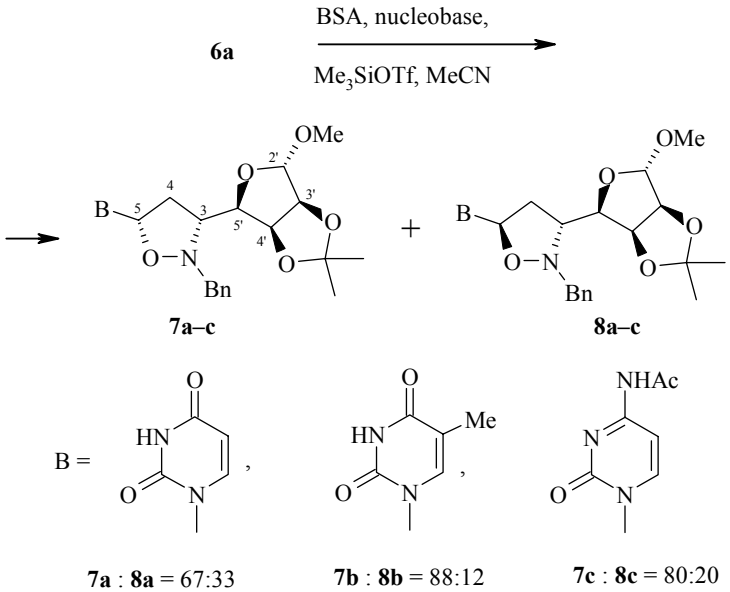


6a : **6b** : **6c** : **6d** = 47 : 21 : 18 : 14; *anti : syn* = 68 : 32, *cis : trans* = 65 : 35

Cycloaddition of nitrone **3** to vinyl acetate proceeded regioselectively and led to isoxazolidines **6a**–**d** as a mixture of diastereoisomers in 86% yield. Purification by flash chromatography allowed the isolation of pure *exo*-adduct **6a**, with C-3/C-5 *cis* relative configuration and *endo*-adduct **6b**, with C-3/C-5 *trans* relative configuration identified by spectroscopic analysis, particularly NOE difference experiments. Based on our previous results from 1,3-dipolar cycloadditions of sugar nitrones bearing a protected hydroxy group in the α-position [8-15] as well as to the fact that 1,3-dipolar cycloaddition of electron-rich alkenes to chiral α-alkoxy nitrones gave preferentially *anti* adducts [3], we assigned to isomer **6a** (and similarly **6b**) a C-1'/C-3 *anti* relationship as a result of dipolarophile attack from the less sterically hindered *si* diastereotopic face of nitrone **3** [8].

Next, the major *anti-cis* cycloadduct **6a** was coupled with silylated nucleobases according to the Vorbrüggen methodology [19]. The condensation with silylated uracil, thymine, and N-acetylcytosine at 70°C in the presence of 0.4 equiv of trimethylsilyltriflate as a catalyst proceeded with good yields and from moderate to good stereoselectivity with the formation of the expected isoxazolidinyl β- and α-nucleosides (Scheme 3). For N-acetylcytosine and thymine, the β-anomers clearly predominate, while in the case of uracil a significant amount of α-anomer has been obtained. It was reported that the anomeric distribution obtained depends on the attacking nucleobase [20-23]. Evidently, in this case, attack on the intermediate oxonium from either α- or β-side is possible, and hence the product distribution is sensitive to the structural changes of the reactants. Purification by flash chromatography allowed the isolation of pure nucleoside **7a**; its assigned stereochemistry is supported by NMR analysis. In fact, NOE measurements performed on β-anomers **7a-c** show a positive NOE effect for protons H-3 when irradiating H-5, thus indicating a *cis* relationship between these protons.

Scheme 3



In conclusion**,** two strategies for the synthesis of isoxazolidinyl nucleosides as potential antiviral agents are reported: the one-step approach based on 1,3-dipolar cycloaddition of D-lyxosyl nitrone **3** with N,N-dibenzyl-substituted vinyl adenine **4,** and the two-step methodology based on the Vorbrüggen nucleosidation of 5-acetoxyisoxazolidine **6a**. The chiral nitrone **3** undergoes regioselective 1,3-dipolar cycloadditions with adenine **4** and vinyl acetate giving 5-substituted isoxazolidines **5a-d** and **6a-d** as a mixture of four diastereoisomers in good yields. The condensation of acetoxyisoxazolidine **6a** with silylated uracil, thymine, and N-acetylcytosine proceeded with good yields and from moderate to good stereoselectivity with the formation of the expected isoxazolidinyl β- and α-nucleosides **7a-c** and **8a-c**. Biological evaluation of the compounds obtained is in progress.

EXPERIMENTAL

All commercially available starting materials and reagents (Fluka, Merck, Across, or Aldrich) were used without further purification. Solvents were dried before use. Thin-layer chromatography (TLC, ALUGRAM Sil G/UV_{254} Macherey-Nagel) was used for monitoring of reaction courses; eluents are given in the text. For column chromatography the flash chromatography technique was employed using silica 60 (0.040-0.063 mm, Merck). IR spectra were recorded on FTIR NICOLET MAGNA 750 instrument. The ^{1}H and ^{13}C NMR spectra of deuterochloroform solutions were obtained using Varian INOVA-600 (600 and 150 MHz respectively) and VXR-300 (300 and 75 MHz respectively) instruments, TMS being the internal reference. Specific rotations [α] were measured on an IBZ Messtechnik Polar-LμP polarimeter at the sodium D line (589 nm) using a 1 dm cell. Elemental analyses were conducted using the Fisons EA 1108 Analysator. Nitrone **3** was prepared from the corresponding aldehyde by the reaction with N-benzylhydroxylamine according to the procedure already described [16].

1,3-Dipolar cycloaddition of nitrone 3 with vinyl adenine 4. A mixture of nitrone **3** (1 g, 3.25 mmol) and vinyl adenine **4** (1.11 g, 3.25 mmol) was stirred in toluene (10 ml) for 24 h under reflux. When the starting nitrone had been consumed (TLC), the solvent was evaporated under vacuum, and the mixture of diastereoisomers **5a-d** in 98% yield was separated by column chromatography (silica gel, hexanes : AcOEt = 90 : 10).

N,N-Dibenzyl-9-{(3*S*,5*S*)-2-benzyl-3-[2,3-O-isopropylidene-1-O-methyl-α-D-lyxotetrafuranose]isoxazolidin-5-yl}adenine (**5a**). Yield 38%, colorless oil, R_f 0.47 (hexanes : AcOEt, 50 : 50). $[\alpha]_D^{25}$ = +75 (*c* = 0.12, CH_2Cl_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.42, 8.39 (2 × 1H, 2 × s, H-2", H-8"); 7.27 (15H, m, H-arom); 6.58 (1H, dd, *J* = 7.7, *J* = 2.9, H-5); 5.63–4.92 (4H, br.s, N(C$\underline{H}_2$Ph)$_2$); 4.88 (1H, s, H-2'); 4.65 (1H, dd, *J* = 5.8, *J* = 2.9, H-4'); 4.52 (1H, d, *J* = 5.8, H-3'); 4.27 (1H, d, *J* = 14.4, NC$\underline{H}_2$Ph); 4.07 (1H, d, *J* = 14.4, NC$\underline{H}_2$Ph); 3.93 (1H, dd, *J* = 3.8, *J* = 3.9, H-5'); 3.49 (1H, m, H-3); 3.20 (3H, s, OCH_3); 3.12 (1H, m, H-4b); 3.00 (1H, m, H-4a); 1.41 (3H, s, CH_3); 1.27 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 152.02, 137.61 (C-2", C-8"); 154.67, 150.42, 138.08, 127.24, 119.12 (NCH_2Ph, N(CH_2Ph)$_2$, C-adenine); 112.54 ($\underline{C}(CH_3)_2$); 106.60 (C-2'); 84.65 (C-3'); 80.89 (C-5); 79.72 (C-4'); 77.95 (C-5'); 63.80 (C-3); 61.88 (N$\underline{C}H_2$Ph); 54.58 (OCH_3); 38.82 (C-4); 25.66 (CH_3); 24.28 (CH_3). Found, %: C 68.44; H 6.22; N 13.00. $C_{37}H_{40}N_6O_5$. Calculated, %: C 68.50; H 6.21; N 12.95.

N,N-Dibenzyl-9-{(3*S/3R*,5*S/5R*)-2-benzyl-3-[2,3-O-isopropylidene-1-O-methyl-α-D-lyxo-tetrafuranose]isoxazolidin-5-yl}adenine (5b). Yield 20%, colorless oil, R_f 0.43 (hexanes : : AcOEt = 50 : 50). $[\alpha]_D^{25}$ = +39 (*c* = 0.10, CH_2Cl_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.44, 7.92 (2 × 1H, 2 × s, H-2", H-8"); 7.28 (15H, m, H-arom); 6.41 (1H, dd, *J* = 7.0, *J* = 3.4, H-5); 5.64–4.92 (4H, br.s, N(C$\underline{H}_2$Ph)$_2$); 4.91 (1H, s, H-2'); 4.74 (1H, dd, *J* = 5.9, *J* = 3.4, H-4'); 4.58 (1H, d, *J* = 5.9, H-3'); 4.26 (1H, d, *J* = 13.8, NC$\underline{H}_2$Ph); 4.19 (1H, d, *J* = 13.8, NC$\underline{H}_2$Ph); 4.09 (1H, m, H-5'); 4.00 (1H, m, H-3); 3.36 (3H, s, OCH_3); 3.26 (1H, m, H-4b); 3.14 (1H, m, H-4a); 1.40 (3H, s, CH_3); 1.27 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 154.69, 137.51 (C-2", C-8"); 152.37, 150.50, 137.13, 127.29, 120.01 (NCH_2Ph, N(CH_2Ph)$_2$, C-adenine); 112.46 ($\underline{C}(CH_3)_2$); 106.95 (C-2'); 85.05 (C-3'); 83.94 (C-5); 79.60 (C-4'); 79.17 (C-5'); 62.57 (C-3); 61.78 (N$\underline{C}H_2$Ph); 54.79 (OCH_3); 37.79 (C-4); 25.89 (CH_3); 24.55 (CH_3). Found, %: C 68.58; H 6.51; N 13.19. $C_{37}H_{40}N_6O_5$. Calculated, %: C 68.50; H 6.21; N 12.95.

N,N-Dibenzyl-9-{(3*R*,5*R*)-2-benzyl-3-[2,3-O-isopropylidene-1-O-methyl-α-D-lyxo-tetrafuranose]isoxazolidin-5-yl}adenine (**5c**). Yield 19%, colorless oil, R_f 0.57 (hexanes : AcOEt = 50 : 50). $[\alpha]_D^{25}$ = -12 (*c* = 0.20, CH_2Cl_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.36, 8.06 (2 × 1H, 2 × s, H-2", H-8"); 7.33 (15H, m, H-arom); 6.41 (1H, m, H-5); 5.60-4.95 (4H, br.s, N(C$\underline{H}_2$Ph)$_2$); 4.95 (1H, s, H-2'); 4.77 (1H, d, *J* = 14.4, NC$\underline{H}_2$Ph); 4.65 (1H, dd, *J* = 6.3, 3.8, H-4'); 4.53 (1H, d, *J* = 6.7, H-3'); 4.09 (1H, m, H-5'); 3.93 (1H, d, *J* = 14.4, NC$\underline{H}_2$Ph); 3.43 (2H, m, H-4b, H-3); 3.32 (3H, s, OCH_3); 2.39 (1H, m, H-4a); 1.49 (3H, s, CH_3); 1.29 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 154.63, 137.53 (C-2", C-8"); 152.08, 149.83, 136.88, 127.23, 119.37 (NCH_2Ph, N(CH_2Ph)$_2$, (C-adenine); 112.72 ($\underline{C}(CH_3)_2$); 107.44 (C-2'); 84.26 (C-3'); 81.56 (C-5); 81.23 (C-4'); 80.82 (C-5'); 64.73 (C-3); 61.88 (NC$\underline{H}_2$Ph); 54.55 (OCH_3); 41.55 (C-4); 26.03 (CH_3); 24.70 (CH_3). Found, %: C 68.03; H 6.61; N 12.69. $C_{37}H_{40}N_6O_5$. Calculated, %: C 68.50; H 6.21; N 12.95.

N,N-Dibenzyl-9-{(3*S/3R*,5*S/5R*)-2-benzyl-3-[2,3-O-isopropylidene-1-O-methyl-α-D-lyxotetrafuranose]-isoxazolidin-5-yl}adenine (**5d**). Yield 18%, colorless oil, R_f 0.23 (hexanes : : AcOEt = 50 : 50). $[\alpha]_D^{25}$ = –29.2 (*c* = 0.12, CH_2Cl_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.39, 7.77 (2 × 1H, 2 × s, H-2", H-8"); 7.32 (15H, m, H-arom); 6.37 (1H, dd, *J* = 7.7, *J* = 2.9, H-5); 5.63–4.92 (4H, br.s, N(C$\underline{H}_2$Ph)$_2$); 4.99 (1H, s, H-2'); 4.73 (1H, dd, *J* = 5.8, *J* = 3.8, H-4'); 4.60 (1H, d, *J* = 14.4, NC$\underline{H}_2$Ph); 4.58 (1H, d, *J* = 5.8, H-3'); 4.15 (1H, m, H-5'); 4.15 (1H, d, *J* 14.4, NC$\underline{H}_2$Ph); 3.76 (1H, m, H-3); 3.37 (3H, s, OCH_3); 2.96 (1H, ddd, *J* = 8.6, *J* = 6.7, *J* = 1.9, H-4b); 2.78 (1H, m, H-4a); 1.46 (3H, s, CH_3); 1.28 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 154.80, 137.67 (C-2", C-8"); 152.55, 150.44, 136.76, 127.24, 119.70 (NCH_2Ph, N(CH_2Ph)$_2$, C-adenine; 112.71 ($\underline{C}(CH_3)_2$); 107.42 (C-2'); 84.34 (C-3'); 81.40 (C-5); 80.71 (C-4'); 80.56 (C-5'); 62.66 (C-3); 61.15 (N$\underline{C}H_2$Ph); 54.66 (OCH_3); 39.27 (C-4); 26.08 (CH_3); 24.73(CH_3).

1,3-Dipolar cycloaddition of nitrone 3 with vinyl acetate. A mixture of nitrone **3** (0.5 g, 1.60 mmol) and vinyl acetate (5 ml) was stirred for 24 h under reflux. When the starting nitrone had been consumed (TLC), solvent was evaporated under vacuum and the mixture of diastereoisomers in the ratio 47 : 21 : 18 : 14 in 86% yield was separated by column chromatography (silica gel, hexanes : AcOEt = 90 : 10).

(3*R*,5*S*)-5-Acetoxy-2-benzyl-3-(2,3-O-isopropylidene-1-O-methyl-α-D-lyxotetrafuranose)isoxazolidine (**6a**). Yield 35%, colorless oil, R_f 0.54 (hexanes : AcOEt = 50 : 50). $[\alpha]_D^{25}$ = +154.5 (*c* = 0.10, CH_2Cl_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.32 (5H, m, H-arom); 6.45 (1H, d, *J* = 5.3, H-5); 4.83 (1H, s, H-2');

4.74 (1H, dd, J = 5.9, J = 3.5, H-4'); 4.54 (1H, d, J = 5.9, H-3'); 4.17 (1H, d, J = 14.1, NC$\underline{H}_2$Ph,); 4.16 (1H, dd, J = 9.4, J = 3.5, H-5'); 4.05 (1H, d, J = 14.1, NC$\underline{H}_2$Ph); 3.72 (1H, ddd, J = 8.8, J = 1.8, J = 9.4, H-3); 3.30 (3H, s, OCH_3); 2.45 (1H, dd, J = 14.1, J = 2.4, H-4b); 2.30 (1H, ddd, J = 14.1, J = 5.3, J = 8.8, H-4a); 2.03 (3H, s, $OCOCH_3$); 1.41 (3H, s, CH_3); 1.26 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm (J, Hz): 170.04 (O$\underline{C}$OCH$_3$); 136.18–127.50 (C-arom); 112.18 ($\underline{C}(CH_3)_2$); 106.73 (C-2'); 96.95 (C-5); 85.08 (C-3'); 79.43 (C-5'); 79.28 (C-4'); 62.29 (NC$\underline{H}_2$Ph); 59.79 (C-3); 54.11 (OCH_3); 37.78 (C-4); 25.95 (CH_3); 24.60 (CH_3); 21.28 (OCO$\underline{C}H_3$). Found, %: C 61.31; H 7.26; N 3.72. $C_{20}H_{27}NO_7$. Calculated, %: C 61.06; H 6.92; N 3.56.

(3*R*,5*R*)-5-Acetoxy-2-benzyl-3-(2,3-O-isopropylidene-1-O-methyl-α-D-lyxo-tetrafuranose)isoxazolidine (**6b**). Yield 20%, colorless oil, R_f 0.46 (hexanes : AcOEt = 50 : 50). $[\alpha]_D^{25}$ = –82 (c = 0.10, CH_2Cl_2). ^{1}H NMR spectrum, δ, ppm (J, Hz): 7.34 (5H, m, H-arom); 6.35 (1H, dd, J = 2.3, J = 7.0, H-5); 4.96 (1H, s, H-2'); 4.67 (1H, dd, J = 5.9, J = 3.5, H-4'); 4.61 (1H, d, J = 14.7, NC$\underline{H}_2$Ph,); 4.56 (1H, d, J = 5.9, H-3'); 4.12 (1H, dd, J = 8.5, J = 3.5, H-5'); 4.00 (1H, d, J = 14.7, NC$\underline{H}_2$Ph); 3.66 (1H, m, H-3); 3.33 (3H, s, OCH_3); 2.94 (1H, ddd, J = 14.1, J = 8.2, J = 6.5, H-4b); 2.12 (1H, ddd, J = 11.7, J = 2.3, J = 9.4, H-4a); 2.06 (3H, s, $OCOCH_3$); 1.44 (3H, s, CH_3); 1.29 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm (J, Hz): 170.60 (O$\underline{C}$OCH$_3$); 136.69-127.08 (C-arom); 112.60 ($\underline{C}(CH_3)_2$); 107.41 (C-2'); 95.02 (C-5); 84.38 (C-3'); 81.26 (C-5'); 80.85 (C-4'); 63.19 (NC$\underline{H}_2$Ph); 61.09 (C-3); 54.61 (OCH_3); 39.85 (C-4); 26.02 (CH_3); 24.77 (CH_3); 21.35 (OCO$\underline{C}H_3$). Found, %: C 61.21; H 7.16; N 3.80. $C_{20}H_{27}NO_7$. Calculated, %: C 61.06; H 6.92; N 3.56.

(3*S*,5*S*)-5-Acetoxy-2-benzyl-3-(2,3-O-isopropylidene-1-O-methyl-α-D-lyxo-tetrafuranose)isoxazolidine (**6d**). Yield 7%, colorless oil, R_f 0.43 (hexanes : AcOEt = 50 : 50). ^{1}H NMR spectrum, δ, ppm (J, Hz): 7.31 (5H, m, H-arom); 6.28 (1H, d, J = 4.7, H-5); 4.92 (1H, s, H-2'); 4.66 (1H, dd, J = 5.9, J = 3.5, H-4'); 4.57 (1H, d, J = 5.9, H-3'); 4.43 (1H, d, J = 13.5, NC$\underline{H}_2$Ph,); 4.11 (1H, d, J = 14.1, NC$\underline{H}_2$Ph); 4.00 (1H, dd, J = 8.8, J = 3.5, H-5'); 3.60 (1H, m, H-3); 3.35 (3H, s, OCH_3); 2.63 (1H, dd, J = 12.6, J = 6.2, H-4b); 2.31 (1H, ddd, J = 11.1, J = 4.7, J = 10.6, H-4a); 2.06 (3H, s, $OCOCH_3$); 1.49 (3H, s, CH_3); 1.31 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm (J, Hz): 170.01 (O$\underline{C}$OCH$_3$); 137.48-127.15 (C-arom); 112.58 ($\underline{C}(CH_3)_2$); 107.15 (C-2'); 96.23 (C-5); 84.75 (C-3'); 81.99 (C-5'); 80.19 (C-4'); 64.61 (NC$\underline{H}_2$Ph); 61.83 (C-3); 54.41 (OCH_3); 38.95 (C-4); 26.05 (CH_3); 24.77 (CH_3); 21.42 (OCO$\underline{C}H_3$).

From the enriched fraction of the inseparable mixture of **6c** with **6a** it is possible to establish the corresponding signals for diastereoisomer **6c**. Yield 22%, colorless oil, R_f 0.66 (hexanes : :AcOEt = 50 : 50). ^{1}H NMR spectrum, δ, ppm (J, Hz): 7.32 (5H, m, H-arom); 6.44 (1H, m, H-5); 4.83 (1H, s, H-2'); 4.68 (1H, dd, J = 5.9, J = 3.5, H-4'); 4.52 (1H, d, J = 6.4, H-3'); 4.27 (1H, d, J = 13.5, NC$\underline{H}_2$Ph,); 4.20 (1H, d, J = 14.7, NC$\underline{H}_2$Ph); 4.17 (1H, m, H-5'); 3.82 (1H, m, H-3); 3.30 (3H, s, OCH_3); 2.71 (2H, m, H-4); 2.10 (3H, s, $OCOCH_3$); 1.37 (3H, s, CH_3); 1.23 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm (J, Hz): 169.92 (O$\underline{C}$OCH$_3$); 137.44, 127.25 (C-arom); 112.18 ($\underline{C}(CH_3)_2$); 107.03 (C-2'); 98.46 (C-5); 85.07 (C-3'); 81.05 (C-5'); 79.38 (C-4'); 64.09 (NC$\underline{H}_2$Ph); 61.53 (C-3); 54.47 (OCH_3); 39.75 (C-4); 25.89 (CH_3); 24.57 (CH_3); 21.41 (OCO$\underline{C}H_3$).

Nucleosidation (General procedure). A suspension of the nucleobase (0.58 mmol) in dry acetonitrile (2 ml) was treated with bis(trimethylsilyl)acetamide (2.32 mmol) and heated at 70°C for 15 min under stirring. Isoxazolidine **6a** (0.48 mmol) in dry acetonitrile (2 ml) and TMSOTf (0.72 mmol) were added to the clear solution obtained. The reaction mixture was stirred at 70°C for 2 h. After cooling at 0°C the solution was neutralized by addition of aqueous 5% sodium bicarbonate and then concentrated in vacuo. After addition of dichloromethane (8 ml) the organic phase was separated, washed with water, dried over sodium sulfate, filtered off, and evaporated to dryness. The residue was purified by column chromatography using AcOEt : hexanes = 60 : 40.

1-{(3*S*,5*S*)-2-Benzyl-3-[2,3-O-isopropylidene-1-O-methyl-α-D-lyxotetrafuranose]isoxazolidin-5-yl}-1H-pyrimidine-2,4-dione (**7a**). Flash chromatography of the mixture of isoxazo-lidinyl β- and α-nucleosides **7a** and **8a** formed in the ratio of 67 : 33 in 89% yield on silica-gel gave pure β-nucleoside **7a** and a mixture of both β- and α-nucleosides **7a** and **8a**. Yield 26%, colorless oil, $[\alpha]_D^{25}$ = +94.1 (c = 0.06, CH_2Cl_2). ^{1}H NMR spectrum, δ, ppm (J, Hz): 9.10 (1H, br.s, NH); 7.85 (1H, d, J = 8.2, H-6''); 7.34 (5H, m, H-arom); 6.19 (1H, dd, J = 2.9, J = 7.6, H-5); 5.63 (1H, dd, J = 8.2, J = 1.8, H-5''); 4.88 (1H, s, H-2'); 4.64 (1H, dd, J = 5.9, J = 3.5, H-4'); 4.55 (1H, d, J = 5.9, H-3'); 4.26 (1H, d, J = 14.1, NC$\underline{H}_2$Ph); 3.96 (1H, d, J = 14.1,

NCH_2Ph); 3.91 (1H, m, H-5'); 3.43 (1H, ddd, J = 9.4, J = 7.3, J = 4.7, H-3); 3.29 (3H, s, OCH_3); 3.01 (1H, dd, J = 14.4, J = 7.6, H-4b); 2.63 (1H, ddd, J = 10.3, J = 2.9, J = 7.3, H-4a); 1.44 (3H, s, CH_3); 1.28 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm (J, Hz): 163.54 (CO); 150.54 (CO); 141.08 (C-6"); 136.54-127.68 (C-arom); 112.67 ($\underline{C}(CH_3)_2$); 106.66 (C-2'); 101.42 (C-5"); 84.76 (C-5); 83.28 (C-3'); 79.53 (C-5'); 78.37 (C-4'); 63.48 (C-3); 61.45 ($N\underline{C}H_2Ph$); 54.60 (OCH_3); 39.45 (C-4); 25.74 (CH_3); 24.35 (CH_3). Found, %: C 59.44; H 6.27; N 9.59. $C_{22}H_{27}N_3O_7$. Calculated, %: C 59.32; H 6.11; N 9.43.

1-{(3*S*,5*S*)-2-Benzyl-3-[2,3-O-isopropylidene-1-O-methyl-α-D-lyxotetrafuranose]isoxa-zolidin-5-yl}-5-methylpyrimidine-2,4-dione (**7b**). Flash chromatography of the mixture of isoxazolidinyl β- and α-nucleosides **7b** and **8b** formed in the ratio of 88 : 12 in 91% yield on silicagel gave pure β-nucleoside **7b** and a mixture of both β- and α-nucleosides **7b** and **8b**. Yield 61%, colorless oil. ^{1}H NMR spectrum, δ, ppm (J, Hz): 9.19 (1H, br.s, NH); 7.71 (1H, d, J = 1.2, H-6"); 7.35 (5H, m, H-arom); 6.18 (1H, dd, J = 2.1, J = 7.8, H-5); 4.90 (1H, s, H-2'); 4.67 (1H, dd, J = 5.9, J = 3.6, H-4'); 4.57 (1H, d, J = 5.9, H-3'); 4.26 (1H, d, J = 14,3, $NC\underline{H}_2Ph$); 3.96 (1H, m, H-5'); 3.94 (1H, d, J = 14.2, $NC\underline{H}_2Ph$); 3.42 (1H, m, H-3); 3.31 (3H, s, OCH_3); 3.02 (1H, m, H-4b); 2.60 (1H, ddd, J = 10.7, J = 3.2, J = 7.5, H-4a); 1.85 (3H, s, CH_3); 1.44 (3H, s, CH_3); 1.29 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm (J, Hz): 164.11 (CO); 150.65 (CO); 136.79 (C-6"); 137.16–127.62 (C-arom); 112.67 ($C(CH_3)_2$); 109.59 (C-5"); 106.68 (C-2'); 84.78 (C-5); 83.72 (C-3'); 79.52 (C-5'); 78.45 (C-4'); 63.52 (C-3); 61.11 ($N\underline{C}H_2Ph$); 54.58 (OCH_3); 39.49 (C-4); 25.72 (CH_3); 24.33 (CH_3); 12.49 (CH_3).

1-{(3*S*,5*S*)-2-Benzyl-3-[2,3-O-isopropylidene-1-O-methyl-α-D-lyxotetrafuranose]isoxazolidin-5-yl}-4-acetylaminopyrimidine-2-one (**7c**). Flash chromatography of the mixture of isoxazolidinyl β- and α-nucleosides **7c** and **8c** formed in the ratio of 80 : 20 in 98% yield on silica-gel gave pure β-nucleoside **7c** and a mixture of both β- and α-nucleosides **7c** and **8c**. Yield 73%, colorless oil. ^{1}H NMR spectrum, δ, ppm (J, Hz): 10.11 (1H, br.s, NH); 8.03 (1H, d, J = 8.1, H-6"); 7.33 (5H, m, H-arom); 7.31 (1H, d, J = 7.3, H-5"); 6.10 (1H, dd, J = 2.9, J = 7.3, H-5); 4.81 (1H, s, H-2'); 4.63 (1H, dd, J = 5.9, J = 3.7, H-4'); 4.53 (1H, d, J = 5.9, H-3'); 4.32 (1H, d, J = 14.7, $NC\underline{H}_2Ph$); 3.96 (1H, d, J = 13.9, $NC\underline{H}_2Ph$); 3.82 (1H, m, H-5'); 3.47 (1H, m, H-3); 3.23 (3H, s, OCH_3); 3.13 (1H, m, H-4b); 2.62 (1H, ddd, J = 9.5, J = 2.9, J = 6.6, H-4a); 2.23 (3H, s, $COCH_3$); 1.43 (3H, s, CH_3); 1.28 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm (J, Hz): 171.02 (CO); 162.59 (CO); 155.34 (CO); 145.29 (C-6"); 136.73-127.76 (C-arom); 112.63 ($C(CH_3)_2$); 106.50 (C-2'); 95.77 (C-5"); 85.21 (C-5); 84.89 (C-3'); 79.41 (C-5'); 78.74 (C-4'); 63.38 (C-3); 61.78 ($N\underline{C}H_2Ph$); 54.56 (OCH_3); 40.64 (C-4); 25.76 ($CO\underline{C}H_3$); 24.78 (CH_3); 24.41 (CH_3).

The authors are grateful to the Slovak Grant Agency (No. 13549/06) and APVV (No. 20/000305). The NMR experimental part was facilitated by the support of the Slovak National Research (No. 2003SP200280203).

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