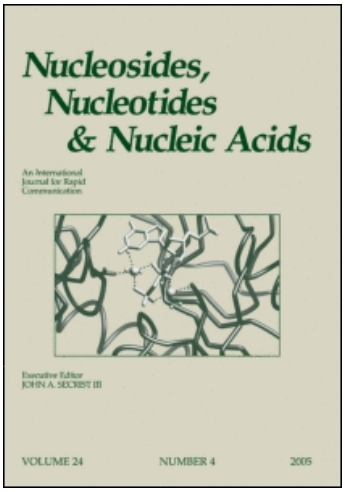

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Jean M. J. Tronchet[a]; Imre Kovacs[a]; Françoise Barbalat-Rey[a]; Naz Dolatshahi[a]
[a] Department of Pharmaceutical Chemistry, Faculty of Sciences, Geneva, Switzerland

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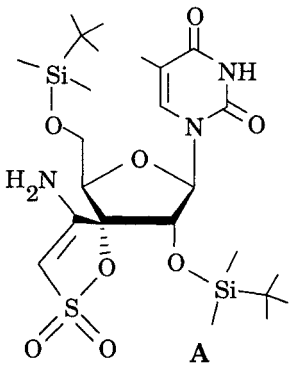
A NOVEL TYPE OF SPIRONUCLEOSIDES: 2',5'-*O*-BIS-TBDMS URIDINE-3'-SPIRO-3"-ISOXAZOLIDIN-5"-ONE AND ITS THYMIDINE CONGENER+

Jean M. J. Tronchet,* Imre Kovacs, Françoise Barbalat-Rey, and Naz Dolatshahi

Department of Pharmaceutical Chemistry, Faculty of Sciences, 30 Quai Ernest Ansermet, 1211 Geneva 4, Switzerland

Abstract: TSAO analogues, 2',5'-*O-bis*-TBDMS uridine-3'-spiro-3"-isoxazolidin-5"-one (**9**) and its thymidine congener **10**, as well as model spiro sugar derivatives (**3** and **4**) have been prepared from the corresponding nitrones through a stereospecific tandem nucleophilic attack. Compounds **9** and **10** which are bioisosters of TSAO-U and T respectively but which lack an amino group on the spiro ring, were found inactive against both HIV-1 and HIV-2.

TSAO derivatives, *i.e.* TSAO-T (**A**), constitute very efficient noncompetitive inhibitors of HIV reverse transcriptase (RT).[1] These compounds induce very rapidly a viral resistance expressed as a mutation in the amino acid sequence of RT. From the nature and position of the mutated amino acids a hypothesis on the site of action of these compounds and their specific association with certain RT amino acid residues has been established.[2]



A

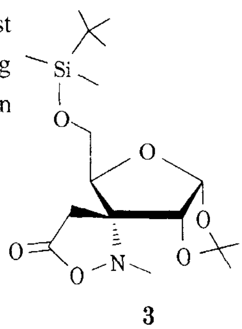
An isoxazolidinone ring should be roughly bioisosteric to the oxathiolene dioxide ring of the native TSAO derivatives. To check the deemed importance of the amino group of TSAO derivatives, we prepared spiro isoxazolidinones bearing a methyl group at the position corresponding to that of the amino group of TSAO derivatives. The starting material for the elaboration of the isoxazolidinone ring was a ketonitrone: a sugar

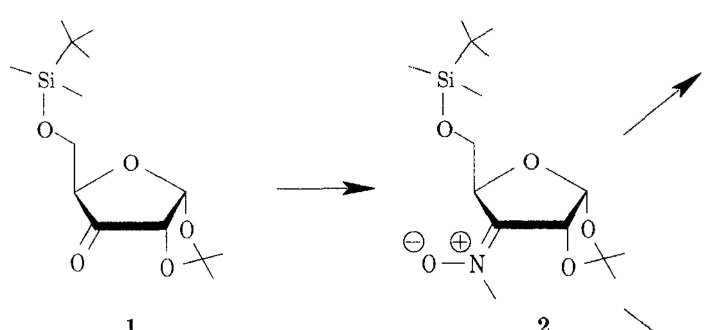
+ This paper is dedicated to Prof. Y. Mizuno on the occasion of his 75th birthday.

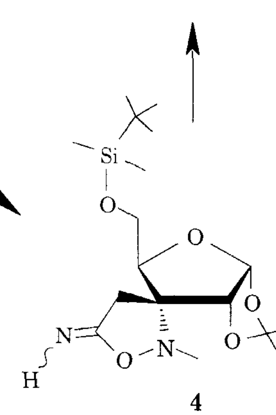
ketonitrone used in the model reactions and a nucleoside ketonitrone in the final nucleoside series. Treated with the conjugate base of ethyl acetate or ethanenitrile, the nitrone underwent a stereospecific tandem nucleophilic attack leading to the spiro derivative.

The ketosugar derivative **1**[3] was converted to the nitrone **2** (80%). As previously observed[4] for furanose derivatives bearing a sp^2 C-3 carbon atom, a $^4J_{2,4}$ long-range coupling was observed. In this case, two extra long range couplings ($^5J_{2,NMe}$ and $^5J_{4,NMe}$) were also present. From the chemical shifts of H-2 and H-4, a *E* configuration could be assigned to the unique diastereoisomer obtained.

Upon treatment with the conjugate base of ethyl acetate, **2** gave a unique compound **3**, isolated in 67% yield (Scheme 1). Its structure was assigned from its spectroscopic data, in particular the presence of a methylenic AB signal (*J* 17 Hz, δ 3.15 and 2.59). The spiro derivative **3** was formed *via* a *tandem* nucleophilic attack of the sugar: nucleophilic addition of the carbanion onto C-3 from the most accessible β face followed by a nucleophilic ring closure proceeding through an attack of the oxygen atom of the former nitrone function

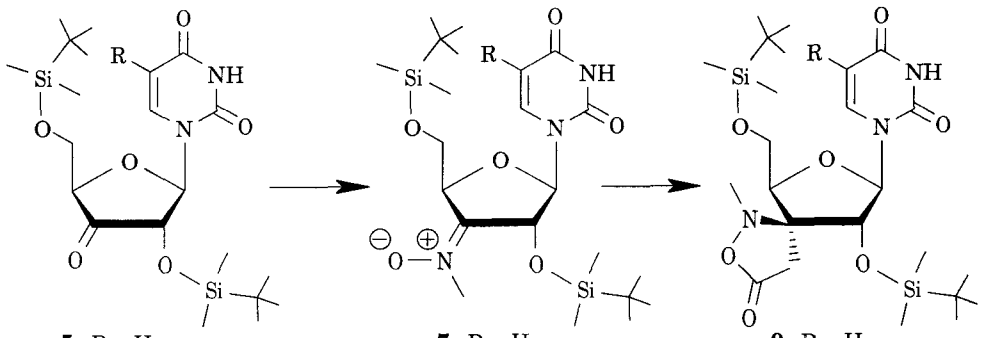






Scheme 1

onto the carbonyl group. The α-D-*ribo* configuration of **3** was confirmed by NOE experiments (see below). When reacted with the conjugate base of ethanenitrile, **2** led in 94% yield to a mixture of the geometrical isomers of the imino derivative **4**. They slowly interconverted to reach different equilibrium compositions in different solvents (^{1}H NMR) and both were integrally converted into **3** upon chromatography on silica gel (hexane/acetone).



5 R = H
6 R = Me

7 R = H
8 R = Me

9 R = H
10 R = Me

Scheme 2

The same reaction (Scheme 2) was applied to 3'-ketonucleosides **5**[5] and **6**, the latter compound previously described as a foam,[6] being obtained in crystalline form. From **5** and **6**, we obtained the *E* nitrones **7** (77%) and **8** (75%) as crystals . Compound **8** had been previously prepared[7] but characterized only by ^{1}H and ^{13}C NMR. Upon treatment with the conjugate base of ethyl acetate, **7** and **8** gave respectively **9** (90%), and **10** (86%). The reaction was highly stereoselective and only one diastereoisomer was isolated. In both cases, β-D-*xylo* isomers were obtained as shown by NOE experiments (see below).

From NOE experiments (TABLE 1), it appears that the 4' methylene group of compounds **3** and **4** resides on the β face of the sugar (signal enhancement upon irradiation of H-2) thus assessing the α-D-*ribo* configuration of these compounds. The same NOE observations also allow the assignment of the more upfield of the two H_2-4' signals to the $H_{pro\text{-}S}$-4' proton. Contrarily to the $H_{pro\text{-}R}$-4', the $H_{pro\text{-}S}$-4' proton is almost unaffected by the position of the conformational equilibrium around the C4-C5 bond and hence constitutes a meaningful indicator of the geometrical configuration of **4**. On this basis, we assigned the *Z* configuration to the more abundant isomer of **4** (δ $H_{pro\text{-}S}$-4' 2.70 ppm at 20 °C *versus* 2.51 for the *E* isomer).

In the case of the nucleoside analogues **9** and **10**, no intensity enhancement of H_2-4" signals was noted upon irradiation of H-2', thus establishing their β-D-*xylo* configuration. On the other hand, large enhancements of the H-6 signals upon irradiation of H-2' indicated an important contribution of the *anti* conformer around the base-sugar bond.

TABLE 1. NOE Signal Enhancements.

Compound	temp °C	Irradiated proton	Signal Enhancements[a]
3	+25	H-1	H-2 (m), $H_{pro\text{-}R}$-4' (s)
		H-2	H-1 (l), $H_{pro\text{-}S}$-4' (m), N-Me (s)
		N-Me	H-2 (s), $H_{pro\text{-}S}$-4' (l), H-4 (l)
(2'R)-**3**	-40	H-1	H-2 (l)
		H-2	H-1 (l)
		N-Me	H-2 (l), H-4 (s), $H_{pro\text{-}S}$-4' (l)
		Me_{exo}-*i*-Pr	H-1 (m), H-2 (l)
		Me_{endo}-*i*-Pr	H-1 (s), H-4 (m)
(2'S)-**3**	-40	N-Me	H-4 (l)
		Me_{exo}-*i*-Pr	H-1 (m), H-2 (l)
		Me_{endo}-*i*-Pr	H-1 (m), H-4 (s)
Z-**4**	+25	H-2	H-1 (l), $H_{pro\text{-}S}$-4' (m)
		N-Me	H-2 (s), H-4 (s), $H_{pro\text{-}S}$-4' (m)
E-**4**	+25	H-2	H-1 (l), $H_{pro\text{-}S}$-4' (s)
9	+25	H-2'	H-1' (l), H-6 (l)
		N-Me	H-2' (l), $H_{pro\text{-}R}$-4'' (l)
10	+25	H-2'	H-1' (l), H-6 (l), N-Me (m)
		H-6	H-2' (m), Me-5 (m)
		N-Me	H-2' (l), $H_{pro\text{-}R}$-4'' (l)

[a] The enhancements of signals are expressed as l (large, *ca.* 20%), m (medium, *ca.* 10%), or s (small, 5% or less).

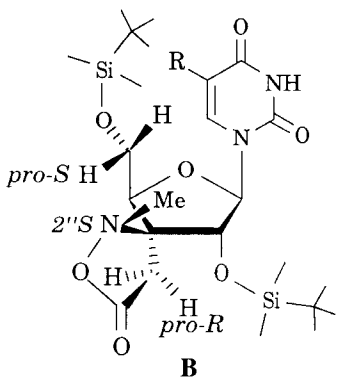
The nitrogen inversion barrier is known to be much higher for hydroxylamines than for amines.[8] Variable temperature ^{1}H NMR experiments allowed the observation of the frozen invertomers of **3** and *Z*-**4** and the determination of a nitrogen inversion activation free energy of *ca.* 50 kJ/mol (TABLE 2). In the case of nucleosides **9** and **10**, no coalescence was observed indicating that one of the invertomers was considerably more stable than the other.

TABLE 2. Thermodynamic and Kinetic Data Concerning the Nitrogen Inversion of Isoxazolidine Derivatives.

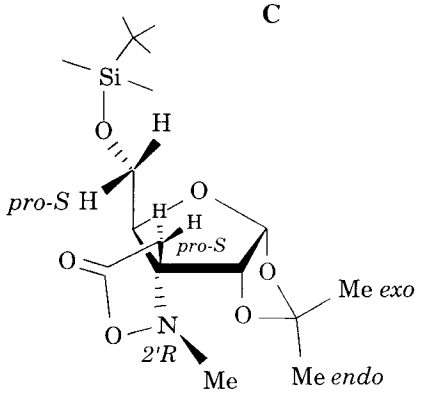
Compd	temp/°C	Invertomer *ratio* S/R	$\Delta G^{\neq}$ [a] (T/K)
3	-50	0.5	52.7 ± 0.9 (253)
Z-**4**	-50	0.4	54.4 ± 0.9 (253)
9	-50	>20	n/a
10	-50	>20	n/a

[a] kJ/mol

The configuration of the invertomers could be established using the results of the NOE experiments collected in TABLE 1. At room temperature, the unique invertomer of both **9** and **10** directs its *N*-methyl group toward H-2' as indicated by the H-2' signal enhancement and the absence of effect on H-5' upon irradiating the *N*-methyl group. This establishes its *(2''S)* configuration (**B**).



B



C

For compound **3**, at room temperature, irradiation of the *N*-methyl group enhances the signals of both H-2 and H-4, reflecting the fact that both invertomers are present, and that even for the *2'R* invertomer (*N*-methyl facing H-2) the *N*-methyl group is not very far from H-4. When irradiating the *N*-methyl group of each frozen invertomers, a large enhancement of the H-2 signal and a small one for the H-4 signal were observed for the major *(2'R)* invertomer (**C**), whereas in the case of the minor *(2'S)* invertomer, only the H-4 signal was affected.

The conformational equilibrium around the bond between the two last sugar carbon atoms has been computed using the procedure of Haasnoot et al.[9] The results collected in TABLE 3 show in particular that for **3**, the population distribution between the conformers is very notably dependent upon the configuration of the asymmetric nitrogen of the isoxazolidinone ring.

Compounds **7**-**10** were submitted to anti-HIV-1 and anti-HIV-2 testing and all were found inactive.[10] The inactivity of **9** and **10** confirms the important role played by the amino group of the spiro ring of TSAO derivatives in the binding to the HIV-1 reverse transcriptase.

Nucleoside analogues **7**-**10** were also tested for their inhibitory activity against the SV_{40} oncovirus grown on CV1 cells following a previously described procedure.[11] The nitrones **7** and **8** were even less cytotoxic (300 μM and > 300 μM) than the spironucleosides **9** and **10** (185 and 126 μM respectively). The TSAO analogues **9** and **10** exhibited no activity against SV_{40}, contrarily to **7** which provoked a partial inhibition at a 80 μM concentration and **8** which, at the same concentration, was responsible for a 48 h delay in the growth of SV_{40}.

EXPERIMENTAL

General methods.[12]

***(3E)*-5-*O*-*tert*-Butyldimethylsilyl-3-deoxy-1,2-*O*-isopropylidene-3-(*N*-methylimino)-α-D-*erythro*-pentofuranose *N*-oxide (2).** *N*-Methylhydroxylamine hydrochloride (1.04 g, 12.5 mmol) and pyridine (1.01 mL, 12.5 mmol) were added to a solution of **1**[3] (3.02 g, 10.0 mmol) in dry CH_2Cl_2 (100 mL) and ethanol (40 mL). The reaction mixture was stirred at room temperature for 24 h, evaporated, dissolved in CH_2Cl_2 (150 mL), and washed with water (30 mL). The aqueous phase was reextracted with CH_2Cl_2 (30 mL) and the combined organic phases were dried (Na_2SO_4), concentrated, and submitted to a column chromatography (4:1 CH_2Cl_2/EtOAc) to give **2** (2.65 g, 80%): mp 38.2-38.8 °C; R_F 0.22 (4:1 CH_2Cl_2/EtOAc); $[\alpha]_D^{27}$ 234.2° (*c* 1.0, $CHCl_3$); ν_{max}^{KBr} 2990-2850 (CH), 1631 (C=N), 1462, 1382, 1325, 1213, and 1125 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.09 (*d*, 1 H, $J_{1,2}$ = 4.5 Hz, H-1), 5.17 (*m*, 1 H, $J_{2,4}$ = 2 Hz, $J_{4,5a}$ = 2 Hz, $J_{4,5b}$ = 1.5 Hz, $J_{4,NMe}$ ~1 Hz, H-4), 5.08 (*m*, 1 H, $J_{2,NMe}$ ~1 Hz, H-2), 4.25 (*dd*, 1 H, $J_{5a,5b}$ = 10.5 Hz, H-5b), 3.85 (*dd*, 3 H, NMe), 3.70 (*dd*, 1 H, H-5a), 1.47 (*s*, 6 H, CMe_2), 0.87 (*s*, 9 H, *t*-Bu), 0.06 and 0.04 (2 *s*, each 3 H, Me_2Si). EIMS: *m/z* (%) 73 (100), 89 (77), 274 (58, $M^{\cdot+}$ - *t*-Bu), 174 (38), 115 (18, TBDMS), 316 (15, $M^{\cdot+}$ - Me), 216 (8, $M^{\cdot+}$ - TBDMS), and 331 (5, $M^{\cdot+}$).

Anal. Calcd for $C_{15}H_{29}NO_5Si$ (331.49): C, 54.35; H, 8.82; N, 4.23. Found: C, 54.10; H, 8.64; N, 4.29.

TABLE 3. Conformational Equilibrium around the C4-C5 (C4'-C5') Bond.

Compd	temp/°C	$J_{4,5a}$	$J_{4,5b}$	γ^+	γ^-	γ^t
3	+20	3.8	4.0	59%	19%	22%
(2'R)-**3**	-50	2.0	3.0	87%	7%	6%
(2'S)-**3**	-50	4.0	7.0	30%	58%	12%
Z-**4**	+55	5.0	4.0	47%	19%	34%
Z-$\mathbf{4}_{maj}$	-40	5.2	5.2	33%	33%	33%
Z-$\mathbf{4}_{min}$	-40	7.0	3.8	27%	16%	57%
E-**4**	+55	7.0	4.0	25%	18%	57%
E-**4**	-40	8.2	3.5	16%	12%	72%
9	+20	5.5	4.0	40%	18%	42%
10	+20	5.0	5.0	37%	31%	32%

[5-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose]-3-spiro-3'-2'-methylisoxazolidin-5'-one (3). A solution of lithium bis(trimethylsilyl)amide (2.0 mmol) in dry THF (4.0 mL) under argon was cooled to -78 °C and EtOAc (2.0 mL of a 1.0 M solution in dry THF, 2.0 mmol) was added dropwise (5 min). After stirring at that temperature for 15 min, a solution of **2** (331 mg, 1.0 mmol) in dry THF (1.5 mL) was added dropwise (10 min). After 10 min, the reaction mixture was poured into CH_2Cl_2 (80 mL), washed with a saturated NaCl solution (15 mL), dried (Na_2SO_4), and filtered. The filtrate was evaporated and the residue purified by column chromatography (85:15 hexane/EtOAc) to yield 250 mg (67%) of **3**: mp 45.7-47.2 °C; R_F 0.21 (4:1 hexane/EtOAc); $[\alpha]_D^{32}$ 13.3° (*c* 0.9, $CHCl_3$); ν_{max}^{KBr} 2990-2860 (CH), 1791 (C=O), 1464, 1376, 1253, and 1067 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.73 (*d*, 1 H, $J_{1,2}$ = 3.4 Hz, H-1), 4.48 (*d*, 1 H, H-2), 4.30 (*dd*, 1 H, $J_{4,5a}$ = 3.8 Hz, $J_{4,5b}$ = 4 Hz, H-4), 3.98 (*dd*, 1 H, $J_{5a,5b}$ = 11.8 Hz, H-5b), 3.92 (*dd*, 1 H, H-5a), 3.15 (*d*, 1 H, $J_{4'pro\text{-}R,4'pro\text{-}S}$ = 17 Hz, $H_{pro\text{-}R}$-4'), 3.10 (*s*, 3 H, NMe), 2.59 (*d*, 1 H, $H_{pro\text{-}S}$-4'), 1.59 (*s*, 3 H, $\mathbf{Me}_{endo}$-CMe), 1.35 (*s*, 3 H, $\mathbf{Me}_{exo}$-CMe), 0.91 (*s*, 9 H, *t*-Bu), and 0.09 (*s*, 6 H, Me_2Si). EIMS: *m/z* (%) 327 (100), 274 (57), 258 (42, $M^{\cdot+}$ - TBDMS), 358 (38, $M^{\cdot+}$ - Me), 316 (25, $M^{\cdot+}$ - *t*-Bu), and 373 (23, $M^{\cdot+}$).

Anal. Calcd for $C_{17}H_{31}NO_6Si$ (373.53): C, 54.67; H, 8.37; N, 3.75. Found: C, 54.66; H, 8.27; N, 4.03.

(5'*E* and 5'*Z*)-[5-*O*-(*tert*-Butyldimethylsilyl)-1,2-*O*-isopropylidene-α-D-ribofuranose]-3-spiro-3'-(5'-imino-2'-methylisoxazolidine) (4). Acetonitrile (2.0 mL of

a 1.0 M solution in dry THF, 2.0 mmol) was added in 3 min to a mixture of LDA (1.33 mL of a 1.5 M solution in cyclohexane, 2.0 mmol), and THF (3.0 mL) under argon atmosphere at -78 °C. After 10 min, compound **2** (331 mg, 1.0 mmol) was added in dry THF (1.5 mL) to the suspension (the lithium salt precipitates). The reaction mixture was further stirred for 10 min, quenched with MeOH (200 μL), poured into CH_2Cl_2 (100 mL), and washed with a saturated NaCl solution (20 mL). After drying over anhydrous $MgSO_4$, the solvents were evaporated and the residue purified by chromatography on a Florisil column (60:40:3-->50:50:4 hexane/EtOAc/TEA) to yield **4** (350 mg, 94%) as a syrup: R_F 0.16 (50:50:2); $[\alpha]_D^{30}$ 18.7° (equilibrium, *c* 0.7, $CHCl_3$); ν_{max}^{KBr} 3250 (NH), 2970-2835 (CH), 1676 (C=N), 1452, 1374, 1245, and 1210 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.87 and 6.15 (2 *bs*, each 1 H, NH), 5.85 and 5.74 (2 *d*, each 1 H, $J_{1,2}$ = 3.8 Hz and 3.5 Hz, H-1), 4.72 and 4.45 (2 *d*, each 1 H, H-2), 4.38-4.23 (*m*, 1 H, H-4), 4.02-3.78 (*m*, 2 H, H-5), 3.22 and 3.14 (2 d, each 1 H, $J_{4'pro\text{-}R,4'pro\text{-}S}$ = 17.4 Hz and 16.8 Hz, $H_{pro\text{-}R}$-4'), 3.03 and 2.88 (2 *s*, each 3 H, NMe), 2.69 and 2.50 (2 *d*, each 1 H, $H_{pro\text{-}S}$-4'), 1.62, 1.37, and 1.58, 1.34 (2x2 *s*, 6 H, CMe_2), 0.89 (s, 9 H, *t*-Bu), 0.11 and 0.07 (2 *s*, each 6 H, Me_2Si). EIMS: *m/z* (%) 215 (100), 240 (52), 315 (27, $M^{\cdot+}$ - *t*-Bu), 357 (13, $M^{\cdot+}$ - Me), and 372 (4, $M^{\cdot+}$).

Anal. Calcd for $C_{17}H_{32}N_2O_5Si$ (372.54): C, 54.81; H, 8.66; N, 7.52. Found: C, 55.22; H, 8.70; N, 7.30.

1-[2,5-bis(*O*-*tert*-Butyldimethylsilyl)-β-D-*erythro*-pentofuran-3-ulosyl]thymine (6). This compound was synthesized by oxidation of 1-[2,5-bis-(*O*-*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]thymine[6] with the Dess-Martin periodinane reagent as described for the synthesis of **5**.[4] Yield 88%; mp 130.5-131.8 °C; $[\alpha]_D^{24}$ 85.1° (*c* 1.0, $CHCl_3$); white foam, $[\alpha]_D$ 72° (*c*, 0.5, $CHCl_3$).[5]

1-[(3 *E*)-2,5-bis(*O*-*tert*-Butyldimethylsilyl)-3-deoxy-3-(*N*-methylimino)]uridine *N*-oxide (7). A mixture of **5**[5] (2.35 g, 5.0 mmol), *N*-methylhydroxylamine hydrochloride (1.25 g, 15.0 mmol) and pyridine (1.21 mL, 15.0 mmol) in acetonitrile (100 mL) was stirred at 5 °C. After 60 h, the solvent was evaporated and the residue submitted to a column chromatography (CH_2Cl_2 ---> 100:2 CH_2Cl_2/MeOH) to give **5** (0.74 g, 31%) and **7** as a syrup. Its crystallization from ether/hexane afforded **7** (1.32 g, 77% corrected for recovered **5**) as colourless microcrystals with mp 141.8-142.6 °C; R_F 0.25 (4:1 CH_2Cl_2/EtOAc); $[\alpha]_D^{30}$ 151.4° (*c* 0.9, $CHCl_3$); λ_{max}^{EtOH} 205 nm (ε 8521) and 259 (17442); ν_{max}^{KBr} 3400 (NH), 2955-2870 (CH), 1720, 1698 (C=O), 1635 (C=N), 1462, 1380, 1258, and 1124 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.85 (*bs*, 1 H, NH), 7.90 (*d*, 1 H, $J_{5,6}$ = 8.2 Hz, H-6), 6.13 (*d*, 1 H, $J_{1',2'}$ = 5.8 Hz, H-1'), 5.69 (*d*, 1 H, H-5), 5.09 (*m*, 1 H, $J_{2',4'}$ = 2.5 Hz, $J_{4',5'a}$ = 1.8 Hz, $J_{4',5'b}$ = 2.0 Hz, $J_{4',NMe}$ ~1 Hz, H-4'), 4.87 (*m*, 1 H, $J_{2',NMe}$ ~1.0 Hz, H-2'), 4.47 (*dd*, 1 H, $J_{5'a,5'b}$ = 11 Hz, H-5'b), 3.83 (*dd*, 1 H, H-5'a) 3.68 (*dd*, 3 H, NMe), 0.90 (*s*, 18 H, *t*-Bu), 0.12, 0.10, 0.08, and

0.00 (4 *s*, each 3 H, Me_2Si). EIMS: *m/z* (%) 75 (100), 112 (85, uracil), 169 (13), 211 (10), 301 (6), 391 (5), 442 (1, $M^{\cdot+}$ - *t*-Bu), and 499 (1, $M^{\cdot+}$).

Anal. Calcd for $C_{22}H_{41}N_3O_6Si_2$ (499.76): C, 52.87; H, 8.27; N, 8.41. Found: C, 52.71; H, 8.14; N, 8.44.

1-[(3 *E*)-2,5-bis(*O*-*tert*-Butyldimethylsilyl)-3-deoxy-3-(*N*-methylimino)]-thymine *N*-oxide (8). The reaction was performed by applying the reaction conditions described for **7** to compound **6** (2.42 g, 5.0 mmol) to obtain **8** [1.25 g, 75% corrected for recovered **6** (0.85 g, 35%)]: mp 162.4-162.9 °C; R_F 0.22 (1:1 hexane/EtOAc); $[\alpha]_D^{31}$ 114.1° (*c* 0.7, $CHCl_3$); ν_{max}^{KBr} 3400 (NH), 3925-2830 (CH), 1683 (C=O), 1626 (C=N), 1450, 1369, 1265, and 1110 cm^{-1}. The ^1H NMR data for **8** agreed with the data from the literature.[5] EIMS: *m/z* (%) 73 (100), 330 (80), 359 (42), 301 (38), 456 (10, $M^{\cdot+}$ - *t*-Bu), and 513 (3, $M^{\cdot+}$).

Anal. Calcd for $C_{23}H_{43}N_3O_6Si_2$ (513.79): C, 53.77; H, 8.44; N, 8.18. Found: C, 53.68, H, 8.38; N, 8.16.

[1-[2',5'-bis-(*O*-*tert*-Butyldimethylsilyl)-3'-deoxy-β-D-xylofuranosyl]uracil]-3'-spiro-3''-(2''-methylisoxazolidin-5''-one) (9). A solution of lithium bis(trimethylsilyl)amide (1.5 mmol) in dry THF (4.0 mL) under argon was cooled to -78 °C and EtOAc (1.0 mL of a 1.0 M solution in dry THF, 1.0 mmol) was added in 5 min. After stirring at that temperature for 15 min, a solution of **7** (250 mg, 0.5 mmol) in dry THF (1.5 mL) was added dropwise (10 min). After 15 min, the reaction mixture was poured into EtOAc (50 mL), washed with a saturated $NaHCO_3$ solution (10 mL), dried (Na_2SO_4), filtered and concentrated. Column chromatography 70:30 ---> 65:35 hexane/EtOAC) of the residue afforded **9** (243 mg, 90%): mp 205.3-206.5 °C; R_F 0.24 (6:4 hexane/EtOAc); $[\alpha]_D^{24}$ 0.0° (*c* 0.9, $CHCl_3$); ν_{max}^{KBr} 3400 (NH), 2930-2830 (CH), 1791, 1695 (C=O), 1450, 1250, and 1092 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.82 (*bs*, 1 H, NH), 7.88 (*d*, 1 H, $J_{5,6}$ = 8 Hz, H-6), 5.28 (*d*, 1 H, H-5), 5.23 (*d*, 1 H, $J_{1',2'}$ = 3.2 Hz, H-1'), 4.56 (*d*, 1 H, H-2'), 4.19 (*dd*, 1 H, $J_{4',5'a}$ = 5.5 Hz, $J_{4',5'b}$ = 4 Hz, H-4'), 4.02 (*dd*, 1 H, $J_{5'a,5'b}$ ~12 Hz, H-5'b), 3.95 (*dd*, 1 H, H-5'a), 3.29 (d, 1 H, $J_{4''pro\text{-}R,4''pro\text{-}S}$ = 17.6 Hz, $H_{pro\text{-}R}$-4''), 2.62 (s, 3 H, NMe), 2.58 (d, 1 H, $H_{pro\text{-}S}$-4''), 0.92 and 0.90 (2 s, each 9 H, *t*-Bu), 0.13 (s, 12 H, Me_2Si). EIMS: *m/z* (%) 73 (100), 216 (94), 484 (78, $M^{\cdot+}$ - *t*-Bu), 269 (35), 372 (15, $M^{\cdot+}$ - uracil - *t*-Bu), and 541 (8, $M^{\cdot+}$).

Anal. Calcd for $C_{24}H_{43}N_3O_7Si_2$ (541.80): C, 53.21; H, 8.00; N, 7.76. Found: C, 53.44; H, 8.01; N, 7.59.

[1-[2',5'-bis-(*O*-*tert*-Butyldimethylsilyl)-3'-deoxy-β-D-xylofuranosyl]thymine]-3'-spiro-3''-2''-methylisoxazolidin-5''-one) (10). **8** (257 mg, 0.5 mmol) was converted to **10** (240 mg, 86%) following the procedure described for **9**: mp 148.7-149.4 °C; R_F 0.21 (7:3 hexane/EtOAc); $[\alpha]_D^{25}$ -58.0° (*c* 1.5, $CHCl_3$): ν_{max}^{KBr} 3450 (NH), 2930-2860 (CH), 1800, 1698 (C=O), 1471, 1260, and 1121 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.87 (*bs*, 1 H, NH), 7.52 (*q*,

1 H, $J_{Me\text{-}5,6}$ = 1.2 Hz, H-6), 5.70 (*d*, 1 H, $J_{1',2'}$ = 3.2 Hz, H-1'), 4.54 (*d*, 1 H, H-2'), 4.19 (*t*, 1 H, $J_{4',5'a} \sim J_{4',5'b}$ ~5 Hz, H-4'), 4.02 (*d*, 2 H, H-5'a and H-5'b), 3.27 (*d*, 1 H, $J_{4''pro\text{-}R,4''pro\text{-}S}$ = 18 Hz, $H_{pro\text{-}R}$-4''), 2.72 (*s*, 3 H, NMe), 2.58 (*d*, 1 H, $H_{pro\text{-}S}$-4''), 1.98 (*d*, 3 H, Me-5), 0.96 and 0.92 (2 *s*, each 9 H, *t*-Bu), 0.17 (*s*, 12 H, Me_2Si). EIMS: *m/z* (%) 73 (100), 216 (73), 498 (40, $M^{\cdot+}$ - *t*-Bu), 283 (33), 372 (11, $M^{\cdot+}$ - *t*-Bu - thymine), and 555 (5, $M^{\cdot+}$).

Anal. Calcd for $C_{25}H_{45}N_3O_7Si_2$ (555.83): C, 54.02; H, 8.16; N, 7.56. Found: C, 54.42; H, 8.18; N, 7.56.

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REFERENCES

1. Balzarini, J.; Karlson, A.; Vandamme, A.-M.; Perez-Perez, M.- J.; Zhang, H.; Wrang, L.; Öberg, B.; Bäckbro, K.; Unge, T.; San-Felix, A.; Velazquez, S.; Camarasa, M.-J.; De Clercq, E., *Proc. Natl. Acad. Sci. USA*, **1993**, *90*, 6952.
2. a) Balzarini, J.; Perez-Perez, M.-J; San-Felix, A.; Velazquez, S.; Camarasa, M.-J.; Vandamme, A.-M.; Karlsson, A.; De Clercq, E., in "Antibiotics and Antiviral Compounds", Krohn, K.; Kirst, H. A.; Maag, H., Ed., VCH, Weinheim, 1993, pp 403-420.
   b) Balzarini, J.; Karlsson, A.; Perez-Perez, M.-J.; Vrang, L.; Walbers, J.; Zhang, H.; Öberg, B.; Vandamme, A.-M.; Camarasa, M.-J.; De Clercq, E., *Virology*, **1993**, *192*, 246.
   c) Balzarini, J.; Kleim, J.-P.; Riess, G.; Camarasa, M.-J.; De Clercq, E.; Karlsson, A., *Biochem. Biophys. Res. Commun.*, **1994**, *201*, 1305.
3. Yoshimura, Y.; Sano, T.; Matsuda, A.; Ueda, T., *Chem. Pharm. Bull.*, **1988**, *36*, 162.
4. Tronchet, J. M. J.; Barbalat-Rey, F.; Bourgeois, J.-M.; Graf, R.; Tronchet, J., *Helv. Chim. Acta*, **1972**, *55*, 803.
5. Samano, V.; Robins, M. J., *J. Org. Chem.*, **1990**, *55*, 5186.
6. Calvo-Mateo, A.; Camarasa, M.-J.; Diaz-Ortiz, A.; De la Heras, F. G., *Tetrahedron*, **1988**, *44*, 4895.

7. Hossain, N.; Papchikhin, A.; Plavec, J.; Chattopadhyaya, J., *Tetrahedron*, **1993**, *44*, 10133.
8. Tronchet, J. M. J.; Komaromi, I., *J. Comput. Chem.*, **1994**, *15*, 1091, and ref. cited.
9. Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; de Leeuw, H. P. M.; Altona, C., *Rec. J. R. Nether. Chem. Soc.*, **1979**, *98*, 576.
10. Personal communication from Profs. E. De Clercq and J. Balzarini.
11. Tronchet, J. M. J.; Iznaden, M.; Barbalat-Rey, F.; Dhimane, H; Ricca, A.; Balzarini, J.; De Clercq, E., *Eur. J. Med. Chem.*, **1992**, *27*, 555, and ref. cited.
12. Tronchet, J. M. J.; Benhamza, R.; Bernardinelli, G., *Nucleosides Nucleotides*, **1993**, *12*, 55.