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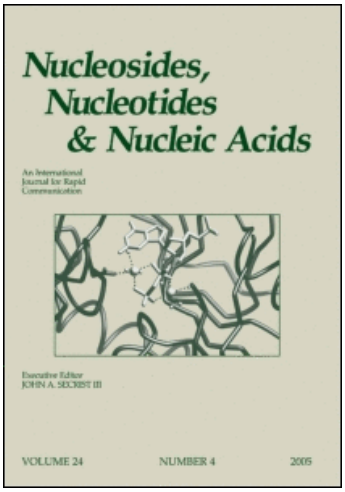


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Jean M. J. Tronchet[a]; Imre Kovacs[a]; Michel Seman[b]; Pierre Dilda[b]; Erik De Clercq[c]; Jan Balzarini[c]
[a] Department of Organic Pharmaceutical Chemistry, University of Geneva, Sciences II, Geneva 4, Switzerland [b] Research Department, Laboratoires Mayoly Spindler, Chatou Cedex, France [c] Rega Institute for Medical Research, Leuven, Belgium

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NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 19(4), 775–794 (2000)

# HIGHLY STEREOSELECTIVE SYNTHESIS AND BIOLOGICAL PROPERTIES OF NUCLEOSIDE ANALOGUES BEARING A SPIRO INSERTED OXIRANE RING

Jean M. J. Tronchet,*[1] Imre Kovacs,[1] Michel Seman,[2] Pierre Dilda,[2] Erik De Clercq,[3] and Jan Balzarini,[3]

[1]Department of Organic Pharmaceutical Chemistry, University of Geneva, Sciences II, CH-1211 Geneva 4, Switzerland

[2]Laboratoires Mayoly Spindler, Research Department, 6, avenue de l'Europe, F-78401 Chatou Cedex, France

[3]Rega Institute for Medical Research, Minderbroedersstraat 10, B-3000 Leuven, Belgium

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**ABSTRACT.** Starting from 2',5'-di-*O*-TBDMS-3'-ketouridine **1** or its thymine analogue **2**, both *xylo* (**3-10**) and *ribo* (**20**) epimers of a series of 3"-substituted 3'-spironucleosides have been obtained in good yields and with a total stereoselectivity. Most new compounds were moderately cytotoxic with in some cases slightly selective antiproliferative activities. None of these compounds was active against HIV, but some other antiviral activities against HSV-2, CMV, EBV, or VZV, in the micromolar range, were noted in specific cases.

## INTRODUCTION

*O*-Silylated spironucleosides of the TSAO family[1] exhibit high inhibitory activity at the non-nucleoside allosteric site of HIV-1 reverse transcriptase (RT). The major chemical features of TSAO thought to intervene in the interaction with the target site, are the silyl groups, the $SO_2$ group, and a weakly basic amino group.[2] Even if the structural exigence of the RT allosteric site toward spironucleoside derivatives is strict,[3,4] we prepared a novel type of nucleoside derivatives bearing *O*-silyl groups and an oxirane moiety *spiro* inserted in 3', some examples possessing a carbonyl (a sulfonyl bioisostere) and a NH group. Methods were developed to prepare highly stereoselectively nucleosides of either a *ribo* or a *xylo* configuration. None of these compounds exhibited any anti-HIV activity but some of them showed other biological activities and represent the starting point for a more general study[5] of the cytotoxic and antiproliferative properties of *O*-silylated nucleoside derivatives.



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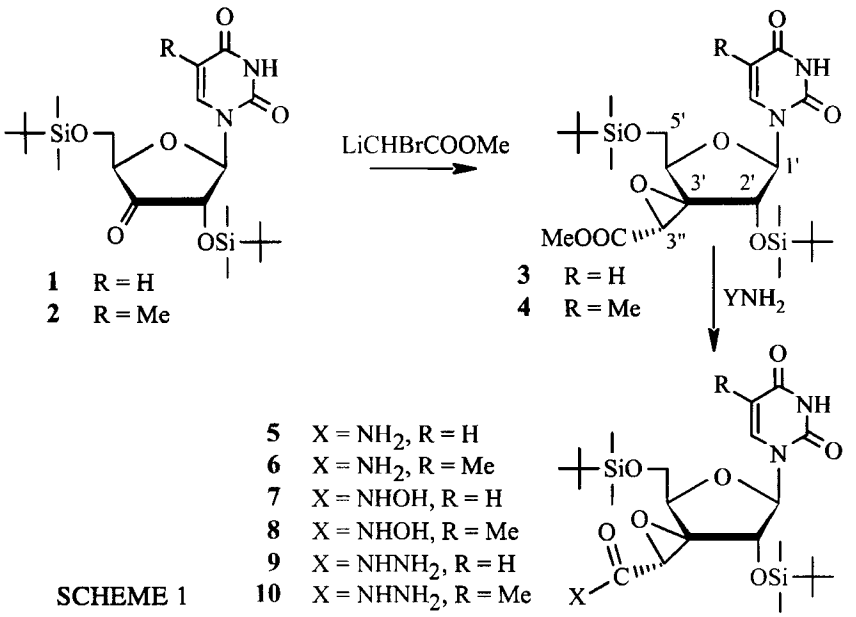
## RESULTS AND DISCUSSION

When submitted to a Darzens reaction[6] with methyl bromoacetate and using lithium bis(trimethylsilyl)amide as a base,[7] the 3'-ketonucleoside derivatives **1**[8] and **2**[3,9] led to **3** (78%) and **4** (88%), respectively (SCHEME 1).




SCHEME 1

No formation of "dimers" of bromoacetate was observed contrarily to observations made in other cases.[6] The reactions were both highly stereoselective, only one [the (3"*R*)-*xylo*] of the four possible diastereoisomers being formed in each case. This implies, for the coordination of the methyl bromoacetate conjugate base onto the carbonyl carbon atom, a substrate face stereoselectivity (α preferred over β), and a concurrent diastereoselectivity of the *E*/*Z* enolate formation and of the attacking (*Re*/*Si*) face of the enolate anionic carbon atom. If the enolate configuration is kinetically controlled, which is the most probable, the *Z* ($O^-$) isomer would be formed[10] and should attack from its *Si* face to avoid steric interaction between the bromine atom and the *O*-2'-TBDMS group (Fig. 1).

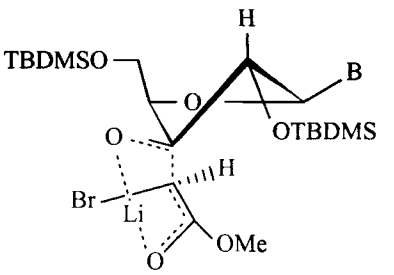



**FIG. 1** Proposed transition state for the Darzens reaction (C-C bond formation).

This will lead to the (*3"S*) open-chain intermediate which, upon $S_N2$ ring closure will afford **(3"*R*)-3** or **(3"*R*)-4**. This was indeed the case and the (3"*R*)-*xylo* configuration of **3** and **4** was established by large NOE between H-3" and H-1'. On the

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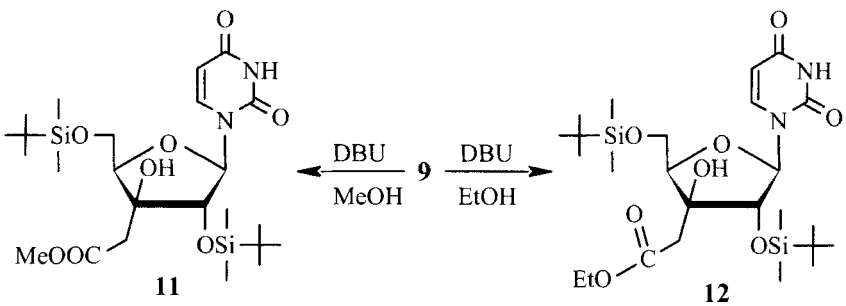
other hand, large $J_{1',2'}$ couplings indicated a $^{2'}T_{3'}$ conformation of the furanose ring and a NOE between H-2' and H-6 an *anti* conformation around the glycosyl bond.

As expected,[11] upon treatment of **3** and **4** with methanolic ammonia, ester ammoniolysis preceded oxirane opening and **5** (90%) and **6** (89%) were obtained from **3** and **4,** respectively. In the same way, treatment of **3** and **4** with hydroxylamine afforded respectively **7** (79%) and **8** (75%), whereas upon hydrazinolysis **3** and **4** led to **9** (87%) and **10** (88%), respectively. A solution of **8** in diglyme spontaneously oxidized in the air to a small stationary concentration of the corresponding *N*-acylaminoxyl radical, which gave rise to the expected EPR signal (g 2.0069, $a_N$ 5.6 G, $a_H$ 10.7 G).

The feasibility of an intramolecular opening of the oxirane ring by the nucleophilic hydroxy group of **7** or amino group of **9** to afford respectively an isoxazolidone or a pyrrolidone was tested in a variety of conditions implying either Lewis acid catalysis or base catalysis. In no case, such reactions took place. Conversely, when treated with an excess DBU in refluxing methanol for 30 min (method A), **9** underwent a ring opening leading to **11** (37%) (SCHEME 2). When the reaction was performed at room temperature for 30 days with a default of DBU (method B), the yield of **11** was increased to 74%. The same reaction (method A) performed in ethanol afforded **12** (55%). The proposed mechanism (Fig. 2) implies a hydride transfer from the hydrazide moiety. Compound **12** was also obtained in 93% yield by nucleophilic addition of the conjugate base of ethyl acetate upon **1**.




SCHEME 2

Ring openings of 2-carbamoyloxiranes with azide ion have been shown to take place at C-3 of the oxirane[12] even in the case of a geminal substitution at this position.[13] In our case, the reaction exhibited the alternate regioselectivity and only compounds **13** and **14** were formed both regio- and stereoselectively (SCHEME 3). As shown in Table1, the major incidence of changes in reaction conditions concerns the extent of the 5'-de-*O*-silylation leading to **14**. When using a chloride ion as nucleophile, the reaction followed the same totally regio- and stereoselective course leading to **15** (77%).

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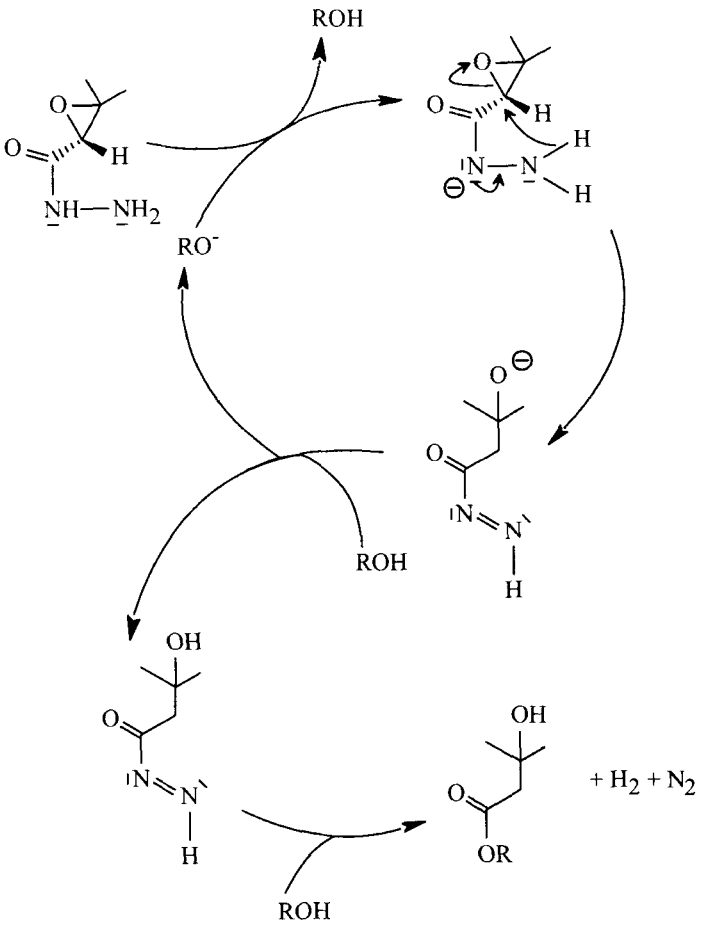


**FIG. 2** Proposed mechanism for the reductive oxirane opening of **9**.

To access to spirooxiranes of the *ribo* configuration, we started from **16**, which, after reduction to **19**, was submitted to a peracid epoxidation leading to **20**. The compound 16 was prepared as follows: the Wittig reaction between **1** and methoxycarbonylmethylenetriphenylphorphorane was totally stereoselective as it afforded only the (*E*)-isomer **16** in 99% yield, configuration of which was established by NOE experiments performed on **20** (see below). Applied to thymidine derivative **2**, the same Wittig reaction afforded **17** in 96% yield. Methylation (iodomethane) of **17** led to **18** (93%). Upon reduction [$NaH_2Al(OCH_2CH_2OMe)_2$], **16** gave **19** (83%) which, submitted to epoxidation using 3-chloroperbenzoic acid, afforded the (3"*S*) *ribo* spirooxirane **20**. NOE experiments on **20** (SCHEME 4) established the proximity of H-2' and H-3", hence its configuration, whereas an *anti* conformation of the glycosyl bond was proven by a

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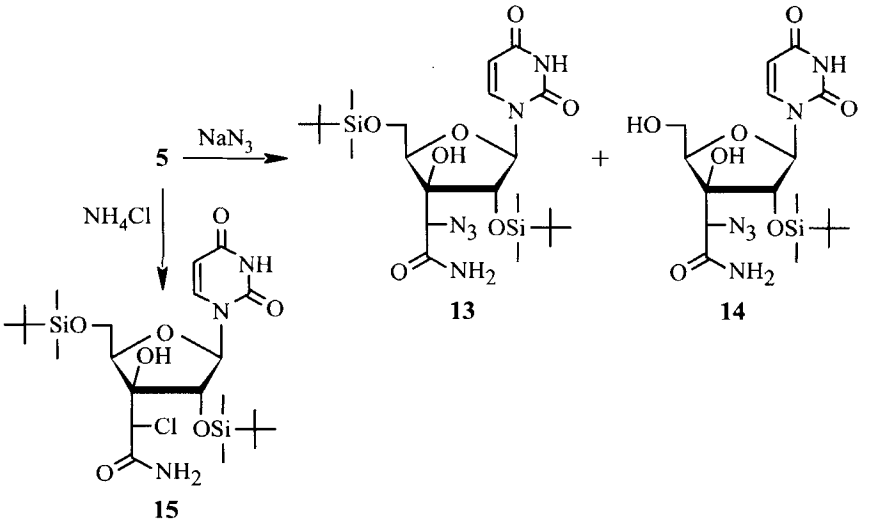
**TABLE 1.** Oxirane ring opening of **5** using azide ion.

| Method | t/°C | time/h | unreacted **5** | **13** | **14** |
|---|---|---|---|---|---|
| A[a] | 100 | 4.5 | 6% | 61% | 33% |
| A | 60 | 67 | 6% | 61% | 33% |
| A | 100 | 45 | 0% | 0% | 33% |
| B[b] | 64[c] | 30 | 10% | 79% | 10% |

[a] $NaN_3$, $NH_4Cl$, 8:1 propanol/water. [b] $MgSO_4$, $NaN_3$, MeOH. [c] Refluxing MeOH.




SCHEME 3

NOE effect between H-2' and H-6. All the spiro nucleosides described exhibited large $J_{1',2'}$ couplings (7.8-8.2 Hz) indicative of a 2'-*endo* (probably $^{2'}T_{3'}$) conformation of the furanose ring, whereas branched-chain nucleosides **11**, **12**, **13**, and **15** had null values of $J_{1',2'}$ (2'-*exo*). The 5'-de-*O*-silylated compound **14** exhibited an intermediate value (4.7 Hz) of $J_{1',2'}$. The unsaturated branched-chain nucleosides **16**-**19** preferred a 2'-*endo* conformation.

The nucleoside analogues have been tested for the $CT_{50}$ (cytotoxic concentration) and $CS_{50}$ (cytostatic concentration) on CEM cells as described in the experimental section (Table 2). Excepted for **14**, which is the nucleoside bearing only one TBDMS, all the compounds tested had similar $CT_{50}$ and $CS_{50}$ comprised between 3 and 26 µM and 1.7 and 21 µM respectively. Antiproliferative activities of each compound against cancer and normal cell lines were compared in order to determine their selectivity. The ratio

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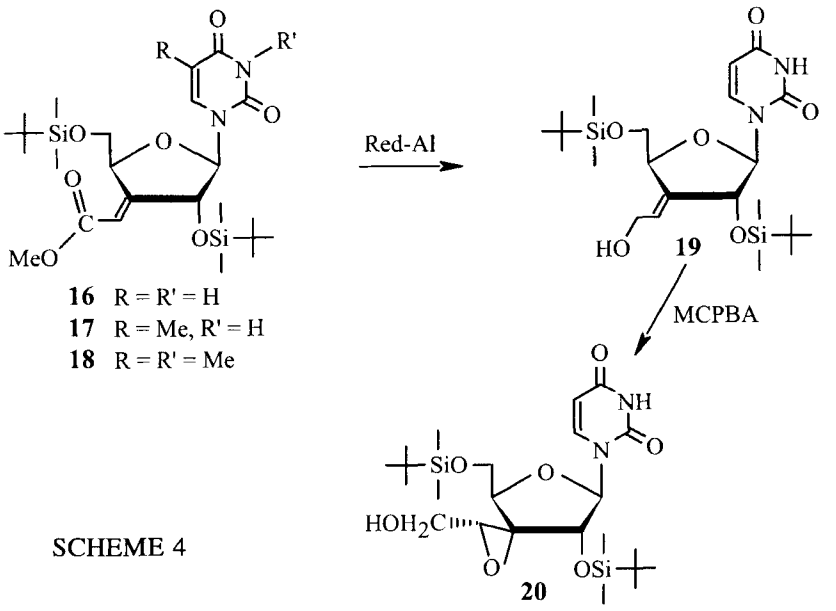


SCHEME 4

**TABLE 2.** Cytotoxic ($CT_{50}$) and cytostatic ($CS_{50}$) values (in μM) in CEM cells for modified nucleosides.

| Compd | $CT_{50}$ | $CS_{50}$ | Compd | $CT_{50}$ | $CS_{50}$ |
|---|---|---|---|---|---|
| **1** | 21.0 | 21.0 | **11** | 4.8 | 4.4 |
| **2** | 22.0 | 20.0 | **12** | 25.0 | 11.0 |
| **3** | 11.0 | 4.2 | **13** | 20.0 | 4.4 |
| **4** | 22.0 | 7.6 | **14** | >50 | >50 |
| **5** | 20.0 | 5.8 | **15** | 8.0 | 4.0 |
| **6** | 5.0 | 4.0 | **16** | 25.0 | 10.0 |
| **7** | 4.5 | 4.0 | **17** | 22.0 | 6.8 |
| **8** | 3.1 | 1.7 | **18** | 41.0 | 21.0 |
| **9** | 10.0-50.0[a] | 10.0 | **19** | 24.0 | 5.0 |
| **10** | 5.0 | 4.3 | **20** | 26.0 | 8.0 |

[a] Value between 10.0 and 50.0.

between $IC_{50}$ for non tumoral (MRC5-prol) and tumoral cells is then representative of an in vitro selectivity index. As was observed on CEM cells, **14** had no antiproliferative activity against the cell lines tested even at 100 μM. Some nucleosides such as **8**, **12**, **15**, **16**, **17** and **19** exhibited a moderate selective activity toward one or more cancer cell line(s). The thymine derivative **8** showed a better activity against colon carcinoma cells

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**TABLE 3.** Antiproliferative activities [$CC_{50}$ (μM)] of nucleoside derivatives **1-20** against representative cell lines.

| Compd | MRC5_Tox[a] | MRC5_prol.[b] | NCI H460[b] | HT29[b] | Caki-1[b] | HL60[b] |
|---|---|---|---|---|---|---|
| **1** | >100 | >100 | 32 | 32 | 100 | 23 |
| **2** | 30 | 30 | 30 | 30 | 30 | 30 |
| **3** | > 100 | 37.0 | 9.0 | 20.0 | 32.0 | 38.0 |
| **4** | > 100 | 32.0 | 4.0 | 25.0 | 26.0 | 12.0 |
| **5** | 33.0 | 33.0 | 5.0 | 4.1 | 25.0 | 20.0 |
| **6** | 32.0 | 30.0 | 3.1 | 3.8 | 30.0 | 3.3 |
| **7** | 23.0 | 20.0 | 2.6 | 3.8 | 15.0 | 4.3 |
| **8** | 23.0 | 21.0 | 1.7 | 2.0 | 2.0 | 2.0 |
| **9** | 30.0 | 22.0 | 13.5 | 20.0 | 29.0 | 16.5 |
| **10** | 32.0 | 30.0 | 14.0 | 28.0 | 21.0 | 22.0 |
| **11** | 21.0 | 3.1 | 2.5 | 3.0 | 13.0 | 3.1 |
| **12** | 8.0 | 30.0 | 2.0 | 2.0 | 2.0 | 2.0 |
| **13** | 28.0 | 30.0 | 4.0 | 3.8 | 18.0 | 4.6 |
| **14** | >100 | >100 | >100 | >100 | >100 | >100 |
| **15** | 25.0 | 35.0 | 2.9 | 4.0 | 25.0 | 6.0 |
| **16** | 39.0 | 39.0 | 3.7 | 3.1 | 4.2 | 2.0 |
| **17** | 39.0 | 39.0 | 3.2 | 4.0 | 4.0 | 3.3 |
| **18** | >100 | 72.0 | 30.0 | 25.0 | >100 | 30.0 |
| **19** | 32.0 | 35.0 | 2.1 | 3.0 | 5.5 | 9.0 |
| **20** | 35.0 | 40.0 | 19.0 | 20.0 | 35.0 | 35.0 |

[a]Cytotoxic concentration. [b]Antiproliferative concentration.

(HT29) as compared to its uracil analogue **7** (Table 3). Although **11** and **12** had similar effects on cancer cell lines, the compound bearing a 3-*C*-methoxycarbonylmethyl group **11** exhibited a ten-fold higher toxicity for normal cells than its 3-*C*-ethoxycarbonylmethyl analogue **12**. The methylation of **17** to give a 3-methylthymidine derivative **18** induced the loss of the antiproliferative activity in all cells tested.

The novel nucleoside derivatives were also evaluated for their antiviral activity against HIV-1, HIV-2, HSV-1, HSV-2, CMV, EBV and VZV (Table 4). None exhibited $EC_{50}$ values notably inferior to the micromolar range whatever the virus considered. However, in the following cases, antiviral activities were observed : **3** against EBV (0.83 μM), **5** against EBV (3.4 μM), **7** against HSV-2 (3 μM), **8** against CMV (4 μM), **16**

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**TABLE 4.** Activities [$EC_{50}$ (μM)] of nucleoside derivatives **3-20** against several viruses (NA, no activity).

| Compd | HIV-1 | HIV-2 | HSV-1 | HSV-2 | CMV | EBV | VZV |
|---|---|---|---|---|---|---|---|
| **3** | NA[a]; >10[b] | >10[b] | 23.0 | 26.0 | >20[b] | 0.83[c] | >20[c] |
| **4** | NA[a]; >10[b] | >10[b] | >23 | >23 | 12[b] | | >20[b] |
| **5** | NA[a]; >10[b] | >10[b] | >8[c] | >8[c] | >8[b,c] | 3.4[c] | >8[c] |
| **6** | >2[b]; 7 | >2[b] | >2.7 | >2.7 | | | |
| **7** | NA[a]; >10[b] | >2[b] | 27.0 | 3.0 | 24.0 | NA[c] | 13.0 |
| **8** | NA[a]; >2[b] | >2[b] | >3 | >3 | 4[b] | | >5[b] |
| **9** | NA[a]; >2[b] | >2[b] | 33.0 | 30.0 | 23.0 | >92[c] | 4.0 |
| **10** | NA[a]; >10[b] | >10[b] | >5.5 | >5.5 | >5[b] | | 3.9[b] |
| **11** | >10 | | >3.2 | >3.2 | | | |
| **12** | NA[a]; >10[b] | >10[b] | >3.4 | >3.4 | >2[b] | | >5[b] |
| **13** | NA[a]; >10[b] | >10[b] | >3.6 | >3.6 | >5[b] | | >5[b] |
| **14** | NA; ≥250[b] | >250[b] | >100 | >100 | | | |
| **15** | NA[a]; >2[b] | >2[b] | >3.8 | >3.8 | >5[b] | | >5[b] |
| **16** | NA[a]; >2[b] | >2[b] | >38[c] | 10.0 | 1[b] | 82[c] | 1.6[b] |
| **17** | NA[a]; >2[b] | >2[b] | >35 | >35 | 1.5 | | 4.4; 1.3[b] |
| **18** | NA[a] | | >100 | >100 | >36[c] | | >7[c] |
| **19** | NA[a]; >2[b] | >2[b] | >5 | >5 | 2.1; 3.8[c] | >100[c] | 3[b]; 6.4[c] |
| **20** | NA[a]; >10[b] | >10[b] | 20.0 | 24.0 | >5[b] | 76[c] | >194[c] |

Results from [a] NIH/NCI; [b] Rega Institute, Leuven; [c] NIH/NIAID.

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against CMV (1 μM) and VZV (1.6 μM), **17** against CMV (1.5 μM) and VZV (1.3-4.4 μM), and **19** against VZV (3-6.4 μM).

In conclusion, these compounds, in the rule moderately cytotoxic, exhibit in some cases, selective antiproliferative properties as well as some antiviral activities. They clearly do not behave as TSAO analogues.

## EXPERIMENTAL

**General Synthetic procedures.**[14]

**Biological testings.** Results from the Rega Institute for Medical Research have been obtained following previously described procedures.[15] Methods used in the

Mayoly-Spindler Laboratories are described below. Antiproliferative activities of the compounds were determined after 3 days using four cancer cell lines in exponential growth rate [NCI-H460 (lung large cell carcinoma, ATCC # HTB-177), HT29 (colon adenocarcinoma, ATCC # HTB-38), Caki-1 (kidney carcinoma, ATCC # HTB-46) and HL60s (promyelocytic leukemia, ATCC # CCL-240)]. A normal cell line [MRC5 (fœtal lung fibroblast, ATCC # CCL-171)] was used as control. With MRC5 cells, cytotoxic (MRC5-tox) and antiproliferative (MRC5-antip) effects of each compound were determined in stationary and exponential growth rate conditions, respectively. After 3 days of culture, the quantitation of growth was determined using the MTT assay as previously described by Park *et al.*[16] Briefly, the MTT test is based on the enzymatic reduction of the tetrazolium salt MTT [3-(4,5-dimetylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide] in living, metabolically active cells but not in dead cells. The reaction product, a purple-colored formazan soluble in dimethylsulfoxide, were measured colorimetrically at 550 nm, using multiwell plate reader. Measurements were done in duplicate. These results were issued from two distinct manipulations.

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$CT_{50}$ (cytotoxic concentration) and $CS_{50}$ (cytostatic concentration) of each compound were determined on the human T lymphoblastoid cell line CEM (ATCC # CL119) after 4 days of culture at exponential rate. At the end of this period, cells were incubated with propidium iodide that stained only dead cells. The distinction between cytotoxic and cytostatic effects of compounds was made by using a flow cytometry cell analyzer (Facscalibur, Becton Dockinson). The total cell number and ratio between living and dead cells were representative of the cytostatic and cytotoxic properties of the compounds, respectively. Measurements were currently duplicated.

Activities against HSV-1 and 2 virus were determined on Vero cells (kidney, African green monkey, ATCC # CCL-81). Cells were infected by HSV-1 or 2. One hour after infection, dilutions of each compound, or DMSO for control, were added. After 3 days, the cell layer was fixed by trichloroacetic acid and colored by sulforhodamine B. After dissolution, optical density which was inversely proportional to the virus activity was measured at 520 nm, using a multiwell plate reader. Measurements were currently duplicated.

Anti-CMV and anti-VZV activities of the compounds were determined on the MRC5 cell line (fœtal lung fibroblast, ATCC # CCL-171). Cells were infected by either CMV or VZV. One hour after infection, dilutions of each compound, or DMSO for control, were added. After 7 and 3 days, for CMV and VZV, respectively, the cell layer was fixed by acetone and incubated with primary antibodies against CMV or VZV (Argene Biosoft, Varilhes France). A goat polyclonal anti mouse antibody labeled with horseradish peroxidase and diaminobenzidine was used to stain infected cells. The number of plaques was counted using an inverted light microscope.

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Peripheral blood mononuclear cells from healthy patients were used to determine the compound's activity on HIV-1 Lai. Cells activated by PHA and $IL_2$ were treated by dilutions of each compound tested, or DMSO for control, one hour before infection by 100 $TCID_{50}$. After 7 days, the reverse transcriptase activity in the culture supernatant was measured using the RetroSys kit (Innovagen, Lund Sweden).

**(3"*R*)-1-[2',5'-Bis(*O*-*tert*-butyldimethylsilyl)-3'-deoxy-β-D-xylofuranosyl]uracil-3'-spiro-2"-(3"-methoxycarbonyloxirane) (3).** A solution of lithium bis(trimethylsilyl)amide (30.0 mmol) in dry THF (120 mL) under argon was cooled to -78 °C and methyl bromoacetate (4.60 g, 2.84 mL, 30.0 mmol) was added dropwise (10 min). After stirring at that temperature for 10 min, a solution of **1** (5.64 g, 12.0 mmol) in dry THF (30 mL) was added dropwise (15 min). After 30 min at -78 °C, the reaction mixture was stirred without cooling bath for an additional 25 min, poured into a saturated $NaHCO_3$ solution (80 mL) and extracted with $Et_2O$ (500 mL). The organic layer was washed with a saturated NaCl solution (80 mL), dried ($Na_2SO_4$), filtered, concentrated, and the residue purified by column chromatography (93:7 --> 17:3 toluene/EtOAc) to yield 5.06 g (78%) of **3**: mp 71.8-72.8 °C; $R_F$ 0.23 (4:1 toluene/EtOAc); $[\alpha]_D^{29}$ -19.0° (*c* 0.9, $CHCl_3$); $\nu_{max}^{KBr}$ 3415 (NH), 2958-2860 (CH), 1754, 1719, and 1700 (C=O), 1463, 1288, 1257, 1208, 1122, and 839 $cm^{-1}$. $^1H$ NMR ($C_6D_6$): δ 9.24 (*bs*, 1 H, NH), 8.07 (*d*, 1 H, $J_{5,6}$ 8.2 Hz, H-6), 6.44 (*d*, 1 H, $J_{1',2'}$ 7.8 Hz, H-1'), 5.76 (*dd*, 1 H, $J_{5,NH}$ 1.8 Hz, H-5), 4.55 (*d*, 1 H, H-2'), 4.08 (*bdd*, 1 H, H-4'), 3.97 (*s*, 1 H, H-3"), 3.92 (*dd*, 1 H, $J_{5'a,5'b}$ 11.0 Hz, $J_{4',5'b}$ 1.0 Hz, Hb-5'), 3.71 (*dd*, 1 H, $J_{4',5'a}$ 2.0 Hz, Ha-5'), 3.26 (*s*, 3 H, OMe), 0.95 and 0.92 (2 *s*, 18 H, $CMe_2$), 0.12, 0.04, and 0.01 (3 *s*, 12 H, $SiMe_2$). $^{13}C$ NMR ($C_6D_6$): δ ($CO_2Me$), 162.9 (C-2), 151.1 (C-4), 139.5 (C-6), 102.6 (C-5), 85.1 (C-1'), 75.3 and 74.5 (C-2' and C-4'), 69.0 (C-3'), 63.6 (C-5'), 53.6 (C-3"), 52.0 (OMe), 25.9 and 25.5 ($CMe_2$), 18.5 and 18.0 ($CMe_3$), -5.1, -5.4, and -5.7 ($SiMe_2$). EIMS: *m/z* (%) 73 (100), 89 (48), 169 (45), 485 (44, $M^{\cdot+}$ - *t*-Bu), 343 (23), 241 (22), 373 (21), and 527 (1, $M^{\cdot+}$ - Me).

*Anal.* Calcd for $C_{24}H_{42}N_2O_8Si_2$ (542.78): C, 53.11; H, 7.80; N, 5.16. Found: C, 53.03; H, 7.83; N, 5.05.

**(3''*R*)-1-[2',5'-Bis(*O*-*tert*-butyldimethylsilyl)-3'-deoxy-β-D-xylofuranosyl]thymine-3'-spiro-2''-(3''-methoxycarbonyloxirane) (4).** The reaction was performed by applying the reaction conditions described for **3** to **2** (4.85 g, 10.0 mmol) to obtain **4** (4.90 g, 88%): mp 74.3-75.1 °C; $R_F$ 0.24 (4:1 toluene/EtOAc); $[\alpha]_D^{27}$ -27.8° (*c* 1.0, $CHCl_3$); $\nu_{max}^{KBr}$ 3425 (NH), 2955-2858 (CH), 1755, 1719 and 1695 (C=O), 1472, 1462, 1288, 1260, 1215, 1123, 1072, 838, and 779 $cm^{-1}$. $^1H$ NMR ($C_6D_6$): δ 10.46 (*bt*, 1 H, NH), 7.24 (*q*, 1 H, $J_{Me-5,6}$ 1 Hz, H-6), 6.48 (*d*, 1 H, $J_{1',2'}$ 8.1 Hz, H-1'), 4.57 (*d*, 1 H, H-2'), 4.08 (*bt*, 1 H, H-4'), 3.97 (*s*, 1 H, H-3"), 3.95 (*dd*, 1 H, $J_{4',5b}$ 1.0 Hz, $J_{5'a,5'b}$ 11.5

Hz, Hb-5'), 3.77 (*dd*, 1 H, $J_{4',5'a}$ 1.5 Hz, Ha-5'), 3.27 (*s*, 3 H, OMe), 1.98 (*d*, 3 H, Me-5), 0.98 and 0.89 (2 *s*, 18 H, $CMe_3$), 0.17, 0.15, and 0.01 (3 *s*, 12 H, $SiMe_2$). EIMS: *m/z* (%) 73 (100), 499 (36, $M^+$ - *t*-Bu), 183 (23), 343 (19), 373 (12), 241 (11), and 525 (1).

*Anal.* Calcd for $C_{25}H_{44}N_2O_8Si_2$ (556.81): C, 53.93; H, 7.97; N, 5.03. Found: C, 53.78; H, 8.01; N, 4.92.

**(3''*R*)-1-[2',5'-Bis(*O-tert*-butyldimethylsilyl)-3'-deoxy-β-D-xylofuranosyl]uracil-3'-spiro-2''-(3''-carbamoyloxirane) (5).** Compound **3** (2.31 g, 4.2 mmol) dissolved in a saturated methanolic solution of ammonia (20 mL) was kept at room temperature for a night, the solvent was evaporated and the residue submitted to a column chromatography (3:2-->2:3 hexane/EtOAc) to give **5** (2.03 g, 90%): mp 173.4-174.4 °C; $R_F$ 0.16 (2:3 hexane/EtOAC); $[\alpha]_D^{29}$ +4.5° (*c* 1.0, $CHCl_3$); $\nu_{max}^{KBr}$ 3476, 3418, and 3345 (NH), 2956-2859 (CH), 1701 (C=O), 1464, 1389, 1284, 1255, 1121, 1070, 839, and 782 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 8.80 (*bs*, 1 H, NH), 8.02 (*d*, 1 H, $J_{5,6}$ 8.2 Hz, H-6), 6.17 and 6.10 (2 *bs*, 2 H, $CONH_2$), 6.15 (*d*, 1 H, $J_{1',2'}$ 7.8 Hz, H-1'), 5.78 (*dd*, 1 H, $J_{5,NH}$ 2.0 Hz, H-5), 4.46 (*d*, 1 H, H-2'), 4.04 (*bdd*, 1 H, H-4'), 3.96 (*dd*, 1 H, $J_{5'a,5'b}$ 11.3 Hz, $J_{4',5'b}$ 2.0 Hz, Hb-5'), 3.87 (*s*, 1 H, H-3''), 3.65 (*dd*, 1 H, $J_{4',5'a}$ ~ 1 Hz, Ha-5'), 1.00 and 0.85 (2 *s*, 18 H, $CMe_3$), 0.17-0.03 and 0.08 (3 *s*, 12 H, $SiMe_2$). EIMS: *m/z* (%) 73 (100, 89 (25), 169 (9), 470 (2, $M^+$ - *t*-Bu).

*Anal.* Calcd for $C_{23}H_{41}N_3O_7Si_2$ (527.77): C, 52.34; H, 7.83; N, 7.96. Found: C, 51.98; H, 7.94; N, 7.79.

**(3''*R*)-1-[2',5'-Bis(*O-tert*-butyldimethylsilyl)-3'-deoxy-β-D-xylofuranosyl]thymine-3'-spiro-2''-(3''-carbamoyloxirane) (6).** Compound **4** (557 mg, 1.0 mmol) was converted to **6** (480 mg, 89%) following the procedure described for **5**: mp 112.6-115.4 °C; $R_F$ 0.14 (2:3 hexane/EtOAc); $[\alpha]_D^{27}$ -23.2° (*c* 0.6, $CHCl_3$); $\nu_{max}^{KBr}$ 3480, 3414, and 3338 (NH), 2955-2857 (CH), 1700 (C=O), 1472, 1388, 1262, 1123, 1069, 839, and 781 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 9.46 (*s*, 1 H, NH-3), 7.62 (*s*, 1 H, H-6), 6.61 and 6.48 (2 *bs*, 2 H, $CONH_2$), 6.12 (*d*, 1 H, $J_{1',2'}$ 8.2 Hz, H-1'), 4.42 (*d*, 1 H, H-2'), 4.02 (*bt*, 1 H, H-4'), 3.95 (*dd*, 1 H, $J_{4',5'b}$ 1.5 Hz, $J_{5'a,5'b}$ 11.0 Hz, Hb-5'), 3.87 (*s*, 1 H, H-3''), 3.68 (*d*, 1 H, Ha-5'), 1.97 (*s*, 3 H, Me-5), 0.99 and 0.82 (2 *s*, 18 H, $CMe_3$), 0.20, 0.19, -0.02, and -0.09 (4 *s*, 12 H, $SiMe_2$). EIMS: *m/z* (%) 73 8100), 484 (35, $M^+$ - *t*-Bu), 183 (28), 343 (26), 226 (15), and 358 (14).

*Anal.* Calcd for $C_{24}H_{43}N_3O_7Si_2$ (541.80): C, 53.21; H, 8.00; N, 7.76. Found: C, 53.34; H, 8.06; N, 7.53.

**(3''*R*)-1-[2',5'-Bis(*O-tert*-butyldimethylsilyl)-3'-deoxy-β-D-xylofuranosyl]uracil-3'-spiro-2''-[3''-(*N*-hydroxycarbamoyl)oxirane] (7).** Hydroxylamine hydrochloride (2.08 g, 30.0 mmol) and triethylamine (4.18 mL, 30.0 mmol) were added to a solution of **3** (814 mg, 1.5 mmol) in dry methanol (15 mL). The reaction micture was stirred at

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room temperature for 6 h, evaporated (bath temperature: 25 °C), dissolved in cold EtOAc (40 mL) and washed with ice-cold 1.0 N hydrochloric acid. The aqueous phase was reextracted with cold EtOAc (2x40 mL) and the combined organic phases were washed with saturated $NaHCO_3$ (40 mL) and NaCl (40 mL), dried ($Na_2SO_4$), concentrated, and submitted to a column chromatography (50:3--> 25:1 $CH_2Cl_2$/MeOH) to give **7** (640 mg, 79%): mp 142.0-143.8 °C; $R_F$ 0.31 (10:1 $CH_2Cl_2$/MeOH); $[\alpha]_D^{26}$ +6.0° (*c* 1.0, $CHCl_3$); $\nu_{max}^{KBr}$ 3410 and 3240 (NH, OH), 2956-2858 (CH), 1691 (C=O), 1464, 1256, 1121, 1067, 838, and 781 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 11.51 and 11.26 (2 *bs*, 2 H, CONHOH), 9.2 (*bs*, 1 H, NH-3), 7.86 (*d*, 1 H, $J_{5,6}$ 8.2 Hz, H-6), 5.93 (*d*, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 5.77 (*d*, 1 H, H-5), 4.34 (*d*, 1 H, H-2'), 4.08 (*bt*, 1 H, H-4'), 3.84 (*dd*, 1 H, $J_{5'a,5'b}$ 11 Hz, $J_{4',5'b}$ 2 Hz, Hb-5'), 3.76 (*dd*, 1 H, $J_{4',5'a}$ 2 Hz, Ha-5'), 3.57 (*s*, 1 H, H-3''), 0.93 and 0.86 (2 *s*, 18 H, $CMe_3$), 0.13, -0.05, and -0.13 (3 *s*, 12 H, Si $Me_2$). EIMS: *m/z* (%) 73 (100), 169 (24), 425 (15), 470 (9), 343(7), and 486 (3, $M^{\cdot+}$ - *t*-Bu).

*Anal.* Calcd for $C_{23}H_{41}N_3O_2Si_2$ (543.77): C, 50.88; H, 7.60; N, 7.73. Found: C, 50.51; H, 7.66; N, 7.62.

**(3''*R*)-1-[2',5'-Bis(*O*-*tert*-butyldimethylsilyl)-3'-deoxy-β-D-xylofuranosyl]thymine-3'-spiro-2''-[3''-(*N*-hydroxycarbamoyl)oxirane] (8).** The reaction was performed by applying the reaction conditions described for **7** to **4** (557 mg, 10 mmol) to obtain **8** (420 mg, 75%): mp127.0-128.5 °C; $R_F$ 0.26 (10:1 $CH_2Cl_2$/MeOH); $[\alpha]_D^{28}$ -9.6° (*c* 1.0 $CHCl_3$); $\nu_{max}^{KBr}$ 3411 and 3237 (NH, OH), 2957-2859 (CH), 1724, 1693, and 1664 (C=O), 1472, 1388, 1282, 1258, 1122, 839, and 780 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 9.7-9.3 (*bs*, 3 H, NH-3, CONHOH), 7.65 (*s*, 1 H, H-6), 6.12 (*d*, 1 H, H-1'), 4.41 (*d*, 1 H $J_{1',2'}$ 8 Hz, H-2'), 4.01 (*bm*, 1 H, H-4'), 3.94 (*d*, 1 H, $J_{5'a,5'b}$ 11 Hz; $J_{4',5'b}$ 1-2 Hz, Hb-5'), 3.87 (*s*, 1 H, H-3''), 3.72 (*d*, 1 H, $J_{4',5'a}$ ~ 2 Hz, Ha-5'), 1.96 (*s*, 3 H, Me-5), 0.98 and 0.87 (2 *s*, 18 H, $CMe_3$), 0.21, 0.19, -0.06, and -0.12 (4 *s*, 12 H, $SiMe_2$). EIMS: *m/z* (%) 75 (100), 183 (23), 126 (16), 482 (8, $M^{\cdot+}$ - *t*-Bu), 439 (5), and 301 (5).

*Anal.* Calcd for $C_{24}H_{43}N_3O_8Si_2$ (557.80): C, 51.68; H, 7.77; N, 7.53. Found: C, 51.84; H, 7.97; N, 7.26.

**(3''*R*)-1-[2',5'-Bis(*O*-*tert*-butyldimethylsilyl)-3'-deoxy-β-D-xylofuranosyl]uracil-3'-spiro-2''-[3''-(*N*-aminocarbamoyl)oxirane (9).** A solution of **3** (814 mg, 1.50 mmol) and hydrazine hydrate (364 mL, 7.5 mmol) in dry methanol (6 mL) was stirred at room temperature for 2 h. Evaporation (bath temperature: 25 °C) and chromatography on silica gel (25:1 --> 50:3 $CH_2Cl_2$/MeOH) afforded **9** (710 mg, 87%): mp 117.8-120.2 °C; $R_F$ 0.46 (9:1 $CH_2Cl_2$/MeOH); $[\alpha]_D^{26}$ +2.1° (*c* 1.0, $CHCl_3$); $\nu_{max}^{KBr}$ 3410, 3328, and 3288 (NH), 2956-2858 (CH), 1694 (C=O), 1463, 1256, 1120, 1067, 838, and 781 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 11.50 (*bs*, 1 H, $CONHNH_2$), 9.79 (*bs*, 1 H, NH-3), 7,87 (*d*, 1 H, $J_{5,6}$ 8.2 Hz, H-6), 5.92 (*d*, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 5.77 (*d*, 1 H, H-5), 4.44 (*bs*, 2 H, $NH_2$), 4.34

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(*d*, 1 H, H-2'), 4.08 (*bt*, 1 H, H-4'), 3.82 (*dd*, 1 H, $J_{5'a,5'b}$ 11 Hz, $J_{4',5'b}$ 2 Hz, Hb-5'), 3.77 (*dd*, 1 H, $J_{4',5'a}$ 2 Hz, Ha-5'), 3.53 (*s*, 1 H, H-3''), 0.92 and 0.88 (2 *s*, 18 H, $CMe_2$), 0.13, -0.06, and -0.12 (3 *s*, 12 H, $SiMe_2$). EIMS: *m/z* (%) 73 (100), 485 (24, $M^{\cdot+}$ - *t*-Bu), 169 (19), 241 (13), 343 (12), 373 (6), and 542 (1, $M^{\cdot+}$).

*Anal.* Calcd for $C_{23}H_{42}N_4O_7Si_2$ (542.79): C, 50.90; H, 7.80; N, 10.32. Found: C, 50.72; H, 7.91; N, 10.09.

**(3''*R*)-1-[2',5'-Bis(*O*-*tert*-butyldimethylsilyl)-3'-deoxy-β-D-xylofuranosyl]thymine-3'-spiro-2''-[3''-(*N*-aminocarbamoyl)oxirane] (10).** **4** (557 mg, 1.0 mmol) was converted to **10** (490 mg, 88%) following the procedure described for **9**: mp 171.5-173.3 °C; $R_F$ 0.40 (10:1 $CH_2Cl_2$/MeOH); $[\alpha]_D^{28}$ -14.8° (*c* 1.0, $CHCl_3$); $\nu_{max}^{KBr}$ 3418 and 3326 (NH), 2956-2858 (CH), 1696 (C=O), 1471, 1387, 1257, 1121, 1069, 838, and 781 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 9.34 (*s*, 1 H, NH-3), 7.87 (*s*, 1 H, $CONHNH_2$), 7.62 (*q*, 1 H, $J_{Me-5,6}$ 1 Hz, H-6), 6.12 (*d*, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.42 (*d*, 1 H, H-2'), 4.02 and 3.97 (2 *m*, 3 H, H-4' and $CONHNH_2$), 3.92 (*d*, 1 H, $J_{4',5'b}$ 1.5 Hz, $J_{5'a,5'b}$ 12 Hz, Hb-5'), 3.85 (*s*, 1 H, H-3''), 3.70 (*dd*, 1 H, $J_{4',5'a}$ 2.0 Hz, Ha-5'), 1.96 (*d*, 3 H, Me-5), 1.00 and 0.82 (2 *s*, 18 H, $CMe_3$), 0.20, 0.19, -0.05, and -0.02 (4 *s*, 12 H, $SiMe_2$). EIMS: *m/z* (%) 73 (100), 183 (29), 225 (17), 343 (17), 499 (17, $M^{\cdot+}$ - *t*-Bu), 301 (13), 283 (10), 469 (8), and 556 (0.3, $M^{\cdot+}$).

*Anal.* Calcd for $C_{24}H_{44}N_4O_7Si_2$ (556.81): C, 51.77; H, 7.97; N, 10.06. Found: C, 51.68; H, 8.05; N, 9.90.

**1-[2,5-Bis(*O*-*tert*-butyldimethylsilyl)-3-*C*-methoxycarbonylmethyl-β-D-xylofuranosyl]uracil (11).**

**Method A**: A solution of **9** (27.1 mg, 0.05 mmol) and DBU (19.3 μL, 0.13 mmol) in dry methanol (1.0 mL) was refluxed for 30 min. The solvent was evaporated and the residue submitted to a column chromatography (2:1 hexane/EtOAc) to give **11** (10.2 mg, 37%).

**Method B**: A solution of **9** (109.0 mg, 0.20 mmol) and DBU (3.0 μL, 0.02 mmol) in dry methanol (3.0 mL) was kept at room temperature for 30 days. Purification as described in method A, afforded **11** (80.8 mg, 74%): mp 48.8-50.6 °C; $R_F$ 0.40 (1:1 hexane/EtOAc); $[\alpha]_D^{26}$ +29.7° (*c* 0.8, $CHCl_3$); $\nu_{max}^{KBr}$ 3417 (NH, OH), 2955-2855 (CH), 1711 and 1691 (C=O), 1471, 1464, 1265, 1168, 838, and 782 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 8.46 (*bs*, 1 H, NH-3), 7.88 (*d*, 1 H, $J_{5,6}$ 8.2 Hz, H-6), 5.74 (*s*, 1 H, H-1'), 5.65 (*dd*, 1 H, $J_{NH-3,5}$ 1.5 Hz, H-5), 4.50 (*bs*, 1 H, OH), 4.28 (*s*, 1 H, H-2'), 4.17 (*dd*, 1 H, $J_{5'a,5'b}$ 11 Hz, $J_{4',5'b}$ 4.5 Hz, Hb-5'), 4.04 (*dd*, 1 H, $J_{4',5'a}$ 3.4 Hz, Ha-5'), 3.97 (*dd*, 1 H, H-4'), 3.72 (*s*, 3 H, OMe), 2.86 and 2.71 (*AB system*, 2 H, $J_{gem}$ 16.5 Hz, $CH_2CO_2Me$), 0.95 and 0.90 (2 *s*, 18 H, $CMe_3$), 0.23, 0.15, and 0.08 (3 s, 12 H, $SiMe_2$). $^{13}C$ NMR ($CDCl_3$): δ 172.3 ($CO_2Me$), 163.1 (C-2), 150.1 (C-4), 141.2 (C-6), 100.9 (C-5), 91.4 (C-1'), 83.7, 82.4, and

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79.5 (C-2', C-3', and C-4'), 61.0 (C-5'), 51.9 (OMe), 36.0 ($\mathbf{CH_2}CO_2Me$), 25.8 and 25.7 ($\mathbf{CMe_3}$), 18.2 and 17.9 ($\mathbf{CMe_3}$), -4.4, -5.6, and -5.8 ($SiMe_2$). EIMS: *m/z* (%) 73 (100), 89 (63), 269 (39), 169 (33), 213 (31), 487 (21, $M^+$ - *t*-Bu), 375 (14), 243 (12), 301 (11), and 357 (7).

*Anal.* Calcd for $C_{24}H_{44}N_2O_8Si_2$ (544.80): C, 52.91; H, 8.14; N, 5.14. Found: C, 53.02; H, 8.18; N, 5.04.

**1-[2,5-bis(*O*-*tert*-Butyldimethylsilyl)-3-*C*-ethoxycarbonylmethyl-β-D-xylofuranosyl]uracil (12).** **9** (27.1 mg, 0.05 mmol) was converted to **12** (15.1 mg, 55%) following method A (solvent EtOH) described for **11**. **12** was also prepared by an independent procedure (see below). The $^1H$ NMR spectra of the products coming from the two different methods were superimposable.

To a cooled (-78 °C) and stirred solution of lithium bis(trimethylsilyl)amide (3.0 mmol) in dry THF (7 mL) EtOAc (294 μL, 3.0 mmol) was added dropwise in 5 min. The yellow solution was stirred at -78 °C for 15 min, then a solution of **1** (470 mg, 1.0 mmol) in dry THF (3 mL) was added in 10 min and stirring was continued for 10 min. The reaction mixture was poured into EtOAc (40 mL), washed with a saturated $NaHCO_3$ solution (10 mL), water (10 mL), saturated NaCl (10 mL), dried ($Na_2SO_4$), filtered, and concentrated. Column chromatography (7:3 hexane/EtOAc) of the residue afforded **12** (520 mg, 93%): mp 53.8-55.2 °C; $R_F$ 0.32 (3:2 hexane/EtOAc); $[\alpha]_D^{27}$ +28.1° (*c* 1.0, $CHCl_3$); $\nu_{max}^{KBr}$ 3434 (NH, OH), 2955-2854 (CH), 1712 and 1690 (C=O), 1470, 1462, 1265, 1116, 839, and 781 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 8.95 (*d*, 1 H, $J_{NH\text{-}3,5}$ 2.2 Hz, NH-3), 7.87 (*d*, 1 H, $J_{5,6}$ 8.3 Hz, H-6), 5.72 (*s*, 1 H, H-1'), 5.65 (*dd*, 1 H, H-5), 4.47 (*s*, 1 H, OH), 4.28 (s, 1 H, H-2'), 4.16 (*dq*, 2 H, $J_{CH2,CH3}$ 7 Hz, extra J 1 Hz, $OCH_2$), 4.12 (*dd*, 1 H, $J_{5'a,5'b}$ 10 Hz, $J_{4',5'b}$ 3.2 Hz, Hb-5'), 4.02 (*dd*, 1 H, $J_{4',5'a}$ 3.8 Hz, Ha-5'), 3.97 (*dd*, 1 H, H-4'), 2.84 and 2.69 (*AB system*, 2 H, $J_{gem}$ 16.5 Hz, $\mathbf{CH_2}CO_2Et$), 1.27(*t*, 3 H, $OCH_2\mathbf{CH_3}$), 0.92 and 0.87 (2 *s*, 18 H, $CMe_3$), 0.22, 0.15, and 0.04 (3 *s*, 12 H, $SiMe_2$. $^{13}C$ NMR ($CDCl_3$): δ 172.1 ($\mathbf{CO_2}Et$), 163.3 (C-2), 150.2 (C-4), 141.2 (C-6), 100.8 (C-5), 91.4 (C-1'), 84.0, 82.3, and 79.4 (C-2', C-3', C-4'), 61.0 (C-5' and $\mathbf{OCH_2}CH_3$), 35.9 ($\mathbf{CH_2}CO_2Et$), 25.8 and 25.7 ($\mathbf{CMe_3}$), 18.2 and 17.9 ($\mathbf{CMe_3}$), 14.1 ($\mathbf{OCH_2CH_3}$), -4.4, -5.5, and -5.8 ($SiMe_2$). EIMS: *m/z* (%) 73 (100), 269 (39), 501 (35, $M^+$ - *t*-Bu), 169 (34), 297 (27), and 389 (16).

*Anal.* Calcd for $C_{25}H_{46}N_2O_8Si_2$ (558.83): C, 53.73; H, 8.30; N, 5.01. Found: C, 53.60; H, 8.36; N, 4.86.

**1-[2,5-Bis(*O*-tert-butyldimethylsilyl)-3-*C*-[(1 *S*)-2-amino-1-azido-2-oxoethyl]-β-D-xylofuranosyl]uracil (13).** A solution of **5** (320 mg, 0.60 mmol) in dry methanol (5 mL) was refluxed for 30 h with $NaN_3$ (390 mg, 6.0 mmol) and anhydrous $MgSO_4$ (361 mg, 3.0 mmol). The reaction mixture was cooled and then concentrated to dryness. The

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residue was taken up in EtOAc (60 mL) and washed with a mixture of water (20 mL) and a saturated NaCl solution (10 mL). The aqueous phase was back-extracted with EtOAc (20 mL) and the combined organic phases were washed with saturated NaCl, dried ($Na_2SO_4$), concentrated and purified by column chromatography (11:9 hexane/EtOAc) to afford **13** (270 mg, 79%) along with recovered **5** (30 mg, 10%), and the 5'-desilylated product **14** (26 mg, 10%). Properties of **13** : mp 99.2-101.5 °C; $R_F$ 0.39 (2:3 hexane/ EtOAc); $[\alpha]_D^{29}$ +34.5 (*c* 1.0, $CHCl_3$); $\nu_{max}^{KBr}$ 3410 and 3350 (NH, OH), 2956-2859 (CH), 2127 and 2111 ($-N_3$), 1692 (C=O), 1464, 1263, 1120, 1060, 839, and 782 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 9.41 (*d*, 1 H, $J_{NH-3,5}$ 2 Hz, NH-3), 8.02 (*d*, 1 H, $J_{5,6}$ 8.0 Hz, H-6), 6.88 and 6.27 (2 *d*, 2 H, $J_{gem}$ 2.5 Hz, $CONH_2$), 5.80 (*s*, 2 H, H-1' and OH), 5.66 (*dd*, 1 H, H-5), 4.33 (*dd*, 1 H, $J_{4',5'b}$ 2.0 Hz, $J_{5'a,5'b}$ 11.5 Hz, Hb-5'), 4.32 (*d*, 1 H, $J_{1',2'}$ 2.2 Hz, H-2'), 4.23 (*dd*, 1 H, $J_{4',5'a}$ 1.5 Hz, Ha-5'), 4.20 (*s*, 1 H, $N_3CH$), 4.14 (*t*, 1 H, H-4'), 0.95 and 0.89 (2 *s*, 16 H, $CMe_3$), 0.10, 0.08, 0.06, and 0.04 (4 *s*, 12 H, Si $Me_2$). EIMS: *m/z* (%) 73 (100).301 (75), 169 (31), 413 (7), 513 (2, $M^{\cdot+}$ - *t*-Bu), and 478 (1).

*Anal.* Calcd for $C_{23}H_{42}N_6O_7Si_2$ (570.80): C, 48.40; H, 7.42; N, 14.72. Found: C, 48.64; H, 7.52; N, 14,40.

**1-[2-*O*-*tert*-Butyldimethylsilyl-3-*C*-[(1*S*)-2-amino-1-azido-2-oxoethyl]-β-D-xylofuranosyl]uracil (14).** A solution of **5** (320 mg, 0.60 mmol), $NaN_3$ (234 mg, 3.6 mmol), and $NH_4Cl$ (96 mg, 1.8 mmol) in 2-methoxyethanol (8.0 mL) and water (10 mL) was stirred at 100 °C (bath) for 45 h. The reaction mixture was cooled to room temperature, concentrated, and coevaporated with toluene (3x10 mL). The residue was taken up in EtOAc (40 mL), washed with a mixture of a saturated NaCl solution (10 mL) and $H_2O$ (5 mL), and the combined organic phases were washed with saturated NaCl (10 mL), dried $Na_2SO_4$), evaporated, and purified by column chromatography (1:1 hexane/ acetone) to afford **14** (180 mg, 66%): mp 112.5-114.3 °C; $R_F$ 0.14 (1:1 hexane/acetone); $[\alpha]_D^{26}$ +38.5° (*c* 0.5, EtOH); $\nu_{max}^{KBr}$ 3415 and 3239 (NH, OH), 2956-2857 (CH), 2126 ($-N_3$), 1694 and 1681 (C=O), 1464, 1390, 1266, 1118, 840, and 784 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 40 °C): δ 11.15 (*bs*, 1 H, NH-3), 7.88 (*d*, 1 H, $J_{5,6}$ 8.0 Hz, H-6), 7.80 and 7.55 (2 *bs*, 2 H, $CONH_2$), 5.77 (*d*, 1 H, $J_{1',2'}$ 4.7 Hz, H-1'), 5.71 (*bs*, 1 H, OH-3'), 5.54 (*d*, 1 H, H-5), 4.82 (*bs*, 1 H, OH-5'), 4.38 (*d*, 1 H, H-2'), 4.14 (*dd*, 1 H, $J_{4',5'a}$ 5 Hz, $J_{4',5'b}$ 3 Hz, H-4'), 4.03 (*s*, 1 H, $N_3CH$), 0.87 (*s*, 9 H, $CMe_3$), 0.08 and 0.04 (2 *s*, 6 Hz, $SiMe_2$). EIMS: *m/z* (%) 75 (100), 187 (58), 169 (55), 112 (41 ), 211 (10), 259 (5), 287 (4), 353 (3), and 399 (2, $M^{\cdot+}$ - *t*-Bu).

*Anal.* Calcd for $C_{17}H_{28}N_6O_7Si$ (456.53): C, 44.73; H, 6.18; N, 18.41. Found: C, 44.50; H, 6.23; N, 18.36.

**1-{2,5-Bis-(*O*-*tert*-butyldimethylsilyl)-3-*C*-[(1*S*)-2-amino-1-chloro-2-oxoethyl]-β-D-xylofuranosyl}uracil (15).** A mixture of **5** (320 mg, 0.60 mmol),

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tetrabutylammonium chloride (88.8) mg, 0.30 mmol), and ammonium chloride (64.2 mg, 1.20 mmol) in MeCN (2.0 mL) was boiled under reflux for 40 h, partitioned between EtOAc (50 mL) and water (10 mL), and the organic phase was washed with a saturated NaCl solution (10 mL), dried ($Na_2SO_4$), and evaporated. Column chromatography of the residue 9:11 hexane/EtOAc) afforded **15** (260 mg, 77%): mp 106.2-107.3 °C; $R_F$ 0.45 (2:3 hexane/EtOAc); $[\alpha]_D^{29}$ +48.4° (*c* 0.8, $CHCl_3$); $\nu_{max}^{KBr}$ 3415 and 3354 (NH, OH), 2955-2857 (CH), 1691 (C=O), 1464, 1389, 1266, 1118, 839, and 784 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 9.45 (*bs*, 1 H, NH-3), 8.02 (*d*, 1 H, $J_{5,6}$ 8.3 Hz, H-6), 6.87 (*bs*, 1 H, CONH**a**H**b**), 6.02 (*bs*, 2 H, CONH**a**Hb), OH), 5.67 (*s*, 1H, H-1'), 5.62 (*dd*, 1 H, $J_{NH\text{-}3,5}$ 2.1 Hz, H-5), 4.61 and 4.42 (2 *s*, 2 H, H-2' and ClCH), 4.56 (*dd*, 1 H, $J_{4',5'b}$ 2.0 Hz, $J_{5'a,5'b}$ 12 Hz, Hb-5), 4.33 (*dd*, 1 H, $J_{4',5'b}$ 1.3 Hz, Ha-5'), 4.21 (*bs*, 1 H, H-4'), 0.95 and 0.92 (2 *s*, 18 H, $CMe_3$), 0.27 and 0.17 (2 *s*, 12 H, $SiMe_2$).. EIMS: *m/z* (%) 73 (100), 301 (48), 89 (45), 169 (23), 506 (10), 394 (9), 343 (5), 470 (4), and 376 (4).

*Anal.* Calcd for $C_{23}H_{42}ClN_3O_7Si_2$ (564.23): C, 48.96; H, 7.50; Cl, 6.28; N, 7.45. Found: C, 49.38; H, 7.64; Cl, 6.52; N, 7.20.

**(*E*)-2',5'-Bis(*O*-*tert*-butyldimethylsilyl)-3'-deoxy-3'-*C*-(methoxycarbonylmethylene)uridine (16).** Compound **1** (4.00 g, 8.5 mmol) and (methoxycarbonylmethylene)triphenylphosphorane (8.53 g, 26.5 mmol) were dissolved in a mixture of anhydrous benzene (85 mL) and $CH_2Cl_2$ (18 mL) and the solution was stirred at room temperature for one day. The solvents were removed under reduced pressure, the residue treated with ether (60 mL), filtered, concentrated, and subjected to column chromatography (3:1 hexane/EtOAc) to afford **16** (4.44 g, 99%). Mp 123.6-124.8 °C; $R_F$ 0.28 (7:3 hexane/EtOAc); $[\alpha]_D^{27}$ +126.0° (*c* 1.1, $CHCl_3$); $\nu_{max}^{KBr}$ 3192 (NH), 2955, 2530, and 2859 (CH), 1718 and 1694 (C=O), 1635, 1461, 1222, and 838 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 8.70 (*bs*, 1 H, NH), 8.02 (*d*, 1 H, $J_{5,6}$ 8 Hz, H-6), 5.99 (*d*, 1 H, $J_{1',2'}$ 7.5 Hz, H-1'), 5.92 (*t*, 1 H, $J_{1'',2'}$ 2 Hz, $J_{1'',4'}$ 2 Hz, H-1''), 5.78 (*dd*, 1 H, $J_{3NH,5}$ 2.5 Hz, H-5), 5.38 (*m*, 1 H, H-4'), 4.70 (dt, 1 H, $J_{2',4'}$ 2 Hz, H-2'), 4.17 (*dd*, 1 H, $J_{5'a,5'b}$ 11.2 Hz, $J_{4',5'b}$ 1.2 Hz, Hb-5'), 3.96 (*dd*, 1 H, $J_{4',5'a}$ 2 Hz, Ha-5'), 3.77 (*s*, 3 H, $CO_2Me$), 0.90 (*s*, 18 H, $CMe_3$), 0.09, 0.04, and -0.06 (3 *s*, 12 H, $SiMe_2$). EIMS: *m/z* (%) 73 (100), 357 (37, $M^{\cdot+}$ + 1 - $CMe_3$ - B), 169 (21), 386 (16), 225 (12), and 469 (6, $M^{\cdot+}$ - $CMe_3$).

*Anal.* Calcd for $C_{24}H_{42}N_2O_7Si_2$ (526.78): C, 54.72; H, 8.04; N, 5.32. Found: C, 54.75; H, 8.00; N, 5.36.

**(*E*)-2',5'-Bis(*O*-*tert*-butyldimethylsilyl)-3'-deoxy-3'-*C*-(methoxycarbonylmethylene)thymidine (17).** Compound **17** was prepared from **2** (830 mg, 1.5 mmol) as described for **16**. Yield: 890 mg (96%): mp 140.6-142.4 °C; $R_F$ 0.28 (7:3 hexane / EtOAc); $[\alpha]_D^{27}$ + 170.5° (*c* 0.9, $CHCl_3$); $\nu_{max}^{KBr}$ 3190 (NH), 2954, 2929, and 2858 (CH), 1718, 1727, and 1694 (C=O), 1464, 1223, and 838 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 8.42 (*bs*,

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1 H, NH), 7.66 (*q*, 1 H, $J_{5\text{-Me},6}$ 1 Hz, H-6), 5.95 (*d*, 1 H, $J_{1',2'}$ 7.8 Hz, H-1'), 5.83 (*t*, 1 H, $J_{1'',2'} \sim J_{1'',4'} \sim 2$ Hz, H-1''), 5.33 (*m*, 1 H, H-4'), 4.70 (*dt*, 1 H, $J_{2',3'} \sim 2$ Hz, H-2'), 4.22 (*dd*, 1 H, $J_{4',5'b}$ 1.5 Hz, $J_{5'a,5'b}$ 11.2 Hz, Hb-5'), 3.97 (*dd*, 1 H, $J_{4',5'a}$ 2 Hz, Ha-5'), 3.77 (*s*, 3 H, $CO_2Me$), 1.96 (*d*, 3 H, 5-Me), 0.95 and 0.92 (2 *s*, 18 H, $CMe_3$), 0.08, 0.06, 0.05, and -0.08 (4 *s*, 12 H, $SiMe_2$). EIMS: *m/z* (%) 73 (100), 357 (30), 183 (18), 386 (15), 225 (11), 483 (4, M.+ - *t*-Bu), and 525 (1).

*Anal.* Calcd for $C_{25}H_{44}N_2O_7Si_2$ (540.81): C, 55.52; H, 8.20; N, 5.18. Found: C, 55.45; H, 8.20; N, 5.25.

**(*E*)-2',5'-Bis(*O*-*tert*-butyldimethylsilyl)-3'-deoxy-3'-*C*-(methoxycarbonylmethylene)-3-methylthymidine (18).** A mixture of **17** (541 mg, 1.0 mmol), $K_2CO_3$ (160 mg, 1.2 mmol) and methyl iodide (312 mL, 5.0 mmol) in acetone (12 mL) was vigorously stirred for a night. After the solvent was evaporated, ether (50 mL) was added, the solution was washed with saturated $NaHCO_3$ and processed as usual. The residue was purified by column chromatography (4:1 hexane/EtOAc) to afford **18** (517 mg, 93%) as a syrup; $R_F$ 0.36 (7:3 hexane/EtOAc; $[\alpha]_D^{27}$ +104.6° (*c* 1.0, $CHCl_3$); $\nu_{max}^{KBr}$ 2955, 2931, and 2859 (CH), 1709, 1670, and 1646 (C=O), 1470, 1223, 1106, and 839 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 7.65 (*q*, 1 H, $J_{5\text{-Me},6}$ 1.3 Hz, H-6), 6.04 (*d*, 1 H, $J_{1',2'}$ 7.8 Hz, H-1'), 5.94 (*t*, 1 H, $J_{1'',2'} \sim J_{1'',4'} \sim 2.2$ Hz, H-1''), 5.35 (*m*, 1 H, H-4'), 4.68 (*dt*, 1 H, $J_{2',4'}$ -2 Hz, H-2'), 4.22 (*dd*, 1 J, $J_{4',5'b}$ 1.6 Hz, $J_{5'a,5'b}$ 11.0 Hz, Hb-5'), 3.97 (*dd*, 1 H, $J_{4',5'a}$ 1.8 Hz, Ha-5'), 3.77 (*s*, 3 H, $CO_2Me$), 3.37 (*s*, 3 H, N-Me), 1.98 (*d*, 3 H, 5-Me), 0.93 and 0.89 (2 *s*, 18 H, $CMe_3$), 0.08, 0.05, 0.02 and -0.15 (4 *s*, 12 H, $SiMe_2$). EIMS: *m/z* (%) 73 (100), 105 (52), 357 (48), 386 (27), 397 (18), 254 (14), and 497 (7, $M^{\cdot+}$ - *t*-Bu).

*Anal.* Calcd for $C_{26}H_{46}N_2O_7Si_2$ (554.84): C, 56.28; H, 8.36; N, 5.05. Found: C, 56.36; H, 8.35; N, 4.96.

**(*E*)-2',5'-Bis(*O*-*tert*-butyldimethylsilyl)-3'-deoxy-3'-*C*-(2-hydroxyethylidene)uridine (19).** To a stirred solution of **16** (2.64 g, 5.0 mmol) in toluene (50 mL) Red-Al (Fluka) (7.1 mL, 25.0 mmol) was added in 20 min at -15 to -20 °C. The reaction mixture was stirred at that temperature for 30 min and quenched by successive slow addition of EtOAc (50 mL), saturated $NaHCO_3$ (50 mL), and $NH_4Cl$ (50 mL) solutions. The aqueous layer was separated and extracted with EtOAc (2x30 L). The combined organic layers were washed successively with saturated $NH_4Cl$ (25 mL) and NaCl (2x25 mL), dried ($Na_2SO_4$), and concentrated. The residue was purified by column chromatography (3:1 --> 3:2 hexane/EtOAc) to give **19** (2.07 g, 83%): mp 64.7-65.5 °C; $R_F$ 0.13 (3:2 hexane/EtOAc); $[\alpha]_D^{23}$ (*c* 1.0, $CHCl_3$); $\nu_{max}^{KBr}$ 3440 and 3150 (OH, NH), 2974, 2930 and 2858 (CH), 1691 (C=O), 1463, 1254, 1114, and 838 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 9.23 (*bs*, 1 H, NH), 7.93 (*d*, 1 H, $J_{5,6}$ 8.1 Hz, H-6), 5.87 (*d*, 1 H, $J_{1',2'}$ 7.4 Hz, H-1'), 5.75 (*d*, 1 H, H-5), 5.70 (*m*, 1 H, $J_{1'',2''b}$ 6.6 Hz, $J_{1'',2''a}$ 4.5 Hz, $J_{1'',2'}$ 2 Hz,

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$J_{1'',4'}$ 1.7 Hz, H-1''), 4.92 (*bm*, 1 H, H-4'), 4.58 (*m*, 1 H, $J_{2',4'} \sim J_{2',2''a} \sim J_{2',2''b} \sim 2$ Hz, H-2'), 4.28 (*ddd*, 1 H, $J_{2''a,2''b}$ 13.2 Hz, Hb-2''), 4.17 (*ddd*, 1 H, Ha-2''), 3.92 (*dd*, 1 H, $J_{5'a,5'b}$ 11.1 Hz, $J_{4',5'b}$ 2.7 Hz, Hb-5'), 3.73 (*dd*, 1 H, $J_{4',5'a}$ 1.7 Hz, Ha-5'), 2.18 (*bs*, 1 H, OH), 0.90 and 0.87 (2 *s*, 18 H, $CMe_3$), 0.08, 0.06, 0.02, and -0.08 (4 *s*, 12 H, $SiMe_2$). Electrospray-MS: *m/z* (%) 557 (100, [M + acetone + H]$^+$), 499 (48, [M + H]$^+$), and 521 (39, [M + Na]$^+$).

*Anal.* Calcd for $C_{23}H_{42}N_2O_6Si_2$ (498.97): C, 55.39; H, 8.49; N, 5.62. Found: C, 55.28; H, 8.62; N, 5.41.

**(3''*S*)-1-[2',5'-Bis(*O*-tert-butyldimethylsilyl)-3'-deoxy-β-D-ribofuranosyl]uracil-3'-spiro-2''-(3''-hydroxymethyloxirane) (20).** Compound **19** (1.25 g, 2.5 mmol) was dissolved in dry $CH_2Cl_2$ (50 mL) and cooled to 0 °C. MCPBA (Fluka, 70%, 1.12 g, 4.5 mmol) was added with stirring, and the mixture was allowed to warm slowly to room temperature. After 15 h, the mixture was diluted with EtOAc (150 mL), and washed with 0.2 M $Na_2SO_4$ (50 mL), saturated aqueous $NaHCO_3$ (25 mL), water (25 mL), and saturated aqueous NaCl (25 mL) successively. The organic layer was dried ($Na_2SO_4$), and filtered. Evaporation of the solvents followed by recrystallization from EtOAc/hexane gave **20** (1.15 g, 89%): mp 183.2-184.0 °C; $R_F$ 0.42 (2:3 hexane/EtOAc); $[\alpha]_D^{23}$ +63.8° (*c* 1.0, $CHCl_3$); $\nu_{max}^{KBr}$ 3491 and 3202 (OH, NH), 2954, 2921, and 2858 (CH), 1204 (C=O), 1464, 1252, 1111, and 837 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ 9.39 (*bs*, 1 H, NH), 7.87 (*d*, 1 H, $J_{5,6}$ 8.1 Hz, H-6), 6.14 (*d*, 1 H, $J_{1',2'}$ 7.9 Hz, H-1'), 5.77 (*d*, 1 H, $J_{3NH,5}$ 1 Hz, H-5), 4.43 (*d*, 1 H, H-2'), 4.22 (*t*, 1 H, $J_{4',5'a}$ 1.8 Hz, $J_{4',5'b}$ 1.8 Hz, H-4'), 4.07 (*dd*, 1 H, $J_{gem}$ 13 Hz, $J_{Hb,3''}$ 3 Hz, $CH_aH_bOH$), 3.88 (*dd*, 1 H, $J_{5'a,5'b}$ 11.4 Hz, Hb-5'), 3.80 (*dd*, 1 H, Ha-5'), 3.76 (*dd*, 1 H, $J_{Ha,3''}$ 3.5 Hz, $CH_aH_bOH$), 3.17 (*t*, 1 H, H-3''), 2.46 (*s*, 1 H, $CH_2OH$), 0.95 and 0.83 (2 *s*, 18 H, $CMe_3$), 0.14, -0.03, and -0.12 (3 *s*, 12 H, $SiMe_2$). Electrospray-MS: *m/z* (%) 515 (100, [M + H]$^+$), and 537 (10, [M + Na]$^+$).

*Anal.* Calcd for $C_{23}H_{42}N_2O_7Si_2$ (514.77): C, 53.67; H, 8.22; N, 5.44. Found: C, 53.41; H, 8.23; N, 5.38.

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