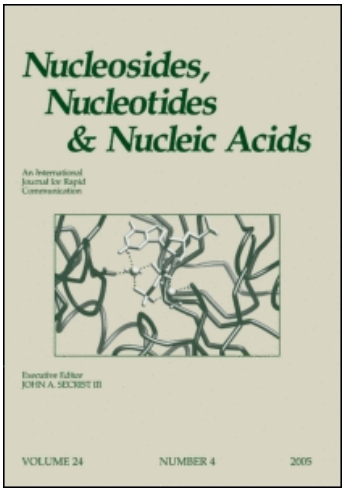



**Nucleosides, Nucleotides and Nucleic Acids**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

# Synthesis and Conformational Analysis of A Novel Type of Spin Labelled Bicyclonucleoside Based on A Tetrahydrofurano[2,3-c]Pyrrolidine Sugar Skeleton

Jean M. J. Tronchet[a]; Laetitia Brenas[a]; Françoise Barbalat-Rey[a]; Martina Zsély[a]; Michel Geoffrey[b]
[a] Departments of Organic Pharmaceutical Chemistry, University of Geneva, Geneva 4, Switzerland [b] Departments of Physical Chemistry, University of Geneva, Geneva 4, Switzerland

**To cite this Article** Tronchet, Jean M. J. , Brenas, Laetitia , Barbalat-Rey, Françoise , Zsély, Martina and Geoffrey, Michel(1998) 'Synthesis and Conformational Analysis of A Novel Type of Spin Labelled Bicyclonucleoside Based on A Tetrahydrofurano[2,3-c]Pyrrolidine Sugar Skeleton', Nucleosides, Nucleotides and Nucleic Acids, 17: 6, 1019 — 1031
**To link to this Article: DOI:** 10.1080/07328319808004218
**URL:** http://dx.doi.org/10.1080/07328319808004218

NUCLEOSIDES & NUCLEOTIDES, 17(6), 1019-1031 (1998)

# SYNTHESIS AND CONFORMATIONAL ANALYSIS OF A NOVEL TYPE OF SPIN LABELLED BICYCLONUCLEOSIDE BASED ON A TETRAHYDROFURANO[2,3-c]PYRROLIDINE SUGAR SKELETON

Jean M. J. Tronchet,*[1] Laetitia Brenas,[1] Françoise Barbalat-Rey,[1] Martina Zsély,[1] and Michel Geoffroy[2]

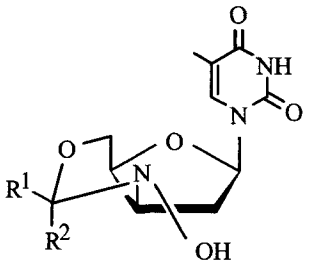
Departments of Organic Pharmaceutical Chemistry[1] and Physical Chemistry,[2] University of Geneva, Sciences II, CH-1211 Geneva 4, Switzerland

Abstract: Bicyclonucleosides bearing a 5-deoxy-5-*N*-hydroxyamino-3,$N^5$-(1,1-ethano)-β-D-furanosyl sugar moiety (**15-18**) have been prepared by glycosidation of the corresponding bicyclosugars obtained *via* an intramolecular *reverse* Cope elimination. The configuration of the asymmetric carbon of the 1,1-ethano bridge is the most important factor directing the conformation of the *N*-hydroxypyrrolidine ring and its invertomers ratio as shown by variable temperature H NMR experiments.



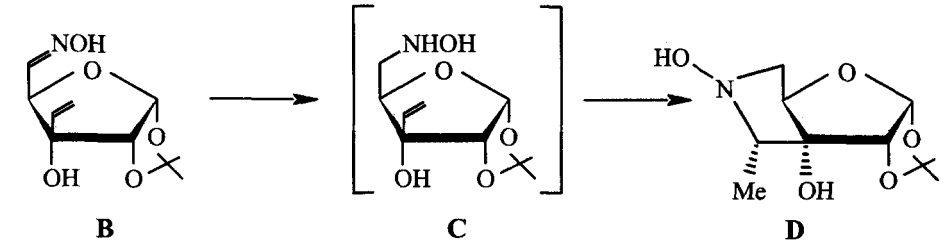
## INTRODUCTION

Some bicyclonucleosides of type **A** (tetrahydrofurano[3,2-d]perhydro-1,3-oxazine based sugar moiety) have been found active against HIV[1] or VZV.[2] On the other hand, we described a new synthetic pathway toward another type of bicyclosugars[3] *via* a *reverse* Cope elimination for which a one step slightly dissymmetric reaction mechanism was established from ab initio quantum mechanics.[4]




**A**

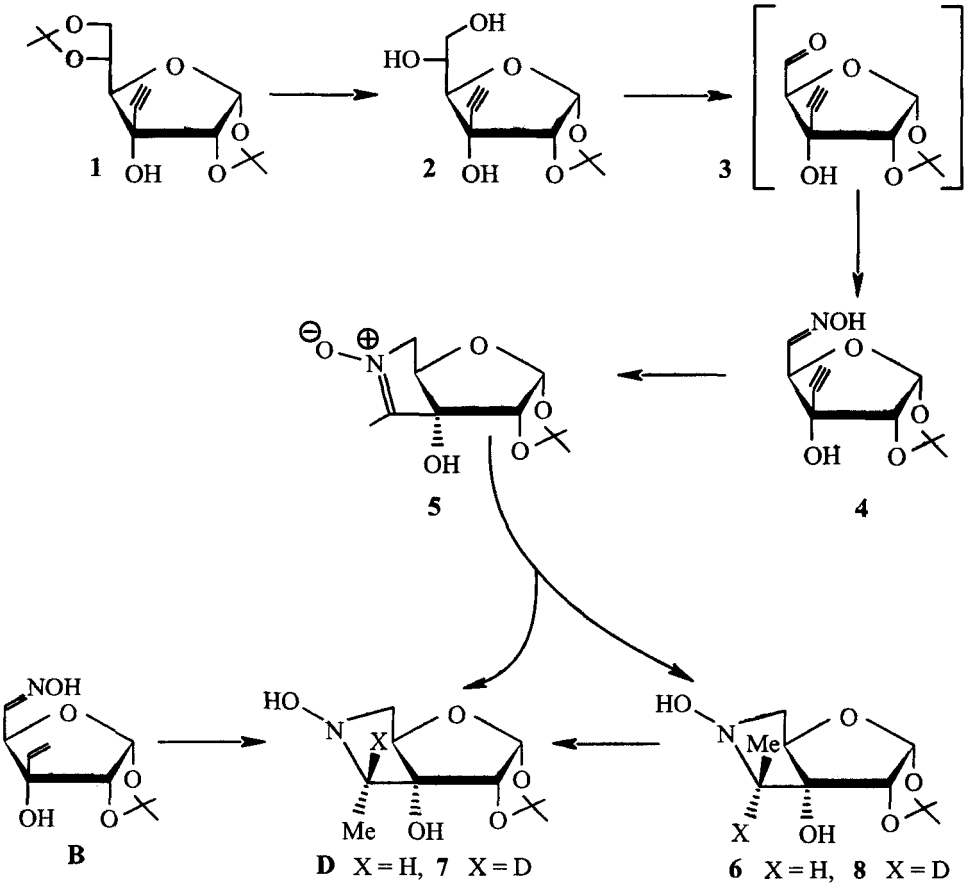
The previously described intramolecular *reverse* Cope elimination of 5-deoxy-3-*C*-ethenyl-5-(*N*-hydroxyamino)-1,2-*O*-isopropylidene-α-D-ribofuranose **C** (obtained by reduction of **B**) proceeded stereospecifically affording the (*3'S*) epimer **D** of the bicyclosugar derivative. In order to obtain both epimers, we applied the same type of reaction to the 3-*C*-ethynyl analogue of **B**. The epimeric pair obtained from the reduction of the intermediate cyclic nitrone was glycosylated to the corresponding uracil and thymine nucleosides, spectroscopic properties of which were investigated.




B C D

## RESULTS AND DISCUSSION

The acetylenic sugar derivative **1**[5] was mono-de-*O*-isopropylidenated to **2** (93%) which upon treatment with lead tetraacetate afforded **3** which was not fully characterized



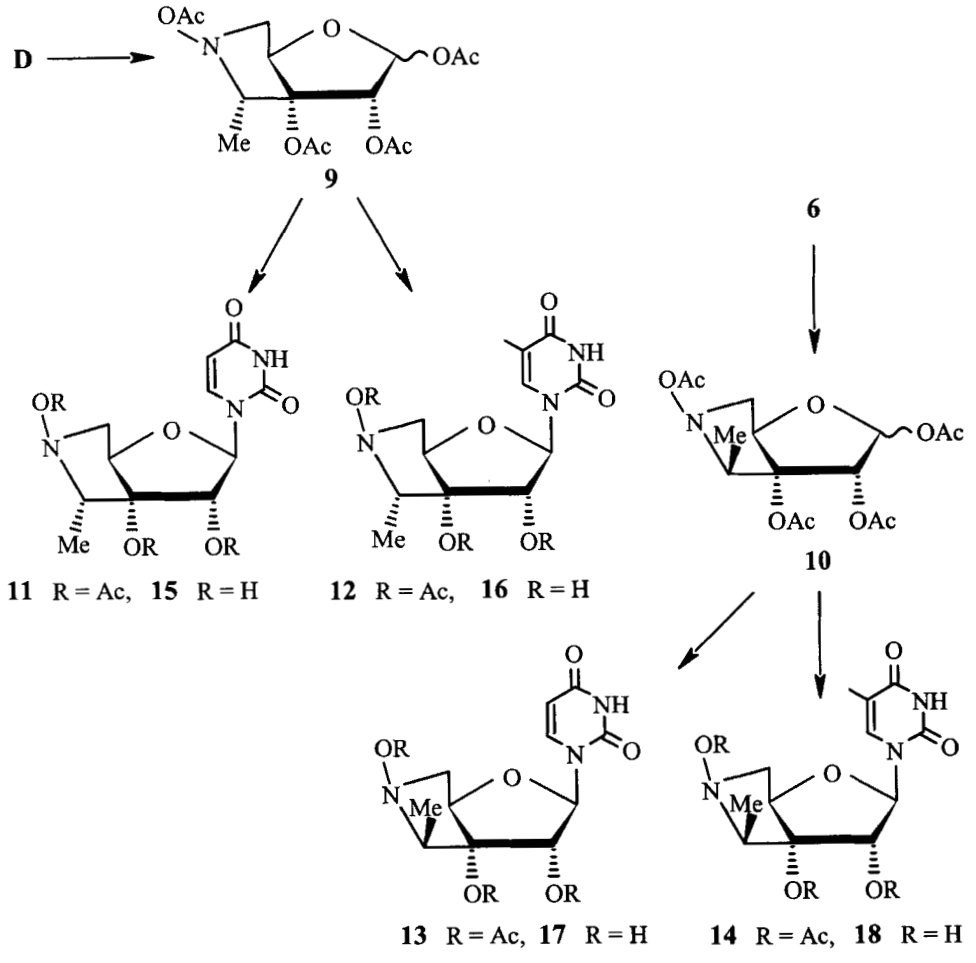

but directly converted to the oxime **4** (as a *ca* 7:2 *E*/*Z* mixture in chloroform) obtained in 69% yield from **2**. Upon reduction ($NaBH_3CN$, pH 2-3), **4** led to the corresponding hydroxylamine which upon heating at 60 °C for 2 hours underwent a *reverse* Cope

elimination to the cyclic nitrone **5** (50%) yield). The structure of **5** was established by IR [intense peak at 1606 $cm^{-1}$ ($\nu_{C=N}$)] and H NMR [a methyl peak at δ 2.11 long-range coupled to $H_2$-5 and a large (14.75 Hz) geminal coupling constant for $H_2$-5]. Sodium borohydride reduction of **5** proceeded almost quantitatively affording a 1:1 mixture of **D** and **6**. To check that the reduction proceeded at the same rate from each of the two diastereotopic faces of **5** and that the obtention of a 1:1 epimeric mixture was not the result of a double bond migration from C-3'-N to N-C-5 preceding the reduction, the same reaction was performed using sodium borodeuteride. A 1:1 mixture of **7** and **8** was obtained confirming the somewhat unexpected similar reactivity of the *endo* and *exo* faces of the bicyclic nitrone. The configuration of the novel epimer **6** could be inferred from the known *(3'S)* configuration of **D**. It was nevertheless confirmed by NOE experiments, in particular reciprocal signal enhancements upon irradiation of H-2 and $CH_3$-3' on one hand an H-1 and $CH_3$-3' on the other hand. One of the most salient differences, in the H NMR spectra of **D** and **6** resides in the relative chemical shifts of the diastereotopic $H_2$-5 protons, the more shielded being the *pro-S* ($H_{exo}$-5) in **D** and the *pro-R* in **6**. This shielding is due to an almost antiparallel nitrogen lone pair[6] in the more stable invertomer in each case (see below) and reflects the conformational change induced by the configurational inversion at C-3'.



Upon acid hydrolysis followed by acetylation, **D** afforded **9** in 74% yield as a *ca.* 2:1 β/α mixture whereas in the same conditions **6** was converted into a 3:1 α/β mixture of **10** (64%). Glycosylation of **9** with uracil in the presence of hexamethyldisilazane[7] led to **11** in 40% yield. Using thymine instead of uracil afforded **12** (60% yield). From **10**, **13** (44%) and **14** (50%) were obtained. Deacetylation of compounds **11-14** led in good yields to the corresponding nucleoside analogues **15-18**.

H NMR data concerning the core protons of bicyclosugars are collected in TABLE 1, whereas the corresponding data relative to bicyclonucleosides are found in TABLE 2. For each compound a spectrum was recorded at room temperature or, when badly resolved at that temperature, the temperature was increased to 50-80 °C. As shown by the $^3J_{4,5}$ ($^3J_{4',5'}$ for nucleosides) values, the conformation of the pyrrolidine ring depends almost exclusively on the configuration of the carbon atom bearing the methyl group: *N-endo* for a *R* configuration, *N-exo* in the opposite case. This corresponds to an essentially equatorial[8] disposition of the methyl group. At room or higher temperatures, the compound consists in a mixture of rapidly interconverting invertomers, the more abundant bearing an equatorial OR group [(*NR*) for (3'*R*) bicyclosugars and (3''*R*) bicyclonucleosides, (*NS*) for (3'*S*) bicyclosugars and (3''*S*) bicyclonucleosides]. From this, it follows that in the more abundant invertomer, an axial lone pair on nitrogen shields the antiperiplanar protons: $H_{exo}$-5$^{(')}$ and H-3'$^{(')}$ for (3'$^{(')}$*R*) compounds, $H_{endo}$-5$^{(')}$ and H-3'$^{(')}$ for (3'$^{(')}$*S*) compounds. On the other hand, an axial nitrogen lone pair decreases the






absolute value of the geminal coupling constant of the neighbour methylene group.[9] The experimental time-averaged value of $^2J_{5exo,5endo}$, comprised between 10 Hz (an axial lone pair) and 15 Hz (no axial lone pair) is an indicator of the invertomers ratio. A direct observation of each invertomer has been performed in selected cases by variable temperature H NMR. The influence of an axial lone pair on both $^2J_{5exo,5endo}$ and δ H-5 (*exo* and *endo*) is clearly apparent from TABLES 1 and 2.

Invertomers ratios and free energies of activation of the nitrogen inversion, estimated using the Gutowsky's approximation,[10] are collected in TABLE 3.

Upon UV irradiation of solutions of these novel *N*-hydroxypyrrolidine derivatives, small stationary concentrations of the corresponding *N*-oxyl free radicals are obtained. Representative examples of these aminoxyls - identified by the same number as the parent molecule but primed - have been studied by EPR spectroscopy (TABLE 4). In pyrrolidine

TABLE 1. Selected H NMR data ($CDCl_3$, 200 MHz, δ in ppm, J in Hz) of bicyclosugar derivatives.

| | | Chemical shifts | | | | | | Coupling constants | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cmpd | Temp | H-1 | H-2 | H-4 | $H_{exo\text{-}5}$ | $H_{endo\text{-}5}$ | H-3' | $J_{1,2}$ | $J_{4,5exo}$ | $J_{4,5endo}$ | $J_{5exo,5endo}$ |
| **5**[a] | 25 °C | 5.92 | 4.50 | 4.49 | 4.45 | 3.98 | , | 4.0 | 4.5 | 0 | 14.75 |
| **D** | 25 °C | 5.94 | 4.26 | 4.34 | 3.80 | 2.94 | 2.77 | 4.0 | 6.0 | 2.5 | 12.2 |
| ***(NS)*-D** | -40 °C | 5.96 | 4.32 | 4.32 | 3.80 | 2.92 | 2.79 | 4.0 | 6.0 | 1.5 | 12.0 |
| ***(NR)*-D** | -40 °C | 5.87 | 4.32 | 4.82 | 3.71 | 3.20 | 2.77 | 4.0 | 6.0 | 2.0 | 15.0 |
| **6** | 55 °C | 5.80 | 4.48 | 4.40 | 2.97 | 3.35 | 3.00 | 3.8 | 4.8 | 0 | 11.0 |
| ***(NR)*-6** | -40 °C | 5.78 | 4.48 | 4.38 | 2.93 | 3.39 | 2.97 | 3.8 | 4.0 | 0 | 10.5 |
| ***(NS)*-6** | -40 °C | 6.03 | 4.73 | 4.66 | 3.33 | ~3.40 | 3.21 | 4.0 | 4.0 | 0 | 14.0 |
| **β-9** | 25 °C | 6.29 | 5.48 | 5.10 | 3.89 | 3.10 | 3.80 | 1.0 | 7.3 | 5.0 | 12.5 |
| **α-10** | 55 °C | 6.39 | 5.42 | 5.11 | 3.35 | 3.66 | 3.79 | 4.0 | 5.5 | 0 | 11.3 |
| ***(NR)*-α-10** | -40 °C | 6.33 | 5.30 | 5.10 | 3.27 | 3.70 | 3.78 | 4.0 | 6.0 | 0.5 | 10.5 |
| ***(NS)*-α-10** | -40 °C | 6.42 | 5.61 | 5.24 | 3.87 | 3.57 | 4.00 | 4.0 | 5.0 | 0 | 15.5 |
| **β-10** | 25 °C | 6.16 | 5.62 | 4.95 | 3.13 | 3.67 | 3.41 | 2.0 | 5.5 | 1.0 | 11.0 |

[a] $J_{Me\text{-}3',5exo}$ 2.5; $J_{Me\text{-}3',5endo}$ 1.0.



*N*-oxyls, the nitrogen atom is planar, or very nearly so, as shown by both experimental measurements and quantum mechanical computations.[11] From data collected in TABLE 4, it appears that, contrarily to what was observed for the H NMR spectra, the C-3'() configuration is not the only, or even major factor directing the conformation of the pyrrolidine ring as shown by the notable differences between the spectra of the bicyclosugar derivatives on one hand, and those of the bicyclonucleosides on the other hand. For bicyclosugar derivatives, the deuterium labelling allows the unambiguous assignment of the $a_{H\text{-}3'}$ hyperfine coupling constant. For **D'**, $a_{H\text{-}3'}$ corresponds to the largest (23.5 G) $a_H^\beta$ value. From the classical relationship[12] between $a_H^\beta$ and the dihedral angle between the H-C bond and the axis of the p orbital of nitrogen, it appears that the pyrrolidine ring of **D'** adopts a C-3' *endo* conformation. A $^4E$ conformation of the pyrrolidine ring of **6'** would be in accordance with the EPR data. For both **D'** and **6'**, a $^3T_2$ conformation of the furanose ring is the most compatible with the conformation of the pyrrolidine *N*-oxyl ring. (3"*S*)-Bicyclonucleosides **15'** and **16'** adopt a planar conformation of the pyrrolidine ring and their (3"*R*) epimers a 3"*exo* conformation.

TABLE 2. Selected H NMR data (δ in ppm, J in Hz) of bicyclonucleosides and their peracetylated derivatives.

| Cmpd | Temp | H-1' | H-2' | H-4' | $H_{exo\text{-}5'}$ | $H_{endo\text{-}5'}$ | H-3'' | $J_{1',2'}$ | $J_{4',5'exo}$ | $J_{4',5'endo}$ | $J_{5'exo,5'endo}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **11**[a] | 60 °C | 6.45 | 5.45 | 4.94 | 3.45 | 3.38 | 4.15 | 6.5 | 5.5 | 2.5 | 11.0 |
| ***(NS)*-11**[b] | -60 °C | 6.62 | 5.10 | 5.09 | 3.40 | 3.30 | 4.28 | 6.0 | 4.5 | 1.0 | 10.0 |
| ***(NR)*-11**[b] | -60 °C | 6.62 | 5.33 | 5.18 | 3.79 | 3.16? | 3.92 | 6.0 | 6.0 | | 11.5[c] |
| **11**[b] | 60 °C | 6.53 | 5.41 | 5.09 | 3.55 | 3.31 | 4.18 | 6.8 | 6.0 | 2.0 | 11.0 |
| **12**[a] | 60 °C | 6.42 | 5.48 | 4.93 | 3.42[d] | 3.42[d] | 4.20 | 7.0 | 3.5[d] | 3.5[d] | ?[d] |
| **13**[a] | 60 °C | 6.48 | 5.39 | 4.97 | 2.99 | 3.70 | 3.29 | 6.5 | 5.5 | 0 | 10.5 |
| ***(NR)*-13**[a] | -50 °C | 6.48 | 5.29 | 4.95 | 2.90 | 3.69 | 3.21 | 6.0 | 5.5 | 0 | 10.0 |
| ***(NS)*-13**[a] | -50 °C | 6.54 | 5.49 | 5.23 | *3.6 to 3.8* | | | ? | ? | ? | ? |
| **14**[a] | 60 °C | 6.48 | 5.40 | 4.97 | 2.98 | 3.70 | 3.29 | 6.5 | 5.5 | 0 | 10.5 |
| **15**[e] | 80 °C | 5.79 | 4.02 | 4.11 | 3.37 | 2.76 | 2.98 | 7.7 | 6.5 | 4.5 | 10.5 |
| **16**[e] | 80 °C | 5.85 | 4.07 | 4.10 | 3.48 | 2.82 | 3.02 | 8.0 | 6.5 | 4.5 | 10.5 |
| **17**[e] | 80 °C | 5.71 | 3.89 | 4.18 | 2.72 | 3.18 | 2.51 | 8.2 | 6.5 | 0 | 11.2 |
| **18**[e] | 80 °C | 5.79 | 3.93 | 4.19 | 2.77 | 3.20 | 2.53 | 8.0 | 6.5 | 0 | 11.0 |

[a] In $CDCl_3$. [b] In acetone-$d_6$. [c] Obtained at -40 °C, signal hidden at -60 °C.
[d] Isochronous 5' protons. [e] In DMSO-$d_6$.

TABLE 3. Equilibrium and kinetic data relative to nitrogen inversion ($CDCl_3$ solutions).

| Cmpd | **D** | **6** | **α-10** | **11**[a] | **13** |
|---|---|---|---|---|---|
| *NS/NR* (T) | 2.5 (233) | 0.15 (233) | 0.33 (233) | 3 (213) | 0.1 (233) |
| $\Delta G^{\ddagger}$/kJ.mol$^{-1}$ (T) | 56.5 (263) | 56.2 (273) | 54.8 (263) | 57.7 (283 | 60.7 (293) |

[a] In acetone-$d_6$.

Bicyclonucleosides **17** and **18** exhibited no antiviral activity against HIV-1, HIV-2, HSV-1, HSV-2, HCMV, and VZV. This lack of activity was expected from compounds bearing hydroxy groups at the 2' and 3' position. We are preparing their 2',3'-dideoxy analogues which are more promising.

TABLE 4. EPR data (hyperfine coupling constants in G) of aminoxyl radicals obtained upon UV irradiation of solutions of *N*-hydroxypyrrolidine derivatives.

| Cmpd | Temp | Solvent | g | $a_N$ | $a_D$ | $a_H^\beta$ | | | $a_H^\gamma$ | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **D'** | 60 °C | diglyme | 2.0063 | 14.4 | | 15.4 | 20.9 | 23.5 | 0.6 | 0.6 | 0.6 | |
| **7'** | 90 °C | diglyme | 2.0061 | 14.4 | 3.55 | 15.4 | 21.0 | | 0.5 | 0.5 | 0.5 | |
| **6'** | 80 °C | diglyme | 2.0059 | 14.4 | | 14.4 | 17.7 | 23.0 | 0.5 | 0.5 | 0.5 | 0.5 |
| **8'** | 90 °C | diglyme | 2.0057 | 14.4 | 2.7 | 14.4 | 22.8 | | 0.5 | 0.5 | 0.5 | 0.5 |
| **15'** | 140 °C | DMSO | 2.0060 | 15.0 | | 18.0 | 19.8 | 19.8 | 0.45 | 0.45 | 0.45 | 0.45 |
| **16'** | 80 °C | DMSO | 2.0061 | 14.7 | | 19.0 | 19.5 | 19.7 | 0.45 | 0.45 | 0.45 | 0.45 |
| **17'** | 50 °C | DMSO | | 14.5 | | ~16.5 | ~21.0 | ~24.8 | 0.4 | 0.4 | 0.4 | |
| **18'** | 120 °C | DMSO | 2.0060 | 15.2 | | 16.0 | 21.0 | 24.5 | 0.45 | 0.45 | 0.45 | 0.45 |



## EXPERIMENTAL

**General Methods.**[13] Antiviral assays have been performed using standard or already described procedures.[14]

**3-*C*-Ethynyl-1,2-*O*-isopropylidene-α-D-allo-1,4-furanose (2).** A solution of **1** (0.3 g, 1.05 mmol) in 80% AcOH (4.4 mL) is kept at 50 °C for 2 h, concentrated and the remaining solvent coevaporated with toluene (3x10 mL). Silica gel column chromatography (9:1 $CHCl_3$/MeOH) followed by crystallization (ether) afforded **2** (0.24 g, 93%). Mp 160-163 °C; $R_F$ 0.29 (9:1 $CHCl_3$/MeOH); $[\alpha]_D^{21}$ +47.1° (*c* 0.9, MeOH); IR (KBr) 3451 (OH), 2114 $cm^{-1}$ (C≡C). H NMR ($CDCl_3$): δ 1.39 and 1.61 (2 *s*, 2x3 H, $CMe_2$), 2.10, 2.65, and 3.47 (3 *bs*, 3x1 H, OH), 2.70 (*s*, 1 H, HC≡C), 3.78 (*dd*, 1 H, $J_{5,6a}$ 5.0 $J_{6a,6b}$ 11.5 Hz, Ha-6), 3.90 (*d*, 1 H, $J_{4,5}$ 8.5 Hz, H-4), 4.01 (*dd*, 1 H, $J_{5,6b}$ 3.5 Hz, Hb-6), 4.15 (*ddd*, 1 H, H-5), 4.62 (*d*, 1 H, $J_{1,2}$ 4 Hz, H-2), and 5.87 (*d*, 1 H, H-1). EIMS: *m/z* (%) 229 (2, $M^{+}$ - Me), 183 (5), 149 (8), 128 (1), 109 (10), 97 (55), 85 (2), 71 (9), 59 (100), and 51 (13).

*Anal. Calcd* for $C_{11}H_{16}O_6$ (244.25): C, 54.09; H, 6.60. Found: C, 54.01; H, 6.62.

**5-Deoxy-3-*C*-ethynyl-5-(*N*-hydroxyimino)-1,2-*O*-isopropylidene-α-D-ribofuranose (4).** To a solution of **2** (360 mg, 1.47 mmol) in toluene (10 mL), lead tetraacetate (780 mg, 1.76 mmol) was added. After 30 min stirring at 25 °C, 0.5 mL ethane-1,2-diol was added and the mixture stirred for 15 min was filtered (Celite), concentrated, then submitted to a silica gel column chromatography (9:1 $CH_2Cl_2$/MeOH) to afford 263 mg (84%) of **3** [H NMR δ 9.73 (*d*, 1 H, $J_{5,4}$ 1.5 Hz, H-5)] which was not

further characterized but directly used for the next step. To a solution of **3** (263 mg, 1.24 mmol) in a mixture of methanol (8 mL) and pyridine (0.21 mL) hydroxylamine hydrochloride (102 mg, 1.47 mmol) was added and the solution stirred for 14 h at 25 °C, concentrated and the solvent removed by codistillation with toluene (2x10 mL). The residue was dissolved in AcOEt (20 mL), washed ($H_2O$, 10 mL), concentrated, then submitted to a silica gel column chromatography (9:1 $CH_2Cl_2$/MeOH) to give **4** (192 mg, 69% from **2**). Mp 138.0-140.0 °C; $R_F$ 0.27 (9:1 $CH_2Cl_2$/MeOH); $[\alpha]_D^{23}$ -40° (*c* 1.0, MeOH); IR (KBr) 3474, 3292 (OH), and 2128 $cm^{-1}$ (C≡C). H NMR ($CDCl_3$): *E* isomer (75%): δ 1.40 and 1.61 (2 *s*, 2x3 H, $CMe_2$), 2.69 (*s*, 1 H, HC≡C), *ca* 3.65 (*bs*, 1 H, HO-3), 4.41 (*d*, 1 H, $J_{4,5}$ 7 Hz, H-4), 4.61 (*d*, 1 H, $J_{1,2}$ 3.5 Hz, H-2), 5.94 (*d*, 1 H, H-1), 7.55 (*d*, 1 H, H-5), *ca.* 8.60 (*bs*, 1 H, HO-N). *Z* isomer (25%): δ 1.40 and 1.63 (2 *s*, 2x3 H, $CMe_2$), 2.61 (*s*, 1 H, HC≡C), 3.65 (*bs*, 1 H, HO-3), 4.66 (*d*, 1 H, $J_{1,2}$ 3.5 Hz, H-2), 5.23 (*d*, 1 H, $J_{4,5}$ 4.0 Hz, H-4), 5.92 (*d*, 1 H, H-1), 6.93 (*d*, 1 H, H-5), and 7.97 (*bs*, 1 H, HO-N). EIMS: *m/z* (%) 228 (17, M + 1), 212 (5, $M^{\cdot+}$ - Me), 183 (4), 170 (17), 111 (20), 96 (27), 86 (50), 80 (18), 59 (100), and 53 (18).

*Anal. Calcd* for $C_{10}H_{13}NO_5$ (227.22): C, 52.86; H, 5.77; N, 6.16. Found: C, 53.02; H, 5.96; N, 6.10.

**5-Amino-5-deoxy-1,2-*O*-isopropylidene-3',$N^5$-didehydro-3,$N^5$-(1,1-ethano)-α-D-ribofuranose *N*-oxide (5).** To a solution of **4** (260 mg, 1.14 mmol) in methanol (33 mL), sodium cyanoborohydride (0.77 g, 12.5 mmol) was added in small fractions over 5 min. In the same time, methanolic 3 M HCl was added dropwise to keep the pH between 2 and 3. When the pH remained at 2-3 without addition of hydrochloric acid, the reaction was completed. After neutralization, the reaction mixture was concentrated, then rapidly passed over a silica gel column (elution 9:1 $CHCl_3$/MeOH) concentrated, dissolved in toluene (20 mL) and kept at 60 °C for 2 h. A column chromatographic separation (silica gel, 19:1 AcOEt/MeOH) afforded **5** (131 mg, 50%). Mp >300 °C; $R_F$ 0.45 (9:1 $CHCl_3$/MeOH); $[\alpha]_D^{21}$ +56° (*c* 0.6, MeOH); UV (MeOH) 233.5 nm (ε 9640). IR (KBr) 1606 $cm^{-1}$ (C=N). H NMR ($CDCl_3$) see TABLE 1 and δ 1.45 and 1.62 (2 *s*, 2x3 H, $CMe_2$), 2.11 (*dd*, 3 H, $J_{Me,5exo}$ 2.5 Hz, $J_{Me,5endo}$ 1.0, Me-3'), and 2.45 (*bs*, 1 H, HO-3). EIMS: *m/z* (%) 229 (4, $M^{\cdot+}$), 214 (2, $M^{\cdot+}$ - Me), 171 (11), 155 (0.2), 113 (100), 96 (15), 85 (10), 59 (19), and 55 (80).

*Anal. Calcd* for $C_{10}H_{15}NO_5$ (229.23): C, 52.40; H, 6.60; N, 6.11. Found: C, 52.20; H, 6.61; N, 6.12.

**(*3'S*)-5-Deoxy-5-(*N*-hydroxyamino)-1,2-*O*-isopropylidene-3,$N^5$-(1,1-ethano)-α-D-ribofuranose (D).** To a solution of **5** (100 mg, 0.436 mmol) in methanol (5 mL) sodium borohydride (50 mg, 1.33 mmol) was added and the solution stirred for 30 min at 25 °C. The reaction mixture, concentrated, was submitted to silica gel column

chromatography (7:3:0.3 ethyl ether/petroleum ether/methanol) to afford **D** (43.3 mg, 43%) and **6** (43 mg, 43%). Mp 96.0-98.0 °C; $R_F$ 0.16 (7:3:0.3 ethyl ether/petroleum ether/MeOH); $[\alpha]_D^{20}$ +78° (*c* 0.7, $CHCl_3$). H NMR.[3] EIMS: *m/z* (%) 232 (4, M + 1), 216 (5.5, $M^{\cdot+}$ - Me), 198 (0.4), 173 (6), 156 (7), 102 (20), 97 (20), 73 (22), 60 (60), and 56 (100).

*Anal. Calcd* for $C_{10}H_{17}NO_5$ (231.25): C, 51.94; H, 7.41; N, 6.06. Found: C, 51.70; H, 7.35; N, 6.07.

**(*3'R*)-5-Deoxy-5-(*N*-hydroxyamino)-1,2-*O*-isopropylidene-3,$N^5$-(1,1-ethano)-α-D-ribofuranose (6).** Prepared as described for **D**. Mp 109.0-111.0 °C; $R_F$ 0.35 (7:3:0.3 ethyl ether/petroleum ether/MeOH); $[\alpha]_D^{20}$ +29.9° (*c* 0.8, MeOH); IR (KBr) 3536, 3395, and 3250 $cm^{-1}$ (OH). H NMR ($CDCl_3$, 55 °C): cf TABLE 1, and δ 1.28 (*d*, 3 H, J 6.5 Hz, Me-3'), 1.41 and 1.60 (2 *s*, 2x3 H, $CMe_2$), 3.35 (*bs*, 1 H, HO-3), and 4.12 (*bs*, 1 H, HO-N). EIMS: *m/z* (%) 232 (7, M + 1), 216 (5, $M^{\cdot+}$ - Me), 186 (1), 173 (7.5), 156 (8), 102 (20), 97 (23), 73 (30), 60 (58), and 56 (100).

*Anal. Calcd* for $C_{10}H_{17}NO_5$ (231.35): C, 51.94; H, 7.41; N, 6.06. Found: C, 51.75; H, 7.38; N, 5.98.

**Deuterated derivatives 7 and 8.** Prepared as described for **D** and **6** substituting sodium borodeuteride to sodium borohydride, they showed the expected features in H NMR and EIMS spectra.

**(*3'S*)-5-(*N*-Acetoxyamino)-1,2,3-tri-*O*-acetyl-5-deoxy-3,$N^5$-(1,1-ethano)-(β + α)-D-ribofuranose (9).** A solution of **D** (100 mg, 0.432 mmol) in a 80% aqueous trifluroacetic acid solution (11 mL) was stirred 14 h at 25 °C, then concentrated and the last traces of solvent removed by codistillation with toluene (20 mL). To the residue dissolved in dichloromethane (7 mL), 4-dimethylaminopyridine (11 mg, 0.09 mmol), triethylamine (0.36 mL, 2.57 mmol), then after 5 min, acetic anhydride (0.2 mL, 2.16 mol) were added. After 4 h stirring at 25 °C, dichloromethane (15 mL) was added and the organic phase washed (2x15 mL $H_2O$, 2x15 mL saturated aqueous $NaHCO_3$ solution, then 10 mL $H_2O$), concentrated and submitted to a column chromatography (7:3:0.3 ethyl ether/petroleum ether/MeOH) affording **9** (115 mg, 74%) as a 2:1 β/α mixture from which β-9 was recrystallized (ethyl ether/petroleum ether). Mp 185-187 °C; $R_F$ 0.48 (7:3:0.3 ethyl ether/petroleum ether/MeOH); $[\alpha]_D^{23}$ -30.7° (*c* 1, MeOH). IR (KBr) 1749 $cm^{-1}$ (CO). H NMR ($CDCl_3$, 25 °C), see TABLE 1 and δ 1.28 (*d*, 3 H, J 6.5 Hz, Me-3'), 2.08, 2.09, 2.11, and 2.12 (4 *s*, 4x3 H, OAc). EIMS: *m/z* (%) 360 (0.6, M + 1), 317 (12), 300 ($M^{\cdot+}$ - OAc), 257 (100), 240 (22), 198 (32), 155 (47), 138 (31), 96 (49), 73 (58), and 56 (75).

*Anal. Calcd* for $C_{15}H_{21}NO_9$ (359.34): C, 50.14; H, 5.89; N, 3.90. Found: C, 50.07; H, 5.88; N, 3.96.

**(3'*R*)-5-(*N*-Acetoxyamino)-1,2,3-tri-*O*-acetyl-5-deoxy-3,$N^5$-(1,1-ethano)-(α + β)-D-ribofuranose (10).** Treated as described for the preparation of **9**, **6** (100 mg, 0.432 mmol) afforded **10** (99 mg, 64%) of a 3:1 mixture of α and β anomers. Syrup; $R_F$ 0.35 (α) and 0.38 (β) (7:3:0.3 ethyl ether/petroleum ether/MeOH); IR (film) 1755 $cm^{-1}$ (CO). An essentially pure sample of **α-10** was obtained by column chromatography (7:3:0.3 ethyl ether/petroleum ether/MeOH). H NMR ($CDCl_3$, 55 °C) of α anomer: see TABLE 1 and δ 1.25 (*d*, 3 H, J 6.5 Hz, Me-3'), 2.07, 2.09, 2.11, and 2.17 (4 *s*, 4x3 H, 4 OAc). H NMR ($CDCl_3$, 25 °C) of β anomer: see TABLE 1 and δ 1.46 (*d*, 3 H, J 6,5 Hz, Me-3'), 2.08, 2.10, 2.12, and 2.16 (4 *s*, 4x3 H, 4 OAc). EIMS: *m/z* (%) 360 (0.6, M + 1), 316 (0.3, $M^{\cdot+}$ - Ac), 300 (13.6, $M^{\cdot+}$ - OAc), 257 (11), 240 (100), 198 (54.5), 155 (60), 138 (44), 96 (68), 73 (56.5), and 56 (88).

*Anal. Calcd* for $C_{15}H_{21}NO_9$ (359.34): C, 50.14; H, 5.89; N, 3.90. Found: C, 50.23; H, 5.97; N, 3.89.

**(3"*S*)-5'-(*N*-Acetoxyamino)-2',3'-di-*O*-acetyl-5'-deoxy-3',$N^{5'}$-(1,1-ethano)-uridine (11).** A mixture of uracil (249 mg, 2.22 mmol), 1,1,1,3,3,3-hexamethyldisilazane (HDMS) (11 mL, 52.4 mmol) and ammonium sulfate (3 mg, 22.7 mmol) was treated under reflux for 14 h with exclusion of moisture. The excess of HMDS was removed by distillation under vacuum and to the residue, transferred under argon atmosphere, a solution of **9** (200 mg, 0.557 mmol) in dichloromethane (9 mL), then trimethylsilyl triflate (0.4 mL, 2.21 mmol) were added. After 6 h stirring at 25 °C, dichloromethane (20 mL) was added and the organic solution washed with an aqueous saturated solution of sodium hydrogenocarbonate (2x10 mL), dried ($Na_2SO_4$), then concentrated , was submitted to column chromatography (4:1 AcOEt/petroleum ether) affording **11** (91 mg, 40%). Mp 140-144 °C; $R_F$ 0.3 (4:1 AcOEt/petroleum ether); $[\alpha]_D^{25}$ -25.2° (*c* 0.9, MeOH). UV (MeOH) 244 (ε 8800) and 258 nm (ε 9320). IR (KBr) 1757 and 1696 $cm^{-1}$ (CO). H NMR ($CDCl_3$, 60 °C): see TABLE 2 and δ 1.17 (*d*, 3 H, J 6.5 Hz, Me-3"), 2.08 (*s*, 6 H, 2 OAc), 2.15 (*s*, 3 H, OAc), 5.88 (*dd*, 1 H, $J_{5,6}$ 8.0 Hz, $J_{3,5}$ 2.0 Hz, H-5), 7.88 (*d*, 1 H, H-6), and 7.90 (*bs*, 1 H, H-3). EIMS: *m/z* (%) 352 ($M^{\cdot+}$ - OAc), 291 (6), 250 (16), 240 (100, $M^{\cdot+}$ - AcOH - Base), 180 (20), 140 (42), 138 (62), 112 (16, B + H), 98 (38), and 55 (52).

*Anal. Calcd* for $C_{17}H_{21}N_3O_9$ (411.37): C, 49.64; H, 5.15; N, 10.21. Found: C, 49.25; H, 5.34; N, 9.71.

**1-[(3'*S*)-5-Acetoxyamino-2,3-di-*O*-acetyl-5-deoxy-3,$N^5$-(1,1-ethano)-β-D-ribofuranosyl]thymine (12).** Treatment of **9** (200 mg, 0.557 mmol) with thymine (278 mg, 2.21 mmol) as described for the preparation of **11** afforded **12** (142 mg, 60%). Mp 86-90 °C; $R_F$ 0.34 (4:1 AcOEt/petroleum ether); $[\alpha]_D^{25}$ -43.8° (*c* 1.1, AcOEt). UV (MeOH) 208.5 (ε 8680), and 265 nm (ε 8480). IR (KBr) 1756 and 1696 $cm^{-1}$ (CO). H NMR ($CDCl_3$, 60 °C): see TABLE 2 and δ 1.19 (*d*, 3 H, J 6,5 Hz, Me-3"), 2.01 (*bs*,

3 H, Me-5), 2.09, 2.10, and 2.16 (3 *s*, 3x3 H, 3 OAc), 7.61 (*bs*, 1 H, H-6), and 8.00 (*bs*, 1 H, H-3). EIMS: *m/z* (%) 366 (5, $M^{\cdot+}$ - OAc), 305 (3), 240 (100, $M^{\cdot+}$ - AcOH - Base), 198 (10), 138 (44), 60 (30), and 45 (42).

*Anal. Calcd* for $C_{18}H_{23}N_3O_9$ (425.40): C, 50.82; H, 5.45; N, 9.88. Found: C, 50.57; H, 5.53; N, 9.40.

**(3"*R*)-5'-(*N*-Acetoxyamino)-2',3'-di-*O*-acetyl-5'-deoxy-3',$N^{5'}$-(1,1-ethano)-uridine (13).** Treatment of **10** (200 mg, 0.557 mmol) with uracil (249 mg, 2.22 mmol) as described for the preparation of **11** afforded **13** (100.8 mg, 44%). Syrup, $R_F$ 0.35 (4:1 AcOEt/petroleum ether); $[\alpha]_D^{23}$ +1.7° (*c* 1.0, MeOH). UV (MeOH), 242 (ε 8740), and 255 nm (ε 9400). IR (film) 1769 and 1693 $cm^{-1}$ (CO). H NMR ($CDCl_3$, 60 °C): see TABLE 2 and δ 1.23 (*d*, 3 H, J 6.5 Hz, Me-3"), 2.09, 2.10, and 2.17 (3 *s*, 3x3 H 3 OAc), 5.86 (*dd*, 1 H, $J_{5,6}$ 8.0 Hz, $J_{3,5}$ 2.0 Hz, H-5), 7.73 (*bs*, 1 H, H-3), and 7.90 (*d*, 1 H, H-6). EIMS: *m/z* (%) 412 (9, M + 1), 369 (2, $M^{\cdot+}$ - $CH_2CO$), 352 (8, $M^{\cdot+}$ - OAc), 300 (6), 257 (8), 240 (18, $M^{\cdot+}$ - AcOH - Base), 198 (10), 138 (30), 73 (50), and 56 (100).

*Anal. Calcd* for $C_{17}H_{21}N_3O_9$ (411.37): C, 49.64; H, 5.15; N, 10.21. Found: C, 49.36; H, 5.21; N. 9.96.

**1-[(3'*R*)-5-(*N*-Acetoxyamino)-2,3-di-*O*-acetyl-5-deoxy-3,$N^5$-(1,1-ethano)-β-D-ribofuranosyl]thymine (14).** Treatment of **10** (200 mg, 0.557 mmol) with thymine (228 mg, 2.2 mmol) as described for the preparation of **11** afforded **14** (118 mg, 50%). Mp 240-245 °C (dec); $R_F$ 0.46 (4:1 AcOEt/petroleum ether); $[\alpha]_D^{27}$ -36.3° (*c* 1.0, pyridine). UV ($CH_2Cl_2$) 226 (ε 2620) and 263 nm (ε 6180). IR (KBr) 1766 and 1693 $cm^{-1}$ (CO). H NMR ($CDCl_3$, 60 °C): see TABLE 2 and δ 1.28 (*d*, 3 H, J 6.5 Hz, Me-3"), 2.05 (*bs*, 3 H, Me-5), 2.09, 2.10, and 2.19 (3 *s*, 3x3 H, 3 OAc), 7.66 (*bs*, 1 H, H-6), and 7.80 (*bs*, 1 H, H-3). EIMS: *m/z* (%) 383 (1.7, $M^{\cdot+}$ - Ac), 366 (15, $M^{\cdot+}$ - OAc), 300 (3.5, $M^{\cdot+}$ - Base), 257 (6), 240 (100, $M^{\cdot+}$ - AcOH - Base), 198 (17), 156 (13), 138 (51), 82 (18), and 56 (32).

*Anal. Calcd* for $C_{18}H_{23}N_3O_9$ (425.40): C, 50.82; H, 5.45; N, 9.88. Found: C, 49.93; H, 5.40; N, 9.53.

**(3"*S*)-5'-Deoxy-5'-(*N*-hydroxyamino)-3',$N^{5'}$-(1,1-ethano)uridine (15).** A solution of **11** (50 mg, 0.12 mmol) in a 8:1:1 methanol/$Et_3N$/$H_2O$ mixture (4 mL) was stirred at 25 °C for 14 h. The reaction mixture was concentrated, $H_2O$ (5 mL) added and the solvents removed by codistillation with toluene (10 mL). Silica gel column chromatography (4:1 $CH_2Cl_2$/MeOH) afforded **15** (28.4 mg, 83 %). Mp *ca* 200 °C dec; $R_F$ 0.44 (4:1 $CH_2Cl_2$/MeOH); $[\alpha]_D^{24}$ -30.0° (*c* 1.0, MeOH); UV (MeOH) 206 (ε 9600) and 260 nm (ε 9700): IR (KBr) 3450-3200 (OH) and 1691 $cm^{-1}$ (CO). H NMR (DMSO-$d_6$, 80 °C): see TABLE 2 and δ 1.01 (*d*, 3 H, J 6.5 Hz, Me-3"), 4.60 (*bs*, 1 H, OH), 5.67 (*d*, 1 H, $J_{5,6}$ 8.0 Hz, H-5), 7.61 (*d*, 1 H, H-6), 7.73 (*bs*, 1 H, HON), and 11.62 (*bs*, 1 H, H-

3). EIMS: *m/z* (%) 270 (1.6, $M^{\cdot+}$ - Me), 268 (72, $M^{\cdot+}$ - OH), 171 (5), 156 (18, $M^{\cdot+}$ - $H_2O$ - B), 113 (72, B + 2 H), 98 (69), 56 (100), and 53 (11).

*Anal. Calcd* for $C_{11}H_{15}N_3O_6$, 1.5$H_2O$ (285.26, 27): C, 42.31; H, 5.81; N, 13.46. Found: C, 42.56; H, 5.34; N, 13.45.

**1-[(3'*S*)-5-Deoxy-5-(*N*-hydroxyamino)-3,$N^5$-(1,1-ethano)-β-D-ribofuranosyl] thymine (16).** Upon de-*O*-acetylation following the procedure described for **15**, **12** (100 mg, 0.235 mmol) afforded **16** (55 mg, 78%). Mp 210-215 °C dec; $R_F$ 0.45 (4:1 $CH_2Cl_2$/MeOH); $[\alpha]_D^{23}$ -38.4° (*c* 1.0, MeOH). UV (MeOH) 208 (ε 8700), and 264 nm (ε 8900). IR (KBr) 3430-3000 (OH), and 1682 $cm^{-1}$ (CO). H NMR (DMSO-$d_6$, 80 °C): see TABLE 2 and δ 1.07 (*d*, 3 H, J 6.5 Hz, Me-3"), 1.90 (*bs*, 3 H, Me-5), 4.58 (*s*, 1 H, HO-3'), 5.42 (*d*, 1 H, $J_{2',OH}$ 6.0 Hz, HO-2'), 7.58 (*bs*, 1 H, H-6), 7.80 (*s*, 1 H, HON), 11.06 (*s*, 1 H, H-3), and also δ 3.20 (*d*, 1 H, J 5.0 Hz, MeOH), and 3.80 (*q*, 1/3 H, MeOH) corresponding to 1/3 mol crystallization MeOH. EIMS: *m/z* (%) 282 (100, $M^{\cdot+}$ - OH), 185 (7), 156 (22, $M^{\cdot+}$ - $H_2O$ - Base), 127 (57), and 56 (34).

*Anal. Calcd* for $C_{12}H_{17}N_3O_6$, 1/3 MeOH (299.29, 10.66): C, 47.79; H, 5.96; N, 13.56. Found: C, 47.44; H, 5.72; N, 13.76.

**(3"*R*)-5'-Deoxy-5'-(*N*-hydroxyamino-3',$N^{5'}$-(1,1-ethano)-uridine (17).** Deacetylation of **13** (50 mg, 0.121 mmol) as described for the preparation of **15** afforded **17** (27.6 mg, 80%). Mp 210 °C dec; $R_F$ 0.5 (4:1 $CH_2Cl_2$/MeOH); $[\alpha]_D^{24}$ +10.2° (*c* 0.95, MeOH). UV (MeOH) 204 (ε 8600) and 260 nm (ε 9110). IR (KBr) 3420-3200 (OH) and 1684 $cm^{-1}$ (CO). H NMR (DMSO-$d_6$, 80 °C): see TABLE 2 and δ 1.11 (*d*, 3 H, J 6.5 Hz, Me-3"), 5.10 (*s*, 1 H, HO-3'), 5.19 (*bd*, 1 H, $J_{2',OH}$ 7.0 Hz, HO-2'), 5.77 (*d*, 1 H, $J_{5,6}$ 8.0 Hz, H-5), 7.37 (*d*, 1 H, H-6), 7.71 (*s*, 1 H, HON), and *ca* 11 (*bs*, 1 H, H-3). EIMS: *m/z* (%) 268 (2, $M^{\cdot+}$ - OH), 249 (0.3), 113 (22, B + 2 H), 98 (20), 86 (15), 73 (24), and 56 (100).

*Anal. Calcd* for $C_{11}H_{15}N_3O_6$, $H_2O$ (285.26; 18): C, 44.90; H, 5.48; N, 14.28. Found: C, 45.04; H, 5.34; N, 14.12.

**1-[(3'*R*)-5-Deoxy-5-(*N*-hydroxyamino)-3,$N^5$-(1,1-ethano)-β-D-ribofuranosyl] thymine (18).** Deacetylation of **14** (100 mg, 0.235 mmol) following the procedure described for the preparation of **15** afforded **18** (65.4 mg, 93%). Mp 218.0-220.0 °C dec; $R_F$ 0.53 (4:1 $CH_2Cl_2$/MeOH); $[\alpha]_D^{22}$ -20.78° (*c* 0.987, MeOH). UV (MeOH) 207.7 (ε 9130) and 266 nm (ε 7910). IR (KBr) 3450-3000 (OH) and 1700 $cm^{-1}$ (CO). H NMR (DMSO-$d_6$, 80 °C): see TABLE 2 and δ 1.15 (*d*, 3 H, J 6.5 Hz, Me-3"), 1.83 (*bd*, 3 H, $J_{6,Me}$ 1.0 Hz, Me-5), 5.11 (*bs*, 2 H, HO-2' and HO-3'), 7.20 (*bq*, 1 H, H-6), 7.72 (*bs*, 1 H, HON), and 11.08 (*bs*, 1 H, H-3). EIMS: *m/z* (%) 299 (5, $M^{\cdot+}$), 282 (58, $M^{\cdot+}$ - OH), 185 (4), 156 (19), 127 (98, B + 2 H), 98 (32), and 56 (100).

*Anal. Calcd* for $C_{12}H_{17}N_3O_6$, 1/2 $H_2O$ (299.29; 9): C, 46.75; H, 5.89; N, 13.63. Found: C, 46.62; H, 5.98; N, 13.23.

ACKNOWLEDGEMENTS

The authors thank Dr H. Eder for the elemental analyses, Profs E. De Clercq and J. Balzarini (Rega Institute for Medical Research, Leuven, Belgium), Prof. M. Seman and Dr. P. Dilda (Mayoly-Spindler Laboratories, Chatou, France) for the antiviral assays, and Mr. J. Dirrig for his technical assistance. This work was supported by the Swiss National Research Foundation (grants # 3139-037156 and 20-43352.95).

REFERENCES

1. Tronchet, J. M. J.; Zsély, M.; Lassout, O.; Barbalat-Rey, F.; Komaromi, I.; Geoffroy, M. *J. Carbohydr. Chem.* **1995** *14*, 575-588; Tronchet, J. M. J.; Zsély, M.; Cápek, K.; Komaromi, I.; De Clercq, E.; Balzarini, J. *Nucleosides Nucleotides*, **1994** *13*, 1871-1889 and ref. cited.
2. Tronchet, J. M. J.; Zsély, M. unpublished results.
3. Tronchet, J. M. J.; Zsély, M.; Nadra Yazji, R.; Barbalat-Rey, F.; Geoffroy, M. *Carbohydr. Lett.*, **1995** *1*, 343-348.
4. Komaromi, I.; Tronchet, J. M. J. *J. Phys. Chem. A.*, **1997** *101*, 3554-3560.
5. Baker, D. C.; Brown, D. K.; Horton, D.; Nickol, R. G. *Carbohydr. Res.*, **1974** *32*, 299-319.
6. Lambert, J. B.; Keske, R. G. *J. Am. Chem. Soc.*, **1966** *88*, 620-622.
7. Wilson, L. J.; Hager, M. W.; El-Kattan, Y. A.; Liotta, D. C. *Synthesis*, **1995** 1465-79; Vorbrüggen, H.; Bennua, B. *Chem. Ber.*, **1981** *114*, 1279-86.
8. Following the most classical conformational nomenclature: B. Fuchs, *Topics in stereochemistry*, **1978** *10*, 1-94, and ref. cited.
9. Pople, S. A.; Bothner-By, A. A. *J. Chem. Phys.*, **1965** *42*, 1339-49.
10. Allerhand, A.; Gutowsky, H. S.; Jonas, J.; Meinzer, R. A. *J. Am. Chem. Soc.*, **1966** *88*, 3285-94.
11. Komaromi, I.; Tronchet, J. M. J. *J. Phys. Chem.*, **1995** *99*, 10213-220 and ref. cited.
12. Rassat, A.; Lemaire, H. *J. Chim. Phys. Phys. Chim. Biol.*, **1964** *61*, 1576-79; Rassat, A.; Lemaire, H.; Ramasseul, R. *Mol. Phys.*, **1964** *8*, 557-560; Tronchet, J. M. J.; Bizzozero, N.; Koufaki, M.; Habashi, F.; Geoffroy, M. *J. Chem. Res., Synop.* **1989**, 334, *Miniprint* **1989**, 2601-2619; Ricca, A.; Tronchet, J. M. J.; Weber, J.; Ellinger, Y. *J. Phys. Chem.*, **1992** *96*, 10779-84.
13. Tronchet, J. M. J.; Benhamza, R.; Bernardinelli, G. *Nucleosides Nucleotides*, **1993** *12*, 55-71.
14. Tronchet, J. M. J.; Iznaden, M.; Barbalat-Rey, F.; Dhimane, H.; Ricca, A.; Balzarini, J.; De Clercq, E. *Eur. J. Med. Chem.*, **1992** *27*, 555-560, and ref. cited.