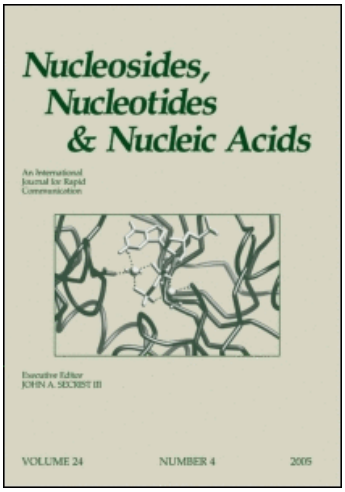



**Nucleosides, Nucleotides and Nucleic Acids**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

# Novel Spironucleosides: 1'',3''-Thiazolidine-2''-Spiro-3'-3'-Deoxyuridine Derivatives

Jean M. J. Tronchet[a]; Imre Kovács[a]; Françoise Barbalat-Rey[a]; Margarita VegaHolm[a]
[a] Department of Pharmaceutical Chemistry Sciences II, University of Geneva, Geneva 4, Switzerland

**To cite this Article** Tronchet, Jean M. J. , Kovács, Imre , Barbalat-Rey, Françoise and VegaHolm, Margarita(1998) 'Novel Spironucleosides: 1'',3''-Thiazolidine-2''-Spiro-3'-3'-Deoxyuridine Derivatives', Nucleosides, Nucleotides and Nucleic Acids, 17: 6, 1115 — 1123
**To link to this Article: DOI:** 10.1080/07328319808004224
**URL:** http://dx.doi.org/10.1080/07328319808004224

NUCLEOSIDES & NUCLEOTIDES, 17(6), 1115-1123 (1998)

# NOVEL SPIRONUCLEOSIDES: 1",3"-THIAZOLIDINE-2"-SPIRO-3'-3'-DEOXYURIDINE DERIVATIVES

Jean M. J. Tronchet,* Imre Kovács, Françoise Barbalat-Rey, and Margarita Vega Holm

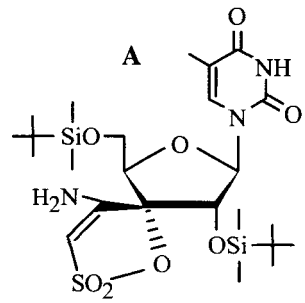
Department of Pharmaceutical Chemistry, Sciences II, University of Geneva, CH-1211 Geneva 4 (Switzerland)

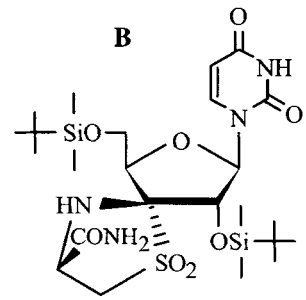
Abstract : Reaction of 2',5'-di-*O*-TBDMS-3'-ketouridine **1** with L-cysteine yielded in good yield a resolvable mixture of the two expected epimeric spironucleosides **2** and **3**. Amidification of their carboxylic group took place readily and the *ribo* carboxamide **4** was oxidized to the corresponding sulfoxide **6**. Despite their similarity to TSAO derivatives these compounds did not exhibit usable anti-HIV activity.



## INTRODUCTION

TSAO derivatives,[1] *i.e.* TSAO-T (**A**), relatively rigid molecules which bind selectively to the non-nucleoside site of HIV-1 reverse transcriptase (RT), can be used as an indicator of the inhibitor-bound conformation of the allosteric RT site. Their mechanism of action as well as, most probably, their binding features have been proved[2] different from those observed for nevirapine, contrarily to the more generally accepted view[3] of an uniform mechanism of action of all NNRTIs (non-nucleoside RT inhibitors). From the mutations observed in RT, following treatment of the virus with TSAO-T, aided by molecular modelling, the following binding interactions between **A** and RT were proposed:[4] each oxygen atom of the sulfonyl group with one of the tyrosines 181 and 188, the 2'-*O*-TBDMS group with Val-106 and the amino group on the oxathiolane ring with Glu-138. To test the effect of structural modifications upon activity, we considered the synthesis of compound **B** in



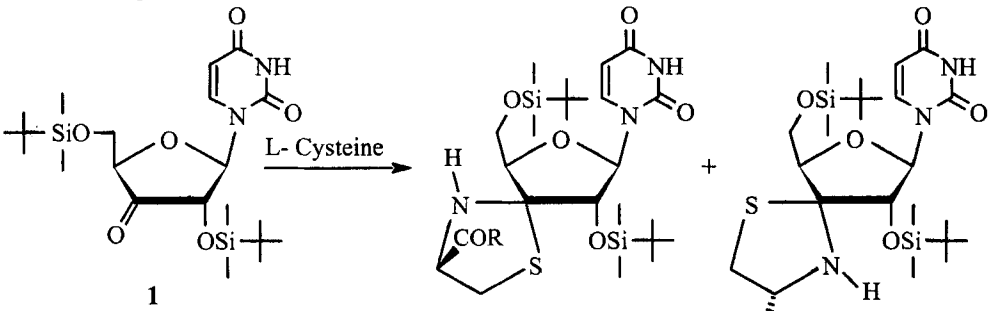



which the sulfonyl group was shifted closer to the furanose ring and the very slightly basic amino group of **A** replaced with a still less basic carboxamido group shifted toward the exterior of the molecule. Unfortunately **B** was too unstable to be isolated. The nucleofugal properties of the alkylsulfonyl group assisted by the formation of a C=N double bond probably promoted the opening of the ring leading to a reversion to the 3'-ketonucleoside. We thus resorted to the preparation of the sulfoxide analogue of **B**.

## RESULTS AND DISCUSSION

Condensation of cysteine or penicillamine with carbonyl derivatives to afford thiazolidines has been described, *inter alia*, for aldehydosugar derivatives,[5] aromatic aldehydes,[6] and propanone.[7] We describe the application of this condensation reaction to the somewhat encumbered ketonucleoside derivative **1**[8] to afford thiazolidine spironucleosides.

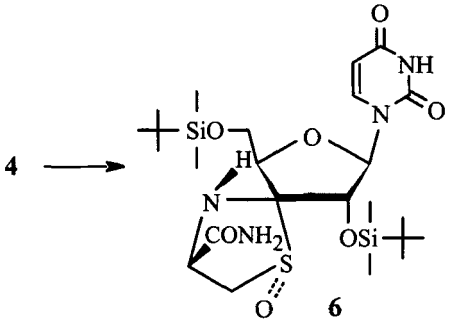
Upon reaction with L-cysteine, in hydroethanolic solution and under argon at 90 °C for three hours, the ketouridine derivative **1** afforded mainly a mixture of the epimeric spiro derivatives **2** and **3**. As some de-*O*-silylation took place, the reaction mixture was resilylated before a tedious column chromatography leading to pure **2** (31%) and **3** (29%). Amidification of **2** and **3** led respectively to **4** (86%) and **5** (96%). It was somewhat more convenient not to separate the two acids **2** and **3** but to submit their mixture to amidification then to proceed to the separation of **4** and **5** obtained in 30 and 35% yields (from **1**) respectively.




A number of reagents promoting a somewhat selective oxidation of sulfides to sulfoxides are known.[9] We selected three oxidizing reagents: osmium tetraoxide-*N*-methylmorpholine *N*-oxide,[10] hydrogen peroxide on silica gel we developed from the successful use of other silica gel supported oxidizing reagents,[11,12] and *m*-chloroperbenzoic acid (MCPBA) which proved selective in some occasions.[13] Upon oxidation with either osmium tetraoxide or hydrogen peroxide/silica gel, the *xylo* compound **5** afforded neither a sulfoxide nor a sulfone. Instead, it reverted to the

ketonucleoside **1**. The readily accessible thioether function on the β face of the furanose ring was most probably oxidized to the unstable sulfone which would undergo an elimination reaction, implying the nucleofugal sulfonyl group, to an imine, readily hydrolyzed to **1**. Using the more selective MCPBA, some sulfoxide was formed [H NMR δ 5.92 (*d*, 1 H, $J_{1',2'}$ 7.4 Hz, H-1'), 2.90 (*dd*, 1 H, $J_{4'',5''\text{-}pro\text{-}S}$ 9.1 Hz, $J_{5''\text{-}pro\text{-}S,5''\text{-}pro\text{-}R}$ 14.0 Hz, H-*pro*-*S*-5''), 3.08 (*dd*, 1 H, $J_{4'',5''\text{-}pro\text{-}R}$ 6.5 Hz, H-*pro*-*R*-4'')], but could not be isolated in a pure form. The *ribo* thiazolidine **4** was stereospecifically converted to the (*R*) sulfoxide **6**, the reagent attacking the more accessible face of the thiazolidine ring. The yields obtained [osmium tetraoxide (52%), hydrogen peroxide/silica gel (80%), MCPBA at -40 °C (85%)] reflect the selectivity of the oxidizing reagent owing probably to the fact that an oxidation to the unstable sulfone leads to a reversion to the ketonucleoside. The observation that when using MCPBA at temperature higher than -40 °C, the yield decreased and the only isolable by-product was the ketonucleoside **1** is also in favor of this hypothesis. It is also worth noting that these oxidation reactions do not affect the secondary amine group. Such groups were protected in such sulfide to sulfoxide oxidation reactions previously described in the literature.






**6**

Most pertinent H NMR data concerning compounds **2-6** are collected in TABLES 1 and 2. When reacting **1** with L-cysteine, the existing asymmetric atoms kept their original configuration and two new asymmetric centers C-3' and N-3'' were created, an extra one (S-1'') being formed upon oxidation of **4** to **6**. The C-3' configuration of unoxidized thiazolidines **2-5** exhibited a large influence upon the conformation of the furanose moiety, the sulfur atom adopting a position as close as possible to an equatorial one, i.e. $E_{4'}$ for **2** and **4**, $^{2'}T_{3'}$ for **3** and **5**. This is shown by the $J_{1',2'}$ coupling constants small for the *ribo* and larger for the *xylo* epimers. The *ribo* sulfoxide **6** does not follow this rule.

In the H NMR spectra (DMSO-$d_6$) of carboxylic acid derivatives **2** and **3**, the H-$N^{3''}$ signal was badly resolved. On the contrary, for the carboxamides **4-6**, H-$N^{3''}$ gave rise to a sharp doublet with a large (10.5-11.6 Hz) $J_{3'',4''}$ coupling. This indicates that these compounds exist as a preponderant invertomer of (*3''R*) configuration. The position of H-$N^{3''}$ relative to the rest of the thiazolidine ring being established, this proton could be used in NOE experiments to assess the topographical relationships between the thiazolidine ring and the rest of the molecule, particularly the C-3' configuration. Reciprocal signal enhancements were noted for **4** between H-$N^{3''}$ on one hand and H-2'

TABLE 1. H NMR (200 MHz, DMSO-$d_6$) Chemical Shifts (δ in ppm) of the Sugar Moiety of Compounds **2**-**6**.

| Cmpd | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| H-1' | 5.69 | 5.90 | 5.60 | 5.92 | 5.97 |
| H-2' | 4.31 | 4.09 | 4.40 | 4.13 | 4.66 |
| H-4' | 4.08 | 4.29 | 4.03 | 4.29 | 4.55 |
| Ha-5' | 3.81 | 3.80 | 3.90 | 3.80 | 3.84 |
| Hb-5' | 3.92 | 3.90 | 4.01 | 3.87 | 3.98 |
| H-N$^{3"}$ | 2.82 | ~3.50 | 3.21 | 3.20 | 3.16 |
| H-4" | 3.46 | 3.93 | 3.73 | 4.09 | 4.07 |
| $H_{pro\text{-}S\text{-}5"}$ | 2.61 | 2.72 | 2.65 | 2.87 | 2.31 |
| $H_{pro\text{-}R\text{-}5"}$ | 3.12 | 3.09 | 3.09 | 3.03 | 3.26 |

TABLE 2. Selected H NMR (200 MHz, DMSO-$d_6$) Interproton Coupling Constants (in Hz) of Compounds **2**-**6**.

| Cmpd | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| $J_{1',2'}$ | 2.4 | 7.8 | 1.5 | 7.5 | 6.5 |
| $J_{4',5'a}$ | 6.0 | ~1.5 | 6.0 | 1.5 | 3.0 |
| $J_{4',5'b}$ | 3.0 | ~1.5 | 2.0 | 1.0 | 2.0 |
| $J_{5'a,5'b}$ | 11.0 | ~11.0 | 12.0 | 11.5 | 11.5 |
| $J_{3",4"}$ | | | 11.0 | 10.5 | 11.5 |
| $J_{4",5"\text{-}pro\text{-}S}$ | 8.5 | 8.0 | 9.0 | 7.5 | 10.5 |
| $J_{4",5"\text{-}pro\text{-}R}$ | 6.5 | 6.5 | 6.0 | 6.5 | 4.5 |
| $J_{5"\text{-}pro\text{-}R,5"\text{-}pro\text{-}S}$ | 10.0 | 10.0 | 10.0 | 9.5 | 13.5 |

and H-6 on the other hand establishing the (*3'R*) configuration (*ribo*) of **2** and **4**. This was confirmed by NOE experiments on **5** showing signal enhancements between H-N$^{3"}$ on one hand and H-4' and H-1' on the other hand assessing its *xylo* configuration. The (*1"R*) configuration of the sulfur atom of **6** has been established from the known[7] strong deshielding effect of the S-O bond on the *syn* 1,3-diaxial protons (H-4' and H-4"), the small deshielding of the *cis* α-proton and the small shielding of the *trans* α-proton (TABLE 1).

The low absolute value (9.5-10.0 Hz) of the geminal coupling constant of the 5" protons indicates that one of the lone pairs on the sulfur atom is antiperiplanar or synperiplanar to one of the neighbour protons.[14] Upon oxidation of **4** to **6**, the absolute value of this coupling constant increases to 13.5 Hz establishing the axial position of the S-O bond which is then antiperiplanar to $H_{pro\text{-}S}$-5" itself antiperiplanar to H-4", which confirms the configuration of the sulfur atom. For each compounds of the series, the two $J_{4",5"}$ coupling constants correspond to one large and one medium values respectively. This indicates that the H-C4" bond projects along the C'4"-C5" bond outsides the H-C4"-H angle and that the larger coupling constant corresponds to the $H_{pro\text{-}S}$-5" proton. The conformation of the thiazolidine ring implies a puckering of C5" toward the face bearing the COR group. The $J_{4",5"\text{-}proS}$ value reflects the extent of that puckering.

Compound **4** did not exhibit any anti-HIV activity. Compound **6** is not sufficiently stable in aqueous solutions and too cytotoxic to warrant further biological testing. Compounds **2-5** are being tested against other viruses.



## EXPERIMENTAL

General.[15]

***(3'R,4"R)*-2',5'-Bis(*O-tert*-butyldimethylsilyl)-3'-deoxyuridine-3'-spiro-2"-thiazolidine-4"-carboxylic acid (2).** To a solution of L-cysteine (5.81 g, 48.0 mmol) in water (distilled, reboiled and cooled under Ar, 60 mL) kept at 90 °C under Ar, ethanol (120 mL) was slowly added then, after 5 min, **1** (5.64 g, 12.0 mmol) in one portion and the reaction was kept at 90 °C under slight reflux for 3 h. After cooling and distillation of ethanol, the remaining aqueous solution was treated with EtOAc (400 mL), $H_2O$ (60 mL) and a saturated aqueous NaCl solution (120 mL). The aqueous phase was reextracted with EtOAc (2x100 mL) and the combined organic phases dried ($Na_2SO_4$), concentrated to a syrup which was dried in vacuum over $P_2O_5$ for one day. To a solution of the residue (5.5 g) in pyridine (36 mL), kept at 0 °C, TBDMSCl (5.33 g, 36 mmol) was added in three portions. After 30 min at that temperature, the reaction mixture was allowed to warm to 20 °C, and stirred for 10 h. The reaction was quenched at 0 °C by dropwise addition of water (1 mL). After concentration, coevaporation with toluene (3x50 mL), the residue dissolved in EtOAc (250 mL) was washed with a mixture of water (30 mL) and a saturated aqueous NaCl solution (60 mL), the aqueous phase was reextracted with AcOEt (2x50 mL) and the combined organic phases dried ($Na_2SO_4$), concentrated, and submitted to column chromatography [(50:7:1 $CH_2Cl_2$/MeOH/25% aqueous $NH_3$) on silica gel chromagel 60 A CC (<325 mesh)]. The separated products were further purified by column chromatography (15:1 --> 10:1 $CH_2Cl_2$/MeOH) to yield **2** (2.11 g, 31%) and **3** (2.01 g, 29%). Mp 215-225 °C dec; $R_F$ 0.32 (50:5:1 $CH_2Cl_2$/

MeOH/25% aqueous $NH_3$), 0.42 (5:1 $CH_2Cl_2$/MeOH); $[\alpha]_D^{25}$ +9.3° (*c* 0.5, pyridine). IR $\nu_{max}^{KBr}$ 3600-2900 (NH,OH), 2960-2840 (CH), 1702, 1695, and 1690 (CO) $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): see TABLES 1 and 2, and δ 11.36 (*s*, 1 H, H-3), 7.95 (*d*, 1 H, $J_{5,6}$ 8.2 Hz, H-6), 5.56 (*d*, 1 H, H-5), 0.88 (*s*, 18 H, $CMe_3$), 0.14, 0.10, and 0.07 (3 *s*, 12 H, $Me_2Si$). $^{13}C$ NMR (DMSO-$d_6$): δ 174.3 (COOH), 163.2 (C-4), 150.6 (C-2), 141.0 (C-5), 100.6 (C-5), 89.1 (C-1'), 88.8 (C-4'), 86.8 (C-3'), 81.1 (C-2'), 69.1 (C-4''), 61.9 (C-5'), 37.4 (C-5''), 25.8 and 25.7 (**Me**$_3$C), 18.1 and 17.7 (**C**$Me_3$), -4.6, -4.7, -5.1, and -5.4 ($SiMe_3$). Electrospray-MS: *m/z* (%) 574.2 (100, M), 462.0 (21, M + 2 *t*-Bu - TBDMS - B).

*Anal. Calcd* for $C_{24}H_{43}N_3O_7SSi_2.H_2O$ (591.88): C, 48.70; H, 7.66; N, 7.10; S, 5.42. Found: C, 48.59; H, 7.66, N, 7.00; S, 5.43.

***(3'S,4''R)*-2',5'-Bis(*O-tert*-butyldimethylsilyl)-3'-deoxyuridine-3'-spiro-2''-thiazolidine-4''-carboxylic acid (3).** Obtained as described for the preparation of **2**. Mp 160-170 °C dec; $R_F$ 0.23 (50:5:1 $CH_2Cl_2$/MeOH/25% aqueous $NH_3$), 0.28 (5:1 $CH_2Cl_2$/MeOH); $[\alpha]_D^{27}$ -96.4° (*c* 0.9, pyridine). IR $\nu_{max}^{KBr}$ 3600-2800 (NH,OH), 2950-2858 (CH), and 1702 (C=O) $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): see TABLES 1 and 2, and δ 10.50 (*s*, 1 H, H-3), 7.75 (*d*, 1 H, $J_{5,6}$ 8.2 Hz, H-6), 5.68 (*d*, 1 H, H-5), 0.95 and 0.80 (2 *s*, 18 H, $CMe_3$), 0.13, 0.07, and -0.14 (3 *s*, 12 H, $Me_2Si$). $^{13}C$ NMR (DMSO-$d_6$): δ 172.5 (COOH), 162.6 (C-4), 150.7 (C-2), 139.6 (C-6), 102.5 (C-5), 85.6 (C-1'), 83.9, 83.2, and 81.7 (C-2', C-3', and C-4'), 66.7 and 65.2 (C-5' and C-4''), 25.8 and 25.4 (**C**$Me_3$), 18.0 and 17.5 (**C**$Me_3$), -4.3, -5.4, -5.5, and -5.7 ($SiMe_2$). Electrospray-MS: *m/z* (%) 574.2 (100, M), and 462.0 (94, M + 2 *t*-Bu - TBDMS - B).

*Anal. Calcd* for $C_{24}H_{43}N_3O_7SSi_2.2\ H_2O$ (609.89): C, 47.27; H, 7.77; N, 6.89; S, 5.26. Found: C, 47.38; H, 7.51; N, 6.77; S, 5.48.

***(3'R,3''R,4''R)*-2',5'-Bis(*O-tert*-butyldimethylsilyl)-3'-deoxyuridine-3'-spiro-2''-thiazolidine-4''-carboxamide (4).**

*A. From isolated* **2**: to a solution of **2** (688 mg, 1.2 mmol) and *N*-hydroxysuccinimide (207 mg, 1.8 mmol) in DMF (12 mL), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (345 mg, 1.8 mmol) was added at 0 °C under Ar. After 6 h stirring at that temperature and 18 h at 22 °C, the reaction mixture was cooled to 0 °C and a saturated methanolic solution of ammonia (6.0 mL) was added. After 1 h, the reaction mixture was concentrated (oil pump), the residue dissolved in EtOAc (50 mL), washed ($H_2O$, 2x10 mL, saturated aqueous NaCl 10 mL), dried ($Na_2SO_4$), filtered and concentrated. Column chromatography (3:97 --> 4.5:95.5 MeOH/$CH_2Cl_2$) afforded **4** (590 mg, 86%).

*B. From* **1** *without separation of* **2** *and* **3**: **1** (4.70 g, 10.0 mmol) was converted to **2** and **3** following the procedure described for the preparation of **2**. The crude product

was purified by column chromatography (3:47 --> 13:87 MeOH/$CH_2Cl_2$) to yield a mixture of **2** and **3** (4.49 g, 78.5%) which was amidified as described for the synthesis of **4**. A column chromatography (93:7 hexane/EtOH) afforded **4** and **5**. After a further purification (7:93 MeOH/$CH_2Cl_2$) **4** (1.70 g, 30% from **1**) and **5** (2.02, 35% from **1**) were obtained.

*Properties of* **4**: mp 120-122 °C; $R_F$ 0.47 (10:1 $CH_2Cl_2$/MeOH), 0.34 (4:1 hexane/EtOH); $[\alpha]_D^{25}$ +43.2° (*c* 0.5, EtOH). IR $\nu_{max}^{KBr}$ 3464, 3324, 3255, and 3200 (NH), 2953-2857 (CH), 1700 and 1678 (C=O) $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): see TABLES 1 and 2, and δ 11.31 (*s*, 1 H, H-3), 7.96 (*d*, 1 H, $J_{5,6}$ 8.2 Hz, H-6), 7.28 (*s*, 1 H, $CONH_2$), 5.52 (*d*, 1 H, H-5), 0.88 (*s*, 18 H, $CMe_3$), 0.12, 0.11, and 0.07 (3 *s*, 12 H, $SiMe_2$). $^{13}C$ NMR (DMSO-$d_6$): δ 171.2 ($CONH_2$), 163.3 (C-4), 150.5 (C-2), 141.2 (C-6), 100.0 (C-5), 89.4 (C-1'), 87.5 (C-4'), 86.1 (C-3'), 80.6 (C-2'), 66.4 (C-4''), 61.1 (C-5'), 36.3 (C-5''), 25.8 and 25.7 ($CMe_3$), 17.9 and 17.7 ($CMe_3$), -4.5, -4.8, -5.3, and -5-5 ($Me_2Si$). EIMS: *m/z* (%) 73 (100), 211 (16), 169 (5), 303 (5), and 403 (3, $M^{\cdot+}$ + *t*-Bu - TBDMS - B).

*Anal. Calcd* for $C_{24}H_{44}N_4O_6SSi_2$ (572.88): C, 50.32; H, 7.74; N, 9.78; S, 5.60. Found: C, 50.55; H, 7.89; N, 9.61; S, 5.88.

***(3'S,3''R,4''R)*-2',5'-Bis(*O-tert*-butyldimethylsilyl)-3'-deoxyuridine-3'-spiro-2''-thiazolidine-4''-carboxamide (5).** Obtained as described for the preparation of **4** [*method A* afforded **5** (770 mg, 96%) from **3** (688 mg, 1.2 mmol)]. Mp 132-134 °C; $R_F$ 0.47 (10:1 $CH_2Cl_2$/MeOH), 0.25 (4:1 hexane/EtOH); $[\alpha]_D^{25}$ -11.0° (*c* 0.5, EtOH). IR $\nu_{max}^{KBr}$ 3457, 3313.5 and 3209 (NH), 2952-2858 (CH), 1723, 1696, and 1669 (C=O) $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): see TABLES 1 and 2, and δ 11.47 (*s*, 1 H, H-3), 7.74 (*d*, 1 H, $J_{5,6}$ 8.0 Hz, H-6), 7.54 and 7.25 (2 *s*, 1 H, $CONH_2$), 5.71 (*d*, 1 H, H-5), 0.93 and 0.80 (2 *s*, 18 H, $CMe_3$), 0.12, 0.10, and -0.13 (3 *s*, 12 H, $Me_2Si$). $^{13}C$ NMR (DMSO-$d_6$): δ 171.7 ($CONH_2$), 162.6 (C-4), 150.7 (C-2), 139.5 (C-6), 102.5 (C-5), 85.5 (C-1'), 84.0, 82.9, and 80.7 (C-2', C-3', and C-4'), 65.4 and 65.1 (C-5' and C-4''), 37.3 (C-5''), 25.8 and 25.4 ($CMe_3$), 18.0 and 17.5 ($CMe_3$), -4.1, -5.3, and -5.7 ($SiMe_2$). EIMS: *m/z* (%) 73 (100), 211 (14), 169 (5), 303 (3), and 403 (3, $M^{\cdot+}$ + *t*-Bu, - TBDMS - B).

*Anal. Calcd* for $C_{24}H_{44}N_4O_6SSi_2$ (572.88): C, 50.32; H, 7.74; N, 9.78; S, 5.60. Found: C, 50.59, H, 7.97; N, 9.58; S, 5.78.

***(3'R,1''R,3''R,4''R)*-2',5'-Bis(*O-tert*-butyldimethysilyl)-3'-deoxyuridine-3'-spiro-2''-thiazolidine-4''-carboxamide *S*-oxide (6).**

*A. By oxidation of* **4** *with* $OsO_4$/N-*methylmorpholine* N-*oxide (NMO).* A 0.1 M *tert*-butanolic solution of $OsO_4$ (50 μL, 0.005 mol) was added at 0 °C to a solution of **4** (57.2 mg, 0.1 mmol) and NMO (27.0 mg, 0.2 mmol) in a mixture of acetone (2.0 mL) and water (0.4 mL). After 5.5 h stirring at 0 °C a 1 M solution of $Me_2S$ in acetone (0.3 mL, 0.3 mmol) was added and the stirring continued for 40 min. To the reaction mixture

AcOEt (40 mL) was added at 0 °C and the organic phase washed [cold saturated aqueous $NaHCO_3$ solution (2x5 mL), then saturated aqueous NaCl solution (5 mL)], dried ($Na_2SO_4$) was submitted to column chromatography (1:24 $MeOH/CH_2Cl_2$), then recrystallized from $CH_2Cl_2$ to afford **6** (30.4 mg, 52%).

*B. By oxidation of* **4** *with* $H_2O_2$ *on silica gel.* To a solution of **4** (172 mg, 0.3 mmol) in acetone (5.0 mL), 30% aqueous $H_2O_2$ (0.28 mL, *ca* 2.7 mol) and silica gel for chromatography (1.7 g) was added and the solvent removed by vacuum distillation at 35 °C. After 75 min at 25 °C, the silica gel was washed with acetone (10x5 mL), and the combined acetone extracts, concentrated, were treated as described under *A* to give, after crystallization in $CH_2Cl_2$, 140 mg (80%) of **6**.

*C. Oxidation of* **4** *with* m-*chloroperbenzoic acid (MCPBA).* To a solution of **4** (172 mg, 0.3 mmol) in acetone (9 mL), a 0.4 M solution of MCPBA in acetone (0.97 mL, 0.39 mmol) was added dropwise in 3 min at -40 °C. The reaction mixture was stirred at that temp for 30 min, then quenched with a 1 M solution of $Me_2S$ in acetone (0.2 mL, 0.2 mmol) ice-cold EtOAc (80 mL) was added and the organic phase treated as described under *A* gave, after crystallization in $CH_2Cl_2$ 150 mg (85%) of **6**: mp 111.5-113.5 °C; $R_F$ 0.33 (10:1 $CH_2Cl_2$/MeOH); $[\alpha]_D^{23}$ +3.5° (*c* 1.0, EtOH). IR: $\nu_{max}^{KBr}$ 3456, 3356, and 3200 (NH), 2960-2856 (CH), 1699 and 1690 (C=O) $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, see TABLES 1 and 2, and δ 11.52 (*s*, 1 H, H-3), 8.03 (*d*, 1 H, $J_{5,6}$ 8.2 Hz, H-6), 5.71 (*d*, 1 H, H-5), 7.74 and 7.44 (2 *s*, 2 H, $CONH_2$), 0.88 and 0.78 (2 *s*, 18 H, $CMe_3$), 0.08, 0.04, and -0.12 (3 *s*, 12 H, $SiMe_2$). $^{13}C$ NMR (DMSO-$d_6$): δ 170.7 ($CONH_2$), 162.6 (C-4), 150.7 (C-2), 139.9 (C-6), 102.6 (C-5), 96.8 (C-3'), 85.9 (C-1'), 77.0 (C-2'), 74.5 (C-4'), 63.9 (C-5'), 62.0 (C-4''), 56.9 (C-5''), 25.8 and 25.4 ($C\mathbf{Me}_3$), 18.1 and 17.4 ($\mathbf{C}Me_3$), -4.8, -5.3, and -5.7 ($Si\mathbf{Me}_2$). Electrospray-MS: *m/z* (%) 611.2 (100, M + $Na^+$), and 589.2 (41, M + $H^+$).

*Anal. Calcd* for $C_{24}H_{44}N_4O_7SSi_2$ (588.88): C, 48.95; H, 7.53; N, 9.51; S, 5.44. Found: C, 48.80; H, 7.55; N, 9.43; S, 5.62.

## ACKNOWLEDGEMENTS

The authors thank Dr H. Eder for the elemental analyses. This work was supported by the Swiss National Research Foundation (grants # 3139-037156 and 20-43352.95).

## REFERENCES

1. Balzarini, J.; Perez-Perez, M.-J.; San-Felix, A.; Schols, D.; Perno, C.-F.; Vandamme, A.-M.; Camarasa, M.-J.; De Clercq, E. *Proc. Natl. Acad. Sci. USA* **1992** *89*, 4392-96.

2. Arion, D.; Fletcher, R. S.; Borkow, G.; Camarasa, M.-J.; Balzarini, J.; Dmitrienko, G. I.; Parniak, M.A. *Mol. Pharmacol.* **1996** *50*, 1057-64.
3. Mager, P. P. *Med. Res. Rev.* **1997** *17*, 235-76.
4. Balzarini, J. *Mem. Acad. R. Med. Belg.* **1995** *57*, 575-600.
5. Bognár, R.; Györgydeák, Z.; Szilágyi, L.; Czira, G.; Tamás, J. *Liebiegs Ann. Chem.* **1977**, 1536-46 .
6. Györgydeák, Z.; Kajtár, J.; Kajtár, M.; Kajtár-Peredy, M. *Liebiegs Ann. Chem.* **1990**, 281-86.
7. Iwakawa, M.; Pinto, B. M.; Szarek, W. A. *Can. J. Chem.* **1978** *56*, 326-35.
8. Samano, V.; Robins, M. J. *J. Org. Chem.* **1990** *55*, 5186-88; Tronchet, J. M. J.; Kovács, I.; Barbalat-Rey, F.; Dolatshahi, N. *Nucleosides Nucleotides* **1996** *15*, 337-47.
9. Madesclaire, M. *Tetrahedron* **1986** *42*, 5459-95.
10. Priebe, W.; Grynkiewicz, G. *Tetrahedron Lett.* **1991** *32*, 7353-56; Ghosh, A. K.; Lee, H. Y.; Thompson, W. J.; Culberson, C.; Holloway, M. K.; McKee, S. P.; Munson, P. M.; Duong, T. T.; Smith, A. M.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1994** *37*, 1177-88.
11. Pautet, F.; Daudon, M. *Tetrahedron Lett.* **1991** *32*, 1457-58.
12. Hirano, M.; Komiya, K.; Yakabe, S.; Clark, J. H.; Morimoto, T. *OPPI Briefs* **1996** *28*, 705-708.
13. Ando, W.; Huang, L. *Tetrahedron Lett.* **1986** *27*, 3391-94.
14. Pople, S. A.; Bothner-By, A. A. *J. Chem. Phys.* **1965** *42*, 1339-49.
15. Tronchet, J. M. J.; Benhamza, R.; Bernardinelli, G. *Nucleosides Nucleotides* **1993** *12*, 55-71.