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The Synthesis and Conformation of 2'- and 3'-Hypermodified Tricyclic Nucleosides and Their Use in the Synthesis of Novel 2'- or 3'-Isomeric 4(7)-Substituted Isoxazolidine-nucleosides

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Abstract. *Intramolecular 1,3-dipolar cycloadditon reactions of a number of C-alkenyl nitrones of nucleoside derivatives* ***7, 9, 19*** *and* ***28*** *afforded 2'- and 3'-hypermodified tricyclic nucleoside derivatives* ***10*** *(56%),* ***11*** *(43%),* ***20*** *(91%) and* ***29*** *(75%), respectively. The solution structures of these tricyclic nucleoside derivatives have been investigated using the* $^3J_{HH}$ *(^1H at 500 MHz) and the NMR-derived torsion angle constrained energy minimizations with the aid of MacroModel's AMBER force field. Subsequent Tamao oxidation of the hypermodified nucleoside derivatives* ***20*** *and* ***29*** *gave spiro-4(7)-substituted isoxazolidine-nucleoside derivatives* ***21*** *and* ***30***, *respectively.*

A recent report by Camarasa and coworkers[1] has indicated that nucleosides with a 3'-spiro-unit, in conjunction with other structural features, possess anti-HIV-1 activity. Studies by Tronchet and coworkers[2,3] have described the synthesis of a 3'-deoxy-3'-*N*-hydroxyaminonucleoside derivative which has been tested to be moderately active against HIV-1 and may still prove to be a new lead compound in the combat against HIV infection. It was these reports that prompted us to investigate the synthesis of both 2'- and 3'-spironucleosides through the intermediacy of an *N*-methylnitrone.

Recent work carried out in this laboratory[4] has employed the use of an intermolecular 1,3-dipolar cyclisation of a 2'- or 3'-*N*-methylnitrone, with both electron-deficient and electron-rich dipolarophiles, to produce 5-substituted spiro-isoxazolidine nucleosides. The intramolecular 1,3-dipolar cycloaddition reaction of both oximes and nitrones with various dipolarophiles has been used extensively in the synthesis of fused 4-substituted isoxazolidines,[5a-c] and in particular with the synthesis of many natural products.[6a-c] In this paper, we report the first synthesis of *cis*-fused 4-substituted isoxazolidines as a means to introduce C2' or C3' functionality to nucleosides, by way of an intramolecular cycloaddition reaction of a tethered olefin with a vicinal *N*-methylnitrone. The use of the *N*-methylnitrone as the dipole clearly overcame the problem encountered by Tronchet *et al,*[7a] where the 2'-oxime employed in their system underwent intramolecular nucleophilic reactions with the aglycone.

This report constitutes the first synthesis of an isomeric pair of tricyclic *cis*-fused-spiro-isoxazolidine nucleosides **10** and **11.** They occured smoothly through a tandem intramolecular 1,3-dipolar cycloaddition[8] of the isomeric pair of 2'- or 3'-*N*-methylnitrones **7** and **9**, generated *in situ* from their parent ketones (**2** → **6** → **7** → **10** and **3** → **8** → **9** → **11**), and were found to be both regio and diastereospecific in their formation. It is worth pointing out that these tricyclic fused systems **10** and **11** were extremely rigid molecules which allowed for the assignment of their configuration and conformation *(vide infra)*. While the synthesis of hypermodified nucleosides **10** and **11** clearly illustrated the facility and stereospecfic nature of the above cycloaddition reaction they could not, however, be used further for the stereospecific synthesis of new 4-substituted spiro-isoxazolidine nucleosides.

Work also carried out in this laboratory[9] has successfully shown the utility of the silyl-tether approach to stereospecifically direct an intramolecular free-radical trapping reaction by an olefin. We herein extend our above synthesis of tricyclic-spiro-isoxazolidine thymidines **10** and **11**, by incorporating a silyl-tethered alkene into the isoxazolidine synthesis (Scheme 2). This approach utilized the existing β-hydroxy functional group, as in **18** or **27**, to undergo first silylation with a suitable vinylchlorosilane to give intermediary **19** or **28**, respectively, which in turn undergoes an *in situ* intramolecular cycloaddition reaction. The products resulting from this approach, **20** and **29**, have silicon containing heterocycles which are readily cleavable under the Tamao oxidation conditions.[10a-c] The products of this oxidative cleavage, the 4(7)-substituted-[1(9), 2(10)-isoxazolidines] **21** and **30**, are unique 1,3-dihydroxy functionalized nucleoside derivatives (note that the actual numbering of all atoms used for NMR and NOE assignments are shown in parenthesis and are also shown in the formulae in Schemes 1 and 2). This 4(7)-hydroxyl group of the spiro moiety of both **20** and **29**, which is not accessible by an intermolecular means, is then amenable to further modification.

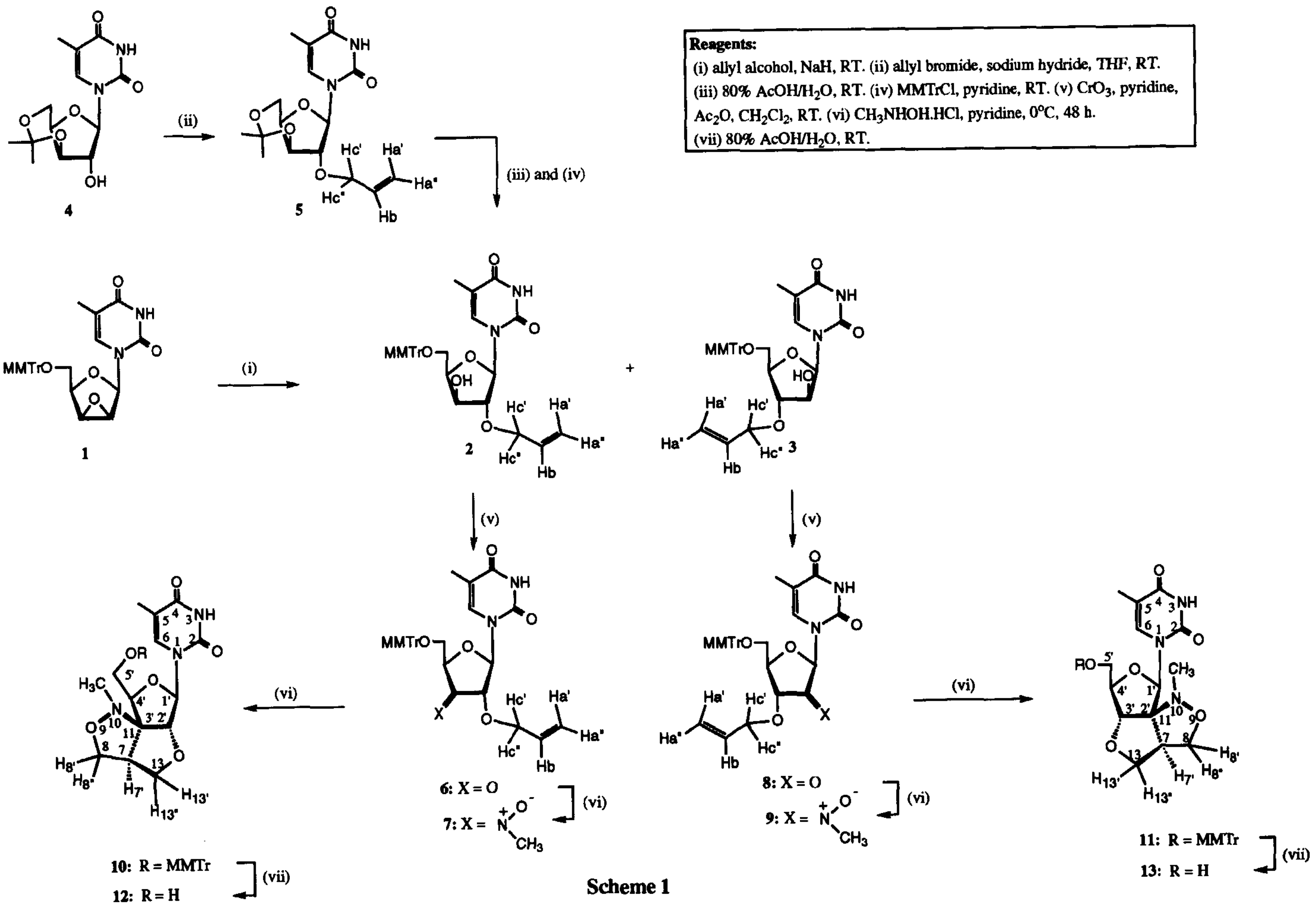
Result and Discussion

Synthesis of an isomeric pair of tricyclic cis-fused-spiro-isoxazolidine nucleosides 10 and 11.

The precursors for the intramolecular nitrone-olefin cycloaddition reaction were the 2'- and 3'-*O*-allyl nucleosides **2** (30%) and **3** (44%), respectively, and were readily synthesized by the opening of the 2',3'-epoxy ring of 1-(5'-*O*-MMTr-2',3'-*O*-anhydro-β-D-*lyxo*furanosyl)thymine[9] (**1**) with allyl alcohol (2:3 ratio, NMR) under a basic condition at room temperature, followed by simple column chromatography. The assignment of regio and stereochemistry of **2** and **3** was based on a comparison with an authentic sample of the 2'-*O*-allyl derivative **2**, which was obtained from 3',5'-*O*-*iso*propylidine-*xylo*thymidine (**4**), *via* specific 2'-*O*-allylation, removal of the *iso*propylidine group under an acidic condition and subsequent protection of the 5'-hydroxyl group as the 4-monomethoxytrityl ether [**4** → **5** → **2**].

Oxidation of the nucleosides **2** and **3**, using the reaction conditions described by Hansske *et al.*[11] afforded the corresponding 2'- and 3'-ulosides **6** and **8**. Treatment of the crude 2'- or 3'-*O*-allyl ulosides **6** and **8** with *N*-methylhydroxylamine hydrochloride in pyridine at 0°C gave the corresponding putative *N*-methylnitrones **7** and **9**, which underwent *in situ* intramolecular cycloaddition to afford the corresponding isomeric pair of tricyclic *cis*-fused-spiro-isoxazolidine nucleosides **10** (56%) and **11** (43%), respectively. Of particular interest to us was the regio and stereochemical outcome of this cyclisation reaction. ^{1}H NMR spectroscopy of these derivatives indicated that the *cis*-fused products were isolated in each case as the sole product. Confirmation of the regiochemical and hence the stereochemical outcome of the reaction was on the basis of 1D NOE difference spectroscopy *(vide infra)*.

Removal of the 5'-*O*-MMTr-protecting group from the tricyclic nucleosides **10** and **11** was affected by stirring each nucleoside with an 80% aqueous acetic acid mixture at room temperature overnight. The respective nucleoside derivatives **12** (93%) and **13** (91%) were isolated as the sole product of the deprotection reaction and were characterised on the basis of their spectral characteristics. Again, the regio and



Reagents:
(i) allyl alcohol, NaH, RT. (ii) allyl bromide, sodium hydride, THF, RT.
(iii) 80% $AcOH/H_2O$, RT. (iv) MMTrCl, pyridine, RT. (v) CrO_3, pyridine,
Ac_2O, CH_2Cl_2, RT. (vi) $CH_3NHOH.HCl$, pyridine, 0°C, 48 h.
(vii) 80% $AcOH/H_2O$, RT.

Scheme 1

stereochemistry of the nucleoside derivatives was confirmed on the basis of 1D NOE difference spectroscopy and is discussed in detail below.

Structural assignment of tricyclic cis-fused 2'- and 3'-spiro-isoxazolidine nucleosides 10 and 13

The saturation of H7' (Fig. 1 [panel A2]) in *cis*-fused 3'-spiro-isoxazolidine **10** shows enhancements at H1' (0.4%), H4' (4.3%), H13' (2.4%), H13" (0.3%) and H8' (1.2%) which prove C2'*(R)*, C3'*(S)*, C7*(S)* configurations, whereas saturation of NMe in **10** (Fig. 1 [panel A1]) gives key enhancement at H2' (2.5%) which proves N10*(S)* configuration. The orientation of thymine base is *anti* which was clear from the results of saturation at H1' and H2' giving 0.3% and1.6% NOE enhancements at H6, respectively. The saturation of H1' in *cis*-fused 2'-spiro-isoxazolidine **13** (Fig. 1 [panel B2]) shows key NOE enhancement at H7' (3.5%) which proves that cyclization underwent on the α-face of pentofuranosyl moiety and C2'*(S)*, C3'*(S)*, C7*(R)* configurations. The NOE enhancements at H3' (1.5%) and H8" (0.3%) upon saturation of NMe (Fig. 1 [panel B1]) in **13** prove N10*(R)* configuration.

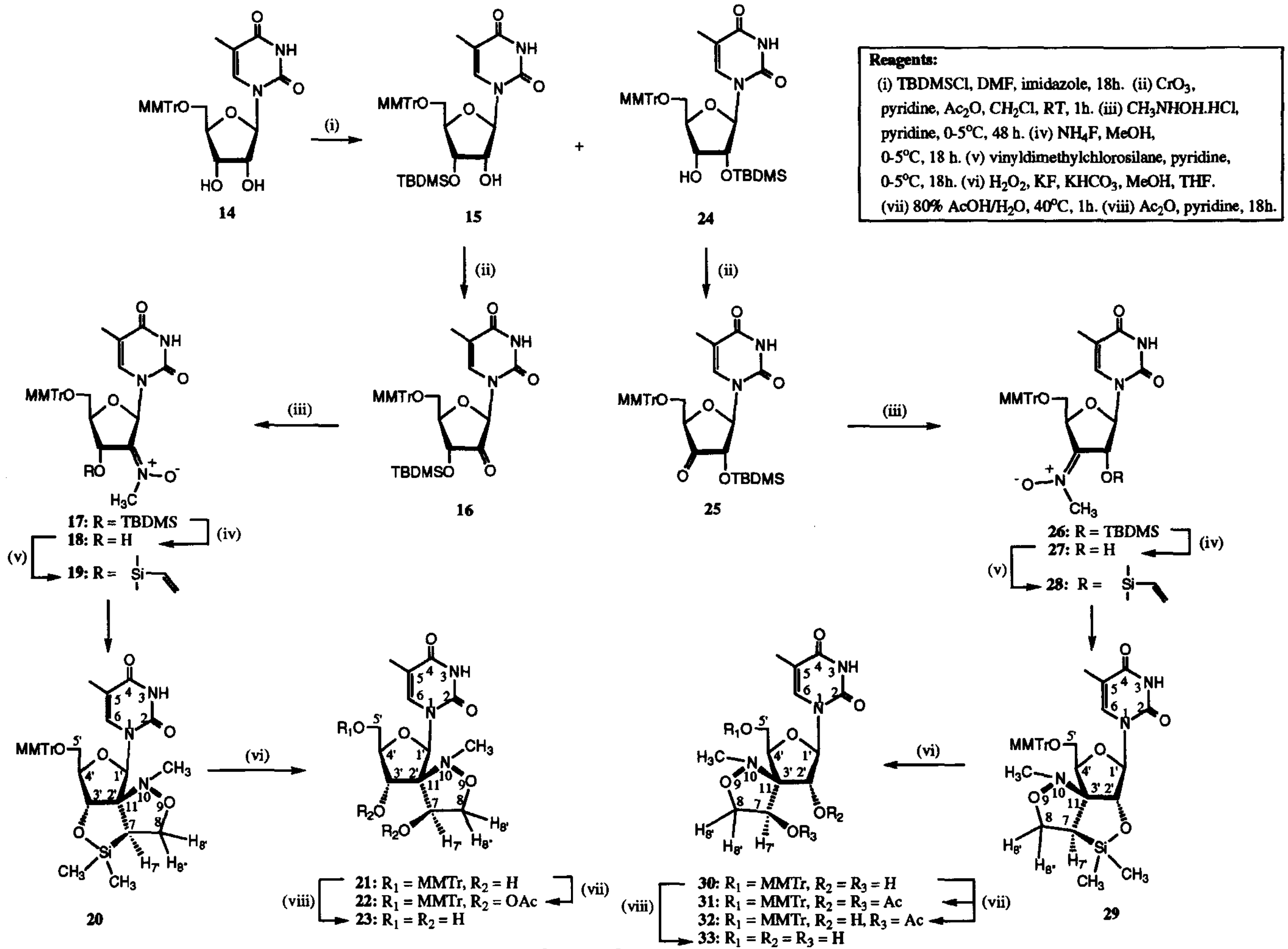
Synthesis of tricyclic cis-fused-silicon-tethered-2'- and 3'-spiro-isoxazolidine nucleosides 20 and 29

While it was clear from the above described work that the intramolecular 1,3-dipolar cyclisation affords products with high regio and stereoselectivity, the procedure is of limited utility unless it is applicable to the synthesis of nucleosides bearing a free hydroxyl group at the C4(7) position of the spiro moiety and at the 2'- or 3'-positions of the furanose moiety. The availability of these 1,3-dihydroxy derivatives will clearly pave the way for specific deoxygenation or further functionalization at either of these centres, thus enabling structure-activity studies against HIV reverse transcriptase to be carried out. Consequently, the introduction of the silyl-tethered alkene was investigated.

1-(5'-*O*-MMTr-β-D-*ribo*furanosyl)thymine[9] (**14**), when treated with *tert*-butyldimethylsilylchloride and imidazole under the reaction conditions described by Matsuda and coworkers,[12] afforded a 3:4 mixture of the 3'- and 2'-*O*-TBDMS-protected nucleosides **15** (33%) and **24** (42%), respectively, which were separated by column chromatography (Scheme 2). Recycling of the 2'-*O*-TBDMS-protected derivative **24** to prepare additional 3'-*O*-TBDMS-protected derivative **15** was possible by partial isomerization affected by heating the 2'-*O*-TBDMS-derivative **24** in methanol for several hours at reflux.[13]

Both 3'- and 2'-*O*-TBDMS protected nucleoside derivatives **15** and **24**, respectively, were oxidized under similar conditions to those described for nucleosides **2** and **3**. The reaction of **15** and **24** with the chromium trioxide/pyridine/acetic anhydride reagent gave the corresponding 2'- and 3'-ulosides **16** and **25** respectively. These were in turn separately treated with *N*-methylhydroxylamine hydrochloride in pyridine to afford the corresponding 2'- and 3'-*N*-methylnitrones **17** (67%) and **26** (69%). Removal of the 3'- or 2'-*O*-TBDMS group by the treatment of a methanolic solution of the nucleoside derivative **17** or **26** with ammoniun fluoride at 0°C for 6 h afforded the 2'- or 3'-*N*-methylnitrones **18** (67%) and **27** (84%), respectively. It was essential that the reaction be carried out at low temperature and with the exclusion of moisture for an optimal yield of the *N*-methylnitrones. The assignment of the configuration of *N*-methylnitrone **27** was on the basis of 1D NOE difference spectroscopy. The saturation of NMe group in **27** shows a key NOE enhancement at H2' (0.4%) which proves the *(Z)*-configuration along the nitrone double bond. Assignment of the configuration of *N*-methylnitrone **17** was not possible owing to the broadness of H1' and H3' peaks[7b,c] in the 1D proton spectrum and the almost isochronous chemical shifts of the NMe and OMe groups (Δδ = 0.06 ppm).

2'- or 3'-*N*-methylnitrone **18** or **27** was then dissolved in dry pyridine and treated with one equivalent of vinyldimethylchlorosilane to give the intermediary vinylsilanes **19** and **28** which underwent tandem [3 +2] cycloaddition with the vicinal *N*-methylnitrones. The reaction mixture was maintained at 0°C for 1 h before



Reagents:
(i) TBDMSCl, DMF, imidazole, 18h. (ii) CrO_3, pyridine, Ac_2O, CH_2Cl, RT, 1h. (iii) $CH_3NHOH.HCl$, pyridine, 0-5°C, 48 h. (iv) NH_4F, MeOH, 0-5°C, 18 h. (v) vinyldimethylchlorosilane, pyridine, 0-5°C, 18h. (vi) H_2O_2, KF, $KHCO_3$, MeOH, THF. (vii) 80% $AcOH/H_2O$, 40°C, 1h. (viii) Ac_2O, pyridine, 18h.

Scheme 2

being allowed to warm slowly to room temperature. The sole product isolated from the reaction mixture after 6 h at room temperature was the tricyclic adduct **20** (70%) or **29** (75%), respectively. The sterochemical and the structural assignment of each isomer was on the basis of its NMR spectral properties and 1D NOE difference spectroscopy and is discussed in detail below.

The hydrogen peroxide mediated Tamao Oxidation[10] was used to oxidatively cleave the silylheterocycle of **20** or **29** in a stereospecific manner to afford the respective 1,3-diols **21** (91%) or **30** (64%). The retention of the stereochemical integrity of the isoxazolidines **21** and **30** is consistent with the findings of Tamao and coworkers that the oxidative cleavage takes place with retention of stereochemistry. This fact was confirmed by 1D NOE difference spectroscopy. To our knowledge, this constitutes the first time that the Tamao reaction has been performed in concert with the 1,3-dipolar cyclisation reaction to generate 1,3-dihydroxy isoxazolidine derivatives stereospecifically. Formation of the di-acetates **22** and **31** was further evidence in support of the formation of the respective diols **21** and **30**. Removal of the 5'-*O*-MMTr-protecting group from the tricyclic nucleosides **21** and **30** was affected by stirring each nucleoside with an 80% aqueous mixture at room temperature overnight. The respective nucleoside derivatives **23** (87%) and **33** (90%) were isolated as the sole product of the deprotection reaction.

Structural assignment of tricyclic cis-fused-2'- and 3'-spiro-isoxazolidine nucleosides 20 and 29, and the products resulting from Tamao Oxidation 21 and 30.

The saturation of H1' in **20** (Fig. 1 [panel C2]) shows key NOE enhancement at H7' (6.9%), whereas saturation of H3' (Fig. 1 [panel C1]) shows enhancement at NMe (5.0%) which prove the C2'*(S)*, C3'*(S)*, C7*(S)* and N10*(R)* configurations of **20**. The saturation of H7' in **29** (Fig. 1 [panel D1]) shows key NOE enhancements at H1' (0.1%), H4' (1.3%), H8' (0.7%), H8" (0.1%) which are consistent with C2'*(R)*, C3'*(S)*, C7*(R)* configurations, whereas saturation of H2' (Fig. 1 [panel D2]) gives NOE enhancement at NMe (3.7%) which proves N10*(S)* configuration.

The regiochemical outcome of the cycloaddition reaction is consistent with the findings of Baldwin *et al.*[14] Their study concentrated on the intramolecular cycloaddition of 5-alkenyl nitrones, in which the sole product isolated from the intramolecular cycloaddition of unsubstituted alkenes were the *cis*-fused adducts. Based on the configuration of the starting *N*-methylnitrone **27** (*i.e.* *(Z)*) and the orientation of the *N*-methyl group in the isoxazolidine **29**, it is possible to draw some conclusions on the transition state geometry. Clearly, the *cis*-fused isoxazolidine **29**, which is consistent with our 1D NOE difference spectroscopy *(vide infra)*, results from the interaction of the terminal carbon of the alkene with the oxygen atom of the nitrone and interaction between the C_α-carbon of the alkene and C3' of the nitrone. The stereochemistry of the final product **29** suggests that the cycloaddition proceeds exclusively through an *endo*-transition state,[15] with the *N*-methyl group adopting a relative cisoid orientation towards both H2' and C4(7) substituent in both the reactant **27** and the product **29**. The cycloaddition of putative **19** to adduct **20** also similarly suggests the involvement of*endo*-transition state.

The saturation of H7' in **21** shows key NOE enhancement at H1' (4.8%), H8' (1.5%), H8" (0.3%), whereas saturation of NMe shows enhancement at H3' (2.5%) and H8" (0.5%) which prove C2'*(S)*, C3'*(S)*, C7*(S)* and N10*(R)* configuration. The saturation of H7' in **30** shows key NOE enhancements at H1' (0.9%), H4' (4.3%), H8' (0.2%), H8" (2.3%), whereas saturation of NMe gives NOE enhancement at H2' (2.9%), H8' (0.9%) and H6 (0.3%) which prove C2'*(R)*, C3'*(R)*, C7*(R)*, N10(S) configurations.

Conformation of tricyclic nucleoside derivatives 10, 13, 20 and 29.

The $^3J_{HH}$ measured at 500 MHz were translated into corresponding proton-proton torsion angles (Φ_{HH}) with

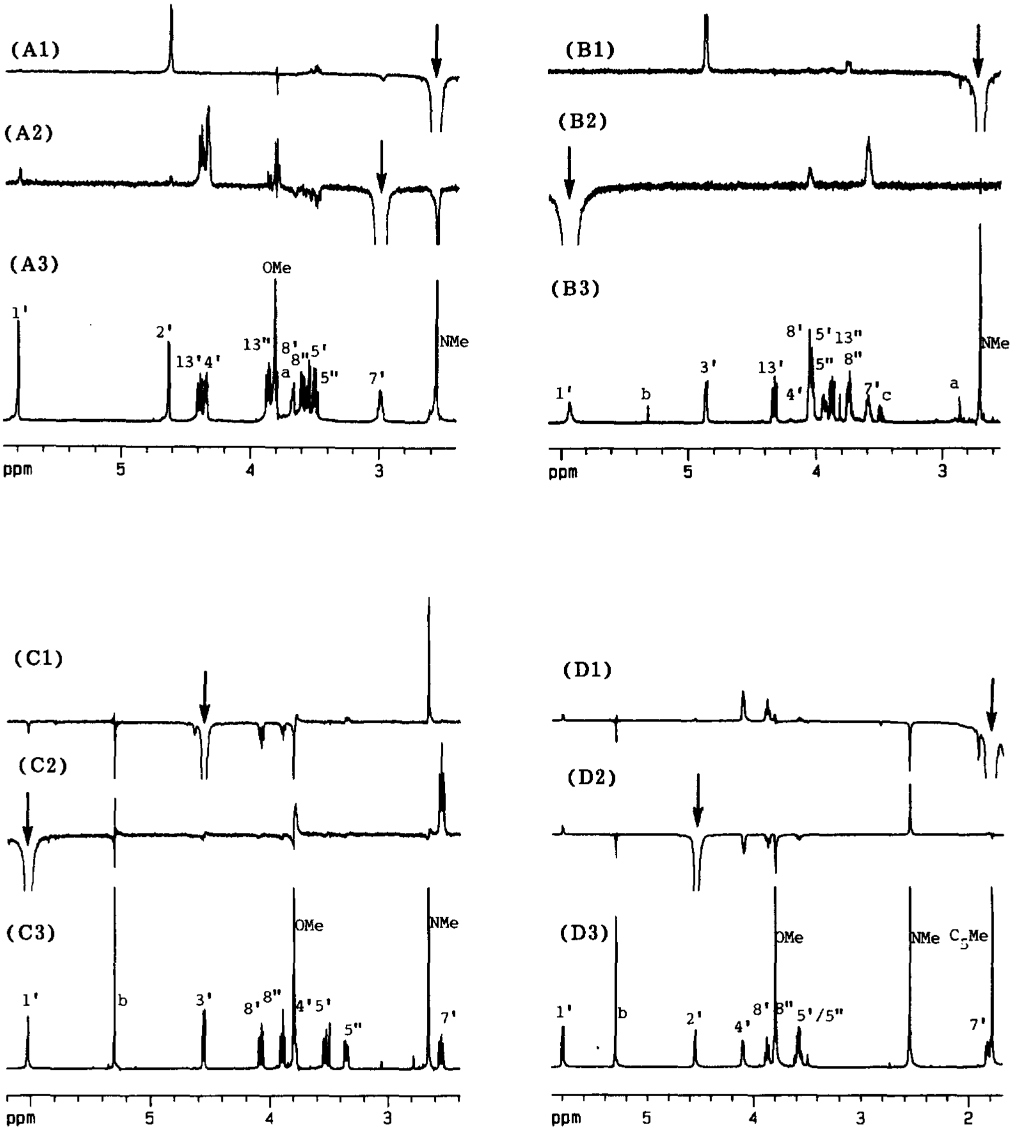


Figure 1. Expansions of the 500 MHz ^{1}H-NMR 1D NOE difference spectra and off-resonance spectra of compounds **10** [panels A1-A3], **13** [panels B1-B3], **20** [panels C1-C3] and **29** [panels D1-D3]. The arrows shown in NOE difference spectra, which were obtained upon subtraction of on- and off-resonance spectra, indicate the saturated proton. The observed NOE enhancements are discussed in the text. The signals labeled with a - c are due to: (a) unidentified impurity, (b) residual CH_2Cl_2 and (c) q of residual EtOH.

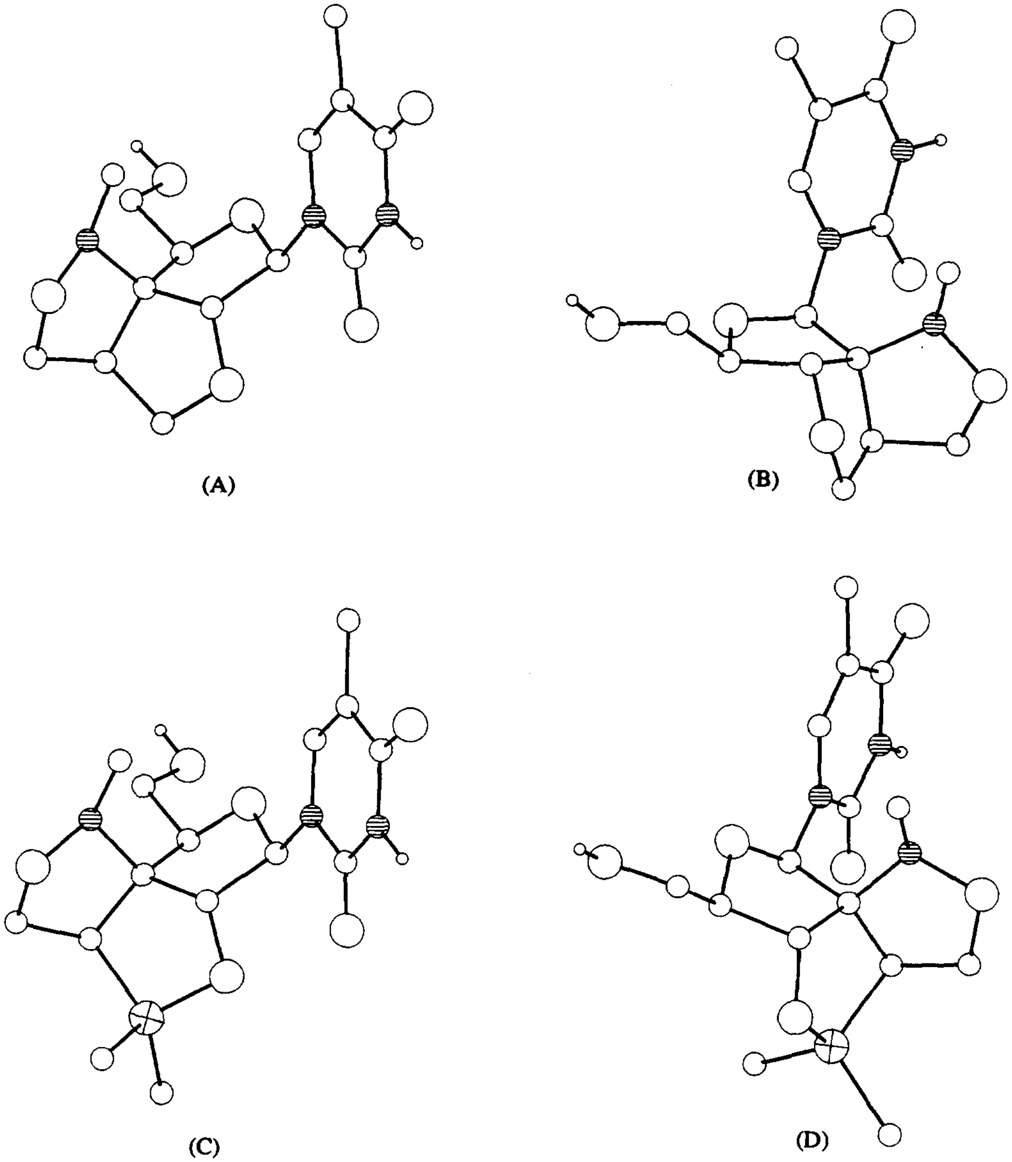


Figure 2. The conformers of **10** (panel: A), **13** (panel: B), **20** (panel: D) and **29** (panel: C) as obtained through energy minimisation (the generalized AMBER force field parameters as implemented in the computer program MacroModel V3.5a[19] were used) with constraints on Φ_{HH} to build structures that fulfil all torsional angles derived from $^3J_{HH}$ measured at 500 MHz NMR. For clarity, carbon bonded hydrogen atoms are not shown. In the case of **10**, **20** and **29** 5'-O-MMTr groups were replaced by hydrogen atoms. Details about the translation of $^3J_{HH}$ into Φ_{HH} are given in note 17. Detailed structural information is given in the text. Note the similarity in the overall conformation between **10** (panel: A) and **29** (panel: C), and between **13** (panel: B) and **20** (panel: D).

the use of generalised Karplus-Altona equation,[16] which includes a correction term due to electronegativities of substituents.[17] The computer program MacroModel[19] with its generalised AMBER force field parameters has been used to build structural models of **10**, **13**, **20** and **29**. The conformational study was restricted due to the absence of high quality force field parameters for C_8-O_9-N_{10}-Me structural fragments in all four compounds and additionally for C_7-Si-O fragments in **20** and **29**. The fused, rigid tricyclic structures of **10**, **13**, **20** and **29** were energy minimised with constraints on Φ_{HH} to yield conformers that fulfill all torsion angles derived from $^3J_{HH}$ values. The flat region of ±5° was used in which no energy penalty is paid, whereas the constraint energy outside the allowed region was calculated by $E = 1000$ kJ mol^{-1} rad^{-1} [1 - cos (deviation)]. In all energy minimised conformers of **10**, **13**, **20** and **29** presented in Figure 2 the Φ_{HH} were inside the allowed regions.

In the case of **10** five torsion angles were constrained to mutually consistent values ($\Phi_{1'2'} = 132°$, $\Phi_{7'8'} = 334°$, $\Phi_{7'8''} = 115°$, $\Phi_{7'13'} = 23°$, $\Phi_{7'13''} = 239°$) and resulting energy minimised conformer which satisfies all constraints is shown in Figure 2A (for clarity 5'-O-MMTr group and carbon bonded protons are not shown). The pentofuranose moiety in **10** (Fig. 2A) adopts East conformation ($P = 66°$, $\Psi_m = 38°$),[18] thymine is *anti* (χ[O4'-C1'-N1-C2] = 191°) and orientation across C4'-C5' is *trans* (γ[O5'-C5'-C4'-C3'] = 187°, experimental $^3J_{4'5'} = 3.9$ Hz and $^3J_{4'5''} = 6.8$ Hz show[21] 55% γ^t and 28% γ^+). The isoxazolidine moiety in **10** adopts O_9-*endo*-N_{10}-*exo* conformation ($P = 109°$, $\Psi_m = 46°$), whereas the pentofuranose fused to C2'-C3' is in $C_{2'}$-*endo*-$C_{3'}$-*exo* conformation ($P = 217°$, $\Psi_m = 20°$). Energy minimisation of **29** was performed by constraining three torsion angles ($\Phi_{1'2'} = 136°$, $\Phi_{7'8'} = 343°$, $\Phi_{7'8''} = 117°$). The resulting conformer of **29** (Fig. 2C) is characterised by East sugar geometry ($P = 62°$, $\Psi_m = 45°$), *anti* orientation of thymine ($\chi = 188°$) and *trans* orientation across C4'-C5' ($\gamma = 187°$, experimental $^3J_{4'5'} = 3.4$ Hz and $^3J_{4'5''} = 6.3$ Hz show[20] 51% γ^t and 38% γ^+). The isoxazolidine moiety in **29** is in O_9-*endo*-N_{10}-*exo* conformation ($P = 107°$, $\Psi_m = 42°$) and *cis*-fused silanofurane ring is in $C_{2''}$-*endo*-$O_{2'}$-*exo* conformation ($P = 254°$, $\Psi_m = 32°$). Note that **10** (Fig. 2A) and **29** (Fig. 2C) adopt similar overall conformation with only minor structural variations owing to different bond lengths and bond angles due to the presence of CH_2 group in **10** and $SiMe_2$ fragment in **29**.

The conformer of **13** (Fig. 2B) was obtained after energy minimisation with five torsion angles constrained to mutually consistent values ($\Phi_{3'4'} = 222°$, $\Phi_{7'8'} = 24°$, $\Phi_{7'8''} = 245°$, $\Phi_{7'13'} = 340°$, $\Phi_{7'13''} = 123°$).[17] The pentofuranose moiety in **13** (Fig. 2B) adopts North conformation ($P = 17°$, $\Psi_m = 25°$), thymine is *anti* ($\chi = 207°$) and orientation across C4'-C5' is *trans* ($\gamma = 182°$). The isoxazolidine moiety in **13** adopts envelope conformation close to O_9-*exo* ($P = 263°$, $\Psi_m = 34°$), whereas the pentofuranose fused to $C_{2'}$-$C_{3'}$ is in East conformation close to $O_{3'}$-*endo*-$C_{3'}$-*exo* twist conformation ($P = 101°$, $\Psi_m = 29°$). Energy minimisation of **20** was performed by constraining three torsion angles ($\Phi_{3'4'} = 208°$, $\Phi_{7'8'} = 336°$, $\Phi_{7'8''} = 228°$). The pentofuranose moiety in the energy minimised conformer of **20** (Fig. 2D) is characterised by geometry close to O4'-*endo* envelope ($P = 97°$, $\Psi_m = 44°$), *anti* orientation of thymine ($\chi = 209°$) and *trans* orientation across C4'-C5' ($\gamma = 184°$, experimental $^3J_{4'5'} = 2.4$ Hz and $^3J_{4'5''} = 4.9$ Hz show[20] 38% γ^t and 62% γ^+). The isoxazolidine moiety in **20** is in C_7-*endo*-C_{11}-*exo* conformation ($P = 6°$, $\Psi_m = 26°$) and *cis*-fused silanofurane ring is in Si-*endo*-C_7-*exo* conformation ($P = 320°$, $\Psi_m = 27°$).

Experimental

^1H NMR spectra were recorded using a Jeol JNM-GX 270 spectrometer operating at 270 MHz or a Bruker AMX-500 spectrometer operating at 500 MHz. Unless otherwise stated, spectra were recorded in the solvents indicated and at 20°C, using tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded at 67.8

MHz using both ^{1}H-coupled and ^{1}H-decoupled modes. Chemical shifts are quoted as δ in parts per million. Multiplicities are abbreviated to: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. A Jeol DX 303 spectrometer was used to record high resolution mass spectra. T.l.c. was carried out using Merck pre-coated silica gel F254 plates. Column chromatographic separations were carried out on Merck G60 silica gel using a gradient of methanol and dichloromethane. All solvents were distilled before use. Drying and purification of all solvents and reagents was accomplished by standard laboratory procedures.[21]

1-(5'-*O*-MMTr-2'-*O*-allyl-β-D-*xylo*furanosyl)thymine (2) and 1-(5'-*O*-MMTr-3'-*O*-allyl-β-D-*arabino*furanosyl)thymine (3) Sodium hydride (0.11 g, 4.5 mmol) was added slowly to a stirred solution of allyl alcohol (5 ml) maintained at 0-5°C and allowed to stir for a further 15 mins. A solution of 1-(5'-*O*-MMTr-2',3'-*O*-anhydro-β-D-*lyxo*furanosyl)thymine[9] (1) (0.77 g, 1.5 mmol) in allyl alcohol (3 ml) was then added and the resulting solution was sonicated for 72 h at room temperature. The reaction was quenched by the slow addition of saturated aqueous NH_4Cl to the mixture. Concentration of the reaction mixture to remove allyl alcohol followed by extraction of the aqueous phase with dichloromethane afforded a 2:3 mixture of the title compounds **2** and **3** as a foam, which was subsequently chromatographed on silica gel to give compound **2** (245 mg, 30%) and compound **3** (380 mg, 44%), as colourless foams. Compound **2**: ^{1}H NMR ($CDCl_3$) 9.04 (br s, 1H) NH; 7.59 (q, $J_{6,5Me}$ = 1.1 Hz) H6; 7.45-6.84 (m, 14H) arom.; 5.96-5.81 (m, 1H) Hb; 5.88 (d, $J_{1',2'}$ = 1.0 Hz, 1H) H1'; 5.30 (dq, $J_{a',a''}$, $J_{a,c'}$ and $J_{a,c''}$ = 1.6 Hz and J_{trans} = 17.2 Hz, 1H) Ha'; 5.24 (dq, $J_{a'',c'}$ and $J_{a'',c''}$ = 1.6 Hz and J_{cis} = 10.4 Hz, 1H) Ha"; 4.32-4.10 (m, 4H) Hc', Hc", H3' and H4'; 3.98 (d, 1H) H2'; 3.79 (s, 3H) OMe; 3.66 (dd, $J_{5',4'}$ = 4.4 Hz and $J_{5',5''}$ = 10.3 Hz, 1H) H5'; 3.58 (dd, $J_{5'',4'}$ = 4.2 Hz, 1H) H5"; 1.76 (d, 3H) 5Me. ^{13}C NMR ($CDCl_3$) 163.9 (s) C2; 158.8; 150.2 (s) C4; 143.4; 136.9 (d, J_{CH} = 185.9 Hz) C6; 134.5; 133.6 (d, J_{CH} = 157.5 Hz) Cb; 130.2; 128.0; 127.2; 117.7 (t, J_{CH} = 156.5 Hz) Ca; 113.3 (d, J_{CH} = 163.3 Hz) C-MMTr; 110.0 (s) C5; 90.2 (d, J_{CH} = 172.1 Hz) C1'; 87.6 (s) C-MMTr; 87.5 (d, J_{CH} = 152.6 Hz) C2'; 81.0 (d, J_{CH} = 150.7 Hz) C4'; 75.3 (d, J_{CH} = 154.6 Hz) C3'; 70.9 (t, J_{CH} = 143.8 Hz) Cc; 62.0 (t, J_{CH} = 143.8 Hz) C5'; 55.1 (q, J_{CH} = 143.5 Hz) OMe; 12.4 (q, J_{CH} = 129.1 Hz) NMe. MS (FAB$^-$) calc. for $(M-H)^-$ 569.2288, found 569.2300. Compound **3**: ^{1}H NMR ($CDCl_3$) 10.94 (br s, 1H) NH; 7.43-6.72 (m, 15H) H6 and arom.; 6.06 (d, $J_{1',2'}$ = 3.3 Hz, 1H) H1'; 5.80 (m, 1H) Hb; 5.20 (dq, $J_{a',a''}$, $J_{a',c'}$ and $J_{a',c''}$ = 1.3 Hz and J_{trans} = 17.1 Hz, 1H) Ha'; 5.09 (dq, J_{cis} = 10.5 Hz, 1H) Ha"; 4.80 (br d, $J_{OH,2'}$ = 4.3 Hz, 1H) OH; 4.68 (m, 1H) H2'; 4.15 (ddt, $J_{c',a}$ = 1.3 Hz, $J_{c',b}$ = 5.4 Hz and $J_{c'',c'}$ = 12.6 Hz, 1H) Hc'; 4.06 (m, 1H) H4'; 3.94 (ddt, $J_{c'',b}$ = 5.7 Hz, 1H) Hc"; 3.89 (d, $J_{3',4'}$ = 3.9 Hz, 1H) H3'; 3.62 (s, 3H) OMe; 3.36 (dd, $J_{5',4'}$ = 4.4 Hz and $J_{5'5''}$ = 10.3 Hz, 1H) H5'; 3.30 (dd, $J_{5'',4'}$ = 5.9 Hz, 1H) H5"; 1.48 (s, 3H) 5Me. ^{13}C NMR ($CDCl_3$) 165.8 (s) C2; 158.5; 150.4 (s) C4; 144.2; 139.3 (d, J_{CH} = 180.5 Hz) C6; 135.3; 134.0 (d, J_{CH} = 155.8 Hz) Cb; 130.2; 128.3; 127.7; 126.9; 117.3 (t, J_{CH} = 157.2 Hz) Ca; 113.0 (d, J_{CH} = 163.13 Hz) C-MMTr; 107.4 (s) C5; 86.9 (d, J_{CH} = 168.6 Hz) C1'; 86.5 (s) C-MMTr; 84.5 (d, J_{CH} = 150.3 Hz) C3'; 82.2 (d, J_{CH} = 149.4 Hz) C4'; 73.2 (d, J_{CH} = 154.9 Hz) C2'; 70.5 (t, J_{CH} = 142.5 Hz) Cc; 63.3 (t, J_{CH} = 142.9 Hz) C5'; 55.0 (q, J_{CH} = 143.0 Hz) OMe; 12.1 (q, J_{CH} = 125.6 Hz) 5Me. MS (FAB$^-$) calc. for $(M-H)^-$ 569.2288, found 569.2327.

1-(5'-*O*-MMTr-2'-*O*-allyl-β-D-*xylo*furanosyl)thymine (2) 3',5'-*O*-*iso*propylidene-β-D-5-methyluridine (4) (1.0 g, 3.4 mmol) was dissolved in THF and treated with sodium hydride (80% in parrafin oil) (0.3 g, 10 mmol). The resulting solution was stirred vigorously at room temperature for 15 minutes before a THF solution of allyl bromide (1.2 g, 10 mmol) was added in a dropwise fashion. The resulting mixture was stirred at room temperature for 7 h. The reaction was quenched by the addition of saturated ammonium chloride and then partitioned with dichloromethane. The organic phase was concentrated and the residue chromatographed on silica gel to afford 3',5'-*O*-*iso*propylidene-2'-*O*-allyl-β-D-5-methyluridine (**5**) (0.91 g, 80%) as a colourless foam. ^{1}H NMR ($CDCl_3$) 9.17 (s, 1H) NH; 7.93 (q, $J_{6,5Me}$ = 1.1 Hz, 1H) H6; 5.92 (m, 1H) Hb; 5.89 (s, 1H) H1'; 5.33 (dq, $J_{a',a''}$, $J_{a,c'}$ and $J_{a,c''}$ = 1.5 Hz and J_{trans} = 17.5 Hz, 1H) Ha'; 5.22 (dq, $J_{a'',c'}$ and $J_{a'',c''}$ = 1.5 Hz and J_{cis} = 10.4 Hz, 1H) Ha"; 4.39 (ddt, $J_{c',b}$ = 5.2 Hz and $J_{c',c''}$ = 12.9 Hz, 1H) Hc'; 4.31 (d, $J_{3',2'}$ = 2.1 Hz, 1H) H3'; 4.26-4.18 (m, 3H) Hc", H5' and H5"; 4.11-4.13 (m, 1H) H4'; 3.95 (m, 1H) H2'; 1.95 (d, 3H) 5Me; 1.48 (s, 3H) Me; 1.33 (s, 3H) Me. ^{13}C NMR ($CDCl_3$) 164.1 (s) C2; 150.3 (s) C4; 137.0 (d, J_{CH} = 185.1 Hz) C6; 133.6 (d, J_{CH} = 156.7 Hz) Cb; 117.8 (t, J_{CH} = 157.2 Hz) Ca; 108.8 (s) C5; 97.8 (s) C-*iso*propylidene acetal; 89.7 (d, J_{CH} = 168.6 Hz) C1'; 87.2 (d, J_{CH} = 149.4 Hz) C2'; 74.6 (d, J_{CH} = 149.5 Hz) C4'; 72.7 (d, J_{CH} = 156.7 Hz) C3'; 71.0 (t, J_{CH} = 156.7 Hz) Cc; 60.3 (t, J_{CH} = 146.2 Hz) C5'; 28.6 (q, J_{CH} = 127.4 Hz) Me; 18.4 (q, J_{CH} = 126.4 Hz) Me; 12.4 (q, J_{CH} = 128.3 Hz) 5Me. MS (FAB$^-$) calc. for $(M-H)^-$ 337.1400, found 337.1409. The allyl derivative **5** (320 mg, 1.0 mmol) was dissolved in 80% $AcOH/H_2O$ and stirred at room temperature overnight. The solution was concentrated under reduced pressure to give an oil which was chromatographed on silica gel to afford 2'-*O*-allyl-β-D-5-methyluridine (280 g, 97%) as a colourless oil. This oil was dissolved in pyridine (4 ml) and then treated with MMTrCl (400 mg, 1.3 mmol). The solution was stirred at room temperature overnight. The resulting yellow solution was poured into ice water and allowed to stir for several minutes. The suspension was then extracted with dichloromethane and the organic layer concentrated to give an oil which was chromatographed on silica gel to yield compound **2** (460 mg, 83%) as a colourless foam. This compound had spectral characteristics consistent with those reported above.

1-[5'-*O*-MMTr-3'-*C*,2'-*O*-ethylidene-3'-deoxy-3'-dehydro-spiro[3'*(S)*,11-(7*(S)*,10-*N*-*(S)*-methyl-9,10-isoxazolidine)-β-D-*ribo*furanosyl]thymine (10). Compound **2** (400 mg, 0.72 mmol), as a concentrated solution in CH_2Cl_2, was added to an already prepared complex of CrO_3/pyridine/Ac_2O, as desribed by Hansske *et al.* [11] The resulting ketonucleoside **6** was isolated as a yellow foam and used without further purification. Uloside **6**: ^{1}H NMR ($CDCl_3$) 8.55 (s, 1H) NH; 7.41 (s, 1H) H6; 7.28-6.72 (m, 14H) arom.; 6.19 (d, $J_{1',2'}$ = 7.6 Hz, 1H) H1'; 5.80 (m, 1H) Hb; 5.20 (m, 2H) Ha' and Ha"; 4.33 (d, 1H) H2'; 4.24 (m, 2H) Hc' and Hc"; 4.17 (m, 1H) H4'; 3.69 (s, 3H) OMe; 3.50 (dd, $J_{5',4'}$ = 2.6 Hz and $J_{5',5''}$ = 10.5 Hz, 1H) H5'; 3.29 (dd, $J_{5'',4'}$ = 1.9 Hz, 1H) H5"; 1.29 (s, 3H) 5Me. The crude ketonucleoside **6** was dissolved in dry pyridine (4 ml) and *N*-methylhydroxylamine hydrochloride (185 mg, 2.2 mmol) was added, with the resulting solution being maintained at 0-5°C for 48 h. The solvent was then removed under reduced pressure, the concentrate resuspended in dichloromethane and partitioned with water. The organic phase was concentrated under reduced pressure to yield a foam which was chromatographed on silica gel to afford the *title compound* **10** (220 mg, 56%): ^{1}H NMR ($CDCl_3$) 8.77 (br s, 1H) NH; 7.50-6.83 (m, 15 H) H6 and arom.; 5.80 (d, $J_{1',2'}$ = 4.1 Hz, 1H) H1'; 4.64 (d, 1H) H2'; 4.38 (dd, $J_{13',7'}$ = 7.3 Hz and $J_{13',13''}$ = 9.6 Hz, 1H) H13'; 4.34 (m, 1H) H4'; 3.86 (dd, $J_{13'',7'}$ = 5.3 Hz, 1H) H13"; 3.81 (dd, $J_{8',7'}$ = 6.8 Hz and $J_{8',8''}$ = 8.7 Hz, 1H) H8'; 3.80 (s, 3H) OMe; 3.59 (dd, $J_{8'',7'}$ = 2.3 Hz, 1H) H8"; 3.55 (dd, $J_{5',4'}$ = 4.0 Hz and $J_{5',5''}$ = 11.0 Hz, 1H) H5'; 3.48 (dd, $J_{5'',4'}$ = 6.8 Hz, 1H) H5"; 2.98 (m, 1H) H7'; 2.56 (s, 3H) NMe; 1.80 (d, $J_{5Me,6}$ = 1.1 Hz, 3H) 5Me. ^{13}C NMR ($CDCl_3$) 163.2 (s) C2; 158.6 (s); 150.0 (s) C4; 144.0; 143.92; 135.1; 134.8 (d, J_{CH} = 176.0 Hz) C6; 130.3; 128.4; 127.8; 127.0; 113.1 (d, J_{CH} = 158.5 Hz) C-MMTr; 110.9 (s) C5; 88.0 (d, J_{CH} = 166.8 Hz) C1'; 87.1 (s) C-MMTr; 85.6 (s) C3' ; 84.2 (d, J_{CH} = 154.9 Hz) C2'; 81.7 (d, J_{CH} = 147.6 Hz) C4'; 74.5 (t, J_{CH} = 146.2 Hz) C13; 70. 0 (t, J_{CH} = 145.3 Hz) C8; 61.9 (t, J_{CH} = 144.3 Hz) C5'; 55.1 (q, J_{CH} = 143.9 Hz) OMe; 54.2 (d, J_{CH} = 138.4 Hz) C7; 40.4 (q, J_{CH} = 135.6 Hz) NMe; 12.31 (q, J_{CH} = 132.9 Hz) 5Me. MS (FAB$^-$) calc. for (M-H)$^-$ 596.2397, found 596.2377.

1-[5'-*O*-MMTr-2'-*C*,3'-*O*-ethylidene-2'-deoxy-2'-dehydro-spiro[2'*(S)*,11-(7*(R)*,10-*N*-*(R)*-methyl-9,10-isoxazolidine)-β-D-*ribo*furanosyl]thymine (11). Compound **3** (160 mg, 0.29 mmol) was oxidized, as for compound **2** above, to yield crude ketonucleoside **8**. ^{1}H NMR ($CDCl_3$) 8.65 (br s, 1H) NH; 7.51-6.70 (m, 15H) H6 and arom.; 5.82 (m, 1H) Hb; 5.30-5.16 (m, 3H) Ha',Ha" and H1'; 4.49 (d, $J_{3',4'}$ = 7.9 Hz, 1H) H3'; 4.40 (ddt, $J_{c'a'}$ and $J_{c'a''}$ = 1.5 Hz, $J_{c',b}$ = 5.6 Hz and $J_{c',c''}$ = 12.6 Hz, 1H) Hc'; 4.21-4.00 (m, 2H) Hc" and H4'; 3.79 (s, 3H) OMe; 3.56 (dd, $J_{5',4'}$ = 3.3 Hz and $J_{5'5''}$ = 10.7 Hz, 1H) H5'; 3.47 (dd, $J_{5'',4'}$ = 5.1 Hz, 1H) H5"; 1.86 (d, $J_{5Me,6}$ = 1.2 Hz, 3H) 5Me. Crude ketonucleoside **8** was then treated with *N*-methylhydroxylamine as described above for the reaction of 2'-*O*-allyl nucleoside **2**. Following work up and chromatography on silica, the *title compound* **11** was isolated as a white solid (100 mg, 43%). ^{1}H NMR ($CDCl_3$) 8.70 (br s, 1H) NH; 7.48-6.83 (m, 15H) H6 and arom.; 6.06 (s, 1H) H1'; 4.75 (d, $J_{3',4'}$ = 5.8 Hz, 1H) H3'; 4.30 (dd, $J_{13',7'}$ = 7.5 and $J_{13',13''}$ = 9.2 Hz, 1H) H13'; 4.12 (m, 1H) H4'; 3.98 (dd, $J_{8',7'}$ = 6.2 and $J_{8',8''}$ = 8.6 Hz, 1H) H8'; 3.81 (dd, $J_{13'',7'}$ = 6.2, 1H) H13"; 3.67 (dd, $J_{8'',7'}$ = 2.9, 1H) H8"; 3.60 (m, 1H) H7'; 3.46 (m, 2H) H5' and H5"; 2.58 (s, 3H) NMe; 1.76 (d, $J_{5Me,6}$ = 1.0 Hz, 3H) 5Me; ^{13}C NMR ($CDCl_3$) 163.4 (s) C2; 158.8 (s); 150.2 (s) C4; 143.8; 135.7 (d, J_{CH} = 178.0 Hz) C6; 134.9; 130.3; 128.3; 127.8; 127.1; 113.2 (d, J_{CH} = 159.4 Hz) C-MMTr; 109.7 (s) C5; 89.2 (d, J_{CH} = 168.7 Hz) C1'; 87.1 and 86.8 (2 x (s)) C-MMTr and C2'; 81.1 (d, J_{CH} = 154.0 Hz) C3'; 80.2 (d, J_{CH} = 146.8 Hz) C4'; 73.8 (t, J_{CH} = 154.0 Hz) C13; 69.5 (t, J_{CH} = 150.3Hz) C8; 62.8 (t, J_{CH} = 142.1 Hz) C5'; 56.6 (d, J_{CH} = 137.4 Hz) C7; 55.1 (q, J_{CH} = 143.0 Hz) OMe; 40.6 (q, J_{CH} = 135.6Hz) NMe; 12.2 (q, J_{CH} = 130.2 Hz) 5Me. MS (FAB$^-$) calc. for (M-H)$^-$ 596.2397, found 596.2417

1-[3'-*C*,2'-*O*-ethylidene-3'-deoxy-3'-dehydro-spiro[3'*(S)*,11-(7*(S)*,10-*N*-*(S)*-methyl-9,10-isoxazolidine)-β-D-ribofuranosyl]thymine (12). Fused-tricyclic nucleoside **10** (60 mg) was treated with 80% aqueous acetic acid (2 ml) at room temperature overnight. The solvent was then removed under reduced pressure and the residue submitted to column chromatography to give deprotected nucleoside derivative **5** (31 mg, 93%) as a white solid. ^{1}H NMR ($CDCl_3$) 7.35 (s, 1H) NH; 5.83 (d, $J_{1',2'}$ = 4.8 Hz, 1H) H1'; 4.78 (d, 1H) H2'; 4.45 (dd, $J_{13',7'}$ = 7.5 Hz and $J_{13',13''}$ = 9.8 Hz, 1H) H13'; 4.34 (t, $J_{5',4'}$ and $J_{5'',4'}$ = 5.2 Hz, 1H) H4'; 4.04 (dd, $J_{8',7'}$ = 7.1 Hz and $J_{8',8''}$ = 9.0 Hz, 1H) H8'; 3.98 (m, 1H) H5'; 3.95 (dd, $J_{13'',7'}$ = 5.0 Hz, 1H) H13"; 3.91 (m, 1H) H5"; 3.79 (dd, $J_{8'',7'}$ = 3.8 Hz, 1H) H8"; 3.30 (m, 1H) H7'; 2.82 (s, 3H) NMe; 1.95 (s, 3H) 5Me. ^{13}C NMR ($CDCl_3$/CD_3OD) 164.2 (s) C2 ; 150.4 (s) C4; 135.9 (d, J_{CH} = 181.0 Hz) C6; 110.7 (s) C5; 87.8 (d, J_{CH} = 165.3 Hz) C1'; 85.9 (s) C3'; 84.1 (d, J_{CH} = 156.5 Hz) C2'; 82.3 (d, J_{CH} = 144.8 Hz) C4'; 73.4 (t, J_{CH} = 145.3 Hz) C13; 70.5 (t, J_{CH} = 149.7 Hz) C8; 59.8 (t, J_{CH} = 143.3 Hz) C5'; 54.5 (d, J_{CH} = 142.3 Hz) C7 40.3 (q, J_{CH} = 127.2 Hz) NMe; 11.6 (q, J_{CH} = 125.2 Hz) 5Me. MS (FAB$^-$) calc. for (M-H)$^-$ 324.1196, found 324.1164.

1-[2'-*C*,3'-*O*-ethylidene-2'-deoxy-2'-dehydro-spiro[2'*(S)*,11-(7*(R)*,10-*N*-*(R)*-methyl-9,10-isoxazolidine)-β-D-*ribo*furanosyl]thymine (13). Treatment of spiro-nucleoside **11** (40 mg) with 80% aqueous acetic acid (2 ml) as described above for the preparation of **12**, gave compound **13** (22 mg, 91%) as a white solid. ^{1}H NMR ($CDCl_3$) 7.25 (s, 1H) NH; 5.95 (br s, 1H) H1'; 4.86 (d, $J_{3',2'}$ = 5.9 Hz, 1H) H3'; 4.33 (dd, $J_{13',7'}$= 7.7 Hz and

$J_{13',13''}$ = 9.5 Hz, 1H) H13'; 4.04 (m, 3H) H4', H8' and H5'; 3.93 (m, 1H) H5"; 3.87 (dd,$J_{13'',7'}$ = 5.7 Hz, 1H) H13"; 3.75 (dd, $J_{8'',7'}$ = 4.2 Hz and $J_{8''8'}$ = 8.9 Hz, 1H) H8"; 3.59 (m, 1H) H7'; 3.72 (s, 3H) NMe; 1.97 (s, 3H) 5Me. ^{13}C NMR ($CDCl_3/CD_3OD$) 164.0 (s) C2; 150.4 (s) C4; 135.5 (d, J_{CH} = 181.9 Hz) C6; 111.0 (s) C5; 87.6 (d, J_{CH} = 165.3 Hz) C1'; 85.7 (s) C2'; 84.3 (d, J_{CH} = 156.5 Hz) C3'; 82.9 (d, J_{CH} = 146.8 Hz) C4'; 73.6 (t, J_{CH} = 149.7 Hz) C13; 70.0 (d, J_{CH} = 148.2 Hz) C8; 60.6 (t, J_{CH} = 143.8 Hz) C5'; 55.6 (d, J_{CH} = 138.9 Hz) C7; 40.4 (q, J_{CH} = 136.3Hz) NMe; 12.2 (q, J_{CH} = 128.5 Hz) 5Me. MS (FAB^-) calc. for $(M\text{-}H)^-$ 324.1196, found 324.1229.

1-(5'-*O*-MMTr-3'-*O*-TBDMS-β-D-*ribo*furanosyl)thymine (15) and 1-(5'-*O*-MMTr-2'-*O*-TBDMS-β-D-*ribo*furanosyl)thymine (24).[12] *tert*-Butyldimethylsilylchloride (0.71 g,9.4 mmol) was slowly added to a stirred solution of 1-(5'-*O*-MMTr-β-D-*ribo*furanosly)thymine[9] (**14**) (2.0 g, 3.8 mmol) and imidazole (0.64 g, 9.4 mmol) in dimethylformamide (4 ml). The mixture was stirred overnight at room temperature. The resulting mixture was poured into ice water and extracted with dichloromethane. The organic layer was concentrated under reduced pressure to yield an oil which consisted of three components. These components were separated by chromatography on silica. 1-(5'-*O*-MMTr-2',3'-*bis*-*O*-TBDMS-β-D-*ribo*furanosyl)thymine was isolated in 12 % yield while compound **15** was isolated in 33 % and compound **24** was isolated in 42 % yield. The isolated 2'-*O*-TBDMS protected derivative **24** was then dissolved in methanol and refluxed for 3 h. The reaction mixture was concentrated under reduced pressure and the concentrate chromatographed on silica to afford further **15**. Compound **15:** ^{1}H NMR ($CDCl_3$) 8.88 (br s, 1H) NH; 7.58 (q, $J_{6,5Me}$ = 1.1 Hz, 1H) H6; 7.43-6.83 (m, 14H) arom.; 5.98 (d, $J_{1',2'}$ = 5.6 Hz, 1H) H1'; 4.39 (dd, $J_{3',4'}$ = 3.8 and $J_{3',2'}$ = 5.6Hz, 1H) H3'; 4.28 (dt, $J_{2',OH}$ = 7.9 Hz, 1H) H2'; 4.06 (dt, $J_{4',5'}$ and $J_{4',5''}$ = 2.6 Hz, 1H) H4'; 3.80 (s, 3H) OMe; 3.54 (dd, $J_{5',5''}$ = 10.9 Hz, 1H) H5'; 3.26 (dd, 1H) H5"; 2.83 (d, 1H) OH; 1.50 (d, $J_{5Me,6}$ = 1.1 Hz, 3H) 5Me; 0.87 (s, 9H) $C(\underline{Me})_3$; 0.06 (s, 3H) SiMe; -0.03 (s, 3H) SiMe.^{13}C NMR ($CDCl_3$) 163.6 (s) C2; 158.7 (s) C4; 143.6; 135.5 (d, J_{CH} = 179.9 Hz) C6; 134.7; 130.2; 128.2; 127.3; 127.2; 113.2 (d, J_{CH} = 163.4 Hz) C-MMTr; 111.2 (s) C5; 88.8 (d, J_{CH} = 168.2 Hz) C1'; 87.1 (s) C-MMTr; 84.2 (d, J_{CH} = 151.6 Hz) C4'; 74.7 (d, J_{CH} = 151.5 Hz) and 71.7 (d, J_{CH} = 150.63 Hz) C2' and C3'; 62.8 (t, J_{CH} = 142.8 Hz) C5'; 55.1 (q, J_{CH} = 144.3 Hz) OMe; 25.6 (q, J_{CH} = 125.1 Hz) $C(\underline{Me})_3$; 17.9 (s) $\underline{C}(Me)_3$; 11.7 (q, J_{CH} = 129.1 Hz) 5Me; -4.9 (q, J_{CH} = 118.0 Hz) SiMe; -4.9 (q, J_{CH} = 118.0 Hz) SiMe. MS (FAB^-) calc. for $(M\text{-}H)^-$ 643.2840, found 643.2849. Compound **24**: ^{1}H NMR ($CDCl_3$) 8.57 (br s, 1H) NH; 7.65 (q, $J_{6,5Me}$ = 1.0 Hz, 1H) H6; 7.43-6.84 (m, 14H) arom.; 6.05 (d, $J_{1',2'}$ = 5.4 Hz, 1H) H1'; 4.50 (t, $J_{2',3'}$ = 5.4 Hz, 1H) H2'; 4.30 (ddd, $J_{3',4'}$ = 5.4 Hz and $J_{3',OH}$ = 4.0 Hz, 1H) H3'; 4.17 (m, 1H) H4'; 3.80 (s, 3H) OMe; 3.53 (dd, $J_{5',4'}$ = 2.2 Hz and $J_{5',5''}$ = 10.9 Hz, 1H) H5'; 3.49 (dd, $J_{5'',4'}$ = 2.0 Hz, 1H) H5"; 2.79 (d, 1H) OH; 1.37 (d, 3H) 5Me; 0.93 (s, 9H) $C(Me)_3$; 0.15 (s, 3H) SiMe; 0.14 (s, 3H) SiMe.^{13}C NMR ($CDCl_3$) 163.4 (s) C2; 158.8; 150.2 (s) C4; 143.6; 135.4 (d, J_{CH} = 177.5 Hz) C6; 134.5; 130.3; 128.2; 127.3; 113.3 (d, J_{CH} = 160.4 Hz) C-MMTr; 111.2 (s) C5; 87.8 (d, J_{CH} = 174.4 Hz) C1'; 87.3 (s) C-MMTr; 83.7 (d, J_{CH} = 150.5 Hz) C4'; 75.5 (d, J_{CH} = 149.4 Hz) C2'; 71.3 (d, J_{CH} = 158.8 Hz) C3'; 63.3 (t, J_{CH} = 145.9 Hz) C5'; 55.2 (q, J_{CH} = 143.2 Hz) OMe; 25.5 (q, J_{CH} = 130.8 Hz) $C(\underline{Me})_3$; 17.9 (s) $\underline{C}(Me)_3$; 11.5 (q, J_{CH} = 127.7 Hz) 5Me; -4.8 (q, J_{CH} = 120.4 Hz) SiMe; -5.2 (q, J_{CH} = 117.3 Hz) SiMe. MS (FAB^-) calc. for $(M\text{-}H)^-$ 643.2840, found 643.2825.

5'-*O*-MMTr-3'-*O*-TBDMS-2'-deoxy-2'-dehydro-(*E*)-(*N*-methyloximino)-5-methyluridine (17). Compound **15** (250 mg, 0.39 mmol) was oxidized to the corresponding 1-(5'-*O*-MMTr-3'-*O*-TBDMS-β-D-*erythro*pentafuran-2-ulosyl)thymine (**16**) using the oxidation procedure described by Hansske *et al.*[11] Uloside **16.** ^{1}H NMR ($CDCl_3$) 8.67 (br s, 1H) NH; 7.47-6.79 (m, 15H) H6 and arom.; 5.12 (s, 1H) H1'; 4.71 (d, $J_{3',4'}$ = 8.5 Hz, 1H) H3'; 4.05 (ddd, $J_{4',5'}$ = 2.3 Hz and $J_{4',5''}$ = 6.0 Hz, 1H) H4'; 3.80 (s, 3H) OMe; 3.53 (dd, $J_{5'5''}$ = 10.7 Hz, 1H) H5'; 3.35 (dd, 1H) H5"; 1.89 (s, 3H) NMe; 0.78 (s, 9H) $C(Me)_3$; 0.09 (s, 3H) SiMe; -0.07 (s, 3H) SiMe. The crude ketonucleoside **16** was in turn dissolved in pyridine. *N*-Methylhydroxylamine hydrochloride (100 mg, 1.2 mmol) was added to the pyridine solution and the mixture was kept at 0-5°C for 48 h. The reaction mixture was then concentrated under reduced pressure and at low temperature. The concentrate was partially dissolved in toluene and the supernatant decanted from the insoluable pyridinium hydrochloride. The toluene solution was concentrated under reduced pressure to yield 2'-nitrone **17**, which was isolated as a pale yellow foam after chromatography on silica (200 mg, 69%). ^{1}H NMR ($CDCl_3$) 8.37 (br s, 1H) NH; 7.44-6.78 (m, 15H) H6 and arom.; 6.21 (br s, 1H) H1'; 4.91 (br m, 1H) H3'; 4.30 (m, 1H) H4'; 3.78 (s, 3H) OMe; 3.71 (s, 3H) NMe; 3.54 (dd, $J_{5',4'}$ = 7.7 Hz and $J_{5',5''}$ = 10.5 Hz, 1H) H5'; 3.25 (d, 1H) H5"; 1.83 (br s, 3H) 5Me; 0.84 (s, 9H) $C(\underline{Me})_3$; 0.06 (s, 3H) SiMe; -0.16 (s, 3H) SiMe. ^{13}C NMR ($CDCl_3$) 164.0 (s) C2; 158.4; 149.7 and 146.9 (2 x (s)) C4 and C2'; 143.7; 139.6 (br d, J_{CH} = 176.3 Hz) C6; 134.9; 130.1; 128.2; 127.5; 126.7; 112.8 (d, J_{CH} = 157.5 Hz) C-MMTr; 110.4 (s) C5; 87.1 (br d) C1'; 87.1 (d, J_{CH} = 146.5 Hz) C4'; 86.3 (s) C-MMTr; 70.3 (d, J_{CH} = 153.1 Hz) C3'; 63.7 (t, J_{CH} = 142.7 Hz) C5'; 54.9 (q, J_{CH} = 144.3 Hz) OMe; 49.1 (q, J_{CH} = 144.3 Hz) NMe; 25.4 (q, J_{CH} = 125.6 Hz) $C(\underline{Me})_3$; 17.8 (s) $\underline{C}(Me)_3$; 11.92 (q, J_{CH} = 128.9 Hz) 5Me; -4.1 (q, J_{CH} = 119.0 Hz) SiMe; -5.0 (q, J_{CH} = 119.0 Hz) SiMe. MS (FAB^-) calc. for $(M\text{-}H)^-$ 670.2949, found 670.2939

5'-*O*-MMTr-2'-deoxy-2'-dehydro-(*E*)-(*N*-methyloximino)-5-methyluridine (18). Compound **17** (180 mg, 0.27 mmol) was added to a stirred suspension of NH_4F (150 mg, 4.1 mmol) in dry MeOH (5 ml) maintained at 0-5°C. The suspension was maintained at this temperature overnight. The reaction mixture was then treated with dichloromethane (5 ml) and filtered through a bed of silica using dichloromethane as the eluant. The filtrate was concentrated under reduced pressure to afford the *title compound* **18** (100 mg, 67%) as a colourless foam. ^1H NMR ($CDCl_3$) 8.86 (br s, 1H) NH; 7.44-6.82 (m, 15H) H6 and arom.; 6.30 (br s, 1H) H1'; 5.02 (m, 1H) H3'; 4.10 (m, 1H) H4'; 3.84 (s, 3H) NMe; 3.79 (s, 3H) OMe, 3.55 (m, 2H) H5',H5"; 1.74 (s, 3H) 5Me. ^{13}C NMR ($CDCl_3$) 164.0 (s) C2; 158.5; 150.0 and 149.1 (2 x (s)) C2 and C2'; 143.8; 138.7 (br d) C6; 135.0; 130.3; 128.3; 127.7; 127.0; 113.1 (d, J_{CH} = 160.3 Hz) C-MMTr, 111.0 (s) C5; 86.7 (s) C-MMTr; 84.9 (br d) C1'; 84.9 (d, J_{CH} = 155.7 Hz) C4'; 69.1 (d, J_{CH} = 157.5 Hz) C3'; 63.3 (t, J_{CH} = 144.3 Hz) C5'; 55.1 (q, J_{CH} = 145.3 Hz) OMe; 49.1 (q, J_{CH} = 144.2 Hz) NMe; 11.9 (q, J_{CH} = 129.8 Hz) 5Me. MS (FAB^-) calc. for $(M-H)^-$ 556.2084, found 556.2036

1-[5'-*O*-MMTr-2'-*C*,3'-*O*-dimethylsilamethylidene-2'-deoxy-2'-dehydro-spiro[2'*(S)*,11-(7*(S)*,.10-*N*-*(R)*-methyl-9,10-isoxazolidine)-β-D-ribofuranosyl]thymine (20). Compound **18** (100 mg. 0.18 mmol) was dissolved in pyridine (2 ml) and the solution was kept a 0-5°C. Vinyldimethylchlorosilane (22 mg, 0.18 mmol) was added in a dropwise fashion to the cooled solution and allowed to stir at this temperature overnight. The reaction mixture was concentrated under reduced pressure and then partially dissolved in toluene. The supernatant was removed and concentrated to give a yellow residue which was chromatographed on silica and crystallised from CH_2Cl_2/hexane to afford the *title compound* **20** (80 mg, 70%) as colourless plates. ^1H NMR ($CDCl_3$) 8.51 (br s, 1H) NH; 7.49-6.83 (m, 15H) H6 and arom.; 6.04 (s, 1H) H1'; 4.57 (d, $J_{3',4'}$ = 7.5 Hz, 1H) H3'; 4.08 (dd, $J_{8',7'}$ = 9.6 Hz and $J_{8',8''}$ = 8.2 Hz, 1H) H8'; 3.89 (dd, 1H) H8"; 3.80 (s, 3H) OMe; 3.79 (m, 1H) H4'; 3.54 (dd, $J_{5',4'}$ = 2.4 Hz and $J_{5',5''}$ = 10.7 Hz, 1H) H5'; 3.35 (dd, $J_{5'',4'}$ = 4.9, 1H) H5"; 2.66 (s, 3H) NMe; 2.56 (dd, $J_{7',8''}$ = 7.6 Hz, 1H) H7'; 1.81 (d, $J_{5Me,6}$ = 1.1 Hz, 3H) 5Me; 0.38 (s, 3H) SiMe; 0.31 (s, 3H) SiMe. ^{13}C NMR ($CDCl_3$) 164.0 (s) C2, 158.5, 143.9, 137.4 (d, J_{CH} = 191.7 Hz) C6; 134.9; 130.1; 128.1; 127.6; 126.8; 112.9 (d, J_{CH} = 164.3 Hz) C-MMTr; 108.4 (s) C5; 91.4 (d, J_{CH} = 173.12 Hz) C1'; 86.5 and 85.8 (2 x (s)) C-MMTr and C2'; 82.1 (d, J_{CH} =145.7 Hz) C4'; 79.6 (d, J_{CH} = 155.5 Hz) C3'; 65.6 (t, J_{CH} = 149.2 Hz) C8; 62.6 (t, J_{CH} = 144.3 Hz) C5'; 54.9 (q, J_{CH} = 143.8 Hz) OMe; 40.2 (d, J_{CH} = 131.7 Hz) C7; 39.6 (q, J_{CH} = 135.9 Hz) NMe; 12.2 (q, J_{CH} = 129.1 Hz) 5Me; 1.2 (q, J_{CH} = 119.3 Hz) SiMe; -2.8 (q, J_{CH} = 119.3 Hz) SiMe. MS (FAB^-) calc. for $(M-H)^-$ 640.2479, found 640.2498.

5'-*O*-MMTr-2'-deoxy-2'-dehydro-spiro[2'-*(S)*,11-(7*(S)*-hydroxy-10-*N*-*(R)*-methyl-9,10-isoxazolidine)] thymidine (21) Thymidine derivative **20** (80 mg, 0.12 mmol) was dissolved in a 1:1 mixture of MeOH and THF (2 ml). Potassium fluoride (28 mg, 0.48 mmol), $KHCO_3$ (48 mg, 0.48 mmol) and 30% H_2O_2 (0.12 ml) were added at once and at 5°C and the stirred solution was allowed to warm slowly to room temperature overnight. The reaction mixture was then concentrated under reduced pressure and the residue dissolved in dichloromethane, washed with water and again concentrated to give an oil which was chromatographed on silica to give the *title compound* **21** (71 mg, 91%) as a foam: ^1H NMR ($CDCl_3$) 7.39-6.75 (m, 15H) H6 and arom.; 6.09 (s, 1H) H1'; 5.09 (dd, $J_{7',8'}$ = 3.7 Hz and $J_{7',8''}$ = 6.1 Hz, 1H) H7'; 4.45 (d, $J_{3',4'}$ = 2.3 Hz, 1H) H3'; 4.17 (m, 1H) H4'; 3.93 (dd, $J_{8',8''}$ = 8.9 Hz, 1H) H8'; 3.83 (dd, 1H) H8"; 3.70 (s, 3H) OMe; 3.38 (dd, $J_{5',4'}$ = 4.6 Hz and $J_{5',5''}$ = 9.7 Hz, 1H) H5'; 3.16 (dd, $J_{5'',4'}$ = 7.4 Hz, 1H) H5"; 2.51 (s, 3H) NMe; 1.67 (d, $J_{5Me,6}$ = 1.1 Hz, 3H) 5Me; ^{13}C NMR ($CDCl_3$) 164.4 (s) C2; 158.7; 151.27 (s) C4; 143.8; 138.0 (d, J_{CH} = 85.1 Hz) C6; 135.0; 130.2; 128.2; 127.9, 113.2 (d, J_{CH} = 159.5 Hz) C-MMTr; 108.6 (s) C5; 88.4 (d, J_{CH} = 163.2 Hz) C1'; 86.8 (s) C-MMTr; 83.1 (d, J_{CH} = 152.2 Hz) C4'; 80.1 (d, J_{CH} = 153.9 Hz) C7; 79.6 (s) C2'; 75.1 (d, J_{CH} = 158.5 Hz) C3'; 73.6 (t, J_{CH} = 149.4 Hz) C8; 62.5 (t, J_{CH} = 144.8 Hz) C5'; 55.2 (q, J_{CH} = 135.6 Hz) OMe; 40.4 (q, J_{CH} = 137.5 Hz) NMe; 12.4 (q, J_{CH} = 130.2 Hz) 5Me. MS (FAB^-) calc. for $(M-MMTr)^-$ 328.1145, found 328.1171.

5'-*O*-MMTr-3'-*O*-acetyl-2'-deoxy-2'-dehydro-spiro[2'-*(S)*,11-(7(S)-acetyloxy-10-*N*-*(R)*-methyl-9,10-isoxazolidine]thymidine (22) Spiro-nucleoside derivative **21** (20 mg, 0.03 mmol) was co-evaporated with dry pyridine twice, redissolved in dry pyridine (2 ml) and then treated with acetic anhydride (100 µl, 1 mmol) at room temperature overnight. Pyridine was then removed under vacuum, the residue dissolved in 20 ml dichloromethane, washed with saturated aq. sodium bicarbonate solution and water, then evaporated to dryness. Residual pyridine was removed by coevaporating with toluene and dichloromethane. The concentrate was purified by preperative TLC to afford the diacetate **22** (12 mg, 58%). ^1H NMR ($CDCl_3$) 7.69 (br s, 1H) NH; 7.47-6.84 (m, 15H) arom. and H6; 6.26 (s, 1H) H1'; 5.92 (dd, $J_{7',8''}$ = 2.8 Hz and $J_{7',8'}$ = 6.1 Hz, 1H) H7'; 5.75 (s, 1H) H3'; 4.19 (dd, $J_{4',5'}$ = 6.5 Hz and $J_{4',5''}$ = 8.4 Hz, 1H) H4'; 4.10 (dd, $J_{8',8''}$ = 10.0 Hz, 1H) H8'; 3.80 (s, 3H) OMe; 3.77 (dd, 1H) H8"; 3.53 (dd, $J_{5',5''}$= 10.0 Hz, 1H) H5'; 3.16 (dd, 1H) H5"; 2.41 (s, 3H) NMe; 2.13 (s, 3H) $\underline{C}$OMe; 2.03 (s, 3H) $\underline{C}$OMe; 2.03 (s, 3H) 5Me. ^{13}C NMR ($CDCl_3$) 168.9 (s) $\underline{C}$OMe; 168.5 (s) $\underline{C}$OMe; 163.3 (s) C2; 158.8 (s); 150.5 (s) C4; 143.5; 137.0 (d, J_{CH} = 185.8 Hz) C6; 134.9; 130.1; 128.3; 127.9; 127.2; 113.2 (d, J_{CH} = 159.5 Hz) C-MMTr; 108.7 (s) C5; 88.4 (d, J_{CH} = 172.3 Hz) C1'; 87.04 (s) C-MMTr; 82.8 (d, J_{CH} = 153.6 Hz) C4'; 79.6 (d, J_{CH} = 162.4 Hz) C7; 78.6 (s) C2'; 75.0 (d, J_{CH} = 156.2 Hz) C3'; 72.4 (t, J_{CH} = 151.1 Hz) C8; 62.1 (t, J_{CH} =145.0 Hz) C5'; 55.2 (q, J_{CH} = 143.8 Hz) OMe; 39.9 (q, J_{CH} = 136.7 Hz) NMe; 20.8 (q, J_{CH} = 130.1 Hz) CO$\underline{Me}$; 20.59 (q, J_{CH} = 130.1 Hz) CO$\underline{Me}$; 12.49 (q, J_{CH} = 129.4 Hz) 5Me. MS

(FAB$^-$) calc. for (M-H)$^-$ 684.2557, found 684.2544 .

2'-Deoxy-2'-dehydro-spiro[2'-*(S)*,11-(7-*(S)*-hydroxy-10-*N*-*(R)*-methyl-9,10-isoxazolidine)]thymidine (23) Spiro nucleoside derivative **21** (70 mg, 0.12 mmol) was treated with 80% aqueous acetic acid (2 ml) at room temperature overnight. The solvent was then removed under reduced pressure and the residue submitted to column chromatography to give deprotected nucleoside derivative **23** (39 mg, 87%) as a white solid: ^{1}H NMR ($CDCl_3/CD_3OD$) 7.45 (s, 1H) H6; 6.00 (s, 1H) H1'; 5.12 (dd, $J_{7',8'}$ = 2.9 and$J_{7',8''}$= 5.9 Hz, 1H) H7'; 4.56 (d, $J_{3',4'}$ = 4.8 Hz, 1H) H3'; 4.12-3.82 (m, 5H) H4',H5',H5",H7' and H7"; 2.93 (s, 3H) NMe; 1.89 (s, 3H) 5Me. ^{13}C NMR ($CDCl_3/CD_3OD$) 164.5 (s) C2; 150.9 (s) C4; 138.3 (d, J_{CH} = 178.7 Hz) C6; 108.6 (s) C5; 87.84 (d,J_{CH} = 168.3 Hz) C1'; 83.69 (d, J_{CH} = 149.4 Hz) C4'; 80.1 (d, J_{CH} = 152.13 Hz) C7; 77.4 (s) C2'; 73.6 (t, J_{CH} = 149.8 Hz) C8; 72.4 (d, J_{CH} = 151.21 Hz) C3'; 60.0 (t, J_{CH} = 143.0 Hz) C5'; 40.7 (q, J_{CH} = 136.9 Hz) NMe; 12.03 (q, J_{CH} = 128.6 Hz) 5Me. MS (FAB$^-$) calc. for (M-H)$^-$ 328.1145, found 328.1169

5'-*O*-MMTr-3'-deoxy-3'-dehydro-(*Z*)-(*N*-methyloximino)-5-methyluridine (27). To a solution of 5'-*O*-MMTr-2'-*O*-TBDMS-3'-deoxy-3'-dehydro-*(Z)*-(*N*-methyloximino)-5-methyluridine (**26**) (200 mg, 0.3 mmol), obtained from 3-ketonucleoside **25** by a literature procedure,[4] in dry methanol (6 ml), NH_4F (160 mg, 4.3 mmol) was added. The reaction mixture was stirred at 0°C for 6 h. Dichloromethane (15 ml) was added and the resulting suspension was passed through a silica gel pad. The filtrate was concentrated and the residue purified by silica gel chromatography to afford *title compound* **27** (139 mg, 84%): ^{1}H NMR ($CDCl_3/CD_3OD$): 7.51 (q, $J_{H6,5Me}$ = 1.0 Hz, 1H) H6; 7.38-6.84 (m, 14H) arom.; 6.14 (d, $J_{1',2'}$ = 6.4 Hz, 1H) H1'; 5.07 (m, $J_{4',NMe}$ = 1.3 Hz, $J_{4',5''}$ = 1.8 Hz, $J_{4',5'}$ = 2.0 Hz and $J_{4',2'}$ = 2.8 Hz, 1H) H4'; 5.03 (m, $J_{2',NMe}$ = 1.3 Hz, 1H) H2'; 4.12 (dd, $J_{5',5''}$ = 10.1 Hz, 1H) H5'; 4.00 (t, 3H) NMe; 3.80 (s, 3H) OMe; 3.30 (dd, 1H) H5"; 1.32 (s, 3H) 5Me. ^{13}C NMR ($CDCl_3$): 163.6 (s) C4; 159.0 (s); 151.4 (s) C2; 148.1 (s); 144.1 (s); 143.7 (s); 135.0 (d, J_{CH} = 180.5 Hz) C6; 134.9 (s); 130.1; 128.0; 127.1; 113.3 (d, J_{CH} = 159.5 Hz) C-MMTr; 112.3 (s) C5; 87.7 (d, J_{CH} = 170.5 Hz) C1'; 87.0 (s) C-MMTr; 78.7 (d, J_{CH} = 158.6 Hz) and 73.1 (d, J_{CH} = 151.2 Hz) C2' and C4'; 61.4 (t, J_{CH} = 146.6 Hz) C5'; 55.1 (q, J_{CH} = 143.9 Hz) OMe; 48.9 (q, J_{CH} = 144.2 Hz) NMe; 11.5 (q, J_{CH} = 130.1 Hz) 5Me. MS (FAB$^-$) calc. for (M-H)$^-$ 556.2084, found 556.2104.

1-[5'-*O*-MMTr-3'-*C*,2'-*O*-dimethylsilamethylidene-3'-deoxy-3'-dehydro-spiro[3'*(S)*,11-(7*(R)*,10-*N*-*(S)*-methyl-9,10-isoxazolidine)-β-D-*ribo*furanosyl]thymine (29). Nucleoside derivative **26** (570 mg, 1.02 mmol) was coevaporated with dry pyridine two times, and redissolved in dry pyridine (5 ml). Vinyldimethylchlorosilane (123 mg, 11.02 mmol) was added dropwise to the pyridine solution maintained at 0°C. The reaction mixture was stirred at room temperature overnight, and then evaporated to dryness under vacuum. The residue was redissolved in CH_2Cl_2, washed (H_2O), dried over anhydrous $MgSO_4$ then concentrated. The residue was purified by silica gel chromatography and afforded *title compound* **29** (489 mg, 75%):^{1}H NMR ($CDCl_3$) 8.55 (br s, 1H) NH; 7.50-6.83 (m, 15H) H6 and arom.; 5.80 (d, $J_{1',2'}$ = 4.4 Hz) H1'; 4.55 (d, 1H) H2'; 4.10 (t, $J_{4',5'}$ and $J_{4',5''}$ = 4.8Hz, 1H) H4'; 3.93-3.78 (m, $J_{8',7'}$= 4.6 Hz, $J_{8',8''}$= 8.4 Hz and $J_{8'',7'}$ = 9.0 Hz, 5H) H8', H8" and OMe; 3.58 (d, 2H) H5' and H5"; 2.55 (s, 3H) NMe; 1.82 (dd, 1H) H7'; 1.78 (s, 3H) 5Me; 0.42 (s, 3H) SiMe; 0.30 (s, 3H) SiMe. ^{13}C NMR ($CDCl_3$): 163.2 (s) C4; 158.6 (s); 150.1 (s) C2; 144.2 (s); 144.1 (s); 135.3 (d, J_{CH} = 180.5 Hz) C6; 130.3; 128.4; 127.8; 127.0; 113.1 (d, J_{CH} = 163.1 Hz) C-MMTr; 110.9 (s) C5; 90.0 (d, J_{CH} = 166.8 Hz) C1'; 87.2 (s) C-MMTr; 84.1 (d, J_{CH} = 147.8 Hz) C4'; 83.0 (d, J_{CH} = 154.9 Hz) C2'; 66.3 (t, J_{CH} = 148.5 Hz) C8; 62.3 (t, J_{CH} = 144.8 Hz) C5'; 55.1 (q, J_{CH} = 143.9 Hz) OMe; 39.8 (q, J_{CH} = 135.6 Hz) NMe; 38.5 (d, J_{CH} = 128.3 Hz) C7; 12.3 (q, J_{CH} = 129.2 Hz) 5Me; 0.8 (q, J_{CH} = 120.1 Hz) SiMe; -2.5 (q, J_{CH} = 120.1 Hz) SiMe. MS (FAB$^-$) calc. for (M-H) 640.2479, found 640.2441.

5'-*O*-MMTr-3'-deoxy-3'-dehydro-spiro[3'-*(S)*,11-(7-*(R)*-hydroxy-10-*(S)*-*N*-methyl-9,10-isoxazolidine)]-5-methyluridine (30). Compound **29** (295 mg, 0.46 mmol), potassium fluoride (107 mg, 1.84 mmol), and potassium bicarbonate (184 mg, 1.84 mmol) were added to a solution of CH_3OH/THF (*v/v*, 1:1, 10 ml) maintained at 0°C, quickly followed by the addition of 30% H_2O_2 (0.46 ml, 4.6 mmol). The reaction mixture was then allowed to warm to room temperature over 4 h. The suspension was then passed throuh a silica gel pad and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford nucleoside derivative **30** (180 mg, 64%): ^{1}H NMR ($CDCl_3$): 7.69 (s, 1H) H6; 7.50-6.82 (m, 14H) arom.; 6.32 (d, $J_{OH,2' or 6'}$ = 1.7 Hz, 1H) OH; 5.94 (s, 1H) H1'; 4.66 (dd, $J_{7',8''}$= 5.3 Hz, $J_{7',8'}$ = 6.1 Hz, 1H) H7'; 4.56 (s, 1H) H2'; 4.53 (dd, $J_{4',5''}$ = 2.6 Hz, $J_{4',5'}$ = 7.9 Hz, 1H) H4'; 3.92 (dd, $J_{8',8''}$ = 9.4 Hz, 1H) H8'; 3.89 (s, 1H) OH; 3.86 (d, 1H) H8"; 3.80 (s, 3H) OMe; 3.65 (dd, $J_{5',5''}$ = 10.7 Hz, 1H) H5'; 3.12 (dd, 1H) H5"; 2.54 (s, 3H) NMe; 1.83 (s, 3H) 5Me. ^{13}C NMR ($CDCl_3$): 164.9 (s) C4; 158.5 (s); 150.6 (s) C2; 144.3 (s); 144.0 (s); 137.0 (d, J_{CH} = 175.1 Hz) C6, 135.4; 130.3; 128.5; 128.4; 127.7; 126.8; 113.0 (d, J_{CH} = 159.5 Hz) C-MMTr; 109.5 (s) C5; 91.8 (d, J_{CH} = 175.0 Hz) C1'; 86.8 (s) C-MMTr; 86.1 (d, J_{CH} = 151.2 Hz) C4'; 79.4 (s) C3'; 79.0 (d, J_{CH} = 152.1 Hz) C7; 77.7 (d, J_{CH} = 156.7 Hz) C2'; 72.1 (t, J_{CH} = 149.8 Hz) C8; 62.6 (t, J_{CH} = 145.3 Hz) C5'; 55.1 (q, J_{CH} = 143.9 Hz) OMe; 40.3 (q, J_{CH} = 134.7 Hz) NMe; 12.3 (q, J_{CH} = 128.3 Hz) 5Me. MS (FAB$^-$) calc. for (M-H) 600.2346, found 600.2294.

5'-*O*-MMTr-2'-*O*-acetyl-3'-deoxy-3'-dehydro-spiro[3'-*(S)*,11-(7-*(R)*-acetoxy-10-*N*-*(S)*-methyl-9,10-

isoxazolidine)]-5-methyluridine (31) and 5'-*O*-MMTr-3'-deoxy-3'-dehydro-spiro[3'-(*S*),11-(7(*R*)-acetoxy-10-N-(*S*)-methyl-9,10-isoxazolidine)]-5-methyluridine (32). The compound **30** (61 mg, 0.1 mmol) was co-evaperated with dry pyridine twice, redissolved in dry pyridine (2 ml), and then treated with acetic anhydride (100 µl, 1 mmol) at room temperature overnight. The solvent was removed in *vacuo*. The residue was dissolved in 20 ml dichloromethane, washed with saturated aq. sodium bicarbonate solution and water, repectively, dried over anhydrouse magnium sulphate, and then evaperated to dryness, co-eveperated with toluene and dichloromethane, respectively, purified with preperative TLC to afford the compound **31** (30 mg, 43%), and **32** (18 mg, 28%). Compound **31:** ^{1}H NMR ($CDCl_3$): 8.72 (s, 1H) NH; 7.58-6.84 (m, 15H) H6 and arom.; 5.82 (s, 1H) H1'; 5.71 (s, 1H) H2'; 5.38 (dd, $J_{7',8''}$= 3.3 Hz and $J_{7',8'}$ = 6.9 Hz, 1H) H7'; 4.33 (dd, $J_{4',5'}$ = 3.4 Hz and $J_{4',5''}$ = 7.7 Hz, 1H) H4'; 3.96 (dd, $J_{8',8''}$ = 10.3 Hz, 1H) H8'; 3.80-3.68 (m, 5H) H8", OMe, H5'; 3.14 (dd, 1H) H5"; 2.52 (s, 3H) NMe; 2.12 (s, 3H) COMe; 2.00 (s, 3H) COMe; 1.85 (s, 3H) 5Me. ^{13}C NMR ($CDCl_3$): 169.4 (s) $\underline{C}$OMe; 167.6 (s) C4; 158.6 (s); 149.9 (s) C2; 144.2 (s); 143.8 (s); 135.6 (d, J_{CH} = 190.6 Hz) C6; 135.2 (s); 130.3; 128.4; 128.3; 127.8; 127.0; 113.1 (d, J_{CH} = 154.9 Hz) C-MMTr; 109.3 (s) C5; 89.4 (d, J_{CH} = 177.8 Hz) C1'; 87.1 (s) C-MMTr; 85.7 (d, J_{CH} = 144.8 Hz) C4'; 78.4 (d, J_{CH} = 140.2 Hz) C7; 77.8 (s) C3'; 76.1 (d, J_{CH} = 174.1 Hz) C2'; 72.4 (t, J_{CH} = 150.3 Hz) C8; 62.4 (t, J_{CH} = 145.7 Hz) C5'; 55.1 (q, J_{CH} = 143.9 Hz) OMe; 40.0 (q, J_{CH} = 136.6 Hz) NMe; 20.6 (q, J_{CH} = 129.2 Hz) CO$\underline{Me}$; 20.5 (q, J_{CH} = 130.1 Hz) CO$\underline{Me}$; 12.4 (q, J_{CH} = 129.2 Hz) 5Me. MS (FAB$^-$) calc. for (M-H)$^-$ 684.2557, found 684.2560. Compound **32**: ^{1}H NMR ($CDCl_3$): 7.65-6.83 (m, 15H) H6 and arom.; 5.78 (s, 1H) H1'; 5.55 (dd, $J_{7',8'}$ = 3.4 Hz, $J_{7',8''}$ = 7.1 Hz, 1H) H7'; 5.19 (br s, 1H) 2'-OH; 4.58-4.52 (m, $J_{4',5''}$ = 2.8 Hz, $J_{4',5'}$ = 8.4 Hz, 2H) H2', H4'; 3.94-3.74 (m, $J_{8',8''}$ = 10.0 Hz, 5H) H8',H8", OMe; 3.65 (dd, $J_{5',5''}$ = 10.7 Hz, 1H) H5'; 3.11 (dd, 1H) H5"; 2.41 (s, 3H) NMe; 2.06 (s, 3H) 6'-$COCH_3$; 1.85 (s, 3H) 5Me. ^{13}C NMR ($CDCl_3$) 169.7 (s) $\underline{C}$OMe; 164.6 (s) C4; 158.5 (s); 150.8 (s) C2; 144.3 (s); 144.0 (s); 136.7 (d, J_{CH} = 188.8 Hz) C6; 135.3 (s); 130.3; 128.5; 128.3; 128.1; 127.7; 126.9; 113.0 (d, J_{CH} = 159.4 Hz) C-MMTr; 109.2 (s) C5; 92.5 (d, J_{CH} = 177.0 Hz) C1'; 86.8 (s) C-MMTr; 85.8 (d, J_{CH} = 152.6 Hz) C4'; 78.7 C7; 78.6 (s) C3'; 76.7 (d, J_{CH} = 155.5 Hz) C2'; 71.9 (t, J_{CH} = 150.6 Hz) C8; 62.6 (t, J_{CH} = 144.9 Hz) C5'; 55.1 (q, J_{CH} = 143.8 Hz) OMe; 39.9 (q, J_{CH} = 136.0 Hz) NMe; 20.7 (q, J_{CH} = 130.1 Hz) CO$\underline{Me}$; 12.5 (q, J_{CH} = 129.1 Hz) 5Me. MS (FAB$^-$) calc. for (M-C_2H_3O)$^-$ 600.2346, found 600.2372.

3'-deoxy-3'-dehydro-spiro[3'-(*S*),11-(7(*R*)-hydroxy-10-*N*-(*S*)-methyl-9,10-isoxazolidine)]-5-methyluridine (33) Treatment of **30** (50 mg, 0.08 mmol) with 80% aqueous acetic acid (2 ml) as described above for the preparation of **23**, afforded compound **33** (25 mg, 90%): ^{1}H NMR ($CDCl_3$ /CD_3OD): 7.90 (s, 1H) H6; 5.99 (d, $J_{1',2'}$ = 3.7 Hz, 1H) H1'; 5.39 (br s, 1H) OH; 4.92 (dd, $J_{7',8''}$ = 3.4 Hz and $J_{7',8'}$ = 6.6 Hz, 1H) H7'; 4.61 (d, 1H) H2'; 4.23 (dd, $J_{8',8''}$ = 10.1 Hz, 1H) H8'; 4.10 (dd, 1H) H8"; 4.04 (dd, $J_{4',5''}$ = 3.6 Hz, $J_{4',5'}$ = 4.6 Hz, 1H) H4'; 3.88 (dd, $J_{5',5''}$ = 12.9 Hz, 1H) H5'; 3.75 (dd, 1H) H5"; 3.45 (br s, 1H) OH; 2.80 (s, 3H) NMe; 1.92 (s, 3H) 5Me. ^{13}C NMR ($CDCl_3$/CD_3OD): 165.0 (s) C4; 151.0 (s) C2; 136.0 (d, J_{CH} = 185.8 Hz) C6; 109. (s) C5; 88.83 (d, J_{CH} = 171.3 Hz) C1'; 85.1 (d, J_{CH} = 147.4 Hz) C4'; 79.6 (d, J_{CH} = 151.6 Hz) C7; 76.1 (s) C3'; 75.9 (d, J_{CH} = 152.6 Hz) C2'; 73.0 (t, J_{CH} = 149.0 Hz) C8; 60.4 (t, J_{CH} = 143.8 Hz) C5'; 39.9 (q, J_{CH} = 137.0 Hz) NMe; 11.3 (q, J_{CH} = 128.7 Hz) 5Me MS (FAB$^-$) calc. for (M-H) 328.1145, found 328.1172.

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$$^3J_{HH} = P_1 \cos^2\Phi_{HH} + P_2 \cos\Phi_{HH} + P_3 + \sum \Delta\chi_i \{P_4 + P_5 \cos^2(\zeta_i \Phi_{HH} + P_6 |\Delta\chi_i|)\}$$

where P_1 - P_6 are parameters which were determined empirically with the use of a large coupling constant data set,[16] $\Delta\chi_i$ is a difference in Huggins electronegativity between the substituent and hydrogen and ζ_i denotes the orientation of the substituent relative to the coupled protons in H-C-C-H fragment. For **10** ($CDCl_3$, 20°C): (i) $J_{1'2'} = 4.1$ Hz ($\Phi_{1'2'} = 45°, 132°, 235°, 323°$), (ii) $J_{7'8'} = 6.8$ Hz ($\Phi_{7'8'} = 43°, 144°, 231°, 334°$), (iii) $J_{7'8''} = 2.3$ Hz ($\Phi_{7'8''} = 74°, 115°, 258°, 303°$), (iv) $J_{7'13'} = 7.3$ Hz ($\Phi_{7'13'} = 23°, 132°, 214°, 321°$), (v) $J_{7'13''} = 5.3$ Hz ($\Phi_{7'13''} = 52°, 135°, 239°, 324°$). For **13** ($CDCl_3$, 20°C): (i) $J_{3'4'} = 5.9$ Hz ($\Phi_{3'4'} = 31°, 138°, 222°, 329°$, (ii) $J_{7'8'} = 7.1$ Hz ($\Phi_{7'8'} = 24°, 131°, 215°, 320°$), (iii) $J_{7'8''} = 4.2$ Hz ($\Phi_{7'8''} = 59°, 129°, 245°, 317°$), (iv) $J_{7'13'} = 7.7$ Hz ($\Phi_{7'13'} = 36°, 148°, 226°, 340°$), (v) $J_{7'13''} = 5.7$ Hz ($\Phi_{7'13''} = 34°, 123°, 223°, 311°$. For **20** ($CDCl_3$, 20°C): (i) $J_{3'4'} = 7.5$ Hz ($\Phi_{3'4'} = 9°, 149°, 208°, 348°$), (ii) $J_{7'8'} = 9.6$ Hz ($\Phi_{7'8'} = 13°, 144°, 206°, 336°$), (iii) $J_{7'8''} = 7.6$ Hz ($\Phi_{7'8''} = 41°, 146°, 228°, 335°$). For **29** ($CDCl_3$, 20°C): (i) $J_{1'2'} = 4.4$ Hz ($\Phi_{1'2'} = 43°, 136°, 234°, 329°$), (ii) $J_{7'8'} = 9.1$ Hz ($\Phi_{7'8'} = 28°, 151°, 219°, 343°$), (iii) $J_{7'8''} = 4.6$ Hz ($\Phi_{7'8''} = 41°, 117°, 229°, 303°$).
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