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Synthesis of 2'- and 3'-Spiro-isoxazolidine Derivatives of Thymidine & Their Conversions to 2',3'-dideoxy-2',3'-didehydro-3'-C-substituted nucleosides by Radical Promoted Fragmentation.

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Abstract: *We herein report the synthesis of a new class of 2'- and 3'-spiro-nucleosides (3 - 19, 38 - 55) by the 1,3-dipolar cycloaddition reaction of 2'- or 3'-methylnitrone (2, 36 or 37) with ethyl vinyl ether and acrylonitrile It has been also shown that the free-radical promoted deoxygenation of 3'-hydroxy group vicinal to the 2'-spiro function in the free-radical precursor 15, 17 or 19 gives a mixture of 2',3'-dideoxy-2',3'-didehydro-2'-C-substituted thymidines (20, 21, 24 , 26, 28 or 32) and/or 2',3'-dideoxy-2'-spiro- derivatives (30) Similarly, the deoxygenation of 2'-hydroxy group vicinal to the 3'-spiro function in the free-radical precursor 49, 52 or 55 gives a mixture of 2',3'-dideoxy-2',3'-didehydro-3'-C-substituted nucleosides (59, 60 or 62) and/or 2',3'-dideoxy-3'-spiro-nucleosides (56 and 57) The results described herein constitute the first report of the synthesis of spiro-(1,2-isoxazolidine) derivatives of nucleosides and their use in the unique free-radical cleavage reactions to give 2',3'-dideoxy-2',3'-didehydro-C-branched nucleosides*

Recent biochemical studies have clearly shown that multiple drug chemotherapy is perhaps the treatment of choice against AIDS in order to avoid the severe drug resistance problems. This means that, despite the availability of three FDA approved nucleoside based drugs (AZT[1], ddI[2] and ddC[3]) which are specific against HIV specific reverse transcriptase, new types of 2'/3'-deoxy-3'/2'-substituted nucleoside derivatives should be available as candidate drugs for effective treatment against AIDS and AIDS related syndromes.

We herein report the synthesis of a new class of 2'- and 3'-spiro nucleosides (**3 - 19, 38 - 55**) by the 1,3-dipolar cycloaddition reaction of 2'- and 3'-methylnitrones (**2, 36** or **37**) with ethyl vinyl ether and acrylonitrile. It has been also shown that the free-radical promoted deoxygenation of 3'-hydroxy group vicinal to the 2'-spiro function in the free-radical precursor **15, 17** or **19** gives a mixture of 2',3'-dideoxy-2',3'-didehydro-2'-C-substituted nucleosides (**20, 21, 24, 26, 28** or **32**) and/or 2',3'-dideoxy-2'-spironucleoside (**30**). Similarly, the deoxygenation of 2'-hydroxy group vicinal to the 3'-spiro function in the free-radical precursor **49, 52** or **55** gives a mixture of 2',3'-dideoxy-2',3'-didehydro-3'-C-substituted nucleosides (**59, 60** or **62**) and/or 2',3'-dideoxy-3'-spironucleosides (**56** and **57**) The results described herein constitute the first report of the synthesis of spiro-(1,2-isoxazolidine) derivatives of nucleosides and their use in the unique free-radical cleavage reactions to give 2',3'-dideoxy-2',3'-didehydro-C-branched nucleosides Nitrone chemistry as means to form simple isoxazolidines or fused bicyclic isoxazolidines through 1,3-dipolar cycloaddition reactions has been extensively utilized[4] and the stereochemical studies of these cycloaddition reactions have been also well documented.[4,5,6i,7,9] Tronchet and co-workers[6a-f] have outlined the preparation of nitrone derivatives of pentofuranose and the corresponding isoxazolidines or isoxazolines sugar derivatives by the dipolar cycloaddition reactions with appropriate ethylenes or ethynes. Vasella *et al.* [6g-i] has reported the cycloaddition

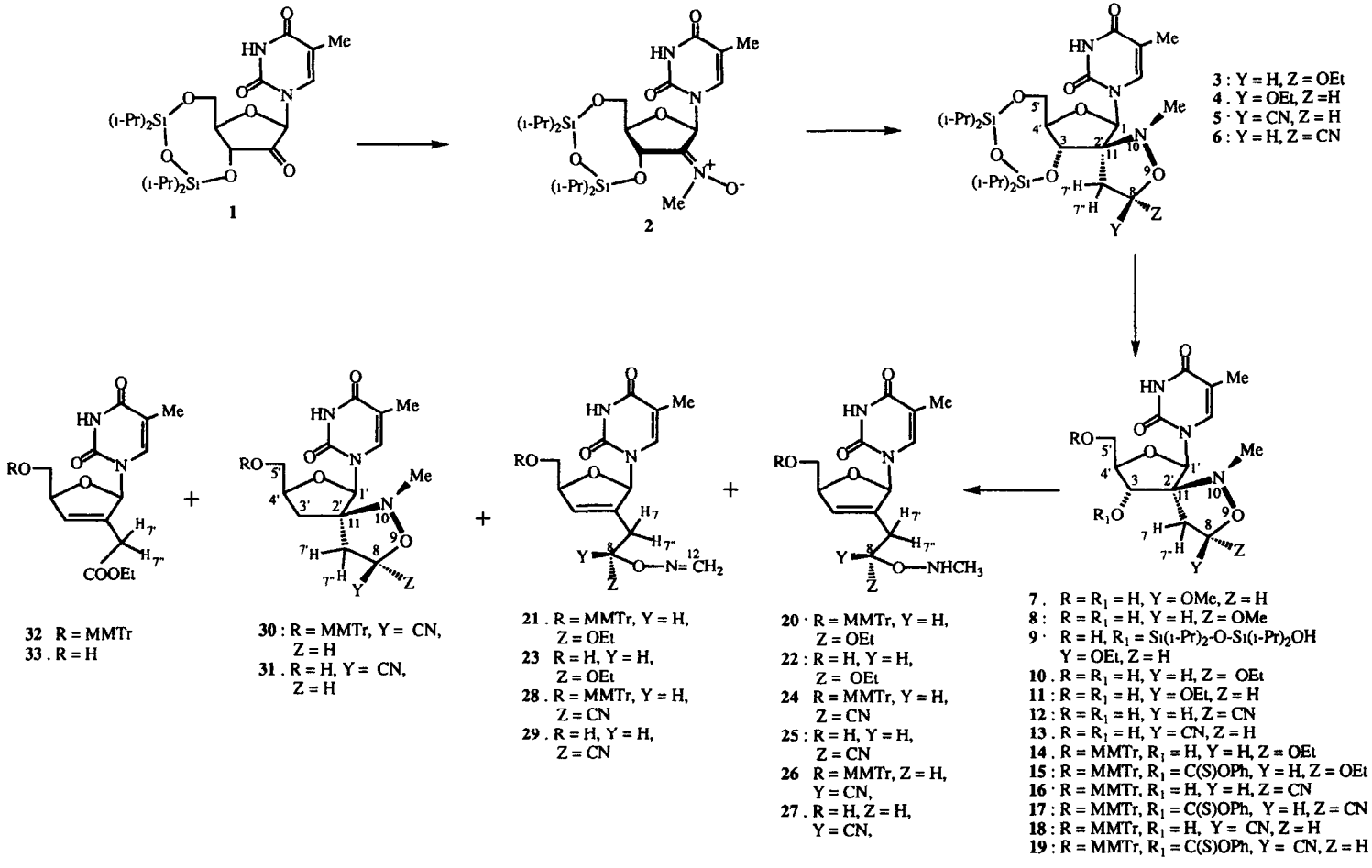
reaction of nitrone in carbohydrate chemistry for the modification of the anomeric center. Earlier, isoxazolidine chemistry[7] has been used for the homologation of simple aldehydes to α,β-unsaturated aldehydes or acyclic amino alcohols. Other groups have focused their attention on the synthesis of C1-spiro[8,9] and C3-spiro[10] pentofuranose derivatives. Ueda *et al.*[11] first introduced spiroepoxide derivatives in the nucleoside chemistry. Robins *et al.* have made 2'-spiropyrazoline derivatives of nucleoside by the dipolar cycloaddition of 2'-deoxy-2'-methylene adenosine with CH_2N_2 [12] Reaction of O-mesylcyanohydrin-3-uloses of furanose[10] or thymidine[14] has also afforded 3(3')-spiro-(1,2-oxathiole-2,2-dioxide) derivatives.

[A] Preparation of the 2'- and 3'-methylnitrone derivatives of ribothymidine. The 3',5'-O-[tetraisopropyldisiloxane-1,3-diyl (Tipsil)][15] protected β-D-ribothymidine[13] was oxidised by pyridiniumdichromate (PDC)[16] in CH_2Cl_2 to its corresponding 2'-uloside **1** which was treated with N-methylhydroxylamine hydrochloride in pyridine solution to give the corresponding 2'-(Z)-methylnitrone **2** as the sole product which was isolated in 75% yield. A reaction with 3'-ketone **34**[16,17] or **35**[16,17] with N-methylhydroxylamine hydrochloride under identical condition however gave the 3'-(E)-methylnitrone **36** (59%) or **37** (52%), respectively.

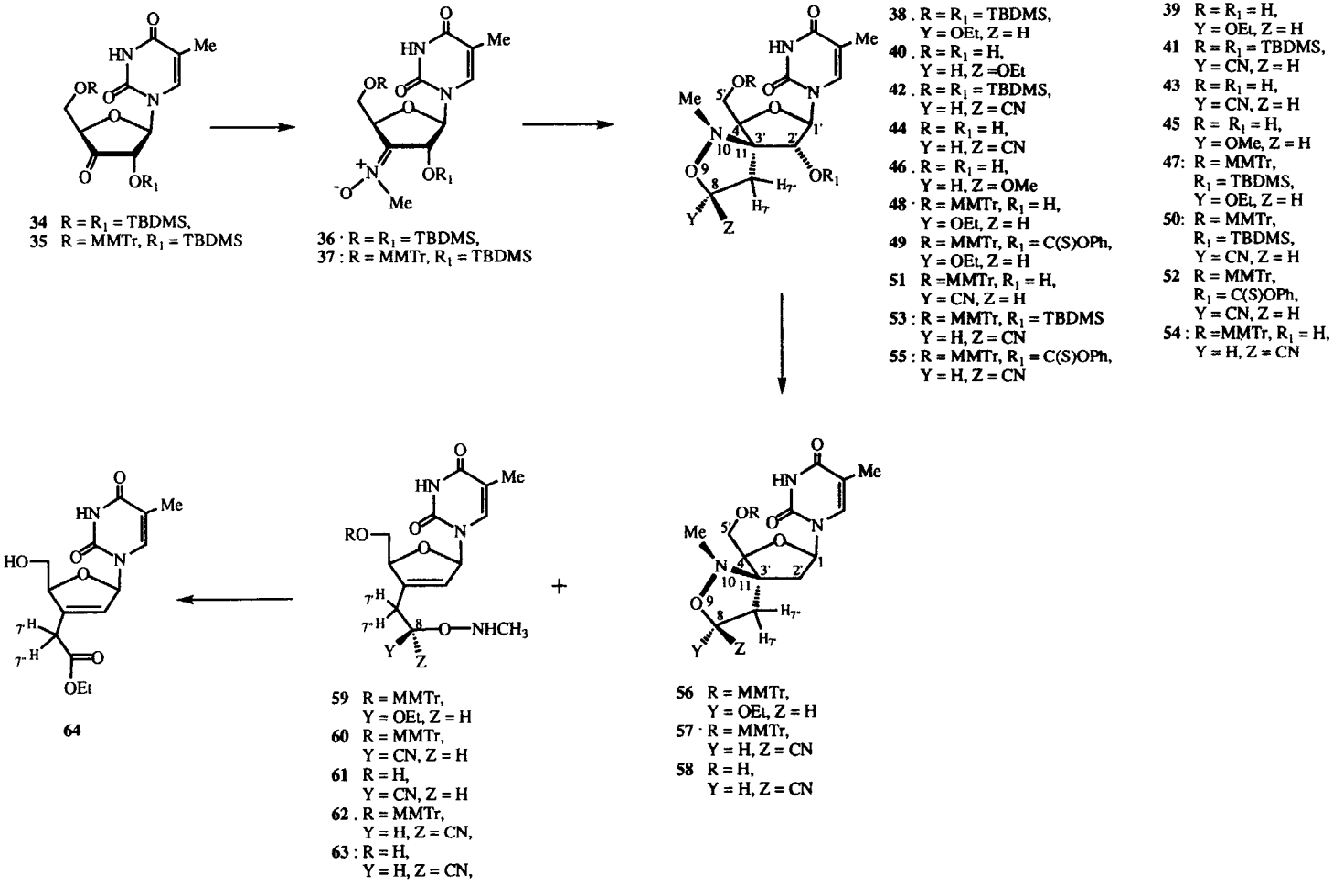
The configurations of **2** and **36** were determined through one-dimensional (1D) NOE difference spectroscopy [^{1}H-NMR at 500 MHz]. Upon saturation of 2'-NMe in **2**, H3' showed 0.8% enhancement which indicates Z configuration along 2'C=N bond. In a similar way, the E configuration across 3'C=N double bond in **36** has been confirmed by NOE enhancement at NMe (1.1%) upon saturation of H2'. The stereospecific formation of the above single isomer as the sole product is probably due to the steric and hydrophobic interaction between N-methyl group of alkylnitrone with the silyl groups at 2' or 3' positions.

[B] Reaction of 2'-methylnitrone 2 and 3'-methylnitrone 36 with olefins. Methylnitrone **2** or **36** was treated with electron-rich (ethyl vinyl ether) and electron-deficient (acrylonitrile) olefins. The [2+3]-cycloaddition reaction of **2** or **36** with ethyl vinyl ether at RT gave only adduct **3** (97%) or **38** (95%), respectively, in a diastereospecific manner. Clearly, adducts **3** and **38** were formed through the mediation of the *exo* transition state,[5a] in which the two large substituents (*i.e. N*-Me and *C*-OEt) are in trans-1,3-dipseudoaxial orientation.[5a] On the other hand, the reaction of **2** with acrylonitrile gave **5** (42%) and **6** (53%) in 45:55 ratio, whereas the corresponding reaction with **36** gave **41** (53%) and **42** (24%) in 2:1 ratio. The major diastereomer formed in the latter reaction was found to be in 1,3-trans-pseudoaxial orientation due to the kinetically favoured *exo* transition state.[5a] All of these cycloaddition reactions proceed through the transition states formed exclusively at the α-face of the sugar moiety (*vide infra*). This is consistent with both diazomethane cycloaddition[12] to 2'-methylenadenosine and dipolarophile addition to the sugar-nitrone[9] which also proceed preferentially from the α-face of the pentofuranose ring. All cycloadducts reported in this paper were stable and resistant to the isomerization even at a higher temperature (~90 °C). The structural integrity of 5(8)-substituted-[1(9),2(10)-isoxazolidines] (note that the actual numbering of all atoms used for NMR and NOE assignments are shown in parenthesis which are also shown in the formulae in *Schemes 1 and 2*) is corroborated by the chemical shifts of H8 and H7'/H7" protons at δ 5.49-4.74 and δ 3.43-2.18 ppm, respectively, which are consistent with the literature NMR data on simple 5-substituted-1,2-isoxazolidines[5a,9,18,19] and also through the independent characterization of 2',3'-dideoxy-2',3'-didehydro-*C*-branched nucleosides (*e.g.* **20** and **59**), *vide infra*

[C] Assignment of stereoconfigurations of spiro-isoxazolidines. The C2'-(S) configuration in spiro-isoxazolidines **3**, **5** and **6** was proved by 1D NOE difference spectroscopy. Saturation of H7" in **3** gives key


1
2
3 : Y = H, Z = OEt
4 . Y = OEt, Z =H
5 · Y = CN, Z = H
6 : Y = H, Z = CN
7 . R = R1 = H, Y = OMe, Z = H
8 : R = R1 = H, Y = H, Z = OMe
9 · R = H, R1 = Si(i-Pr)2-O-Si(i-Pr)2OH
Y = OEt, Z = H
10 . R = R1 = H, Y = H, Z = OEt
11 : R = R1 = H, Y = OEt, Z = H
12 : R = R1 = H, Y = H, Z = CN
13 . R = R1 = H, Y = CN, Z = H
14 . R = MMTr, R1 = H, Y = H, Z = OEt
15 : R = MMTr, R1 = C(S)OPh, Y = H, Z = OEt
16 · R = MMTr, R1 = H, Y = H, Z = CN
17 : R = MMTr, R1 = C(S)OPh, Y = H, Z = CN
18 : R = MMTr, R1 = H, Y = CN, Z = H
19 : R = MMTr, R1 = C(S)OPh, Y = CN, Z = H
20 · R = MMTr, Y = H, Z = OEt
22 : R = H, Y = H, Z = OEt
24 R = MMTr, Y = H, Z = CN
25 : R = H, Y = H, Z = CN
26 R = MMTr, Z = H, Y = CN,
27 . R = H, Z = H, Y = CN.
21 . R = MMTr, Y = H, Z = OEt
23 R = H, Y = H, Z = OEt
28 . R = MMTr, Y = H, Z = CN
29 . R = H, Y = H, Z = CN
30 : R = MMTr, Y = CN, Z = H
31 . R = H, Y = CN, Z = H
32 R = MMTr
33 . R = H

Scheme 1


34 R = R1 = TBDMS,
35 R = MMTr, R1 = TBDMS
36 · R = R1 = TBDMS,
37 : R = MMTr, R1 = TBDMS
38 . R = R1 = TBDMS, Y = OEt, Z = H
40 . R = R1 = H, Y = H, Z = OEt
42 . R = R1 = TBDMS, Y = H, Z = CN
44 R = R1 = H, Y = H, Z = CN
46 . R = R1 = H, Y = H, Z = OMe
48 · R = MMTr, R1 = H, Y = OEt, Z = H
49 R = MMTr, R1 = C(S)OPh, Y = OEt, Z = H
51 R = MMTr, R1 = H, Y = CN, Z = H
53 : R = MMTr, R1 = TBDMS Y = H, Z = CN
55 : R = MMTr, R1 = C(S)OPh, Y = H, Z = CN
39 R = R1 = H, Y = OEt, Z = H
41 R = R1 = TBDMS, Y = CN, Z = H
43 R = R1 = H, Y = CN, Z = H
45 R = R1 = H, Y = OMe, Z = H
47: R = MMTr, R1 = TBDMS, Y = OEt, Z = H
50: R = MMTr, R1 = TBDMS, Y = CN, Z = H
52 R = MMTr, R1 = C(S)OPh, Y = CN, Z = H
54 : R = MMTr, R1 = H, Y = H, Z = CN
56 R = MMTr, Y = OEt, Z = H
57 · R = MMTr, Y = H, Z = CN
58 R = H, Y = H, Z = CN
59 R = MMTr, Y = OEt, Z = H
60 R = MMTr, Y = CN, Z = H
61 R = H, Y = CN, Z = H
62 . R = MMTr, Y = H, Z = CN,
63 : R = H, Y = H, Z = CN,
64

Scheme 2

NOE enhancements at H1' (5.3%) and H4' (2 1%) which prove C2'-(S) configuration. Saturation of NMe in **3** gives NOE enhancements at H3' (1.9%), which proves N10-(R) configuration, and at H7' (0.7%) and H8 (0.5%) which prove that NMe, H7' and H8 are on the same side of isoxazolidine moiety. The saturation of H8 in **3** also results in 1D NOE enhancements at cisoid H7' (3.6%) and transoid H7" (0 9%), which additionally prove C8-(S) configuration. The configurations at newly formed chiral centres in **5** [C2'-(S), C8-(R), N10-(R)] have been confirmed by key NOE enhancements at H8 (1.8%) and H7" (4.3%) upon saturation of H1', and at NMe (3.6%) upon saturation of H3'. The C2'-(S) configuration in **6** has been established through NOE enhancements at H7" (5.2%) upon saturation of H1' and at H7' (0.4%) and H7" (0.9%) upon saturation of H4'. NOE enhancements observed between cisoid H7' and H8 (6.0%) and transoid H7" and H8 (0.8%) prove C8-(S) configuration in **6**. The spatial proximity of H3' and NMe in **6** is consistent with N10-(R) configuration and is clearly established by 4.8% NOE enhancement upon saturation of H3'. Saturation of H7' in 1D NOE spectra of **38** gives key NOE enhancements at H1' (2 0%) and H4' (5.7%) which prove C3'-(S) configuration. Saturation of NMe in **38** gives NOE enhancements at H2' (3.0%), H7" (0 6%) and H8 (0.7%) which prove N10-(S) configuration and show that NMe, H7" and H8 are on the same face of isoxazolidine ring. This is consistent with C8-(R) configuration in **38** and has been additionally confirmed through saturation of H8 and key NOE enhancements observed at cisoid H7" (3.2%) and transoid H7' (0.5%). Spatial proximity of H2' and NMe group in stereoisomers **41** [C3'-(S), C8-(R), N10-(S)] and **42** [C3'-(S), C8-(S), N10-(S)] has been confirmed by NOE enhancements at NMe in both **41** (3.5%) and **42** (4 0%) upon saturation of H2'. That H7' and H7" in **41** are located on the α-face of pentofuranose moiety [C3'-(S)] have been shown through NOE enhancements at H7' (1.6%) and H7" (0.5%) upon saturation of H1'. Saturation of H7" in **41** yields key NOE enhancement at cisoid H8 (6.5%), which confirms C8-(R) configuration. Saturation of H1' in **42** yields NOE enhancement at H7' (0.8%) and saturation of H4' gives key enhancements at H7' (2.4%) and H8 (0.8%) which clearly prove that H7' and H7" are on the α-face of pentofuranose moiety [C3'-(S) configuration in **42**]. The C8-(S) configuration in **42** has been proved by NOE enhancements between cisoid H7" and H8 (2.7%) and transoid H7' and H8 (0.3%) upon saturation of H8.

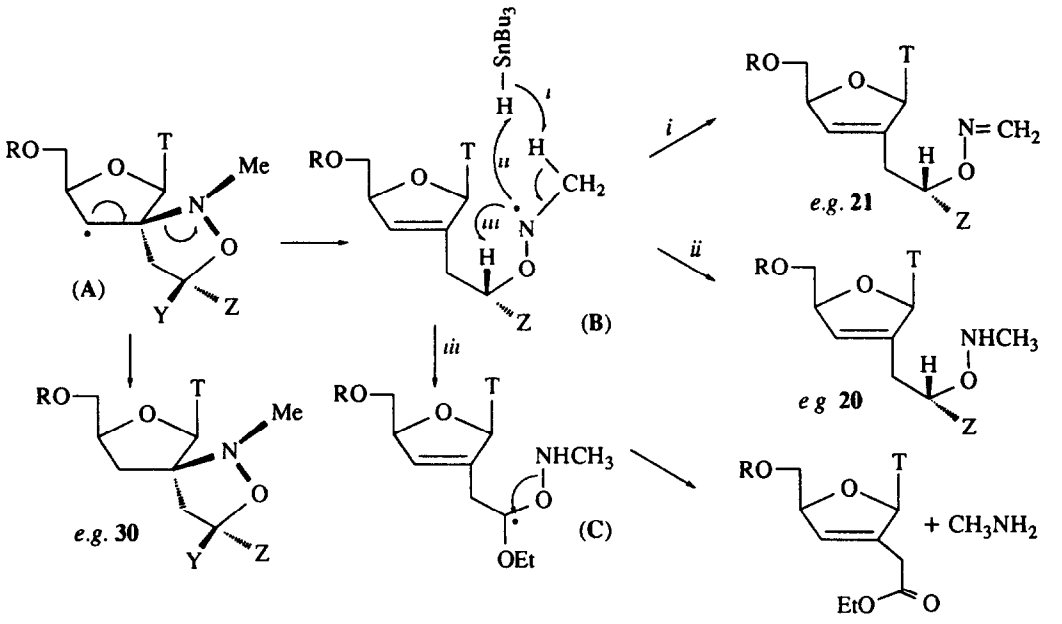
[D] Acid catalyzed isomerization at the chiral C8 center of 2'- and 3'-spiroisoxazolidines. The treatment of 2'-spirothymidine **10** (C8-S) in dry *methanol* containing 20% CF_3CO_2H at 45 °C for 70 h gave an equilibrium mixture of diastereomeric **7** (C8-R) and **8** (C8-S) in 10·1 ratio (^{1}H-NMR at 270 MHz). Similarly, the treatment of 2'-spirothymidine **10** (C8-S) in dry *ethanol* containing 20% CF_3CO_2H at 45 °C for 70 h gave an equilibrium mixture of **11** (C8-R) and **10** (C8-S) in ~5.1 ratio (^{1}H-NMR at 270 MHz). It appears from the product distribution that 3'-hydroxy group exerts more steric and electronic influence on the direction of approach of the alcohol than thymine base because the less bulky methoxide prefers to attack the C8 carboxonium ion of 2'-spiroisoxazolidine from the opposite side (pro-R) of thymine base more effectively (R : S = 10:1) than the relatively more bulky ethoxide ion (R : S = 5:1). This has been actually assessed by the acid catalyzed isomerization of **3** (C8-S) with bulky 3'-O-silyl group, which under the latter acidic condition gave an equilibrium mixture of **3** (C8-S) (30%), **4** (C8-R) (23%) and **9** (C8-R) (20%) The product distribution in the this reaction shows that the ratio of C8-(S) versus C8-(R) is now 3.4. This also suggests that the steric and electronic influence of the 3'-substituent (*i e* 3'-OH or 3'-O-silyl) is more dominant than thymine base for the above reaction of 2'-spirothymidine **3** or **10** due to the fact that thymine at the β-face of the sugar ring is oriented further away from the 2'-isoxazolidine ring whereas the 3'-OH or 3'-O-silyl group and 2'-isoxazolidine are all on the same α-face In contrast, a treatment of 3'-spirothymidine **39** (C8-R) in dry *methanol* containing

20% CF_3CO_2H at 45 °C for 70 h gave the equilibrium mixture of diastereomeric **45** (C8-R) and **46** (C8-S) in 1: 1.2 ratio (^{1}H-NMR at 270 MHz) whereas in dry *ethanol* the equilibrium mixture of **39** (C8-R) and **40** (C8-S) in 1: 1.5 ratio (^{1}H-NMR at 270 MHz) were obtained. This clearly shows that 2'-OH has no significant influence on the direction of approach of methoxide and ethoxide ion at the C8-carboxonium ion of 3'-spiroisoxazolidine, although the distance between 2'-OH and C8 in **39** are quite comparable to the distance between 3'-OH and C8 in **3** and **10**. This suggests that 2'-OH in 3'-spirothymidine **39** is most probably involved in some intramolecular hydrogen bonding with the carbonyl function of thymine residue and can not therefore interact with the incoming alcohol.

[E] Assignment of stereoconfigurations of acid-isomerized spiro-isoxazolidines. Saturation of H7" in 1D difference NOE spectra of **10** gives key NOE enhancements at both H1' (2.8%) and H4' (1.1%) which are consistent with C2'-(S) configuration. The N10-(R) configuration in **10** has been proved by key NOE enhancement at NMe (3.5%) upon saturation of H3'. The saturation of NMe in **10** gives NOE enhancements at H3' (1.6%), H7' (0.8%) and H8 (0.2%), which confirm that NMe, H7' and H8 are on the same face of the isoxazolidine moiety. The saturation of H8 in **10** also results in NOE enhancement at cisoid H7' (2.3%) and transoid H7" (0.7%), which additionally prove C8-(S) configuration. The saturation of H1' in **7** gives key NOE enhancement at H8 (0.9%) and H7" (4.7%), and saturation of H7" results in key NOE enhancements at H1' (7.9%), H4' (1.3%) and cisoid H8 (5.5%) which prove C8-(R) configuration. Similarly, saturation of H1' in **11** gives NOE enhancements at H8 (0.7%) and H7" (3.4%), and saturation of H7" results in NOE enhancements at H1' (4.7%), H4' (0.8%) and cisoid H8 (4.0%) which are consistent with C8-(R) configuration. It is noteworthy that N10-(R) configuration in both **7** and **11** has been retained during the acid-catalyzed isomerization, which has been confirmed by the observation of key NOEs between H3' and NMe in both **7** (3.9%) and **11** (3.8%) upon saturation of H3'. The assignment of chiral centres of the isoxazolidine ring has been found to be C3'-(S), C8-(R), N10-(S) in **39** and C3'-(S), C8-(S), N10-(S) in **40** on the basis of the following NOE connectivities. Saturation of H7" in **39** gives NOE enhancement at H1' (0.7%) and saturation of H7' gives enhancements at H1' (2.4%) and H4' (4.8%) which are consistent with C3'-(S) configuration. Saturation of H8 in **39** also gives enhancements at cisoid H7" (3.4%) and transoid H7' (0.7%), which are in agreement with C8-(R) configuration. The C8-(S) configuration in **40** was confirmed by saturation of H8 which produced key NOE enhancements at H4' (0.9%), cisoid H7' (2.6%) and transoid H7" (0.3%). That H7' and H7" are located on the α-face of pentofuranose moiety (*i.e.* C3'-(S) configuration) has been confirmed by NOE contacts between H1' and H7" (0.7%, H7" saturated) and by enhancements at H1' (1.3%) and H4' (4.1%) upon saturation of H7'.

[F] Preparation of the free radical precursors and the radical promoted ring-opening reaction of spiroisoxazolidines. The 5'-hydroxyl group of **10** was protected with 4-monomethoxytrityl (MMTr) to give **14** (93%) which was subsequently converted to the radical precursor **15** (91%) upon treatment with phenoxythiocarbonyl chloride in dry acetonitrile in presence of N,N-dimethylaminopyridine. Similarly, the mixture of **12** and **13** was also converted to the corresponding 5'-O-MMTr protected derivatives, **16** (55%) and **18** (33%), which were separated and subsequently converted to the corresponding 3'-phenoxythiocarbonyl nucleosides **17** (61%) and **19** (82%). For the preparation of 5'-O-MMTr protected 3'-spiroisoxazolidine-2'-O-phenoxythiocarbonyl nucleosides **49** , the following procedure has been used: 2'-O-TBDMS group was removed from **47** by a treatment of NH_4F in boiling methanol[20] to give **48** (93%) which was then treated with phenoxythiocarbonyl chloride under a condition described for **15** to give **49** (85%). Similarly, **50** and **53** were also converted to the corresponding radical precursors **52** [**50** → **51** (94%) → **52** (49%)] and **55** [**53** → **54** (77%)

→ **55** (88%)] (see experimental section for details). Compound **15** was then treated with tributyltin hydride and azobisisobutyronitrile (AIBN) in toluene at 100 °C for 30 min to yield **20** (45%), **21** (9%) and **32** (8%). The treatment of **17** under the latter free-radical condition for 60 min gave only **24** (60%) and **28** (5%). The tributyltin hydride treatment of **19** under the above radical condition produced **26** (45%) and **30** (20%). Compound **49**, upon treatment with tributyltin hydride and AIBN in toluene at 100 °C for 30 min, gave **56** (22%), **59** (30%) and **48** (9%). The treatment of **52** under the latter free-radical condition for 60 min gave only



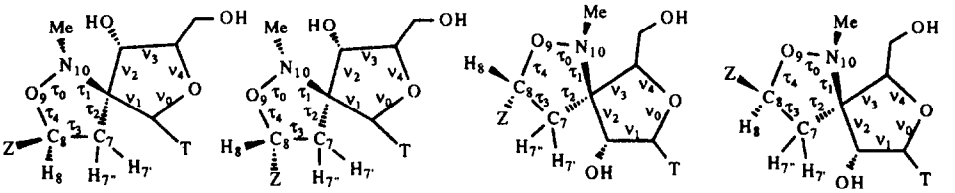
Scheme 3

60 (56%). The tributyltin hydride treatment of **55** under an identical condition produced **62** (45%) and **57** (30%). The distribution of various radical-reaction products in the above reactions suggests that radical reaction pathways of 2'- and 3'-spiroisoxazolidines involve a C3'- or C2'-radical intermediate, respectively, which are summarized in *Scheme 3* using the fragmentation pathways of 2'-spiroisoxazolidine[27] as an example. The abstraction of a hydrogen atom by C3' radical [intermediate (A) in *Scheme 3*], giving 3'-deoxy-2'-spiro-thymidine (*e.g.* **30**), competes with the breaking of C2'-N10 bond of the 2'-spiro-isoxazolidine ring [shown by arrows in intermediate (A)] to give the N10-nitrogen-radical [intermediate (B) in *Scheme 3*]. The intermediate (B) can then abstracts a hydrogen atom from Bu_3SnH [fragmentation pathway (ii) in intermediate (B)] to give **20** or Bu_3Sn radical abstract a hydrogen atom from NMe [fragmentation pathway (i) in intermediate (B)] to give **21**, or a 1,3-hydrogen abstraction from C8 center [fragmentation pathway (iii) in intermediate (B)] leads to **32** through C8-radical intermediate (C).

Removal of 5'-O-MMTr group from **20**, **21**, **24**, **26**, **28**, **30**, **32**, **57**, **59**, **60** and **62** by a brief treatment of 80 % aqueous acetic acid at RT gave the corresponding 5'-hydroxy derivative **22** (27%), **23** (86%), **25** (56%), **27** (68%), **29** (88%), **31** (94%) and **33** (94%), **58** (78%), **64** (75%), **61** (84%) and **63** (87%) respectively. Removal of silyl protections from **3**, **5** and **6** by a brief treatment of TBAF solution in THF give 3',5'-dihydroxy

analogues **10** (98 %), **13** (90%) and **12** (92%), respectively. The configurations at C2', C8 and N10 in **12** and **13** under the latter deprotection condition have been retained, which have been substantiated by detailed 1D difference NOE experiments (data not shown). The silyl protections in **38**, **41** and **42** were removed by treatment of NH_4F[20] in boiling CH_3OH to give the corresponding 2',5'-dihydroxy analogues **39** (82%), **43** (80%) and **44** (83%), respectively. Detailed one dimensional NOE difference spectroscopy was also used to prove that the configuration at C3', C8 and N10 in **43** and **44** remained unchanged in the latter deprotection condition and were identical to those of the parent compounds **41** and **42** (data not shown).

[G] Conformational analysis of 2'- and 3'-spironucleosides. Saturated five-membered rings are generaly puckered. In the case of spironucleosides, we are faced with two heterocyclic rings (*i.e.* ribofuranose and isoxazolidine) which only share one common atom of the sugar ring (C2'/C3'). The conformation of both ribofuranosyl and isoxazolidine rings is described by the pseudorotation concept.[21] A phase angle of pseudorotation (P) defines the part of the ring which is mostly puckered and a puckering amplitude (Ψ_m) indicates the extent of puckering. Note that the phase angle (P^{IS}) and puckering amplitude (Ψ_m^{IS}) are related to the endocyclic torsion angles (τ_0 - τ_4) of isoxazolidine moiety,[22] while P^R and Ψ_m^R are related to ν_0 - ν_4 of ribofuranosyl moiety as shown in *Scheme 4*.



10: Z = OEt
12: Z = CN

11: Z = OEt
13: Z = CN

39: Z = OEt
43: Z = CN

40: Z = OEt
44: Z = CN

T = thymine-1-yl

Scheme 4

Conformational analysis of both the ribofuranose and isoxazolidine rings in solution is based on the experimental vicinal proton-proton coupling constants ($^3J_{HH}$) measured from 233K - 318K presented in Table I. The experimental $^3J_{3'4'}$ in **10**, **11**, **12** and **13** (Table I) show that the ribofuranose moiety adopts preferentially (> 90%) North conformation at 293K (limiting $^3J_{3'4'}$ = 8.6 Hz for P^R = 0° and 1.0 Hz for P^R = 165° at Ψ_m^R = 39°). The $^3J_{1'2'}$ in **39** and **43** show that their ribofuranose moieties prefer the South conformation by approximately 90% at 293K (limiting $^3J_{1'2'}$ = 1.0 Hz for P^R = 0° and 7.5 Hz for P^R = 165° at Ψ_m^R = 39°), whereas ribofuranose rings in **40** and **44** are involved in ≈1:2 and ≈1:4 North ⇄ South equilibria, respectively. The populations of the three staggered rotamers across C4'-C5' (γ^+, γ^t and γ^-) presented in Table I were calculated from $^3J_{4'5'}$ and $^3J_{4'5''}$.[23] Two observables ($^3J_{7'8}$ and $^3J_{7''8}$) are available from ^{1}H-NMR measurements for the isoxazolidine rings in spiro compounds (Table I) which clearly can not define five unknowns [P_N^{IS}, P_S^{IS}, $\Psi_m^{IS}(N)$, $\Psi_m^{IS}(S)$ and X_S]. We have therefore used a graphical method to translate $^3J_{7'8}$ and $^3J_{7''8}$ into a rough structural model. The variation of $^3J_{7'8}$ and $^3J_{7''8}$ with the phase angle of pseudorotation of the isoxazolidine ring (P^{IS}) at fixed puckering amplitude (Ψ_m^{IS} = 39°) has been calculated by the use of generalised Karplus equation.[24,25] The curves correlating $^3J_{7'8}$ and $^3J_{7''8}$ as a function of P^{IS} were specifically

generated for both OEt and CN substituted isoxazolidine moieties with C8-(R) and C8-(S) configurations in **10**,

Table 1 : $^3J_{HH}$ coupling constants[a] for **10, 11, 12, 13, 39, 40, 43** and **44**

Compound	Temp. (K)	$^3J_{1'2'}$ (Hz)	$^3J_{3'4'}$ (Hz)	$^3J_{7'8}$ (Hz)	$^3J_{7''8}$ (Hz)	$^3J_{4'5'}$ (Hz)	$^3J_{4'5''}$ (Hz)	x (γ^+)	x (γ^-)	x (γ^t)
	233		8.1	5 6	<0.7	b	b	-	-	-
10	263		b	6 1	<0 7	b	b	-	-	-
	293		8 6	6 3	<0 7	2.3	2.9	0.84	0.00	0.16
	313		8 6	6 3	0.7	2 6	3.1	0 79	0.02	0.19
	233		8.7	4.4	6.3	2.2	2.7	0.87	0.00	0.13
11	263		8 3	4 3	6 3	2 6	b	-	-	-
	293		8 1	4 2	6 3	2 9	3.2	0.75	0.06	0.19
	318		8 0	4 1	6 3	3.2	3.5	0.70	0.09	0.21
	233		8 5	10 4	4 4	b	b	-	-	-
12	263		b	b	b	b	b	-	-	-
	293		8.4	10 4	4.4	2 6	3 0	0 80	0.02	0.18
	318		8.1	10 3	4.4	2.8	3.2	0.76	0.04	0.20
	233		8.8	8 1	8.9	2.0	2.6	0.90	0 00	0.10
13	263		8 7	8 1	9 0	2 2	3 0	0.84	0.00	0.16
	293		8 6	8.0	8 9	2 4	3.3	0.79	0.00	0.21
	318		8.4	8 0	8.8	2 6	3 4	0 76	0.02	0.22
	233	7 4		0 8	6.4	2 7	2 3	0 87	0 03	0.10
39	263	7 2		0 9	6 4	2.9	2 8	0 79	0.06	0.15
	293	7.0		1 0	6 4	3.3	3 1	0 73	0 10	0 17
	313	6.9		1.2	6 4	3.3	3.2	0 72	0.11	0 17
	233	5.4		6 4	4 3	b	b	-	-	-
40	263	5 4		6 4	4 2	b	b	-	-	-
	293	5 5		6.5	4 2	b	b	-	-	-
	318	5 4		6.4	4.2	b	b	-	-	-
	233	7.3		3 4	10 4	2 3	2.4	0 90	0.00	0.10
43	263	7 1		3 5	10 3	2.7	2.6	0.83	0.03	0.14
	293	6 9		3.6	10.2	3 0	2 7	0 80	0.07	0.13
	318	6 7		3 7	10 1	3.3	2.9	0.75	0.11	0.14
	233	6 6		9.3	7 8	2 5	2 8	0.83	0.01	0.16
44	263	6.4		9 2	7 7	2 9	3 3	0.74	0 06	0 20
	293	6.3		9 1	7 7	3 2	3 4	0.70	0.09	0.21
	318	6 1		9 1	7 6	3.4	3.6	0.67	0.11	0.22

[a] 500 MHz ^{1}H-NMR spectra were recorded in $CDCl_3$-CD_3OD solution. [b] Could not be assessed.

11, 12, 13, 39, 40, 43 and **44** (Fig. 1).[22,24,25] It is noteworthy that the experimental $^3J_{7'8}$ and $^3J_{7''8}$ in **10** and **39** lie close to the calculated curves (Fig 1) which show that conformational equilibria of their isoxazolidine moieties are strongly biased to the South (C2'-*endo*-C7-*exo*, $P^{IS} \approx 180°$) or West (C8-*endo*-O-*exo*, $P^{IS} \approx 252°$) in the case of **10** (Fig. 1B) and to the North (C2'-*exo*-C7-*endo*, $P^{IS} \approx 3°$) or East (O-*endo*-C8-*exo*, $P^{IS} \approx 75°$) in the case of **39** (Fig. 1A). The isoxazolidine moieties in **11** and **40** are involved in ≈1:1 conformational equilibria (Fig. 1, panels A and B) The experimental $^3J_{7'8}$ for **11** and **39** clearly show variation with temperature (Fig. 1A). The North (or East) to South alignment of experimental $^3J_{7'8}$ and $^3J_{7''8}$ in **11** and **39** suggests that their isoxazolidine moieties are involved in the two-state North ⇄ South (or East ⇄ South) equilibria (Fig 1A) By constructing the conode through the experimental data points for **11** four possible two-state equilibria are anticipated: ($P^{IS}_N \approx -5°$) ⇄ ($P^{IS}_S \approx -175°$), ($P^{IS}_N \approx -75°$) ⇄ ($P^{IS}_S \approx -175°$), ($P^{IS}_N \approx -5°$) ⇄ ($P^{IS}_S \approx -225°$) or ($P^{IS}_N \approx -75°$) ⇄ ($P^{IS}_S \approx -225°$) and in all of them the relative populations are in ≈ 1:1 ratio.

The experimental $^3J_{7'8}$ and $^3J_{7''8}$ for CN substituted **12, 13, 43** and **44** reveal that their isoxazolidine moieties are conformationally pure (Fig. 1, panels C and D). The location of experimental $^3J_{7'8}$ and $^3J_{7''8}$ couplings, relative to the calculated curves in Fig. 1 (panels C and D), shows that the isoxazolidine ring in **13**

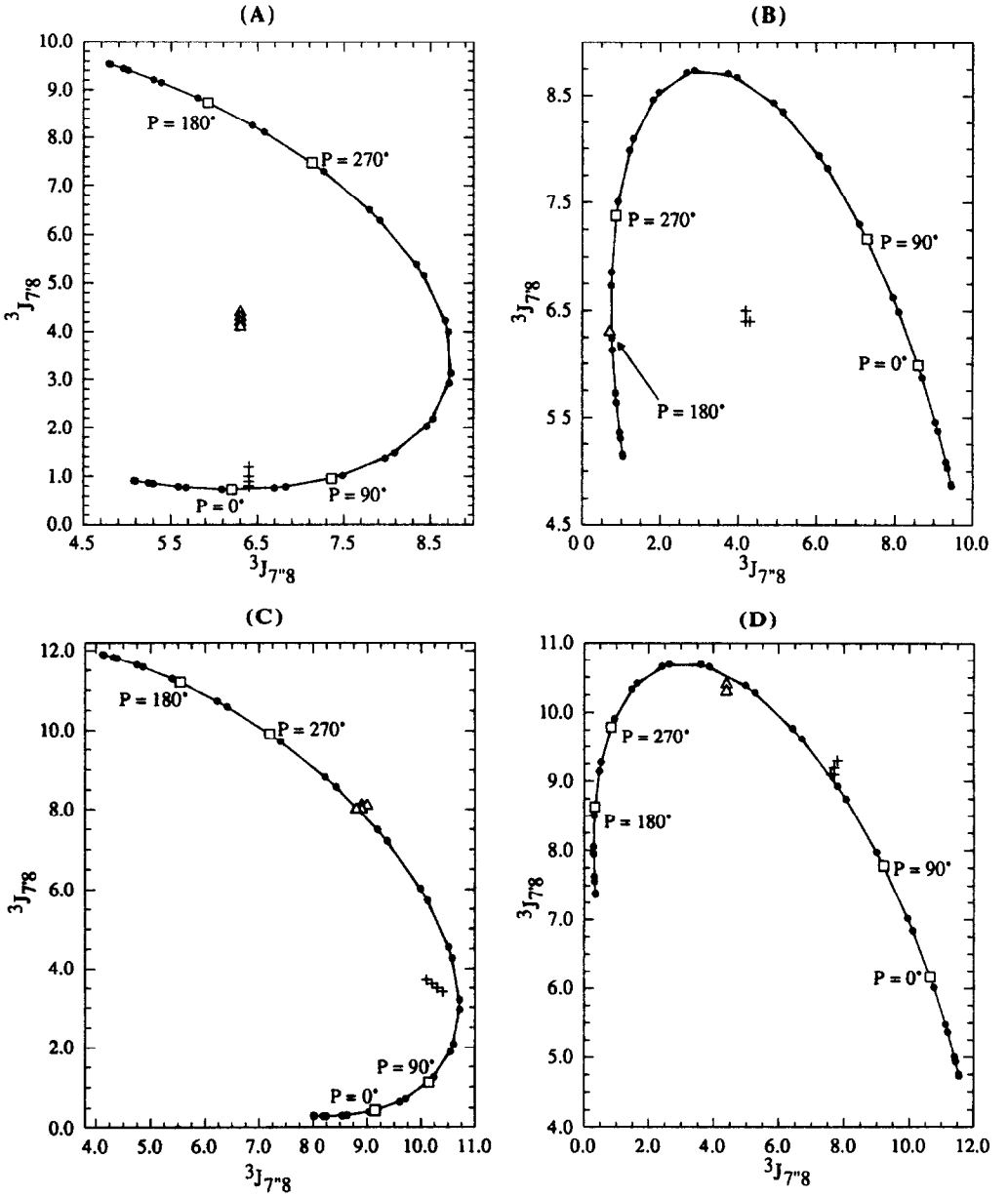


Figure 1: Curves correlating $^3J_{7'8}$ and $^3J_{7''8}$ were calculated by varying the phase angle (P^{IS}) of isoxazolidine moiety between 0° (C_7-*endo*-C_2-/C_3-*exo*) and 360° (in 10° steps) via 180° (C_7-*exo*-C_2-/C_3-*endo*) at fixed puckering amplitude Ψ_m^{IS} = 39° for C8-(R) [panel (A) for OEt and (C) for CN] and C8-(S) [panel (B) for OEt and (D) for CN] configurations by the use of generalised Karplus equation.[24,25] In panel (A) the experimental $^3J_{7'8}$ and $^3J_{7''8}$ for **11** and **39** at four temperatures in the range 233K - 318 K (see Table I) are represented by Δ and +, respectively. In panel (B) the experimental $^3J_{7'8}$ and $^3J_{7''8}$ for **10** and **40** in the range 233 - 318 K are represented by Δ and +, respectively. In panel (C) the experimental $^3J_{7'8}$ and $^3J_{7''8}$ for **13** and **43** (Table I) in the range 233K - 318 K are represented by Δ and +, respectively. In panel (D) experimental $^3J_{7'8}$ and $^3J_{7''8}$ for **12** and **44** in the range 233 - 318 K are represented by Δ and +, respectively (Table I).

adopts (≈ 100%) either N10-*exo*-C2'-*endo* (P^{IS} ≈ 145°) or N10-*endo*-O9-*exo* (P^{IS} ≈ 287°) twist conformation (Fig. 1C). In **12**, the isoxazolidine ring is in either N10-*exo* (P^{IS} ≈ 125°) or N10-*endo* (P^{IS} ≈ 305°) envelope conformation (Fig. 1D). The conformation of isoxazolidine ring in **43** is either biased (>95%) to O9-*endo*-N10-*exo* (P^{IS} ≈ 110°) or N10-*endo*-C3'-*exo* (P^{IS} ≈ 320°) (Fig. 1C). Figure 1D shows that the isoxazolidine moiety in **44** prefers (≈ 100%) either O9-*endo*-N10-*exo* (P^{IS} ≈ 103°) or N10-*endo*-C3'-*exo* (P^{IS} ≈ 328°) twist conformation. $^3J_{7'8}$ and $^3J_{7''8}$ for all CN substituted compounds **12**, **13**, **43** and **44** show some variation with temperature, but their alignment does not suggest North (C2'/C3'-*exo*-C7-*endo*) ⇄ South (C2'/C3'-*endo*-C7-*exo*) conformational equilibium of C8-CN substituted isoxazolidine moieties (Fig. 1).

A comparison of the conformational behaviour in **10**, **11**, **12**, **13**, **39**, **40**, **43** and **44** in solution suggests distinct steric and stereoelectronic effects that drive the pseudorotational equilibrium of isoxazolidine moiety in both 2'- and 3'-spiro compounds depending upon the nature of the substituent (CN *vs.* OEt). The lone pair (Lp) on the N10 would preferably orient itself in such a way to adopt a gauche orientation to both lone pairs on O9 (gauche effect of Lp-N_{10}-O_9-Lp fragment).[5a] Gauche orientations in the N10-(R) invertomers **10**, **11**, **12** and **13** are optimally achieved at P^{IS} ≈ 110° [Φ(Lp-N_{10}-O_9-Lp_1) = 80°, Φ(Lp-N_{10}-O_9-Lp_2) = -40°, Ψ_m^{IS} = 39°], whereas the N10-(S) invertomers **39**, **40**, **43** and **44** should prefer conformation with P^{IS} ≈ 290° [Φ(Lp-N_{10}-O_9-Lp_1) = -40°, Φ(Lp-N_{10}-O_9-Lp_2) = 80°, Ψ_m^{IS} = 39°]. There are however other stereoelectronic factors operating, especially anomeric effects in C8-OEt substituted isoxazolidine moieties of **10**, **11**, **39** and **40**. The endo-anomeric effect (*i e.* preference for antiperiplanar orientation of Lp-O_9-C_8-QEt fragment) stabilizes the conformers in which OEt group occupies axial orientation. In **10** and **40** with C8-(S) configuration one of the Lp on O9 approaches antiperiplanar orientation with OEt group at P^{IS} = 250° [Φ(Lp-O_9-C_8-QEt) = -160°, Ψ_m^{IS} = 39°], while in **11** and **39** with C8-(R) configuration that is achieved at P^{IS} = 70° [Φ(Lp-O_9-C_8-QEt) = 160°, Ψ_m^{IS} = 39°]. The exo-anomeric effect (*i e.* antiperiplanar orientation of Lp-QEt-C_8-O fragment) further influences the conformation of isoxazolidine through a rotation around C8-OEt bond.

EXPERIMENTAL

^{1}H-NMR spectra were recorded (in δ scale) with Jeol JNM-GX 270 at 270 MHz or Bruker AMX-500 at 500 MHz NMR spectrometers using TMS (0.0 ppm) as reference at 25 °C unless it is mentioned. ^{13}C-NMR were recorded at 67.8 MHz using both ^{1}H-coupled and H-decoupled or INEPT modes. Jeol DX 303 instrument was used for recording high resolution mass spectra Tlc was carried out using Merck pre-coated silica gel F254 plates.The column chromatographic separations were carried out using Merck G60 silica gel. For **21**, **23**, **28** and **29** the N = CH_2 protons are noted as 12' and 12"

3',5'-O-(Tetraisopropyldisiloxane-1,3-diyl)-2'-deoxy-2'-dehydro-2'-(Z)-(N-methyloximino)-5-methyl-uridine (2). The 3',5'-bis protected-(5-methyluridine) (4 g, 8 mmol) was oxidized to corresponding keto derivative 1[(3,5-O-tetraisopropyldisiloxane-1,3-diyl)-β-D-*erythro*-pentofuran-2-ulosyl]thymine[16] (**1**) which was dissolved in dry pyridine (40 mL), N-methylhydroxylamine hydrochloride (2 g, 24 mmol) was added and the reaction mixture was stirred and kept at ~5 °C for 48 h. The solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (150 mL), washed with water (2 x 50 mL). The solvent was removed in vacuo, the residue was co-evaporated with toluene to give a foam which was subjected to silica gel column chromatography to give **2** (2 53 g, 75%, two steps) and **1** (800 mg) ^{1}H NMR ($CDCl_3$): 8.84 (*br, s*, 1H) NH; 7.08 (*d*, J = 1.1 Hz, 1H) H6; 5.9 (*m*, $J_{1',3'}$ = 2.0 Hz, 1H) H1'; 5.46 (*m*, $J_{3',4'}$ = 4.8 Hz, 1H) H3'; 4.21-3.98 (*m*, 3H) H4', H5', H5"; 3.85 (*m*, 3H) NCH_3; 1.88 (*d*, 3H) $5CH_3$; 1.2 (m, 28 H) Tipsil. ^{13}C NMR ($CDCl_3$): 163.9 (*s*) C4, 149.5, 147.8 (2 x *s*) C2 and C2'; 139.9 (*d*, J_{CH} = 179.6 Hz) C6; 110.5 (*s*) C5; 87.9 (*d*, J_{CH} = 167.7 Hz) C1'; 86.9 (*d*, J_{CH} = 150.3 Hz) C4'; 72 0 (*d*, J_{CH} = 158.5 Hz) C3'; 63.8 (*t*, J_{CH} = 146.2 Hz) C5'; 48.6 (*q*, J_{CH} = 143.0 Hz) NCH_3. MS (FAB$^+$): calc. for M^+ 528.2562, found 528.2573.

3',5'-O-(Tetraisopropyldisiloxane-1,3-diyl)-2'-didehydro-spiro[2'-(S),11-(8-(S)-ethoxy-10-(R)-N-methyl-

9,10-isoxazolidine)]thymidine (3). Compound **2** (1.32 g, 2.5 mmol) was treated with ethyl vinyl ether (10 mL) at RT for 48 h. The solvent was removed in vacuo to give a foam which was separated by silica gel column chromatography to give **3** (1.45 g, 97%). ^{1}H NMR ($CDCl_3$): 7.94 (*br, s*, 1H) NH; 7.17 (*s*, 1H) H6; 6.0 (*br, s* 1H) H1', 5.32 (*d*, $J_{7',8}$ = 6.4 Hz, 1H) H8; 4.77 (*br, s* 1H) H3'; 4.12 (*dd*, $J_{4',5'}$ = 3.9 Hz, $J_{5',5''}$ = 13.0 Hz, 1H) H5'; 4.03 (*dd*, $J_{4',5''}$ = 3.0 Hz, 1H) H5''; 3,74 (*m*, 1H) H4'; 3.65, 3.39 (2 x *m*, 2H) OCH_2CH_3; 3.06 (*dd*, $J_{7',7''}$ = 13.7 Hz, 1H) H7'; 2.66 (*s*, 3H) NCH_3; 2.30 (*d*, 1H) H7''; 1.89 (*d*, J = 1.0 Hz, 3H) $5CH_3$; 1.18 (*t*, 3H) OCH_2CH_3; 1.1 (*m*, 28 H) Tipsil. ^{13}C NMR ($CDCl_3$): 164.0 (*s*) C4; 150.2 (*s*) C2; 138.5 (*d*, J_{CH} = 187.9 Hz) C6; 108.6 (*s*) C5; 101.9 (*d*, J_{CH} = 170.5 Hz) C8; 82.7 (*d*, J_{CH} = 151.2 Hz) C4'; 75.4 (*s*) C2'; 71.8 (*d*, J_{CH} = 151.2 Hz) C3'; 63.5 (*t*, J_{CH} = 140.7 Hz) OCH_2CH_3; 61.6 (*t*, J_{CH} = 140.7 Hz) C5'; 41.7 (*q*, J_{CH} = 135.6 Hz) NCH_3; 38.9 (*t*, J_{CH} = 134.5 Hz) C7.

3',5'-O-(Tetraisopropyldisiloxane-1,3-diyl)-2'-didehydro-spiro[2'-(S),11-(8-(R)-ethoxy-10-(R)-N-methyl-9,10-isoxazolidine)]thymidine (4) and **3'-O-(Tetraisopropyldisiloxane-1,3-diyl)-2'-didehydro-spiro[2'-(S),11-(8-(R)-ethoxy-10-(R)-N-methyl-9,10-isoxazolidine)]thymidine (9).** Compound **3** (300 mg, 0.5 mmol) was treated with 20% trifluoroacetic acid in dry C_2H_5OH (10 mL) at 45 °C for 70 h. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give **4** (70 mg, 23%), **3** (90 mg, 30%) and **9** (60 mg, 20%). Compound **4**, ^{1}H NMR ($CDCl_3$): 8.43 (*br, s*, 1H) NH; 7.13 (*d*, J = 1.0 Hz, 1H) H6; 5.93 (*s*, 1H) H1'; 5.27 (*dd*, $J_{7',8}$ = 4.1 Hz, $J_{7'',8}$ = 6.5 Hz, 1H) H8; 4.45 (*d*, $J_{3',4'}$ = 8.0 Hz, 1H) H3'; 4.11 (*dd*, $J_{4',5'}$ = 3.2 Hz, $J_{5',5''}$ = 13.2 Hz, 1H) H5'; 4.05 (*dd*, $J_{4',5''}$ = 2.9 Hz, 1H) H5''; 3.70 (*m*, 2H) H4' and OCH_2CH_3; 3.46 (*m*, 1H) OCH_2CH_3; 2.86 (*dd*, $J_{7',7''}$ = 14.1 Hz, 1H) H7'; 2.85 (*s*, 3H) NCH_3; 2.62 (*dd*, 1H) H7''; 1.90 (*d*, 3H) $5CH_3$; 1.18 (*m*, 31 H) Tipsil and OCH_2CH_3. ^{13}C NMR ($CDCl_3$): 163.7 (*s*) C4; 150.5 (*s*) C2; 137.7 (*d*, J_{CH} = 180.5 Hz) C6; 108.4 (*s*) C5; 105.3 (*d*, J_{CH} = 176.0 Hz) C8; 89.8 (*d*, J_{CH} = 172.3 Hz) C1'; 81.6 (*d*, J_{CH} = 143.9 Hz) C4'; 76.3 (*s*) C2'; 70.0 (*d*, J_{CH} = 147.5 Hz) C-3'; 64.0 (*t*, J_{CH} = 142 5 Hz) OCH_2CH_3; 60.2 (*t*, J_{CH} = 144.8 Hz) C5'; 42.6 (*q*) NCH_3; 39.4 (*t*, J_{CH} = 134.3 Hz) C7. Compound **9**, ^{1}H NMR ($CDCl_3$): 8.69 (*br, s*, 1H) NH; 7.27 (*s*, 1H) H6; 6.02 (*s*, 1H) H1'; 5.12 (*dd*, $J_{7',8}$ = 4.2 Hz, $J_{7'',8}$ = 5.8 Hz, 1H) H8; 4.73 (*d*, $J_{3',4'}$ = 4.1 Hz, 1H) H3'; 4.01 (*m*, 1H) H4'; 3.87 (*m*, 2H) H5', 5''; 3.70, 3.44 (2 x *m*, 2H) OCH_2CH_3; 2.88 (*s*, 3H) NCH_3; 2.88 (*dd*, $J_{7',7''}$ = 14.0 Hz, 1H) H7', 2.78 (*dd*, 1H) H7''; 1.88 (*s*, 3H) $5CH_3$; 1.15 (*m*, 31 H) Tipsil and OCH_2CH_3. ^{13}C NMR ($CDCl_3$): 164.0 (*s*) C4; 150.7 (*s*) C2; 138.2 (*d*, J_{CH} = 181.5 Hz) C6; 108.5 (*s*) C5; 105.0 (*d*, J_{CH} = 173.2 Hz) C8; 90.3 (*d*, J_{CH} = 162.2 Hz) C1'; 84.2 (*d*, J_{CH} = 149.4 Hz) C4'; 78.2 (*s*) C2'; 72.9 (*d*, J_{CH} = 149.4 Hz) C3'; 64.0 (*t*, J_{CH} = 142.5 Hz) OCH_2CH_3; 60.5 (*t*, J_{CH} = 144.3 Hz) C5'; 43.0 (*q*, J_{CH} = 136.5 Hz) NCH_3; 40.0 (*t*, J_{CH} = 134.7 Hz) C7.

3',5'-O-(Tetraisopropyldisiloxane-1,3-diyl)-2'-didehydro-spiro[2'-(S),11-(8-(R)-cyano-10-(R)-N-methyl-9,10-isoxazolidine)]thymidine (5) and **3',5'-O-(Tetraisopropyldisiloxane-1,3-diyl)-2'-didehydro-spiro[2'-(S),11-(8-(S)-cyano-10-(R)-N-methyl-9,10-isoxazolidine)]thymidine (6).** Compound **2** (300 mg, 0.57 mmol) was treated with acrylonitrile (3 mL) overnight at RT. The solvent was removed in vacuo to give a foam which was purified by silica gel column chromatography to give **5** (140 mg, 42%) and **6** (175 mg, 53%) (The ^{1}H NMR investigation of the crude reaction mixture showed that the ratio of **5** and **6** was 45 : 55). Compound **5**, ^{1}H-NMR ($CDCl_3$): 8.22 (*br, s*, 1H) NH; 7.06 (*d*, J = 1.2 Hz, 1H) H6; 5.85 (*s*, 1H) H1'; 4.80 (*dd*, $J_{7',8}$ = 8.0 Hz, $J_{7'',8}$ = 8.7 Hz, 1H) H8; 4.45 (*d*, $J_{3',4'}$ = 8.4 Hz, 1H) H3'; 4.11 (*d*, 2H) H5', H5''; 3.71 (*m*, 1H) H4'; 3.22 (*dd*, $J_{7',7''}$ = 12.9 Hz, 1H) H7'; 2.81 (*s*, 3H) NCH_3; 2.80 (*dd*, 1H) H7''; 1.90 (*d*, 3H) $5CH_3$; 1.20 (*m*, 28 H) Tipsil. ^{13}C NMR ($CDCl_3$): 163.8 (*s*) C4; 151.0 (*s*) C2; 136.7(*d*, J_{CH} = 183.3 Hz) C6; 119.3 (*s*) CN; 109.3 (*s*) C5; 89.0 (*d*, J_{CH} = 167.7 Hz) C1'; 81.2 (*d*, J_{CH} = 145.7 Hz) C4'; 77.3 (*s*) C2'; 69.2 (*d*, J_{CH} = 146.6 Hz) C3'; 63.4 (*d*, J_{CH} = 164.0 Hz) C8; 59.6 (t, J_{CH} = 143.9 Hz) C5'; 41.0 (*q*, J_{CH} = 136.9 Hz) NCH_3; 37.2 (*t*, J_{CH} = 138.4 Hz) C7 Compound **6**, ^{1}H NMR ($CDCl_3$)· 8.18 (*br, s*, 1H) NH; 7.21 (*d*, J = 1.1 Hz, 1H) H6; 6.12 (*br, s*, 1H) H1'; 4.85 (*dd*, $J_{7',8}$ = 9.8 Hz, $J_{7'',8}$ = 4 6 Hz, 1H) H8; 4.60 (*br, s*, 1H) H3'; 4.07 (2 x *d*, $J_{4',5'}$ = 3.1 Hz, $J_{4',5''}$ = 3.2 Hz, 2H) H5', H5'', 3.77 (*m*, $J_{3',4'}$ = 6.7 Hz, 1H) H4'; 3.35 (*dd*, $J_{7',7''}$ = 13 4 Hz, 1H) H7'; 2.65 (*s*, 3H) NCH_3, 2.27 (*dd*, 1H) H7''; 1.92 (*d*, 3H) $5CH_3$, 1.07 (*m*, 28 H) Tipsil. ^{13}C NMR ($CDCl_3$): 163.4 (*s*) C4; 150.1 (*s*) C2; 136.5 (*d*, J_{CH} = 183.3 Hz) C6, 117.3 (*s*) CN; 109.8 (*s*) C5, 87.6 (*d*, J_{CH} = 174.0 Hz) C1', 82.2 (*d*, J_{CH} = 141 2 Hz) C4'; 70.4 (*d*, J_{CH} = 150.3 Hz) C3', 63.0 (*d*, J_{CH} = 144.3 Hz) C8; 60.6 (*t*, J_{CH} = 144.3 Hz) C5'; 40.1 (*q*, J_{CH} = 136.8 Hz) NCH_3; 38.1 (*t*, J_{CH} = 137.9 Hz) C7

2'-Didehydro-spiro[2'-(S),11-(8-(R)-methoxy-10-(R)-N-methyl-9,10-isoxazolidine)]thymidine (7) and **2'-Didehydro-spiro[2'-(S),11-(8-(S)-methoxy-10-(R)-N-methyl-9,10-isoxazolidine)]thymidine (8).** Compound **10** (100 mg, 0.28 mmol) was treated with 20% trifluoroacetic acid in dry CH_3OH (6 mL) at 45 °C for 70 h. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give compound **7** (70 mg, 73%) and **8** (10 mg, 7%) contaminated with starting material. ^{1}H-NMR study of the crude reaction mixture showed that the ratio between **7/8** is 10:1. Compound **7**, ^{1}H NMR ($CDCl_3$ + CD_3OD): 7.32 (*d*, J = 1.2 Hz) H6, 5 91 (*s*, 1H) H1'; 5 15 (*dd*, $J_{7',8}$ = 4.2 Hz, $J_{7'',8}$ = 6.3 Hz, 1H) H8; 4.25 (*d*, $J_{3',4'}$ = 8.2 Hz, 1H) H3'; 3.91 (*dd*, $J_{4',5'}$ = 2.7 Hz, $J_{5',5''}$ = 12.5 Hz, 1H) H5', 3.76 (*dd*, $J_{4',5''}$ = 3.4 Hz, 1H) H5'', 3.67 (*m*, 1H) H4', 3 36 (*s*, 3H) OMe; 2.91 (*dd*, $J_{7',7''}$ = 14 0 Hz, 1H) H7'; 2.84 (*s*, 3H) NCH_3; 2.62 (*dd*, 1H) H7''; 1.89 (*d*, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$ + CD_3OD): 164.6 (*s*) C4; 150.8 (*s*) C2; 138.6 (*d*, J_{CH} = 187.9 Hz) C6; 108.2 (*s*) C5; 106.7 (*d*, J_{CH} = 172 3 Hz) C8, 90 4 (*d*, J_{CH} = 173.2 Hz) C1'; 81.9 (*d*, J_{CH} = 144 8 Hz) C4'; 76 6 (*s*) C2'; 68.6

(*d*, J_{CH} = 145.7 Hz) C3'; 59.4 (*t*, J_{CH} = 142.5 Hz) C5'; 55.7 (*q*, J_{CH} = 143.0 Hz) OMe; 42.0 (*q*) NCH_3; 39.0 (*t*) C7; 11.9 (*q*, J_{CH} = 128.9 Hz) $5CH_3$. MS (FAB^-): calc. for $(M-H)^-$ 342.1301, found 342.1299. Compound **8**, ^1H NMR ($CDCl_3$ + CD_3OD): 7.12 (*s*, 1H) H6; 5.78 (*br, s*, 1H) H1'; 5.28 (*d*, $J_{7',8}$ = 5.9 Hz, 1H) H8; 4.68 (*br, d*, 1H) H3'; 3.94 (*m*, 1H) H4'; 4.75 (*m*, 2H) H5',5"; 3.30 (*s*, 3H) OMe; 3.07 (*dd*, $J_{7',7"}$ = 13.5 Hz, 1H) H7'; 2.67 (*s*, 3H) NMe; 2.23 (*d*, 1H) H7"; 1.88 (*s*, 3H) $5CH_3$.

2'-Didehydro-spiro[2'-(S),11-(8-(S)-ethoxy-10-(R)-N-methyl-9,10-isoxazolidine)]thymidine (10). Compound **3** (1.2 g, 2 mmol) was dissolved in dry THF (20 mL), 0.5 M TBAF solution in THF (4.2 mL) was added and kept at RT for 5 min. The solvent was removed in vacuo. The residue was purified by silica gel column chromatography to give **10** (615 mg, 98%). ^1H NMR ($CDCl_3$ + CD_3OD): 7.14 (*d*, J = 1.1 Hz) H6; 5.78 (*br, s*, 1H) H1'; 5.42 (d, $J_{7',8}$ = 6.3 Hz, 1H) H8; 4.70 (*d*, $J_{3',4'}$ = 8.3 Hz, 1H) H3'; 3.92 (*dd*, $J_{4',5'}$ = 2.5 Hz, $J_{5',5"}$ = 12.3 Hz, 1H) H5'; 3.78 (*dd*, $J_{4',5"}$ = 2.8 Hz, 1H) H5"; 3.74 (*m*, 1H) H4'; 3.68, 3.44 (2 x *m*, 2H) OCH_2CH_3; 3.09 (*dd*, $J_{7',7"}$ = 13.7 Hz, 1H) H7'; 2.66 (*s*, 3H) NCH_3; 2.23 (*d*, 1H) H7"; 1.88 (*d*, 3H) $5CH_3$; 1.22 (*t*, 3H) OCH_2CH_3. ^{13}C NMR ($CDCl_3$ + CD_3OD): 164.9 (*s*) C4; 151 0 (*s*) C2; 141.1 (*d*, J_{CH} = 180.5 Hz) C6; 108.4 (*s*) C5; 102.5 (*d*, J_{CH} = 174.1 Hz) C8; 82.8 (*d*, J_{CH} = 146.6 Hz) C4', 74.8 (*s*) C2'; 68.0 (*d*, J_{CH} = 149.4 Hz) C3'; 63.8 (*t*, J_{CH} = 143.0 Hz) OCH_2CH_3; 60.0 (*t*, J_{CH} = 144.8 Hz) C5'; 41.5 (*q*, J_{CH} = 136.8 Hz) NCH_3; 37.7 (*t*, J_{CH} = 135.2 Hz) C7; 14.6 (*q*, J_{CH} = 126.8 Hz) OCH_2CH_3; 11.6 (*q*, J_{CH} = 128.9 Hz) $5CH_3$. MS (FAB^-): calc. for $(M-H)^-$ 356.1458, found 356.1443.

2'-Didehydro-spiro[2'-(S),11-(8-(R)-ethoxy-10-(R)-N-methyl-9,10-isoxazolidine)]thymidine (11). Compound **10** (120 mg, 0.33 mmol) was treated with 20% trifluoroacetic acid (6 mL) in C_2H_5OH at 45 °C for 70 h. The solvent was removed in vacuo. The residue was purified by silica gel column chromatography to give **11** (95 mg, 79%) and **10** (16 mg, 13%). The ^1H NMR spectrum of the crude reaction mixture showed the ratio between **11** and **10** was approximately (5:1). ^1H NMR ($CDCl_3$ + CD_3OD): 7.31 (*d*, J = 1.1 Hz, 1H) H6; 5.91 (*s*, 1H) H1'; 5.26 (*dd*, $J_{7',8}$ = 4.3 Hz, $J_{7",8}$ = 6.1 Hz, 1H) H8; 4.25 (*d*, $J_{3',4'}$ = 8.0 Hz, 1H) H4'; 3.91 (*dd*, $J_{4',5'}$ = 2.8 Hz, $J_{5',5"}$ = 12.6 Hz, 1H) H5'; 3.70 (*m*, 3H) H5", H4' and OCH_2CH_3; 3.50 (*m*, 1H) OCH_2CH_3; 2.92 (*dd*, $J_{7',7"}$ = 14.0 Hz, 1H) H7'; 2.84 (*s*, 3H) NCH_3; 2.61 (*dd*, 1H) H7"; 1.89 (*d*, 3H) $5CH_3$; 1.17 (*t*, 3H) OCH_2CH_3. ^{13}C NMR ($CDCl_3$ + CD_3OD): 165.0 (*s*) C4; 151.1 (*s*) C2; 138.6 (*d*, J_{CH} = 185.0 Hz) C6; 108.2 (*s*) C5; 105.5 (*d*, J_{CH} = 175.0 Hz) C8; 90.5 (*d*, J_{CH} = 169.5 Hz) C1'; 81.9 (*d*, J_{CH} = 146.6 Hz) C4'; 76.5 (*s*) C2'; 68.6 (*d*, J_{CH} = 144.8 Hz) C3'; 63.9 (*t*, J_{CH} = 142.0 Hz) OCH_2CH_3, 59 5 (*t*, J_{CH} = 142.5 Hz) C5'; 42.0 (*q*) NCH_3; 39.1 (*d*) C7, 14.7 (*q*, J_{CH} = 126.8 Hz) OCH_2CH_3; 11.9 (*q*, J_{CH} = 129.5 Hz) $5CH_3$ MS (FAB^-): calc. for $(M-H)^-$ 356.1458, found 356.1431.

2'-Didehydro-spiro[2'-(S),11-(8-(S)-cyano-10-(R)-N-methyl-9,10-isoxazolidine)]thymidine (12). Compound **6** (100 mg, 0.18 mmol) was dissolved in dry THF (2 mL), 0.5 M TBAF solution in dry THF (380 µL) was added and the reaction mixture kept at RT for 5 min. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give **12** (52 mg, 90%). ^1H NMR ($CDCl_3$ + CD_3OD): 7.35 (*d*, J = 1.0 Hz, 1H) H6, 5.96 (*br, s*, 1H) H1', 4.96 (*dd*, $J_{7',8}$ = 10.4 Hz, $J_{7",8}$ = 4.4 Hz, 1H) H8; 4.47 (*br, s*, 1H) H3'; 3.93 (*dd*, $J_{4',5'}$ = 2.6 Hz, $J_{5',5"}$ = 12.7 Hz, 1H) H5'; 3.80 (*dd*, $J_{4',5"}$ = 2 9 Hz, 1H) H5"; 3.75 (*m*, 1H) H4'; 3.43 (*dd*, $J_{7',7"}$ = 13.6 Hz, 1H) H7', 2.67 (*dd*, 1H) H7"; 2.61 (*s*, 3H) NCH_3; 1.88 (*d*, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$ + CD_3OD): 165.0 (*s*) C4; 151.0 (*s*) C2; 138.8 (*d*, J_{CH} = 193 5 Hz) C6; 117.3 (*s*) CN; 109.1 (*s*) C5; 82.7 (*d*, J_{CH} = 145.7 Hz) C4'; 77.8 (*s*) C2'; 67.8 (*d*, J_{CH} = 150.3 Hz) C3'; 62.7 (*d*) C8; 59.4 (*t*, J_{CH} = 142.0 Hz) C5'; 39.7 (*q*, J_{CH} = 136.8 Hz) NCH_3, 37.1 (*t*, J_{CH} = 139.3 Hz) C7; 11.9 (*q*, J_{CH} = 128.6 Hz) $5CH_3$. MS (FAB^-): calc. for $(M-H)^-$ 337.1148, found 337.1143.

2'-Didehydro-spiro[2'-(S),11-(8-(R)-cyano-10-(R)-N-methyl-9,10-isoxazolidine)]thymidine (13). Compound **5** (80 mg, 0.14 mmol) was dissolved in dry THF (1.5 mL), 0.5 M TBAF solution in dry THF (290 µL) was added and the reaction mixture kept at RT for 5 min. The solvent was removed in vacuo. The residue was purified by silica gel column chromatography to give **13** (43 mg, 92%). ^1H NMR ($CDCl_3$ + CD_3OD): 7.36 (*d*, J = 1.2 Hz, 1H) H6; 5.90 (*s*, 1H) H1', 4.83 (*dd*, $J_{7',8}$ = $J_{7",8}$ = 8.0 Hz, 1H) H8; 4.27 (*d*, $J_{3',4'}$ = 8.2 Hz, 1H) H3'; 3.96 (*dd*, $J_{4',5'}$ = 2.3 Hz, $J_{5',5"}$ = 12.5 Hz, 1H) H5'; 3.79 (*dd*, $J_{4',5"}$ = 3.2 Hz, 1H) H5"; 3.71 (*m*, 1H) H4'; 3 27 (*dd*, $J_{7',7"}$ = 13.4 Hz, 1H) H7'; 2.80 (*s*, 3H) NCH_3; 2.8 (*dd*, 1H) H7"; 1.89 (*d*, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$ + CD_3OD) 165.0 (*s*) C4; 151.2 (*s*) C2; 137.9 (*d*, J_{CH} = 180.5 Hz) C6; 119.1 (*s*) CN; 108.4 (*s*) C5; 89.2 (*d*) C1'; 81.5 (*d*, J_{CH} = 145 7 Hz) C4'; 77.7 (*s*) C2', 67 7 (*d*, J_{CH} = 146.3 Hz) C3'; 63.0 (*d*, J_{CH} = 163.1 Hz) C8; 58.9 (*t*, J_{CH} = 142.0 Hz) C5', 40.3 (*q*, J_{CH} = 136 5 Hz) NCH_3; 36.7 (*t*, J_{CH} = 137.9 Hz) C7; 11.5 (*q*, J_{CH} = 128.9 Hz) $5CH_3$. MS (FAB^-): calc. for $(M-H)^-$ 337.1148, found 337.1183

5'-O-MMTr-2'-didehydro-spiro[2'-(S),11-(8-(S)-ethoxy-10-(R)-N-methyl-9,10-isoxazolidine)]thymidine (14). Compound **10** (670 mg, 1 9 mmol) was treated with monomethoxytrityl chloride (771 mg, 2.5 mmol) in pyridine (10 mL) overnight at RT. The reaction mixture was quenched with water (10 mL) which was extracted with ethyacetate (3 x 50 mL) The combined organic phase was concentrated in vacuo, co-evaporated with toluene. The residue was purified by silica gel column chromatography to give **14** (1.1g, 93%). ^1H NMR ($CDCl_3$): 8.99 (br, *s*, 1H) NH, 7 47-6.81 (*m*, 15 H) arom and H6, 5.93 (*br, s*, 1H) H1'; 5.34 (*d*, $J_{7',8}$ = 6.0 Hz,

1H) H8; 4.56 (br, *s*, 1H) H3'; 3.81 (*m*, 1H) H4'; 3.77 (*s*, 3H) MMTr; 3.39-3.69 (*m*, 4H) H5', 5" and OCH_2CH_3; 2.99 (*dd*, $J_{7',7"}$= 13.4 Hz, 1H) H7'; 2.80 (*d*, 1H) 3'OH; 2.57 (*s*, 3H) NMe; 2.22 (*d*, 1H) H7"; 1.78 (*s*, 3H) $5CH_3$; 1.17 (*t*, 3H) OCH_2CH_3. ^{13}C NMR ($CDCl_3$ + CD_3OD): 164.0 (*s*) C4; 150.2 (*s*) C2; 108.6 (*s*) C5; 102.6 (*d*, J_{CH} = 173.4 Hz) C8; 87.0 (*s*) MMTr; 80.9 (*d*, J_{CH} = 148.5 Hz) C4'; 75.2 (*s*) C2'; 72.4 (*d*, J_{CH} = 147.5 Hz) C3'; 63.9 (2 x *t*, J_{CH} = 142.0 Hz) C5' and OCH_2CH_3; 55.0 (*q*, J_{CH} = 143.9 Hz) MMTr; 42.0 (*q*, J_{CH} = 136.2 Hz) NMe; 38.0 (*t*, J_{CH} = 134.7 Hz) C7; 15.0 (*q*, J_{CH} = 125.9 Hz) OCH_2CH_3; 12.1 (*q*, J_{CH} = 129.2 Hz) $5CH_3$.

5'-O-MMTr-3'-O-(phenoxythiocarbonyl)-2'-didehydro-spiro[2'-(S),11-(8-(S)-ethoxy-10-(R)-N-methyl-9,10-isoxazolidine)]thymidine (15). Compound **14** (1.0 g, 1.6 mmol) was treated with phenoxythio carbonyl chloride (445 µL, 3.2 mmol) and 4-dimethylaminopyridine (488 mg, 4.0 mmol) in acetonitrile (16 mL) at RT for 24 h. The solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 (150 mL), washed with aqueous NH_4Cl solution (3 x 10 mL). The organic phase was removed in vacuo to give a foam which was purified by silica gel column chromatography to give **15** (1.1 g, 91%). ^1H NMR ($CDCl_3$): 8.11 (*br, s*, 1H) NH; 7.52-6.82 (*m*, 20 H) arom and H6; 6.32 (2 x *br, s*, 2H) H1' and H3'; 5.35 (*d*, $J_{7',8}$ = 6.2 Hz, 1H) H8; 4.18 (*m*, 1H) H4'; 3.78 (*s*, 3H) MMTr; 3.56, 3.40 (2 x *m*, 4H) H5', 5" and OCH_2CH_3; 2.94 (*dd*, $J_{7',7"}$ = 13.3 Hz, 1H) H7'; 2.59 (*s*, 3H) NMe; 2.42 (*d*, 1H) H7"; 1.86 (*s*, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$): 163.8 (*s*) C4; 108.6 (*s*) C5; 102.3 (*d*, J_{CH} = 170.5 Hz) C8; 86.9 (*s*) MMTr; 82.9, 80.1 (2 x *d*, J_{CH} = 154.0 Hz) C3' and C4'; 75.2 (*s*) C2'; 64.5 (*t*, J_{CH} = 142.5 Hz) OCH_2CH_3; 63.0 (*t*, J_{CH} = 144.8 Hz) C5'; 55.0 (*q*, J_{CH} = 143.6 Hz) MMTr; 42.8 (*q*, J_{CH} = 135.9 Hz) NMe; 37.9 (*t*) C7; 14.9 (*q*, J_{CH} = 126.8 Hz) OCH_2CH_3; 12.2 (*q*, J_{CH} = 130.1 Hz) $5CH_3$.

5'-O-MMTr-2'-didehydro-spiro[2'-(S),11-(8-(S)-cyano-10-(R)-N-methyl-9,10-isoxazolidine)]thymidine (16) and 5'-O-MMTr-2'-didehydro-spiro[2'-(S),11-(8-(R)-cyano-10-(R)-N-methyl-9,10-isoxazolidine)] thymidine (18). A mixture of **12** and **13** (1 g, 2.96 mmol) gives **16** (900 mg, 55%) and **18** (600 mg, 33%) in an identical reaction condition described for **14**. ^1H NMR ($CDCl_3$, 50 °C): Compound **16**, 9.0 (*br, s*,1H) NH; 7.49-6.79 (*m*, 15 H) arom and H6; 5.99 (*br, s*, 1H) H1'; 4.81 (*dd*, $J_{7',8}$ = 10.1 Hz, $J_{7",8}$ = 4.5 Hz, 1H) H8; 4.36 (*br, s*, 1H) H3'; 3.86 (*m*, $J_{3',4'}$ = 7.0 Hz, 1H) H4'; 3.76 (*s*, 3H) MMTr; 3.53 (*m*, 2H) H5", 5"; 3.32 (*dd*, $J_{7',7"}$ = 13.4 Hz, 1H) H7'; 2.67 (*dd*, 1H) H7"; 2.53 (*s*, 3H) NMe; 1.75 (*s*, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$): 164.0 (*s*) C4; 150.5 (*s*) C2; 138.2 (*d*, J_{CH} = 176.9 Hz) C6; 117.1 (*s*) CN; 109.2 (*s*) C5; 90.8 (br, *d*) C1'; 87.0 (*s*) MMTr; 81.4 (*d*, J_{CH} = 149.4 Hz) C4'; 78.2 (*s*) C2'; 71.4 (*d*, J_{CH} = 151.2 Hz) C3'; 62.8 (*d*, J_{CH} = 161.3 Hz) C8; 62.7 (*t*, J_{CH} = 143.0 Hz) C5'; 55.0 (*q*, J_{CH} = 143.9 Hz) MMTr; 40.0 (*q*, J_{CH} = 136.5 Hz) NMe; 37.3 (*t*, J_{CH} = 138.8 Hz) C7; 12.0 (*q*, J_{CH} = 129.5 Hz) $5CH_3$. Compound **18**, ^1H NMR ($CDCl_3$ + CD_3OD): 7.48-6.85 (*m*, 15 H) arom and H6; 5.93 (*s*, 1H) H1'; 4.81 (*dd*, $J_{7',8}$ = 7.8 Hz, $J_{7",8}$ = 9.0 Hz, 1H) H8; 4.30 (*d*, $J_{3',4'}$ = 8.2 Hz, 1H) H3'; 3.87 (*m*, 1H) H4'; 3.80 (*s*, 3H) MMTr; 3.55 (*dd*, $J_{4',5'}$ = 2.5 Hz, $J_{5',5"}$ = 10.6 Hz, 1H) H5'; 3.38 (*dd*, $J_{4',5"}$ = 3.8 Hz, 1H) H5"; 3.23 (*dd*, $J_{7',7"}$ = 13.6 Hz, 1H) H7'; 2.79 (*s*, 3H) NMe; 2.77 (*dd*, 1H) H7"; 1.68 (*d*, J = 1.1 Hz, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$ + CD_3OD): 164.4 (*s*) C4; 150.8 (*s*) C2; 137.5 (*d*; J_{CH} = 183.3 Hz) C6; 119.2 (*s*) CN; 108.6 (*s*) C5; 89.5 (*d*, J_{CH} = 166.8 Hz) C1'; 86.4 (*s*) MMTr; 80.7 (*d*, J_{CH} = 145.7 Hz) C4'; 78.1 (*s*) C2'; 69.7 (*d*, J_{CH} = 146.6 Hz) C3'; 63.2 (*d*, J_{CH} = 164.0 Hz) C8; 61.5 (*t*, J_{CH} = 143.4 Hz) C5'; 54.8 (*q*, J_{CH} = 143.9 Hz) MMTr; 40.6 (*q*, J_{CH} = 136.8 Hz) NMe; 37.0 (*t*, J_{CH} = 137.0 Hz) C7; 11.6 (*q*, J_{CH} = 128.7 Hz) $5CH_3$.

5'-O-MMTr-3'-O-(phenoxythocarbonyl)-2'-didehydro-spiro[2'-(S),11-(8-(S)-cyano-10-(R)-N-methyl-9,10-isoxazolidine)]thymidine (17). The reaction condition was used described for **15** using **16** (800 mg, 1.3 mmol) phenoxythiocarbonyl chloride (364 µL, 2.62 mmol) and 4-dimethylaminopyridine (396 mg, 3.25 mmol) in acetonitrile to give **17** (600 mg, 61%). ^1H NMR ($CDCl_3$, at 50 °C): 8.18 (*br, s*, 1H) NH; 7.52-7.28 (*m*, 16 H) arom and H6; 7.04 (*m*, 2H) arom; 6.84 (*m*, 2H) arom; 6.25 (*br, s*, 1H) H1'; 6.15 (*br, s*, 1H) H3'; 4.80 (*dd*, $J_{7',8}$ = 6.6 Hz, $J_{7",8}$ = 6.1 Hz, 1H) H8; 4.23 (*m*, $J_{3',4'}$ = 3.4 Hz, 1H) H4'; 3.79 (*s*, 3H) MMTr; 3.53 (*dd*, $J_{4',5'}$ = 4.5 Hz, $J_{5',5"}$ = 10.5 Hz, 1H) H5'; 3.47 (*dd*, $J_{4',5"}$ = 5.0 Hz, 1H) H5"; 3.05 (*m*, 2H) H7', H7"; 2.58 (*s*, 3H) NMe; 1.85 (*d*, J = 1.0 Hz, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$, 50 °C): 163.0 (*s*) C4; 150.5 (*s*) C2; 109.7 (*s*) C5; 88.6 (*d*) C1'; 87.4 (*s*) MMTr; 83.0, 80.7 (2 x *d*) C3' and C4'; 78.2 (*s*) C2'; 62.7 (*d*, J_{CH} = 157.6 Hz) C8; 62.5 (*t*, J_{CH} = 143.9 Hz) C5'; 55.2 (*q*, J_{CH} = 143.9 Hz) MMTr; 41.0 (*q*, J_{CH} = 137.2 Hz) NMe; 36.9 (*t*, J_{CH} = 137.5 Hz) C7; 12.3 (*q*, J_{CH} = 128.6 Hz) $5CH_3$.

5'-O-MMTr-3'-O-(phenoxythocarbonyl)-2'-didehydro-spiro[2'-(S),11-(8-(R)-cyano-10-(R)-N-methyl-9,10-isoxazolidine)]thymidine (19). Compound **18** (500 mg, 0.82 mmol) was treated with phenoxythiocarbonyl chloride (228 µL, 1.64 mmol), DMAP (244 mg, 2.0 mmol) in acetonitrile (16 mL) at RT for 8 h. The solvent was removed in vacuo, residue dissolved in CH_2Cl_2 (50 mL), washed with aqueous NH_4Cl (3 x 8 mL). The organic phase was concentrated in vacuo to give a foam which was purified by silica gel column chromatography to give **19** (500 mg, 82%). ^1H NMR ($CDCl_3$): 9.08 (*br, s*, 1H) NH; 7.54-6.84 (*m*, 20 H) arom and H6; 6.17 (*d*, $J_{3',4'}$ = 3.7 Hz, 1H) H3'; 6.13 (*s*, 1H) H1', 4.77 (dd, $J_{7',8}$ = 7.7 Hz, $J_{7",8}$ = 8.3 Hz, 1H) H8; 4.27 (*m*, 1H) H4'; 3.78 (*s*, 3H) MMTr; 3.55 (*dd*, $J_{4',5'}$ = 4.4 Hz, $J_{5',5"}$ = 10.4 Hz, 1H) H5'; 3.44 (*dd*, $J_{4',5"}$ = 3.5 Hz, 1H) H5"; 3.17 (*dd*, $J_{7',7"}$ = 14.1 Hz, 1H) H7'; 3.08 (*dd*, 1H) H7"; 2.83 (*s*, 3H) NMe; 1.78 (*s*, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$): 163.7 (*s*) C4; 151.1 (*s*) C2; 119.0 (*s*) CN; 109.5 (*s*) C5, 89.9 (*d*, J_{CH} = 163.1 Hz) C1'; 87.2 (*s*) MMTr; 82.4, 80.9 (2 x *d*, J_{CH} = 157.6, 152.1 Hz) C3' and C4'; 78.7 (*s*) C2'; 63.4 (*d*, J_{CH} = 165.0 Hz) C8; 62.1 (*t*, J_{CH} = 144.3 Hz) C5'; 55.0 (*q*, J_{CH} = 143.9 Hz) MMTr; 42.4 (*q*, J_{CH} = 137.5 Hz) NMe; 38.0 (*t*, J_{CH} =

137.9 Hz) C7; 12.2 (*q*, J_{CH} = 129.2 Hz) $5CH_3$.

5'-O-MMTr-3'-deoxy-2',3'-didehydro-2'-*C*-(ethyl-8-(S)-ethoxy-8-O-hydroxylamino-N-methyl)thymidine (20), 5'-O-MMTr-3'-deoxy-2',3'-didehydro-2'-*C*-(ethyl-8-(S)-ethoxy-8-O-hydroxylamino-N-methylene) thymidine (21) and 5'-O-MMTr-3'-deoxy-2',3'-didehydro-2'-*C*-(ethylacetyl)thymidine (32). Compound **15** (500 mg, 0.65 mmol) was treated with tributyltin hydride (264 μL, 0.98 mmol), AIBN (82 mg, 0.32 mmol) in toluene (12 mL) in a stopper sealed round bottom flask at 100 °C for 30 min. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give **20** (180 mg, 45%) and **21** (35 mg, 9%) and **32** (30 mg, 8%). Compound **20**, ^{1}H NMR ($CDCl_3$, 500 MHz): 8.17 (*br, s*, 1H) NH; 7.46-7.2 (*m*, 13 H) arom and H6; 6.96 (*m*, $J_{1',3'}$ = 1.8 Hz, $J_{1',4'}$ = 3.6 Hz, 1H) H1'; 6.82 (*m*, 2H) arom; 6.12 (*m*, $J_{3',4'}$ = 1.1 Hz, 1H) H3'; 5.51 (*q*, 1H) NHNMe; 4.95 (*m*, 1H) H4'; 4.80 (*dd*, $J_{7',8}$ = 5.8 Hz, $J_{7'',8}$ = 5.0 Hz, 1H) H8; 3.85, 3.58 (2 x *m*, 2H) OCH_2CH_3; 3.78 (*s*, 3H) MMTr; 3.35 (*dd*, $J_{4',5'}$ = 3.0 Hz, $J_{5',5''}$ = 10.4 Hz, 1H) H5'; 3.30 (*dd*, $J_{4',5''}$ = 4.2 Hz, 1H) H5''; 2.72 (d, $J_{CH_3,NH}$ = 6.6 Hz, 3H) NMe; 2.53 (*m*, $J_{1',7'}$ = 0.7 Hz, $J_{3',7'}$ = 1.9 Hz, $J_{4',7'}$ = 1.9 Hz, $J_{7',7''}$ = 15.7 Hz, 1H) H7'; 2.30 (*m*, $J_{1',7''}$ = 0.6 Hz, $J_{3',7''}$ = 1.2 Hz, $J_{4',7''}$ = 1.2 Hz, 1H) H7''; 1.21 (*m*, 6H) $5CH_3$ and OCH_2CH_3. ^{13}C NMR ($CDCl_3$): 163.7 (*s*) C4; 150.9 (*s*) C2; 130.5 (*d*) C3'; 111.3 (*s*) C5'; 103.4 (*d*, J_{CH} = 163.1 Hz) C8; 90.6 (*d*, J_{CH} = 170.5 Hz) C1'; 86.4 (*s*) MMTr; 84.7 (*d*, J_{CH} = 152.1 Hz) C4'; 65.0 (*t*, J_{CH} = 142.0 Hz) C5'; 63.7 (*t*, J_{CH} = 142.5 Hz) OCH_2CH_3; 55.0 (*q*, J_{CH} = 143.6 Hz) MMTr; 39.6 (*q*, J_{CH} = 135.0 Hz) NMe; 30.5 (*t*, J_{CH} = 128.8 Hz) C7; 15.2 (*q*, J_{CH} = 126.2 Hz) OCH_2CH_3; 11.2 (*q*, J_{CH} = 128.9 Hz) $5CH_3$. MS (FAB^-): calc. for $(M-H)^-$ 612.2710, found 612.2691. Compound **21**, ^{1}H NMR ($CDCl_3$): 8.31 (*br, s*, 1H) NH; 7.46-7.2 (m, 13 H) arom and H6; 7.07 (d, $J_{12',12''}$ = 8.2 Hz, 1H) H12'; 6.97 (*m*, $J_{1',3'}$ = 1.8 Hz, $J_{1',4'}$ = 3.7 Hz, 1H) H1'; 6.81 (*m*, 2H) arom; 6.49 (*d*, 1H) H12''; 6.10 (*m*, 1H) H3'; 5.30 (*dd*, $J_{7',8}$ = 5.1 Hz, $J_{7'',8}$ = 5.1 Hz, 1H) H8; 4.94 (*m*, 1H) H4'; 3.83, 3.60 (2 x *m*, 2H) OCH_2CH_3; 3.78 (*s*, 3H) MMTr; 3.35 (*dd*, $J_{4',5'}$ = 2.9 Hz, $J_{5',5''}$ = 10.5 Hz, 1H) H5'; 3.30 (*dd*, $J_{4',5''}$ = 3.9 Hz, 1H) H5''; 2.59 (*m*, 1H) H7'; 2.41 (*m*, 1H) H7''; 1.21 (*m*, 6H) $5CH_3$ and OCH_2CH_3. ^{13}C NMR ($CDCl_3$): 163.5 (*s*) C4; 150.7 (*s*) C2; 138.3 (*t*, J_{CH} = 173.7 Hz) C12; 130.3 (*d*) C3'; 111.3 (*s*) C5'; 103.9 (*d*, J_{CH} = 167.7 Hz) C8; 90.6 (*d*, J_{CH} = 175.0 Hz) C1'; 86.5 (*s*) MMTr; 84.8 (*d*, J_{CH} = 154.0 Hz) C4'; 64.8, 64.3 (2 x *t*, J_{CH} = 143.0, 142.0 Hz) OCH_2CH_3 and C5'; 55.1 (*q*, J_{CH} = 143.9 Hz) MMTr; 31.0 (*t*, J_{CH} = 128.8 Hz) C7; 15.0 (*q*, J_{CH} = 126.5 Hz) OCH_2CH_3; 11.2 (*q*, J_{CH} = 128.3 Hz) $5CH_3$. Compound **32**, ^{1}H NMR ($CDCl_3$): 8.38 (*br, s*, 1H) NH, 7.47.7.18 (*m*, 13 H) arom and H6; 7.0 (m, $J_{1',3'}$ = 1.8 Hz, $J_{1',4'}$ = 3.8 Hz, 1H) H1'; 6.82 (*m*, 2H) arom; 6.24 (*m*, 1H) H3'; 4.98 (*m*, 1H) H4'; 4.15 (*m*, 2H) $COOCH_2CH_3$; 3.79 (*s*, 3H) MMTr; 3.44 (*dd*, $J_{4',5'}$ = 2.5 Hz, $J_{5',5''}$ = 10.4 Hz, 1H) H5'; 3.38 (*dd*, $J_{4',5''}$ = 4.0 Hz, 1H) H5''; 3.11 (br, *s*, 2H) H7', H7''; 1.26 (*m*, 6H) $COOCH_2CH_3$ and $5CH_3$. ^{13}C NMR ($CDCl_3$): 169.8 (*s*) COO; 164.0 (*s*) C4; 150.2 (*s*) C2; 135.7 (*d*, J_{CH} = 179.6 Hz) C6; 131.2 (*d*, J_{CH} = 174.1 Hz) C3'; 111.5 (*s*) C5; 90.3 (*d*, J_{CH} = 176.0 Hz) C1'; 86.6 (*s*) MMTr; 85.0 (*d*, J_{CH} = 150.3 Hz) C4'; 64.6, 61.3 (2 x *t*, J_{CH} = 143.0 Hz, 148.9 Hz) $COOCH_2CH_3$ and C5'; 55.1 (*q*, J_{CH} = 143.9 Hz) MMTr, 31.9 (*t*, J_{CH} = 130.1 Hz) C7; 14.0 (*q*, J_{CH} = 127.4 Hz) $COOCH_2CH_3$; 11.1 (*q*, J_{CH} = 128.6 Hz) $5CH_3$. MS (FAB^-): calc. for $(M-H)^-$ 581.2288, found 581.2286.

3'-Deoxy-2',3'-didehydro-2'-*C*-(ethyl-8-(S)-ethoxy-8-O-hydroxylamino-N-methyl)thymidine (22). Compound **20** (100 mg, 0.16 mmol) was treated with 80% aqueous acetic acid (3 mL) at RT for 2 h. The solvent was removed in vacuo, co-evaporated with toluene and CH_3OH. The residue was purified by silica gel column chromatography to give **22** (15 mg, 27%). When the reaction was continued for overnight under identical condition an unidentified compound was formed as a major product along with trace amount of **33**. ^{1}H NMR ($CDCl_3$): 7.38 (*d*, J = 1.2 Hz, 1H) H6; 6.90 (*m*, $J_{1',3'}$ = 1.6 Hz, $J_{1',4'}$ = 3.5 Hz, 1H) H1'; 6.07 (*m*, 1H) H3'; 4.88 (*m*, 1H) H4'; 4.76 (*dd*, $J_{7',8}$ = $J_{7'',8}$ = 5.4 Hz, 1H) H8; 3.92 (*dd*, $J_{4',5'}$ = 2.7 Hz, $J_{5',5''}$ = 12.4 Hz, 1H) H5'; 3.80, 3.52 (2 x *m*, 2H) OCH_2CH_3; 3.75 (*dd*, $J_{4',5''}$ = 3.0 Hz, 1H) H5''; 2.71 (*s*, 3H) NMe; 2.52 (*m*, 1H) H7'; 2.26 (*m*, 1H) H7''; 1.85 (*d*, 3H) $5CH_3$; 1.21 (*t*, 3H) OCH_2CH_3. ^{13}C NMR ($CDCl_3$): 163.8 (*s*) C4; 150.7 (*s*) C2; 136.9 (*d*, J_{CH} = 183.9 Hz) C6; 134.9 (*s*) C2'; 129.6 (*d*, J_{CH} = 172 1 Hz) C3'; 110.7 (*s*) C5; 103.4 (*d*, J_{CH} = 165.3 Hz) C8; 91.3 (*d*, J_{CH} = 178.0 Hz) C1', 86.3 (*d*, J_{CH} = 149.7 Hz) C4'; 63.9, 63.5 (2 x *t*, J_{CH} = 142.3, 143.3 Hz) OCH_2CH_3 and C5'; 39.6 (*q*, J_{CH} = 135.0 Hz) NMe; 30.8 (*t*, J_{CH} = 129.6 Hz) C7; 15.2 (*q*, J_{CH} = 125.5 Hz) OCH_2CH_3; 12.3 (*q*, J_{CH} = 128.8 Hz) $5CH_3$. MS (FAB^-)· calc. for $(M-H)^-$ 340.1508, found 340.1519.

3'-Deoxy-2',3'-didehydro-2'-*C*-(ethyl-8-(S)-ethoxy-8-O-hydroxylamino-N-methylene)thymidine (23). Compound **21** (20 mg, 0.03 mmol) was treated with 80% aqueous acetic acid (3 mL) at RT for 90 min. The solvent was removed in vacuo, co-evaporated with toluene and CH_3OH. The residue was purified by flash chromatography to give **23** (9.5 mg, 86%). ^{1}H NMR ($CDCl_3$): 7.35 (*d*, J = 1.2 Hz, 1H) H6; 7.07 (*d*, $J_{12',12''}$ = 8.2 Hz, 1H) H12'; 6.96 (*m*, $J_{1',3'}$ = 1.7 Hz, $J_{1',4'}$ = 3.4 Hz, 1H) H1'; 6.49 (*d*, 1H) H12''; 6.07 (*m*, 1H) H3'; 5.22 (*t*, $J_{7',8}$ = 5.5 Hz, $J_{7'',8}$ = 5.2 Hz, 1H) H8; 4.89 (*m*, 1H) H4'; 3.92 (*dd*, $J_{4',5'}$ = 2.6 Hz, $J_{5',5''}$ = 12.6 Hz, 1H) H5'; 3.81, 3.57 (2 x *m*, 2H) OCH_2CH_3; 3.74 (*dd*, $J_{4',5''}$ = 3.2 Hz, 1H) H5''; 2.59 (*m*, 1H) H7'; 2.33 (*m*, 1H) H7''; 1.84 (*d*, 3H) $5CH_3$; 1.19 (*t*, 3H) OCH_2CH_3. ^{13}C NMR ($CDCl_3$): 163.8 (*s*) C4; 150.5 (*s*) C2; 138.4 (*t*, J_{CH} = 173.7 Hz) C12; 136.9 (*d*, J_{CH} = 186.0 Hz) C6; 134.2 (*s*) C2'; 130 3 (*d*, J_{CH} = 169.5 Hz) C3'; 110.7 (*s*) C5; 103.7 (*d*, J_{CH} = 166.8 Hz) C8; 91.2 (*d*, J_{CH} = 177.8 Hz) C1'; 86.4 (*d*, J_{CH} = 147.5 Hz) C4'; 64.5, 63.4 (2 x *t*, J_{CH} = 143.4, 142.5 Hz) C5' and OCH_2CH_3; 31.3 (*t*, J_{CH} = 128.3 Hz) C7; 15.0 (*q*, J_{CH} = 126.5 Hz) OCH_2CH_3; 12.2 (*q*, J_{CH} = 129.2 Hz) $5CH_3$. MS (FAB^-): calc. for $(M-H)^-$ 338.1352, found 338.1375.

5'-O-MMTr-3'-deoxy-2',3'-didehydro-2'-*C*-(ethyl-8-(S)-cyano-8-O-hydroxylamino-N-methyl)thymidine (24) and 5'-O-MMTr-3'-deoxy-2',3'-didehydro-2'-*C*-(ethyl-8-(S)-cyano-8-O-hydroxylamino-N-methylene)thymidine (28). Reaction condition was used described for **20** using **17** (500 mg, 0.67 mmol), tributyltin hydride (269 μL, 1.0 mmol) and AIBN 28 mg, 0.17 mmol) in toluene (7 mL) at 100 °C for 60 min. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give **24** (240 mg, 60%) and **28** (20 mg, 5%). Compound **24**, ^{1}H NMR ($CDCl_3$): 8.61 (*br, s*, 1H) NH; 7.48-7.18 (*m*, 13 H) arom and H6; 6.98 (*m*, $J_{1',3'}$ = 1.8 Hz, $J_{1',4'}$ = 3.8 Hz, 1H) H1'; 6.83 (*m*, 2H) arom; 6.25 (m, 1H) H3'; 6.07 (*q*, 1H) NHMe; 4.99 (*m*, 1H) H4'; 4.63 (*dd*, $J_{7',8}$ = 5.2 Hz, $J_{7'',8}$ = 5.0 Hz, 1H) H8; 3.79 (*s*, 3H) MMTr; 3.45 (*dd*, $J_{4',5'}$ = 2.4 Hz, $J_{5',5''}$ = 10.6 Hz, 1H) H5'; 3.36 (*dd*, $J_{4',5''}$ = 3.7 Hz, 1H) H5''; 2.79 (*d*, $J_{CH_3,NH}$ = 7.0 Hz, 3H) NMe; 2.68 (*m*, 1H) H7'; 2.54 (*m*, 1H) H7''; 1.2 (*s*, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$): 163.7 (*s*) C4; 151.0 (*s*) C2; 117.8 (*s*) CN; 112.0 (*s*) C5; 90.1 (*d*, J_{CH} = 171.4 Hz) C1'; 86.6 (*s*) MMTr; 84.9 (*d*, J_{CH} = 148.5 Hz) C4'; 69.8 (*d*, J_{CH} = 154.0 Hz) C8; 64.5 (*t*, J_{CH} = 143.0 Hz) C5'; 55.0 (*q*, J_{CH} = 143.6 Hz) MMTr; 39.3 (*q*, J_{CH} = 136.2 Hz) NMe; 28.8 (*t*, J_{CH} = 131.0 Hz) C7; 11.0 (*q*, J_{CH} = 127.7 Hz) $5CH_3$. Compound **28**, ^{1}H NMR ($CDCl_3$): 8.36 (*br, s*, 1H) NH; 7.47 (*d*, J = 1.2 Hz, 1H) H6; 7.42-7.20 (*m*, 12 H) arom; 7.13 (*d*, $J_{12',12''}$ = 7.0 Hz, 1H) H12'; 6.99 (*m*, $J_{1',3'}$ = 1.7 Hz, $J_{1',4'}$ = 3.9 Hz, 1H) H1'; 6.83 (*m*, 2H) arom; 6.65 (*d*, 1H) H12''; 6.27 (*m*, 1H) H3'; 5.08 (*dd*, $J_{7',8}$ = 6.8 Hz, $J_{7'',8}$ = 5.1 Hz, 1H) H8; 4.99 (*m*, 1H) H4'; 3.79 (*s*, 3H) MMTr; 3.45 (*dd*, $J_{4',5'}$ = 2.6 Hz, $J_{5',5''}$ = 10.7 Hz, 1H) H5'; 3.36 (*dd*, $J_{4',5''}$ = 3.3 Hz, 1H) H5''; 2.81 (*m*, 1H) H7'; 2.67 (*m*, 1H) H7''; 1.19 (*d*, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$): 163.3 (*s*) C4; 150.6 (*s*) C2; 141.1 (*t*, J_{CH} = 175.0 Hz) C12; 135.3 (*d*, J_{CH} = 183.3 Hz) C6; 131.9 (*d*, J_{CH} = 171.4 Hz) C3'; 116.8 (*s*) CN; 111.9 (*s*) C5; 90.2 (*d*, J_{CH} = 172.3 Hz) C1'; 86.7 (*s*) MMTr; 85.0 (*d*, J_{CH} = 145.7 Hz) C4'; 69.4 (*d*, J_{CH} = 156.7 Hz) C8; 64.4 (*t*, J_{CH} = 143.4 Hz) C5'; 55.1 (*q*, J_{CH} = 143.9 Hz) MMTr; 29.0 (*t*, J_{CH} = 131.5 Hz) C7; 11.0 (*q*, J_{CH} = 129.5 Hz) $5CH_3$.

3'-Deoxy-2',3'-didehydro-2'-*C*-(ethyl-8-(S)-cyano-8-O-hydroxylamino-N-methyl)thymidine (25). Compound **24** (100 mg, 0.17 mmol) was treated with 80% aqueous acetic acid (3 mL) at RT for 2 h. The solvent was removed in vacuo, co-evaporated with CH_3OH and toluene. The residue was purified by silica gel column chromatography to give **25** (30 mg, 56%). ^{1}H NMR ($CDCl_3$): 9.09 (*br, s*, 1H) NH; 7.49 (*d*, J = 1.1 Hz, 1H) H6; 6.96 (*m*, $J_{1',3'}$ = 1.6 Hz, $J_{1',4'}$ = 3.6 Hz, 1H) H1'; 6.23 (*m*, 1H) H3'; 6.12 (*q*, 1H) NHMe; 4.95 (*m*, 1H) H4'; 4.61 (*dd*, $J_{7',8}$ = 5.2 Hz, $J_{7'',8}$ = 6.3 Hz, 1H) H8; 3.96 (*dd*, $J_{4',5'}$ = 2.6 Hz, $J_{5',5''}$ = 12.5 Hz, 1H) H5'; 3.81 (*dd*, $J_{4',5''}$ = 2.9 Hz, 1H) H5''; 3.10 (br, *s*, 1H) 5'-OH; 2.78 (d, $J_{NH,Me}$ = 6.7 Hz, 3H) NMe; 2.65 (*m*, 1H) H7'; 2.46 (*m*, 1H) H7''; 1.85 (*d*, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$): 163.9 (*s*) C4; 150.8 (*s*) C2, 136.4 (*d*, J_{CH} = 180.5 Hz) C6; 133.0 (*s*) C2'; 131.6 (*d*, J_{CH} = 170.5 Hz) C3'; 117.7 (*s*) CN; 111.3 (*s*) C5; 90.7 (*d*, J_{CH} = 171.4 Hz) C1'; 86.5 (*d*, J_{CH} = 151.2 Hz) C4'; 69.9 (*d*, J_{CH} = 155.8 Hz) C8; 63.0 (*t*, J_{CH} = 142.5 Hz) C5'; 39.3 (*q*, J_{CH} = 135.9 Hz) NMe; 28.9 (*t*, J_{CH} = 132.0 Hz) C7; 12.2 (*q*, J_{CH} = 129.5 Hz) $5CH_3$. MS (FAB^-): calc. for $(M-H)^-$ 321.1199, found 321.1233.

5'-O-MMTr-3'-deoxy-2',3'-didehydro-2'-*C*-(ethyl-8-(R)-cyano-8-O-hydroxylamino-N-methyl)thymidine (26). and **5'-O-MMTr-3'-deoxy-2'-didehydro-spiro[2'-(R),11-(8-(R)-cyano-10-(R)-N-methyl-9,10-isoxazolidine)]thymidine (30).** The reaction condition was used described for **24** using **19** (450 mg, 0.6 mmol), tributyltin hydride (242 μL, 0.9 mmol) AIBN (24 mg, 0.15 mmol) in toluene for 30 min to obtain **26** (160 mg, 45%) and **30** (70 mg, 20%). Compound **26**, ^{1}H NMR ($CDCl_3$): 8.51 (*br, s*, 1H) NH; 7.48-7.20 (*m*, 13 H) arom; 6.95 (*m*, $J_{1',3'}$ = 1.7 Hz, $J_{1',4'}$ = 3.9 Hz, 1H) H1'; 6.83 (*m*, 2H) arom; 6.25 (*m*, 1H) H3'; 6.05 (*q*, 1H) NHMe; 4.98 (*m*, 1H) H4'; 4.60 (*t*, $J_{7',8}$ = 6.9 Hz, $J_{7'',8}$ = 6.8 Hz, 1H) H8; 3.79 (*s*, 3H) MMTr; 3.46 (*dd*, $J_{4',5'}$ = 2.7 Hz, $J_{5',5''}$ = 10.9 Hz, 1H) H5'; 3.36 (*dd*, $J_{4',5''}$ = 3.8 Hz, 1H) H5''; 2.79 (*d*, $J_{NH,Me}$ = 6 8 Hz, 3H) NMe; 2.69 (*m*, 1H) H7'; 2.53 (*m*, 1H) H7''; 1.20 (*d*, J = 1.1 Hz, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$): 163.8 (*s*) C4; 151.2 (*s*) C2; 117.8 (*s*) CN; 111.9 (*s*) C5; 90.0 (*d*, J_{CH} = 168.6 Hz) C1'; 86.6 (*s*) MMTr; 84.9 (*d*, J_{CH} = 147.5 Hz) C4'; 70.2 (*d*, J_{CH} = 155.8 Hz) C8; 64.4 (*t*, J_{CH} = 143.4 Hz) C5'; 55.0 (*q*, J_{CH} = 144.2 Hz) MMTr; 39.3 (*q*, J_{CH} = 135.6 Hz) NMe; 28.9 (*t*, J_{CH} = 131.0 Hz) C7; 11.0 (*q*, J_{CH} = 128.6 Hz) $5CH_3$.

3'-Deoxy-2',3'-didehydro-2'-*C*-(ethyl-8-(R)-cyano-8-O-hydroxylamino-N-methyl)thymidine (27). Compound **26** (60 mg, 0.1 mmol) was treated with 80% aqueous acetic acid (3 mL) at RT for 5 h. The solvent was removed in vacuo, co-evaporated with methanol and toluene. The residue was purified by silica gel column chromatography to give **27** (22 mg, 68%). ^{1}H NMR ($CDCl_3$): 9.01 (*br, s*, 1H) NH; 7.50 (*d*, J= 1.2 Hz, 1H) H6; 6.94 (*m*, $J_{1',3'}$ = 1.8 Hz, $J_{1',4'}$ = 3.6 Hz, 1H) H1'; 6.22 (*m*, 1H) H3', 6.14 (*q*, 1H) NHMe, 4.93 (*m*, 1H) H4'; 4.56 (dd, $J_{7',8}$ = 6.0 Hz, $J_{7'',8}$ = 7.6 Hz, 1H) H8; 3.96 (br, *d*, $J_{4',5'}$ = 2.6 Hz, $J_{5',5''}$ = 12.5 Hz, 1H) H5'; 3.81 (br, *d*, $J_{4',5''}$ = 3.0 Hz, 1H) H5''; 3.03 (br, *s*, 1H) 5'-OH; 2.77 (*d*, $J_{Me,NH}$ = 6.7 Hz, 3H) NMe; 2.65 (*m*, 1H) H7'; 2.47 (*m*, 1H) H7''; 1.85 (*d*, 3H) $5CH_3$ ^{13}C NMR ($CDCl_3$): 163.8 (*s*) C4; 150.8 (*s*) C2; 136.3 (*d*, J_{CH} = 181.5 Hz) C6; 133.3 (*s*) C2'; 131.4 (*d*, J_{CH} = 170 5 Hz) C3'; 117.8 (*s*) CN; 111.3 (*s*) C5; 90.5 (*d*, J_{CH} = 175.9 Hz) C1'; 86.4 (*d*, J_{CH} = 148.5 Hz) C4'; 70.2 (*d*, J_{CH} = 155.8 Hz) C8; 63.0 (*t*, J_{CH} = 142.0 Hz) C5'; 39.4 (*q*, J_{CH} = 136.8 Hz) NMe; 29.0 (*t*, J_{CH} = 132.0 Hz) C7; 12.2 (*q*, J_{CH} = 129.5 Hz) $5CH_3$. MS (FAB^-): calc. for $(M-H)^-$ 321.1199, found 321.1174.

3'-Deoxy-2',3'-didehydro-2'-*C*-(ethyl-8-(S)-cyano-8-O-hydroxylamino-N-methylene)thymidine (29). Compound **28** (15 mg, 0.02 mmol) was treated with 80% aqueous acetic acid (1.5 mL) at RT for 2 h. After

usual work up the residue was purified by silica gel column chromatography to give **29** (7 mg, 88%). ^{1}H NMR ($CDCl_3$): 8.29 (*br, s*, 1H) NH; 7.49 (d, J = 1.3 Hz, 1H) H6; 7.15 (*d*, $J_{12',12''}$ = 7.0 Hz, 1H) H12'; 6.99 (*m*, $J_{1',3'}$ = 1.8 Hz, $J_{1',4'}$ = 3.7 Hz, 1H) H1'; 6.66 (*d*, 1H) H12''; 6.26 (*m*, 1H) H3'; 5.04 (*dd*, $J_{7',8}$ = 6.0 Hz, $J_{7'',8}$ = 5.3 Hz, 1H) H8; 4.96 (*m*, 1H) H4'; 3.98 (br,*d*, $J_{4',5'}$ = 2.7 Hz, $J_{5',5''}$ = 12.4 Hz, 1H) H5'; 3.83 (br,*d*, $J_{4',5''}$ = 2.8 Hz, 1H) H5''; 2.76 (br,*dd*, 1H) H7'; 2.59 (br,*dd*, 1H) H7''; 2.37 (*t*, 1H) 5'OH; 1.87 (*d*, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$): 163.4 (*s*) C4; 150.5 (*s*) C2; 141.3 (*t*, J_{CH} = 175.0 Hz) C12; 136.1 (*d*, J_{CH} = 179.6 Hz) C6; 132.9 (*s*) C2'; 132.2 (*d*, J_{CH} = 173.2 Hz) C3'; 116.7 (*s*) CN; 111.5 (*s*) C5; 90.7 (*d*, J_{CH} = 174.1 Hz) C1'; 86.2 (*d*, J_{CH} = 155.8 Hz) C4'; 69.6 (*d*, J_{CH} = 156.7 Hz) C8; 63.2 (*t*, J_{CH} = 143.4 Hz) C5'; 29.1 (*t*, J_{CH} = 132.4 Hz) C7; 12.3 (*q*, J_{CH} = 129.2 Hz) $5CH_3$. MS (FAB^-): calc. for $(M-H)^-$ 319.1042, found 319.1034.

3'-Deoxy-2'-didehydro-spiro[2'-(R),11-(8-(R)-cyano-10-(R)-N-methyl-9,10-isoxazolidine)]thymidine (31). Compound **30** (60 mg, 0.1 mmol) was treated with 80% aqueous acetic-acid (3 mL) at RT for 3 h. After usual workup the residue was purified by silica gel column chromatography to give **31** (30 mg, 94%). ^{1}H NMR ($CDCl_3$ + CD_3OD): 7.44 (s, 1H) H6; 5.84 (*s*, 1H) H1'; 4.80 (*dd*, $J_{7',8}$ = 8.8 Hz, $J_{7'',8}$ = 7.8 Hz, 1H) H8; 4.15 (*m*, 1H) H4'; 3.91 (*dd*, $J_{4',5'}$ = 3.0 Hz, $J_{5',5''}$ = 12.3 Hz, 1H) H5'; 3.69 (*dd*, $J_{4',5''}$ = 3.5 Hz, 1H) H5''; 3.11 (*dd*, $J_{7',7''}$ = 13.0 Hz, 1H) H7'; 2.86 (*dd*, 1H) H7''; 2.78 (*s*, 3H) NMe; 2.39 (*dd*, $J_{3',4'}$ = 9.9 Hz, $J_{3'',4'}$ = 5.9 Hz, 1H) H3'; 2.11 (*dd*, $J_{3',3''}$ = 13.1 Hz, 1H) H3'', 1.89 (*s*, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$ + CD_3OD): 164.5 (*s*) C4; 151.0 (*s*) C2; 137.4 (*d*, J_{CH} = 184.2 Hz) C6; 119.0 (*s*) CN; 109.0 (*s*) C5; 89.9 (*d*, J_{CH} = 168.6 Hz) C1'; 77.7 (*d*, J_{CH} = 149.4 Hz) C4'; 76.6 (*s*) C2'; 63.7 (*d*, J_{CH} = 166.8 Hz) C8; 61.4 (*t*, J_{CH} = 142.0 Hz) C5'; 42.1 (*t*, J_{CH} = 137.5 Hz) C7; 41.5 (*q*, J_{CH} = 136.5 Hz) NMe; 32.2 (*t*, J_{CH} = 133.8 Hz) C3'; 12.0 (*q*, J_{CH} = 128.9 Hz) $5CH_3$. MS (FAB^-): calc. for $(M-H)^-$ 321.1199, found 321.1195.

3'-Deoxy-2',3'-didehydro-2'-*C*-(ethylacetyl)thymidine (33). Compound **32** (10 mg. 0.02 mmol) was treated with 80% aqueous acetic acid (1.5 mL) at RT for 4 h. The solvent was removed in vacuo, co-evaporated with toluene and CH_3OH. The residue was purified by flash chromatography to give **33** (5 mg, 94%). ^{1}H NMR ($CDCl_3$ + CD_3OD): 7.58 (*d*, J= 1.2 Hz, 1H) H6; 6.91 (*m*, $J_{1',3'}$ = 1.6 Hz, $J_{1',4'}$ = 3.6 Hz, 1H) H1'; 6.20 (*m*, 1H) H3'; 4.91 (*m*, 1H) H4'; 4.14 (*m*, 2H) $COO\underline{CH_2}CH_3$; 3.89 (*dd*, $J_{4',5'}$ = 2.6 Hz, $J_{5',5''}$ = 12.1 Hz. 1H) H5': 3.79 (*dd*, $J_{4',5''}$ = 3.0 Hz, 1H) H5''; 3.08 (2 x br, *d*, 2H) H7', H7''; 1.88 (*d*, 3H) $5CH_3$; 1.26 (*t*, 3H) $COOCH_2\underline{CH_3}$. ^{13}C NMR ($CDCl_3$ + CD_3OD): 169.4 (*s*) $\underline{C}OO$; 163.8 (*s*) C4; 150.9 (*s*) C2; 136.5 (*d*, J_{CH} = 186.0 Hz) C6; 132.2 (*s*) C2'; 130.9 (*d*, J_{CH} = 174.1 Hz) C3'; 111.1 (*s*) C5; 90.9 (*d*, J_{CH} = 174.1 Hz) C1'; 86.5 (*d*, J_{CH} = 154.0 Hz) C4'; 63.0, 61.4 (2 x *t*, JCH = 142.5, 150.3 Hz) $COO\underline{C}H_2CH_3$ and C5'; 31.9 (*t*, J_{CH} = 130.1 Hz) C7; 13.9 (*q*, J_{CH} = 127.4 Hz) $COOCH_2\underline{C}H_3$; 12.2 (*q*, J_{CH} = 128.6 Hz) $5CH_3$. MS (FAB^-): calc. for $(M-H)^-$ 309.1086, found 309.1095.

1-[2, 5-Bis -O-TBDMS-β-D-*erythro*-pentofuran-3-ulosyl]thymine (34). The reaction was performed using a reaction condition described for **1** (2', 5'-Bis -O-TBDMS-xylothymidine, 1.5 g, 3.09 mmol). ^{1}H NMR ($CDCl_3$): 9.44 (*br, s*, 1H) NH; 7.51 (*d*, 1H) H6; 6.27 (*d*, $J_{1',2'}$ = 8.2 Hz, 1H) H1'; 4.23 (*s*, 1H) H4'; 4.19 (*d*, 1H) H2'; 3.93 (*s*, 2H) H-5', H-5''; 1.97 (*d*, J = 1 Hz, 3H) $5CH_3$; 0.92 (*s*, 9H), 0.85 (*s*, 9H), 0.11 (*s*, 6H), 0.08 (*s*, 6H) TBDMS. ^{13}C NMR ($CDCl_3$): 208.1 (*s*) C3'; 163.6 (*s*) C4; 150.5 (*s*) C2; 133.9 (*d*, J_{CH} = 180.6 Hz) C6; 112.1 (*s*) C5; 84.1 (*d*, J_{CH} = 168.2 Hz) C1'; 81.6 (*d*, J_{CH} = 149.5 Hz) C4'; 76.8 (*d*, J_{CH} = 140.1 Hz) C2'; 62.3 (*t*, J_{CH} = 145.3Hz) C5'; 12.1 (*q*, J_{CH} = 129.4Hz) $5CH_3$; 25.6, 25.1, 18.0, 17 8, -5.0, -5.6, -5,7, -5.9 TBDMS.

1-[5-O-MMTr-2-O-TBDMS-β-D-*erythro*-pentofuran-3-ulosyl]thymine (35). The reaction was performed using a reaction condition described for **1** (5'-O-MMTr-2'-TBDMS-xylothymidine[17], 2.0 g, 3.1 mmol). ^{1}H NMR ($CDCl_3$): 9.82 (*br, s*, 1H) NH; 7.54 (*d*, 1H) H6; 7.37-7.19 (*m*, 12H) MMTr; 6.85 (*m*, 2H) MMTr; 6.29 (*d*, $J_{1',2'}$ = 8.1 Hz, 1H) H1'; 4.63 (*d*, 1H) H2', 4.24 (*m*, 1H) H4'; 3 79 (*s*, 3H) MMTr; 3.59 (*dd*, $J_{4',5'}$ = 1.4 Hz, $J_{5',5''}$ = 10.4 Hz, 1H) H-5', 3.40 (*dd*, $J_{4',5''}$ = 1 8 Hz, 1H) H-5''; 1.40 (*d*, J = 1 Hz, 3H) $5CH_3$; 0.90 (*s*, 9H), 0.18 (*s*, 3H), 0.11 (*s*, 3H), TBDMS ^{13}C NMR ($CDCl_3$): 208.6 (*s*) C3'; 163 3 (*s*) C4; 150.4 (*s*) C2; 134.4 (*d*, J_{CH} = 180.0 Hz) C6; 112.4 (*s*) C5; 84 59 (*d*, J_{CH} = 173 1 Hz) C1'; 80 2 (*d*, J_{CH} = 154.5 Hz) C4'; 76.4 (*d*, J_{CH} = 139.9 Hz) C2'; 63.0 (*t*, J_{CH} = 146.2 Hz) C5'; 55.1 (*q*, J_{CH} = 143.8 Hz) MMTr; 11.5 (*q*, J_{CH} = 129.4 Hz) $5CH_3$; 25.3, 18.0, -4.8, -5.5, TBDMS.

2',5'-Bis-O-TBDMS-3'-deoxy-3'-dehydro-3'-(E)-(N-methyloximino)-5-methyluridine (36). The reaction was performed using a reaction condition described for **2** (compound **34** without purification) to give **36** (0.93 g, 59%). ^{1}H NMR ($CDCl_3$) 9.18 (*br, s*, 1H) NH; 7.54 (*d*, 1H) H6; 6.15 (*d*, $J_{1',2'}$ = 6 5 Hz, 1H) H1'; 5.11 (*m*, $J_{4',Me}$ =1.0 Hz, 1H) H4'; 4 93 (*m*, $J_{2',Me}$ =1.0 Hz, $J_{2',4'}$ =2.5 Hz, 1H) H2'; 4.51 (*dd*, $J_{4',5'}$ = 2.0 Hz, $J_{5',5''}$ = 11.0 Hz, 1H) H5'; 3.89 (*dd*, $J_{4',5''}$ = 1.7 Hz, 1H) H5'', 3.85 (*dd* , 3H) NMe, 2.02 (*d*, J = 0.8 Hz, 3H) $5CH_3$; 0.99 (*s*, 9H), 0.97 (*s*, 9H), 0.17 (*s*, 6H), 0.05 (*s*, 6H) TBDMS ^{13}C NMR ($CDCl_3$): 163.5 (*s*) C4; 150.6 (*s*) C2; 145.6 (*s*) C3'; 134.4 (*d*, J_{CH} = 179 0 Hz) C6; 112.0 (*s*) C5; 87.3 (*d*, J_{CH} = 171.2 Hz) C1'; 79.6 (*d*, J_{CH} = 157.6 Hz) C4'; 72.9 (*d*, J_{CH} = 147.7 Hz) C2'; 60.6 (*t*, J_{CH} = 145 7 Hz) C5'; 48.0 (*q* J_{CH} = 142.5 Hz) NMe; 12.0 (*q*, J_{CH} = 129.4 Hz) $5CH_3$; 25.6, 25.2, 17.9, 17.5, -4.7, -5 10, -5,7, -5.80 TBDMS.

5'-O-MMTr-2'-O-TBDMS-3'-deoxy-3'-dehydro-3'-(E)-(N-methyloximino)-5-methyluridine (37). The reaction was performed using a reaction condition described for **2** (compound **35** without purification) to give

37 (0.74 g, 52%) and 0.63 g of initial **35**. ^{1}H NMR ($CDCl_3$): 8.87 (*br, s*, 1H) NH; 7.45 (*d*, 1H) H6; 7.40-7.22 (*m*, 12H) MMTr; 6.86 (*m*, 2H) MMTr; 6.14 (*d*, $J_{1',2'}$ = 6.5 Hz, 1H) H1'; 5.26 (*m*, $J_{2',Me}$ =0.5 Hz, $J_{2',4'}$ =2.6 Hz, 1H) H2'; 5.18 (*m*, 1H) H4'; 4.12 (*dd*, $J_{4',5'}$ = 2.2 Hz, $J_{5',5''}$ = 10.1 Hz, 1H) H5'; 3.95 (*m*, 3H) NMe; 3.81 (*s*, 3H) MMTr; 3.29 (*dd*, $J_{4',5''}$ = 1.8 Hz, 1H) H5''; 1.32(*d*, J = 1.0 Hz, 3H) $5CH_3$; 0.97 (*s*, 9H), 0.24 (*s*, 3H), 0.02 (*s*, 3H) TBDMS. ^{13}C NMR ($CDCl_3$): 163.46 (*s*) C4; 150.5 (*s*) C2; 145.5 (*s*) C3'; 135.0 (*d*, J_{CH} = 180.0 Hz) C6; 112.32 (*s*) C5; 87.6 (*d*, J_{CH} = 172.1Hz) C1'; 78.2 (*d*, J_{CH} = 156.5 Hz) C4'; 72.8 (*d*, J_{CH} = 146.7 Hz) C2'; 61.7 (*t*, J_{CH} = 147.2 Hz) C5'; 55.0 (*q*, J_{CH} = 143.8 Hz) MMTr; 48.4 (*q* J_{CH} = 142.5 Hz) NMe; 11.2 (*q*, J_{CH} = 129.4 Hz) $5CH_3$; 25.4, 17.6,-4.6, -4.9 TBDMS.

2',5'-Bis-O-TBDMS-3'-deoxy-3'-dehydro-spiro[3'-(S),11-(8-(R)-ethoxy-10-(S)-N-methyl-9,10-isoxazolidine)]-5-methyluridine (38). The reaction was performed using a reaction condition described for **3** (compound **36**, 0.40 g, 0.8 mmol) to give **38** (0.44 g, 95%). ^{1}H NMR ($CDCl_3$): 8.44 (*br, s*, 1H) NH; 7.70 (*q*, 1H) H6; 5.79 (*d*, $J_{1',2'}$ = 4.5 Hz, 1H) H1'; 5.35 (*dd*, $J_{7',8}$ = 1.9 Hz, $J_{7'',8}$ = 6.7 Hz, 1H) H8; 4.41 (*d*, 1H) H2'; 4.31 (*dd*, $J_{4',5'}$ = 2.4 Hz, $J_{4',5''}$ = 5.4 Hz, 1H) H4'; 4.10 (*dd*, $J_{5',5''}$ = 11.6 Hz, 1H) H5'; 3.97 (*dd*, 1H) H5''; 3.73 (*m*, 1H) and 3.45 (m, 1H) CH_3CH_2O; 2.98 (*dd*, $J_{7',7''}$ = 13.8 Hz, 1H) H7'; 2.59 (*s*, 3H) NMe; 2.18 (*dd*, 1H) H7''; 1.96 (*d*, J = 1.1 Hz, 3H) $5CH_3$; 1.19 (*t*, J = 7.0 Hz, 3H) CH_3CH_2O; 0.96 (*s*, 9H), 0.89 (*s*, 9H), 0.17 (*s*, 6H), 0.07 (*s*, 6H) TBDMS. ^{13}C NMR ($CDCl_3$): 163.8 (*s*) C4; 150.7 (*s*) C2; 136.2 (*d*, J_{CH} = 180.9 Hz) C6; 110.3 (*s*) C5; 102.9 (*d*, J_{CH} = 162.2 Hz) C8; 88.6 (*d*, J_{CH} = 170.2 Hz) C1'; 85.9 (*d*, J_{CH} = 148.7 Hz) C4'; 75.8 (*d*, J_{CH} = 150.6 Hz) C2'; 74.85 (*s*) C3'; 64.3 (*t*, J_{CH} = 141.8 Hz) CH_3CH_2O; 62.6 (*t*, J_{CH} = 143.3 Hz) C5'; 42.2 (*q*, J_{CH} = 136.0 Hz) NMe; 38.3 (*t*, J_{CH} = 134.5 Hz) C7; 15.0 (*q*, J_{CH} = 126.2Hz) CH_3CH_2O; 12.3 (*q*, J_{CH} = 129.1 Hz) $5CH_3$; 26.0 25.7, 18.6, 17.8, -4.2, -5.0, -5.5 TBDMS.

3'-Deoxy-3'-dehydro-spiro[3'-(S),11-(8-(R)-ethoxy-10-(S)-N-methyl-9,10-isoxazolidine)]-5-methyluridine (39). Compound **38** (0.40 g, 0.68 mmol), NH_4F (500 mg) and CH_3OH (3 mL) was refluxed 18 h then silica gel was added and reaction mixture was evaporated. Compound was purified by silica gel column chromatography to give **39** (0.20 g, 82%). ^{1}H NMR ($CDCl_3$ + CD_3OD): 7.83 (*q*, 1H) H6; 5.83 (*d*, $J_{1',2'}$ = 6.8 Hz, 1H) H1'; 5.49 (*dd*, $J_{7',8}$ = 0.6 Hz, $J_{7'',8}$ = 6.4 Hz, 1H) H8; 4.37 (*dd*, $J_{4',5'}$ = 2.9 Hz, $J_{4',5''}$ = 3.2 Hz, 1H) H4'; 4.33 (*d*, 1H) H2'; 3.98 (*dd*, $J_{5',5''}$ = 12.4 Hz, 1H) H5'; 3.80 (*dd*, 1H) H5''; 3.73 (*m*, 1H) and 3.48 (*m*, 1H) CH_3CH_2O; 3.07 (*dd*, $J_{7',7''}$ = 13.5 Hz, 1H) H7'; 2.68 (*s*, 3H) NMe; 2.22 (*dd*, 1H) H7''; 1.93 (*d*, J = 1.1 Hz, 3H) $5CH_3$; 1.20 (*t*, J = 7.1 Hz, 3H) CH_3CH_2O. ^{13}C NMR ($CDCl_3$): 163.8 (*s*) C4; 150.7 (*s*) C2; 136.2 (*d*, J_{CH} = 180.9 Hz) C6; 110.3 (*s*) C5; 102.9 (*d*, J_{CH} = 162.2 Hz) C8; 88.6 (*d*, J_{CH} = 170.2 Hz) C1'; 85.9 (*d*, J_{CH} = 148.7 Hz) C4'; 75.8 (*d*, J_{CH} = 150.6 Hz) C2'; 74.8 (*s*) C3'; 64.3 (*t*, J_{CH} = 141.8 Hz) CH_3CH_2O; 62.6 (*t*, J_{CH} = 143.3 Hz) C5'; 42.2 (*q* J_{CH} = 136.0 Hz) NMe; 38.3 (*t*, J_{CH} = 134.5 Hz) C7; 15.0 (*q*, J_{CH} = 126.2Hz) CH_3CH_2O; 12.3 (*q*, J_{CH} = 129.1 Hz) $5CH_3$; 26.0 25.7, 18.6, 17.8, -4.2, -5.0, -5,5 TBDMS. MS (FAB^-): calc. for $(M-H)^-$ 356.1458, found 356.1475.

3'-Deoxy-3'-dehydro-spiro[3'-(S),11-(8-(S)-ethoxy-10-(S)-N-methyl-9,10-isoxazolidine)]-5-methyluridine (40). Compound **39** (20 mg, 0.06 mmol) was treated with 20% trifluoroacetic acid in C_2H_5OH (1 ml) at 45 °C for 70 h. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give mixture of initial compound **39** and **40** in 2:3 ratio. Compound **40**, ^{1}H NMR ($CDCl_3$ + CD_3OD): 7.84 (*q*, 1H) H6; 5.34 (*d*, $J_{1',2'}$ = 5.5 Hz, 1H) H1'; 5.24 (*dd*, $J_{7',8}$ = 6.3 Hz, $J_{7'',8}$ = 4.3 Hz, 1H) H8; 4.36 (*d*, 1H) H2'; 4.34 (*m*, $J_{4',5'}$ = 2.7 Hz, $J_{4',5''}$ = 3.3 Hz, 1H) H4'; 3.96 (*dd*, $J_{5',5''}$ = 12.4 Hz, 1H) H5'; 3.73 (*m*, 1H) and 3.48 (*m*, 1H) CH_3CH_2O; 3.78 (*dd*, 1H) H5''; 2.95 (*dd*, $J_{7',7''}$ = 14.1 Hz, 1H) H7'; 2.82 (*s*, 3H) NMe; 2.54 (*dd*, 1H) H7''; 1.93 (*d*, J = 1.1 Hz, 3H) $5CH_3$.

2',5'-Bis-O-TBDMS-3'-deoxy-3'-dehydro-spiro[3'-(S),11-(8-(R)-cyano-10-(S)-N-methyl-9,10-isoxazolidine)]-5-methyluridine (41) and **2',5'-Bis-O-TBDMS-3'-deoxy-3'-dehydro-spiro[3'-(S),11-(8-(S)-cyano-10-(S)-N-methyl-9,10-isoxazolidine)]-5-methyluridine (42).** The reaction was performed using a reaction condition described for **5** (compound **36**, 0.50 g, 0.97 mmol) to give **41** (0.29 g, 53%) and **42** (0.13 g, 24%). Compound **41**, ^{1}H NMR ($CDCl_3$): 8.77 (*br, s*, 1H) NH; 7.67 (*q*, 1H) H6; 5.86 (*d*, $J_{1',2'}$ = 5.6 Hz, 1H) H1'; 4.86 (*dd*, $J_{7',8}$ = 4.3 Hz, $J_{7'',8}$ = 10.0 Hz, 1H) H8; 4.53 (*d*, 1H) H2'; 4.15 (*dd*, $J_{4',5'}$ = 3.7 Hz, $J_{4',5''}$ = 2.9 Hz, 1H) H4'; 3.98 (*dd*, $J_{5',5''}$ = 11.6 Hz, 1H) H5'; 3.91 (*dd*, 1H) H5''; 3.27 (*dd*, $J_{7',7''}$ = 13.4 Hz, 1H) H7'; 2.66 (*dd*, 1H) H7''; 2.60 (*s*, 3H) NMe; 1.97 (*d*, J = 1.0 Hz, 3H) $5CH_3$; 0.97 (*s*, 9H), 0.88 (*s*, 9H), 0.18 (*s*, 6H), 0.05 (*s*, 6H) TBDMS. ^{13}C NMR ($CDCl_3$): 163.6 (*s*) C4; 150.8 (*s*) C2; 135.4 (*d*, J_{CH} = 180.0 Hz) C6; 117.6 (*s*) CN; 111.1 (*s*) C5; 87.8 (*d*, J_{CH} = 170.2 Hz) C1'; 85.5 (*d*, J_{CH} = 151.6 Hz) C4'; 76.1 (*s*) C3'; 74.0 (*d*, J_{CH} = 150.0 Hz) C2'; 62.6 (*d*, J_{CH} = 160.4 Hz) C8; 62.2 (*t*, J_{CH} = 143.3 Hz) C5'; 40.6 (*q* J_{CH} = 136.6 Hz) NMe; 37.6 (*t*, J_{CH} = 134.6 Hz) C7; 12.3 (*q*, J_{CH} = 130.1 Hz) $5CH_3$; 26.0, 25.6, 18.6, 17.7, -4.2, -5.0, -5.6 TBDMS. Compound **42**, ^{1}H NMR ($CDCl_3$): 8.85 (*br, s*, 1H) NH; 7.53 (*q*, 1H) H6; 5.70 (*d*, $J_{1',2'}$ = 2.7 Hz, 1H) H1'; 4.74 (*dd*, $J_{7',8}$ = 9.3 Hz, $J_{7'',8}$ = 6.8 Hz, 1H) H8; 4.44 (*d*, 1H) H2'; 4.03 (*m*, 1H) H4'; 3.93-3.87 (*m*, 2H) H5', H5''; 3.08 (*dd*, $J_{7',7''}$ = 13.4 Hz, 1H) H7'; 2.70 (*dd*, 1H) H7''; 2.66 (*s*, 3H) NMe; 1.95 (*d*, J = 1.1 Hz, 3H) $5CH_3$; 0.93 (*s*, 9H), 0.92 (*s*, 9H), 0.15 (*s*, 6H), 0.11 (*s*, 6H) TBDMS. ^{13}C NMR ($CDCl_3$): 163.6 (*s*) C4; 150.4 (*s*) C2; 135.5 (*d*, J_{CH} = 180.9 Hz) C6; 119.6 (*s*) CN; 110.03 (*s*) C5; 89.2 (*d*, J_{CH} = 173.1 Hz) C1'; 86.6 (*d*, J_{CH} = 150.6 Hz) C4'; 77.5 (*d*, J_{CH} = 151.6 Hz) C2'; 63.3 (*d*, J_{CH} = 165.3 Hz) C8; 61.2 (*t*, J_{CH} = 144.3 Hz) C5'; 41.9 (*q*, J_{CH} = 136.3 Hz) NMe; 37.8 (*t*, J_{CH} = 137.4 Hz) C7; 12.4 (*q*, J_{CH} = 128.8 Hz) $5CH_3$; 25.9, 25.7, 25.2, 18.4, 17.8, -0 13, -4.1, -5.2, -5.6 TBDMS.

3'-Deoxy-3'-dehydro-spiro[3'-(S),11-(8-(R)-cyano-10-(S)-N-methyl-9,10-isoxazolidine)]-5-methyluridine (43). The reaction was performed using a reaction condition described for **39** (compound **41**, 50 mg, 0.09 mmol) to give **43** (24 mg, 80%). ^{1}H NMR ($CDCl_3$ + CD_3OD): 7.82 (*q*, 1H) H6; 5.83 (*d*, $J_{1',2'}$ = 6.6 Hz, 1H) H1'; 5.04 (*dd*, $J_{7',8}$ = 3.6 Hz, $J_{7'',8}$ = 10.3 Hz, 1H) H8; 4.40 (*d*, 1H) H2'; 4.21 (*dd*, $J_{4',5'}$ = $J_{4',5''}$ = 2.6 Hz, 1H) H4'; 3.99 (*dd*, $J_{5',5''}$ = 12.9 Hz, 1H) H5'; 3.79 (*dd*, 1H) H5''; 3.42 (*dd*, $J_{7',7''}$ = 13.4 Hz, 1H) H7'; 2.66 (*s*, 3H) NMe; 2.61 (*dd*, 1H) H7''; 1.93 (*d*, J = 1.0 Hz, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$ + CD_3OD): 164.0 (*s*) C4; 151.5 (*s*) C2; 135.7 (*d*, J_{CH} = 189.7 Hz) C6; 117.5 (*s*) CN; 111.0 (*s*) C5; 89.1 (*d*, J_{CH} = 166.8 Hz) C1'; 86.7 (*d*, J_{CH} = 145.7 Hz) C4'; 76.0 (*s*) C3'; 73.3 (*d*, J_{CH} = 147.5 Hz) C2'; 63.3 (*d*, J_{CH} = 162.2 Hz) C8; 61.5 (*t*, J_{CH} = 144.8 Hz) C5'; 40.8 (*q* J_{CH} = 137.2 Hz) NMe; 36.6 (*t*, J_{CH} = 138.4 Hz) C7; 12.2 (*q*, J_{CH} = 128.3 Hz) $5CH_3$.

3'-Deoxy-3'-dehydro-spiro[3'-(S),11-(8-(S)-cyano-10-(S)-N-methyl-9,10-isoxazolidine)]-5-methyluridine (44). The reaction was performed using a reaction condition described for **39** (compound **42**, 50 mg, 0.09 mmol) to give **44** (25 mg, 83%) ^{1}H NMR ($CDCl_3$ + CD_3OD). 7.83 (*q*, 1H) H6; 5.86 (*d*, $J_{1',2'}$ = 6.1 Hz, 1H) H1'; 4.86 (*dd*, $J_{7',8}$ = 9.0 Hz, $J_{7'',8}$ = 7.7 Hz, 1H) H8; 4.44 (*d*, 1H) H2'; 3.91 (*m*, $J_{4',5'}$ = 3.2 Hz, $J_{4',5''}$ = 3.4 Hz, 1H) H4'; 3.84 (*dd*, $J_{5',5''}$ = 12.3 Hz, 1H) H5'; 3.71 (*dd*, 1H) H5''; 3.36 (*dd*, $J_{7',7''}$ = 12.6 Hz, 1H) H7'; 2.83 (*s*, 3H) NMe; 2.77 (*dd*, 1H) H7''; 1.93 (*d*, J = 1.0 Hz, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$ + CD_3OD): 164.3 (*s*) C4; 151.2 (*s*) C2; 135.9 (*d*, J_{CH} = 186.0 Hz) C6; 119.1 (*s*) CN; 110.7 (*s*) C5; 88.4 (*d*, J_{CH} = 169.5 Hz) C1'; 86.2 (*d*, J_{CH} = 152.1 Hz) C4'; 76.0 (*s*) C3'; 72.7 (*d*, J_{CH} = 148.5 Hz) C2'; 63.4 (*d*, J_{CH} = 166.8 Hz) C8; 60.9 (*t*, J_{CH} = 143.9 Hz) C5'; 41.3 (*q* J_{CH} = 137.2 Hz) NMe; 36.4 (*t*, J_{CH} = 138.4 Hz) C7; 11.7 (*q*, J_{CH} = 129.2 Hz) $5CH_3$. MS (FAB$^-$): calc. for (M-H)$^-$ 337.1148, found 337.1134.

3'-Deoxy-3'-dehydro-spiro[3'-(S),11-(8-(R)-methoxy-10-(S)-N-methyl-9,10-isoxazolidine)]-5-methyluridine (45) and 3'-Deoxy-3'-dehydro-spiro[3'-(S),11-(8-(S)-methoxy-10-(S)-N-methyl-9,10-isoxazolidine)]-5-methyluridine (46). Compound **39** (20 mg, 0.06 mmol) was treated with 20% trifluoroacetic acid in CH_3OH (1 mL) at 45 °C for 70 h. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give mixture of **45** and **46** in 1:1.2 ratio. Compound **45**, ^{1}H NMR ($CDCl_3$ + CD_3OD): 7.81 (*q*, 1H) H6; 5.82 (*d*, $J_{1',2'}$ = 6.6 Hz, 1H) H1'; 5.37 (*dd*, $J_{7',8}$ = 0.6 Hz, $J_{7'',8}$ = 5.9 Hz, 1H) H8; 4.26 (*d*, 1H) H2'; 3.94 (*dd*, $J_{4',5'}$ = 3.6 Hz, $J_{5',5''}$ = 11.5 Hz, 1H) H5'; 3.87 (*m*, $J_{4',5''}$ = 3.4 Hz, 1H) H4'; 3.75 (*dd*, 1H) H5''; 3.40 (*s*, 3H) NMe; 3.07 (*dd*, $J_{7',7''}$ = 13.5 Hz, 1H) H7'; 2.70 (*s*, 3H) OMe; 2.21 (*dd*, 1H) H7''; 1.93 (*d*, J = 1.1 Hz, 3H) $5CH_3$. Compound **46**, ^{1}H NMR ($CDCl_3$ + CD_3OD): 7.84 (*q*, 1H) H6; 5.82 (*d*, $J_{1',2'}$ = 5.5 Hz, 1H) H1'; 5.24 (*dd*, $J_{7',8}$ = 6.4 Hz, $J_{7'',8}$ = 4.1 Hz, 1H) H8; 4.37 (*d*, 1H) H2'; 4.34 (*m*, $J_{4',5'}$ = 2.7 Hz, $J_{4',5''}$ = 3.3 Hz, 1H) H4'; 3.96 (*dd*, $J_{5',5''}$ = 12.4 Hz, 1H) H5'; 3.78 (*dd*, 1H) H5''; 3.43 (*s*, 3H) NMe; 2.95 (*dd*, $J_{7',7''}$ = 14.2 Hz, 1H) H7'; 2.81 (*s*, 3H) OMe; 2.55 (*dd*, 1H) H7''; 1.93 (*d*, J = 1.1 Hz, 3H) $5CH_3$.

5'-O-MMTr-2'-O-TBDMS-3'-deoxy-3'-dehydro-spiro[3'-(S),11-(8-(R)-ethoxy-10-(S)-N-methyl-9,10-isoxazolidine)]-5-methyluridine (47). The reaction was performed using a reaction condition described for **3** (compound **37** 0.21 g, 0.3 mmol) to give **47** (0.21 g, 94%). ^{1}H NMR ($CDCl_3$): 8.38 (*br, s*, 1H) NH; 7.65 (*q*, 1H) H6; 7.57-7.19 (*m*, 12H) and 6.83 (*m*, 2H) MMTr; 5.81 (*d*, $J_{1',2'}$ = 3.7 Hz, 1H) H1'; 5 38 (*dd*, $J_{7',8}$ = 2.0 Hz, $J_{7'',8}$ = 6.7 Hz, 1H) H8; 4.45 (*d*, 1H) H2'; 4.36 (*dd*, $J_{4',5'}$ = 5.5 Hz, $J_{4',5''}$ = 2.9 Hz, 1H) H4'; 3.78 (*s*, 3H) MMTr; 3.66 (*dd*, $J_{5',5''}$ = 11.3 Hz, 1H) H5'; 3.59 (*dd*, 1H) H5''; 3.46 (*m*, 1H) and 3.27 (*m*, 1H) $CH_3\underline{CH_2}O$; 2.91 (*dd*, $J_{7,7''}$ = 13.9 Hz, 1H) H7'; 2.51 (s, 3H) NMe; 2.06 (*dd*,1H) H7''; 1.51 (*d*, J = 0.5 Hz, 3H) $5CH_3$; 1.19 (*t*, J = 7.0 Hz, 3H) $\underline{CH_3}CH_2O$; 0.92 (*s*, 9H), 0.15 (*s*, 3H), 0.12 (*s*, 3H) TBDMS. ^{13}C NMR ($CDCl_3$): 164.0 (*s*) C4; 150.7 (*s*) C2; 136.3 (*d*, J_{CH} = 180.5 Hz) C6; 110.0 (*s*) C5; 102.5 (*d*, J_{CH} = 171.2 Hz) C8; 82.0 (*d*, J_{CH} = 171.2 Hz) C1'; 85.3 (*d*, J_{CH} = 151.1 Hz) C4'; 76.7 (*d*, J_{CH} = 151.1 Hz) C2'; 75.4 (*s*) C3'; 64.2 (*t*, J_{CH} = 142.1 Hz) $CH_3\underline{CH_2}O$; 63.0 (*t*, J_{CH} = 144.8 Hz) C5'; 41.7 (*q* J_{CH} = 135.8 Hz) NMe; 38.8 (*t*, J_{CH} = 130.0 Hz) C7; 14.8 (*q*, J_{CH} = 126.2Hz) $\underline{C}H_3CH_2O$; 11.7 (*q*, J_{CH} = 129.3 Hz) $5CH_3$; 25.7, 17.8, -4.1, -5.2, TBDMS.

5'-O-MMTr-3'-deoxy-3'-dehydro-spiro[3'-(S),11-(8-(R)-ethoxy-10-(S)-N-methyl-9,10-isoxazolidine)]-5-methyluridine (48). The reaction was performed using a reaction condition described for **39** (compound **47**, 0.23 g, 0.27 mmol) to give **48** (0.18 g, 93%). ^{1}H NMR ($CDCl_3$): 9.41(*br, s*, 1H) NH; 7.77 (*q*, 1H) H6; 7.50-7.18 (*m*, 12H) and 6.81 (*m*, 2H) MMTr; 5.58 (*d*, $J_{1',2'}$ = 4.9 Hz, 1H) H1'; 5.40 (*dd*, $J_{7',8}$ = 0.8 Hz, $J_{7'',8}$ = 6.4 Hz, 1H) H8; 4.84 (*dd*, $J_{4',5'}$ = 2.9 Hz, $J_{4',5''}$ = 8.4 Hz, 1H) H4'; 4.64 (*bs*, 1H) OH; 4.28 (*d*, 1H) H2'; 3.78 (*s*, 3H) MMTr; 3.66 (*m*, 1H) and 3.39 (*m*, 1H) $CH_3\underline{CH_2}O$; 3.56 (*dd*, $J_{5',5''}$ = 10.5 Hz, 1H) H5'; 3.06 (*dd*, $J_{7',7''}$ = 13.5 Hz, 1H) H7'; 3.05 (*dd*, 1H) H5''; 2.53 (*s*, 3H) NMe; 2.19 (*dd*, 1H) H7''; 1.57 (*d*, J = 1.1 Hz, 3H) $5CH_3$; 1.18 (*t*, J = 7.1 Hz, 3H) $\underline{CH_3}CH_2O$. ^{13}C NMR ($CDCl_3$). 164.2 (*s*) C4; 151.8 (*s*) C2; 135.8 (*d*, J_{CH} = 183.3 Hz) C6; 110.3 (*s*) C5; 102.8 (*d*, J_{CH} = 171.4Hz) C8; 91 8 (*d*, J_{CH} = 171.4 Hz) C1'; 86.0 (*d*, J_{CH} = 154.9 Hz) C4'; 75.4 (*d*, J_{CH} = 148.5 Hz) C2'; 74.3 (*s*) C3'; 63.9 (*t*, J_{CH} = 142.5 Hz) $CH_3\underline{CH_2}O$; 63.0 (*t*, J_{CH} = 143.9 Hz) C5'; 55.0 (*q*, J_{CH} = 143.6 Hz) MMTr; 42.5 (*q* J_{CH} = 136.2 Hz) NMe; 37.2 (*t*, J_{CH} = 134.7 Hz) C7; 15.1 (*q*, J_{CH} = 126.2 Hz) $\underline{C}H_3CH_2O$; 12.0 (*q*, J_{CH} = 129.2 Hz) $5CH_3$.

5'-O-MMTr-2'-O-(phenoxythiocarbonyl)-3'-deoxy-3'-dehydro-spiro[3'-(S),11-(8-(R)-ethoxy-10-(S)-N-methyl-9,10-isoxazolidine)]-5-methyluridine (49). The reaction was performed using a reaction condition described for **15** (compound **48**, 176 mg, 0.28 mmol) to give **49** (183 mg, 85%). ^{1}H NMR ($CDCl_3$): 8 33 (*br, s*, 1H) NH; 7.85 (*q*, 1H) H6; 7 58-6.81 (*m*, 19H) MMTr; 6.52 (*d*, $J_{1',2'}$ = 7.3 Hz, 1H) H1'; 6.26 (*d*, 1H) H2'; 5.35 (*dd*, $J_{7',8}$ <0.5 Hz, $J_{7'',8}$ = 6.1 Hz, 1H) H8; 4.57 (*m*, 1H) H4', 3.78 (*s*, 3H) MMTr; 3.66 (*dd*, $J_{4',5'}$ = 2.3 Hz, $J_{5',5''}$

= 11.0 Hz, 1H) H5'; 3.60 (*m*, 1H) and 3.37 (*m*, 1H) $CH_3\underline{CH_2}O$; 3.40 (*dd*, $J_{4',5''}$ = 2.6 Hz, 1H) H5''; 3.05 (*dd*, $J_{7',7''}$ = 13.3 Hz, 1H) H7'; 2.77 (*s*, 3H) NMe; 2.42 (*dd*, 1H) H7''; 1.19 (*d*, J = 0.9 Hz, 3H) $5CH_3$; 1.07 (*t*, J = 7.1 Hz, 3H) $\underline{CH_3}CH_2O$. ^{13}C NMR ($CDCl_3$): 194.5 (*s*) C=S; 163.3 (*s*) C4; 150.6 (*s*) C2; 135.8 (*d*, J_{CH} = 181.5 Hz) C6; 111.5 (*s*) C5; 102.0 (*d*, J_{CH} = 172.3 Hz) C8; 85.0 (*d*, J_{CH} = 154.9 Hz) C4'; 84.2 (*d*, J_{CH} = 169.5 Hz) C1'; 80.4 (*q*, J_{CH} = 154.9 Hz) C2'; 71.7 (*s*) C3'; 63.8 (*t*, J_{CH} = 142.5 Hz) $CH_3\underline{CH_2}O$; 62.6 (*t*, J_{CH} = 144.3 Hz) C5'; 55.1 (*q*, J_{CH} = 143.9 Hz) MMTr; 42.0 (*q*, J_{CH} = 136.2 Hz) NMe; 40.3 (*t*, J_{CH} = 134.3 Hz) C7; 15.1 (*q*, J_{CH} = 126.2 Hz) $\underline{CH_3}CH_2O$; 12.0 (*q*, J_{CH} = 129.5 Hz) $5CH_3$.

5'-O-MMTr-2'-O-TBDMS-3'-deoxy-3'-dehydro-spiro[3'-(S),11-(8-(R)-cyano-10-(S)-N-methyl-9,10-isoxazolidine)]-5-methyluridine (50) and **5'-O-MMTr-2'-O-TBDMS-3'-deoxy-3'-dehydro-spiro[3'-(S),11-(8-(S)-cyano-10-(S)-N-methyl-9,10-isoxazolidine)]-5-methyluridine (53)**. The reaction was performed using a reaction condition described for **5** (compound **37**, 0.55 g, 0.82 mmol) to give **50** (0.36 g, 61%) and **53** (0.21 g, 35%). Compound **50**, ^1H NMR ($CDCl_3$): 8.62 (*br, s*, 1H) NH; 7.64 (*q*, 1H) H6; 7.54-7.24 (*m*, 12H) and 6.85 (*m*, 2H) MMTr; 5.86 (*d*, $J_{1',2'}$ = 4.9 Hz, 1H) H1'; 4.77 (*dd*, $J_{7',8}$ = 4.5 Hz, $J_{7'',8}$ = 9.9 Hz, 1H) H8; 4.63 (*d*, 1H) H2'; 4.24 (*dd*, $J_{4',5'}$ = 4.9 Hz, $J_{4',5''}$ = 2.7 Hz, 1H) H4'; 3.79 (*s*, 3H) MMTr; 3.62 (*dd*, $J_{5',5''}$ = 11.1 Hz, 1H) H5'; 3.39 (*dd*, 1H) H5''; 3.22 (*dd*, $J_{7',7''}$ = 13.5 Hz, 1H) H7'; 2.58 (*s*, 3H) NMe; 2.46 (*dd*, 1H) H7''; 1.40 (*d*, J = 0.9 Hz, 3H) $5CH_3$; 0.90 (*s*, 9H), 0.17 (*s*, 6H), 0.08 (*s*, 6H) TBDMS. ^{13}C NMR ($CDCl_3$): 163.8 (*s*) C4; 150.8 (*s*) C2; 135.7 (*d*, J_{CH} = 183.9 Hz) C6; 117.0 (*s*) CN; 110.8 (*s*) C5; 88.2 (*d*, J_{CH} = 170.2 Hz) C1'; 84.6 (*d*, J_{CH} = 149.6 Hz) C4'; 76.2 (*s*) C3'; 74.7 (*d*, J_{CH} = 149.6 Hz) C2'; 62.3 (*d*, J_{CH} = 159.4 Hz) C8; 62.3 (*t*, J_{CH} = 144.3 Hz) C5'; 54.9 (*q*, J_{CH} = 143.8 Hz) MMTr; 40.1 (*q* J_{CH} = 136.6 Hz) NMe; 38.0 (*t*, J_{CH} = 137.4 Hz) C7; 11.4 (*q*, J_{CH} = 130.1 Hz) $5CH_3$; 25.5, 17.7, -4.2, -5.2, TBDMS. Compound **53**, ^1H NMR ($CDCl_3$): 8.78 (*br, s*, 1H) NH; 7.52-7.23 (*m*, 13H) and 6.85 (*m*, 2H) MMTr and H-6; 5.71 (*d*, $J_{1',2'}$ = 2.2 Hz, 1H) H1'; 4.48 (*m*, 2H) H8 and H2'; 3.99 (*m*, 1H) H4'; 3.80 (*s*, 3H) MMTr; 3.63 (*dd*, $J_{4',5'}$ = 5.2 Hz, $J_{5',5''}$ = 10.6 Hz, 1H) H5'; 3.21 (*dd*, $J_{4',5'}$ = 4.5 Hz, 1H) H5''; 3.03 (*dd* , $J_{7',8}$ = 9.5 Hz, $J_{7',7''}$ = 13.7 Hz, 1H) H7'; 2.64 (*s*, 3H) NMe; 2.56 (*dd*, $J_{7'',8}$ = 6.8 Hz, 1H) H7''; 1.63 (*d*, J = 0.9 Hz, 3H) $5CH_3$; 0.94 (*s*, 9H), 0.20 (*s*, 6H), TBDMS. ^{13}C NMR ($CDCl_3$): 163.7 (*s*) C4; 150.4 (*s*) C2; 135.7 (*d*, J_{CH} = 185.8 Hz) C6; 119.4 (*s*) CN; 109.9 (*s*) C5; 89.7 (*d*, J_{CH} = 174.1 Hz) C1'; 85.8 (*d*, J_{CH} = 151.6 Hz) C4'; 77.4 (*s*) C-3'; 77.4 (*d*, J_{CH} = 151.6 Hz) C2'; 63.0 (*d*, J_{CH} = 169.2 Hz) C8; 62.2 (*t*, J_{CH} = 144.3 Hz) C5'; 55.1 (*q*, J_{CH} = 143.8 Hz) MMTr; 41.7 (*q* J_{CH} = 136.6 Hz) NMe; 37.6 (*t*, J_{CH} = 138.4 Hz) C7; 12.0 (*q*, J_{CH} = 129.1Hz) $5CH_3$; 25.7, 17.9, -4.1, -5.2, TBDMS.

5'-O-MMTr-3'-deoxy-3'-dehydro-spiro[3'-(S),11-(8-(R)-cyano-10-(S)-N-methyl-9,10-isoxazolidine)]-5-methyluridine (51). The reaction was performed using a reaction condition described for **39** (compound **50**, 350 mg, 0.48 mmol) to give **51** (276 mg, 94%). ^1H NMR ($CDCl_3$): 9.91 (*br, s*, 1H) NH; 7.73 (*q*, 1H) H6; 7.49-7.20 (*m*, 12H) and 6.83 (*m*, 2H) MMTr; 5.65 (*d*, $J_{1',2'}$ = 5.0 Hz, 1H) H1'; 4.95 (*bs*, 1H) OH; 4.89 (*dd*, $J_{7',8}$ = 3.9 Hz, $J_{7'',8}$ = 10.1 Hz, 1H) H8; 4.45 (*dd*, $J_{4',5'}$ = 3.0, $J_{4',5''}$ = 7.3 Hz, 1H) H4'; 4.41 (*d*, 1H) H2'; 3.78 (*s*, 3H) MMTr; 3.48 (*dd*, $J_{5',5''}$ = 11.4 Hz, 1H) H5'; 3.37 (*dd*, $J_{7',7''}$ = 13.4 Hz, 1H) H7'; 3.23 (*dd*, 1H) H5''; 2.54 (*s*, 3H) NMe; 2.53 (*dd*, 1H) H7''; 1.57 (*d*, J = 0.9 Hz, 3H) $5CH_3$.

5'-O-MMTr-2'-O-(phenoxythiocarbonyl)-3'-deoxy-3'-dehydro-spiro[3'-(S),11-(8-(R)-cyano-10-(S)-N-methyl-9,10-isoxazolidine)]-5-methyluridine (52). The reaction was performed using a reaction condition described for **15** (compound **51**, 270 mg, 0.44 mmol) to give **52** (160 mg, 49%). ^1H NMR ($CDCl_3$): 8.87 (*br, s*, 1H) NH; 7.85 (*q*, 1H) H6; 7.56-7.03 and 6.83 (*m*, 19H) MMTr; 6.62 (*d*, $J_{1',2'}$ = 7.4 Hz, 1H) H1'; 6.31 (*d*, 1H) H2'; 4.93 (*dd*, $J_{7',8}$ = 3.5 Hz, $J_{7'',8}$ = 9.8 Hz, 1H) H8; 4.30 (*m*, 1H) H4'; 3.79 (*s*, 3H) MMTr; 3.66 (*dd*, $J_{4',5'}$ = 2.0 Hz, $J_{5',5''}$ = 11.0 Hz, 1H) H5'; 3.43 (*dd*, $J_{4',5''}$ = 2.9 Hz, 1H) H5''; 3.36 (*dd*, $J_{7',7''}$ = 13.4 Hz, 1H) H7'; 2.80 (*dd*, 1H) H7''; 2.75 (*s*, 3H) NMe; 1.24 (*d*, J = 0.9 Hz, 3H) $5CH_3$.

5'-O-MMTr-3'-deoxy-3'-dehydro-spiro[3'-(S),11-(8-(S)-cyano-10-(S)-N-methyl-9,10-isoxazolidine)]-5-methyluridine (54). The reaction was performed using a reaction condition described for **39** (compound **53**, 200 mg, 0.28 mmol) to give **54** (130 mg, 77%) ^1H NMR ($CDCl_3$): 10.43 (*br, s*, 1H) NH; 7.65 (*q*, 1H) H6; 7.49-7.20 (*m*, 12H) and 6.83 (*m*, 2H) MMTr; 5.79 (*d*, $J_{1',2'}$ = 4.3 Hz, 1H) H1'; 5 40 (*bs*, 1H) OH; 4.51 (*bd*, 1H) H2'; 4.50 (*dd*, $J_{7',8}$ = 8.9 Hz, $J_{7'',8}$ = 7.3 Hz, 1H) H8; 3.93 (*m*, $J_{4',5'}$ = 5.6 Hz, $J_{4',5''}$ = 3.9 Hz, 1H) H4'; 3.78 (*s*, 3H) MMTr; 3.44 (*dd*, $J_{5',5''}$ = 11.2 Hz, 1H) H5'; 3.35 (*dd*, $J_{7',7''}$ = 13.6 Hz, 1H) H7'; 3.29 (*dd*, 1H) H5''; 2.77 (*s*, 3H) NMe; 2.68 (*dd*, 1H) H7''; 1.58 (*d*, J = 0.9 Hz, 3H) $5CH_3$.

5'-O-MMTr-2'-O-(phenoxythiocarbonyl)-3'-deoxy-3'-dehydro-spiro[3'-(S),11-(8-(S)-cyano-10-(S)-N-methyl-9,10-isoxazolidine)]-5-methyluridine (55). The reaction was performed using a reaction condition described for **15** (compound **54**, 120 mg, 0.20 mmol) to give **55** (130 mg, 88%). ^1H NMR ($CDCl_3$): 9.13 (*bs*, 1H) NH; 7.76 (*q*, 1H) H6; 7.56-7.18 and 6.84 (*m*, 19H) MMTr; 6.62 (*d*, $J_{1',2'}$ = 6.7 Hz, 1H) H1'; 6.29 (*d*, 1H) H2'; 4.65 (*dd*, $J_{7',8}$ = 9.0 Hz, $J_{7'',8}$ = 7.3 Hz, 1H) H8; 3.92 (*m*, 1H) H4'; 3.78 (*s*, 3H) MMTr; 3.60 (*dd*, $J_{4',5'}$ = 2.2 Hz, $J_{5',5''}$ = 10.9 Hz, 1H) H5'; 3.29 (*dd*, $J_{7',7''}$ = 13 3 Hz, 1H) H7'; 3.23 (*dd*, $J_{4',5''}$ = 3.4 Hz, 1H) H5''; 2.95 (*s*, 3H) NMe; 2.88 (*dd*, 1H) H7''; 1.26 (*d*, J = 1.0 Hz, 3H) $5CH_3$.

5'-O-MMTr-3'-deoxy-2',3'-didehydro-3'-*C*-(ethyl-8-(R)-ethoxy-8-O-hydroxylamino-N-methyl)thymidine (59), 5'-O-MMTr-3'-deoxy-3'-dehydro-spiro[3'-(S),11-(8-(R)-ethoxy-10-(S)-N-methyl-9,10-isoxazolidine)] thymidine (56). Compound **49** (170 mg, 0.22 mmol) was treated with tributyltin hydride (100 µL, 0.4 mmol), AIBN (40 mg) in toluene (3 mL) in a stopper-sealed round bottom flask at 100 °C for 1 h. The solvent was

removed in vacuo and the residue was purified by silica gel column chromatography to give **59** (40 mg, 30%), **56** (30 mg, 22%) and **48** (12 mg, 9%). Compound **59,** ^{1}H NMR ($CDCl_3$, 500 MHz): 8.08 (*br, s*, 1H) NH; 7.69 (*q*, 1H) H6; 7.45-7.19 and 6.81 (*m*, 19H) MMTr; 7.02 (*m*, $J_{1',2'}$ = 1.8 Hz, $J_{1',4'}$ = 3.8 Hz, 1H) H1'; 5.67 (*m*, $J_{2',4'}$ = 1.7 Hz, $J_{2',7'}$ = 1.7 Hz, $J_{2',7''}$ = 1.1 Hz, 1H) H2'; 4.83 (*m*, $J_{4',5'}$ = 2.2 Hz, $J_{4',5''}$= 3.0 Hz, $J_{4',7'}$ = 1.0 Hz, $J_{4',7''}$ = 1.1 Hz, 1H) H4'; 4.72 (*dd*, $J_{7',8}$ = 5.7 Hz, $J_{7'',8}$ = 5.1 Hz, 1H) H8; 3.79 (*s*, 3H) MMTr; 3.76 (*m*, 1H) and 3.47 (*m*, 1H) $CH_3C\underline{H}_2O$; 3.63 (*dd*, $J_{5',5''}$ = 10.9 Hz, 1H) H5'; 3.26 (*dd*, 1H) H5"; 2.67 (*s*, 3H) NMe; 2.66 (*m*, $J_{7',7''}$ = 15.7 Hz, 1H) H-7'; 2.30 (*m*, 1H) H-7"; 1.16 (*t*, J = 7.1 Hz, 3H) $C\underline{H}_3CH_2O$; 1.07 (*d*, J = 0.9 Hz, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$): 163.9 (*s*) C4; 150.8 (*s*) C2; 143.9 (*s*) C3'; 136.4 (*d*, J_{CH} = 179.6 Hz) C6; 121.7 (*d*, J_{CH} = 175.9 Hz) C2'; 111.0 (*s*) C5; 103.7 (*d*, J_{CH} = 164.0 Hz) C8; 88.5 (*d*, J_{CH} = 180.5 Hz) C1'; 86.4 (*d*, J_{CH} = 150.3 Hz) C4'; 63.7 (*t*, J_{CH} = 142.5 Hz) $CH_3\underline{C}H_2O$; 63.0 (*t*, J_{CH} = 143.0 Hz) C5'; 55.0 (*q*, J_{CH} = 135.3 Hz) MMTr; 39.6 (*q*, J_{CH} = 135.3 Hz) NMe; 31.4 (*t*, J_{CH} = 128.8 Hz) C7; 15.1 (*q*, J_{CH} = 126.2 Hz) $\underline{C}H_3CH_2O$; 10.8 (*q*, J_{CH} = 129.8 Hz) $5CH_3$. MS (FAB$^-$): calc. for (M-H)$^-$ 612.2710, found 612.2680. Compound **56,** ^{1}H NMR ($CDCl_3$): 8.33 (*br, s*, 1H) NH; 7.71 (*q*, 1H) H6; 7.55-7.19 (*m*, 12H) and 6.82 (*m*, 2H) MMTr; 6.07 (*d*, $J_{1',2'}$ = 5.7 Hz, $J_{1',2''}$ = 6.9 Hz, 1H) H1'; 5.36 (*dd*, $J_{7',8}$ = 1.2 Hz, $J_{7'',8}$ = 6.2 Hz, 1H) H8; 4.45 (*dd*, $J_{4',5'}$ = 2.6 Hz, $J_{4',5''}$ = 7.1 Hz, 1H) H4'; 3.78 (*s*, 3H) MMTr; 3.58 (*dd*, $J_{5',5''}$ = 11.7 Hz, 1H) H5'; 3.55 (*m*, 1H) and 3.33 (*m*, 1H) $CH_3C\underline{H}_2O$; 3.36 (*dd*, 1H) H5"; 2.53 (*dd*, $J_{7',7''}$ = 13.7 Hz, 1H) H7'; 2.48 (*s*, 3H) NMe; 2.39 (*dd*, $J_{2',2''}$ = 13.0 Hz, 1H) H2'; 2.35 (*dd*, 1H) H7"; 2.25 (*dd*, 1H) H2"; 1.56 (*d*, J = 1.0 Hz, 3H) $5CH_3$; 1.07 (*t*, J = 7.1 Hz, 3H) $C\underline{H}_3CH_2O$. ^{13}C NMR ($CDCl_3$): 163.5 (*s*) C4; 150.1 (*s*) C2; 135.5 (*d*, J_{CH} = 186.3 Hz) C6; 110.2 (*s*) C5; 102.9 (*d*, J_{CH} = 171.4 Hz) C8; 86.0 (*d*, J_{CH} = 154.0 Hz) C4'; 84.6 (*d*, J_{CH} = 172.3 Hz) C1'; 72.0 (*s*) C3'; 64.0 (*t*, J_{CH} = 142.5 Hz) $CH_3\underline{C}H_2O$; 63.3 (*t*, J_{CH} = 144.3Hz) C5'; 55.1 (*q*, J_{CH} = 143.6 Hz) MMTr; 43.2 (*d*, J_{CH} = 133.3 Hz) C2'; 42.6 (*q* J_{CH} = 135.6 Hz) NMe; 38.8 (*t*, J_{CH} = 134.7 Hz) C7; 15.0 (*q*, J_{CH} = 126.2 Hz) $\underline{C}H_3CH_2O$; 11.9 (*q*, J_{CH} = 129.2 Hz) $5CH_3$.MS (FAB$^-$): calc. for (M-H)$^-$ 612.2710, found 612.2687.

3'-Deoxy-3'-dehydro-spiro[3'-(S),11-(8-(S)-cyano-10-(S)-N-methyl-9,10-isoxazolidine)]thymidine (58). Compound **57** (40 mg, 0.07 mmol) was treated with 90% aqueous acetic acid (2 mL) at RT over night. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give **58** (18 mg, 78%). ^{1}H NMR ($CDCl_3$): 9.36 (*br, s*, 1H) NH, 7.80 (*q*, 1H) H6; 6.26 (*dd*, $J_{1',2'}$ = 5.9 Hz, $J_{1',2''}$ = 7.7 Hz, 1H) H1'; 4.79 (*dd*, $J_{7',8}$ = 8.9 Hz, $J_{7'',8}$ = 7 9 Hz, 1H) H8; 3.92 (*dd*, $J_{4',5'}$ = 2.4 Hz, $J_{5',5''}$ = 12.4 Hz, 1H) H5'; 3.79 (*dd*, $J_{4',5''}$ = 3.4 Hz, 1H) H5"; 3.74 (*dd*, 1H) H4'; 3.01 (*dd*, $J_{7',7''}$ = 12.9 Hz, 1H) H7'; 2.89 (*dd*, 1H) H7"; 2.69 (*s*, 3H) NMe; 2.48 (*dd*, $J_{2',2''}$ = 13.2 Hz, 1H) H2'; 2.41 (*dd*, 1H) H2"; 1.94 (*d*, J = 0.9 Hz, 3H) $5CH_3$.^{13}C NMR ($CDCl_3$): 163.8 (*s*) C4; 150.5 (*s*) C2, 135 1 (*d*, J_{CH} = 182.4 Hz) C6; 118.8 (*s*) CN; 111.3 (*s*) C5; 86.6 (*d*, J_{CH} = 148.4 Hz) C4'; 83.3 (*d*, J_{CH} = 172.3 Hz) C1', 75.3 (*s*) C3'; 64.3 (*d*, J_{CH} = 165.9 Hz) C8; 62.2 (*t*, J_{CH} = 143.9 Hz) C5'; 42.5 (*t*, J_{CH} = 137.0 Hz) C2'; 42.2 (*q*, J_{CH} = 136.9 Hz) NMe; 37.7 (*t*, J_{CH} = 135.2 Hz) C7; 12.5 (*q*, J_{CH} = 129.2 Hz) $5CH_3$. MS (FAB$^-$): calc. for (M-H)$^-$ 321.1199, found 321.1201.

5'-O-MMTr-3'-deoxy-2',3'-didehydro-3'-*C*-(ethyl-8-(R)-cyano-8-O-hydroxylamino-N-methyl) thymidine (60). Compound **52** (160 mg, 0.21 mmol) was treated with tributyltin hydride (100 μL, 0.4 mmol), AIBN (40 mg) in toluene (3 mL) in a stopper sealed round bottom flask at 100 °C for 1 h. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give **60** (71 mg, 56%). ^{1}H NMR ($CDCl_3$): 8.65 (*br, s*, 1H) NH; 7.68 (*q*, 1H) H6; 7 41-7.21 and 6.84 (*m*, 19H) MMTr; 7.06 (*m*, $J_{1',2'}$ = 1.4 Hz, $J_{1',4'}$ = 3.8 Hz, 1H) H1'; 5.91 (*q*, J = 2.9 Hz, 1H) N$\underline{H}$Me; 5.86 (*m*, $J_{2',4'}$ = 1.8 Hz, 1H) H2'; 4.81 (*m*, 1H) H4'; 4.56 (*dd*, $J_{7',8}$ = 6.8 Hz, $J_{7'',8}$ = 5.7 Hz, 1H) H8; 3.80 (*s*, 3H) MMTr,,3.65 (*dd*, $J_{4',5'}$ = 2.3 Hz, $J_{5',5''}$ = 11.1 Hz, 1H) H5'; 3.22 (*dd*, $J_{4',5''}$ = 2.8 Hz, 1H) H5", 2 62 (*d*, 3H) NMe; 2.74 (*m*, $J_{7',7''}$ = 15.9 Hz, 1H) H7'; 2.46 (*m*, 1H) H7"; 1.17 (*d*, J = 1.1 Hz, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$): 163.7 (*s*) C4, 150.6 (*s*) C2, 143.2 (*s*) C3'; 136.0 (*d*, J_{CH} = 179.6 Hz) C6; 123 7 (*d*, J_{CH} = 174.1 Hz) C2'; 117.8 (*s*) CN; 111.3 (*s*) C5; 88.5 (*d*, J_{CH} = 169.5 Hz) C1'; 86.0 (*d*, J_{CH} = 148.5 Hz) C4'; 69.8 (*d*, J_{CH} = 156.7 Hz) C8; 62.9 (*t*, J_{CH} = 143.4 Hz) C-5'; 55.1 (*q*, J_{CH} = 143.9 Hz) MMTr; 39.4 (*q*, J_{CH} = 135.9 Hz) NMe, 29.6 (*t*, J_{CH} = 131.5 Hz) C7; 11.0 (*q*, J_{CH} = 129.2 Hz) $5CH_3$.

5'-O-MMTr-3'-deoxy-2',3'-didehydro-3'-*C*-(ethyl-8-(S)-cyano-8-O-hydroxylamino-N-methyl) thymidine (62), 5'-O-MMTr-3'-deoxy-3'-dehydro-spiro[3'-(S),11-(8-(S)-cyano-10-(S)-N-methyl-9,10-isoxazolidine)] thymidine (57) Compound **55** (125 mg, 0.21 mmol) was treated with tributyltin hydride (100 μL, 0.4 mmol), AIBN (40 mg) in toluene (3 mL) in a stopper sealed round bottom flask at 100 °C for 1 h. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give **62** (45 mg, 45%) and **57** (30 mg, 30%). Compound **62**· ^{1}H NMR ($CDCl_3$): 8.49 (*br, s*, 1H) NH; 7.67 (*q*, 1H) H6; 7.45-7.18 and 6.85 (*m*, 19H) MMTr; 7 05 (*m*, $J_{1',2'}$ = 1.5 Hz, $J_{1',4'}$ = 3.9 Hz, 1H) H1'; 5.91 (*q*, J = 6.9 Hz, 1H) N$\underline{H}$Me; 5.82 (*m*, $J_{2',4'}$ = 2.0 Hz, 1H) H2'; 4.81 (*m*, 1H) H4'; 4.55 (*dd*, $J_{7',8}$ = 7.5 Hz, $J_{7'',8}$ = 5 9 Hz, 1H) H8; 3.80 (*s*, 3H) MMTr;,3.68 (*dd*, $J_{4',5'}$ = 2 3 Hz, $J_{5',5''}$ = 11.1 Hz, 1H) H5', 3.22 (*dd*, $J_{4',5''}$ = 2.8 Hz, 1H) H5"; 2.75 (*d*, 3H) NMe; 2.62 (*m*, 1H) H7'; 2.38 (*m*, 1H) H7"; 1.16 (*d*, J = 0.9 Hz, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$): 163.7 (*s*) C4; 150.7 (*s*) C2; 143.2 (*s*) C3'; 136.0 (*d*, J_{CH} = 179.6 Hz) C6; 123.1 (*d*, J_{CH} = 176.0 Hz) C2'; 117.8 (*s*) CN; 111.4 (*s*) C5; 88.5 (*d*, J_{CH} = 180 5 Hz) C1'; 86.2 (*d*, J_{CH} = 155.8 Hz) C4'; 69.8 (*d*, J_{CH} = 156.7 Hz) C8; 62.7 (*t*, J_{CH} = 143.4 Hz) C5'; 55 1 (*q*, J_{CH} = 143 9 Hz) MMTr; 39.4 (*q*, J_{CH} = 135.9 Hz) NMe; 29.5 (*t*, J_{CH} = 131.0 Hz) C7; 10.9 (*q*, J_{CH} = 129.2 Hz) $5CH_3$ Compound **57,** ^{1}H NMR ($CDCl_3$): 8.25 (*br, s*, 1H) NH; 7.61 (*q*, 1H) H6; 7.48-

7.22 (*m*, 12H) and 6.84 (*m*, 2H) MMTr; 6.08 (*t*, 1H) H1'; 4.52 (*dd*, $J_{7',8}$ = 8.9 Hz, $J_{7'',8}$ = 7.5 Hz, 1H) H8; 3.80 (*s*, 3H) MMTr; 3.68 (*dd*, $J_{4',5'}$ = 5.5 Hz, $J_{4',5''}$ = 4.4 Hz, 1H) H4'; 3.49 (*dd*, $J_{5',5''}$ = 10.9 Hz, 1H) H5'; 3.32 (*dd*, 1H) H5''; 2.83 (*dd*, $J_{7',7''}$ = 13.2 Hz, 1H) H7'; 2.76 (*dd*, 1H) H7''; 2.69 (*s*, 3H) NMe; 2.59 (*dd*, $J_{1',2'}$ = 6.2 Hz, $J_{2',2''}$ = 13.8 Hz, 1H) H2'; 2.40 (*dd*, $J_{1',2''}$ = 5.5 Hz, 1H) H2''; 1.65 (*d*, J = 0.9 Hz, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$): 163.7 (*s*) C4; 150.3 (*s*) C2; 135.1 (*d*, J_{CH} = 187.0 Hz) C6; 119.2 (*s*) CN; 110.4 (*s*) C5; 87.6 (*d*, J_{CH} = 146.6 Hz) C4'; 84.0 (*d*, J_{CH} = 173.2 Hz) C1'; 77.4 (*s*) C3'; 63.6 (*d*, J_{CH} = 164.0 Hz) C8; 62.5 (*t*, J_{CH} = 144.8 Hz) C5'; 55.1 (*q*, J_{CH} = 143.9 Hz) MMTr; 41.9 (*q*, J_{CH} = 136.5 Hz) NMe; 41.1 (*t*, J_{CH} = 136.5 Hz) C2'; 38.1 (*t*, J_{CH} = 135.2 Hz) C7; 12.0 (*q*, J_{CH} = 128.9 Hz) $5CH_3$.

3'-Deoxy-2',3'-didehydro-3'-*C*-(ethyl-8-(R)-cyano-8-O-hydroxylamino-N-methyl)thymidine (61). Compound **60** (60 mg, 0.07 mmol) was treated with 90% aqueous acetic acid (3 mL) at RT over night. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give **61** (28 mg, 84%). ^1H NMR ($CDCl_3$ + CD_3OD): 7.73 (*q*, 1H) H6; 6.96 (*m*, $J_{1',2'}$ = 1.5 Hz, $J_{1',4'}$ = 3.4 Hz, 1H) H1'; 5.77 (*m*, $J_{2',4'}$ = 2.1 Hz, 1H) H2'; 4.78 (*m*, 1H) H4'; 4.75 (*t*, J = 6.5 Hz, 1H) H8; 3.87 (*dd*, $J_{4',5'}$ = 2.6 Hz, $J_{5',5''}$ = 12.7 Hz, 1H) H5'; 2.80 (*dd*, $J_{4',5''}$ = 2.2 Hz, 1H) H5''; 2.86 (*m*, 1H) and 2.75 (*m*, 1H) H7', H7''; 2.79 (*s*, 3H) NMe; 1.86 (*d*, J = 1.0 Hz, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$ + CD_3OD): 164.5 (*s*) C4; 151.0 (*s*) C2; 141.5 (*s*) C3'; 137.2 (*d*, J_{CH} = 184.4 Hz) C6; 123.7 (*d*, J_{CH} = 172.3 Hz) C2'; 118.0 (*s*) CN; 110.3 (*s*) C5; 88.6 (*d*, J_{CH} = 170.9 Hz) C1'; 87.8 (*d*, J_{CH} = 151.3 Hz) C4'; 70.1 (*d*, J_{CH} = 158.4 Hz) C8; 61.0 (*t*, J_{CH} = 143.0 Hz) C5'; 39.0 (*q*, J_{CH} = 135.9 Hz) NMe; 29.3 (*t*, J_{CH} = 131.8 Hz) C7; 11.7 (*q*, J_{CH} = 129.4 Hz) $5CH_3$. MS (FAB^-): calc. for $(M-H)^-$ 321.1199, found 321.1223.

3'-Deoxy-2',3'-didehydro-3'-*C*-(ethyl-8-(S)-cyano-8-O-hydroxylamino-N-methyl)thymidine (63). Compound **62** (25 mg, 0.04 mmol) was treated with 90% aqueous acetic acid (3 mL) at RT overnight. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give **63** (12 mg, 87%). ^1H NMR ($CDCl_3$): 8.96 (*br, s*, 1H) NH; 7.54 (*q*, 1H) H6; 6.98 (*m*, $J_{1',2'}$ = 1.5 Hz, $J_{1',4'}$ = 3.4 Hz, 1H) H1'; 5.74 (*m*, $J_{2',4'}$ = 1.8 Hz, 1H) H2'; 4.79 (*m*, 1H) H4'; 4.69 (*dd*, $J_{7',8}$ = 7.7 Hz, $J_{7'',8}$ = 5.6 Hz, 1H) H8; 3.98 (*dd*, $J_{4',5'}$ = 2.4 Hz, $J_{5',5''}$ = 12.9 Hz, 1H) H5'; 2.83 (*dd*, $J_{4',5''}$ = 2.4 Hz, 1H) H5''; 2.96 (*m*, 1H) and 2.74 (*m*, 1H) H7', H7''; 2.81 (*s*, 3H) NMe; 1.83 (*d*, J = 1.2 Hz, 3H) $5CH_3$. ^{13}C NMR ($CDCl_3$): 164.0 (*s*) C4; 150.6 (*s*) C2; 141.8 (*s*) C3'; 137.0 (*d*, J_{CH} = 185.3 Hz) C6; 123.2 (*d*, J_{CH} = 173.2 Hz) C2'; 118.0 (*s*) CN; 110.6 (*s*) C5; 89.0 (*d*, J_{CH} = 171.4 Hz) C1'; 87.9 (*d*, J_{CH} = 152.1 Hz) C4'; 69.9 (*d*, J_{CH} = 157.6 Hz) C8; 61.5 (*t*, J_{CH} = 143.0 Hz) C-5'; 39.4 (*q*, J_{CH} = 135.9 Hz) NMe; 29.6 (*t*, J_{CH} = 131.0 Hz) C7; 12.2 (*q*, J_{CH} = 129.2 Hz) $5CH_3$. MS (FAB^-): calc. for $(M-H)^-$ 321.1199, found 321.1236.

3'-Deoxy-2',3'-didehydro-3'-*C*-(ethylacetyl)thymidine (64). Compound **59** (30 mg, 0.04 mmol) was treated with 90% aqueous acetic acid (3 mL) at RT overnight. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give **64** (11 mg, 75%). ^1H NMR ($CDCl_3$): 8.68 (*br, s*, 1H) NH; 7.67 (*q*, 1H) H6; 6.98 (*m*, $J_{1',2'}$ = 1.4 Hz, $J_{1',4'}$ = 3.5 Hz, 1H) H1'; 5.77 (*m*, $J_{2',4'}$ = 2.3 Hz, 1H) H2'; 4.88 (*m*, 1H) H4'; 4.22 (*q*, J = 7.0 Hz, 2H) $CH_3\underline{C}H_2O$; 3.93 (*dd*, $J_{4',5'}$ = 2.6 Hz, $J_{5',5''}$ = 13.0 Hz, 1H) H5'; 3.83 (*dd*, $J_{4',5''}$ = 2.3 Hz, 1H) H5''; 3.34 (*m*, 2H) H7', H7''; 1.83 (*d*, J = 1.2 Hz, 3H) $5CH_3$; 1.30 (*t*, 3H).$\underline{C}H_3CH_2O$. ^{13}C NMR ($CDCl_3$): 170.0 (*s*) $\underline{C}OO$; 163.8 (*s*) C4; 150.6 (*s*) C2; 140.0 (*s*) C3'; 136.9 (*d*, J_{CH} = 180.5 Hz) C6; 124.6 (*d*, J_{CH} = 174.1 Hz) C2'; 110.5 (*s*) C5; 88.8 (*d*, J_{CH} = 180.5 Hz) C1'; 87.8 (*d*, J_{CH} = 149.4 Hz) C4'; 61.6 (*t*, J_{CH} = 143.0 Hz) C5'; 61.6 (*t*, J_{CH} = 143.0 Hz) $CH_3\underline{C}H_2O$; 32.8 (*t*, J_{CH} = 130.6 Hz) C7'; 14.0 (*q*, J_{CH} = 125.2 Hz) $\underline{C}H_3CH_2O$; 12.2 (*q*, J_{CH} = 128.9 Hz) $5CH_3$. MS (FAB^-): calc. for $(M-H)^-$ 309.1086, found 309.1095.

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22. The observed coupling constants ($^3J_{HH}$) are translated into proton-proton torsion angles (Φ_{HH}) on the basis of the generalised Karplus equation.[24] The Φ_{HH} are related to the corresponding endocyclic torsion angles (τ_k) of isoxazolidine ring by eqn. 1.

$$\Phi_{HH} = A\,\tau_k + B \quad .... \quad (1)$$

Endocyclic torsion angles τ_0[C_8-O_9-N_{10}-$C_{2'}$/$C_{3'}$], τ_1[O_9-N_{10}-$C_{2'}$/$C_{3''}$-C_7], τ_2[N_{10}-$C_{2'}$/$C_{3''}$-C_7-C_8], τ_3[$C_{2'}$/$C_{3''}$-C_7-C_8-O] and τ_4[C_7-C_8-O_9-N_{10}] are directly related to P^{IS} and Ψ_m^{IS} by relation $\tau_k = \Psi_m^{IS} * \cos(P^{IS} + (k-2) * 4\pi/5)$ for k = 0, 1 ...4. Each pair of vicinal ring protons has its own A, B parameter combination. We have calculated the A and B parameters in eqn. 1 specifically for isoxazolidine moieties through a set of molecular mechanics calculations using MacroModel program.[26] Nine conformers for each of **10**, **12**, **13** and **39** were generated through energy minimization by restraining τ_3 in the range -40° < τ_3 < +40° in 10° steps. The proton-proton torsion angles, $\Phi_{7'8}$ and $\Phi_{7''8}$, along with τ_3 were extracted from minimised conformers and used to calculate A and B parameters (eqn. 1) by linear regression. In **10** and **40** $\Phi_{7'8} = 1.08 * \tau_3 - 1.2°$ (correlation coefficient R = 0.999) and $\Phi_{7''8} = 1.11 * \tau_3 - 120.3°$ (R= 0.999), whereas for **11** and **39** $\Phi_{7'8} = 1.09 * \tau_3 + 122.1°$ (R = 0.999) and $\Phi_{7''8} = 1.10 * \tau_3 + 1.6°$ (R = 0.998). For **12** and **44** $\Phi_{7'8} = 1.06 * \tau_3 - 2.4°$ (R = 0.997) and $\Phi_{7''8} = 1.06 * \tau_3 - 120.3°$ (R = 0.995), whereas for **13** and **43** $\Phi_{7'8} = 1.09 * \tau_3 + 124.0°$ (R = 0.998) and $\Phi_{7''8} = 1.06 * \tau_3 + 6.0°$ (R = 0.996).
23. (a) The observed $^3J_{4'5'}$ and $^3J_{4'5''}$ are weighted time-averaged coupling constants related to the couplings of individual conformers and their respective populations. Limiting values for $J_{4'5'}$ and $J_{4'5''}$ in the staggered C4'-C5' rotamers are as follows: $\gamma+$: $J_{4'5'}$ = 2.4 Hz, $J_{4'5''}$ = 1.3 Hz. Rotamer γ' : $J_{4'5'}$ = 2.6 Hz, $J_{4'5''}$ = 10.5 Hz. Rotamer γ : $J_{4'5'}$ = 10.6 Hz, $J_{4'5''}$ = 3.8 Hz. (b) Haasnoot, C.A.G.; de Leeuw, F.A.A.M.;

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25. In the analysis of $^3J_{7'8}$ and $^3J_{7''8}$ of isoxazolidine moieties the generalised Karplus equation[24] with the following P_1 - P_7 parameter set was used: P_1 = 13.7, P_2 = -0.73, P_3 = 0, P_4 = 0.56, P_5 = -2.47, P_6 =16.9° and P_7 = 0.14.[24] The electronegativity of the cyano substituent was taken as follows: $\Delta\chi_{CN}$ = 0.4 - 0.14*(3*0.85) = 0.043.
26. (a) Still, W.C. *et al.*, MacroModel V3.5a **1992**, Columbia University, New York. (b) Mohamadi, F.; Richards, N.G.J.; Guida, W.C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W.C. *J. Comp. Chem.* **1990**, *11*, 440.
27. In **3**, **6**, **8**, **10**, **12**, **14**, **15**, **16** and **17** with C8-(S) configuration, H1', H3' and H6 resonances always appear as broad signals in ^1H NMR spectra. The corresponding ^{13}C resonaces appear also broad in ^1H decoupled INEPT experiments. In contrast, the H1', H3' and H6 the ^1H and corresponding ^{13}C resonances in **4**, **5**, **7**, **9**, **11**, **13**, **18** and **19** with C8-(R) configuration appear as sharp signals (see experimental part). We are presently investigating the temperature-dependent conformational effects and paramagnetic influences of the isoxazolidine moiety that may cause such configuration-dependent line broadening for C1'/H1', C3'/H3' and C6/H6 [see (a) Tronchet, J. M. J.; Benhamza, R.; Bernardinelli, G. *Nucleosides & Nucleotides* **1993**, *12*, 55. (b) Tronchet, J. M. J. *Bioactive Spin Labels*, R. Zhdanov Ed. Springer Verlag: Berlin. **1992**; pp. 355].