



The Synthesis of New 3'-bis-C-substituted-3'-Deoxy-3'-Dehydro-[3.3.0]- α -fused Thymidines by Intramolecular Radical Trapping by Tethered Acetylenes

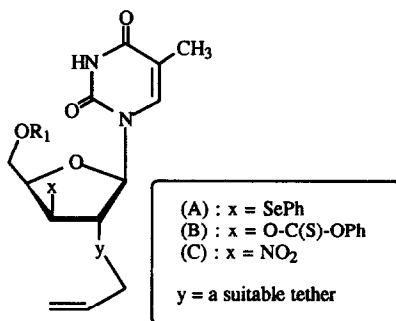
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Abstract: The Michael addition reaction of propargyl alcohol with 3'-nitro-olefin **1** and subsequent Henry reaction at C-3' with electron deficient reagents has produced various diastereomeric mixtures of 2'- Ω -propynyl-3'-deoxy-3'-dehydro-3'-C-substituted-3'-nitro-thymidine derivatives **4** - **7** [α -substitution (major); β -substitution (minor)] in 55-80% yield. Subsequently, the intramolecular cyclization-trapping of carbon radicals by tethered acetylene in **4** - **7** by the treatment with Bu_3SnH and AIBN afforded 3'-bis-C-substituted-[3.3.0]-cis-fused thymidines **8** - **11** in 86-90% yield. The results detailed here represent the first examples of title compounds using a three-step procedure: (1) Michael addition of the propargyl alcohol to nitro-olefin, (2) Henry reaction with electron-deficient reagents, and (3) subsequent intramolecular cyclization-trapping of tertiary carbon radicals by a tethered acetylene.

Several 2',3'-dideoxy-3'-substituted nucleosides have been found to date which are effective inhibitors of HIV-reverse transcriptase (RT). Our own interest in the design of suitable candidate drugs against AIDS is mainly directed in the development of new synthetic methodologies for 2' or/and 3' modifications of the sugar residue of the nucleoside in a stereospecific manner using either ionic or free-radical reactions¹.

Intramolecular free-radical trapping reactions to give stereospecific cyclization reactions have been used extensively to synthesize complex natural products^{2a}. In nucleoside chemistry, we are the first to show that such intramolecular free-radical cyclization reactions provides an easy access to various 2',3'-cis-fused derivatives of nucleosides.^{1(i,j,k,n)} The 2' or 3' free-radical precursor for intramolecular free-radical cyclization that works well as a radical source in nucleoside chemistry is either phenylseleno^{1(i,j,k,n)} (A) or aryloxythiocarbonyl^{1(k)} (B) derivatives as shown in Scheme 1. Recently, we have found¹⁰ that the secondary radical generated from a 3'-nitro group vicinal to a tethered olefin (as in C in Scheme. 1) does not undergo the expected intramolecular cyclization reaction. We have however been able to show that 2',3'-dideoxy-3'-nitro-2'-C-substituted thymidines can be easily denitrated by the action of $n\text{-Bu}_3\text{SnH}$ and AIBN to give 2',3'-dideoxy-2'-C-substituted thymidines in high yields^{1(e)}, which established that the secondary radical can indeed be generated from a secondary nitro group and be quenched intermolecularly by a hydrogen atom. We here report our new methodologies for the first synthesis of 3'-bis-C-substituted-3'-deoxy-[3.3.0]- α -fused nucleoside **8** and **10** by trapping the tertiary free-radical, generated from a tertiary nitro group, by a tethered acetylene function, as in **4** - **7**, in an intramolecular manner.



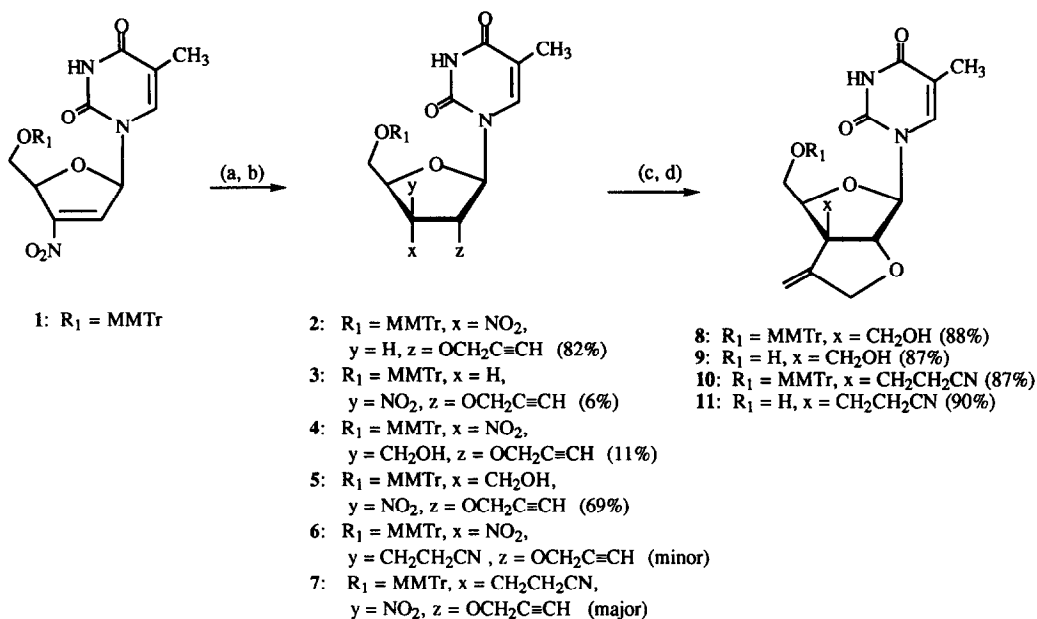
Scheme 1

Thus the Michael addition reaction^{1a-e,l,m} of 2',3'-dideoxy-2',3'-didehydro-3'-nitro-thymidine **1** with propargyl alcohol gave an inseparable diastereomeric mixture of 2'-Q-propenyl-3'-nitro thymidines (**2** + **3**), a subsequent Henry reaction^{1(l,m),3-6} at C3' on this diastereomeric mixture with electron deficient reagents such as formaldehyde or acrylonitrile gave various 2'-Q-propynyl-3'-deoxy-3'-dehydro-3'-C-substituted-3'-nitro-thymidines **4** - **7**, which upon treatment with Bu₃SnH⁷⁻⁹ and AIBN afforded for the first time a 3'-bis-C-substituted [3.3.0]-*cis*-fused nucleoside **8** (88%) or **10** (87%).

(I) *Preparation of 1-(2-O-(2-propynyl)-3-deoxy-3-nitro-β-D-pentofuranosyl)thymines 2 and 3.* 2',3'-Dideoxy-2',3'-didehydro-3'-nitro-thymidine **1** was synthesised by our literature procedure.^{1c} Treatment of **1** with propargyl alcohol in the presence of sodium hydride (2 equiv) at room temperature for 30 min gave an inseparable diastereomeric mixture of **2** (*ribo*) and **3** (*xylo*) in a 13 : 1 ratio (¹H-NMR) in a yield of 88%. Clearly, compounds **2** and **3** were formed due to the attack of the propargyl alkoxide at the C2' center of the 3'-nitro-olefin **1** exclusively from the α-face, which is consistent with our previous observations that the nucleophile preferentially attacks from the less hindered α-face of the 2',3'-double bond in the sugar moiety of a nucleoside in Michael-type addition reactions.^{1(a-e,l,m)} The following trends of chemical shifts and coupling constants were observed in the ¹H-NMR spectra of **2** and **3**. (i) The H-1' was more deshielded (0.13 ppm) in **2** than in the isomer **3**. (ii) The J_{1',2'} of **3** was smaller (1.3 Hz) than that of its epimer **2**. These trends are in accordance with our previous work describing the Michael addition reaction of nitrogen, carbon and oxygen nucleophiles with 2',3'-dideoxy-2',3'-didehydro-3'-nitro thymidine^{1(e,m)} which unambiguously suggest the *ribo* configuration for **2** and the *xylo* configuration for **3**.

(II) *Reaction of 2 + 3 with formaldehyde and acrylonitrile, (The Henry reaction).* Treatment of a mixture of the diastereomeric 1-(2-Q-(2-propynyl)-3-deoxy-3-nitro-β-D-pentofuranosyl)thymines (**2** + **3**) with 35% aqueous formaldehyde in acetonitrile in the presence of 1,1,3,3-tetramethylguanidine (2 equiv) for 30 min at room temperature gave a mixture of diastereomers which were separated on silica gel column to afford pure 2'-Q-(R)-(2-propynyl)-3'-C-(R)-hydroxymethyl-3'-nitro-thymidine **4** (11%) and 2'-Q-(R)-(2-propynyl)-3'-C-(S)-hydroxymethyl-3'-nitro-thymidine **5** (69%). The ¹H-NMR chemical shifts of H-2', H-4', H5'/5'' and 3'-CH₂-OH were remarkably different in **4** and **5** [for **4**: δ4.70 (H-2'), 4.86 (H-4'), 3.75 and 3.51 (H5'/5''), 4.36 - 4.26 (3'-CH₂-OH), and for **5**: δ5.29 (H-2'), 4.25 (H-4'), 3.50 and 3.42 (H5'/5'') and 4.22 (3'-CH₂-OH)] (see the experimental part for the detailed ¹H- and ¹³C-NMR). Treatment of the diastereomeric mixture of **2** and **3** with

acrylonitrile in THF in the presence of tetrabutylammonium fluoride (0.2 equiv) for 60 min gave an inseparable mixture 2'-Q-(R)-(2-propynyl)-3'-C-(R)-(β-cyanoethyl)-3'-nitro-thymidine **6** and 2'-Q-(R)-(2-propynyl)-3'-C-



Conditions: (a): Propargyl alcohol, NaH; (b): HCHO, $\text{CH}_2=\text{CHCN}$, TMG / TBAF, CH_3CN (c): Bu_3SnH , AIBN, Toluene, 100 °C; (d) 80% aqueous acetic acid, RT.

Scheme 2

(S)-(β-cyanoethyl)-3'-nitro-thymidine **7** in 25 : 75 ratio ($^1\text{H-NMR}$). It is also clear from the above results that the incipient carbanion preferentially attacks the electron-deficient reagents from the α-face of the pentofuranose ring [4 / 5 = 1 : 6.3; 6 / 7 = 1 : 3; *vide infra* for NMR arguments for the unequivocal assignment of the configuration at C3']. Again, this is consistent with our earlier results of Michael addition reactions of the 2',3'-enenitrile^{1c}, 2',3'-enesulfone^{1d} and 2',3'-eneselenone^{1b} nucleosides with various carbon or nitrogen nucleophiles in which it has been shown that 2',3'-*trans*-substituted nucleosides are by far the major products formed.

(III) Assignment of configurations in compounds 4 - 7. The following trends of chemical shifts were observed in the $^1\text{H-NMR}$ spectra of 4 - 7: (i) The H-2' was more shielded (0.59 ppm) in the case of 4 and 6 in comparison with their respective epimers 5 and 7. (ii) The H-4' in epimers 4 and 6 was more deshielded (0.61 ppm) than in their corresponding epimers 5 and 7. (iii) The difference in chemical shift of H-5' and H-5'' in 4 was larger ($\Delta\delta = 0.24$ ppm) in comparison with its counterpart 5 ($\Delta\delta = 0.08$ ppm). Above spectroscopic characteristics clearly suggested two distinctly different trends of chemical shifts for the pair of 3'-epimers with C-substituent at the β-face (*i.e.* 4 and 6) or at the α-face (*i.e.* 5 and 7). These spectroscopic results are also

consistent with our previous work on 2',3'-dideoxy-3'-nitro-thymidine that the electron-deficient reagent preferentially react from the relatively unhindered α -face of the pentofuranose ring.^{1(i,m)}

(IV) *Intramolecular free radical cyclization in 2',3'-disubstituted nucleosides.* The free-radical intramolecular cyclization⁷⁻⁹ in 4 - 7 were performed in the following manner. Treatment of 5 with tributyltin hydride (3 equiv) and AIBN (1 equiv) in dry toluene at 100 °C for 30 min gave 2'-Q, 3'-C-((3-Methylidene)ethylene)-3'-deoxy-3'-dehydro-3'-C-(S)-hydroxymethyl-ribothymidine 8 which was isolated in 88% yield upon purification by column chromatography. We have also performed the radical-promoted intramolecular cyclization reaction on the mixture of diastereomeric 4 + 5 to give exclusively 8 in 88% yield. The reaction of diastereomeric mixture 6 + 7 under the above radical reaction conditions gave also only one diastereomer: 2'-Q, 3'-C-((3-Methylidene)ethylene)-3'-deoxy-3'-dehydro-3'-C-(R)-(β -cyanoethyl)ribothymidine 10 (87%). Subsequently, the 5'-Q-MMTr group from 8 and 10 was removed by a brief treatment of 80% aqueous acetic acid at RT to give 9 (87%) and 11 (90%), respectively.

Following points may be noted on the above free-radical intramolecular cyclization procedure: (i) The α -orientation of 2'-O-alkynyl ether dictated the *ribo* configuration of the resultant *cis*-fused five membered rings. (ii) Radical trapping cyclization gave exclusively 5-*exo* ring closure products, no trace of 6-*endo* ring closure^{2(b-g)} products was formed. This implies that the radical cyclizations were kinetically controlled and preferred formation of less stable primary radical is due to pseudochair-like transition state which regioselectively produce the five membered ring. This is consistent with our^{1(i,j,k,n)} and other observations^{2,7} on the radical cyclization in the literature.

EXPERIMENTALS

¹H-NMR spectra were recorded in δ scale with Jeol GX-270 at 270 MHz, using TMS as internal reference (0.0 ppm). ¹³C-NMR were recorded at 67.8 MHz using both ¹H-coupled and ¹H-decoupled or INEPT modes. Jeol DX 303 instrument was used for recording the high resolution mass spectra (HRMS). TLC was carried out using Merck pre-coated silica gel F254 plates. The column chromatography was carried out using Merck G60 silica gel.

1-[5-Q-(MMTr)-2-Q-(R)-(2-propynyl)-3-deoxy-3-(R)-nitro- β -D-pentofuranosyl]thymine (2) & 1-[5-Q-(MMTr)-2-Q-(R)-(2-propynyl)-3-deoxy-3-(S)-nitro- β -D-pentofuranosyl]thymine (3). Sodium hydride (80%, 48 mg, 2.0 mmol) was added in dry propargyl alcohol (4 ml) and was stirred in an ultrasonic bath for 15 min. It was cooled in ice-water bath for a further period of 15 min and then 1 (540 mg, 1.0 mmol) was added. The reaction mixture was stirred in ice-water bath for 30 min and poured into aqueous ammonium chloride solution which was extracted with dichloromethane (3 x 25 ml). The organic phase was pooled and concentrated in vacuo and was subjected to silica gel column chromatography to give an inseparable mixture of 2 and 3 (524 mg, 88%) in 13 : 1 ratio (¹H-NMR). ¹H-NMR (CDCl₃): 8.14 (br. s, 1H) NH; 7.55 (d, 1H) H-6; 7.39-7.24 (m, 12H) arom; 6.87-6.84 (m, 2H) arom; 6.18 (d, $J_{1'2'} = 5.3$ Hz, 1H) H-1' (major); 6.03 (d, $J_{1'2'} = 4.0$ Hz, 1H) H-1' (minor); 5.30 (dd, $J_{3'4'} = 1.6$ Hz, 1H) H-3'; 4.89 (dd, $J_{2'3'} = 6.8$ Hz, 1H) H-2'; 4.81 (ddd, 1H) H-4'; 4.52 (dd, $J_{2'CHa}, 2'CH_2C\equiv CH = 2.3$ Hz, $J_{2'CHa}, 2'CHb = 16.3$ Hz, 1H) 2'-CH_a; 4.35 (dd, $J_{2'CHb}, 2'CH_2C\equiv CH = 2.3$ Hz, 1H) 2'-CH_b; 3.80 (s, 3H) OMe; 3.71 (dd, $J_{4'5'} = 2.6$ Hz, $J_{5'5''} = 11.1$ Hz, 1H) H-5'; 3.38 (dd, $J_{4'5''} = 2.4$ Hz, 1H) H-5''; 2.49 (dd, 1H) 2'-OCH₂C \equiv CH; 1.29 (d, $J_{6,CH_3} = 1.1$ Hz, 3H) 5-CH₃. ¹³C-NMR (CDCl₃): 135.2 (d, $J_{CH} = 180.5$ Hz) C-6; 111.5 (s) C-5; 87.4 (d, $J_{CH} = 172.3$ Hz) C-1'; 87.4 (s) MMTr; 83.9 (d, $J_{CH} = 158.5$ Hz) C-3'; 78.9, 78.7 (2 x d) C-2' & C-4'; 62.4 (t, $J_{CH} = 145.7$ Hz) C-5'; 58.4 (t) 2'-OCH₂; 55.1 (d, $J_{CH} = 150.0$ Hz) OMe; 11.6 (q, $J_{CH} = 129.2$ Hz) 5-CH₃.

1-[5-Q-(MMTr)-2-Q-(R)-(2-propynyl)-3-deoxy-3-dehydro-3-C-(R)-hydroxymethyl-3-nitro- β -D-pentofuranosyl]thymine (4) & 1-[5-Q-(MMTr)-2-Q-(R)-(2-propynyl)-3-deoxy-3-dehydro-3-C-(S)-hydroxymethyl-3-nitro- β -D-pentofuranosyl]thymine (5). To a solution of mixture of 2 and 3 (249 mg, 0.4 mmol) and 35% aqueous formaldehyde (0.5 ml) in acetonitrile (5 ml) was added 1,1,3,3-tetramethylguanidine (92 mg, 0.8 mmol), and kept it standing at RT for 30 min. The reaction mixture was worked-up and purified in

the usual manner^{1m} to give **4** (28 mg, 11%) & **5** (172 mg, 69%). Compound **4**, ¹H-NMR (CDCl₃): 8.03 (br. s, 1H) NH; 7.68 (d, 1H) H-6; 7.42-7.26 (m, 12 H) arom, H-6; 6.88-6.85 (m, 2H) arom; 6.22 (d, J_{1',2'} = 6.9 Hz, 1H) H-1'; 4.86 (dd, 1H) H-4'; 4.70 (d, 1H) H-2'; 4.36-4.26 (m, 2H) 3'-CH₂; 3.81 (s, 3H) OMe; 3.75 (dd, J_{4',5'} = 5.0 Hz, J_{5',5''} = 11.2 Hz, 1H) H-5'; 3.51 (dd, J_{4',5'} = 2.1 Hz, 1H) H-5''; 2.46 (dd, 1H) 2'-OCH₂C≡CH; 1.37 (d, J_{6,CH₃} = 1.2 Hz, 3H) 5-CH₃. HRMS (FAB⁻): calcd. for (M-H)⁻ 626.2139, found 626.2103. Compound **5**, ¹H-NMR (CDCl₃): 8.58 (br. s, 1H) NH; 7.58 (d, J_{6,CH₃} = 1.1 Hz, 1H) H-6; 7.39-7.23 (m, 12H) arom, H-6; 6.87-6.83 (m, 2H) arom; 6.12 (d, J_{1',2'} = 6.2 Hz, 1H) H-1'; 5.29 (d, 1H) H-2'; 4.56 (dd, J_{2'CH_a,C≡CH} = 2.3 Hz, J_{2'CH_a,2'CH_b} = 16.2 Hz, 1H) 2'-CH_a; 4.44 (dd, J_{2'CH_b,2'CH_a} = 2.4 Hz, 1H) 2'-CH_b; 4.25 (dd, 1H) H-4'; 4.22 (m, 2H) 3'-CH₂; 3.80 (s, 3H) OMe; 3.50 (dd, J_{4',5'} = 4.3 Hz, J_{5',5''} = 11.0 Hz, 1H) H-5'; 3.42 (dd, J_{4',5'} = 3.7 Hz, 1H) H-5''; 2.47 (dd, 1H) 2'-OCH₂C≡CH; 1.55 (d, 3H) 5-CH₃; ¹³C-NMR (CDCl₃): 135.2 (d, J_{CH} = 181.5 Hz) C-6; 111.9 (s) C-5; 95.4 (s) C-3'; 86.0 (d, J_{CH} = 168.6 Hz) C-1'; 82.9 (d, J_{CH} = 152.1 Hz), 79.6 (d, J_{CH} = 152.1 Hz) C-2' & C-4'; 77.9 (d) 2'-OCH₂C≡CH; 63.1 (t, J_{CH} = 148.0 Hz) 3'-CH₂OH; 61.8 (t, J_{CH} = 142.3 Hz) C-5'; 59.3 (t, J_{CH} = 151.2 Hz) 2'-OCH₂; 55.1 (q, J_{CH} = 143.9 Hz) OMe; 11.7 (q, J_{CH} = 129.5 Hz) 5-CH₃. HRMS (FAB⁻): calcd. for (M-H)⁻ 626.2139, found 626.2108.

1-[5-Q-(MMTr)-2-Q-(R)-(2-propynyl)-3-deoxy-3-dehydro-3-C-(S)-(β-cyanoethyl)-3-nitro-β-D-pentofuranosyl]thymine (6) & **1-[5-Q-(MMTr)-2-Q-(R)-(2-propynyl)-3-deoxy-3-dehydro-3-C-(R)-(β-cyanoethyl)-3-nitro-β-D-pentofuranosyl]thymine (7)**. To a solution of **2** and **3** (100 mg, 0.17 mmol) and acrylonitrile (100 μl) in acetonitrile (2 ml) was added TBAF (8 mg, 0.03 mmol), and kept it standing at RT for 30 min. The reaction mixture was worked-up and purified in the usual manner^{1m} to give an inseparable mixture of **6** & **7** (60 mg, 55%) in 25 : 75 ratio (from ¹H-NMR). ¹H-NMR (CDCl₃): 8.73 (br. s) NH (major); 8.58 (br. s) NH (minor); 8.56-6.81 (m) arom and H-6; 5.97 (d, J_{1',2'} = 4.5 Hz) H-1' (minor); 5.95 (d, J_{1',2'} = 4.0 Hz) (minor); 5.11 (d) H-2' (major); 4.97 (d) H-2' (minor); 4.55 (m) 2'-OCH₂; 4.16 (m) H-4' (minor); 4.06 (m) H-4' (major); 3.81 (s) OMe; 3.42 (m) H-5', H5''; 2.70-2.22 (m) 3'-CH₂CH₂CN; 2.51 (m) 2'-OCH₂C≡CH; 1.75 (d, J_{6,CH₃} = 1.1 Hz) 5-CH₃. HRMS (FAB⁻): calcd. for (M-H)⁻ 649.2299, found 649.2275.

5'-O-MMTr-2'-Q,3'-C-((3-Methylidene)ethylene)-3'-deoxy-3'-dehydro-3'-C-(S)-hydroxymethyl-ribo thymidine (8). A mixture of **4** & **5** (157 mg, 0.2 mmol), Bu₃SnH (160 μl, 0.6 mmol) and AIBN (33 mg, 0.2 mmol) in toluene (10 ml) was heated at 100 °C for 30 min. The solvent was removed in vacuo and the residue was purified by a silica gel column to give **8** (129 mg, 88%). ¹H-NMR (CDCl₃): 8.43 (br. s, 1H) NH; 7.77 (q, J_{6,CH₃} = 1.2 Hz, 1H) H-6; 7.48-7.23 (m, 12H) arom; 6.89-6.85 (m, 2H) arom; 5.98 (d, J_{1',2'} = 3.4 Hz, 1H) H-1'; 4.91 (br. s, 1H) 3'C=CH_a; 4.77 (d, 1H) H-2'; 4.63 (dt, J_{2'CH_a,2'CH_b} = 13.3 Hz, 1H) 2'-OCH_a; 4.55 (br, 1H) 3'C=CH_b; 4.44 (dt, 1H) 2'-OCH_b; 4.03 (dd, J_{4',5'} = 4.3 Hz, 1H) H-4'; 3.80 (s, 3H) OMe; 3.78 (dd, 1H) H-5'; 3.72 (dd, J_{3'CH_a,OH} = 4.6 Hz, J_{3'CH_a,3'CH_b} = 11.7 Hz, 1H) 3'-CH_a; 3.56 (dd, J_{3'CH_a,OH} = 7.0 Hz, J_{3'CH_a,3'CH_b} = 11.7 Hz, 1H) 3'-CH_a; 3.42 (dd, 1H) OH; 3.28 (dd, J_{4',5'} = 2.9 Hz, J_{5',5''} = 11.0 Hz, 1H) H-5''; 1.91 (d, 3H) 5-CH₃; ¹³C-NMR (CDCl₃): 137.0 (d, J_{CH} = 180.5 Hz) C-6; 111.0 (s) C-5; 105.5 (t, J_{CH} = 158.8 Hz) 3'-C-C=CH₂; 91.2 (d, J_{CH} = 157.8 Hz) C-4'; 89.7 (d, J_{CH} = 165.5 Hz) C-1'; 87.5 (s) MMTr; 82.8 (d, J_{CH} = 145.3 Hz) C-2'; 73.0 (t, J_{CH} = 151.0 Hz) 2'-OCH₂; 63.6 (t, J_{CH} = 143.8 Hz) 3'-CH₂OH; 60.8 (t, J_{CH} = 143.4 Hz) C-5'; 59.7 (s) C-3'; 55.1 (q, J_{CH} = 143.9 Hz) OMe; 12.3 (q, J_{CH} = 129.7 Hz) 5-CH₃.

2'-Q,3'-C-((3-Methylidene)ethylene)-3'-deoxy-3'-dehydro-3'-C-(S)-hydroxymethyl-ribo thymidine (9). Compound **8** (116 mg, 0.1 mmol) was treated with 80% aqueous acetic acid (2.5 ml) overnight at RT. The solvent was removed in vacuo and coevaporated with toluene and ethanol. The residue was purified by a silica gel column to give **9** (54 mg, 87%). ¹H-NMR (CDCl₃ + CD₃OD): 7.74 (q, J_{6,CH₃} = 1.2 Hz, 1H) H-6; 5.91 (d, J_{1',2'} = 3.4 Hz, 1H) H-1'; 5.07 (br, 1H) 3'C=CH_a; 5.00 (br. s, 1H) 3'C=CH_b; 4.77 (d, 1H) H-2'; 4.63 (dt, J_{2'CH_a,2'CH_b} = 13.3 Hz, 1H) 2'-OCH_a; 4.44 (dt, 1H) 2'-OCH_b; 4.03 (dd, J_{4',5'} = 4.3 Hz, 1H) H-4'; 3.80 (s, 3H) OMe; 3.78 (dd, 1H) H-5'; 3.72 (dd, J_{3'CH_a,OH} = 4.6 Hz, J_{3'CH_a,3'CH_b} = 11.7 Hz, 1H) 3'-CH_a; 3.56 (dd, J_{3'CH_a,OH} = 7.0 Hz, J_{3'CH_a,3'CH_b} = 11.7 Hz, 1H) 3'-CH_a; 3.42 (dd, 1H) OH; 3.28 (dd, J_{4',5'} = 2.9 Hz, J_{5',5''} = 11.0 Hz, 1H) H-5''; 1.91 (d, 3H) 5-CH₃; ¹³C-NMR (CDCl₃ + CD₃OD): 137.1 (d, J_{CH} = 182.4 Hz) C-6; 110.7 (s) C-5; 105.8 (t, J_{CH} = 158.5 Hz) 3'-C-C=CH₂; 91.2 (d, J_{CH} = 156.7 Hz) C-4'; 88.6 (d, J_{CH} = 165.9 Hz) C-1'; 84.1 (d, J_{CH} = 146.6 Hz) C-2'; 72.7 (t, J_{CH} = 150.8 Hz) 2'-OCH₂; 63.0 (t, J_{CH} = 144.8 Hz) C-5'; 59.4 (t, J_{CH} = 143.0 Hz) 3'-CH₂OH; 11.6 (q, J_{CH} = 129.2 Hz) 5-CH₃. HRMS (FAB⁻): calcd. for (M-H)⁻ 309.1086, found 309.1125.

5'-O-MMTr-2'-Q,3'-C-((3-Methylidene)ethylene)-3'-deoxy-3'-dehydro-3'-C-(R)-(β-cyanoethyl)ribo thymidine (10). A mixture of **6** & **7** (50 mg, 0.08 mmol), Bu₃SnH (62 μl, 0.23 mmol) and AIBN (3 mg, 0.02

mmol) in toluene (5 ml) was heated at 100 °C for 30 min. The solvent was removed in vacuo and the residue was purified by silica gel column to give **10** (40 mg, 87%). ¹H-NMR (CDCl₃): 8.72 (br. s, 1H) NH; 7.47-7.21 (m, 13H) arom and H-6; 6.86 (m, 2H) arom; 5.72 (d, J_{1'2'} = 3.8 Hz, 1H) H-1'; 5.17 (br. s, 1H) 3'C=CH_a; 4.90 (br. s, 1H) 3'C=CH_b; 4.69 (dt, J_{3'C=CH_a,2'CH_a} = 2.1 Hz, J_{2'CH_a,2'CH_b} = 14.0 Hz, 1H) 2'-OCH_a; 4.61 (d, 1H) H-2'; 4.49 (dt, J_{3'C=CH_b,2'CH_b} = 1.9 Hz, 1H) 2'-OCH_b; 4.15 (t, 1H) H-4'; 3.80 (s, 3H) OMe; 3.40 (m, 2H) H-5', H-5"; 2.21 (m, 2H) 3'-CH₂; 2.10-1.80 (m, 2H) CH₂CN; 1.68 (d, J_{6,CH₃} = 1.1 Hz, 3H) 5-CH₃; ¹³C-NMR (CDCl₃): 163.3 (s) C-4; 150.1 (s) C-2, 136.2 (d, J_{CH} = 178.7 Hz) C-6; 119.0 (s) CN; 111.4 (s) C-5; 107.5 (t, J_{CH} = 158.5 Hz) 3'-C=CH₂; 89.6 (2 x d, J_{CH} = 165.0 Hz) C-1' and C-2'; 87.5 (s) MMTr; 83.6 (d, J_{CH} = 148.5 Hz) C-4'; 72.4 (t, J_{CH} = 155.8 Hz) 2'-OCH₂; 61.6 (t, J_{CH} = 142.1 Hz) C-5'; 57.0 (s) C-3'; 55.1 (q, J_{CH} = 143.9 Hz) OMe; 25.9 (t, J_{CH} = 132.9 Hz) 3'-CH₂; 12.6 (t, J_{CH} = 141.1 Hz) CH₂CN; 12.0 (q, J_{CH} = 129.8 Hz) 5-CH₃.

2'-O,3'-C-((3-Methylidene)ethylene)-3'-deoxy-3'-dehydro-3'-C-(R)-(β-cyanoethyl)ribothymidine (11). Compound **10** (20 mg, 0.03 mmol) was treated with 80% aqueous acetic acid (2 ml) overnight at RT. The solvent was removed in vacuo and coevaporated with toluene and ethanol. The residue was purified by a silica gel column to give **11** (9 mg, 90%). ¹H-NMR (CDCl₃ + CD₃OD): 7.43 (q, J_{6,CH₃} = 1.0 Hz, 1H) H-6; 5.58 (d, J_{1'2'} = 3.9 Hz, 1H) H-1'; 5.27 (br. s, 1H) 3'C=CH_a; 5.13 (br. s, 1H) 3'C=CH_b; 4.74 (d, 1H) H-2'; 4.70 (dt, J_{3'C=CH_a,2'CH_a} = 1.7 Hz, J_{2'CH_a,2'CH_b} = 14.0 Hz, 1H) 2'-OCH_a; 4.53 (dt, J_{3'C=CH_b,2'CH_b} = 1.7 Hz, 1H) 2'-OCH_b; 4.09 (dd, 1H) H-4'; 3.89 (dd, J_{4'5'} = 4.8 Hz, J_{5'5''} = 12.2 Hz, 1H) H-5'; 3.83 (dd, J_{4'5''} = 4.8 Hz, 1H) H-5"; 2.43-2.03 (m, 4H) 3'-CH₂CH₂CN; 1.92 (d, 3H) 5-CH₃; ¹³C-NMR (CDCl₃): 137.3 (d, J_{CH} = 185.8 Hz) C-6; 119.3 (s) CN; 110.9 (s) C-5; 107.0 (t, J_{CH} = 158.3 Hz) 3'-C=CH₂; 90.2 (d, J_{CH} = 163.7 Hz), 89.3 (d, J_{CH} = 160.9 Hz) C-1' and C-2'; 85.0 (d, J_{CH} = 148.4 Hz) C-4'; 72.0 (t, J_{CH} = 148.5 Hz) 2'-OCH₂; 60.2 (t, J_{CH} = 142.7 Hz) C-5'; 56.9 (s) C-3'; 26.4 (t, J_{CH} = 131.8 Hz) 3'-CH₂; 12.6 (t) CH₂CN; 12.0 (q) 5-CH₃. HRMS (FAB⁻): calcd. for (M-H)⁻ 332.1247, found 332.1260.

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