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Diels-Alder Reaction of 2',3'-Unsaturated-3'-Nitro-Thymidine. First Chemical Evidence of Nitroxide Radical Formation in the Radical-Promoted Denitration Reaction

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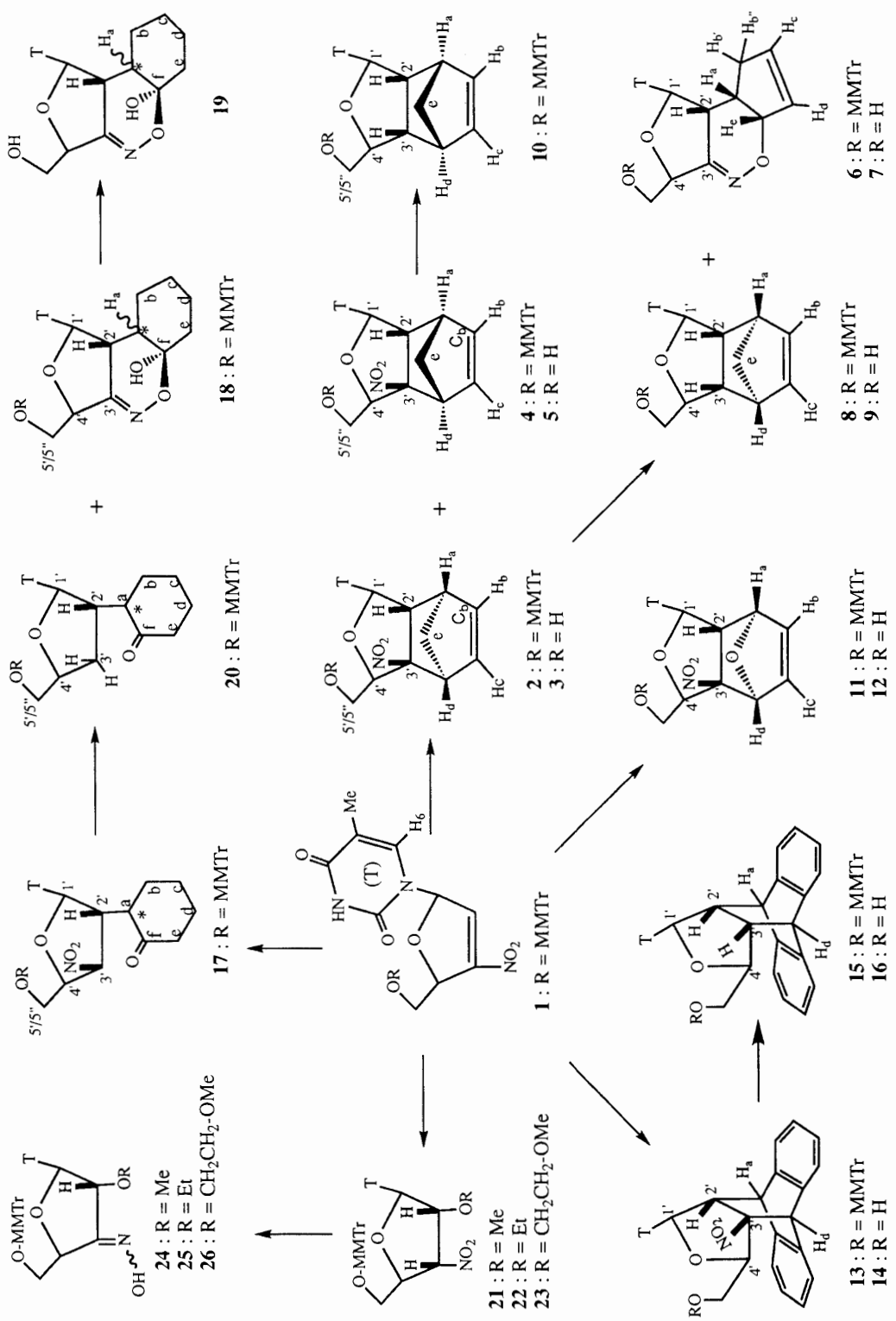
Abstract: *Diels-Alder reaction of an appropriately functionalized nucleoside [2',3'-dideoxy-2',3'-didehydro-3'-nitrothymidine (**1**)] has been used for the first time as a substrate to yield various unique fused 2',3'-dideoxy-2',3'-bis-substituted nucleoside derivatives (**2 - 5, 8 - 16**) which are not hithertofore available through any other known routes. First unequivocal evidence of the formation of nitroxide radical during n-Bu_3SnH promoted denitration reaction has been also presented through the isolation of fused 4H-5,6-dihydro-1,2-oxazine derivatives of the cycloadducts (**6, 7, 18, 19**) which were formed due to the trapping of the nitroxide radical with an olefin or a keto function in an intramolecular reaction.*

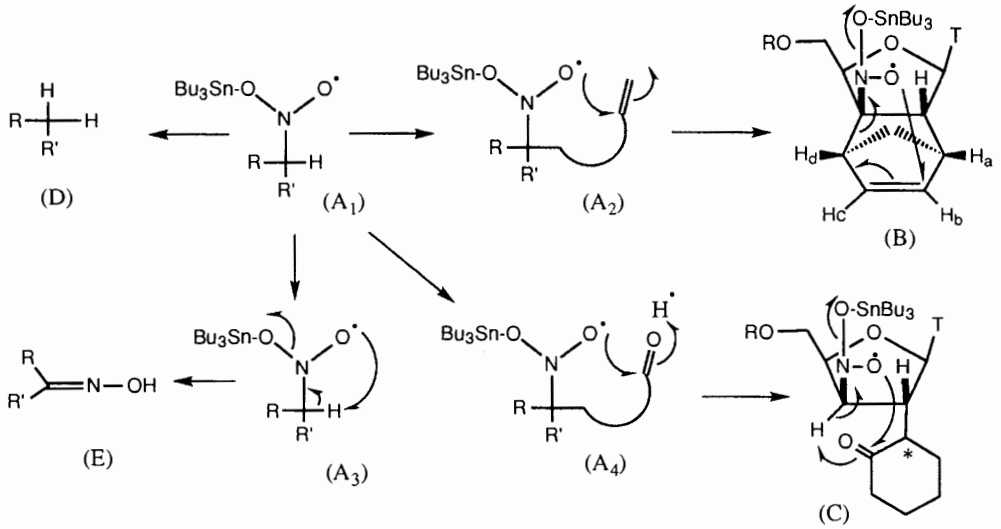
Several 2',3'-dideoxy-3'-substituted nucleoside derivatives [such as 3'-azidothymidine (AZT), 2',3'-dideoxyinosine (ddI) and 2',3'-dideoxycytidine (ddC)] are now available as FDA approved drugs for the treatment of AIDS. The mechanism of action of these 2',3'-dideoxynucleosides is based upon their ability to inhibit HIV-reverse transcriptase in a specific and effective manner. The availability of various 2',3'-unsaturated-nucleosides conjugated with 3'-electron-withdrawing groups, as in 2',3'-ene-3'-nitrile[1a], 2',3'-ene-3'-(phenylsulfonyl)[1b] and 2',3'-ene-3'-(phenylselenonyl)-β-D-nucleosides[1c,1d], provide efficient means to functionalize the 2'- and 3'-carbons as powerful alternatives to standard S_N2 type reactions for preparation of 2',3'-substituted-2',3'-dideoxynucleosides. We have also recently shown[2a] that the strong electron-withdrawing character of nitro group conjugated to a double bond promote nucleophilic addition[3-9] reactions at the β-carbon in 2',3'-dideoxy-2',3'-didehydro-3'-nitrothymidine[2a] (**1**) which has been shown to be synthetically useful[2] for the preparation of various 2'- and 3'-modified nucleosides either through Michael addition reactions[2a] with various oxygen, nitrogen and carbon nucleophiles or by dipolar cycloaddition reaction[2b]. Although Michael-type addition reactions can be performed easily with 2',3'-unsaturated nucleosides[1a-d] in which 2',3'-double bond of the sugar moiety is conjugated with electron-withdrawing groups (CN, $PhSO_2$, $PhSeO_2$ etc) their cycloaddition reactions are generally very sluggish, taking several days to weeks for completion.

We have herein exploited the unique electron-deficient character of 2',3'-dideoxy-2',3'-didehydro-3'-nitrothymidine (**1**) as a powerful dienophile for Diels-Alder reaction[10-22] to give various uniquely fused 2',3'-dideoxy-2',3'-bis-substituted thymidine derivatives **2 - 16** as potential anti-HIV agents. We have also unambiguously demonstrated in this work for the first time that the nitroxide radical is indeed formed at the first step of the radical chain sequence of n-Bu_3SnH promoted denitration reaction[23-27]. This has been shown by the isolation of fused 4H-5,6-dihydro-1,2-oxazine derivatives formed due to the intramolecular trapping of

the nitroxide radical by a neighbouring olefin (**2** → **6**) or a keto function (**17** → **18**). The reaction of 2',3'-unsaturated-3'-nitrothymidine (**1**) in dry toluene with freshly distilled cyclopentadiene at 70 °C overnight gave a mixture of *endo*-**2** and *exo*-**4** addition products which were isolated as pure compounds in 85 and 12% yields, respectively. The 1D difference NOE studies at 500 MHz suggested that *endo*-**2** has 2'(R), 3'(R), C_a(R) and C_d(S) configurations, whereas *exo*-**4** has 2'(R), 3'(R), C_a(S) and C_d(R) configurations. When pure **2** was treated with n-Bu_3SnH overnight in dry benzene at 70 °C, only sugar-fused tricyclic-(4H-5,6-dihydro-1,2-oxazine)-nucleoside **6** (30%) [2'(R), C_a(S) and C_e(R)] was isolated along with the unreacted starting material, and the reaction did not progress further upon prolongation of the reaction time or addition of an excess of n-Bu_3SnH. However, when the same reaction was performed at 105 °C for 3 h in toluene, both sugar-fused tricyclic-nucleoside **6** (45%) and 3'-denitrated product **8** (13%) [2'(R), 3'(S), C_a(R)] and C_d(S)] were obtained. Detailed COSY, two-dimensional ^{13}C-^1H shift correlation, INEPT with ^1H coupled ^{13}C-NMR, ^1H-decouplings and 1D difference NOE studies (*vide infra*, see also experimental) along with high resolution mass spectroscopy clearly substantiated the structure of **6**. The isolation of sugar-fused tricyclic nucleoside **6** provides direct experimental evidence for the first time that the nitroxide radical is indeed formed as an intermediate in n-Bu_3SnH promoted denitration reaction[24-28], which is evidently produced by addition of the tin radical to the oxygen atom of the nitro group (Scheme 1). The fact that at a low temperature (70 °C), only sugar-fused tricyclic nucleoside **6** was formed without any trace of denitrated product **8**, which however was found to have formed at a higher temperature (105 °C), supports Ono's original EPR[24,26] studies that it is the nitroxide radical (A_1 in Scheme 1) which is formed first and subsequently breaks down to the denitrated product (D). Thus from the mechanistic standpoint, the successful trapping of the nitroxide radical in the form of 4H-5,6-dihydro-1,2-oxazine derivative has settled a long debate[23-27] regarding the radical chain sequence of free-radical promoted denitration reaction. The nitroxide radical (A_1) is reasonably stable and can be efficiently trapped intramolecularly if a neighbouring olefin can be set up in a manner shown in (A_2) in Scheme 1. The participation of the intermediate (A_2) indeed explains the mechanism of formation of sugar-fused tricyclic nucleoside **6** which involves the scavenging of the 3'-nitroxide radical by the olefin, followed by concerted carbon-carbon bond cleavage as shown in the intermediate (B). It is noteworthy that *exo*-**4**, upon a treatment of n-Bu_3SnH produces only 3'-denitrated product **10** ([2'(R), 3'(S), C_a(S)] and C_d(R)]. The fact that the nitroxide radical generated from *endo*-**2** can be only scavenged successfully, in contrast to that of *exo*-**4**, is consistent with the fact that the distance between 3'-nitroxide radical and the C_b-carbon of olefin in *endo*-**2** is 3.5 Å whereas it is 4.3 Å in *exo*-**4**[29]. Furthermore, simple model building studies clearly show that the *exo* orientation of the bridgehead methylene in *exo*-**4** sterically hinders the attack of the nitroxide radical to the olefin in comparison with the *endo* orientation of the bridgehead methylene in *endo*-**2**. It is also clear from our temperature-dependent studies *(vide supra)* that the nitroxide radical (A_1) suffers a homolytic cleavage of carbon-nitrogen bond to give denitrated product (D). The formation of (D) is slower than the rate of generation of the nitroxide radical which became clear from the fact that when the nitroxide radical could be trapped effectively *(vide supra)*, then further carbon-nitrogen bond cleavage did not proceed. A treatment of the radical precursor **17** with n-Bu_3SnH has also enabled us to trap the intermediary nitroxide radical by the neighbouring keto function [(A_4) in Scheme 1] in **17** to give sugar-fused tricyclic-(4H-5,6-dihydro-1,2-oxazine)-nucleoside **18**[30] [2'(R), C_a(R), C_f(R)] in 34% yield along with denitrated product **20** [2'(S), C_a(R)] (55%). The isolation of sugar-fused tricyclic nucleoside **18** gave also unequivocal support that the nitroxide radical is indeed formed as an intermediate in radical promoted denitration reaction. The isolation[2a] of the 3'-oximes **24** (35 %), **25** (41 %)


19
18 : R = MMTr
20 : R = MMTr
17 : R = MMTr
4 : R = MMTr
5 : R = H
10 : R = MMTr
2 : R = MMTr
3 : R = H
1 : R = MMTr
8 : R = MMTr
9 : R = H
6 : R = MMTr
7 : R = H
11 : R = MMTr
12 : R = H
15 : R = MMTr
16 : R = H
13 : R = MMTr
14 : R = H
21 : R = Me
22 : R = Et
23 : R = CH2CH2-OMe
24 : R = Me
25 : R = Et
26 : R = CH2CH2-OMe

and **26** (34 %) [general formula (E) in Scheme 1] in the n-Bu_3SnH promoted denitration of 2'-O-alkylsubstituted-3'-nitrothymidines **21**, **22** and **23**, respectively, as major products[2a] along with the corresponding 2',3'-dideoxy-2'-alkoxythymidine (<10%)[2a] allow us for the first time to suggest that the nitroxide intermediate (A_1) also undergoes 1,4-hydrogen shift successfully through the intermediate (A_3) followed by the departure of n-Bu_3SnO• radical in a concerted manner. Different pathways of the radical chain reaction of n-Bu_3SnH promoted denitration are thus summarized in Scheme 1.



Scheme 1

The reaction of 2',3'-unsaturated-3'-nitrothymidine **1** in dry toluene with furan at 70 °C for 48 h gave only *endo*-**11** [2'(S), 3'(S), C_a(R) and C_d(S)] (68%), which upon radical promoted denitration reaction gave an intractable mixture of products from which no pure material could be isolated. The reaction of **1** in dry toluene with anthracene for 90 h at 105 °C gave pure **13** [2'(R), 3'(R)] (57%) which could be subsequently denitrated to give pure **15** [2'(R), 3'(S)] (91%) in sharp contrast with the complex denitration reaction of **11**. It should be noted that detailed 1D NOE difference spectroscopy has shown that the diene in all Diels-Alder reaction reported in this paper approaches 3'-nitro-olefin function in **1** from the α-face with complete diastereofacial specificity (*vide infra*).

Assignment of configurations in compounds 2 - 20 by 1D difference NOE spectroscopy at 500 MHz. The configurations of **2** - **20** were determined through one-dimensional ^{1}H-NMR NOE difference spectroscopy. The reaction of **1** and cyclopentadiene gave two diastereoisomers **2** [2'(R), 3'(R), C_a(R), C_d(S)] and **4** [2'(R), 3'(R), C_a(S), C_d(R)]. Saturation of H2' in **2** showed an enhancement at H6 resonance (5.0%), similarly the saturation of H6 in **4** showed an enhancement at H2' (3.4%). These experiments demonstrated unambiguously that the thymine base and H2' are both on the β-side of the ribofuranosyl ring and the bicyclo-[2.2.1]-pentene system is on the α-face of the pentofuranose ring in both cycloadducts **2** and **4**. The *endo* orientation of -CH_2- bridge at the α-face of the pentofuranose ring in **2** was determined by the NOE observed between H1' and -CH_2- protons (2.8%), whereas the *exo* orientation of -CH_2- bridge in **4** was confirmed by the key NOE enhancement at H1' (2.2%) observed upon saturation of H_b. The free radical reaction of **2** gives 3'-denitrated product **8** which yields **9** after removal of 5'-O-MMTr group. Saturation of H1' in **9** showed the key

NOE at the bridgehead -CH_2- (2.6%), whereas the saturation of H_b and H_c gave enhancement at H2' (0.3%) and H3' (0.2%), which confirmed that H2' and H3' are at the β-face of the sugar ring and -CH_2- bridge is located at the α-face with *endo* orientation [2'(R), 3'(S), C_a(R), C_d(S)]. The 3'-denitration of **4** yielded **10**. The saturation of H6 in **10** showed key NOE enhancements at H2' (3.0%) and H3' (2.0%), which confirmed that both H2' and H3' are on the β-face of the sugar ring [2'(R), 3' (S)]. The NOE enhancements observed at H1' (2.8%) and H4' (2.2%) upon saturation of H_b and H_c in **10**, respectively clearly showed that the fused bicyclo-[2.2.1]-pentene system is at the α-face and -CH_2- bridge is in *exo* orientation [C_a(S), C_d(R)]. The configurations in **6** as 2'(R), C_a(S) and C_e(R) were established through the NOE observed upon saturation of H2' at H6 (4.6%), H_a (4.3%) and H_e (1.3%). The key NOE enhancements at H6 (3.8%), H_b (1.5%) and H_c (0.3%) observed upon saturation of H2' in **11** proved the configurations at the newly created chiral centres which are as follows: 2'(S), 3'(S), C_a(R) and C_d(S). The saturation of H2' in **14** showed NOE enhancement at H6 (3.3%) which clearly demonstrate that H2' is on the β-face of pentofuranose ring and the configuration of C2' is R. The NOE difference spectra of the corresponding denitrated **16** showed the key NOE contacts between H6 and H2' (1.3%) and H3' (1.0%). The H2' and H3' in **16** are therefore on the β-face and configurations of the new chiral centres are 2'(R) and 3'(S). The 2'(S) configuration in **20** has been established by observation of NOE enhancements at H2' (4.5%) upon saturation of H6. The saturation of H1' in **20** results in NOE at H_a (1.8%), $H_{b'}$ and $H_{b''}$ (1.6% and 0.4%), whereas a saturation of H4' gives enhancements at H_a (0.6%) and H_e (0.3%) which suggest (R) configuration for C_a fulfilling all spatial contacts. The synthetic precursor of **20** is **17** which has been isolated as a 7 : 3 mixture of two diastereoisomers[2a] (see NMR in the experimental part). The denitration of **17** yielding C_a(R) diastereoisomer **20** (55%) suggests that the major diastereoisomer of **17** has C_a(R) configuration. On the basis of the NOE enhancements, it was however not possible to unequivocally assign the configuration at C_a in **17**. The NOE enhancement at H3' (3.1%) upon saturation of H4' suggests their *cis* relationship and 3'(R) configuration in the major diastereomer of **17**. The saturation of H6 in **18** has shown an enhancement at H2' (2.6%), which is consistent with 2'(R) configuration in **18**. The C_a(R) configuration in the major (70%) diastereomer of **18** is clearly established by NOE between H1' and H_a (2.5%) and large $^3J_{2',Ha}$ = 11.6 Hz. The C_f(R) configuration in **18** has been assessed through the consideration that the nitroxide radical on the β-face of pentofuranose ring can only attack the carbonyl function from the top and therefore places the C_f-hydroxyl group at the bottom. In this way, two six-membered rings are either *cis*-fused (70%) [C_a(R), C_f(R)] or *trans*-fused (30%) [C_a(S), C_f(R)]. All Diels-Alder adducts and their free-radical promoted reaction products, **2**, **4**, **6**, **8**, **11**, **13**, **15** and **18** were deprotected to the corresponding 5'-hydroxy derivatives in 60 -95 % yields.

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. ^{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. UV absorption spectra were recorded with a Varian Carry 2200 instrument. IR spectra were recorded with Perkin-Elmer 298 spectrometer. Tlc was carried out using Merck pre-coated silica gel F254 plates.The column chromatographic separations were carried out using Merck G60 silica gel. The carbons bearing H_a, H_b, H_c, H_d and H_e are noted as C_a, C_b, C_c, C_d and C_e respectively. The chiral carbon bearing hydroxyl group in **18** and **19** is noted as C_f.

1-[5-*O*-(MMTr)-2,3-dideoxy-3-nitro-2,3-*C*-(*endo*-2-cyclopentene-1,4-yl)-β-D-*ribo*furanosyl]thymine (2) and 1-[5-*O*-(MMTr)-2,3-dideoxy-3-nitro-2,3-*C*-(*exo*-2-cyclopentene-1,4-yl)-β-D-*ribo*furanosyl] thymine (4). *General procedure for Diels Alder reaction*: Compound **1** (540 mg, 1 mmol) was dissolved in toluene (10

mL), freshly distilled cyclopentadiene (3 mL) was added, the reaction mixture was sealed with a stopper and kept at 70 °C overnight. The solvent was removed in vacuo and the residue was subjected to flash chromatography to give an isomeric mixture (85 : 15 from 500 MHz ^{1}H-NMR spectrum) of **2** (520 mg, 85 %) and **4** (70 mg, 12 %). Compound **2**, ^{1}H-NMR (500 MHz, $CDCl_3$) 8.9 (br, 1H) NH; 7.62 (*d*, $J_{CH3,H6}$ = 1.2 Hz, 1H) H6; 7.47-6.78 (*m*, 14 H) arom; 6.35 (*dd*, $J_{Hb,\ Hc}$ = 5.7 Hz, $J_{Ha,Hb}$ = 3.1 Hz, 1H) H_b; 6.17 (*dd*, $J_{Hc,Hd}$ = 2.9 Hz, 1H) H_c; 6.01 (*d*, $J_{1',2'}$ = 5.8 Hz, 1H) H1'; 3.9 (*t*, 1H) H4'; 3.79 (*s*, 3H) MMTr; 3.49 (*dd*, $J_{4',5'}$ = 5.8 Hz, 1H) H5'; 3.31 (*dd*, $J_{4',5''}$ = 5.3 Hz, $J_{5',5''}$ = 10.8 Hz, 1H) H5''; 3.25 (*m*, 1H) H_d; 3.07 (*m*, 1H) H_a; 2.93 (*dd*, $J_{2',He'}$ = 2.3 Hz, 1H) H2'; 1.92 (*m*, 2H) H_e; 1.91 (*d*, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$): 139.3 (*d*, J_{CH} = 174.1 Hz) C_c; 136.0 (*d*, J_{CH} = 179.7 Hz) C_b; 135.3 (*d*, J_{CH} = 179.6 Hz) C6; 112.2 (*s*) C5; 108.1 (*s*) C3'; 87.4 (*s*) MMTr; 85.9 (*d*, J_{CH} = 168.6 Hz) C1'; 82.5 (*d*, J_{CH} = 152.2 Hz) C4'; 62.2 (*t*, J_{CH} = 142.9 Hz) C5'; 60.9 (*d*, J_{CH} = 144.8 Hz) C2'; 55.1 (*q*, J_{CH} = 144.2 Hz) MMTr; 48.0 (*d*, J_{CH} = 161.3 Hz) C_d; 45.1 (*t*, J_{CH} = 137.4 Hz) C_e; 43.4 (*d*, J_{CH} = 152.1 Hz) C_a; 12.5 (*q*, J_{CH} = 129.5 Hz) 5-Me. UV (EtOH): [pH 7] λ_{max} = 264 nm (ε = 9700); [pH 2] λ_{max} = 264 nm (ε = 10000); [pH 12] λ_{max} = 264 nm (ε = 8500). Compound **4**, ^{1}H-NMR (500 MHz, $CDCl_3$) 8.47 (br, 1H) NH; 7.62 (*d*, $J_{CH3,H6}$ = 1.2 Hz, 1H) H6; 7.45-6.82 (*m*, 14 H) arom; 6.59 (*dd*, $J_{Ha,Hb}$ = 3.0 Hz, $J_{Hb,Hc}$ = 5.7 Hz, 1H) H_b; 6.22 (*dd*, $J_{Hc,Hd}$ = 3.4 Hz, 1H) H_c; 5.69 (*d*, $J_{1',2'}$ = 5.9 Hz, 1H) H1'; 3.80 (*s*, 3H) MMTr; 3.74 (*m*, 1H) H_d; 3.71 (*m*, 1H) H4'; 3.58 (*dd*, $J_{H2',Ha}$ = 4.1 Hz, 1H) H2'; 3.45 (*dd*, $J_{4',5'}$ = 5.9 Hz, $J_{5',5''}$ = 10.6 Hz, 1H) H5'; 3.23 (*dd*, $J_{4',5''}$ = 6.4 Hz, 1H) H5''; 3.07 (*m*, 1H) H_a; 2.08 (*ddd*, $J_{He',He''}$ = 9.6 Hz, $J_{Ha,He'}$ = 1.7 Hz, $J_{Hd,He'}$ = 1.7 Hz, 1H) $H_{e'}$; 1.92 (*d*, 3H) 5-Me; 1.73 (*ddd*, $J_{Ha,He''}$ = 1.4 Hz, $J_{Hd,He''}$ = 1.2 Hz, 1H) $H_{e''}$. ^{13}C-NMR ($CDCl_3$): 163.5 (*s*) C4; 150.3 (*s*) C2; 111.9 (*s*) C5; 108.4 (*s*) C3'; 87.4 (*s*) MMTr; 85.5 (*d*, J_{CH} = 167.6 Hz) C1'; 81.9 (*d*, J_{CH} = 151.2 Hz) C4'; 62.9 (*d*, J_{CH} = 143.9 Hz) C2'; 62.1 (*t*, J_{CH} = 143.9 Hz) C5'; 55.0 (*q*, J_{CH} = 144.2 Hz) MMTr; 53.3 (*t*, J_{CH} = 136.0 Hz) C_e; 48.8 (*d*, J_{CH} = 163.1 Hz) C_d; 43.4 (*d*, J_{CH} = 145.7 Hz) C_a; 12.4 (*q*, J_{CH} = 128.9 Hz) 5-Me.

1-[2,3-dideoxy-3-nitro-2,3-*C*-(*endo*-2-cyclopentene-1,4-yl)-β-D-*ribo*furanosyl]thymine (3). Compound **2** (100 mg, 0.16 mmol) was treated with 80 % aqueous acetic acid (2 mL) at RT overnight. The solvent was removed in vacuo, co-evaporated with toluene and methanol. The residue was subjected to flash chromatography to give **3** (54 mg, 98 %). ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD): 7.70 (*d*, $J_{CH3,H6}$ = 1.2 Hz, 1H) H6; 6.41 (*dd*, $J_{Ha,Hb}$ = 3.3 Hz, $J_{Hb,Hc}$ = 5.7 Hz, 1H) H_b; 6.19 (*dd*, $J_{Hc,Hd}$ = 2.7 Hz, 1H) H_c; 6.07 (*d*, $J_{1',2'}$ = 5.9 Hz, 1H) H1'; 4.18 (*t*, 1H) H4'; 3.75 (*d*, $J_{4',5'}$ = 5.3 Hz, 1H) H5'; 3.73 (*d*, $J_{4',5''}$ = 5.0 Hz, 1H) H5''; 3.40 (*m*, 1H) H_d; 3.10 (*m*, 1H) H_a; 3.05 (*dd*, 1H) H2'; 2.06 (*t*, 2H) H_e; 1.96 (*d*, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$ + CD_3OD): 139.7 (*d*, J_{CH} = 176.9 Hz) C_c; 135.6 (*d*, J_{CH} = 182.4 Hz) C_b; 135.4 (*d*, J_{CH} = 182.4 Hz) C6; 112.1 (*s*) C5; 108.0 (*s*) C3'; 85.7 (*d*, J_{CH} = 165.9 Hz) C1'; 83.6 (*d*, J_{CH} = 151.2 Hz) C4'; 60.7 (*t*, J_{CH} = 142.4 Hz) C5'; 60.3 (*d*, J_{CH} = 143.0 Hz) C2'; 48.2 (d) C_d; 45.0 (*t*) C_e; 43.7 (d) C_a; 12.3 (*q*, J_{CH} = 128 Hz) 5-Me. MS (FAB$^-$): calc. for $[(C_{15}H_{17}N_3O_6)-H]^-$ 334.1039, found 334.1018. UV (EtOH): [pH 7] λ_{max} = 265 nm (ε = 8600); [pH 2] λ_{max} = 265 nm (ε = 8800); [pH 12] λ_{max} = 264 nm (ε = 7600).

1-[2,3-dideoxy-3-nitro-2,3-*C*-(*exo*-2-cyclopentene-1,4-yl)-β-D-*ribo*furanosyl]thymine (5). Compound **4** (40 mg, 0.06 mmol) was treated with 80 % aqueous acetic acid (1 mL) overnight at RT. The solvent was removed in vacuo, coevaporated with toluene and methanol. The residue was purified by flash chromatography to give **5** (21 mg, 95 %). ^{1}H-NMR (270 MHz, $CDCl_3$): 8.98 (br, 1H) NH; 7.61 (*d*, $J_{CH3,H6}$ = 1.2 Hz, 1H) H6; 6.65 (*dd*, $J_{Ha,Hb}$ = 2.9 Hz, $J_{Hb,Hc}$ = 5.7 Hz, 1H) H_b; 6.41 (*dd*, $J_{Hc,Hd}$ = 3.6 Hz, 1H) H_c; 5.76 (*d*, $J_{1',2'}$ = 6.1 Hz, 1H) H1'; 3.95-3.62 (*m*, 5H) H5', H5'', H4', H_d and H2'; 3.13 (*m*, 1H) H_a; 2.1 (*m*, 1H) $H_{e'}$; 1.98 (*d*, 3H) 5-Me; 1.73 (*m*, 1H) $H_{e''}$. ^{13}C-NMR ($CDCl_3$ + CD_3OD): 164.1 (*s*) C4; 150.5 (*s*) C2; 139.5, 135.4 C_b, C_c and C6; 111.6 (*s*) C5; 108.5 (*s*) C3'; 85.3 (*d*, J_{CH} = 171.4 Hz) C1'; 83.0 (*d*, J_{CH} = 154.0 Hz) C4'; 61.9 (*d*, J_{CH} = 144.8 Hz) C2'; 60.4 (*t*, J_{CH} = 142.0 Hz) C5'; 52.9 (*t*, J_{CH} = 137.0 Hz) C_e; 49.0 (*d*, J_{CH} = 152.3 Hz) C_d; 43.4 (*d*, J_{CH} = 153.0 Hz) C_a; 12.1 (*q*, J_{CH} = 129.2 Hz) 5-Me. MS (FAB$^-$): calc. for $[(C_{15}H_{17}N_3O_6)-H]^-$ 334.1039, found 334.1050.

Compound 6. *General procedure for radical reaction:* Compound **2** (250 mg, 0.41 mmol) was dissolved in toluene (16 mL), azobisisobutyronitrile(AIBN) (33 mg, 0.2 mmol) was added, followed by tributyltin hydride (330 µL, 1.23 mmol). The reaction mixture was sealed with a stopper and kept at 105 °C for 3 h. The solvent was removed in vacuo and the residue was purified by flash chromatography to give **6** (109 mg, 45 %) and **8** (30 mg, 13 %). Compound **6**, ^{1}H-NMR (500 MHz, $CDCl_3$) 8.36 (br, *s*, 1H) NH; 7.62 (*d*, $J_{CH3,\ H6}$ = 1.2 Hz, 1H) H6; 7.41-6.81 (*m*, 14 H) arom; 6.23 (*d*, $J_{1',2'}$ = 6.4 Hz, 1H) H1'; 5.99 (*ddd*, $J_{Hc,Hd}$ = 5.7 Hz, $J_{Hb',Hc}$ = 2.2 Hz, $J_{Hb'',Hc}$ = 2.3 Hz, 1H) H_c; 5.89 (*m*, $J_{Hb',Hd}$ = 2.2 Hz, $J_{Hb'',Hd}$ = 2.2 Hz, $J_{Hd,He}$ = 2.2 Hz, 1H) H_d; 5.24 (*m*, $J_{Ha,He}$ = 8.6 Hz, $J_{Hb'',He}$ = 2.3 Hz, 1H) H_e; 4.74 (*m*, 1H) H4'; 3.79 (s, 3H) MMTr; 3.67 (*dd*, $J_{4',\ 5'}$ = 3.3 Hz, 1H) H5'; 3.54 (*m*, $J_{Ha,Hb'}$ = 8.4 Hz, $J_{Ha,Hb''}$ = 5.9 Hz, 1H) H_a; 3.46 (*dd*, $J_{4',5''}$ = 2.2 Hz, $J_{5',5''}$ = 10.6 Hz, 1H) H5''; 2.96 (*ddd*, $J_{2',4'}$ = 2.0 Hz, $J_{2',Ha}$ = 7.4 Hz, 1H) H2'; 2.68 (*m*, $J_{Hb',Hb''}$ = 17.1 Hz, 1H) $H_{b'}$; 2.25 (*m*, 1H) $H_{b''}$; 1.35 (*d*, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$): 163.4 (*s*) C4; 150.4 (*s*) C2; 136.0 (*d*, J_{CH} = 165.9 Hz), 130.2 (*d*) C_b and C_c; 134.9 (*d*, J_{CH} = 191.5 Hz) C6; 111.9 (*s*) C5; 87.3 (*d*, J_{CH} = 173.2 Hz) C1'; 87.1 (*s*) MMTr; 83.0 (*d*, J_{CH} = 155.8 Hz) C_e; 79.3 (*d*, J_{CH} = 153.0 Hz) C4'; 64.0 (*t*, J_{CH} = 144.8 Hz) C5'; 55.1 (*q*, J_{CH} = 143.8 Hz) MMTr;

42.5 (*d*, J_{CH} = 134.7 Hz) C2'; 37.9 (*d*, J_{CH} = 144.8 Hz) C_a; 35.0 (*t*, J_{CH} = 134.3 Hz) C_b; 11.5 (*q*, J_{CH} = 130.5 Hz) 5-Me. MS (FAB^-): calc. for $[(C_{35}H_{33}N_3O_6)-H]^-$ 590.2291, found 590.2285. UV (EtOH): [pH 7] λ_{max} = 265 nm (ε = 10400); [pH 2] λ_{max} = 264 nm (ε = 10600); [pH 12] λ_{max} = 270 nm (ε = 10000).

Compound 7. Compound **6** (70 mg, 0.11 mmol) was treated with 80 % aqueous acetic acid (2 mL) at RT for 3 h. The solvent was removed in vacuo, co-evaporated with toluene and methanol. The residue was purified by flash chromatography to give **7** (23 mg, 61 %). ^{1}H-NMR (270 MHz, $CDCl_3$): 8.35 (br, 1H) NH; 7.62 (*d*, $J_{CH3,H6}$ = 1.2 Hz, 1H) H6; 6.2 (*d*, $J_{1',2'}$ = 6.4 Hz, 1H) H1'; 6.0 (*m*, 1H) H_c 5.86 (*m*, 1H) H_d; 5.19 (*m*, $J_{Ha,He}$ = 8.6 Hz, $J_{Hb'',He}$ = 2.3 Hz, 1H) H_e; 4.67 (*m*, 1H) H4'; 4.06 (*m*, 2H) H5', 5''; 3.46 (*m*, 1H) H_a; 2.84 (*ddd*, $J_{2',4'}$ = 2.0 Hz, $J_{2',Ha}$ = 7.3 Hz, 1H) H2'; 2.66 (*m*, 1H) $H_{b'}$; 2.23 (*m*, 1H) $H_{b''}$; 1.94 (*d*, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$): 136.0 (*d*, J_{CH} = 168.6 Hz), 135.0 (*d*, J_{CH} = 181.4 Hz), 130.0 (*d*, J_{CH} = 170.4 Hz); C_c, C_d and C6; 111.8 (*s*) C5; 87.4 (*d*, J_{CH} = 168.6 Hz) C1'; 83.4 (*d*, J_{CH} = 166.8 Hz) C_e; 80.3 (*d*, J_{CH} = 152.1 Hz) C4'; 63.0 (*t*, J_{CH} = 145.2 Hz) C5'; 42.4 (*d*, J_{CH} = 133.8 Hz) C2'; 38.0 (*d*, J_{CH} = 136.5 Hz) C_a, 34.9 (*t*) C_b; 12.5 (*q*, J_{CH} = 129.5 Hz) 5-Me. MS (FAB^-): calc. for $[(C_{15}H_{17}N_3O_5)-H]^-$ 318.1090, found 318.1084.

1-[5-*O*-(MMTr)-2,3-dideoxy-2,3-*C*-(*endo*-2-cyclopentene-1,4-yl)-β-D-*ribo*furanosyl]thymine (8). ^{1}H-NMR (270 MHz, $CDCl_3$): 8.0 (br, 1H) NH; 7.49-6.81 (*m*, 15 H) arom and H6; 6.14 (*m*, 2H) H_b and H_c; 5.82 (*d*, $J_{1',2'}$ = 4.7 Hz, 1H) H1'; 3.89 (*m*, 1H) H4'; 3.79 (*s*, 3H) MMTr; 3.37 (*dd*, $J_{4',5'}$ = 3.4 Hz, 1H) H5'; 3.27 (*dd*, $J_{4',5''}$ = 4.7 Hz, $J_{5',5''}$ = 10.1 Hz, 1H) H5''; 3.06 (*m*, 1H) H_a; 2.65 (*m*, 1H) H_d; 2.48 (*m*, 1H) H3'; 2.31 (*m*, 1H) H2'; 1.67 (*m*, 2H) $H_{e'}$, $H_{e''}$; 1.55 (*d*, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$): 161.1 (*s*) C4; 150.3 (*s*) C2; 135.1 (*d*, J_{CH} = 178.7 Hz) C6; 110.9 (*s*) C5; 88.9 (*d*, J_{CH} = 166.8 Hz) C1'; 86.5 (*s*) MMTr; 83.8 (*d*, J_{CH} = 146.6 Hz) C4'; 65.2 (*t*, J_{CH} = 142.0 Hz) C5'; 55.6 (*d*, J_{CH} = 143.9 Hz) C2'; 55.0 (*q*, J_{CH} = 143.6 Hz) MMTr; 49.8 (*d*, J_{CH} = 143.9 Hz) C3'; 45.2 (*d*, J_{CH} = 150.3 Hz) C_a; 44.7 (*d*, J_{CH} = 159.4 Hz) C_d; 43.2 (*t*, J_{CH} = 136.5 Hz) C_e; 11.8 (*q*, J_{CH} = 129.2 Hz) 5-Me. UV (EtOH): [pH 7] λ_{max} = 266 nm (ε = 6700); [pH 2] λ_{max} = 266 nm (ε = 6700); [pH 12] λ_{max} = 266 nm (ε = 6600).

1-[2,3-dideoxy-2,3-*C*-(*endo*-2-cyclopentene-1,4-yl)-β-D-*ribo*furanosyl]thymine (9). Compound **8** (20 mg, 0.03 mmol) was treated with 80 % aqueous acetic acid (1 mL) at RT overnight. The solvent was removed in vacuo, co-evaporated with toluene and methanol. The residue was purified by flash chromatography to give **9** (9.5 mg, 92 %). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.36 (*d*, $J_{CH3,H6}$ = 1.2 Hz, 1H) H6; 6.16 (*dd*, $J_{Hb,Hc}$ = 5.7 Hz, $J_{Hc,Hd}$ = 2.9 Hz, 1H) H_c; 6.15 (*dd*, $J_{Ha,Hb}$ = 3.0 Hz, 1H) H_b; 5.73 (*d*, $J_{1',2'}$ = 4.7 Hz, 1H) H1'; 3.88 (*dd*, $J_{4',5'}$ = 2.9 Hz, $J_{5',5''}$ = 11.6 Hz, 1H) H5'; 3.85 (*m*, $J_{3',4'}$ = 5.9 Hz, 1H) H4'; 3.72 (*dd*, $J_{4',5''}$ = 4.5 Hz, 1H) H5''; 3.0 (*m*, 1H) H_a; 2.73 (*m*, 1H) H_d; 2.52 (*m*, $J_{2',3'}$ = 8.9 Hz, $J_{3',Hd}$ = 0.8 Hz, $J_{3',He'}$ = 1.7 Hz, 1H) H3'; 2.42 (*dddd*, $J_{2',He'}$ = 1.7 Hz, $J_{2',Ha}$ = 0.9 Hz, 1H) H2'; 1.91 (*d*, 3H) 5-Me; 1.70 (*m*, 1H) $H_{e''}$; 1.65 (*m*, $J_{He',He''}$ = 9.6 Hz, 1H) He'. ^{13}C-NMR ($CDCl_3$): 137.7, 137.4 (2 x d, J_{CH} = 174.1, 172.3 Hz) C_b and C_c; 136.5 (*d*, J_{CH} = 188.8 Hz) C6; 110.9 (*s*) C5; 90 (*d*, J_{CH} = 165 Hz) C1'; 85.1 (*d*, J_{CH} = 147.5 Hz) C4'; 64.3 (*t*, J_{CH} = 142 Hz) C5'; 55 (*d*, J_{CH} = 144.8 Hz) C2'; 48.9 (*d*, J_{CH} = 143.9 Hz) C3'; 45.2, 44.8 (2 x d, J_{CH} = 151.2, 148.5 Hz) C_a and C_d; 43.2 (*t*, J_{CH} = 133.8 Hz) C_e; 12.5 (*q*, J_{CH} = 128.3 Hz) 5-Me. MS (FAB^-): calc. for $[(C_{15}H_{18}N_2O_4)-H]^-$ 289.1188, found 289.1205. UV (EtOH): [pH 7] λ_{max} = 267 nm (ε = 9300); [pH 2] λ_{max} = 266 nm (ε = 9300); [pH 12] λ_{max} = 267 nm (ε = 8100).

1-[5-*O*-(MMTr)-2,3-dideoxy-2,3-*C*-(*exo*-2-cyclopentene-1,4-yl)-β-D-*ribo*furanosyl]thymine (10). Compound **4** (80 mg, 0.13 mmol) was treated with tributyltin hydride (105 µL, 0.39 mmol) and AIBN (21 mg, 0,13 mmol) in benzene (2 mL) at 70 °C for 40 h. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give **10** (10 mg, 14 %). ^{1}H NMR (500 MHz, $CDCl_3$): 8.33 (br, 1H) NH; 7.47 (d) H6; 7.46-6.83 (*m*, 14 H) arom; 6.44 (*dd*, $J_{Ha,Hb}$ = 3.0 Hz, $J_{Hb,Hc}$ = 5.7 Hz, 1H) H_b; 6.29 (*dd*, $J_{Hc,Hd}$ = 3.0 Hz, 1H) H_c; 5.55 (*d*, $J_{1',2'}$ = 4.5 Hz, 1H) H1'; 3.79 (*s*, 3H) MMTr; 3.76 (*m*, $J_{3',4'}$ = 5.6 Hz, 1H) H4'; 3.29 (*dd*, $J_{4',5'}$ = 3.9 Hz, $J_{5',5''}$ = 10.2 Hz, 1H) H5'; 3.24 (*dd*, $J_{4',5''}$ = 5.1 Hz, 1H) H5''; 3.12 (*m*, 1H) H_a; 3.09 (*ddd*, $J_{2',3'}$ = 9.9 Hz, $J_{H3',Hd}$ = 3.9 Hz, 1H) H3'; 3.01 (*ddd*, $J_{H2',Ha}$ = 6.0 Hz, 1H) H2'; 2.85 (*m*, 1H) H_d; 1.71 (*ddd*, $J_{Hd,He'}$ = 1.7 Hz, $J_{Ha,He'}$ = 1.7 Hz, 1H) $H_{e'}$; 1.57 (*d*, $J_{CH3,H6}$ = 1.2 Hz, 3H) 5-Me; 1.53 (*ddd*, $J_{He',He''}$ = 8.5 Hz, $J_{Ha,He''}$ = 1.5 Hz, $J_{Hd,He''}$ = 1.5 Hz, 1H) $H_{e''}$. ^{13}C NMR ($CDCl_3$): 163.5 (*s*) C4; 150.0 (*s*) C2; 110.4 (*s*) C5; 88.6 (*d*, J_{CH} = 167.7 Hz) C1'; 86.5 (*s*) MMTr; 83.3 (*d*, J_{CH} = 147.5 Hz) C4'; 65.5 (*t*, J_{CH} = 141.6 Hz) C5'; 56.8 (*d*, J_{CH} = 139.3 Hz) C2'; 55.1 (*q*) MMTr; 53.1 (*t*, J_{CH} = 134.3 Hz) C_e; 51.0 (*d*, JCH = 143.9 Hz) C3'; 45.0, 44.7 (2 x d) C_a and C_d; 11.9 (*q*, J_{CH} = 128.9 Hz) 5-Me.

1-[5-*O*-(MMTr)-2,3-dideoxy-3-nitro-2,3-*C*-(*endo*-1,4-dihydrofuran-1,4-yl)-β-D-*ribo*furanosyl]thymine (11). Compound **1** (540 mg, 1 mmol) was dissolved in toluene (5 mL), furan (5 mL) was added, and the reraction mixture was kept at 70 °C for 48 h.. The solvent was removed in vacuo and the residue was purified by flash chromatography to give **11** (220 mg, 68 %) and 250 mg of compound **1** was recovered. ^{1}H-NMR (500 MHz, $CDCl_3$): 9.94 (br, 1H) NH; 7.55 (*d*, $J_{CH3,H6}$ = 1.1 Hz, 1H) H6; 7.48-6.8 (*m*, 14 H) arom; 6.61 (*dd*, $J_{Ha,Hb}$ = 1.7 Hz, $J_{Hb,Hc}$ = 5.8 Hz, 1H) H_b; 6.50 (*dd*, $J_{Hc,Hd}$ = 1.7 Hz, 1H) H_c; 6.08 (*d*, $J_{1',2'}$ = 5.6 Hz, 1H) H1'; 5.19 (*d*,

1H) H_a; 5.04 (*d*, 1H) H_d; 4.16 (*dd*, 1H) H4'; 3.80 (*s*, 3H) MMTr; 3.55 (*dd*, $J_{4',5'}$ = 4.9 Hz, 1H) H5'; 3.39 (*dd*, $J_{4',5''}$ = 6.0 Hz, $J_{5',5''}$ = 10.8 Hz, 1H) H5''; 2.98 (*d*, 1H) H2'; 1.9 (*d*, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$): 163.7 (*s*) C4; 150.4 (*s*) C2; 138.6 (d) C_c, 134.8 (d) C_b, 134.5 (d) C6; 112.1 (*s*) C5; 104.4 (*s*) C3'; 87.5 (s) MMTr; 85.5 (*d*, J_{CH} = 168.6 Hz) C1'; 82.1 (*d*, J_{CH} = 154.0 Hz) C4'; 81.6 (*d*, J_{CH} = 171.4 Hz) C_a; 80.0 (*d*, J_{CH} = 174.1 Hz) C_d; 61.1 (*t*, J_{CH} = 144.8 Hz) C5'; 60.8 (*d*, J_{CH} = 145.7 Hz) C2'; 12.4 (*q*, J_{CH} = 128.6 Hz) 5-Me. UV (EtOH): [pH 7] λ_{max} = 264 nm (ε = 9900); [pH 2] λ_{max} = 264 nm (ε = 10100); [pH 12] λ_{max} = 264 nm (ε = 9900).

1-[2,3-dideoxy-3-nitro-2,3-*C*-(*endo*--1,4-dihydrofuran-1,4-yl)-β-D-*ribo*furanosyl]thymine (12). Compound **11** (60 mg, 0.1 mmol) was treated with 80 % aqueous acetic acid (2 mL) at RT overnight. The solvent was removed in vacuo and was co-evaporated with toluene and methanol. The residue was purified by flash chromatography to give **12** (31 mg, 94 %). ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD): 7.6 (*d*, $J_{CH3,\ H6}$ = 1.1 Hz, 1H) H6; 6.66 (*dd*, $J_{Hb,Hd}$ = 1.7 Hz, $J_{Hb,Hc}$ = 5.9 Hz, 1H) H_b; 6.51 (*dd*, $J_{Ha,Hc}$ = 1.5 Hz, 1H) H_c; 6.11 (*d*, $J_{1',2'}$ = 5.7 Hz, 1H) H1'; 5.20 (*d*, 1H) H_a; 5.15 (*d*, 1H) H_d; 4.25 (*t*, 1H) H4'; 3.89 (*dd*, $J_{4',5'}$ = 5.2 Hz, $J_{5',5''}$ = 12.0 Hz, 1H) H5'; 3.79 (*dd*, $J_{4',5''}$ = 5.3 Hz, 1H) H5''; 3.06 (*d*, 1H) H2'; 1.96 (*d*, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$ + CD_3OD): 164.0 (*s*) C4; 150.5 (*s*) C2; 138.6, 135.0, 134.6 (3 x d, J_{CH} = 180.5, 181.5, 183.3 Hz) C6, C_b and C_c; 112.0 (*s*) C5; 104.4 (*s*) C3'; 85.3 (*d*, J_{CH} = 167.7 Hz) C1'; 83.0 (*d*, J_{CH} = 153.0 Hz) C4'; 81.4 (*d*, J_{CH} = 173.2 Hz) C_a; 80.0 (*d*, J_{CH} = 175.9 Hz) C_d; 60.3 (*t*, J_{CH} = 143.0 Hz) C5'; 59.6 (*d*, J_{CH} = 143.9 Hz) C2'; 12.2 (*q*, J_{CH} = 128.9 Hz) 5-Me. MS (FAB$^-$): calc. for $[(C_{14}H_{15}N_3O_7)\text{-}H]^-$ 336.0832, found 336.0847. UV (EtOH): [pH 7] λ_{max} = 264 nm (ε = 6500); [pH 2] λ_{max} = 264 nm (ε = 6400); [pH 12] λ_{max} = 263 nm (ε = 5700).

1-[5-*O*-(MMTr)-2,3-dideoxy-3-nitro-2,3-*C*-(9,10-dihydroanthracene-9,10-yl)-β-D-*ribo*furanosyl]thymine (13). Compound **1** (540 mg, 1 mmol) was dissolved in toluene (12 mL) and anthracene (600 mg, 3.4 mmol) was added to the reaction mixture which was kept at 105 °C for 90 h. The solvent was removed in vacuo and the residue was purified by flash chromatography to give **13** (410 mg, 57 %). ^{1}H-NMR (270 MHz, $CDCl_3$): 8.73 (br, 1H) NH; 7.58-6.83 (*m*, 23 H) arom and H6; 5.68 (*d*, $J_{1',2'}$ = 6.6 Hz, 1H) H1'; 5.11 (*s*, 1H) H_d; 4.45 (*d*, $J_{2',Ha}$ = 3.2 Hz, 1H) H_a; 3.81 (*s*, 3H) MMTr; 3.7 (*t*, 1H) H4'; 3.49 (*dd*, 1H) H2'; 3.34 (*dd*, $J_{4',5'}$ = 5.3 Hz, 1H) H5'; 3.2 (*dd*, $J_{4',5''}$ = 5.9 Hz, $J_{5',5''}$ = 10.5 Hz, 1H) H5''; 1.88 (*d*, $J_{CH3,H6}$ = 1.2 Hz, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$): 163.9 (*s*) C4; 150.8 (*s*) C2; 135 (d) C6; 111.9 (*s*) C5; 104 (*s*) C3'; 87.3 (*s*) MMTr; 84.6 (*d*, J_{CH} = 168.6 Hz) C1'; 80.6 (*d*, J_{CH} = 152.1 Hz) C4'; 61.8 (*t*, J_{CH} = 145.5 Hz) C5'; 59.3 (*d*, J_{CH} = 142.0 Hz) C2'; 54.9 (*q*, J_{CH} = 143.8 Hz) MMTr; 48.7 (*d*, J_{CH} = 146.6 Hz) C_d; 44.5 (*d*, J_{CH} = 138.4 Hz) C_a; 12.3 (*q*, J_{CH} = 128.6 Hz) 5-Me. UV (EtOH): [pH 7] λ_{max} = 264 nm (ε = 13800); [pH 2] λ_{max} = 264 nm (ε = 13800); [pH 12] λ_{max} = 264 nm (ε = 12500).

1-[2,3-dideoxy-3-nitro-2,3-*C*-(9,10-dihydroanthracene-9,10-yl)-β-D-*ribo*furanosyl]thymine (14). Compound **13** (120 mg, 0.16 mmol) was treated with 80 % aqueous acetic acid (3 mL) at RT overnight. After usual work up the residue was purified by flash chromatography to give **14** (70 mg, 91 %). ^{1}H-NMR (500 MHz, $CDCl_3$): 8.81 (br, 1H) NH; 7.58-7.11 (*m*, 8H) arom; 7.52 (*d*, $J_{CH3,H6}$ = 1.2 Hz, 1H) H6; 5.69 (*d*, $J_{1',2'}$ = 6.7 Hz, 1H) H1'; 5.11 (*s*, 1H) H_d; 4.45 (*d*, $J_{2',Ha}$ = 3.2 Hz, 1H) H_a; 3.81 (*s*, 3H) MMTr; 3.74 (*m*, 2H) H5', H5''; 3.67 (*dd*, $J_{4',5'}$ = 5.2 Hz, $J_{4',5''}$ = 6.1 Hz, 1H) H4'; 3.59 (*dd*, 1H) H2'; 1.94 (*d*, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$): 163.9 (*s*) C4; 150.7 (*s*) C2; 135.1 (*d*, J_{CH} = 185.1 Hz) C6; 112.2 (*s*) C5; 104.2 (*s*) C3'; 84.6 (*d*, J_{CH} = 165 Hz) C1'; 81.5 (*d*, J_{CH} = 152.2 Hz) C4'; 60.8 (*t*, J_{CH} = 143.9 Hz) C5'; 59 (*d*, J_{CH} = 143 Hz) C2'; 48.8 (*d*, J_{CH} = 142 Hz) C_d; 44.5 (*d*, J_{CH} = 142 Hz) C_a; 12.5 (*q*, J_{CH} = 129.8 Hz) 5-Me. MS (FAB$^-$): calc. for $[(C_{24}H_{21}N_3O_6)\text{-}H]^-$ 446.1352, found 446.1370. UV (EtOH): [pH 7] λ_{max} = 264 nm (ε = 6500); [pH 2] λ_{max} = 263 nm (ε = 6500); [pH 12] λ_{max} = 264 nm (ε = 5700).

1-[5-*O*-(MMTr)-2,3-dideoxy-2,3-*C*-(9,10-dihydroanthracene-9,10-yl)-β-D-*ribo*furanosyl]thymine (15). Compound **13** (200 mg, 0.28 mmol) was dissolved in toluene (12 mL), AIBN (23 mg, 0.14 mmol) was added, followed by tributyltin hydride (226 µL, 0.84 mmol) and the reaction mixture was kept at 105 °C for 30 min. The solvent was removed in vacuo and the residue was purified by flash chromatography to give **15** (170 mg, 91 %). ^{1}H-NMR (270 MHz, $CDCl_3$): 8.37 (br, 1H) NH; 7.53-6.82 (*m*, 23 H) arom and H6; 5.5 (*d*, $J_{1',2'}$ = 5.9 Hz, 1H) H1'; 4.48 (*d*, $J_{2',Ha}$ = 3 Hz, 1H) H_a; 4.05 (*d*, $J_{3',Hd}$ = 2.8 Hz, 1H) H_d; 3.8 (*s*, 3H) MMTr; 3.53 (*m*, 1H) H4'; 3.39 (*dd*, $J_{4',5'}$ = 3.6 Hz, 1H) H5'; 3.3 (*dd*, $J_{4',5''}$ = 4.4 Hz, $J_{5',5''}$ = 10.0 Hz, 1H) H5''; 2.91 (*ddd*, $J_{3',4'}$ = 7.4 Hz, 1H) H3'; 2.71 (*ddd*, $J_{2',3'}$ = 11.4 Hz, 1H) H2'; 1.65 (*d*, $J_{CH3,\ H6}$ = 1.2 Hz, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$): 164.1 (*s*) C4; 150.7 (*s*) C2; 111 (*s*) C5; 86.8 (*s*) MMTr; 86.6 (*d*, J_{CH} = 168.6 Hz) C1'; 80.7 (*d*, J_{CH} = 149 Hz) C4'; 64.3 (*t*, J_{CH} = 142 Hz) C5'; 55 (*q*, J_{CH} = 143.6 Hz) MMTr; 54 (*d*, J_{CH} = 141.1 Hz) C2'; 48.6 (*d*, J_{CH} = 137.5 Hz) C3'; 46 (*d*, J_{CH} = 139.3 Hz) C_d; 45 (*d*, J_{CH} = 139.5 Hz) C_a; 12 (*q*, J_{CH} = 129.5 Hz) 5-Me. UV (EtOH): [pH 7] λ_{max} = 269, 265 nm (ε = 12400, 11800); [pH 2] λ_{max} = 269, 265 nm (ε = 12800, 12600); [pH 12] λ_{max} = 269, 265 nm (ε = 11200, 11000).

1-[2,3-dideoxy-2,3-*C*-(9,10-dihydroanthracene-9,10-yl)-β-D-*ribo*furanosyl]thymine (16). Compound **15** (130 mg, 0.19 mmol) was treated with 80 % aqueous acetic acid (3 mL) at RT overnight. The solvent was removed in vacuo, co-evaporated with toluene and methanol. The residue was purified by flash chromatography to give **16** (70 mg, 91 %). ^{1}H-NMR (500 MHz, $CDCl_3$): 9.14 (br, 1H) NH; 7.51 (*d*, $J_{CH3,\ H6}$ = 1.1 Hz, 1H) H6; 7.49-7.02 (*m*, 8H) arom; 5.41 (*d*, $J_{1',2'}$ = 6.1 Hz, 1H) H1'; 4.41 (*d*, $J_{2',Ha}$ = 3.0 Hz, 1H) H_a; 4.15 (*d*, $J_{3',\ Hd}$ = 3.0 Hz, 1H) H_d, 3.86 (*dd*, $J_{4',5'}$ = 2.8 Hz,$J_{5',5''}$ = 12.0 Hz, 1H) H5', 3.74 (*dd*, $J_{4',5''}$ = 4.5 Hz, 1H) 5"; 3.48 (*m*, 1H) H4'; 2.95 (*ddd*, $J_{3',\ 4'}$ = 7.5 Hz, $J_{2',3'}$ = 11.3 Hz,1H) H3'; 2.79 (*ddd*, 1H) H2'; 1.86 (*d*, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$): 164 (*s*) C4; 150.5 (*s*) C2; 136.1 (*d*, J_{CH} = 176.9 Hz) C6; 111 (*s*) C5; 87.6 (*d*, J_{CH} = 165 Hz) C1'; 82.1 (*d*, J_{CH} = 143 Hz) C4'; 63 (*t*, J_{CH} = 142 Hz) C5'; 53.5 (*d*, J_{CH} = 143 Hz) C2'; 47.5 (*d*, J_{CH} = 143 Hz)C3'; 45.9 (*d*, J_{CH} = 138.4 Hz) C_d; 45 (*d*, J_{CH} = 144 Hz) C_a; 12.3 (*q*, J_{CH} = 129.5 Hz) 5-Me. MS (FAB$^-$): calc. for [($C_{24}H_{22}N_2O_4$)-H]$^-$ 401.1501, found 401.1489. UV (EtOH): [pH 7] λ_{max} = 267, 264 nm (ε = 9500, 9400); [pH 2] λ_{max} = 267, 263 nm (ε = 9400, 9300); [pH 12] λ_{max} = 267, 264 nm (ε = 7500, 7400).

1-[5-*O*-(MMTr)-2,3-dideoxy-3-nitro-2-(cyclohexanonyl)-β-D-*xylo*furanosyl]thymine (17). Compound **17**[2a] is an inseparable mixture of two diasteriomers (7 : 3 ratio from 500 MHz ^{1}H NMR). ^{1}H NMR (500 MHz, $CDCl_3$): 9.16 (br, *s*, 1H) NH; 7.63 (d) H6(minor); 7.61 (d) H6 (major); 7.40-6.80 (*m*, 14 H) arom; 6.14 (*d*, $J_{1',2'}$ = 6.8 Hz) H1' (minor); 6.13 (*d*, $J_{1',2'}$ = 6.8 Hz) H1' (major); 5.0 (*dd*, $J_{2',3'}$ = 3.2 Hz, $J_{3',4'}$ = 6.2 Hz) H3' (major); 4.95 (*dd*, $J_{2',3'}$ = 3.5 Hz, $J_{3',4'}$ = 6.1 Hz) H3' (minor); 4.61 (m) H4' (major); 4.32 (m) H4' (minor); 3.80 (s) MMTr; 3.51 (*dd*, $J_{4',5'}$ = 5.8 Hz, $J_{5',5''}$ = 10.5 Hz) H5' (minor); 3.50 (*dd*, $J_{4',5'}$ = 5.8 Hz, $J_{5',5''}$ = 10.3 Hz) H-5' (major); 3.33 (*dd*, $J_{4',5'}$ = 5.7 Hz) H5" (minor); 3.31 (*dd*, $J_{4',5''}$ = 6.0 Hz) H5" (major); 3.13 (*m* $J_{2',Ha}$ = 4.0 Hz) H2' (minor); 2.88 (*m*, $J_{Ha,Hb'}$ = 5.1Hz, $J_{Ha,Hb''}$ = 13.2 Hz) H_f (minor); 2.82 (*m*) H2' and H_a (major), 2.45, 2.41 (2 x *m*) H_e; 2.15, 2.12 (2 x *m*) $H_{b'}$ and $H_{d'}$; 1.93 (*d*, $J_{CH3,H6}$ = 1.2 Hz) 5-Me. (major);1.91 (d) 5-Me. (minor); 1.91 (*m*) Hd"; 1.69, 1.67 (2 x *m*) Hc' and Hc"; 1.45 (*m*) Hb". IR ($CHCl_3$): 1680 cm^{-1}.

Compound 18. Compound **17** (150 mg, 0.23 mmol) was dissolved in benzene (10 mL), AIBN (38 mg, 0.23 mmol) was added followed by tributyltin hydride (188 μL, 0.7 mmol) and it was kept at 70 °C overnight. The solvent was removed in vacuo and the residue was purified by flash chromatography to give a mixture of diastereomers (~7 : 3 ratio from ^{1}H NMR spectroscopy), **18** (50 mg, 34 %) and **20** (77 mg, 55 %). Compound **18**, ^{1}H-NMR (500 MHz, $CDCl_3$): 8.72 (br) NH (minor); 8.68 (br, 1H) NH (major); 7.67 (*d*, $J_{CH3,\ H6}$ = 1.2 Hz) H6 (minor); 7.66 (*d*, $J_{CH3,H6}$ = 1.2 Hz) H6 (major); 7.48-6.78 (*m*, 14 H) arom; 6.25 (*d*, $J_{1',2'}$ = 9.3 Hz, 1H) H1' (minor); 6.10 (*d*, $J_{1',2'}$ = 8.9 Hz) H1'(major); 4.65 (*m*, 1H) H4'; 3.79 (*s*, 3H) MMTr; 3.64 (*dd*, $J_{4',5'}$ = 2.1 Hz) H5'(minor); 3.62 (*dd*, $J_{4',5'}$ = 2.0 Hz, $J_{5',5''}$ = 10.3 Hz, 1H) H5' (major); 3.34 (*dd*, $J_{4',5''}$ = 1.7 Hz, 1H) H5"; 3.16 (*m*, $J_{2',Ha}$ = 11.6 Hz, 1H) H2'; 2.69 (br, *s*) O<u>H</u> at C_f; 2.0-1.6 (*m*, 9H) C<u>H</u>C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$; 1.55 (*d*, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$): 163.5 (*s*) C4; 150.2 (*s*) C2; 112.2 (*s*) C5; 95.0 (*s*) C_f; 87.3 (*s*) MMTr; 86 (*d*, J_{CH} = 173 Hz) C1'; 77.5 (*d*, J_{CH} = 152.8 Hz) C4'; 65.4 (*t*, J_{CH} = 143.8 Hz) C5'; 55.2 (*q*, J_{CH} = 143.8 Hz) MMTr; 40.9 (*d*, J_{CH} = 134.8 Hz) C2'; 37.1 (*d*, J_{CH} = 131.4 Hz) C_a; 35.4, 26.5, 24.9, 22.6 (4 x *t*) C<u>H</u>C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$; 11.2 (*q*, J_{CH} = 128.8 Hz) 5-Me. MS (FAB$^-$): calc. for [($C_{36}H_{37}N_3O_7$)-H]$^-$ 622.2553, found 622.2572. UV (EtOH): [pH 7] λ_{max} = 265 nm (ε = 10800); [pH 2] λ_{max} = 264 nm (ε = 10800); [pH 12] λ_{max} = 264 nm (ε = 9100), in IR spectrum no band at 1680 cm^{-1} was observed. Compound **20**,^{1}H NMR (500 MHz, $CDCl_3$) 8.51 (br, 1H) NH; 7.55 (*d*, $J_{CH3,H6}$ = 1.2 Hz, 1H) H6; 7.48-6.83 (*m*, 14 H) arom; 6.05 (*d*, $J_{1',2'}$ = 7.0 Hz, 1H) H1'; 4.28 (*m*, 1H) H4'; 3.78 (*s*, 3H) MMTr; 3.39 (*dd*, $J_{4',5'}$ = 2.9 Hz, $J_{5',5''}$ = 10.3 Hz, 1H) H5'; 3.21 (*dd*, $J_{4',5''}$ = 3.6 Hz, 1H) H5"; 2.68 (*m*, $J_{2',3'}$ = 9.2 Hz, $J_{2',3''}$ = 8.2 Hz, $J_{2',Ha}$ = 7.3 Hz, 1H) H2'; 2.58 (*m*, $J_{Ha,Hb'}$ = 5.3 Hz, $J_{Ha,\ Hb''}$ = 12.2 Hz, 1H) H_a; 2.44 (*m*, $J_{3',4'}$ = 5.8 Hz, 1H) H3'; 2.41 (m) $H_{e'}$, 2.34 (*m*, 1H) $H_{e''}$; 2.19 (*m*, 1H) $H_{b'}$; 2.08 (*m*, 1H) $H_{c'}$; 1.91 (*m*, 1H) $H_{d'}$;1.87 (*m*, 1H) H3"; 1.69 (*m*, 1H) $H_{c''}$; 1.65 (*m*, 1H) $H_{d''}$; 1.52 (*m*, 1H) $H_{b''}$; 1.49 (*d*, 3H) 5-Me. ^{13}C NMR ($CDCl_3$): 211.2 (*s*) <u>C</u>O at C_f; 163.5 (*s*) C4; 150.3 (*s*) C2; 111.1 (*s*) C5; 87.0 (*d*, J_{CH} = 168.5 Hz) C1'; 86.7 (*s*) MMTr; 65.4 (*t*, J_{CH} = 141.5 Hz) C5'; 55.1 (*q*, J_{CH} = 143.8 Hz) MMTr; 52.3 (*d*, J_{CH} = 126.9 Hz) C_a; 43.9 (*d*, J_{CH} = 133.7 Hz) C2'; 31.6 (*t*, J_{CH} = 132.5 Hz) C3'; 42.3, 31.9, 27.9 and 24.9 (4 x *t*) CO<u>C</u>H$_2$<u>C</u>H$_2$<u>C</u>H$_2$<u>C</u>H$_2$; 11.8 (*q*, J_{CH} = 129.2 Hz) 5-Me. MS (FAB$^-$): calc. for [($C_{36}H_{38}N_2O_6$)-H]$^-$ 593.2652, found 593.2632. UV (EtOH): [pH 7] λ_{max} = 266 nm. IR ($CHCl_3$): 1690 cm^{-1}.

Compound 19. Compound **18** (30 mg, 0.05 mmol) was treated with 80 % aqueous acetic acid (1 mL) at RT overnight. The solvent was removed in vacuo, coevaporated with toluene and methanol. The residue was purified by flash chromatography to give **19** (16 mg, 95 %) as an inseparable mixture of two diastereomers in ~ 7 : 3 ratio (^{1}H-NMR). ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD): (Major isomer), 7.89 (*s*, 1H) H6; 6.01 (*d*, $J_{1',2'}$ = 8.7 Hz, 1H) H1'; 4.54 (*m*, 1H) H4'; 3.9 (*m*, 2H) H5',5"; 2.2 (*m*, 1H) H2'; 1.93 (*s*, 3H) 5-Me; 1.85-1.22 (*m*, 9 H) C<u>H</u>C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$. (Minor isomer), 7.83 (*s*, 1H) H6; 6.18 (*d*, $J_{1',2'}$ 8.7 Hz, 1H) H1'; 4.6 (*m*, 1H) H4'; 3.9 (*m*, 2H) H5', 5"; 3.19 (*dd*, $J_{2',4'}$ = 1.3 Hz, 1H) H2'; 1.93 (*s*, 3H) 5-Me; 1.85-1.22 (*m*, 9 H) C<u>H</u>C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$. ^{13}C-NMR ($CDCl_3$ + CD_3OD): 164.6 (*s*) C4; 157.9 (s) C3'; 150.6 (*s*) C2; 135.8 (*d*, J_{CH} = 182.4 Hz) C6; 111.5 (*s*) C5; 94.6 (*s*) C_f; 86.2 (*d*, J_{CH} = 168.3 Hz) C1'; 78.9 (*d*, J_{CH} = 153.0 Hz) C4'; 63.2 (*t*, J_{CH} = 143.9 Hz) C5';

40.2 (*d*, J_{CH} = 137.5 Hz) C2'; 34.3, 26.0, 24.5, 22.3 (4 x *t*) $CH\underline{C}H_2\underline{C}H_2\underline{C}H_2\underline{C}H_2$; 11.7 (*q*, J_{CH} = 129.2 Hz) 5-Me. MS (FAB^-): calc. for $[(C_{16}H_{21}N_3O_6)-H]^-$ 350.1352, found 350.1344.

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29. (a) The molecular models of **2** and **4** were built with the computer program MacroModel V3.5a. The geometries of both **2** and **4** were energy minimised with the generalized all atom AMBER force field parameters using torsion angles derived from $^3J_{1'2'}$ and $^3J_{2',Ha}$ and distance information derived from 1D NOE difference spectra. Upon energy minimization, the conformation of the pentofuranose ring in **2** showed P = 75° and Ψ_m = 19°, $d_{[N\text{-}Cb]}$ = 3.5 Å, and for **4**, it was found to be P = 80° and Ψ_m = 28°, $d_{[N\text{-}Cb]}$ = 4.3 Å. The rotation around C3'-N bond results in the closest distance $d_{[NO\text{-}Cb]}$ of 3.2 Å and 4.7 Å in **2** and **4**, respectively. (b) Still, W. C. *et al.*, MacroModel V3.5a, Columbia University, New York. (c) Mohamadi, F. N.; Richards, G. J.; Guida, W.C. ; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comp. Chem.* **1990**, *11*, 440.
30. ^1H- and ^{13}C-NMR data (see experimental) rule out presence of any corresponding open-chain keto oxime tautomer in any NMR (500 MHz) detectable quantity.