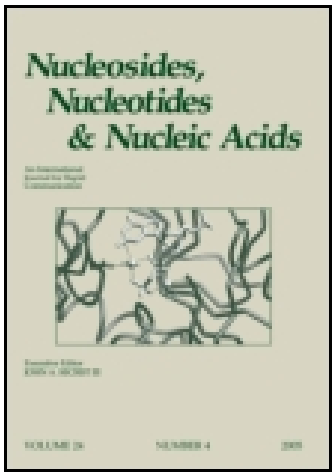

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Synthesis and Antiviral Evaluation of D4T Analogues with a Spacer Arm Between Glucidic and Base Moieties

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Synthesis and Antiviral Evaluation of D4T Analogues with a Spacer Arm Between Glucidic and Base Moieties

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ABSTRACT

The synthesis of a series of d4T analogues bearing an acyclic chains between the sugar and the base moities, is described. New compounds were obtained readily using microwave irradiation and selective deprotection of sugar part. The compounds were characterized by ^{1}H NMR and IR spectroscopy. Antiviral (HIV-1) properties of these compounds were examined.

Key Words: Nucleosides; HIV; Glycosylation; Selective deprotection; Microwave.

INTRODUCTION

2′,3′-didehydro-2′,3′-dideoxythymidine (d4T) is a nucleoside analogue used as a drug according to acquired immunodeficiency syndrome (AIDS). As part of our program to search for new anti-HIV nucleosides, we were interested in the preparation of such analogues where thymine is linked to ribose by an aliphatic chain. It is known

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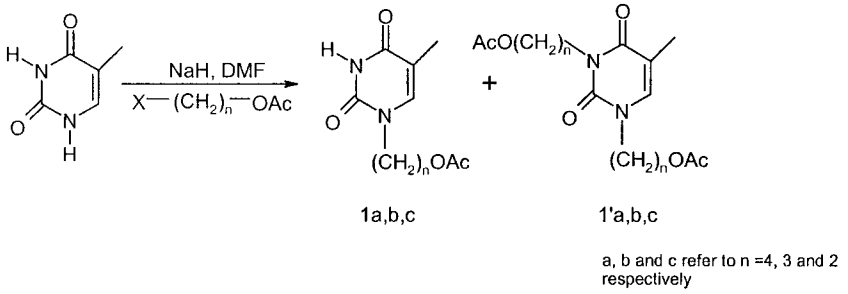


Scheme 1.

that an aliphatic chain not only serves as a neutral linkage but also affects the coiling of DNA. Increasing the length of the spacer arm linkage would thus enhance the bending of DNA, leading to base pair opening where the bases then become susceptible to attack by reactive groups.[1] Spacer arms have also been used in antisense oligomer nucleoside synthesis for preventing the enzymatic degradation of DNA by nucleases.[2] Moreover, a hydrophobic tail was introduced to improve cellular uptake.[3] We prepared a new family of d4T analogues **7a**,**b**,**c** (Scheme 3) to study the influence of the spacer arm and more precisely its length on the biological activities according to human immunodeficiency virus (HIV-1).

RESULTS AND DISCUSSION

General strategy of synthesis is presented on Scheme 3. Compounds **1a**,**b**,**c** were prepared by reaction of thymine with bromobutylacetate for **1a**, chloropropylacetate for **1b** and bromoethylacetate for **1c**.

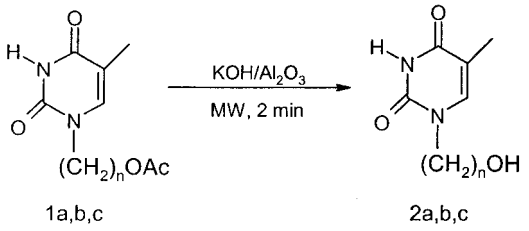
Two methods have been reported for the preparation of *N*-1 substituted thymine. The first includes four steps. Thymine reacts with benzoyl chloride at room temperature to give *N*-1,*N*-3-bis-benzoyl derivative. This compound is then converted in *N*-3 benzoylthymine under basic conditions[4] and, after substitution, the product is debenzoylated to give *N*-1 alkylated thymine.

The other option is the direct alkylation of thymine. This substitution is not regioselective. In addition to *N*-1 alkylation, *N*-2,*N*-3 bis alkylation is also observed (Scheme 1).[5–7]

In a previous work, we proved that, in direct alkylation, an excess of alkylating reagent (bromobutylacetate) in DMF leads to an optimum yield of N-1 monoalkylated thymine (55%).[8] This reaction gave a good yield but involved a longer reaction time (48 h) and high temperature (100°C).

In the present work we have used microwave irradiation to establish a comparison with conventional heating. The microwave heating presents some advantages, such as a remarkable decrease in reaction times and, in some cases, cleaner reactions and a good selectivity.[9]

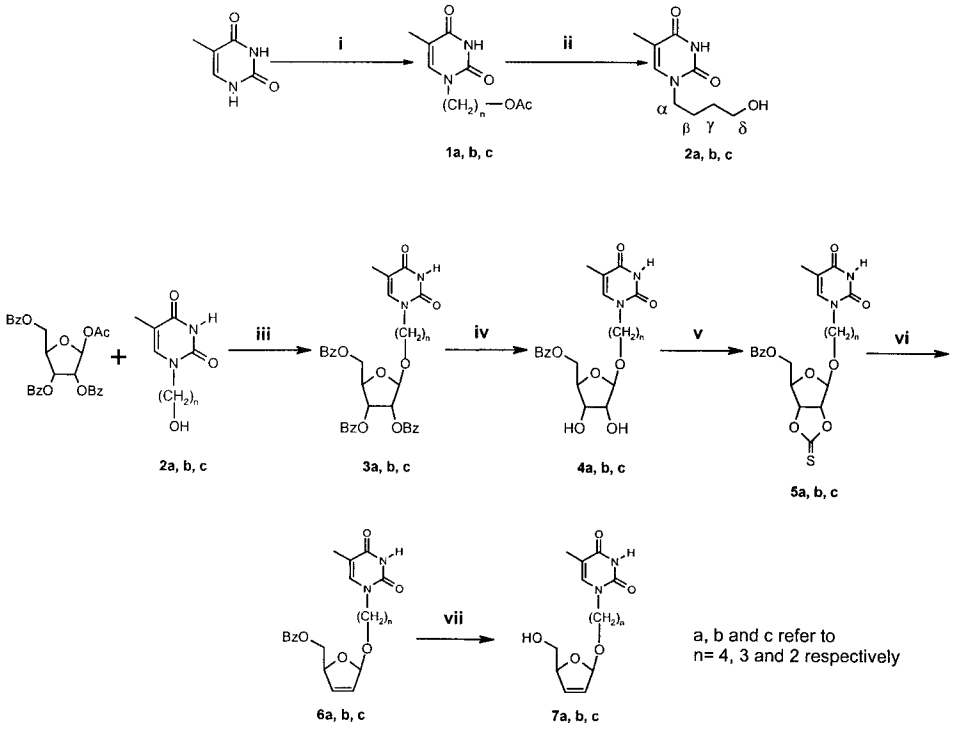
In typical procedure, a solution of thymine with sodium hydride (2 eq) in DMF was irradied 2 min, then bromoalkylacetate or chloropropylacetate (2.3 eq) was added and the mixture irradiated again for 2 min. The results are summarized in Table 1.



Scheme 2.

Saponification of compounds **1a**,**b**,**c** was also achieved under microwave activation (2 min), in dry media, in the presence of an excess of KOH adsorbed on alumina.[10] The deacetylated products **2a**,**b**,**c** were obtained in nearly quantitative yields (96%) (Scheme 2).

The syntheses of **3a**,**b**,**c** were performed by coupling alkylated thymines **2a**,**b**,**c** with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose via Hanessian's procedure[11] (SnCl4/acetonitrile). After purification, compounds **3a**,**b**,**c** were obtained in 69, 77 and 55% yields respectively. Another ratios (β/α = 4) were determined by ^{1}H NMR.



i) NaH, X-$(CH_2)_n$-OAc, DMF. ii) KOH/Al_2O_3, MW. iii) 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose, $SnCl_4$, CH_3CN. iv) NH_3, MeOH. v) $CSCl_2$, CH_2Cl_2, DMAP. vi) $(MeO)_3P$, refluxing. vii) NH_3, MeOH.

Scheme 3.

Table 1. Comparison between conventional heating and microwave activation.

Alkyl halide	Activation	Reaction time	Compound 1	Compound 1′
Br-$(CH_2)_4$-OAc	Δ	48 h	55%	25%
Br-$(CH_2)_4$-OAc	MW	4 min	42%	25%
Cl-$(CH_2)_3$-OAc	Δ	48 h	25%	30%
Cl-$(CH_2)_3$-OAc	MW	4 min	32%	32%
Br-$(CH_2)_2$-OAc	Δ	48 h	21%	26%
Br-$(CH_2)_2$-OAc	MW	4 min	27.7%	24.5%

For the preparation of 2′,3′ unprotected compounds **4a**,**b**,**c**, we found that secondary hydroxyl groups can be efficiently and selectively deprotected using methanolic NH_3. The control amount of NH_3 should be 25 eq per each benzoyl protecting secondary hydroxyl group and a reaction time of 6 hours gives at room temperature unprotected products in acceptable yield. This method achieved at room temperature, requires no particular precaution and implied only an easy work up (concentration of the reaction mixture). In each case, the reaction was checked by TLC and stopped as soon as the trihydroxyl derivatives appeared. After evaporation and purification deprotected compounds **4a**,**b**,**c** were obtained in reasonable yields (about 12% of α analogues were also isolated). IR spectrum displays an hydroxyl band at 3400 cm^{-1} and ^1H NMR indicates the presence of only one benzoyl group.

A large number of methods have been described for obtaining double bond from diol. We tested the Chu's method[12] in order to synthesize unsaturated compounds **5a**,**b**,**c**. The reaction proceeds in two steps. The first one consists in the formation of a bisxanthate intermediate by reaction of the diol with carbon disulfide, sodium hydride and methyl iodide in anhydrous DMF. The following step, which allows the formation of the double bond, is a radical reaction which takes place in anhydrous toluene in the presence of tributylin hydride and 2,2-azobisisobutyronitrile as initiator. In these conditions, reaction of **4** with carbon disulfide (CS_2) gives two products, the bisxantate in a very low yield (30%) and the cyclic thionocarbonate in 30% yield. After numerous attempts, we proceeded to the 2′,3′ diol conversion into the corresponding cyclic thionocarbonate derivative, which was then transformed into the desired olefin by desulfurization-decarboxylation. Thus thionocarbonates **5a**,**b**,**c** were synthesized according to the Corey-Winter[13] procedure in excellent yields (77%). The reaction was carried out in anhydrous dichloromethane with thiophosgene (CSCl2) and dimethylaminopyridine (DMAP). The second step was achieved by refluxing in trimethylphosphite during 4.5 hours. The olefin compounds **6a**,**b**,**c** were obtained in good yields.

The deprotection of the primary hydroxyl group was achieved using ammonia in methanol (7N), the expected compounds were obtained in nearly quantitative yields.

BIOLOGICAL EVALUATION

The synthesized compounds **7a**,**b**,**c** were evaluated for their in vitro inhibitory effects on the replication of RNA virus (HIV-1) (Table 2). The anti HIV-1 activity was tested on CEM-SS and MT_4 cell lines infected respectively with HIV-1 LAI and HIV

Table 2. Biological evaluation.

	CEM-SS		MT-4	
	EC_{50}[a]	CC_{50}[b]	EC_{50}	CC_{50}
7a	3.10^{-2} mg/ml	6.10^{-2} mg/ml	$>CC_{50}$	$3{,}3.10^{-2}$ mg/ml
7b	$3{,}7.10^{-2}$ mg/ml	$5{,}5.10^{-2}$ mg/ml	$>CC_{50}$	2.10^{-2} mg/ml
7c	$2{,}7.10^{-2}$ mg/ml	$5{,}1.10^{-2}$ mg/ml	$>CC_{50}$	$2{,}9.10^{-2}$ mg/ml

[a]50% effective concentration (mg/mL) or concentration required to inhibition the replication of HIV-1 by 50%.
[b]50% cytotoxic concentration (mg/mL) or concentration required to reduce the viability of uninfected cells by 50%.

IIIB according to protocols described previously.[14] In case of CEM-SS cells, the production of virus was measured by quantification of reverse transciptase activity associated with the release of virus particles in the culture supernatant; for MT4 cells the assay was based on the virus induced cytopathogenicity. Cell viability was evaluated by measuring the activity of mitochondrial electron transport by the MTT assay.[15] The antiviral activity is expressed as EC_{50} (mg/mL), the concentration of the compound necessary to reduce virus replication by 50% and was derived from the computer-generated median effect plot of the dose-effect data.[16] The cytotoxicity is expressed as CC_{50}, the concentration of drug needed to reduce the viability of uninfected cells by 50%. The results are summarized in Table 2. For infected CEM-SS cells, the selectivity index (SI = ratio CC_{50}/EC_{50}) is low and close to 2 indicating that the compound has no specific antiviral activity. Similar conclusion can be drawn from the MT4 assay, since the drug failed to bring any protection according to the virus-induced cytopathic effect.

EXPERIMENTAL

All the solvents and chemicals were commercially available and, unless otherwise stated, were used as received. DMF, CH_2Cl_2 and CH_3CN were distilled twice over P_2O_5 and over CaH_2 just before use. Reactions were monitored by thin-layer chromatography (TLC) on precoated 0.2 mm silica gel 60 F_{254} (Merck) plates and visualized in several ways: with an ultraviolet light source at 254 nm, by spraying with sulfuric acid (6N) and heating to 200°C. Silica gel (Merck Kieselgel 60, 15–40 μm) was used for flash chromatography. Microwave irradiations were performed by means of a monomode reactor (Synthewave 402 from Prolabo) with focused waves. ^1H NMR spectra were recorded at 400.13 MHz with a Bruker DPX spectrometer. Chemical shifts (δ) are expressed in ppm with Me_4Si as internal standard (δ = 0). Data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; q, quintet; m, multiplet and br, broad), coupling constants (Hz) and assignment. Melting points (mp) were determined with a Kofler block and are uncorrected. Rotatory dispersions were measured with a Jasco (DIP-370) polarimeter in a 1 dm quartz cell at

22°C. IR spectra were recorded on a Perkin Elmer 1310 grating spectrophotometer and are reported in wave number (cm^{-1}).

1-(4-acetoxybutyl)-thymine (1a). Thymine (757 mg, 6 mmol) was stirred with sodium hydride (2 eq) in DMF (20 mL), under microwave irradiation over 2 minutes (6 × 20 s; P: 300 W). 4-bromobutylacetate (2 mL, 2.3 eq) was then added and the reaction mixture was stirred and irradied 2 minutes (6 × 20 s; P: 300 W). After workup and purification by chromatography with an elution gradient of petroleum ether/acetone, **1a** was recovered in 42% yield as white solid (604 mg). R_f = 0.45 (CH_2Cl_2/MeOH, 95/5, v/v); mp = 95°C; IR: 3150 (NH), 3038 (CH ar.), 2821–2959 (CH alkyl), 1726 (C═O acetyl), 1705 (C═O Thym), 1671 (C═C). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 9.05 (s, 1H, H_3), 6.99 (d, 1H, J = 0.9 Hz, H_6), 1.93 (d, 3H, J = 0.9 Hz, C–CH_3), *N-alkyl*: 4.10 (t, 2H, $J_{\delta,\gamma}$ = 6.2 Hz, H_δ), 3.74 (t, 2H, $J_{\alpha,\beta}$ = 7.1 Hz, H_α), 2.06 (s, 3H, CO–CH_3), 1.72 (m, 4H, H_β and H_γ).

1-(3-acetoxypropyl)-thymine (1b). Compound **1b** was prepared according to the procedure described for **1a** starting from thymine (757 mg, 6 mmol) and 1.69 mL of 3-chloropropylacetate (2.3 eq). Yield: 32% (433 mg); R_f = 0.47 (CH_2Cl_2/MeOH, 95/5, v/v); mp = 88°C; IR: 3149 (NH), 3040 (CH ar.), 2820–2959 (CH alkyl), 1729 (CO acetyl), 1706 (C═O Thym), 1675 (C═C). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 9.27 (s, 1H, H_3), 6.99 (d, 1H, J = 1.08 Hz, H_6), 1.92 (d, 3H, J = 1.08 Hz, C–CH_3), *N-alkyl*: 4.14 (t, 2H, $J_{\gamma,\beta}$ = 6.04 Hz, H_γ), 3.74 (t, 2H, $J_{\alpha,\beta}$ = 6.9 Hz, H_α), 2.07 (s, 3H, CO–CH_3), 2.04 (m, 2H, H_β).

1-(2-acetoxyethyl)-thymine (1c). Compound **1c** was prepared according to the procedure described for **1a** starting from thymine (757 mg, 6 mmol) and 1.52 mL of 2-bromoethylacetate (2.3 eq). Yield: 27.7% (352 mg); R_f = 0.48 (CH_2Cl_2/MeOH, 95/5, v/v); IR: 3152 (NH), 3040 (CH ar.), 2820–2962 (CH alkyl), 1731 (C═O acetyl), 1705 (C═O Thym), 1674 (CC). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.79 (s, 1H, H_3), 6.99 (d, 1H, J = 1.1 Hz, H_6), 1.93 (d, 3H, J = 1.1 Hz, C–CH_3), *N-alkyl*: 4.31 (t, 2H, $J_{\alpha,\beta}$ = 5.28 Hz, H_α), 3.95 (t, 2H, $J_{\beta,\alpha}$ = 5.28 Hz H_β), 2.06 (s, 3H, CO–CH_3).

1-(4-hydroxybutyl)-thymine (2a). The deacetylation of **1a** (545 mg, 2.27 mmol) was performed under microwave irradiation. KOH (381 mg, 3 eq) was dissolved in water and absorbed on alumina (1.143 g). Water was removed by evaporation under vacuum. Compound **1a** was added to the KOH/Al_2O_3 powder and the reaction mixture was stirred over 2 min under microwave irradiation (P: 30 W). The reaction mixture was diluted with CH_3OH and filtered. Compound **2a** was obtained in 96% yield as white solid (431 mg). R_f = 0.47 (CH_2Cl_2/MeOH, 9/1, v/v); mp = 140°C; IR: 3424 (OH), 3158 (NH), 3018 (CH ar.), 2828–2947 (CH alkyl), 1684 (C═O Thym), 1648 (C═C). ^{1}H NMR (400.13 MHz, CD_3OD): δ 7.43 (d, 1H, $J_{6,CH3}$ = 1.1 Hz, H_6), 1.86 (d, 3H, $J_{CH3,6}$ = 1.1 Hz, C–CH_3), *N-alkyl*: 3.74 (t, 2H, $J_{\delta,\gamma}$ = 7.3 Hz, H_δ), 3.57 (t, 2H, $J_{\alpha,\beta}$ = 6.4 Hz, H_α), 1.73 (m, 2H, H_β or H_γ), 1.54 (m, 2H, H_β or H_γ).

1-(3-hydroxypropyl)-thymine (2b). Compound **2b** was prepared according to the procedure described for **2a** starting from **1b** (274 mg, 1.21 mmol). Yield: 95% (211 mg); R_f = 0.5 (CH_2Cl_2/MeOH, 9/1, v/v), mp = 138°C; IR: 3427 (OH), 3150 (NH),

3021 (CH ar.), 2829–2945 (CH alkyl), 1686 (C═O Thym), 1647(C═C). ^{1}H NMR (400.13) MHz, CD_3OD): δ 7.42(d, 1H, $J_{6,CH3}$ = 1.06 Hz, H_6), 1.86 (d, 3H, $J_{CH3,6}$ = 1.06 Hz, C–CH_3), *N-alkyl*: 3.81 (t, 2H, $J_{\gamma,\beta}$ = 6.92 Hz, H_γ), 3.58 (t, 2H, $J_{\alpha,\beta}$ = 6.08 Hz, H_α), 1.86 (m, 2H, H_β).

1-(2-hydroxyethyl)-thymine (2c). Compound **2c** was prepared according to the procedure described for **2a** starting from **1c** (340 mg, 1.3 mmol). Yield: 93% (205 mg); R_f = 0.48 (CH_2Cl_2/MeOH, 9/1, v/v); mp = 158°C; IR: 3427 (OH), 3150 (NH), 3018 (CH ar.), 2829–2945 (CH alkyl), 1686 (C═O Thym), 1647(C═C). ^{1}H NMR (400.13 MHz, CD_3OD): δ 7.51 (d, 1H, $J_{6,CH3}$ = 1.14 Hz, H_6), 1.99 (d, 3H, $J_{CH3,6}$ = 1.14 Hz, C–CH_3), *N-alkyl*: 3.58 (t, 2H, $J_{\alpha,\beta}$ = 6.08 Hz, H_α), 3.9 (m, 2H, H_β).

1-(4-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyloxy)butyl)-thymine (3a). To a dry system of 1-(4-hydroxybutyl)-thymine **2a** (108 mg, 0.547 mmol) in acetonitrile were added 1-O-acetyl, 2,3,5-tri-O-benzoyl-β-D-ribofuranose (276 mg, 1 eq) and tin (IV) chloride (2 eq). After completion of reaction as monitored by TLC, the solution was quenched with the addition of a saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed. The product was purified using flash chromatography with an elution gradient of CH_2Cl_2/MeOH and was recovered in 69% yield (243 mg). R_f = 0.61 (CH_2Cl_2/MeOH, 95/5, v/v); IR: 3155 (NH), 3035 (CH ar.), 2825–2950 (CH alkyl), 1726 (C═O benzoyl), 1705 (C═O Thym), 1598 (C═C), 1266 (C–O–C). ^{1}H NMR (400.13 MHz, $CDCl_3$): *thymine*: δ 8.62 (s, 1H, NH), 7.00 (d, 1H, $J_{6,CH3}$ = 1.1 Hz, H_6), 1.93 (d, 3H, $J_{CH3,6}$ = 1.1 Hz, C–CH_3), *N-alkyl*: 3.82 (dt, 1H, $J_{\alpha,\beta}$ = 6 Hz, $J_{\alpha,\alpha}$ = 9.6 Hz, H_α), 3.67 (t, 2H, $J_{\delta,\gamma}$ = 7.4 Hz, H_δ), 3.47 (dt, 1H, $J_{\alpha,\beta}$ = 6.3 Hz, $J_{\alpha,\alpha}$ = 9.6 Hz, H_α), 1.71 (m, 2H, H_β or H_γ), 1.56 (m, 2H, H_β or H_γ), *ose*: 5.83 (dd, 1H, $J_{3',2'}$ = 4.8 Hz, $J_{3',4'}$ = 6.7 Hz, $H_{3'}$), 5.66 (d, 1H, $J_{2',3'}$ = 4.8 Hz, $H_{2'}$), 5.23 (br s, 1H, $H_{1'}$), 4.72 (m, 2H, $H_{4'}$,$H_{5'}$), 4.52 (m, 1H, $H_{5'}$), *benzoyl groups*: 7.25–8.10 (m, 15H).

1-(3-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyloxy)propyl)-thymine (3b). Compound **3b** was prepared according to t the procedure described for **3a** starting from **2b** (178 mg, 0.97 mmol) and 1-O-acetyl, 2,3,5-tri-O-benzoyl-β-D-ribofuranose (489 mg, 1 eq). Yield: 77% (470 mg); R_f = 0.6 (CH_2Cl_2/MeOH, 95/5, v/v); IR: 3155 (NH), 3035 (CH ar.), 2825–2950 (CH alkyl), 1726 (C═O benzoyl), 1705 (C═O Thym), 1598 (C═C), 1266 (C–O–C). ^{1}H NMR (400.13 MHz, $CDCl_3$): *thymine*: δ 8.51 (br s, 1H, NH), 7.03 (s, 1H, H_6), 1.92 (s, 3H, C–CH_3), *N-alkyl*: 3.82 (dt, 1H, $J_{\alpha,\beta}$ = 5.1 Hz, $J_{\alpha,\alpha}$ = 9.8 Hz, H_α) 3.73 (t, 2H, $J_{\gamma,\beta}$ = 7.4 Hz, H_γ), 3.47 (dt, 1H, $J_{\alpha,\beta}$ = 4.6 Hz, $J_{\alpha,\alpha}$ = 9.8 Hz, H_α), 1.67 (br s, 2H, H_β), *ose*: 5.83 (dd, 1H, $J_{3',2'}$ = 4.96 Hz, $J_{3',4'}$ = 6.3 Hz, $H_{3'}$), 5.66 (d, 1H, $J_{2',3'}$ = 4.96 Hz, $H_{2'}$), 5.22 (br s, 1H, $H_{1'}$), 4.76 (dd, 1H, $J_{5',4'}$ = 3.9 Hz, $J_{5',5'}$ = 12.8 Hz, $H_{5'}$), 4.75 (dt, 1H, $J_{4',5'}$ = 6.3 Hz and 3.9 Hz, $J_{4',3'}$ = 6.3 Hz, $H_{4'}$), 4.51 (dd, 1H, $J_{5',4'}$ = 6.3 Hz, $J_{5',5'}$ = 12.8 Hz, $H_{5'}$), *benzoyl groups*: 7.27–8.11 (m, 15H).

1-(2-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyloxy)ethyl)-thymine (3c). Compound **3c** was prepared according to the procedure described for **3a** starting from **2c** (664 mg, 3.9 mmol) and 1-O-acetyl, 2,3,5-ti-O-benzoyl-β-D-ribofuranose (1.97 g, 1 eq). Yield: 55% (1.32 g); R_f = 0.51 (CH_2Cl_2/MeOH, 95/5, v/v); IR: 3155 (NH), 3035 (CH ar.), 2825–2950 (CH alkyl), 1726 (C═O benzoyl), 1705 (C═O Thym), 1598 (C═C),

1266 (C–O–C). ^{1}H NMR (400.13 MHz, $CDCl_3$): *thymine*: δ 8.25 (br s, 1H, NH), 6.98 (br s, 1H, H_6), 1.92 (s, 3H, C–CH_3), *N-alkyl*: 3.94 (m, 2H, H_α), 3.68 (m, 2H, H_β), *ose*: 5.81 (dd, 1H, $J_{3',2'}$ = 5.04 Hz, $J_{3',4'}$ = 5.88 Hz, $H_{3'}$), 5.64 (d, 1H, $J_{2',3'}$ = 5.04 Hz, $H_{2'}$), 5.25 (br s, 1H, $H_{1'}$) 4.74 (m, 1H, $H_{4'}$), 4.73 (dd, 1H, $J_{5',4'}$ = 3.9 Hz, $J_{5',5'}$ = 11.3 Hz, $H_{5'}$), 4.51 (dd, 1H, $J_{5',4'}$ = 4.9 Hz, $J_{5',5'}$ = 11.3 Hz, $H_{5'}$), *benzoyl groups*: 7.31–8.11 (m, 15H).

1-(4-(5′-*O*-benzoyl-β-D-ribofuranosyloxy)butyl)-thymine (4a). Compound **3a** (160 mg, 0.249 mmol) was stirred with methanolic ammonia (7 N) (50 eq, 1.77 mL) in methanol (3 mL) at room temperature during 6 hours. The solvent was removed under reduced pressure and the crude residue was purified by thin layer preparative chromatography over silica gel (CH_2Cl_2/EtOH) to yield compound **4a** as a viscous oil in 58% (62 mg). R_f = 0.57 (CH_2Cl_2/MeOH, 9/1, v/v); IR: 3300 (OH), 3155 (NH), 3018 (CH ar.), 2840–2945 (CH alkyl), 1716 (C═O benzoyl), 1681 (C═O Thym), 1600 (C═C), 1278 (C–O–C). ^{1}H NMR (400.13 MHz, $CDCl_3$): *thymine*: δ 8.51 (s, 1H, NH), 6.96 (s, 1H, H_6), 1.89 (s, 3H, C–CH_3), *N-alkyl*: 3.75 (dt, 1H, $J_{\alpha,\beta}$ = 5.8 Hz, $J_{\alpha,\alpha}$ = 9.1 Hz, H_α), 3.66 (t, 2H, $J_{\delta,\gamma}$ = 7.7 Hz, H_δ), 3.38 (dt, 1H, $J_{\alpha,\beta}$ = 6.3 Hz, $J_{\alpha,\alpha}$ = 9.1 Hz, H_α), 1.68 (m, 2H, H_β or H_γ), 1.53 (m, 2H, H_β or H_γ), *ose*: 4.99 (s, 1H, $H_{1'}$), 4.59 (dd, 1H, $J_{5',4'}$ = 3.6 Hz, $J_{5',5'}$ = 12 Hz, $H_{5'}$), 4.42 (m, 2H, $H_{3'}$, $H_{5'}$), 4.28 (ddd, 1H, $J_{4',5'}$ = 3.6 Hz, $J_{4',5'}$ = 6 Hz, $J_{4',3'}$ = 6 Hz, $H_{4'}$), 4.12 (d, 1H, $J_{2',3'}$ = 4.7 Hz, $H_{2'}$), *benzoyl group*: 8.05 (dd, 2H, J = 7 Hz, J = 1.3 Hz), 7.55 (t, 1H, J = 7.4 Hz), 7.41 (t, 2H, J = 7.8 Hz).

1-(3-(5′-*O*-benzoyl-β-D-ribofuranosyloxy)propyl)-thymine (4b). Compound **4b** was prepared according to the procedure described for **4a** starting from **3b** (470 mg, 0.748 mmol) and stirred with methanolic ammonia (7 N) (50 eq). Yield: 56% (176 mg); $[\alpha]_D^{22}$ = + 8.99; (0.1; CH_2Cl_2); R_f = 0.57 (CH_2Cl_2/MeOH, 9/1, v/v); IR: 3382(OH), 3192 (NH), 3052 (CH ar.), 2855-2970 (CH alkyl), 1682 (C═O benzoyl), 1678 (C═O Thym), 1472 (C═C), 1277 (C–O–C). ^{1}H NMR (400.13 MHz, CDCl3): *thymine*: δ 9.87 (s, 1H, NH), 6.90 (br s, 1H, H_6), 1.81 (s, 3H, C–CH_3), *N-alkyl*: 3.97 (dt, 1H, $J_{\alpha,\beta}$ = 6.6 Hz, $J_{\alpha,\alpha}$ = 13.9 Hz, H_α), 3.74 (dt, 1H, $J_{\gamma,\beta}$ = 5 Hz, $J_{\gamma,\gamma}$ = 10.46 Hz, H_γ), 3.58 (dt, 1H, $J_{\alpha,\beta}$ = 6 Hz, $J_{\alpha,\alpha}$ = 13.9 Hz, H_α), 3.37 (dt, 1H, $J_{\gamma,\beta}$ = 6 Hz, $J_{\gamma,\gamma}$ = 10.46 Hz, H_γ), 1.79 (m, 2H, H_β), *ose*: 4.95 (s, 1H, $H_{1'}$), 4.59 (dd, 1H, $J_{5',4'}$ = 3.44 Hz, $J_{5',5'}$ = 11.8 Hz, $H_{5'}$), 4.39 (dd, 1H, $J_{5',4'}$ = 5.48 Hz, $J_{5',5'}$ = 11.8 Hz, $H_{5'}$), 4.35 (dd, 1H, $J_{3',2'}$ = 4.9 Hz, $J_{3',4'}$ = 6.3 Hz, $H_{3'}$), 4.26 (m, 1H, $H_{4'}$), 4.09 (d, 1H, $J_{2',3'}$ = 4.9 Hz, $H_{2'}$), *benzoyl group*: 8.04 (br d, 2H, J = 7.6 Hz), 7.55 (t, 1H, J = 7.4 Hz), 7.42 (t, 2H, J = 7.72 Hz).

1-(2-(5′-*O*-benzoyl-β-D-ribofuranosyloxy)ethyl)-thymine (4c). Compound **4c** was prepared according to the procedure described for **4a** starting from **3c** (310 mg, 0.505 mmol) and stirred with methanolic ammonia (7 N) (50 eq). Yield: 55.4% (113.6 mg); $[\alpha]_D^{22}$ = −11.3; (0.7; CH_2Cl_2); R_f = 0.54 (CH_2Cl_2/MeOH, 9/1, v/v); IR: 3382(OH), 3192 (NH), 3052 (CH ar.), 2855–2970 (CH alkyl), 1682 (C═O benzoyl), 1678 (C═O Thym), 1472 (C═C), 1277 (C–O–C). ^{1}H NMR (400.13 MHz, $CDCl_3$): *thymine*: δ 9.87 (s, 1H, NH), 6.90 (br s, 1H, H_6), 1.81 (s, 3H, C–CH_3), *N-alkyl*: 3.97 (ddd, 1H, $J_{\alpha,\beta}$ = 3.9 Hz, $J_{\alpha,\beta}$ = 9.5 Hz, $J_{\alpha,\alpha}$ = 14.1 Hz, H_α), 3.78 (ddd, 1H, $J_{\beta,\alpha}$ = 3.9 Hz, $J_{\beta,\alpha}$ = 5.6 Hz,, $J_{\beta,\beta}$ = 10.6 Hz, H_β), 3.64 (ddd, 1H, $J_{\beta,\alpha}$ = 3.9 Hz, $J_{\beta,\alpha}$ = 6.6 Hz,

$J_{\beta,\beta}$ = 10.6 Hz, H_β), 3.49 (ddd, 1H, $J_{\alpha,\beta}$ = 3.9 Hz, $J_{\alpha,\beta}$ = 6.2 Hz, $J_{\alpha,\alpha}$ = 14.1 Hz, H_α), *ose*: 4.98 (s, 1H, $H_{1'}$), 4.59 (dd, 1H, $J_{5',4'}$ = 2.8 Hz, $J_{5',5'}$ = 11.8 Hz, $H_{5'}$), 4.35 (dd, 1H, $J_{5',4'}$ = 5.6 Hz, $J_{5',5'}$ = 11.8 Hz, $H_{5'}$), 4.31 (dd, 1H, $J_{3',2'}$ = 4.7 Hz, $J_{3',4'}$ = 7.7 Hz, $H_{3'}$), 4.27 (m, 1H, $H_{4'}$), 4.03 (d, 1H, $J_{2',3'}$ = 4.7 Hz, $H_{2'}$), *benzoyl group*: 8.03 (br d, 2H, J = 7.4 Hz), 7.54 (tt, 1H, J = 1.85 Hz J = 7.4 Hz), 7.42 (br t, 2H, J = 7.5 Hz).

1-(4-(2′,3′-*O*-thionocarbonyl-5′-*O*-benzoyl-β-D-ribofuranosyloxy)butyl)-thymine (5a). Compound **4a** (108 mg, 0.244 mmol) was solubilized in 3.5 mL of anhydrous dichloromethane with 4-dimethylaminopyridine (109 mg, 0.886 mmol). This solution was placed at 0°C under argon, and thiophosgene was then added (34 μL, 0.443 mmol). The mixture was stirred 1 hour at 0°C, then 1.5 hours at room temperature. The solvent was removed under reduced pressure and the crude residue purified by thin layer preparative chromatography on silica gel (CH_2Cl_2/MeOH) to yield compound **5a** as a viscous oil in 77% (90 mg). R_f = 0.55 (CH_2Cl_2/MeOH, 95/5, v/v); IR: 3150 (NH), 3028 (CH ar.), 2825–2945 (CH alkyl), 1718 (C═O benzoyl), 1684 (C═O Thym), 1600 (C═C), 1270 (C–O–C), 1025 (C═S). ^{1}H NMR (400.13 MHz, $CDCl_3$): *thymine*: δ 8.6 (s, 1H, NH), 6.96 (d, 1H, $J_{6,CH3}$ = 1 Hz, H_6), 1.91 (s, 3H, C–CH_3), *N-alkyl*: 3.79 (dt, 1H, $J_{\alpha,\beta}$ = 6.2 Hz, $J_{\alpha,\alpha}$ = 9.6 Hz, H_α), 3.67 (t, 2H, $J_{\delta,\gamma}$ = 7.4 Hz, H_δ), 3.51(dt, 1H, $J_{\alpha,\beta}$ = 6.2 Hz, $J_{\alpha,\alpha}$ = 9.6 Hz, H_α), 1.7 (m, 2H, H_β or H_γ), 1.58 (m, 2H, H_β or H_γ), *ose*: 5.48 (d, 1H, $J_{3',2'}$ = 6.7 Hz, $H_{3'}$), 5.34 (s, 1H, $H_{1'}$), 5.3 (d, 1H, $J_{2',3'}$ = 6.7 Hz, $H_{2'}$), 4.81 (dd, 1H, $J_{4',5'}$ = 6.4 Hz, $J_{4',5'}$ = 7.6 Hz, $H_{4'}$), 4.42 (dd, 1H, $J_{5',4'}$ = 7.6 Hz, $J_{5',5'}$ = 11.4 Hz, $H_{5'}$), 4.38 (dd, 1H, $J_{5',4'}$ = 6.4 Hz, $J_{5',5'}$ = 11.4 Hz, $H_{5'}$), *benzoyl group*: 8.02 (dd, 2H, J = 7 Hz, J = 1.2 Hz), 7.61 (tt, 1H, J = 1.2 Hz, J = 7.5 Hz, J = 15 Hz), 7.47 (t, 2H, J = 7.5 Hz).

1-(3-(2′,3′-*O*-thionocarbonyl-5′-*O*-benzoyl-β-D-ribofuranosyloxy)propyl)-thymine (5b). Compound **5b** was prepared according to the procedure described for **5a** starting from **4b** (176 mg, 0.42 mmol) with 4-dimethylaminopyridine (3.6 eq) and thiophosgene (1.8 eq). Yield: 74% (143 mg); $[\alpha]_D^{22}$ = − 1.99; (0.1; CH_2Cl_2); R_f = 0.53 (CH_2Cl_2/MeOH, 95/5, v/v); IR: 3150 (NH), 3028 (CH ar.), 2825–2945 (CH alkyl), 1718 (C═O benzoyl), 1684 (C═O Thym), 1600 (C═C), 1270 (C–O–C), 1025 (C═S). ^{1}H NMR (400.13 MHz, $CDCl_3$): *thymine*: δ 8.16 (s, 1H, NH), 6.92 (d, 1H, $J_{6,CH3}$ = 1 Hz, H_6), 1.91 (d, 3H, $J_{CH3,6}$ = 0.86 Hz, C–CH_3), *N-alkyl*: 3.83 (dt, 1H, $J_{\alpha,\beta}$ = 5.5 Hz, $J_{\alpha,\alpha}$ = 10.32 Hz, H_α), 3.76 (dt, 1H, $J_{\gamma,\beta}$ = 7 Hz, $J_{\gamma,\gamma}$ = 14 Hz, H_γ), 3.72 (dt, 1H, $J_{\gamma,\beta}$ = 7 Hz, $J_{\gamma,\gamma}$ = 14 Hz, H_γ), 3.53 (dt, 1H, $J_{\alpha,\beta}$ = 5.6 Hz, $J_{\alpha,\alpha}$ = 10.32 Hz, H_α), 1.93 (m, 2H, H_β), *ose*: 5.48 (d, 1H, $J_{3',2'}$ = 6.74 Hz, $H_{3'}$), 5.34 (s, 1H, $H_{1'}$), 5.28 (d, 1H, $J_{2',3'}$ = 6.74 Hz, $H_{2'}$), 4.83 (dd, 1H, $J_{4',5'}$ = 6 Hz, $J_{4',5'}$ = 7.8 Hz, $H_{4'}$), 4.46 (dd, 1H, $J_{5',4'}$ = 7.8 Hz, $J_{5',5'}$ = 11.5 Hz, $H_{5'}$), 4.40 (dd, 1H, $J_{5',4'}$ = 6 Hz, $J_{5',5'}$ = 11.5 Hz, $H_{5'}$), *benzoyl group*: 8.04 (dd, 2H, J = 8.4 Hz, J = 1.28 Hz), 7.62 (tt, 1H, J = 1 Hz, J = 7.44 Hz, J = 13.7 Hz), 7.48 (t, 2H, J = 7.88 Hz).

1-(2-(2′,3′-*O*-thionocarbonyl-5′-*O*-benzoyl-β-D-ribofuranosyloxy)ethyl)-thymine (5c). Compound **5c** was prepared according to the procedure described for **5a** starting from **4c** (113 mg, 0.279 mmol) with 4-dimethylaminopyridine (3.6 eq) and thiophosgene (1.8 eq). Yield: 72% (90 mg); $[\alpha]_D^{22}$ = + 9.05; (0.61; CH_2Cl_2); R_f = 0.47 (CH_2Cl_2/MeOH, 95/5, v/v); IR: 3150 (NH), 3028 (CH ar.), 2825–2945 (CH alkyl), 1718 (C═O benzoyl), 1684 (C═O Thym), 1600 (C═C), 1270 (C–O–C),

1025 (C═S). ^{1}H NMR (400.13 MHz, $CDCl_3$): *thymine*: δ 8.71 (s, 1H, NH), 6.79 (d, 1H, $J_{6,CH3}$ = 0.86 Hz, H_6), 1.86 (s, 3H, $J_{CH3,6}$ = 0.86 Hz, C−CH_3), *N-alkyl*: 3.93 (m, 2H, H_β or H_α), 3.72 (m, 2H, H_β or H_α), *ose*: 5.49 (d, 1H, $J_{3',2'}$ = 6.76 Hz, $H_{3'}$), 5.34 (s, 1H, $H_{1'}$), 5.27 (d, 1H, $J_{2',3'}$ = 6.76 Hz, $H_{2'}$), 4.84 (t, 1H, $J_{4',5'}$ = 6.7 Hz, $H_{4'}$), 4.47 (dd, 1H, $J_{5',4'}$ = 6.7 Hz, $J_{5',5'}$ = 11.6 Hz, $H_{5'}$), 4.40 (dd, 1H, $J_{5',4'}$ = 6.8 Hz, $J_{5',5'}$ = 11.6 Hz, $H_{5'}$), *benzoyl group*: 8.02 (dd, 2H, J = 8.4 Hz, J = 1.4 Hz), 7.62 (tt, 1H, J = 1 Hz, J = 7.44 Hz, J = 13.7 Hz), 7.48 (t, 2H, J = 7.9 Hz).

1-(4-(5′-*O*-benzoyl-2′,3′-didehydro-2′,3′-dideoxy-β-D-ribofuranosyloxy)butyl)-thymine (6a). 40 mg (0.084 mmol) of compound **5a** were dissolved in trimethylphosphite (1.1 mL). This system was stirred under argon and immersed in an oil bath at 110°C during 4.5 h. The reaction was evaporated and the crude product was purified using preparative TLC (CH_2Cl_2/MeOH, 98/2, v/v). Pure 1-(4-(5′-O-benzoyl-2′,3′-didehydro-2′,3′-dideoxy-β-D-furanosyloxy)butyl)-thymine (29 mg) was recovered as a viscous oil in 85% yield. R_f = 0.65 (CH_2Cl_2/MeOH, 95/5, v/v); IR: 3155 (NH), 3028 (CH ar.), 2827−2950 (CH alkyl), 1716 (C═O benzoyl), 1685 (C═O Thym), 1600 (C═C), 1272 (C−O−C). ^{1}H NMR (400.13 MHz, $CDCl_3$): *thymine*: δ 8.6 (s, 1H, NH), 6.93 (d, 1H, $J_{6,CH3}$ = 1 Hz, H_6), 1.88 (d, 3H, $J_{CH3,6}$ = 1 Hz, C−CH_3), *N-alkyl*: 3.79 (dt, 1H, $J_{\alpha,\beta}$ = 6.2 Hz, $J_{\alpha,\alpha}$ = 9.6 Hz, H_α), 3.67 (t, 2H, $J_{\delta,\gamma}$ = 7.4 Hz, H_δ), 3.51(dt, 1H, $J_{\alpha,\beta}$ = 6.2 Hz, $J_{\alpha,\alpha}$ = 9.6 Hz, H_α), 1.70 (m, 2H, H_β or H_γ), 1.58 (m, 2H, H_β or H_γ), *ose*: 5.48 (d, 1H, $J_{3',2'}$ = 6.7 Hz, $H_{3'}$), 5.34 (s, 1H, $H_{1'}$), 5.3 (d, 1H, $J_{2',3'}$ = 6.7 Hz, $H_{2'}$), 4.81 (dd, 1H, $J_{4',5'}$ = 6.4 Hz, $J_{4',5'}$ = 7.6 Hz, $H_{4'}$), 4.42 (dd, 1H, $J_{5',4'}$ = 7.6 Hz, $J_{5',5'}$ = 11.4 Hz, $H_{5'}$), 4.38 (dd, 1H, $J_{5',4'}$ = 6.4 Hz, $J_{5',5'}$ = 11.4 Hz, $H_{5'}$), *benzoyl group*: 8.02 (dd, 2H, J = 7 Hz, J = 1.2 Hz), 7.61 (tt, 1H, J = 1.2 Hz, J = 7.5 Hz, J = 15 Hz), 7.47 (t, 2H, J = 7.5 Hz).

1-(3-(5′-*O*-benzoyl-2′,3′-didehydro-2′,3′-dideoxy-β-D-ribofuranosyloxy)propyl)-thymine (6b). Compound **6b** was prepared according to the procedure described for **6a** starting from **5b** (83 mg, 0.175 mmol). Yield: 80% (56 mg); $[\alpha]_D^{22}$ = − 25.1; (0.16; CH_2Cl_2); R_f = 0.60 (CH_2Cl_2/MeOH, 95/5, v/v); IR: 3186 (NH), 3028 (CH ar.), 2827−2950 (CH alkyl), 1719 (C═O benzoyl), 1678 (C═O Thym), 1610 (C═C), 1273 (C−O−C). ^{1}H NMR (400.13 MHz, $CDCl_3$): *thymine*: δ 8.84 (s, 1H, NH), 6.96 (d, 1H, $J_{6,CH3}$ = 1.06 Hz, H_6), 1.85 (d, 3H, $J_{CH3,6}$ = 1.06 Hz, C−CH_3), *N-alkyl*: 3.68−3.84 (m, 3H, H_γ and H_α), 3.58 (dt, 1H, $J_{\alpha,\beta}$ = 5.68 Hz, $J_{\alpha,\alpha}$ = 10.4 Hz, H_α),1.89 (m, 2H, H_β), ose: 6.21 (dt, 1H, $J_{3',2'}$ = 6 Hz, $J_{3',1'}$ = 1.2 Hz $J_{3',4'}$ = 1.2 Hz, $H_{3'}$), 5.92 (ddd, 1H, $J_{2',1'}$ = 1 Hz, $J_{2',3'}$ = 6 Hz, $J_{2',4'}$ = 2.04 Hz, $H_{2'}$), 5.8 (br d, 1H, $J_{1',2'}$ = 1 Hz, $H_{1'}$), 5.04 (m, 1H, $H_{4'}$), 4.49 (dd, 1H, $J_{5',4'}$ = 3.68 Hz, $J_{5',5'}$ = 11.74 Hz, $H_{5'}$), 4.38 (dd, 1H, $J_{5',4'}$ = 5.36 Hz, $J_{5',5'}$ = 11.74 Hz, $H_{5'}$), *benzoyl group*: 8.5 (dd, 2H, J = 1 Hz, J = 8.8 Hz), 7.56 (tt, 1H, J = 1.2 Hz, J = 7.5 Hz, J = 15 Hz), 7.47 (t, 2H, J = 7.5 Hz).

1-(2-(5′-*O*-benzoyl-2′,3′-didehydro-2′,3′-dideoxy-β-D-ribofuranosyloxy)ethyl)-thymine (6c). Compound **6c** was prepared according to the procedure described for **6a** starting from **5c** (173 mg, 0.375 mmol). Yield: 82% (119 mg); $[\alpha]_D^{22}$ = − 8.58; (0.26; CH_2Cl_2); R_f = 0.53 (CH_2Cl_2/MeOH, 95/5, v/v); IR: 3186 (NH), 3028 (CH ar.), 2827−2950 (CH alkyl), 1719 (C═O benzoyl), 1678 (C═O Thym), 1610 (CC), 1273 (C−O−C). ^{1}H NMR (400.13 MHz, $CDCl_3$): *thymine*: δ 8.07 (s, 1H, NH), 6.87 (d, 1H, $J_{6,CH3}$ = 1.18 Hz, H_6), 1.86 (d, 3H, $J_{CH3,6}$ = 1.18 Hz, C−CH_3), *N-alkyl*: 3.99 (ddd, 1H,

$J_{\alpha,\beta}$ = 4.92 Hz, $J_{\alpha,\beta}$ = 3.75 Hz, $J_{\alpha,\alpha}$ = 13.98 Hz, H_α), 3.89 (ddd, 1H, $J_{\beta,\alpha}$ = 4.92 Hz, $J_{\beta,\alpha}$ = 3.84 Hz, $J_{\beta,\beta}$ = 10.56 Hz, H_β), 3.76 (m, 1H, H_β), 3.61 (ddd, 1H, $J_{\alpha,\beta}$ = 7.8 Hz, $J_{\alpha,\beta}$ = 3.84 Hz, $J_{\alpha,\alpha}$ = 13.98 Hz, H_α), *ose*: 6.22 (dt, 1H, $J_{3',2'}$ = 5.97 Hz, $J_{3',1'}$ = 1.16 Hz, $J_{3',4'}$ = 1.16 Hz, $H_{3'}$), 5.92 (ddd, 1H, $J_{2',1'}$ = 1.04 Hz, $J_{2',3'}$ = 5.97 Hz, $J_{2',4'}$ = 2 Hz, $H_{2'}$), 5.76 (br d, 1H, $J_{1',2'}$ = 1.04 Hz, $H_{1'}$), 5.02 (m, 1H, $H_{4'}$), 4.52 (dd, 1H, $J_{5',4'}$ = 3.64 Hz, $J_{5',5'}$ = 11.72 Hz, $H_{5'}$), 4.31 (dd, 1H, $J_{5',4'}$ = 5.4 Hz, $J_{5',5'}$ = 11.72 Hz, $H_{5'}$), *benzoyl group*: 8.05 (dd, 2H), 7.57 (tt, 1H), 7.45 (br t, 2H).

1-(4-(2′,3′-didehydro-2′,3′-dideoxy-β-D-ribofuranosyloxy)butyl)-thymine (7a). Compound **6a** (20 mg, 0.05 mmol) was stirred with methanolic ammonia (7 N) (2 mL) in methanol (5 mL) at room temperature during 3 days. The solvent was removed under reduced pressure and the crude residue was purified by thin layer preparative chromatography on silica gel (CH_2Cl_2/EtOH) to yield compound **7a** as a viscous oil in 75% (11 mg). R_f = 0.51 (CH_2Cl_2/MeOH, 9/1, v/v); IR: 3160 (NH), 3020 (CH ar.), 2825–2950 (CH alkyl), 1690 (C═O Thym), 1597 (C═C), 1272 (C–O–C). ^{1}H NMR (400.13 MHz, $CDCl_3$): *thymine*: δ 8.91 (s, 1H, NH), 7.01 (d, 1H, $J_{6,CH3}$ = 0.9 Hz, H_6), 1.91 (d, 3H, $J_{CH3,6}$ = 1 Hz, C–CH_3), *N-alkyl*: 3.86 (dt, 1H, $J_{\alpha,\beta}$ = 6.16 Hz, $J_{\alpha,\alpha}$ = 9.6 Hz, H_α), 3.72 (t, 2H, $J_{\delta,\gamma}$ = 7.24 Hz, H_δ), 3.6 (dt, 1H, $J_{\alpha,\beta}$ = 6.12 Hz, $J_{\alpha,\alpha}$ = 9.6 Hz, H_α), 1.7 (m, 2H, H_β or H_γ), 1.58 (m, 2H, H_β or H_γ), *ose*: 6.10 (dt, 1H, $J_{3',2'}$ = 5.8 Hz, $J_{3',4'}$ = 1.4 Hz, $J_{3',1'}$ = 1.4 Hz, $H_{3'}$), 5.89 (dt, 1H, $J_{2',3'}$ = 5.8 Hz, $J_{2',4'}$ = 1.4 Hz, $J_{2',1'}$ = 1.4 Hz, $H_{2'}$), 5.73 (d, 1H, $J_{1',2'}$ = 1.4 Hz, $H_{1'}$), 4.93 (m, 1H, $H_{4'}$), 3.77 (dd, 1H, $J_{5',4'}$ = 2.8 Hz, $J_{5',5'}$ = 11.8 Hz, $H_{5'}$), 3.57 (dd, 1H, $J_{5',4'}$ = 3.4 Hz, $J_{5',5'}$ = 11.8 Hz, $H_{5'}$).

1-(3-(2′,3′-didehydro-2′,3′-dideoxy-β-D-ribofuranosyloxy)propyl)-thymine (7b). Compound **7b** was prepared according to the procedure described for **7a** starting from **6b** (40 mg, 0.102 mmol) and stirred with methanolic ammonia (7 N) (1 mL). Yield: 90% (26 mg); $[\alpha]_D^{22}$ = −41.6; (0.12; CH_2Cl_2); R_f = 0.49 (CH_2Cl_2/MeOH, 9/1, v/v); IR: 3190 (NH), 3026 (CH ar.), 2832–2951 (CH alkyl), 1684 (C═O Thym), 1604 (C═C), 1270 (C–O–C). ^{1}H NMR (400.13 MHz, $CDCl_3$): *thymine*: δ 9 (s, 1H, NH), 7.07 (d, 1H, $J_{6,CH3}$ = 0.86 Hz, H_6), 1.91 (d, 3H, $J_{CH3,6}$ = 0.86 Hz, C–CH_3), *N-alkyl*: 3.68–3.84 (m, 3H, H_γ and H_α), 3.58 (dt, 1H, $J_{\alpha,\beta}$ = 5.68 Hz, $J_{\alpha,\alpha}$ = 10.4 Hz, H_α), 1.89 (m, 2H, H_β), *ose*: 6.13 (dt, 1H, $J_{3',2'}$ = 5.96 Hz, $J_{3',1'}$ = 1.36 Hz $J_{3',4'}$ = 1.36 Hz, $H_{3'}$), 5.89 (ddd, 1H, $J_{2',1'}$ = 0.68 Hz, $J_{2',3'}$ = 5.96 Hz, $J_{2',4'}$ = 1.6 Hz, $H_{2'}$), 5.74 (br d, 1H, $J_{1',2'}$ = 0.68 Hz, $H_{1'}$), 4.93 (m, 1H, $H_{4'}$), 3.79 (dd, 1H, $J_{5',4'}$ = 3.2 Hz, $J_{5',5'}$ = 11.7 Hz, $H_{5'}$), 3.61 (dd, 1H, $J_{5',4'}$ = 3 Hz, $J_{5',5'}$ = 11.7 Hz, $H_{5'}$).

1-(2-(2′,3′-dehydro-2′,3′-dideoxy-β-D-ribofuranosyloxy)ethyl)-thymine (7c). Compound **7c** was prepared according to the procedure described for **7a** starting from **6c** (84 mg, 0.226 mmol) and stirred with methanolic ammonia (7 N) (2 mL). Yield: 74% (45 mg); $[\alpha]_D^{22}$ = +11.98; (0.13; CH_2Cl_2); R_f = 0.47 (CH_2Cl_2/MeOH, 9/1, v/v); IR: 3186 (NH), 3021 (CH ar.), 2830–2949 (CH alkyl), 1682 (C═O Thym), 1606 (C═C), 1272 (C–O–C). ^{1}H NMR (400.13 MHz, $CDCl_3$): *thymine*: δ 9.05 (s, 1H, NH), 7.09 (d, 1H, $J_{6,CH3}$ = 1.1 Hz, H_6), 1.9 (d, 3H, $J_{CH3,6}$ = 1.1 Hz, C–CH_3), *N-alkyl*: 3.68–3.84 (m, 3H, H_β and H_α), 3.58 (dt, 1H, $J_{\alpha,\beta}$ = 5.68 Hz, $J_{\alpha,\alpha}$ = 10.4 Hz, H_α), *ose*: 6.13 (dt, 1H, $J_{3',2'}$ = 5.94 Hz, $J_{3',1'}$ = 1.28 Hz $J_{3',4'}$ = 1.28 Hz, $H_{3'}$), 5.89 (ddd, 1H, $J_{2',1'}$ = 0.96 Hz, $J_{2',3'}$ = 5.94 Hz, $J_{2',4'}$ = 1.54 Hz, $H_{2'}$), 5.76 (br d, 1H, $J_{1',2'}$ = 0.96

Hz, $H_{1'}$), 4.89 (m, 1H, $H_{4'}$), 3.75 (dd, 1H, $J_{5',4'}$ = 3 Hz, $J_{5',5'}$ = 11.75 Hz, $H_{5'}$), 3.56 (dd, 1H, $J_{5',4'}$ = 3.1 Hz, $J_{5',5'}$ = 11.75 Hz, $H_{5'}$).

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