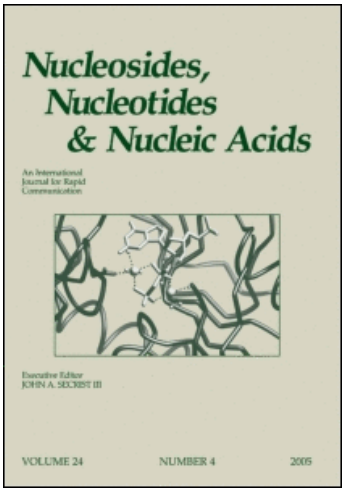

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New Dinucleoside Analogues via Cross-Coupling Metathesis

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NEW DINUCLEOSIDE ANALOGUES VIA CROSS-COUPLING METATHESIS

Vincent Roy, Rachida Zerrouki, and Pierre Krausz ▫ *Laboratoire de Chimie des Substances Naturelles, Faculté des Sciences et Techniques, Université de Limoges, Limoges, France*

▫ *Synthesis of 3′-3′, 5′-5′, and 3′-5′ dimeric thymidine, linked by an olefinic chain between glycosidic moieties is described. Cross metathesis reaction of 3′ or 5′ O-allyl analogues of thymidine led to the expected 3′-3′ and 5′-5′ dimeric compounds, respectively. In order to obtain the 3′-5′ dimer, 5′-O-allyl and 3′-O-allyl monomers were first linked by their free 3′ OH and 5′ OH groups through a glutaryl spacer; ring closing metathesis was then operated upon this temporary dimer, followed by glutaryl removal.*

Keywords Dinucleoside Analogues, Cross Metathesis, Grubbs Catalyst, Selective Allylation

INTRODUCTION

Novel oligonucleotide analogues that can form stable duplexes or triplexes with nucleic acids are being investigated as a new generation of pharmaceuticals.[1–5] One of the most important modifications is the complete substitution of the phosphate internucleoside bridge, in order to achieve stronger affinity for the nucleic acid target, enhanced nuclease resistance, and improved membrane permeability and cellular uptake.

RESULTS AND DISCUSSION

Our research effort in this area has focused on the synthesis and evaluation of three new dinucleoside analogues in which glycosidic moieties are linked by an olefinic chain between positions 3′-3′, 5′-5′, or 3′-5′. The strategy of synthesis of 3′-3′ dimer is presented in Scheme 1.

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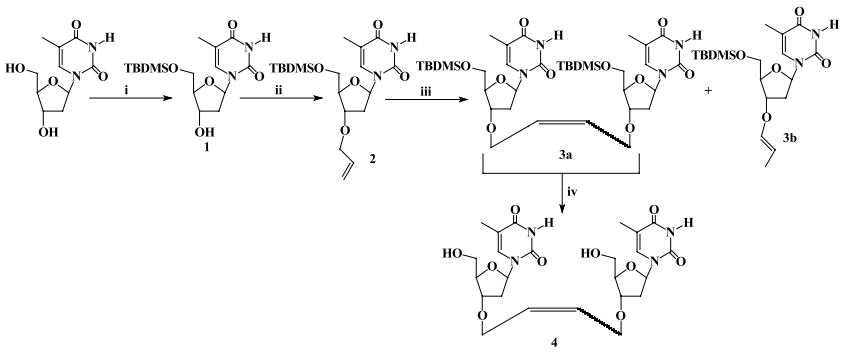


SCHEME 1 (i) TBDMSCl, DMAP, pyridine, 12 h, 90%; (ii) NaH, THF, allylbromide, ultra sonication, 4.5 h, 79%; (iii) metathesis catalyst (see text), CH_2Cl_2, 35°C; 12 h; (iv) TBAF, THF, 2 h, 55%.

First, 5′-hydroxyl of thymidine was protected with a TBDMS group to give 5′-*O*-(tert-butyldimethylsilyl)-thymidine **1**[6,7] (95%). The 3′-hydroxyl was then allylated using Chattopadhyaya method's[8] to give compound **2**. The next step consisted of self-cross metathesis reaction. We chose to use a ruthenium carbene complex catalyst developed by Grubbs and coworkers,[9–14] catalyst Grubbs II, for its strong reactivity, stability, and remarkable functional group tolerance. Metathesis was effected in dry dichloromethane under reflux with 20% mol. catalyst for 8 h. The reaction gave a mixture of two products (Table 1). Structural elucidation of these products indicated that one of them was the expected product **3a** obtained in low yield (35%) and that the second one **3b** (50%) resulted from double bond transposition. Metathesis was then realized using Grubbs I catalyst, leading to the expected compound **3a** in 51% yield (Figure 1).

^{1}H NMR chemical shifts do not allow the identification of Z and E isomers of **3a** but ^{13}C chemical shifts of the carbon atom close to the double bond (C-α) are different for the Z and E isomers.[15] The upper value (δ_α = 69.05 ppm) has been assigned to the E isomer and the lower one (δ_α = 65.07 ppm) to the Z isomer. The Z/E ratio of **3a** was about 15/85 with both catalysts. Deprotection of **3a** was achieved using TBAF/THF system. After 2 h, the solvent was removed and the crude residue purified to give compound **4** in 55% yield.

Synthesis of the 5′-5′ dinucleoside analogue is summarized in Scheme 2. For selective allylation of 5′ hydroxyl, the effect of various activation means was studied (classical stirring, ultrasonication, or microwave activation). The best result was

TABLE 1 Metathesis Yield with Grubbs II or I Catalyst

Metathesis catalyst	Compound **3a** (%)	Compound **3b** (%)
Grubbs II	35	50
Grubbs I	51	7

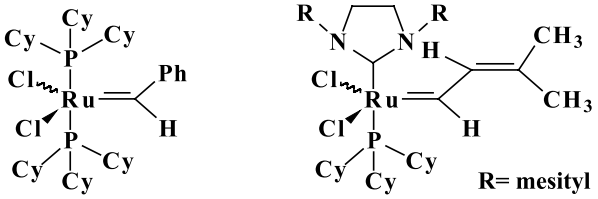
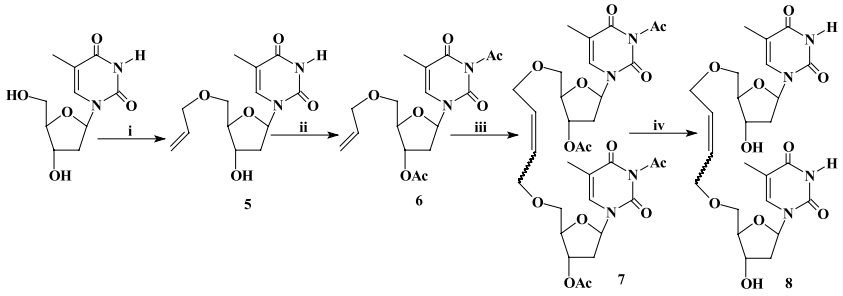


FIGURE 1 Grubbs catalyst used.

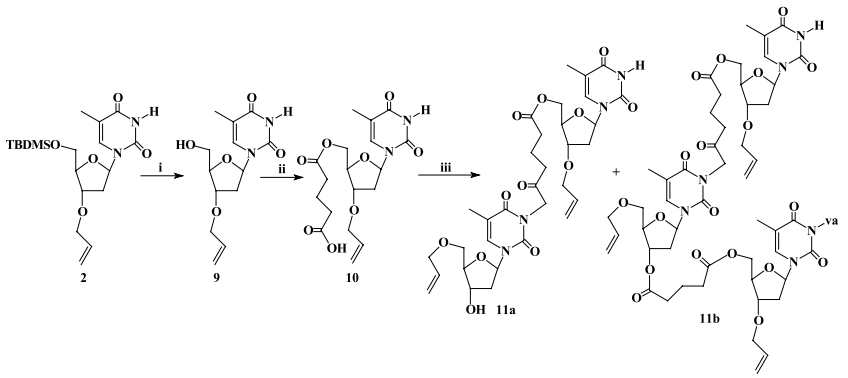
obtained with microwave activation. Starting from thymidine, NaH and 1.2 equiv. of allylbromide in DMF, 5′-*O*-allylthymidine (**5**) was obtained after purification in excellent yield (97%) along with remarkable decrease in reaction time (4 min) and a good selectivity as well.[16] Acetylation was also achieved under microwave activation in the presence of acetic anhydride (20 equiv) during 1 min to give compound **6** in 92% yield.[17] After acetylation, metathesis was realized during 12 h, in dichloromethane, using Grubbs I catalyst, to give dimer product **7** in 61% yield (Z/E = 1/4). Finally, deprotection was achieved using ammonia in methanol (7 N) and the expected compound **8** was obtained in 85% yield.

Synthesis of the 3′-5′ dinucleoside analogue was first performed using cross metathesis reaction between olefinic compounds **2** and **6**. The reaction gave a mixture of three products, 3′-3′, 5′-5′, and 3′-5′ dimers with 5′-5′ dimer as a major product. This result led us to investigate another route. To avoid this self-metathesis drawback, we designed and used ring-closing metathesis (RCM) in conjunction with prearranged *O*-allyl nucleosides, by switching from intermolecular (CM) to intramolecular (RCM) reaction. Glutaryl group was used for the synthesis of spacer-linked *O*-allyl nucleosides. The first test was realized according to Scheme 3.

Compound **2** was deprotected using TBAF in THF during 2 h, to give compound **9** in good yield (92%). The glutaryl spacer was introduced by acylation of primary hydroxyl group of **9** with glutaric anhydride in presence of DMAP; after



SCHEME 2 (i) NaH, DMF, allylbromide, MW, 4 min, 97%; (ii) acetic anhydride, MW, 1 min; (iii) metathesis catalyst Grubbs I, CH_2Cl_2, 35°C; 12 h, 61%; (Z/E: 1/4); (iv) NH_3, MeOH (7N), CH_2Cl_2, 6 h.

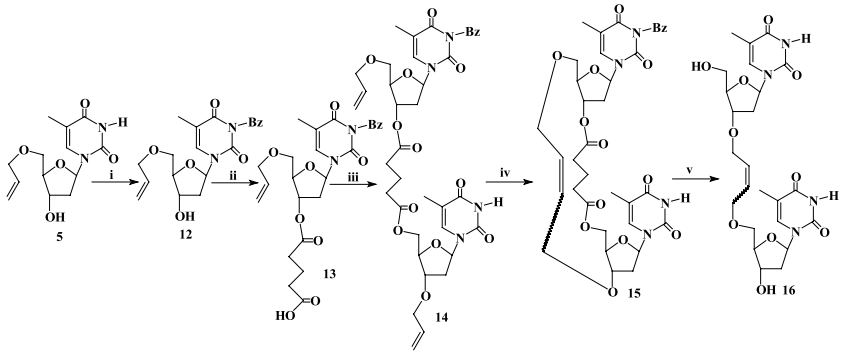


SCHEME 3 (i) TBAF, THF, 2 h, 92%; (ii) DMAP, glutaric anhydride, pyridine, 10 h, 55%; (iii) **5**, DCC, DMAP, CH_2Cl_2, toluene.

10 h, product **10** was isolated in acceptable yield (55%). Compound **10** was then coupled with **5** in the presence of DCC and DMAP in CH_2Cl_2 and toluene as cosolvent.

Two products were obtained, dimer **11a** where the acid function reacted with N-H group of **5**, and compound **11b** that resulted from reaction of **11a** with a second molecule of **10**.

The second strategy is summarized in Scheme 4. Compound **5** was selectively benzoylated[18] on N-H position, to give compound **12** in 53% yield. Reaction with glutaric anhydride gave product **13** in good yield (85%). Esterification, in this case, gave the desired compound **14** in 88% yield. Treated with metathesis Grubbs I catalyst in dichloromethane, compound **14** gave the dimer **15** in 45% yield (E/Z = 2). Finally, deprotection in MeOH with MeONa gave compound **16** in 70% yield.



SCHEME 4 (i) BzCl, Et_3N, 9 h, 53%; (ii) DMAP, glutaric anhydride, pyridine, 10 h, 85%; (iii) DCC, DMAP, CH_2Cl_2, toluene, 88%; (iv) metathesis catalyst Grubbs I, CH_2Cl_2, 39% (E/Z = 2); (v) MeONa (0.5 M in MeOH), CH_2Cl_2, 70%.

The above-mentioned structures were assigned from their ^{1}H- and ^{13}C-NMR spectral data. Additional DEPT experiments and correct assignment were confirmed by ^{1}H-^{13}C heteronuclear correlation experiments.

This article presents a new and efficient route for the synthesis of 3′-3′, 5′-5′, and 3′-5′ thymidine dimers. The approach described herein could be applied to other purines and/or pyrimidines nucleoside analogues.

EXPERIMENTAL SECTION

All 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 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 (MicroSYNTH from Milestone) with focused waves (T = 40°C, P = 100 W). ^{1}H 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; qt, 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}).

***Synthesis of 5′-O-tert-butyldimethylsilylthymidine* (1).** Thymidine (1.5 g, 6.19 mmol) was solubilized in anhydrous pyridine with 0.05 equiv of 4-dimethylaminopyridine (38 mg, 0.309 mmol). This solution was placed under argon, and 1.1 equiv of tertio-butyldimethylsilyl chloride (1.026 g, 6.809 mmol) was then added. The mixture was stirred overnight at room temperature. The solution was removed under reduced pressure and the crude residue purified using flash chromatography with an elution gradient petroleum ether/$CHCl_3$/EtOH. Pure product was recovered as a viscous oil in 95% yield. R_f = 0.44 ($CHCl_3$/EtOH; 9/1; V/V); $[\alpha]_D^{22}$ = +6,957° (c = 1, $CHCl_3$); ^{1}H RMN ($CDCl_3$): *Thymine*: 8.70 (s, 1H, N-H), 7.50 (q, 1H, $J_{H6,CH3}$ = 1.1 Hz, H_6), 1.91 (d, 3H, $J_{CH3,H6}$ = 1.1 Hz, CH_3); *ose*: 6.36 (dd, 1H, J = 5.7 Hz, J = 8.1 Hz, $H_{1'}$), 4.46 (dt, 1H, J = 2.4 Hz, J = 5.4 Hz, $H_{3'}$), 4.03 (q, 1H, J = 2.6 Hz, $H_{4'}$), 3.89 (dd, 1H, J = 2.8 Hz, J = 11.3 Hz, $H_{5'a}$), 3.83 (dd, 1H, J = 2.8 Hz, J = 11.3 Hz, $H_{5'b}$), 2.36 (ddd, 1H, J = 5.7 Hz, J = 2.4 Hz, J = 13.6 Hz, $H_{2'a}$), 2.10 (ddd, 1H, J = 5. 4 Hz, J = 8.1 Hz, J = 13.6 Hz, $H_{2'b}$); *TBDMS*: 0.92 (s, 9H, *tert-but*), 0.12 (s, 3H, CH_3), 0.11 (s, 3H, CH_3).

***3′-O-(prop-2-enyl)-5′-O-tert-butyldimethylsilylthymidine* (2).** To a solution of compound **1** (1.929 g, 5.59 mmol) in dry THF (30 mL), were added 2.1 equivalents of NaH (60%, 470 mg, 11.75 mmol) and the mixture was activated by ultrasonication during 30 min. Two equivalents of allyl bromide (0.994 mL, 11.19 mmol) were then added and the mixture was activated during 4 h. After work-up and purification by chromatography with an elution of petroleum ether/chloroform/ethanol, **2** was recovered in 79% yield (1.723 g) as a viscous oil. R_f = 0.44 ($CHCl_3$/EtOH, 95/5, V/V); $[\alpha]_D^{22}$ = +27.77° (3.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): *thymine*: 9.04 (s, 1H, N-H), 7.5 (q, 1H, J = 1.1 Hz, H_6), 1.91 (d, 3H, J = 1.1 Hz, CH_3); *ose*: 6.30 (dd, 1H, J = 5.6 Hz, J = 8.3 Hz, $H_{1'}$), 4.11 (m, 2H, $H_{3'}$, $H_{4'}$), 3.90 (dd, 1H, J = 2. 4 Hz, J = 11.4 Hz, $H_{5'a}$), 3.78 (dd, 1H, J = 2.1 Hz, J = 11.4 Hz, $H_{5'b}$), 2.44 (ddd, 1H, J = 5.6 Hz, J = 1.8 Hz, J = 12.7 Hz, $H_{2'a}$), 1.93 (ddd, 1H, J = 5.9 Hz, J = 8.3 Hz, J = 12.7 Hz, $H_{2'b}$); *TBDMS*: 0.92 (s, 9H, *tert*-but), 0.11 (s, 6H, CH_3); *allyl*: 5.89 (ddt, 1H, J = 5.5 Hz, J = 10.5 Hz, J = 17.2 Hz, H_β), 5.28 (dd, 1H, J = 1.3 Hz, J = 17.2 Hz, H_γ), 5.21 (dd, 1H, J = 1.2 Hz, J = 10.4 Hz, $H_{\gamma'}$), 4.04 (ddt, 1H, J = 1.2 Hz, J = 5.5 Hz, J = 12.7 Hz, H_α), 3.95 (ddt, 1H, J = 1.3 Hz, J = 5.5 Hz, J = 12.7 Hz, $H_{\alpha'}$).

1,4-bis-O-(5′-O-tert-butyldimethylsilylthymidin-3′-yl)but-2-ene* (3a).** 1.16 mmol of **2** (462 mg) dissolved in 3.5 mL of dry dichloromethane were introduced in a round flask, under argon atmosphere, 216 mg (0.26 mmol) of Grubbs I catalyst dissolved in 2 mL of dry dichloromethane were added slowly. Under stirring, the purple reaction mixture was heated to 35°C for 12 h. The solvent of the resulting dark solution was removed under reduced pressure. The residue was purified by chromatography with an elution of chloroform/ethanol (98/02), **3a** was recovered in 51% yield (227 mg) as colored viscous oil. R_f = 0.35 ($CHCl_3$/EtOH, 95/5, V/V). ^{1}H NMR ($CDCl_3$): ***E isomer: *thymine*: 8.45 (brs, 1H, H_6), 1.89 (d, 3H, J = 1.0 Hz, CH_3); *ose*: 6.27 (dd, 1H, J = 5.5 Hz, J = 8.5 Hz, $H_{1'}$), 4.09–4.11 (m, 2H, $H_{3'}$ and $H_{4'}$), 3.89 (dd, 2H, J = 2.4 Hz, J = 11.3 Hz, $H_{5'a}$), 3.78 (dd, 2H, J = 2.4 Hz, J = 11.3 Hz, $H_{5'b}$), 2.43 (ddd, 1H, J = 1.4 Hz, J = 5.4 Hz, J = 14.4 Hz, $H_{2'a}$), 1.96 (ddd, 1H, J = 5.6 Hz, J = 8.5 Hz, J = 14.4 Hz, $H_{2'b}$); *TBDMS*: 0.92 (s, 9H, *tert*-but), 0.12 (s, 3H, CH_3), 0.11 (s, 3H, CH_3); *butene*: 5.71 (t, 2H, J = 3.8 Hz, H_β), 3.95–4.04 (m, 4H, H_α); ^{13}C NMR ($CDCl_3$): *thymine*: 163.53 (C-4), 150.13 (C-2), 135.33 (C-6), 12.53 (CH_3), 110.83 (C-5); *ose*: 85.13 (C-4′), 85.06 (C-1′), 79.49 (C-3′), 63.68 (C-5′), 37.75 (C-2′); *butene*: 128.94 (C-H_β), 65.07 (C-H_α); *TBDMS*: 25.93 (*tert*-but), −5.32 (CH_3), −5.44 (CH_3). ***Z isomer***: *thymine*: 8.38 (brs, 1H, H_6), 1.91 (d, 3H, J = 1.0 Hz, CH_3); *ose*: 6.26 (dd, 1H, J = 5.5 Hz, J = 8.5 Hz, $H_{1'}$), 4.09–4.11 (m, 2H, $H_{3'}$ and $H_{4'}$), 3.89 (dd, 2H, J = 2.4 Hz, J = 11.3 Hz, $H_{5'a}$), 3.78 (dd, 2H, J = 2.4 Hz, J = 11.3 Hz, $H_{5'b}$), 2.43 (ddd, 1H, J = 1.4 Hz, J = 5.4 Hz, J = 14.4 Hz, $H_{2'a}$), 1.96 (ddd, 1H, J = 5.6 Hz, J = 8.5 Hz, J = 14.4 Hz, $H_{2'b}$); *TBDMS*: 0.92 (s, 9H, *tert*-but), 0.12 (s, 3H, CH_3), 0.11 (s, 3H, CH_3); *butene*: 5.71 (t, 2H, J = 2.7 Hz, H_β), 3.95–4.04 (m, 4H, H_α); ^{13}C NMR ($CDCl_3$): *thymine*: 163.53 (C-4), 150.13 (C-2), 135.33 (C-6), 12.53 (CH_3), 110.83 (C-5); *ose*: 85.13 (C-4′), 85.06 (C-1′), 79.49 (C-3′), 63.68 (C-5′), 37.91

(C-2′); *butene*: 128.86 (C-H_β), 69.05 (C-H_α); *TBDMS*: 25.93 (*tert*-but), −5.32 (CH_3), −5.44 (CH_3).

***1,4-bis-O-(thymidin-3′-yl)but-2-ene* (4).** The deprotection of **3a** (285 mg, 0.373 mmol) was realized in 4 mL of THF. One mL (1 mmol, 2.7 equiv) of a solution of TBAF (1 M) in THF was added. The mixture was stirred at room temperature for 2 h. The solvent was then removed and the crude residue purified by thin-layer preparative chromatography on silica gel ($CHCl_3$/EtOH; 9/1) to yield compound **4** as a white solid in 55% yield (110 mg). R_f = 0.44 ($CHCl_3$/EtOH, 9/1, V/V); mp = 119°C; ^{1}H NMR ($CDCl_3$ + CD_3OD): *thymine*: 7.61 (q, 2H, J = 1.0 Hz, H_6), 1.9 (d, 6H, J = 1.0 Hz, CH_3); *ose*: 6.20 (dd, 2H, J = 5.6 Hz, J = 8.3 Hz, $H_{1'}$), 4.11 (m, 2H, $H_{3'}$, $H_{4'}$), 3.90 (dd, 1H, J = 2. 4 Hz, J = 11.4 Hz, $H_{5'a}$), 3.78 (dd, 1H, J = 2.1 Hz, J = 11.4 Hz, $H_{5'b}$), 2.44 (ddd, 1H, J = 5.6 Hz, J = 1.8 Hz, J = 12.7 Hz, $H_{2'a}$), 1.93 (ddd, 1H, J = 5.9 Hz, J = 8.3 Hz, J = 12.7 Hz, $H_{2'b}$); *TBDMS*: 0.92 (s, 9H, *tert*-but), 0.11 (s, 6H, CH_3); *butene*: 5.89 (ddt, 1H, J = 5.5 Hz, J = 10.5 Hz, J = 17.2 Hz, H_β), 5.28 (dd, 1H, J = 1.3 Hz, J = 17.2 Hz, H_γ), 5.21 (dd, 1H, J = 1.2 Hz, J = 10.4 Hz, $H_{\gamma'}$), 4.04 (ddt, 1H, J = 1.2 Hz, J = 5.5 Hz, J = 12.7 Hz, H_α), 3.95 (ddt, 1H, J = 1.3 Hz, J = 5.5 Hz, J = 12.7 Hz, $H_{\alpha'}$).

***5′-O-(prop-2-enyl) thymidine* (5).** To a solution of thymidine (300 mg, 1.24 mmol) in dry DMF (10 ml) was added NaH (60%, 57 mg, 1.425 mmol) and the mixture was stirred (first activation) under argon. Allyl bromide (129 μL, 1.49 mmol) was then added and the reaction mixture was stirred (second activation). After removal of the solvent, the syrup was purified on a silica gel column, **5** was recovered in 97% yield as a viscous oil (339 mg). R_f = 0.45 ($CHCl_3$/EtOH, 9/1, V/V); mp = 97°C; $[\alpha]_D^{22}$ = 27.96° (c 0.8, EtOH); ^{1}H NMR (400 MHz, CD_3OD, δ ppm): *Thymine*: 7.85 (q, 1-H, $J_{H6,CH3}$ 1.0 Hz, H-6), 1.91 (d, 3H, CH_3); *Ose*: 6.30 (t, 1-H, $J_{1',2'}$ 6.8 Hz, H-1′), 4.39 (dt, 1-H, $J_{3',4'}$ 3.5 Hz, H-3′), 3.91 (q, 1-H, $J_{4',5'}$ 3.5 Hz, H-4′), 3.80 (dd, 1-H $J_{5'b,5'a}$ 12.0 Hz, H-5′$_b$), 3.72 (dd, 1-H, $J_{5'a,5'b}$ 12 Hz, H-5′$_a$), 2.27 (ddd, 1-H, $J_{2'b,3'}$ 6.4 Hz, H-2$_b$′), 2.20 (ddd, 1-H, $J_{2'a,3'}$ 3.6 Hz, $J_{2'a,2'b}$ 13.7 Hz, H-2$_a$′); *Allyl*: 5.86 (ddt, 1-H, $J_{\beta,\gamma}$ 10.4 Hz, $J_{\beta,\gamma'}$ 17.0 Hz, H-β), 5.16 (dq, 1-H, H-γ′), 5.12 (dq, 1-H, $J_{\gamma,\gamma'}$ = 1.4 H-γ), 4.51 (dt, 2H, $J_{\alpha,\beta}$ 5.6 Hz, $J_{\alpha,\gamma}$ 1.4 Hz, H-α). Anal. Calcd for $C_{13}H_{18}O_5N_2$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.36; H, 6.39; N, 9.87.

***3,3′-N,O-diacetyl-5′-O-prop-2-enylthymidine* (6).** To a solution of **5** (157 mg, 0.557 mmol) in excess of acetic anhydride (1.06 mL, 11.14 mmol), was added 4-(dimethylamino)pyridine (20.4 mg, 0.167 mmol) and the mixture was stirred under microwave irradiation over 1 min (P: 100 W). The reaction mixture was quenched by an saturated aqueous $NaHCO_3$ solution and extracted with chloroform. The chloroform solution was dried over $MgSO_4$ and the solvent was removed by evaporation under reduced pressure. The crude product was purified by chromatography on silica gel (elution with a gradient of petroleum ether/ chloroform). Compound **6** was isolated as a viscous oil (189 mg, 92%). R_f = 0.49

($CHCl_3$/EtOH; 98/2; V/V); $[\alpha]_D^{22}$ = +4.799 (0.7, $CHCl_3$); ^1H NMR (CD_3OD): *thymine*: 7.28 (s, 1H, H_6), 1.95 (s, 3H, CH_3); *ose*: 6.35 (dd, 1H, J = 5.7 Hz, J = 8.4 Hz, $H_{1'}$), 5.22 (dt, 1H, J = 2.1 Hz, J = 6.7 Hz, $H_{3'}$), 4.24 (m, 1H, $H_{4'}$), 4.37 (dd, 1H, J = 4.1 Hz, J = 12.2 Hz, $H_{5'a}$), 3.72 (dd, 1H, J = 3.4 Hz, J = 12.2 Hz, $H_{5'b}$), 2.48 (ddd, 1H, J = 2.0 Hz, J = 5.7 Hz, J = 14.5 Hz, $H_{2'a}$), 2.15 (ddd, 1H, J = 6.7 Hz, J = 8.4 Hz, J = 14.5 Hz, $H_{2'b}$); *allyl*: 5.86 (ddt, 1H, J = 5.9 Hz, J = 10.3 Hz, J = 16.8 Hz, H_β), 5.26 (dd, 1H, J = 1.0 Hz, J = 16.8 Hz, H_γ), 5.19 (dd, 1H, J = 1.0 Hz, J = 10.3 Hz, H_γ), 4.55 (br d, 2H, J = 5.9 Hz, H_α); *acetyl*: 2.12 (s, 3H, CH_3), 2.10 (s, 3H, CH_3).

1,4-bis-O-(3′,3-N,O-Diacetylthymidin-5′-yl)but-2-ene* (7).** Compound **7** was prepared according to the procedure described for **3a** starting from **6** (435 mg, 1.15 mmol) using 200 mg (0.242 mmol) of t Grubbs I catalyst. 245 mg of **7** was obtained (61%, Z/E: 1/4). R_f = 0.35 ($CHCl_3$/EtOH; 98/2; V/V); ^1H NMR ($CDCl_3$): ***E isomer: *thymine*: 7.24 (d, 1H, J = 0.9 Hz, H_6), 1.95 (d, 3H, J = 0.9 Hz, CH_3); *ose*: 6.37 (dd, 1H, J = 5.5 Hz, J = 8.5 Hz, $H_{1'}$), 5.21 (dt, 2H, J = 2.3 Hz, J = 6.7 Hz, $H_{3'}$), 4.24 (m, 2H, $H_{4'}$), 4.37 (dd, 2H, J = 4.1 Hz, J = 12.2 Hz, $H_{5'a}$), 4.33 (dd, 2H, J = 3.2 Hz, J = 12.2 Hz, $H_{5'b}$), 2.48 (ddd, 1H, J = 2.1 Hz, J = 5.5 Hz, J = 14.2 Hz, $H_{2'a}$), 2.13 (ddd, 1H, J = 6.7 Hz, J = 8.5 Hz, J = 14.2 Hz, $H_{2'b}$); *allyl group*: 5.66 (t, 2H, J = 4.6 Hz, H_β), 4.82 (m, 4H, H_α); *acetyl groups*: 2.13 (s, 6H, CH_3), 2.10 (s, 6H, CH_3). ***Z isomer***: *thymine*: 7.25 (d, 1H, J = 0.9 Hz, H_6), 1.95 (d, 3H, J = 0.9 Hz, CH_3); *ose*: 6.36 (dd, 1H, J = 5.6 Hz, J = 8.5 Hz, $H_{1'}$), 5.21 (dt, 2H, J = 2.3 Hz, J = 6.7 Hz, $H_{3'}$), 4.24 (m, 2H, $H_{4'}$), 4.37 (dd, 2H, J = 4.1 Hz, J = 12.2 Hz, $H_{5'a}$), 4.33 (dd, 2H, J = 3.2 Hz, J = 12.2 Hz, $H_{5'b}$), 2.48 (ddd, 1H, J = 1.9 Hz, J = 5.5 Hz, J = 14.2 Hz, $H_{2'a}$), 2.13 (ddd, 1H, J = 6.7 Hz, J = 8.5 Hz, J = 14.2 Hz, $H_{2'b}$); *butene*: 5.66 (m, 2H, H_β), 4.82 (m, 4H, H_α); *acetyl groups*: 2.13 (s, 6H, CH_3), 2.10 (s, 6H, CH_3).

1,4-bis-O-(Thymidin-5′-yl)but-2-ene* (8).** A solution of compound **7** (245 mg, 0.348 mmol) in 3 mL of methanol, 2 mL of dichloromethane, and 5 mL of solution of ammonia in methanol (7 M) was stirred at room temperature for 3 h. The solution was evaporated to dryness and the crude product was purified using preparative TLC ($CHCl_3$/EtOH; 8/2; V/V). Pure **8** was recovered as a foam in 85% yield (158 mg). R_f = 0.49 ($CHCl_3$/EtOH; 7/3; V/V); ^1H NMR (CD_3OD): ***E isomer: *thymine*: 7.83 (q, 2H, J = 1.0 Hz, H_6), 1.89 (d, 6H, J = 1.0 Hz, CH_3); *ose*: 6.27 (t, 2H, J = 6.7 Hz, $H_{1'}$), 4.38 (dt, 2H, J = 3.4 Hz, J = 6.4 Hz, $H_{3'}$), 3.89 (q, 2H, J = 3.1 Hz, $H_{4'}$), 3.79 (dd, 2H, J = 3.1 Hz, J = 12.0 Hz, $H_{5'a}$), 3.72 (dd, 2H, J = 3.7 Hz, J = 12.0 Hz, $H_{5'b}$), 2.31–2.22 (m, 2H, $H_{2'a}$), 2.19 (ddd, 2H, J = 6.5 Hz, J = 7.0 Hz, J = 13.5 Hz, $H_{2'b}$); *butene*: 5.73 (m, 2H, H_β), 4.46 (m, 4H, H_α); ^{13}C NMR (CD_3OD): *thymine*: 165.22 (C-4), 152.22 (C-2), 136.75 (C-6), 13.30 (CH_3), 110.88 (C-5); *ose*: 89.00 (C-4′), 87.30 (C-1′), 72.18 (C-3′), 62.88 (C-5′), 41.50 (C-2′); *butene*: 128.76 (C-H_β), 43.29 (C-H_α). ***Z isomer***: *thymine*: 7.83 (q, 2H, J = 1.0 Hz, H_6), 1.91 (d, 6H, J = 1.0 Hz, CH_3); *ose*: 6.30 (t, 2H, J = 6.8 Hz, $H_{1'}$), 4.38 (dt, 2H, J = 3.4 Hz, J = 6.4 Hz, $H_{3'}$), 3.90 (q, 2H, J = 3.1 Hz, $H_{4'}$), 3.80 (dd, 2H, J = 3.1 Hz, J = 12.0 Hz, $H_{5'a}$), 3.73 (dd, 2H,

J = 3.1 Hz, J = 12.0 Hz, $H_{5'b}$), 2.31–2.22 (m, 4H, $H_{2'}$); *butene*: 5.59 (m, 2H, H_β), 4.76 (m, 4H, H_α); ^{13}C NMR (CD_3OD): *thymine*: 165.34 (C-4), 152.34 (C-2), 136.75 (C-6), 13.30 (CH_3), 110.88 (C-5); *ose*: 89.00 (C-4′), 87.30 (C-1′), 72.18 (C-3′), 62.88 (C-5′), 41.50 (C-2′); *butene*: 128.76 (C-H_β), 39.72 (C-H_α).

***3′-O-(prop-2-enyl)thymidine* (9).** Deprotection of **2** (1.723 g, 4.48 mmol) was realized in 30 mL of dry THF. Five mL (5.38 mmol, 1.2 equiv) of a solution of TBAF (1 M) in THF was added. The mixture was stirred at room temperature for 1.5 h. The solvent was then removed and the crude residue purified by flash chromatography on silica gel (elution with a gradient of $CHCl_3$/EtOH) to yield compound **9** in 88% yield (1.191 g). R_f = 0.44 ($CHCl_3$/EtOH, 95/05, V/V); mp = 139°C; $[\alpha]_D^{22}$ = +37.44 (1.8, $CHCl_3$). ^1H NMR (CD_3OD): *thymine*: 7.78 (brs, 1H, H_6), 1.85 (brs, 3H, T-CH_3); *ose*, 6.22 (dd, 1H, J = 5.9 Hz, J = 8.0 Hz, $H_{1'}$), 4.19 (dt, 1H, J = 2.4 Hz, J = 5.6 Hz, $H_{3'}$), 4.05 (m, 3H, H_α, $H_{4'}$, $H_{\alpha'}$), 3.78 (dd, 1H, J = 3.5 Hz, J = 12.0 Hz, $H_{5'a}$), 3.71 (dd, 1H, J = 3.6 Hz, J = 12.0 Hz, $H_{5'b}$), 2.35 (ddd, 1H, J = 2.4 Hz, J = 5.9 Hz, J = 13.8 Hz, $H_{2'a}$), 2.15 (ddd, 1H, J = 5.6 Hz, J = 8.0 Hz, J = 13.8 Hz, $H_{2'b}$); *allyl*: 5.92 (ddt, 1H, J = 5.4 Hz, J = 10.4 Hz, J = 17.1 Hz, H_β), 5.29 (br dd, 1H, J = 1.6 Hz, J = 17.1 Hz, H_γ), 5.21 (br dd, 1H, J = 1.3 Hz, J = 10.4 Hz, $H_{\gamma'}$).

***3-N-benzoyl-3′-O-(prop-2-enyl)thymidine* (12).** To a solution of 1.025 g (3.63 mmol) of **5** in 25 mL of dichloromethane, under argon, was added 1.1 equiv of triethylamine (557 μL, 3.99 mmol). The mixture was stirred for 15 min and then 1.1 equiv of benzoyl chloride (453 μL, 3.99 mmol) was added. After 3 h at room temperature, the solvent was removed and the crude product purified on a silica gel column; compound **12** was recovered in 53% yield as a viscous oil (742 mg). R_f = 0.46 (CH_2Cl_2/EtOH; 95/5; V/V); $[\alpha]_D^{22}$ = −17.628 (2.37, CH_2Cl_2); ^1H NMR, ($CDCl_3$): *thymine*: 7.24 (brs, 1H, H_6), 1.7 (brs, 3H, CH_3); *ose*: 6.35 (t, 1H, J = 6.5 Hz, $H_{1'}$), 4.52 (m, 1H, $H_{3'}$), 4.25 (m, 1H, $H_{4'}$), 4.64 (dd, 1H, J = 3.1 Hz, J = 12.0 Hz, $H_{5'a}$), 4.5 (dd, 1H, J = 4.9 Hz, J = 12.0 Hz, $H_{5'b}$), 2.48 (ddd, 1H, J = 4.3 Hz, J = 6.5 Hz, J = 13.7 Hz, $H_{2'a}$), 2.19 (dt, 1H, J = 6.5 Hz, J = 13.7 Hz, $H_{2'b}$); *allyl*: 5.85 (ddt, 1H, J = 5.8 Hz, J = 10.5 Hz, J = 16.2 Hz, H_β), 5.23 (brd, 1H, J = 16.2 Hz, H_γ), 5.16 (brd, 1H, J = 10.5 Hz, H_γ), 4.63–4.52 (m, 2H, H_α); *benzoyl group*: 8.02 (d, 2H, J = 7.4 Hz, H_{ortho}), 7.6 (brt, 1H, J = 7.4 Hz, H_{para}), 7.46 (t, 2H, J = 7.4 Hz, H_{meta}).

***(3-N-benzoyl-5′-O-allylthymidin-3′-yl)glutaric acid* (13).** Compound **12** (275 mg, 0.712 mmol) was solubilized in 15 mL of anhydrous pyridine with 1.5 equiv of DMAP (243 mg, 2.13 mmol) and 3 equiv of glutaric anhydride (243 mg, 2.13 mmol). The reaction was heated at 60°C during 5 h. The mixture was concentrated and the crude product purified by preparative TLC ($CHCl_3$/EtOH; 95/5; V/V). Compound **13** was recovered in 74% yield (261 mg) as a white solid. R_f = 0.42 (CH_2Cl_2/EtOH; 94/6; V/V); mp = 90°C; $[\alpha]_D^{22}$ = −21.569° (2.25; CH_2Cl_2); ^1H NMR ($CDCl_3$): *thymine*: 7.21 (q, 1H, J = 0.7 Hz, H_6), 1.64 (d, 3H,

J = 0.7 Hz, CH_3); *ose*: 6.37 (brt, 1H, J = 5.8 Hz, $H_{1'}$), 5.39 (de, 1H, J = 5.7 Hz, $H_{3'}$), 4.37 (m, 1H, $H_{4'}$), 4.72 (dd, 1H, J = 2.2 Hz, J = 12.2 Hz, $H_{5'a}$), 4.58 (dd, 1H, J = 2.7 Hz, J = 12.2 Hz, $H_{5'b}$), 2.55 (m, 1H, $H_{2'a}$), 2.22 (m, 1H, $H_{2'b}$); *allyl group*: 5.85 (ddt, 1H, J = 5.7 Hz, J = 10.4 Hz, J = 16.6 Hz, H_β), 5.23 (de, 1H, J = 16.6 Hz, H_γ), 5.17 (brd, 1H, J = 10.4 Hz, H_γ), 4.52 (de, 2H, J = 5.7 Hz, H_α); *benzoyl group*: 8.02 (d, 2H, J = 7.2 Hz, H_{ortho}), 7.6 (brt, 1H, J = 7.4 Hz, H_{para}), 7.46 (t, 2H, J = 7.8 Hz, H_{meta}); *spacer*: 2.43 (m, 4H), 1.96 (m, 2H).

Glutaric anhydride of (3-N-benzoyl-5′-O-allylthymidin-3′-yl) and (3′-O-allylthymidin-5′-yl)* (14).** Compound **13** (200 mg, 0.4 mmol) and **9** (56.5 mg, 0.2 mmol) were solubilized in 6 mL of dry dichloromethane and 3 mL of anhydrous toluene with 0.8 equiv of DMAP (39 mg, 0.32 mmol) and 3 equiv of 1,3-dicyclohexylcarbodiimide (247.5 mg, 1.2 mmol). The solution was stirred under argon during 24 h at room temperature. The reaction mixture was quenched by an acid aqueous solution and extracted with chloroform. The chloroform solution was dried over $MgSO_4$ and solvent was removed by evaporation under reduced pressure. The crude product was purified by preparative TLC (AcOEt/EP; 5/5; 7/3). Compound **14** was recovered in 88% yield as a viscous oil (134.5 mg). R_f = 0.51 (AcOEt/EP; 8/2). ^{1}H NMR ($CDCl_3$): *thymine*: 8.41 (s, 1H, N-H), 7.23 (d, 1H, J = 1.1 Hz, H_6), 7.21 (d, 1H, J = 1.1 Hz, H_6), 1.93 (d, 3H, J = 1.1 Hz, CH_3), 1.65 (d, 3H, J = 1.1 Hz, CH_3); *ose **1: 6.36 (dd, 1H, J = 6.2 Hz, J = 8.0 Hz, $H_{1'}$), 5.38 (dt, 1H, J = 1.7 Hz, J = 6.7 Hz, $H_{3'}$), 4.36 (td, 1H, J = 3.6 Hz, J = 5.7 Hz, $H_{4'}$), 4.71 (dd, 1H, J = 3.6 Hz, J = 12.2 Hz, $H_{5'a}$), 4.58 (dd, 1H, J = 3.6 Hz, J = 12.2 Hz, $H_{5'b}$), 2.53 (ddd, 1H, J = 6.7 Hz, J = 8.0 Hz, J = 14.1 Hz, $H_{2'a}$), 2.22 (ddd, 1H, J = 1.7 Hz, J = 6.2 Hz, J = 14.1 Hz, $H_{2'b}$); *ose **2***: 6.22 (dd, 1H, J = 6.2 Hz, J = 7.3 Hz, $H_{1'}$), 4.05 (m, 1H, $H_{3'}$), 4.36 (dt, 1H, J = 3.5 Hz, J = 5.3 Hz, $H_{4'}$), 4.36 (dd, 1H, J = 3.5 Hz, J = 12.0 Hz, $H_{5'a}$), 4.28 (dd, 1H, J = 3.5 Hz, J = 12.0 Hz, $H_{5'b}$), 2.47 (m, 1H, $H_{2'a}$), 2.04 (ddd, 1H, J = 6.9 Hz, J = 7.3 Hz, J = 14.0 Hz, $H_{2'b}$); *allyl group **1***: 5.84 (ddt, 1H, J = 5.9 Hz, J = 10.2 Hz, J = 17.1 Hz, H_β), 5.24 (dq, 1H, J = 1.3 Hz, J = 17.1 Hz, $H_{\gamma trans}$), 5.17 (dq, 1H, J = 1.2 Hz, J = 10.2 Hz, $H_{\gamma cis}$), 4.52 (brd, 2H, J = 5.9 Hz, H_α); *allyl group **2***: 5.89 (ddt, 1H, J = 5.5 Hz, J = 10.4 Hz, J = 17.2 Hz, H_β), 5.3 (dq, 1H, J = 1.4 Hz, J = 17.2 Hz, $H_{\gamma trans}$), 5.22 (dq, 1H, J = 1.4 Hz, J = 10.4 Hz, $H_{\gamma cis}$), 4.05 (ddt, 1H, J = 1.4 Hz, J = 5.5 Hz, J = 12.6 Hz, H_α), 3.97 (ddt, 1H, J = 1.4 Hz, J = 5.5 Hz, J = 12.6 Hz, H_α); *spacer*: 2.43 (m, 4H), 1.96 (m, 2H); *benzoyl group*: 8.02 (dd, 2H, J = 1.2 Hz, J = 7.8 Hz, H_{ortho}), 7.61 (tt, 1H, J = 1.2 Hz, J = 8.5 Hz, H_{para}), 7.47 (tt, 2H, J = 1.2 Hz, J = 8.0 Hz, H_{meta}).

Compound* (15).** Compound **15** was prepared according to the procedure described for **3a** starting from **14** (136 mg, 0.178 mmol) in 15 mL of CH_2Cl_2 using 44 mg (0.053 mmol) of Grubbs I catalyst. The crude product was purified using preparative TLC (AcOEt/E P; 80/20; V/V) to give compound **15** in 45% yield. Thirty percent of E isomer (39 mg) and 15% of Z isomer (20 mg). ***E isomer: R_f = 0.47 (AcOEt); ^{1}H NMR ($CDCl_3$): *thymine*: 7.25 (d, 1H, J = 0.9 Hz, H_6),

7.19 (d, 1H, J = 0.8 Hz, H_6), 1.93 (d, 3H, J = 0.8 Hz, CH_3), 1.68 (d, 3H, J = 0.9 Hz, CH_3); *ose* ***1***: 6.34 (dd, 1H, J = 4.8 Hz, J = 9.3 Hz, $H_{1'}$), 5.38 (br d, 1H, J = 5.6 Hz, $H_{3'}$), 4.49 (m, 1H, $H_{4'}$), 4.71 (dd, 1H, J = 3.3 Hz, J = 12.2 Hz, $H_{5'a}$), 4.56 (dd, 1H, J = 3.3 Hz, J = 12.2 Hz, $H_{5'b}$), 2.56 (ddd, 1H, J = 1 Hz, J = 4.8 Hz, J = 14.1 Hz, $H_{2'a}$), 2.15 (ddd, 1H, J = 5.6 Hz, J = 9.3 Hz, J = 14.1 Hz, $H_{2'b}$); *ose* ***2***: 6.17 (t, 1H, J = 6.4 Hz, $H_{1'}$), 4.13–4.08 (m, 1H, $H_{3'}$), 4.13–4.08 (m, 1H, $H_{4'}$), 4.32 (dd, 1H, J = 2.2 Hz, J = 12.0 Hz, $H_{5'a}$), 4.23 (dd, 1H, J = 6.9 Hz, J = 12.0 Hz, $H_{5'b}$), 2.35 (ddd, 1H, J = 2.8 Hz, J = 6.4 Hz, J = 13.8 Hz, $H_{2'a}$), 1.96 (m, 1H, $H_{2'b}$); *spacer*: 2.44–2.51 (m, 4H), 2.02–2.10 (m, 2H); *butene*: 5.66 (dt, 1H, J = 4.7 Hz, J = 15.2 Hz, H_β), 5.49 (dddd, 1H, J = 1.7 Hz, J = 5.8 Hz, J = 8.4 Hz, J = 15.2 Hz, H_β), 4.56 (brd, 2H, J = 4.7 Hz, H_α), 4.20 (ddd, 1H, J = 0.8 Hz, J = 5.8 Hz, J = 13 Hz, H_α), 3.81 (dd, 1H, J = 8.4 Hz, J = 13 Hz, H_α); *benzoyl group*: 8.04 (dd, 2H, J = 1.1 Hz, J = 7.9 Hz, H_{ortho}), 7.63 (tt, 1H, J = 7.9 Hz, J = 1.1 Hz, H_{para}), 7.46 (br t, 2H, J = 7.9 Hz, H_{meta}; ***Z isomer:*** R_f = 0.37 (AcOEt); *thymine*: 7.28 (d, 2H, J = 0.9 Hz, H_6), 1.67 (d, 6H, J = 0.9 Hz, CH_3); *benzoyl group*: 8.02 (dd, 2H, J = 1.1 Hz, J = 7.9 Hz, H_{ortho}), 7.62 (brt, 1H, J = 7.9 Hz, H_{para}), 7.48 (brt, 2H, J = 7.9 Hz, H_{meta}); *ose*: 6.33 (dd, 1H, J = 4.7 Hz, J = 10.0 Hz, $H_{1'}$), 5.42 (brd, 1H, J = 5.3 Hz, $H_{3'}$), 4.45 (br t, 1H, J = 3.3 Hz, $H_{4'}$), 4.68 (dd, 1H, J = 3.3 Hz, J = 12.2 Hz, $H_{5'a}$), 4.56 (dd, 1H, J = 3.3 Hz, J = 12.2 Hz, $H_{5'b}$), 2.51 (ddd, 1H, J = 1.3 Hz, J = 4.7 Hz, J = 14.0 Hz, $H_{2'a}$), 2.11 (ddd, 1H, J = 5.3 Hz, J = 10.0 Hz, J = 14.0 Hz, $H_{2'b}$), *ose*: 6.25 (dd, 1H, J = 5.6 Hz, J = 8.5 Hz, $H_{1'}$), 4.32 (m,1H, $H_{3'}$), 4.41 (m, 1H, $H_{4'}$), 4.35 (m, 1H, $H_{5'a}$), 4.28 (dd, 1H, J = 5.8 Hz, J = 11.9 Hz, $H_{5'b}$), 2.45 (m, 1H, $H_{2'a}$), 1.98 (ddd, 1H, J = 6.2 Hz, J = 8.5 Hz, J = 14.3 Hz, $H_{2'b}$); *spacer*: 2.39–2.59 (m, 4H, H_{a1} et H_{a3}), 2.03–2.08 (m, 2H, H_{a2}); *butene*: 5.70 (dt, 1H, J = 6.4Hz, J = 10.5 Hz, H_β), 5.58 (dt, 1H, J = 7.3 Hz, J = 10.5 Hz, H_β), 4.53 (br d, 2H, J = 7.3 Hz, H_α), 4.39 (br dd, 1H, J = 6.4 Hz, J = 13.0 Hz, H_α), 4.29 (dd, 1H, J = 6.4 Hz, J = 13.0 Hz, H_α).

1-(thymidin-3′-yl)-4-(thymidin-5′-yl)but-2-ene (E)* (16).** A solution of **15** (E***) (38 mg, 0.516 mmol) in 4 mL of methanol and 1 mL of CH_2Cl_2 as cosolvent with 3 equiv. of sodium methoxide (0.5 M solution in methanol) was stirred at room temperature for 3 h. The solution was neutralized by addition of Amberlite IRN 77 H^+ resin (Aldrich) and filtered. The solvent was evaporated to dryness and the crude product was purified using preparative TLC ($CHCl_3$/EtOH; 80/20; V/V). Pure **16** (***E***) was recovered in 74% yield (21 mg). R_f = 0.43 ($CHCl_3$/EtOH; 85/15; V/V); mp = 70°C; ^1H NMR (CD_3OD): *thymine*: 7.84 (q, 1H, J = 1.0 Hz, H_6), 7.76 (q, 1H, J = 1.0 Hz, H_6), 1.90 (d, 3H, J = 1.0 Hz, CH_3); 1.87 (d, 3H, J = 1.0 Hz, CH_3); *ose* ***1***: 6.19 (dd, 1H, J = 6.0 Hz, J = 7.8 Hz, $H_{1'}$), 4.14 (dt, 1H, J = 2.6 Hz, J = 6.0 Hz, $H_{3'}$), 3.98 (m, 1H, $H_{4'}$), 3.80 (dd, 1H, J = 3.1 Hz, J = 12.0 Hz, $H_{5'a}$), 3.71 (dd, 1H, J = 3.6 Hz, J = 12.0 Hz, $H_{5'b}$), 2.31 (ddd, 1H, J = 2.6 Hz, J = 6.0 Hz, J = 13.9 Hz, $H_{2'a}$), 2.14 (ddd, 1H, J = 6.0 Hz, J = 7.8 Hz, J = 13.9 Hz, $H_{2'b}$); *ose* ***2***: 6.29 (t, 1H, J = 6.8 Hz, $H_{1'}$), 4.39 (dt, 1H, J = 3.5 Hz, J = 6.4 Hz, $H_{3'}$), 3.90 (q, 1H, J = 3.4 Hz, $H_{4'}$), 3.75 (dd, 1H, J = 3.5 Hz, J = 12.1 Hz, $H_{5'a}$), 3.68 (dd, 1H, J = 3.6 Hz, J = 12.1 Hz, $H_{5'b}$), 2.28 (ddd, 1H, J = 2.6 Hz, J = 6.2 Hz, J = 13.5 Hz, $H_{2'a}$), 2.14

(ddd, 1H, J = 6.6 Hz, J = 7.2 Hz, J = 13.5 Hz, $H_{2'b}$); *butene*: 5.79 (dt, 1H, J = 6.0 Hz, J = 15.6 Hz, H_β), 5.72 (dt, 1H, J = 5.1 Hz, J = 15.6 Hz, H_β), 4.51 (br d, 2H, J = 4.0 Hz, H_α), 4.02 (m, 2H, H_α). ^{13}C NMR (CD_3OD): *thymine*: 166.55 (C-4), 165.21 (C-4), 152.50 (C-2), 152.26 (C-2), 138.28 (C-6), 136.79 (C-6), 111.77 (C-5), 110.89 (C-5), 13.32 (CH3), 12.59 (CH3); *ose*: 89.05 (C-4′), 87.31 (C-1′), 86.83 (C-4′), 86.52 (C-1′), 72.25 (C-3′) 70.36 (C-3′), 63.25 (C-5′), 62.91 (C-5′), 41.49 (C-2′), 38.65 (C-2′); butene: 131.27 (C-β), 127.92 (C-β), 80.21 (C-α), 43.27 (C-α).

1-(thymidin-3′-yl)-4-(thymidin-5′-yl)but-2-ene (Z)* (16).** A solution of **15** (*Z*) (65 mg, 0.088 mmol) in 4 mL of methanol and 1 mL of CH_2Cl_2 as cosolvent with 3 equiv of sodium methoxide (0.5 M solution in methanol) was stirred at room temperature for 3 h. The solution was neutralized by addition of Amberlite IRN 77 H^+ resin (Aldrich) and filtered. The solvent was evaporated to dryness and the crude product was purified using preparative TLC ($CHCl_3$/EtOH; 80/20; V/V). Pure **16** (*Z*) was recovered in 72% yield (34 mg) as a viscous oil. R_f = 0.45 ($CHCl_3$/EtOH; 82/18; V/V); ^{1}H NMR (CD_3OD): *thymine*: 7.83 (q, 1H, J = 1.0 Hz, H_6), 7.81 (q, 1H, J = 1.0 Hz, H_6), 1.90 (d, 3H, J = 1.0 Hz, CH_3), 1.88 (d, 3H, J = 1.0 Hz, CH_3); *ose* ***1: 6.23 (dd, 1H, J = 6.0 Hz, J = 7.8 Hz, $H_{1'}$), 4.25 (dt, 1H, J = 2.7 Hz, J = 5.7 Hz, $H_{3'}$), 4.05 (m, 1H, $H_{4'}$), 3.79 (dd, 1H, J = 3.1 Hz, J = 12.0 Hz, $H_{5'a}$), 3.72 (dd, 1H, J = 3.7 Hz, J = 12.0 Hz, $H_{5'b}$), 2.40 (ddd, 1H, J = 2.7 Hz, J = 6.0 Hz, J = 13.7 Hz, $H_{2'a}$), 2.14–2.26 (m, 1H, $H_{2'b}$). *ose* ***2***: 6.29 (t, 1H, J = 6.8 Hz, $H_{1'}$), 4.39 (dt, 1H, J = 3.4 Hz, J = 6.3 Hz, $H_{3'}$), 3.90 (q, 1H, J = 3.4 Hz, $H_{4'}$), 3.81 (dd, 1H, J = 3.4 Hz, J = 12.0 Hz, $H_{5'a}$), 3.75 (dd, 1H, J = 3.4 Hz, J = 12.0 Hz, $H_{5'b}$), 2.26 (ddd, 1H, J = 3.6 Hz, J = 6.8 Hz, J = 13.7 Hz, $H_{2'a}$), 2.16–2.26 (m, 1H, $H_{2'b}$); *butene*: 5.70 (dt, 1H, J = 6.2 Hz, J = 11.1 Hz, H_β), 5.57 (dt, 1H, J = 6.9 Hz, J = 11.1 Hz, H_β), 4.58 (d, 2H, J = 6.9 Hz, H_α), 4.32 (brd, 2H, H_α). ^{13}C NMR (CD_3OD): *thymine*: 166.47 (C-4), 165.10 (C-4), 152.43 (C-2), 152.16 (C-2), 136.65 (C-6), 138.23 (C-6), 110.64 (C-5), 110.78 (C-5), 13.21 (CH3), 12.51 (CH3); *ose* ***1***: 86.81 (C-4′), 86.47 (C-1′), 80.21 (C-3′), 62.81 (C-5′), 38.54 (C-2′), *ose* ***2***: 87.18 (C-1′), 86.47 (C-4′), 72.14 (C-3′), 63.25 (C-5′), 41.37 (C-2′); *butene*: 131.44 (C-β), 127.75 (C-β), 66.11 (C-α), 39.46 (C-α).

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