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Allylsilanes in the Preparation of 5'-C-Hydroxy or Bromo Alkylthymidines

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Abstract: The reaction of 5'-C-thymidine aldehyde with allytrimethylsilane promoted by BF_3:Et_2O lead stereoselectively to 5'-C(S)-allylthymidine which is converted to 5'-C(S)-hydroxyhexylthymidine. 5'-C-(R or S) hydroxypentylthymidine can be obtained by using ω-tertButyldimethylsilyloxyallyltrimethylsilane in the Sakurai reaction. In the same conditions, ω-Bromoallyltrimethylsilane adds to the aldehyde with a complete transposition of the siliranium intermediate and allows the preparation of the 5'-C(S)-bromopentene derivative.

Keywords: Allylation; rearrangement; diastereoselection; 5'-C-substituted-Nucleosides.

INTRODUCTION

Research in the field of oligodeoxynucleotide analogues which could exhibit activity in antiviral and anticancer therapy by an antisense approach, has received important attention.[1-5]

The major requirements to expect a good activity for antisense oligodeoxynucleotides (ODNs) are good cellular uptake, high specificity and affinity for target RNA and stability towards cytoplasm nucleases.

Our interest is focused on 5'-C substituted nucleosides. This class of compounds appeared recently [6-11] and proved, when incorporated into ODNs, to have a reasonable duplex stability and enhanced nuclease resistance compared to unmodified ODNs.

In this context 5'-C-hydroxyalkyl thymidines should provide a useful tool for introducing additional functionality's on the ODNs to increase membrane permeability or to impart RNase activity (if conjugated with an appropriate catalyst group) leaving the 3' and 5' ends free for further modifications.

We have already described the stereoselective preparation of 5'-C-hydroxyethyl thymidine.[9] With a view to extending the length of the alkyl chain substituted at 5'-C, we explored the condensation of allyltrimethylsilane[12] and ω-silyloxyallyltrimethylsilane[13] with thymidine 5'-C aldehyde **1**.

RESULTS AND DISCUSSION

Promoted by BF_3:Et_2O, the condensation of allyltrimethylsilane with **1** produced in high yield, a single stereoisomer **2** isolated after silylation of the 5' hydroxyl function (scheme 1), titanium tetrachloride did not

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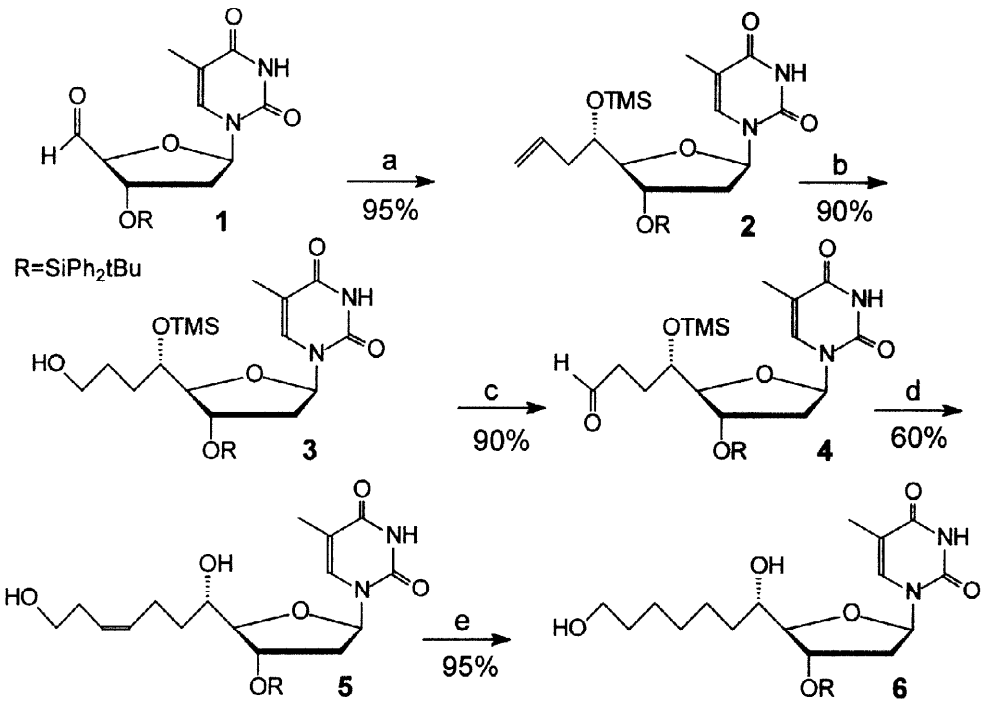
change the stereochemical outcome of the reaction as could be expected.[13] In order to determine the absolute configuration of the newly created asymmetric center, we chose to synthesise a 5'-C-hydroxyhexylthymidine **6** to establish a comparison with the similar compound prepared from the known 5'-C "S" -methylacetate thymidine[9] **7** (scheme 2).

The double bond in **2** is oxidized with borane-methyl sulfide/H_2O_2/NaOH to produce **3** in excellent yield. Aldehyde **4** obtained by the Doering procedure[14] is submitted to a Wittig condensation with $THPO(CH_2)_3PPh_3Br$ to give protected 5'-C-hydroxyhexenyl thymidine with a "Z" double bond. Removal of the protective groups of the 5' and 11' hydroxyl functions in acidic media gave **5** which is submitted to catalytic hydrogenation and thus provide 5'-C-hydroxyhexyl thymidine **6**. At this stage the absolute configuration of 5'-C is not determined, therefore, we synthesised 5'-C(S)-hydroxyhexyl thymidine as a reference product (scheme 2).

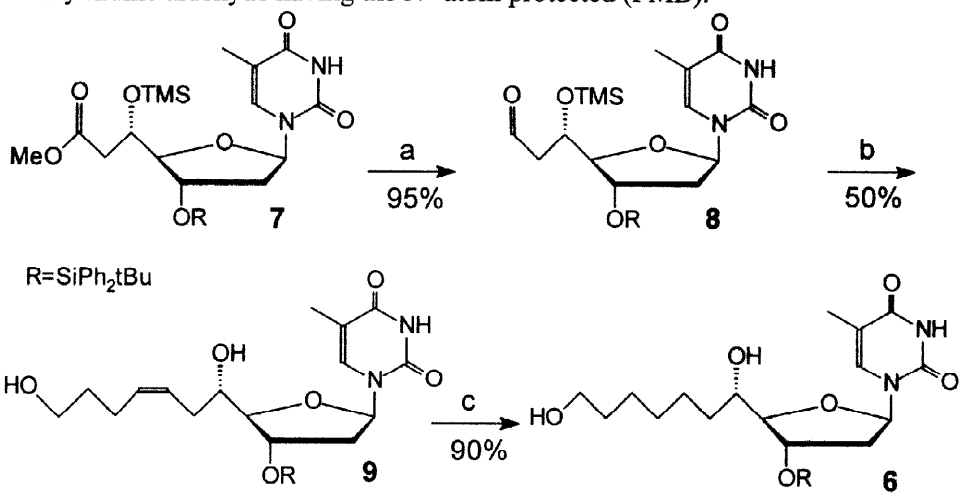


Scheme 1 - a) i- 5 eq allyltrimethylsilane, 5 eq BF_3:Et_2O, 0 °C, 3 h, CH_2Cl_2; ii-TMSCl, HMDS, Pyr; 2 h, b) 6 eq BH_3:DMS,THF, 0 °C, 3 h, then H_2O_2/NaOH; c) Pyr:SO_3, DMSO, Et_3N, CH_2CL_2, 20 min, RT; d) i-8 eq $THPO(CH_2)_3PPh_3Br$, nBuLi, THF,-78 °C to RT; ii- PTSA, MeOH, RT, 3 h; e) H_2/10%Pd/C, MeOH, RT, 5 h.

Mild reduction of the ester moiety of **7** with diisobutylaluminumhydride[15] to the corresponding aldehyde **8** gave the precursor for a Wittig condensation with the non-stabilised ylide generated from $THPO(CH_2)_4PPh_3Br$. The fully protected nucleoside was then obtained; TMS and THP protective groups are removed by acidic hydrolysis to yield compound **9**. Reduction of the double bond of **9** gave 5'-C(S)-hydroxyhexyl thymidine **6**. All spectroscopic data of **6** so obtained were found to be identical with those of **6** synthesized as shown in scheme 1. We can therefore conclude that addition of allyltrimethylsilane promoted by BF_3:Et_2O (or $TiCl_4$) to 5'-C-thymidine aldehyde leads to the formation of the 5'-C "S".

This is quite surprising since Danishefsky[16] reported that when allyltrimethylsilane is added to the 5'-C-aldehyde of a fully protected uridine (N^3 of the base protected by a paramethoxybenzyl) the major adduct (95%) is the "R" stereoisomer at 5'-C. One difference in the two reactions is the protection of the N^3-nitrogen on the

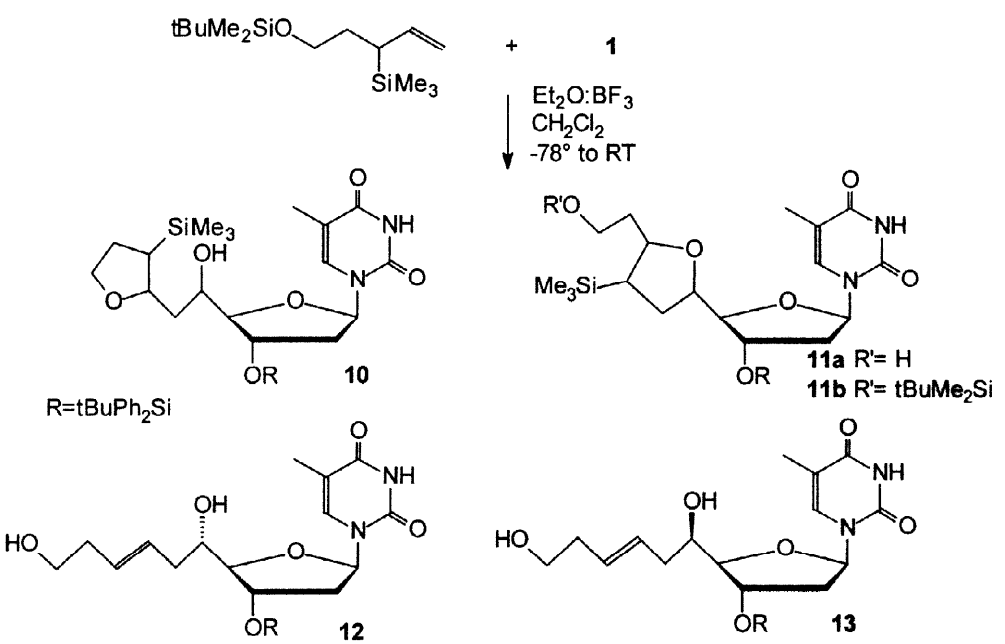
base that could interfere with the Lewis acid to change the stereochemical outcome; thus we ran this reaction again on the 5'-C thymidine aldehyde having the N^3 atom protected (PMB).



Scheme 2 - a) DIBAH, Tol, -78 °C; b) i- 8 eq $THPO(CH_2)_4PPh_3Br$, nBuLi, THF,-78 °C to RT; ii- PTSA, MeOH, RT, 3 h; c) H_2/10% Pd/C, MeOH, RT, 5 h.

After removal of the nitrogen protective group, compound **2** was recovered, indicating that this part of the molecule is not involved in the chelation process. In our case, it seems that the chirality transfer from the furanose ring to the side chain is unusual in this kind of reaction.[13]

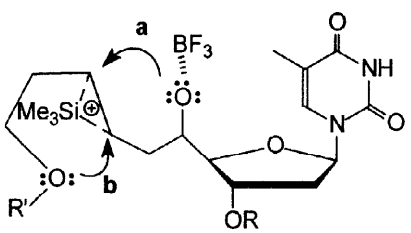
The methodology herein developed towards hydroxyalkylthymidines is stereoselective but still a multi step process. With a view to shortening the synthetic pathway, we explored the reaction between aldehyde **1** and a substituted allyltrimethylsilane, *i.e.* ω-*tert*Butyldimethyl-silyloxyallyltrimethylsilane (scheme 3). Oxepines are usually reported[17] to be the products of this reaction, but we expected a particular behaviour of the aldehyde **1**, *i.e* the nucleophilic attack to the carbonyl center followed by the subsequent transposition of the allylic moiety.[12]



Scheme 3

Using the same conditions as described for the preparation of oxepines (all components in stoechiometric amount), most of the starting aldehyde **1** was not consumed, we therefore carried on with 5 equivalents of Lewis acid and ω-*tert*Butyldimethyl-silyloxyallyltrimethylsilane. Under these conditions, the reaction lead to a mixture of compounds (80% yield) separated on silica gel. The desired 5'-C-substituted nucleosides **12** and **13** can be isolated as the lower Rf products in respectively 6 and 7% yield. The major family of products isolated are five membered ring ether derivatives **10** in 32% yield (high Rf) and **11a,b** in 54% yield (**11a** with a medium Rf and **11b** with the highest Rf). Both of these compounds are mixtures of diastereoisomers since there is formation of three new asymmetric centers. **10** is essentially composed of two isomers and surprisingly **11a** of one. Their structures were assigned after examination of the ^{1}H COSY spectrum of **11a** in which the *tert*Butyldiphenylsilyl has been removed and analysis of ^{13}C NMR spectra of **10** and **11a**.

Already reported additions of chiral substituted allylsilanes to carbonyl compounds invoked the occurrence of a siliranium intermediate.[18]



Following these observations, we can propose that a siliranium ion could collapse by nucleophilic attack either of the oxygen at 5'-C to provide **11** (**a** arrow) or by the oxygen at 10'-C to give **10** (**b** arrow), while elimination of the silicon group leads to **12** and **13**.

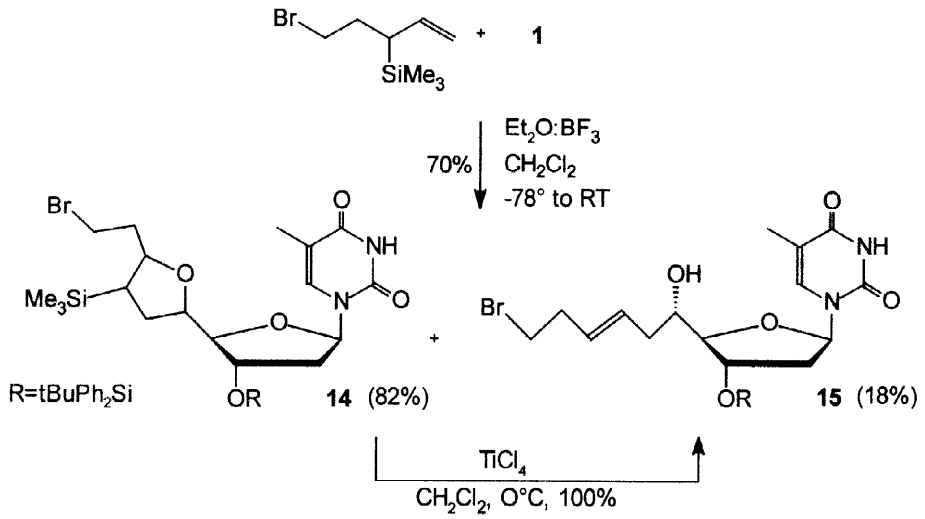
When treated with titanium tetrachloride **10** gave a 1/1 mixture of **12** an **13** in 60% yield, whereas **11** gave a 1/9 ratio in favour of **13** in 80% yield. The overall yield of **12/13** is 60% with a diastereoisomeric ratio of 1/2.8 in favour of the "R" isomer **13**. The stereochemistry can be assigned once again by comparison of **12'** (not shown) obtained either by catalytic hydrogenation of **12** or prepared from **8** in a similar manner as described in scheme 2 where the phosphorus ylide is derived from $THPO(CH_2)_3PPh_3Br$ (step b).

In order to increase the yield of derivatives with a similar structure to **11a** , we studied the reaction of **1** with ω-bromoallyltrimethylsilane (scheme 4), easily prepared from ω-hydroxyallyltrimethylsilane.[13] In that case, replacement of a protected hydroxyl function by a bromine should eliminate the opportunity of the siliranium ion to collapse following route b.

It is noteworthy that in the same time an electrophilic functionality would be added to the nucleoside.

Only two compounds are produced, **15** as the product of elimination and **14** (one isomer) the major adduct, as the expected product of the reaction. The absolute stereochemistry of **14** is not defined but since there is formation of only one isomer, this indicates that there is a chirality transfer during the siliranium ion rearrangement.

The absolute configuration of 5'-C has been assigned by synthesis of **15** from **12** which was tosylated on its primary hydroxyl function and then displacement of the tosyl group with bromine. When treated with $TiCl_4$ **14** gave **15** in 100% yield. This result suggests that the α-silyltetrahydrofurane moiety could be used as a protective group of the 5'-hydroxyl function, instead of the dimethoxytrityl group during an automated synthesis of oligodeoxynucleotides.



Scheme 4

In conclusion, 5'-C-hydroxypropyl-thymidine can be prepared in a stereoselective manner *via* Sakurai's condensation in high yield. Whereas with ω-*tert*Butyldimethyl-silyloxyallyltrimethylsilane, this reaction leads to a mixture of diastereoisomers in favour of 5'-C(R)-hydroxyhexyl-thymidine. ω-bromoallyltrimethylsilane provides a short and stereoselective access to 5'-C(S)-bromopentenyl thymidine. This methodology of synthesis of 5'-C-functionalized thymidine can be applied to all nucleosides with no need of a multi-step process.[19] Incorporation into oligodeoxynucleotides and synthesis of conjugates are in progress and will be reported elsewhere.

EXPERIMENTAL SECTION

Products were purified by medium pressure liquid chromatography on a Jobin et Yvon Modoluprep apparatus by using Amicon 6-35 μm or Merck 15 μm silica. IR spectra were recorded with a Perkin-Elmer 883 spectrometer while for NMR spectra a Bruker AC-80 or AC-250 spectrometers were used (80 or 250 MHz for ^{1}H and 62.9 MHz for ^{13}C). Chemical shifts were referenced to the tetramethylsilane. Mass spectra were recorded on a Nermag R10-10. All solvents were distilled and dried before use.

Compound 2. 5'-O-(trimethylsilyl), 3'-O-(*t*-Butyldiphenylsilyl)-(5S)'-C-allylthymidine. To a solution of 1g (2.09 mmol) of 5'-C-thymidine aldehyde **1** at 0 °C, in anhydrous dichloromethane (18 mL), first allyltrimethylsilane (1.86 mL, 5 eq) and then $Et_2O:BF_3$ are added. After 3h of stirring, the reaction is quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted twice with dichloromethane. The organic layer is dried over $MgSO_4$ and concentrated *in vacuo*. The white foam obtained is treated without purification with trimethylsilylchloride (0.4 mL, 1.5 eq), hexamethyldisylasane (0.645 mL, 1.5 eq) in pyridine (20 mL) for 3 h at room temperature. The reaction mixture is diluted with diethylether (200 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (30 mL) and brine. The organic layer is dried over $MgSO_4$ and the solvent evaporated. **2** (1.17 g, white foam, 95%) is isolated by silica gel chromatography with dichloromethane/ethyl acetate (4/1) as solvent.
IR ($CHCl_3$) ν cm^{-1} : 3399 (NH), 1686 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm: 8.94 (s, 1H, NH); 7.84 (d, 1H, H^6); 7.64-7.61 (m, 4H, Ph); 7.48-7.35 (m, 6H, Ph); 6.60 (dd, 1H, J = 5.4; 9.2 Hz, $H^{1'}$); 5.50 (m, 1H, $H^{7'}$); 5.00 (m, 2H, $H^{8'}$); 4.17 (d, 1H, J = 5.1 Hz, $H^{3'}$); 3.91 (s, 1H, $H^{4'}$); 3.04 (ddd, 1H, J = 1.0; 5.0; 8.5 Hz, $H^{5'}$); 2.27 (m, 2H; $H^{6'}$); 2.09 (m, 1H, $H^{2'}$); 1.84 (m, 4H, CH_3 and $H^{2'}$); 1.08 (s, 9H,tBu); -0.08 (s, 9H, $SiMe_3$). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 164.0, 150.5, 136.4, 135.8, 133.6, 133.4, 133.1, 130.0, 127.9, 118.2, 110.7, 88.7, 85.2, 76.2, 72.6, 40.9, 38.9, 26.9, 19.1, 12.5, 0.20. Analysis (calculated/found): %C 64.83 (64.97), %H 7.48 (7.69), %N 4.72 (4.81).

Compound 3. 5'-O-(trimethylsilyl), 3'-O-(*t*-Butyldiphenylsilyl)-(5S)'-C-(propan-1-ol)-thymidine. To a solution of **2** (1 g, 1.68 mmol) in anhydrous THF, under nitrogen at 0 °C, $BH_3:Me_2S$ (5 mL, sol 2 M in THF, 6 eq) is added. After stirring for 3 h at room temperature, a solution of NaOH (2 N, 16 mL, 18 eq) and a solution of

H_2O_2 (sol 30%, 4 mL, 18 eq) are slowly added and stirred for 15 min. The mixture is diluted with ethyl acetate and washed with water and brine. The organic layer is dried over $MgSO_4$ and the solvent evaporated. **3** (0.922 g, white foam, 90%) is isolated by silica gel chromatography with dichloromethane/ethyl acetate (1/1) as solvent.
IR ($CHCl_3$) ν cm^{-1} : 3400 (NH), 1687 (C=O). ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 8.61 (s, 1H, NH); 7.81 (d, 1H, H^6); 7.66-7.61 (m, 4H, Ph); 7.46-7.37 (m, 6H, Ph); 6.59 (dd, 1H, J = 5.4; 9.2 Hz, $H^{1'}$); 4.20 (d, 1H, J = 5.2 Hz, $H^{3'}$); 3.90 (s, 1H, $H^{4'}$); 3.55 (m, 2H, $H^{8'}$); 3.02 (m, 1H, $H^{5'}$); 2.30 (AB part of an ABX(Y) syst, 1H, J = 5.5; 13 Hz, $H^{2'}$); 1.88-1.80 (m, 4H, $H^{2'}$ and CH_3); 1.61-1.29 (m, 4H, $H^{6'}$ and $H^{7'}$); 1.09 (s, 9H,tBu); -0.08 (s, 9H, $SiMe_3$). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 164.1, 150.6, 136.4, 135.8, 135.7, 133.4, 133.1, 130.0, 127.9, 110.8, 88.9, 85.0, 76.2, 72.7, 62.5, 40.9, 30.5, 28.5, 26.9, 19.1, 12.5, 0.2.
Analysis (calculated/found): %C 62.92 (62.92), %H 7.59 (7.71), %N 4.49 (4.56).

Compound 4. 5'-O-(trimethylsilyl), 3'-O-(*t*-Butyldiphenylsilyl)-(5S)'-C-(oxo-1-propan)-thymidine. To a solution of **3** (1.01 g, 1.65 mmol) in anhydrous dichloromethane (2.5 mL), under nitrogen, anhydrous dimethylsulfoxide (3.3 mL) and triethylamne (1.15 mL, 5eq) are added. Then $Pyr:SO_3$ (1.31 g, 5 eq) is added portionwise. After 25 min the reaction mixture is diluted with diethylether and washed with a saturated aqueous solution of NH_4Cl, water and brine. The organic layer is dried over $MgSO_4$ and the solvent evaporated. **4** (0.9 g, 90%) is obtained as a palish yellow foam and is used without further purification. IR (KBr) ν cm^{-1} : 3421 (NH); 1695 (C=O). ^1H NMR (80 MHz, $CDCl_3$) δ ppm: 9.66 (s, 1H, $H^{8'}$); 8.42 (s, 1H, NH); 7.74-7.36 (m, 11H, Ph and H^6); 6.58 (dd, 1H, J=5.4; 9.1 Hz, $H^{1'}$); 4.21 (d, 1H, J = 4.9 Hz, $H^{3'}$); 3.81 (s, 1H, $H^{4'}$); 3.11 (m, 1H, $H^{5'}$); 2.34-2.00 (m, 3H, $H^{7'}$ and $H^{2'}$); 1.76 (s, 3H, CH_3); 1.75-1.28 (m,3H, $H^{6'}$ and $H^{2'}$); 1.08 (s, 9H,tBu); -0.08 (s, 9H, $SiMe_3$). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 200.0, 163.7, 150.4, 136.0, 135.7, 133.4, 133.0, 111.0, 88.7, 85.0, 76.1, 71.5, 40.7, 39.5, 26.9, 26.4, 19.0, 12.5, 0.1.

Compound 5. 3'-O-(*t*-Butyldiphenylsilyl)-(5S)'-C-(hex-3-ene-1-ol)-thymidine. nBuLi (1.3 mL, sol 1.6 M, 7.9 eq) is added to $THPO(CH_2)_3PPh_3Br$ (0.997 g, 7.9 eq) in anhydrous THF (8 mL) at -78 °C. Then the reaction is allowed to reach room temperature and stirred for 2 h. Then the mixture is cooled to -78 °C and **5** (0.16 g, 0.26 mmol) in anhydrous THF (2 mL) is added drop wise. After 5 min at -78 °C, the reaction is stirred for 2 h at room temperature. The reaction is stopped with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with diethyl ether. The organic layers are combined and washed with water and brine and dried over $MgSO_4$. After evaporation of the solvent, the brown oil obtained is diluted with MeOH (5 mL) and *para*toluene sulfonic acid is added (20 mg). After 2 h of stirring at room temperature, the reaction is stopped with a saturated aqueous solution of $NaHCO_3$ (3 mL) and MeOH is removed in vacuo. The mixture is diluted with ethyl acetate and washed with water and brine. The organic layer is dried over $MgSO_4$ and the solvent evaporated. **5** (90 mg, 60%) is obtained after silica gel chromatography with ethyl acetate/dichloromethane: 1/1 as solvent. IR (KBr) ν cm^{-1} : 3424 (OH); 1692 (C=O). ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 8.78 (s, 1H, NH); 7.68-7.35 (m, 11H, Ph and H^6); 6.27 (dd, 1H, J = 6.0, 8.1 Hz, $H^{1'}$); 5.36 (t, 2H, J = 5.0 Hz, $H^{8'}$ and $H^{9'}$); 4.39 (m, 1H, $H^{3'}$); 3.76 (s, 1H, $H^{4'}$); 3.60 (m, 2H, $H^{11'}$); 3.10 (m, 1H, $H^{5'}$); 2.15 (m, 4H, $H^{7'}$ and $H^{10'}$); 1.95 (m, 2H, $H^{2'}$); 1.83 (s, 3H, CH_3); 1.36 (m, 2H, $H^{6'}$); 1.07 (s, 9H, tBu). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 164.0; 150.0; 135.8; 133.5; 133.2; 132.0; 131.9; 130.0; 128.4; 127.9; 110.8; 90.3; 86.8; 74.8; 69.5; 61.9; 39.9; 33.2; 30.4; 26.9; 23.2; 19.0; 12.5. Analysis (calculated/found): %C 66.41 (65.20), %H 7.31 (7.19), %N 4.84 (4.66).

Compound 6. 3'-O-(*t*-Butyldiphenylsilyl)-(5S)'-C-(hexan-1-ol)-thymidine. A mixture of Pd/C (20 mg) in MeOH (5 mL) is saturated with hydrogen, then **5** (100 mg, 0.17 mmol) is added. An hydrogen flow is maintained for 3 h under stirring. The reaction mixture is filtered through celite and washed with methanol, evaporation of the solvent provide **7** as a white foam in quantitative yield. IR (KBr) ν cm^{-1} : 3399 (NH); 1689 (C=O). ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 8.65 (s, 1H, NH); 7.66-7.60 (m, 4H, Ph); 7.45-7.35 (m, 7H, Ph and H^6); 6.20 (t, 1H, J = 7.2 Hz, $H^{1'}$); 4.43 (m, 1H, $H^{3'}$); 3.79 (t, 1H, J = 2.0 Hz, $H^{4'}$); 3.62 (t, 2H, J = 6.5 Hz, $H^{11'}$); 3.05 (m, 1H, $H^{5'}$);2.22 (m, 3H, OH and $H^{2'}$); 1.85 (s, 3H, CH_3); 1.57-1.48 and 1.37-1.20 (m, 10H, $H^{6',7',8',9',10'}$); 1.06 (s, 9H, tBu). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 164.1, 150.5, 137.4, 135.8, 135.7, 133.4, 133.1, 130.1, 130.0, 127.9, 110.9, 89.5, 87.1, 74.4, 70.9, 62.8, 39.8, 34.1, 32.5, 29.1, 26.9, 25.6, 19.0, 12.5. Analysis (calculated/found): %C 66.18 (66.00), %H 7.64 (7.66), %N 4.82 (4.79).

Compound 8. 5'-O-(trimethylsilyl), 3'-O-(*t*-Butyldiphenylsilyl)-(5S)'-C-(oxo-1-ethane)-thymidine. To a solution of **7** (2.4 g, 3.8 mmol) in anhydrous toluene (9 mL) is added at -78 °C, diisobutylaluminum hydride (7.7 mL, 2 eq). After 2h of stirring, the reaction is stopped by addition of MeOH (10 mL) and water (5 mL). The resulting mixture is filtered and washed with MeOH. After evaporation of the solvent the crude material is diluted with ethyl acetate and washed with brine. The organic layer is dried over $MgSO_4$ and concentrated *in vacuo*. **8** (2.8 g, 95%) is obtained as a white foam. ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 9.65 (t, 1H, J = 1.6 Hz,

H7'); 8.46 (s, 1H, NH); 7.67-7.63 (m, 4H, Ph); 7.47-7.37 (m, 7H, Ph and H^6); 6.(dd, 1H, J = 9.5; 5.5 Hz, $H^{1'}$); 4.19 (d, 1H, J = 5.5 Hz, $H^{3'}$); 3.97 (s, 1H, $H^{4'}$); 3.67 (ddd, 1H, J = 5.5; 1.4; 1.8 Hz, $H^{5'}$); 2.66 and 2.52 (AB part of an ABX(Y) syst, 2H, J = 17.5; 1.8; 1.4 Hz, $H^{6'}$); 2.26 (A part of an ABX syst, 1H, J = 12.9; 5.2; Hz, $H^{2'}$); 1.88-1.80 (m, 4H, $H^{2'}$ and CH_3); 1.10 (S, 9H, tBu); -0.10 (s, 9H, $SiMe_3$). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 199.7, 163.9, 150.6, 135.8, 135.7, 133.1, 133.0, 130.1, 111.1, 90.0, 84.9, 75.7, 67.9, 48.6, 40.7, 26.9, 19.0, 12.5, 0.01.

Compound 9. 3'-O-(*t*-Butyldiphenylsilyl)-(5S)'-C-(hex-4-ene-1-ol)-thymidine. nBuLi (5.6 mL, sol 1.6 M, 6.8 eq) is added to $THPO(CH_2)_4PPh_3Br$ (4.2 g, 6.8 eq) in anhydrous THF (35 mL) at -78 °C. Then the reaction is allowed to reach room temperature and stirred for 2 h. Then the mixture is cooled to -78 °C and **8** (0.737 g, 1.24 mmol) in anhydrous THF (10 mL) is added drop wise. After 5 min at -78 °C, the reaction is stirred for 2 h at room temperature. The reaction is stopped with a saturated aqueous solution of NH_4Cl (100 mL) and extracted with diethyl ether. The organic layers are combined and washed with water and brine and dried over $MgSO_4$. After evaporation of the solvent, the brown oil obtained is diluted with MeOH (50 mL) and *para*toluene sulfonic acid is added (50 mg). After 2 h of stirring at room temperature, the reaction is stopped with a saturated aqueous solution of $NaHCO_3$ (3 mL) and MeOH is removed *in vacuo*. The mixture is diluted with ethyl acetate and washed with water and brine. The organic layer is dried over $MgSO_4$ and the solvent evaporated. **8** (360 mg, 50%) is obtained after silica gel chromatography with ethyl acetate/dichloromethane: 1/1 as solvent. ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 9.44 (s, 1H, NH); 7.69-7.60 (m, 4H, Ph); 7.50-7.30 (m, 7H, Ph and H^6); 6.29 (t, 1H, J = 6.5 Hz, $H^{1'}$); 5.56-5.14 (m, 2H, J = 5.0 Hz, $H^{7'}$ and $H^{8'}$); 4.46 (m, 1H, $H^{3'}$); 3.81 (s, 1H, $H^{4'}$); 3.58 (m, 2H, $H^{11'}$); 3.06 (m, 1H, $H^{5'}$); 2.32-2.01 (m, 6H, $H^{6', 9', 2'}$); 1.95 (m, 2H, $H^{2'}$); 1.83 (s, 3H, CH_3); 1.65-1.1.52 (m, 2H, $H^{10'}$); 1.07 (s, 9H, tBu). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 164.2, 150.6, 137.4, 135.8, 133.4, 133.1, 132.5, 130.2, 127.9, 125.6, 110.9, 89.3, 86.8, 74.8, 70.6, 61.5, 39.8, 32.3, 31.8, 26.9, 23.4, 19.0, 12.4.

To a solution of **1** (1 g, 2.09 mmol) in anhydrous dichloromethane (18 mL), are added $Et_2O:BF_3$ (1.3 mL, 5 eq) and ω-*tert*Butyldimethyl-silyloxyallyltrimethylsilane (2.84 g, 5 eq) at -78 °C. After stirring for 3 h, the reaction mixture is allowed to reach room temperature. The reaction is stopped by addition of a saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted twice with ethyl acetate. The organic layer are dried over $MgSO_4$ and concentrated *in vacuo*. **11b** (67 mg); **10** (335 mg); **11a** (508 mg); **12** (57 mg) and **13** (66 mg) are isolated (80% yield), after silica gel chromatography eluted with a gradient (starting from ethyl acetate/dichloromethane: 1/9 to pure ethyl acetate).

Compound 10. 5'-[(5"-trimetylsilyl-2"-oxacyclopentyl)]methyl-3'-O-(*t*-Butyldiphenylsilyl)-thymidine. IR ($CHCl_3$) ν cm^{-1}: 3400 (NH); 1685 (C=O). ^{13}C NMR (63 MHz, $CDCl_3$) **isomer 1**, δ ppm: 164.1, 150.6, 136.8, 135.9, 135.8, 133.3, 130.0, 127.9, 110.9, 91.4, 84.8, 82.6, 73.4, 73.1, 67.9, 41.2, 38.6, 32.9, 28.8, 26.9, 19.1, 12.7, -2.6. **isomer 2**, δ ppm: 164.0, 150.5, 136.9, 135.9, 135.8, 133.7, 133.1, 130.0, 127.9, 110.7, 90.7, 85.3, 82.6, 75.3, 71.8, 67.8, 40.6, 39.6, 33.5, 29.0, 27.0, 19.0, 12.7, -2.6. MS (FAB>0, MNBA): 659 (100%, M+Na); 637 (18.4%, M+H).

Compound 11a. 5-[3'-(2"-hydroxyethyl)-4'-trimethylsilyl-2'-oxacyclopentyl]-4-*t*-Butyldiphenylsilyl-oxy-2-thyminyl-1-oxacyclopentane. IR ($CHCl_3$) ν cm^{-1}: 3399 (NH); 1689 (C=O). ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 9.10 (s, 1H, NH); 7.68-7.63 (m, 4H, Ph); 7.45-7.36 (m, 7H, Ph and H^6); 6.51 (dd, 1H, $H^{1'}$); 4.31 (d, 1H, J = 4.8 Hz); 4.10 (d, 1H, J = 3 Hz); 3.90 (m, 1H);3.68 (m, 3H); 2.35 (m,1H); 2.20 (A part of an ABX(Y) syst, 1H, $H^{2'}$); 1.87 (s, 3H, CH_3); 1.95-1.56 (m, 5H); 1.06 (s, 9H, tBu); -0.11 (s, 9H, $SiMe_3$). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 163.9, 150.5, 135.9, 135.8, 135.7, 133.2, 132.9, 130.1, 130.0, 128.0, 127.9, 111.2, 89.3, 84.9, 81.6, 79.2, 73.4, 61.0, 40.8, 38.6, 33.1, 31.8, 26.9, 19.1, 12.6, -2.7. MS (FAB>0, MNBA): 659 (100%, M+Na); 637 (17.4%, M+H). Analysis (calculated/found): %C 64.12 (64.76), %H 7.60 (7.26), %N 4.40 (4.92).

Compound 11b. 3'-O-(*t*-Butyldiphenylsilyl)-5'-C-(3-(3-*t*-Butyldimethylsilyloxy-2-trimethylsilyl)-2-ox-etanyl)-thymidine. ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 163.9, 150.5, 136.4, 135.8, 133.3, 133.0, 130.0, 127.9, 110.8, 89.8, 85.2, 79.3, 78.7, 73.5, 60.1, 41.2, 39.9, 32.8, 32.0, 26.9, 25.8, 19.1, 12.6, -2.7, -5.3, -5.5. MS (FAB>0, MNBA): 773 (56.3%,M+Na).

Compound 12. 3'-O-(*t*-Butyldiphenylsilyl)-(5S)'-C-(pent-3-ene-1-ol)-thymidine. IR ($CHCl_3$) ν cm^{-1}: 3398 (NH), 1687 (C=O). ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 8.77 (s, 1H, NH); 7.66-7.60 (m, 4H, Ph); 7.48-7.35 (m, 7H, Ph and H^6); 6.27 (t, 1H, J = 7.1 Hz, $H^{1'}$); 5.42-5.33 (m, 2H, $H^{7'}$ and $H^{8'}$); 4.45 (m, 1H, $H^{3'}$); 3.80 (s, 1H, $H^{4'}$); 3.61 (m, 2H, $H^{10'}$); 3.05 (m, 1H, $H^{5'}$); 2.56 (d, 1H, J = 5.4 Hz, OH); 2.28-2.05 (m, 5H, $H^{2', 6', 9'}$); 1.85 (s, 3H, CH_3); 1.08 (s, 9H, tBu). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 163.8, 150.4, 137.4, 135.8, 133.4, 133.0, 130.5, 130.1, 128.9, 127.9, 110.8, 89.2, 87.1, 74.8, 70.2, 61.7, 39.8, 37.7, 35.9, 26.9, 19.0, 12.5.

Compound 13. 3'-O-(*t*-Butyldiphenylsilyl)-(5R)'-C-(pent-3-ene-1-ol)-thymidine. IR ($CHCl_3$) ν cm^{-1}: 3399 (NH), 1685 (C=O). ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 8.63 (s, 1H, NH); 7.68-7.64 (m, 4H, Ph); 7.48-7.36 (m, 7H, Ph and H^6); 6.31 (dd, 1H, J = 6.0, 8.6 Hz, $H^{1'}$); 5.36-5.31(m, 2H, $H^{7'}$ and $H^{8'}$); 4.49 (d, 1H, J = 4.2 Hz, $H^{3'}$); 3.93 (s, 1H, $H^{4'}$); 3.62 (m, 3H, $H^{10'}$ and $H^{5'}$); 2.79 (d, 1H, J = 2.6 Hz, OH); 2.25-2.11 (m, 5H, $H^{2', 6', 9'}$); 1.84 (s, 3H, CH_3); 1.62-1.49 (m, 1H, $H^{2'}$); 1.07 (s, 9H, tBu). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 164.3, 150.7, 137.5, 135.9, 135.8, 133.1, 130.6, 130.1, 128.7, 127.9, 110.9, 90.7, 86.4, 72.9, 71.1, 61.5, 40.4, 36.6, 35.8, 26.9, 19.1, 12.5. Analysis (calculated/found): %C 65.93 (65.32), %H 7.14 (7.30), %N 4.96 (4.86).

To a solution of **1** (0.705 g, 1.47 mmol) in anhydrous dichloromethane (15 mL), are added $Et_2O:BF_3$ (1 mL, 5 eq) and ω-Bromo-allyltrimethylsilane (1.7 g, 5 eq) at -78 °C. The reaction mixture is allowed to reach room temperature within 4 h. The reaction is stopped by addition of a saturated aqueous solution of $NaHCO_3$ (15 mL) and extracted twice with ethyl acetate. The organic layer are dried over $MgSO_4$ and concentrated *in vacuo*. **14** (513 mg) and **15** (103 mg) with **1** (120 mg) are isolated after chromatography on silica gel with petroleum ether/dichloromethane/ethyl acetate: 2/6.4/1.6 as solvent.

Compound 14. 5-[3'-(2"-bromoethyl)-4'-trimethylsilyl-2'-oxacyclopentyl]-4-*t*-Butyldiphenylsilyloxy-2-thyminyl-1-oxacyclopentane. IR ($CHCl_3$) ν cm^{-1}: 3398 (NH), 1688 (C=O). ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 8.92 (s, 1H, NH); 7.68-7.62 (m, 4H, Ph); 7.46-7.35 (m, 5H, Ph and H^6); 6.39 (dd, 1H, J = 6.0, 7.4 Hz, $H^{1'}$); 4.37 (m, 1H, $H^{3'}$); 3.82 (t, 1H, J = 3.2 Hz, $H^{4'}$); 3.64 (td, 1H, J = 2.5, 9.5 Hz); 3.43-3.31 (m, 3H); 2.35 (A part of an ABX(Y) syst, 1H, J = 3.5, 6.0, 13.5 Hz, $H^{2'}$); 2.04 (m, 1H); 1.94-1.76 (m, 8H); 1.08 (s, 9H, tBu); -0.001 (s, 9H, $SiMe_3$). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 163.8, 150.3, 135.8, 135.5, 133.2, 133.1, 130.1, 127.9, 110.7, 87.5, 84.7, 80.2, 77.3, 73.9, 40.5, 39.5, 31.6, 30.6, 30.5, 26.9, 19.1, 12.6, -2.6. MS (DCI, NH_3): 716 (91.5%), 718 (100%, M+NH_4), 699 (19.0%), 701 (22.2%, M+H). Analysis (calculated/found): %C 58.35 (58.79), %H 6.77 (6.71), %N 4.00 (4.16).

Compound 15. 3'-O-(*t*-Butyldiphenylsilyl)-(5S)'-C-(Bromo-1-pent-3-ene)-thymidine. IR ($CHCl_3$) ν cm^{-1}: 3399 (NH), 1689 (C=O). ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 9.15 (s, 1H, NH); 7.66-7.61 (m, 4H, Ph); 7.52-7.35 (m, 7H, Ph and H^6); 6.33 (dd, 1H, J = 6.1, 8.1 Hz, $H^{1'}$); 5.41-5.33 (m, 2H, $H^{7'}$ and $H^{8'}$); 4.46 (m, 1H, $H^{3'}$); 3.82 (s, 1H, $H^{4'}$); 3.37 (m, 2H, $H^{10'}$); 3.10 (m, 1H, $H^{5'}$); 2.54 (m, 2H,); 2.24-2.08 (m, 5H); 1.85 (s, 3H, CH_3); 1.08 (s, 9H, tBu). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 164.0, 150.5, 137.2, 135.8, 133.4, 133.1, 130.9, 130.1, 129.1, 127.9, 110.8, 88.9, 86.7, 74.8, 70.1, 40.0, 37.5, 35.6, 33.0, 26.9, 19.0, 12.5. MS (DCI, NH_3): 644 (75.6%), 646 (83.3%, M+NH_4), 62 (46.3%), 629 (50.4%, M+H). Analysis (calculated/found): %C 59.32 (59.45), %H 6.26 (6.36), %N 4.46 (4.41).

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