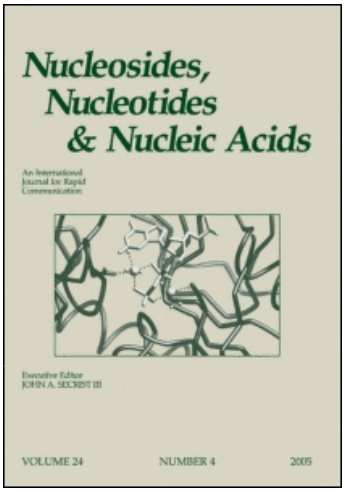

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Total Synthesis of the Thymidine Analogue of Sinefungin

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TOTAL SYNTHESIS OF THE THYMIDINE ANALOGUE OF SINEFUNGIN

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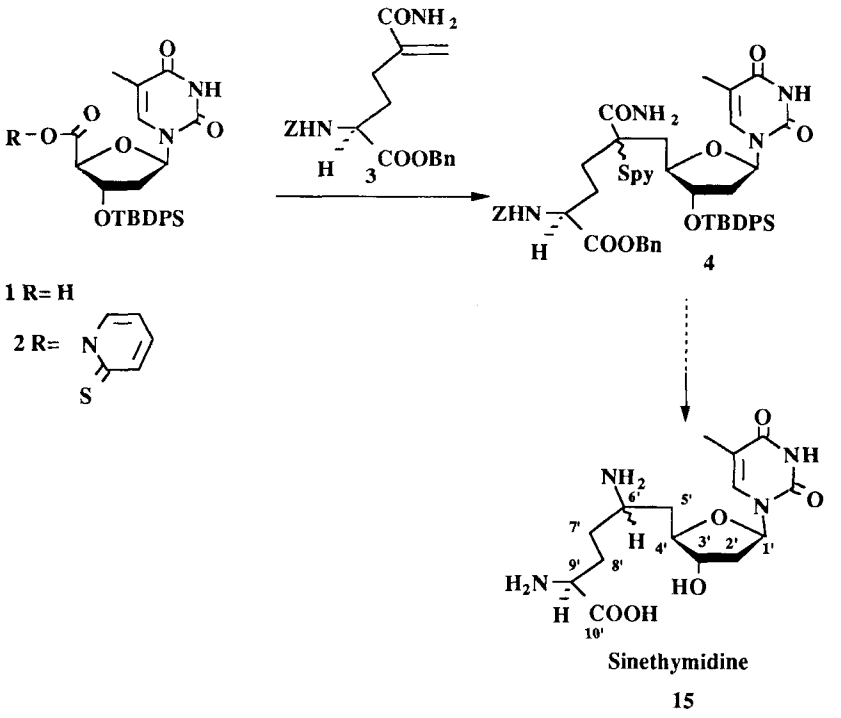
Abstract- The carbon skeleton of "Sinethymidin" **4** was constructed by two radical coupling reaction. The first step was a coupling of the radical derived from **2** and the unsaturated amide **5**. The olefin **6** thus obtained was added to the radical derived from the known *N*-hydroxy-2-thiopyridinone aspartic ester. "Sinethymidin", tested for its antileismanial effect, was devoid of activity.

Natural sinefungin shows a wide variety of biological activity. Its strong antiparasitic effect, especially against various species of *Leishmania*[1] *and Trypanosoma*[2] and its antifungal activity[3] *in vitro* and *in vivo* are of great interest. However, sinefungin has serious toxic side effects in dog and goats. Therefore the synthesis of analogues with potentially improved therapeutic index has been undertaken. Previously, the synthesis of sinefungin[4] and of a series of analogues[5] has been reported, based on known types of ionic chemistry. We described recently a new and simple synthesis of sinefungin[6] (S), epi-sinefungin (R) and "sineuridin" in which the carbon skeleton was formed in one step using radical chemistry[7].

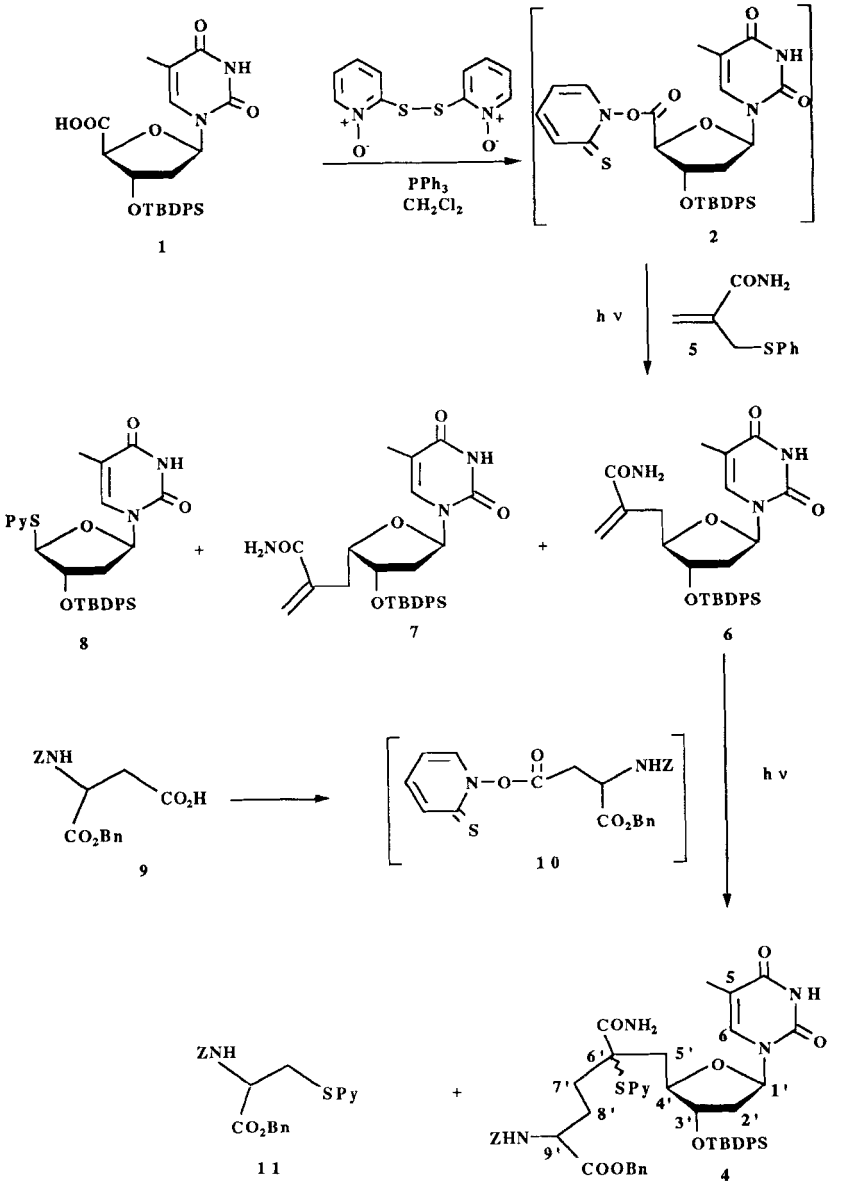
In this paper we report the enantioselective synthesis of "sinethymidine" **15**, an analogue of sinefungin in which adenosine is replaced by thymidine. In this case, the previous procedure using the thiohydroxamic ester[8] **2** and olefin[6] **3** could not be applied to afford the precursor **4** of sinethymidine **15** (Scheme 1).



Scheme 1

The essential carbon skeleton of "sinethymidine" was constructed by two radical reactions (Scheme 2): the first one was the addition of a radical, generated by photolysis of *N*-hydroxy-2-thiopyridone ester of the protected thymidine 5' carboxylic acid[8] **2** to the allylic amide[8] **5** according to a S_H2' reaction[9]. The resulted olefin intermediate **6** undergoes a second addition reaction with the radical derived by irradiation of the known *N*-hydroxy-2-thiopyridone ester of protected *L*-aspartic acid[10] **9** to furnish the skeleton of "sinethymidine" **4**.

In order to increase the overall yield of sinethymidine, we examined a new procedure for the preparation of *N*-hydroxy-2-thiopyridone ester. This new approach, reported recently by Barton[11] *et al.*, proceeds very smoothly. The carboxylic acid **1** in CH_2Cl_2 at 0°C gives in the presence of 2,2'-dithiopyridine-1,1'-di-*N*-oxide and triphenylphosphine the acyl derivative **2**. The irradiation of **2** in the presence of olefin[8] **5** yields the desired product **6** with retention of configuration (67%), the inversion



Scheme 2

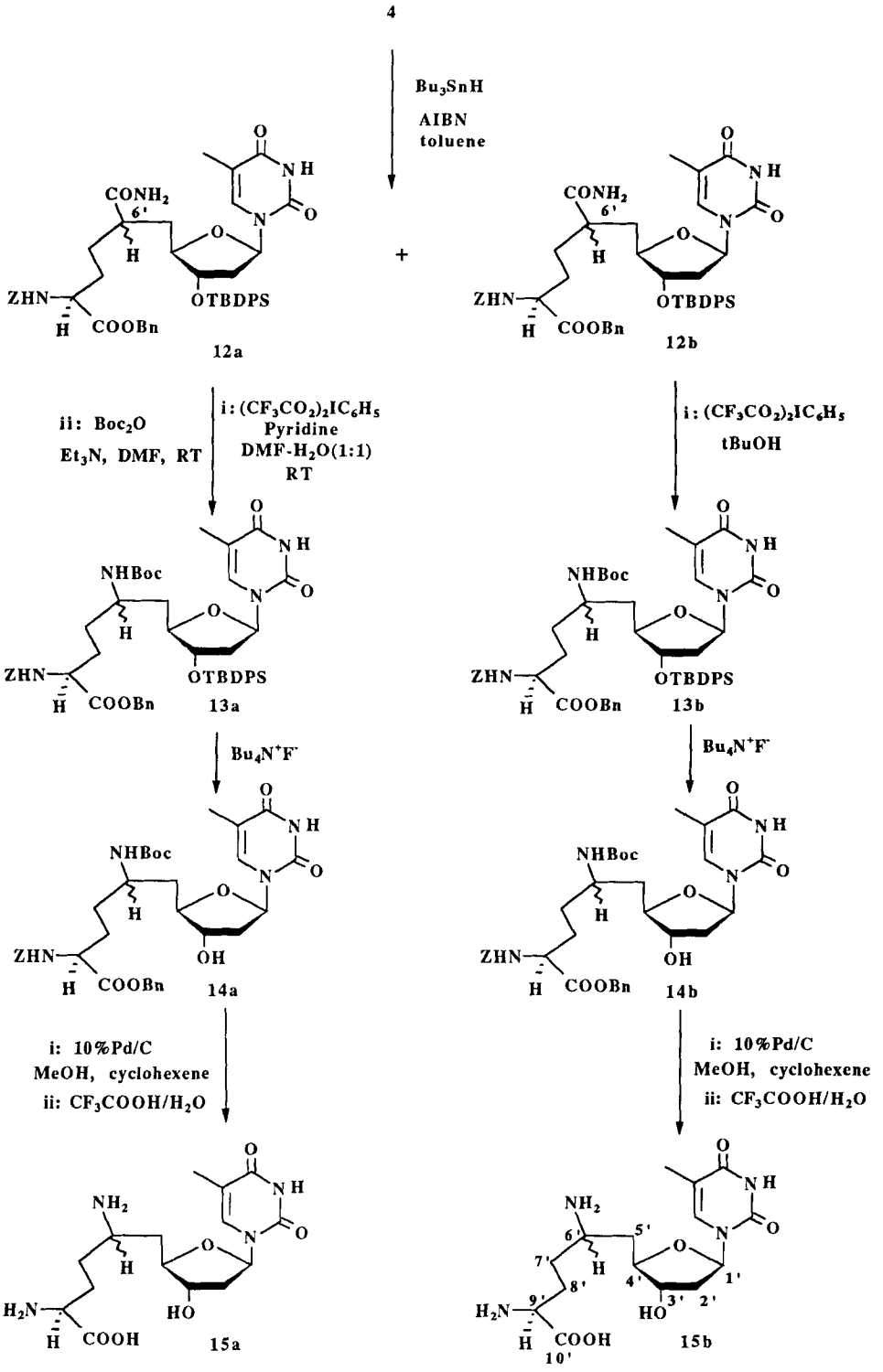
adduct **7** (5%) and the rearranged product **8** (15%). Comparison of NMR data for compounds **6** and **7** shows a chemical shift difference between H4' of **6** ($\delta_{H4'}$= 4.17 ppm) and **7** ($\delta_{H4'}$= 4.37 ppm). This is due to the anisotropy effect of the base on the chemical shift of H4' of inversion product **7**. A similar phenomenon was observed for the α and β ribonucleosides[12]. The second radical reaction consists of the irradiation of *N*-hydroxy-2-thiopyridone ester **10**, prepared from **9** by the usual mixed anhydride method[10,13] in the presence of olefin **6** to afford the adducts **4** (30%) as a mixture of two epimers at C-6'. To improve the yield of this radical reaction, differents reaction conditions were tried using either an excess of olefin **6** (5eq) or an excess of aspartic ester **10** but the major product was the rearranged one[14] **11**.

The thiopyridyl group of **4** was reduced with tributyltin hydride in toluene under reflux with an initiator (Scheme 3). The two products **12a** and **12b** epimeric at C-6' were separated by chromatography over silica gel to give the less polar product **12a** (52%) and the more polar **12b** (37%). The isomer **12a** was treated with [bis(trifluoroacetoxy)-iodo]benzene in DMF-H_2O in the presence of pyridine[15] to give the amide **13a**. This latter was transformed to the tert-butoxycarbonyl derivative **14a**. To improve the Hofmann transformation of **12b**, this latter was treated with bis(trifluoroacetoxy)-iodo]benzene in tert-butanol[16] at 80°C to give directly the *t*-butyl-carbamate **13b** in good yield (65%). Cleavage of silyl groups of **13a** and **13b** with tetrabutylammonium fluoride in tetrahydrofuran afforded the alcohol **14a** (60%) and **14b** (60%) respectively. The two compound **14** were separately deprotected by successive hydrogenolysis using 10% Pd/C and cyclohexene as hydrogen donor to yield **15a** (60%) and **15b** (67%) respectively. The absolute configuration at C-6' of **15a** and **15b** was not determined. However, if we compared the molecular rotation obtained previously for Sinefungin (S) and its epimer (R) we can prelimary conclude that compound **15b** with the lower $[\alpha]_D$ has the configuration (S).

Sinethymidin was tested for its antileismanial effect. This analogue was devoid of antiparasitic activity.

Experimental Section

General.-Column chromatography was carried out on silica gel 60 (0.040 - 0.063 μm). TLC analysis were performed on analytical thin layer plates 60F254 (Merck). ^1H and ^{13}C NMR spectra were recorded on Bruker AC 250 (250 MHz),or WM 400 (400 MHz). Chemical shifts (δ) are expressed in ppm from Me_4Si as internal standard. Coupling constants *J* are in Hz. Most spectra were recorded in $CDCl_3$. In other cases



TBDPS: $SiPh_2tBu$; Bn: CH_2Ph; Z: CO_2Bn; Boc: $CO_2C(CH_3)_3$

Scheme 3

the solvent is specified. Melting points were taken on a Reichert apparatus and are uncorrected. Infra-red spectra were recorded on a Nicolet 205 FT-IR. Routine mass spectra were recorded on AEI MS 50 and Kratos MS 80 (for FAB spectra). Elementary analyses were carried out at the Institut de Chimie des Substances Naturelles.

1'-Thymine-(3'-*O*-t-Butyl-diphenylsilyl-6'-carboxamido-2',5',6',7'-tetradeoxy-β-D-ribo-6'-ene-heptofuranosyl) (6) and 1'-Thymine-(3'-*O*-t-Butyl-diphenylsilyl-6'-carboxamido-2',5',6',7'-tetradeoxy-β-L-ribo-6'-ene-heptofuranosyl) (7)- To a solution of carboxylic acid **1** (0.494 g, 1 mmol) and 2,2'-dithiopyridine-1,1'-di-*N*-oxide (0.302 g, 1.2 mmol) in dry and degassed CH_2Cl_2 (8 ml), triphenylphosphine (0.314 g, 1.2 mmol) was added under argon . The mixture was stirred at room temperature for 30 mn with exclusion of light (aluminium foil). Olefinic amide **5** (0.965 g, 5 mmol.) was then added and the mixture was irradiated with a tungsten light (250 watts) at 10°C for 1 h. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$, water, saturated NaCl and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was subjected to flash chromatography using gradient elution. Elution with ethyl acetate-heptane (8:2) gave the crystalline addition product **6** (72%) and the crystalline inversion product **7** (5%) and the rearranged one **8** (15%).

Compound 6 had mp 170-173°C (from CH_2Cl_2-pentane). $[\alpha]_D^{20}$= +57° (c= 1.2; CH_2Cl_2). Anal. calcd for $C_{29}H_{35}O_5N_3Si$ C, 65.26; H, 6.60. Found C, 64.96; H, 6.82. IRν_{max} (neat) 1718; 1694; 1635; 1475; 1112 cm^{-1}. MS (CI., m/z) 534 $(MH)^+$; 127 $(Base+H)^+$. ^1H NMR (250 MHz, $CDCl_3$) δ 10.08 (sl, 1H, NH); 7.3, 7.60 (m, 10H, Ph); 7.30 (s, 1H, H_6); 6.47 (dd, 1H, $H_{1'}$, $J_{1',2'}$= 8 Hz, $J_{1'2''}$=6 Hz); 6.23 (sl, 2H, NH_2); 5.83 (s, 1H, $H_{7'}$); 5.32 (s, 1H, $H_{7''}$); 4.26 (dt, 1H, $H_{3'}$, $J_{3'4'}$= 6 Hz, $J_{3'2'}$=$J_{3'2''}$= 3 Hz); 4.17 (m, 1H, $H_{4'}$, $J_{4',3'}$= 6 Hz, $J_{4',5'}$= 4 Hz, $J_{4',5''}$= 8 Hz); 2.36 (m, 3H, $H_{2''}$, $H_{5'}$, $H_{5''}$, $J_{5',5''}$= 15 Hz); 1.90 (s, 3H, CH_3); 1.68 (m, 1H, $H_{2'}$); 1.13 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ 170.7 ($CONH_2$); 164.3 (C_4); 150.5 (C_2); 140.5 ($C_{7'}$); 135.7-127.8 (Ph, C_6); 121.4 ($C_{6'}$); 110.9 (C_5); 85.4 ($C_{1'}$); 85.2 ($C_{4'}$); 75.6 ($C_{3'}$); 39.6 ($C_{2'}$); 35.4 ($C_{5'}$); 26.8 [$C(\underline{C}H_3)_3$]; 18.9 [$\underline{C}(CH_3)_3$]; 11.3 (CH_3).

Compound 7 had mp 64-65°C (from ether-pentane). $[\alpha]_D^{20}$= +22° (c= 0.8; CH_2Cl_2). MS (CI, m/z) 534 $(MH)^+$; 127 $(Base+H)^+$. HRMS (C.I. MH^+) Found 534.2413 calcd for $C_{29}H_{36}O_5N_3Si$, requires 534.2424 $(MH)^+$. ^1H NMR (250 MHz, $CDCl_3$) δ 8.3 (s, 1H, NH); 7.80, 7.20 (m, 10H, Ph); 7.3 (s, 1H, H_6); 6.25 (t, 1H, $H_{1'}$); 5.8 (s, 1H, $H_{7'}$); 5.5 (s, 1H, $H_{7''}$); 4.49 (m, 1H, $H_{3'}$); 4.37 (m, 1H, $H_{4'}$); 2.68, 2.35 (2m, 4H, $H_{2'}$, $H_{2''}$, $H_{5'}$, $H_{5''}$); 1.9 (s, 3H, CH_3); 1.10 [s, 9H, $C(C\underline{H}_3)_3$].

Compound 8 had mp 45-46°C (CH_2Cl_2-hexane). Anal. calcd for $C_{30}H_{33}O_4N_3SSi$ C, 64.37; H, 5.94; N, 7.51; S, 5.70. Found C, 64.08; H, 6.21; N, 7.75; S, 5.52. MS (F.A.B.,

m/z) 582 $(M+Na)^+$; 560 $(MH)^+$; 449 $(M-SPy)^+$; 434 $(M-Base)^+$; 127 $(Base+H)^+$; 112 $(PySH+H)^+$. ^1H NMR (250 MHz, $CDCl_3$) 9.15 (s, 1H, NH); 7.40 (m, 15H, Ph, SPy, H_6); 6.68 (dd, 1H, $H_{1'}$, $J_{1'2'}$= 6Hz, $J_{1'2''}$= 9Hz); 6.13 (s, 1H, $H_{4'}$); 4.61 (d, 1H, $H_{3'}$, $J_{3'2'}$= 4Hz); 2.49 (dd, 1H, $H_{2'}$, $J_{2',1'}$=6Hz, $J_{2',2''}$=14Hz); 2.01 (m, 1H, $H_{2''}$, $J_{2'',3'}$=4Hz, $J_{2'',1'}$=9Hz, $J_{2'',2'}$=14Hz); 1.82 (s, 3H, CH_3); 1.05 (s, 9H, $C(C\underline{H}_3)_3$). ^{13}C NMR ($CDCl_3$) δ 163.1 (C_4); 149.7 (C_2); 136.2, 120.3 (Ph, SPy); 133.5 (C_6); 110.7 (C_5); 90.3, 87.1 ($C_{1'}$, $C_{4'}$); 76.1 ($C_{3'}$); 39.8 ($C_{2'}$); 26.5[$C(\underline{C}H_3)_3$]; 18.7[$\underline{C}(CH_3)_3$]; 12.1 (CH_3-5).

Benzyl-[1'-(thymin-1-yl)-[9'(S)-benzyloxycarbonylamino-3'-*O*-*t*-butyldiphenylsilyl-6'(R,S)-carbamoyl-2',5',6',7',8',9'-hexadeoxy-6'-(2-thiopyridyl)]]-β-D-ribo-decofuranuronate 4. To the acid **9** (5.033 g; 14.1 mmol.) in dry and degassed tetrahydrofuran (30 ml), *N*-methylmorpholine (1.55 ml; 14.1 mmol.) and isobutyl chloroformate (1.97 ml; 14.1 mmol.) were added. The reaction mixture was stirred for 15 min under argon at 0°C and the sodium salt of *N*-hydroxy-2-thiopyridone (2.5 g; 16.9 mmol) was added. The mixture was stirred under argon at 0°C for 2 h with exclusion of light (aluminium foil). After the olefin **6** (1.5 g; 2.82 mmoles) was added, the solution was irradiated with a tungsten lamp (250 watts) at 10°C for 3 h. The solvent was evaporated under reduced pressure and the residue was taken up in ethyl acetate and washed with saturated sodium hydrogen carbonate solution and with water. The organic phase was dried over $MgSO_4$ and, after filtration, evaporated under reduced pressure. The residue thus obtained was chromatographed on silica gel using gradient elution. Elution with ethyl acetate-heptane (4-6, 8-2) gave the crystalline derivative **4** (0.720 g, 27%) which was a mixture of two isomers and the crystalline rearranged product **11** (4.7 g).

Compound 4 had MS (F.A.B., m/z) 978 $(M+Na)^+$; 956 $(MH)^+$; 830 $(MH-Base)^+$; 112 $(PySH+H)^+$. ^1H NMR (250 MHz, $CDCl_3$) δ 8.86 (s, 1H, NH); 7.52 (m, 20H, Ph); 6.81 (s, 1H, H_6); 6.19 (t, 1H, $H_{1'}$); 5.78 (d, 1H, NH); 5.08 (m, 4H, $C\underline{H}_2Ph$); 4.23 (m, 2H, $H_{3'}$, $H_{4'}$); 4.01 (m, 1H, $H_{9'}$); 2.3, 2.01, 1.86, 1.18 (m, 8H, $H_{2'}$, $H_{2''}$, $H_{5'}$, $H_{5''}$, $H_{7'}$, $H_{7''}$, $H_{8'}$, $H_{8''}$); 1.80 (s, 3H, $C\underline{H}_3$); 1.5 (s, 9H, $C(C\underline{H}_3)_3$). ^{13}C NMR ($CDCl_3$) δ 175.2 ($\underline{C}ONH_2$); 171.9 ($\underline{C}O_2Bn$); 163.2 (C_4); 156.2 ($NH\underline{C}O_2Bn$); 149.3 (C_2); 136.8, 127.8 (Ph, S$\underline{P}$y); 110.6 (C_5); 84.4, 82.9 ($C_{4'}$, $C_{1'}$); 76.3 (C_3); 66.8 ($\underline{C}H_2Ph$); 58.4 ($C_{6'}$); 54.0 ($C_{9'}$); 39.1, 36.8 ($C_{2'}$, $C_{5'}$); 31.7 ($C_{7'}$, $C_{8'}$); 26.8 ($C(\underline{C}H_3)_3$); 18.9 ($\underline{C}(CH_3)_3$); 12.4 ($\underline{C}H_3$-5).

Benzyl-[1'-(thymin-1-yl)-[9'(S)-Benzyloxycarbonylamino-3'-*O*-*t*-butyldiphenylsilyl-6'(R,S)-carbamoyl-2',5',6',7',8',9'-hexadeoxy]]-β-D-ribo-decofuranuronate 12a and 12b. The mixture of isomers **4** (2 g, 2.09 mmol.) in anhydrous and degassed toluene (12ml) was heated under reflux with tributyltin hydride (1.38 mL, 6.27 mmol.)

and α,α'-azoisobutyronitrile (0.027 g, 0.209 mmol.) for 4 h under argon. The solvent was removed under reduced pressure. The residue was chromatographed on a column of silica gel (ethyl acetate-heptane: 6-4, 7-3, 8-2) permitting separation of crystalline isomers (**12a**) (0.919 g, 52%) and (**12b**) (0.654 g, 37%).

Isomer (12a) had m.p. 66-68°C (CH_2Cl_2-hexane), $[\alpha]_D^{20}$= +22 (c= 0.83; CH_2Cl_2). Anal. calcd for $C_{47}H_{54}O_9N_4Si.\ H_2O$ C, 65.26; H, 6.53; N, 6.48. Found C, 65.63; H, 6.41; N, 6.39. IRν_{max} (neat) 1712; 1687; 1456 cm^{-1}. MS (C.I., m/z) 847 $(MH)^+$; 721 $(MH\text{-base})^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 20H, Ph); 6.91 (s, 1H, H_6); 6.25 (t, 1H, $H_{1'}$, $J_{1',2'}$= $J_{1',2''}$= 6Hz); 5.76 (sl, 1H, $CONH_2$); 5.53 (d, 1H, NH); 5.14, 5.07 (2s, 4H, CH_2Ph); 4.37 (m, 1H, $H_{3'}$); 3.96 (m, 1H, $H_{4'}$); 3.89 (m, 1H, $H_{9'}$); 3.62 (m, 1H, $H_{6'}$); 2.28, 2.19, 1.62, 1.30, 1.20 (m, 8H, $H_{2'}$, $H_{2''}$, $H_{5'}$, $H_{5''}$, $H_{7'}$, $H_{7''}$, $H_{8'}$, $H_{8''}$); 1.82 (s, 3H, CH_3); 1.10 [s, 9H, $C(CH_3)_3$]. ^{13}C NMR ($CDCl_3$) δ 176.5 ($CONH_2$); 172.1 (CO_2Bn); 163.7 (C_4); 156.1 ($NHCO_2Bn$); 150.5 (C_2); 133.3 (C_6); 135.8, 127.9 (Ph); 111.5 (C_5); 84.7, 84.2 ($C_{1'}$, $C_{4'}$); 76.0 ($C_{3'}$); 67.3, 67.0 (CH_2Ph); 53.6 ($C_{9'}$); 41.9 ($C_{6'}$); 39.5 ($C_{2'}$); 36.3 ($C_{5'}$); 30.2 ($C_{7'}$); 28.6 ($C_{8'}$); 26.9 [$C(CH_3)_3$]; 19.1 [$C(CH_3)_3$]; 12.5 (CH_3).

Isomer (12b) had m.p. 69-71°C (CH_2Cl_2-hexane), $[\alpha]_D^{20}$= +30° (c= 0.83; CH_2Cl_2). Anal. calcd for $C_{47}H_{54}O_9N_4Si.\ H_2O$ C, 65.26; H, 6.53; N, 6.48. Found:C, 65.29; H, 6.29; N, 6.35, IRν_{max} (neat) 1712; 1687; 1456 cm^{-1}. MS (F.A.B., m/z) 869 $(M+Na)^+$; 847 $(MH)^+$; 721 $(MH\text{-base})^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 20H, Ph); 7.12 (s, 1H, H_6); 6.25 (dd, 1H, $H_{1'}$, $J_{1',2'}$=6Hz, $J_{1',2''}$=8Hz); 5.84 (sl, 2H, $CONH_2$); 5.56 (d, 1H, NH); 5.18, 5.10 (2s, 4H, CH_2Ph); 4.37 (m, 1H, $H_{3'}$); 4.03 (m, 1H, $H_{4'}$); 3.82 (2m, 2H, $H_{9'}$, $H_{6'}$); 2.26, 2.15, 1.66, 1.54, 1.30 (m, 8H, $H_{2'}$, $H_{2''}$, $H_{5'}$, $H_{5''}$, $H_{7'}$, $H_{7''}$, $H_{8'}$, $H_{8''}$); 1.89 (s, 3H, CH_3); 1.10 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ 177.8 ($CONH_2$); 172.0 (CO_2Bn); 164.1 (C_4); 156.2 ($NHCO_2Bn$); 150.5 (C_2); 136.2 (C_6); 135.7, 128.0 (Ph); 111.0 (C_5); 85.9 ($C_{1'}$, $C_{4'}$); 76.6 ($C_{3'}$); 67.3, 67.1 (CH_2Ph); 53.4 ($C_{9'}$); 42.4 ($C_{6'}$); 39.5 ($C_{2'}$); 35.8 ($C_{5'}$); 30.2 ($C_{7'}$); 28.3 ($C_{8'}$); 26.9[$C(CH_3)_3$]; 19.1 [$C(CH_3)_3$]; 12.3 (CH_3-5).

Benzyl-[1'-(thymin-1-yl)-[9'(S)-benzyloxycarbonylamino-3'-*O*-*t*-butyldiphenylsilyl-6'(R,S)-(*t*-butoxycarbonylamino)-2',5',6',7',8',9'-hexadeoxy]]-β-D-ribo-decofuranuronate 13a and 13b. To the amide (**12a**) (0.8 g, 0.94 mmol.) in a mixture of dimethylformamide (6.0 ml) and water (6.0 ml), iodosobenzene bis-trifluoroacetate (1.3 g, 1.3 mmol) was added. After stirring at room temperature for 30 min pyridine (0.141 ml, 2 eq.) was added. Stirring was continued for 2 h at room temperature. The solvent was removed under reduced pressure and the residue was then treated with toluene which was again removed under reduced pressure to eliminate the last traces of pyridine. The amine obtained was treated at 0°C with di-*t*-butyl dicarbonate (0.228 g,

1.2 eq.) in dimethylformamide (5 ml) with addition of triethylamine (0.122 ml, 1 eq.). After stirring for 2 h at room temperature the solution was evaporated under reduced pressure. The residue was purified on silica gel (ethylacetate-hexane, 7-3) affording the crystalline carbamate **13a** (0.347 g, 36%). This had m.p. 57-59°C (CH_2Cl_2- pentane). $[\alpha]_D^{20}$= +37 (c= 0.8; $CHCl_3$). Anal. calcd for $C_{51}H_{62}O_{10}N_4Si$. 1/2H_2O C, 66.01; H, 6.54; N, 6.01. Found C, 65.99; H, 6.73; N, 6.03. MS (F.A.B., m/z) 941 $(M+Na)^+$; ^1H NMR (400 MHz, $CDCl_3$) 8.51 (s, 1H, NH); 7.45 (m, 20H, Ph); 6.95 (s, 1H, H_6); 6.23 (t, 1H, $H_{1'}$, $J_{1',2'}=J_{1',2''}$=6Hz); 5.40 (d, 1H, N<u>H</u>); 5.16 (d, 2H, C<u>H</u>$_2$Ph); 5.10 (s, 2H, C<u>H</u>$_2$Ph); 4.39 (m, 1H, $H_{3'}$); 4.17 (d, 1H, BocN<u>H</u>); 4.01 (m, 1H, $H_{4'}$); 3.84 (m, 1H, $H_{9'}$); 3.56 (m, 1H, $H_{6'}$); 2.35, 1.62, 1.29 (m, 8H, $H_{2'}$, $H_{2''}$, $H_{5'}$, $H_{5''}$, $H_{7'}$, $H_{7''}$, $H_{8'}$, $H_{8''}$); 2.87 (s, 3H, C<u>H</u>$_3$-5); 1.40 [s, 9H, $NHCO_2C(C\underline{H}_3)_3$]; 1.09 [s, 9H, $OSiC(C\underline{H}_3)_3$]. ^{13}C NMR ($CDCl_3$) δ 172.6 ($NH\underline{C}O_2Bn$); 164.4 (C_4); 156.5 ($\underline{C}O_2Bn$, $\underline{C}O_2tBu$); 150.7 (C_2); 136.8, 129.1 (Ph); 135.7 (C_6); 111.6 (C_5); 85.7 ($C_{4'}$); 84.0 ($C_{1'}$); 78.1 ($NHCO_2\underline{C}(CH_3)_3$); 76.8 ($C_{3'}$); 67.7, 67.5 ($\underline{C}H_2Ph$); 54.2 ($C_{9'}$); 48.1 ($C_{6'}$); 40,6 ($C_{5'}$); 38.8 ($C_{2'}$); 31.4, 30.2 ($C_{7'}$, $C_{8'}$); 28.9[$CO_2C(\underline{C}H_3)_3$]; 2,4 [$C(\underline{C}H_3)_3$]; 19.5 [$\underline{C}(CH_3)_3$]; 13.1 (C<u>H</u>$_3$-5).

To the amide **12b** (0.366 g, 0.432 mmol.) in fresly distilled tert-butanol (30 ml) iodosobenzene bis-trifluoroacetate (0.284 g, 0.648 mmol.) was added. The mixture was heated at 45°C for 18h, under argon. The solvent was evaporated under reduced pressure and the residue purified on a silica gel column using a gradient elution (ethylacetate-hexane) to yield **13b** (0.257 g, 65%). This had m.p. 58-60°C (CH_2Cl_2-hexane). $[\alpha]_D^{20}$= +32° (c= 0.83; CH_2Cl_2). Anal. calcd for $C_{51}H_{62}O_{10}N_4Si$:C, 66.64; H, 6.80; N, 6.10. Found C, 66.94; H, 6.96; N, 5.88. MS (F.A.B., m/z) 941 $(M+Na)^+$. ^1H NMR (250 MHz, $CDCl_3$) δ 8.7 (sl, 1H, NH); 7.38 (m, 21H, Ph, H_6); 6.36 (t, 1H, $H_{1'}$, $J_{1',2'}=J_{1',2''}$=6Hz); 5.60 (d, 1H, N<u>H</u>); 5.13 (2s, 4H, C<u>H</u>$_2$Ph); 4.75 (d, 1H, N<u>H</u>Boc); 4.20 (m,1H, $H_{3'}$); 4.17 (m, 1H, $H_{4'}$); 3.80 (m, 1H, $H_{9'}$); 3.62 (m, 1H, $H_{6'}$); 2.30 (m, 2H, $H_{2'}$, $H_{2''}$); 1.93 (s, 3H, CH_3); 1.85, 1.56 (2m, 6H, $H_{5'}$, $H_{5''}$, $H_{7'}$, $H_{7''}$, $H_{8'}$, $H_{8''}$); 1.35 [s, 9H, $NHCO_2C(C\underline{H}_3)_3$]; 1.06 [s, 9H, $SiC(C\underline{H}_3)_3$]. ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.1 ($NH\underline{C}O_2Bn$); 164.0 (C_4); 156.1, 155.4 ($\underline{C}O_2Bn$, $\underline{C}O_2tBu$); 135.8 (C_6); 133.1, 128.2 (Ph); 111.5 (C_5); 85.1, 84.2 ($C_{4'}$, $C_{1'}$); 79.3 [$NHCO_2\underline{C}(CH_3)_3$]; 76.2 ($C_{3'}$); 67.3, 67.1 ($\underline{C}H_2Ph$); 54.1 ($C_{9'}$); 47.5 ($C_{6'}$); 39.9 ($C_{5'}$); 38.7 ($C_{2'}$); 29.8, 29.2 ($C_{7'}$, $C_{8'}$); 28.4 [$CO_2C(\underline{C}H_3)_3$]; 26.9 [$SiC(\underline{C}H_3)_3$]; 19.1 [$Si\underline{C}(CH_3)_3$]; 12.2 ($CH_3$).

Benzyl-[1'-(thymin-1-yl)-[9'(S)-benzyloxycarbonylamino-6'(R,S)-(*t*-butoxy-carbonylamino)]2',5',6',7',8',9'-hexadeoxy]]-β–D-ribo-decofuranuronate 14a and 14b. The amide **13a** (0.290 g ; 0.31 mmol.) in dry THF (7 ml) was treated with a solution of tetrabutylammonium fluoride 1M in THF (0.61 ml, 0.62 mmol.) for 2h at room temperature under argon. The solvent was evaporated under reduced pressure and

the residue was taken up in dichloromethane. The organic layer was washed with saturated brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified on a silica gel column (ethyl acetate-hexane, 7-3) to yield **14a** (0.126 g, 60%). ^1H NMR (250 MHz, $CDCl_3$) δ 9.7 (s, 1H, NH); 7.45 (s, 10H, Ph); 7.13 (s, 1H, H_6); 6.22 (dd, 1H, $H_{1'}$, $J_{1',2'}$=6Hz, $J_{1',2''}$=8Hz); 5.90 (d, 1H, ZNH); 5.09 (s, 4H, CH_2Ph); 4.68 (d, 1H, NHBoc); 4.45, 4.22, 3.86, 3.64 (4m, 4H, $H_{9'}$, $H_{3'}$, $H_{4'}$, $H_{6'}$); 2.31, 1.59 (2m, 8H, $H_{2'}$, $H_{2''}$, $H_{5'}$, $H_{5''}$, $H_{7'}$, $H_{7''}$, $H_{8'}$, $H_{8''}$) ; 1.94 (s, 3H, CH_3); 1.40 [s, 9H, $C(CH_3)_3$].

The compound **13b** (0.210 g ; 0.22 mmol.) was desilyled as decribed above to give **14b** (0.092 g, 60%). ^1H NMR (250 MHz, $CDCl_3$) δ 9.0 (s, 1H, NH); 7.33 (s, 10H, Ph); 7.16 (s, 1H, H_6); 6.21 (dd, 1H, $H_{1'}$, $J_{1',2'}$=6Hz, $J_{1',2''}$=8Hz); 5.61 (d, 1H, NH); 5.11 (s, 4H, CH_2Ph); 4.55 (d, 1H, NHBoc); 4.42 (m, 1H, $H_{3'}$); 4.19 (m, 1H, $H_{4'}$); 3.80 (m, 1H, $H_{9'}$); 3.64 (m, 1H, $H_{6'}$); 2.33, 1.62 (2m, 8H, $H_{2'}$, $H_{2''}$, $H_{5'}$, $H_{5''}$, $H_{7'}$, $H_{7''}$, $H_{8'}$, $H_{8''}$); 1.95 (s, 3H, CH_3); 1.42 [s, 9H, $C(CH_3)_3$].

1'-Thymin-1-yl-[6'(R,S),9'(S)-diamino-2',5',6',7',8',9'-hexadeoxy]-β-D-ribo-deco-furanoic acid 15a and 15b. The derivative **14a** (0.110 g; 0.160 mmol.) was hydrogenolysed in methanol (4.2 ml) and cyclohexene (1.1 ml) using 10% palladium on charcoal (0.440 g). The reaction mixture was heated under reflux for 30 min. and the solution filtered over celite. The solvent was evaporated under reduced pressure. The Boc protecting group was removed with 80% trifluoroacetic acid (5 ml) at room temperature for 5 h. After evaporation under reduced pressure, the residue was purified on a silica gel column using gradient elution (MeOH, CH_2Cl_2, NH_3, 15-12-4) to yield the oily compound **15a** (0.034 g, 60%). This had $[\alpha]_D^{20}$= +27 (c= 0.83; H_2O). MS (F.A.B, m/z) 357 $(M+H)^+$; 232 $(MH\text{-}Base)^+$; 126 $(Base+H)^+$. HRMS (F.A.B. MH^+) Found 357.1762 calcd for $C_{15}H_{25}O_6N_4$ requires 357.1774. ^{1}HNMR (400 MHz, D_2O) 7.47 (s, 1H, H_6); 6.25 (t, 1H, $H_{1'}$, $J_{1',2'}$=$J_{1',2''}$=6Hz); 4.37 (m, 1H, $H_{3'}$); 4.04 (m, 1H, $H_{4'}$); 3.68 (m, 1H, $H_{9'}$); 3.39 (m, 1H, $H_{6'}$); 2.53, 2.39, 2.06, 1.75 (4m, 8H, $H_{2'}$, $H_{2''}$, $H_{5'}$, $H_{5''}$, $H_{7'}$, $H_{7''}$, $H_{8'}$, $H_{8''}$); 1.4 (s, 3H, CH_3). δ ^{13}C NMR (62.5 MHz, D_2O) 177.2 (C_{10}); 167.4 (C_4); 152.9 (C_2); 139.1 (C_6); 112.8 (C_5); 86.8 ($C_{1'}$); 83.2 ($C_{4'}$); 74.8 ($C_{3'}$); 56.3 ($C_{9'}$); 51.2 ($C_{6'}$); 39.1 ($C_{2'}$) ; 37.7 ($C_{5'}$); 30.9 ($C_{8'}$); 29.3 ($C_{7'}$); 12.8 (CH_3-5).

In exactly the same way, the epimeric derivative **14b** gave the crystalline 6'-epi-sinethymidine **15b** (0.033 g, 68%). This had mp 154°C. $[\alpha]_D^{20}$= +22.5 (c= 1.2, H_2O). MS (F.A.B, m/z) 357 $(M+H)^+$; 232 $(MH\text{-}Base)^+$; 126 $(Base+H)^+$. HRMS (F.A.B. MH^+) Found 357.1763 calcd for $C_{15}H_{25}O_6N_4$. requires 357.1774. ^{1}HNMR (400 MHz, D_2O): 7.40 (s, 1H, H_6); 6.21 (t, 1H, $H_{1'}$, $J_{1',2'}$=$J_{1',2''}$=6Hz); 4.29 (dt, 1H, $H_{3'}$, $J_{3',2'}$=$J_{3',2''}$=5Hz, $J_{3',4'}$=6H); 3.95 (m, 1H, $H_{4'}$); 3.53 (t, 1H, $H_{9'}$, $J_{9',8'}$=$J_{9',8''}$=6Hz); 3.27

(q, 1H, $H_{6'}$, $J_{6',5'}=J_{6',5''}=J_{6',7'}=J_{6',7''}$=6Hz); 2.42 (ddd, 1H, $H_{2'}$, $J_{2',1'}$=6Hz, $J_{2',3'}$=5Hz, $J_{2',2''}$=14Hz); 2.31 (ddd, 1H, $H_{2''}$, $J_{2'',1'}$=6Hz, $J_{2'',3'}$=5Hz, $J_{2'',2'}$=14Hz); 2.09 (dt, 1H, $H_{5'}$, $J_{5',5''}$=14Hz, $J_{5',6'}$=6Hz); 1.88 (s, 3H, CH_3); 1.86 (m, 3H, $H_{5'}$, $H_{8'}$, $H_{8''}$); 1.68 (m, 2H, $H_{7'}$, $H_{7''}$). δ ^{13}C NMR (62.5 MHz, D_2O) 178.5 (C_{10}); 167.3 (C_4); 152.9 (C_2); 138.6 (C_6); 112.7 (C_5); 86.5 ($C_{1'}$); 85.4 ($C_{4'}$); 75.3 ($C_{3'}$) ; 56.5 ($C_{9'}$) ; 51.2 ($C_{6'}$); 39.7, 39.5 ($C_{5'}$, $C_{2'}$) ; 32.4 ($C_{8'}$); 30.3 ($C_{7'}$); 13.1 (CH_3-5).

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