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Short Report

A New Straightforward Synthesis of 2', 3'-Didehydro-2', 3'-dideoxy-2'-(2''-(trimethylsilyl)ethylthio)thymidine, Key Intermediate for the Synthesis of 2'-Substituted Thionucleosides

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We describe herein a straightforward and efficient preparation of 2',3'-dideoxy-2'-(2''-(trimethylsilyl)ethylthio)thymidine, which allows the preparation of diverse potentially antiviral and/or anticancer nucleosides (disulfides, thiols, sulfides, thiocyanates).

Keywords: nucleosides, thionucleosides, antiviral, anticancer

Introduction

Chemical modifications of natural occurring nucleosides and nucleotides have led to a large number of drugs especially antiviral and antitumour agents.[1-7]

In the search for new bioactive agents and tools for biological studies, many sulfur containing nucleosides, nucleotides and oligonucleotides have been synthesized over 50 years.[8-15]

The explosion of interest in thionucleosides was ignited by discovery in early 1990's that L-isomer of 2'-deoxy-3'-thiacytidine [(−)-β-L-3TC, lamivudine)] (**1**) (3TC, Figure 1) is a potent inhibitor of HIV and HBV viruses. Syntheses of 3TC analogues were extensively developed and the chemistry as well as biological activities of such compounds were reviewed.[8-11,16,17] Thionucleosides are also interesting tools for enzymatic mechanistic studies[18- 21] and, when incorporated into RNA or DNA, for the study of nucleic acids structure and functions, for instance, study of their binding to protein and of the mechanism of catalysis performed by ribozymes.[22-24] In synthesis chemistry, nucleosides carrying sulfide functions are valuable intermediates easily converted to other modified nucleosides such as sulfoxides and sulfones.[8-11,21] These functionalities, after achieving their particular synthetic goals, can be readily removed from the final nucleosides either thermally (sulfoxides) or reductively (sulfones).[25]

In the search for antiviral and antitumour nucleosides, one or more hydroxyl functions carried by the ribose and 2'-deoxyribose can be replaced by a thiol function or the corresponding mixed disulfide functions that can be reduced *in vivo*.[20,21,26,27] After phosphorylation, such nucleosides could interfere with the biosynthesis of nucleic acids in viral and cancer cells. The easy oxidizable 2'-deoxy-2'-thiouridine 5'-diphosphate generated *in situ* from the corresponding 2'-propyl disulfide has been found *in vitro* to be a potent inhibitor of a key enzyme in DNA synthesis and cell proliferation, ribonucleoside 5'-diphosphate reductase (RDPR). The inhibition arrives from reaction of the 2'-thiol function at the active site leading to a perthiyl free radical in the protein.[20,21] The corresponding alkyl mixed disulfides showed also antiviral and/or antiproliferative activities.[26,27]

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In order to improve the synthesis of nucleosides bearing an easy oxidizable thiol function on the sugar and of their mixed disulfides, a method of preparation of 2'-deoxy-2'-thionucleosides has been developed using intermediates 2'-deoxy-2'-(2"-(trimethylsilyl)ethylthio)nucleosides.[25,27-29] These 2-(trimethylsilyl)ethylsulfides (TMSES) were efficiently converted to the corresponding mixed disulfides through reaction with dimethyl(methylthio)sulfonium tetrafluoroborate[28] and/or with alkyl- and aryl-sulfinyl chlorides.[29] The isolated mixed disulfides can be reduced *in situ*, for example with dithiothreitol (DTT) or glutathione, to lead to the corresponding thiols.[20,21, 27-29]

This method was applied to the synthesis of mixed disulfides of 2',3'-didehydro-2',3'-dideoxy-2'-(2"-(trimethylsilyl)ethylthio)nucleosides in the uridine, thymine and cytidine series.[29] In the uridine series, the 2'-(4-nitrophenyl) disulfide was converted in one pot to the corresponding 2'-methylsulfide in two steps (*i*) reduction with DTT and (*ii*) alkylation of the obtained vinylthiol with methyl iodide.[29] 2'-Deoxy-2'-(2"-(trimethylsilyl) ethylthio)nucleosides could be also selectively converted in good yields to the corresponding 2'-thiocyanates by treatment with cyanogen bromide in methanol.[30] In regard to the rich chemistry of the TMSES nucleosides which allows the preparation of diverse potentially antiviral and/or anticancer nucleosides (disulfides, thiols, sulfides, thiocyanates and others), we focused our work on the synthesis of the previously described 2',3'-didehydro-2',3'-dideoxy-2'-(2"-(trimethylsilyl)ethylthio)thymidine (**9**), parent compound to the antiviral drug 2',3'-didehydro-2',3'-dideoxythymidine (**2**) (stavudine, D4T, Figure 1).

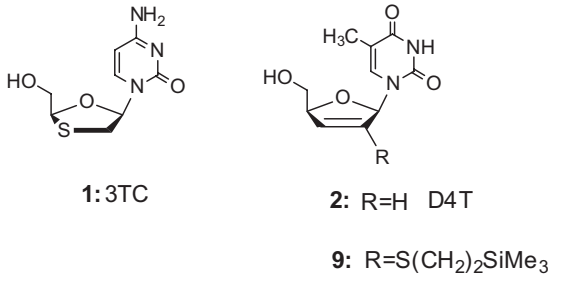


Figure 1. Structures of thionucleosides Lamivudine (3TC), stavudine (D4T) and compound (**9**).

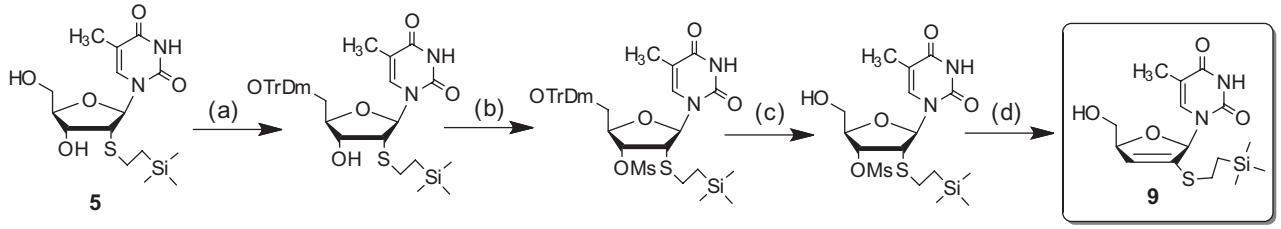
Here, we report on a new straightforward efficient preparation of this nucleoside.

Results and Discussion

2',3'-didehydro-2',3'-dideoxy-2'-(2"-(trimethylsilyl) ethylthio)thymidine **(9)** was previously synthesized from the corresponding saturated TMSE sulfide (**5**) in four steps (64% overall yield): (*i*) 4,4'-dimethoxytritylation of the 5'-hydroxyl function, (*ii*) mesylation at the 3'-position, (*iii*) removal of the trityl group under acidic conditions, and (*iv*) elimination in the presence potassium carbonate in acetonitrile under reflux (Scheme 1).[29] In this synthesis, the good mesyl leaving group has been introduced after selective protection of the 5'-hydroxyl group by tritylation. The detritylation was performed before elimination in order to avoid side reactions observed under acidic conditions during the detritylation of the unsaturated nucleoside.

The saturated TMSE intermediate (**5**) was prepared through the reaction of 2,2'-anhydrothymidine (**4**) with 2-(trimethylsilyl)ethanethiol (prepared from trimethylvinylsilane) at 120 °C in DMF (88% yield). 2,2'-Anhydrothymidine (**4**) can be prepared in 63% yield through (*i*) reaction of 5-methyluridine (**3**) with diphenyl carbonate in the presence of sodium hydrogen carbonate in DMF at reflux (1 h), (*ii*) precipitation from the reaction mixture in diethyl ether (1.8 L for 10 g of starting 5-methyluridine) to remove phenol, (*iii*) filtration and then (iv) crystallization in methanol. The main drawbacks of this synthesis result from the large volume of diethyl ether necessary for phenol removal and from the possible presence of moisture, (**4**) being very hygroscopic. Thus, we developed another method of preparation of (**4**) using dimethyl carbonate as reagent. According to the low boiling point of dimethyl carbonate, the reaction temperature was decreased (130 °C) and the reaction time increased (2 h) in comparison to the reaction performed with diphenyl carbonate. Compound (**4**) was obtained in 78% yield after precipitation in a small volume of diethyl ether, filtration and crystallization from methanol.

Then, from (**5**), we developed a straightforward synthesis of the unsatured thionucleoside (**9**) which was



Scheme 1. (a) 4,4'-dimethoxytrityl chloride, pyridine, room temperature; (b) methanesulfonyl chloride, pyridine, room temperature; (c) dichloroacetic acid, dichloromethane, room temperature; (d) potassium carbonate, acetonitrile, 90 ºC, (64% overall yield).

prepared in three steps (Scheme 2, 48% overall yield): (*i*) mesylation of the 3' and 5'-hydroxyl functions, (*ii*) elimination in the presence of sodium benzoate in DMF at 90 ºC (*iii*) removal of the introduced 5'-benzoyl group under basic conditions (KOH/MeOH).

The saturated TMSE dimesyl intermediate (**6**) was obtained from (**5**) by reaction with methanesulfonyl chloride at room temperature for 1 h (Scheme 2, 87%). The 2',3'-unsaturated nucleoside carrying a benzoyl group at the 5'-position (**8**) was isolated in 65% yield through reaction of (**6**) with sodium benzoate and purification by chromatography on silica gel.

The presence of two mesyl groups in (**6**) could be a source of side reactions decreasing the yield. Since compound (**8**) has a benzoate group at C-5', we rationalized that this compound could also be prepared from a 3',5'-dibenzoate derivative by selective elimination of the 3'-benzoate group. Thus, the saturated TMSE dibenzoyl intermediate (**7**) was prepared from (**5**) by reaction with benzoic anhydride at 60 ºC for 1 h (Scheme 2, 72% yield). Then, the obtained 2',3'-unsaturated nucleoside carrying a benzoyl group at the 5'-position (**8**) was obtained in 62% yield by reaction of (**7**) with potassium carbonate. Finally, (**8**) was treated with potassium hydroxide at room temperature in MeOH to lead in good yield (86%) to corresponding the 2', 3'-unsaturated nucleoside (**9**). Following this synthetic route compound (**9**) was obtained in 38% overall yield.

Both synthetic routes allowed the preparation of unsaturated thionucleoside (**9**) in a very straightforward manner. The main difference between the two methods was the high yield obtained in the preparation of dimesylate (**6**), which could be easily isolated by direct precipitation from the reaction mixture and filtration while the dibenzoate (**7**) needed purification by column chromatography. Side products were detected by TLC and could be due elimination in the presence of pyridine. This led to a higher overall yield (48%) from the former route, compared to the 38% obtained via the second one. Although the synthetic routes depicted in this work had overall yields lower than the previously described method,[29] they are one step shorter and can be easily scaled up, besides making use of cheaper and more stable reagents (methanesulfonyl chloride and benzoyl anhydride) as compared to the more expensive and less stable dimethoxytrityl chloride. Moreover, the new methods of synthesis of nucleoside (**9**) described here led rapidly to the unsaturated nucleoside (**8**) carrying a 5'-benzoyl protective group useful for further modifications of the sugar.

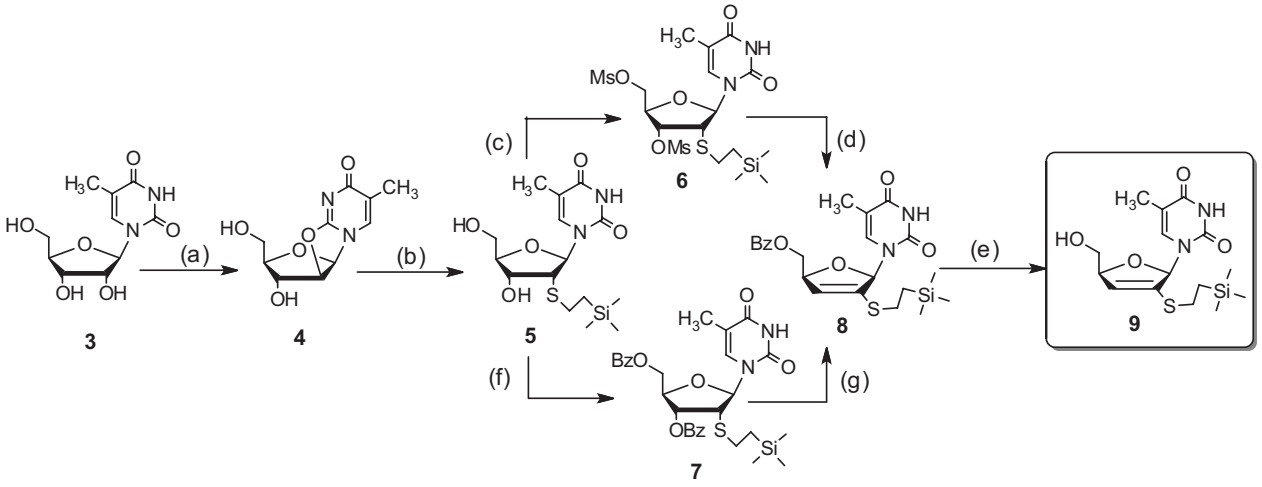
Conclusions

In summary, we have developed two new, simple and efficient methodologies for the synthesis of unsatured thionucleoside (**9**)**,** a key-intermediate in the preparation of potentially antiviral or antiproliferative thionucleosides.

Experimental

General procedures

Thin-layer chromatography (TLC) was carried out on plates precoated with Merck silica gel 60 F_{254} (Darmstad , Germany). Detection was by UV at 254 nm. Column chromatography was carried out on silica gel (230-400 mesh). IR spectra were recorded with a Spectrum One Perkin Elmer (Waltham, USA) spectrometer from the



Scheme 2. (a) dimethyl carbonate, sodium hydrogen carbonate, DMF, 130 ºC (78%); (b) 2-(trimethylsilyl)ethanethiol, DMF, room temperature (88%); (c) methanesulfonyl chloride, pyridine, room temperature (87%); (d) sodium benzoate, DMF, 90 ºC (65%); (e) potassium hydroxide, MeOH, room temperature (86%); (f) benzoic anhydride, pyridine, 60 ºC (72%); (g) potassium carbonate, DMF, 120 ºC (62%).

Laboratory of Medicinal Chemistry, University Federal de Minas Gerais. Nuclear magnetic resonance spectra were obtained using Bruker Avance - 400 MHz spectrometers (Billerica, USA) from the Departément Pharmaco Chimie Molecularie, Université Joseph Fourier-Grenoble and Bruker Avance - 200 MHz (Billerica, USA) spectrometers from the Laboratory of Nuclear Magnetic Resonance, Department of Chemistry, University Federal de Minas Gerais. The assignments were confirmed by proton-proton homocorrelated and carbon-proton heterocorrelated spectra. HRMS experiments were performed using a Shimadzu LC-ITT OF Instrument (Kyoto, Japan) using electrospray ionisation, from the Department of Chemistry, University Federal de Minas Gerais and Shimadzu LC-ITT OF Instrument using electrospray ionisation (Kyoto, Japan) from the Institut de Chimie Organique et Analytique, Université d'Orléans, France. Optical rotations were measured with ADP220 –BS Bellingham Stanley Ltd. Polarimeter (Wales, England) from the Laboratory of Medicinal Chemistry, University Federal de Minas Gerais. Melting points were measured with MQAPF-301 from the Laboratory of Medicinal Chemistry, University Federal Minas de Gerais.

2, 2'-anhydrothymidine (**4**)

5-methyluridine (**3**) (15 g, 58.06 mmol) was dissolved in dry dimethylformamide (100 mL) and treated with dimetyl carbonate (6.95 mL, 81.87 mmol) and sodium hydrogen carbonate (0.31 g, 3.71 mmol). The mixture was heated at 130 °C for 2 h and poured into ether. The precipitated gum was then crystallized from methanol to give the 2,2'-anhydrothymidine (**4**) as colorless prisms (10.9 g, 78%); $[\alpha]_D^{20,5}$ –0.09 (*c* = 0.4, MeOH); mp 240-242 °C; IR ν/cm^{-1} 3070, 2890, 1666, 1550, 1480, 1240, 1060, 990, 790.

2'-Deoxy-2'-(2"-(trimethylsilyl)ethyl)thiothymidine **5**

Prepared according to described procedure [29], in 88% yield.

2'-Deoxy-3', 5'-di-(*O*-methanesulfonyl)-2'-(2"-(trimethylsilyl) ethyl)thiothymidine (**6**)

To a solution of 2'-deoxy-2'-(2''-(trimethylsilyl)ethyl) thiothymidine (**5**) (0.7 g, 1.87 mmol) in anhydrous pyridine (10 mL), at 0 °C under argon, was added methanesulfonyl chloride (1.6 g, 11.25 mmol) and the resulting solution was stirred for 1 h at room temperature. The solution was treated with aqueous hydrochloride acid to pH 1.0. The resulting suspension was filtered. The product (**6**) was obtained as a white solid (0.86 g, 87%); $[\alpha]_D^{23}$ 0.02 (*c* = 0.2, MeOH); mp: 72-74 °C; IR ν/cm^{-1} 2950, 1685, 1350, 1190, 940, 830; ^{1}H NMR (200 MHz, $CDCl_3$), δ 8.65 (s, 1H, NH), 7.35 (s, 1H, H-6), 6.10 (d, 1H, *J* 9.4 Hz, H-1'), 5.24 (d, 1H, *J* 5.8 Hz, H-3'), 4.52 (m, 3H, H-4'+ H-5'a + H-5'b), 3.52 (m, 1H, H-2'), 3.17 (s, 3H, SO_2-CH_3), 3.11 (s, 3H, SO_2-CH_3), 2.57 (m, 2H, S-CH_2), 1.94 (s, 3H, 5-CH_3), 0.77 (m, 2H, Si-CH_2), -0.03 (s, 9H, Si-$(CH_3)_3$); ^{13}C NMR (50 MHz, DMSO-d_6,) δ 163.0 (C-2), 150.2 (C-4), 135.1 (C-6), 112.3 (C-5), 88.7 (C-1'), 81.3 (C-4'), 79.5 (C-3'), 68.2 (C-5'), 48.9 (C-2'), 38.6 (SO_2-CH_3), 37.9 (SO_2-CH_3), 27.9 (S-CH_2), 17.6 (Si-CH_2), 12.1 (5-CH_3), -2.0 (Si-$(CH_3)_3$); HRMS *m/z*, observed: 531.0964; $C_{17}H_{31}N_2O_9S_3Si$ $[M+H]^+$ requires: 531.0916.

2'-Deoxy-3', 5'-di-(*O*-benzoyl)-2'-(2"-(trimethylsilyl)ethyl) thiothymidine (**7**)

To a solution of 2'-deoxy-2'-(2"-(trimethylsilyl) ethyl)thiothymidine (**5**) (1.66 g, 4.45 mmol) in anhydrous pyridine (30 mL), at 0 °C under argon, was added benzoic anhydride (10.1 g, 44.48 mmol) and the resulting solution was stirred for 6 h at 60 ºC, then evaporated. The residue was dissolved in dichloromethane (150 mL), washed twice with water (100 mL) aqueous sodium hydrogenocarbonate (5%; 200 mL), then the combined extracts were dried over MgSO4 and evaporated. The crude compound was purified by chromatography on silica gel in dichloromethane:methanol (95:5) to give compound (**7**) as a white solid (1.86 g, 72%); $[\alpha]_D^{23,5}$ –0.11 (*c* = 0.4, CH_2Cl_2); mp: 68-70 °C; IR ν/cm^{-1} 3060, 2950, 1715, 1680, 1600, 1580, 1450, 1250, 840, 750; ^{1}H NMR (400 MHz, $CDCl_3$,) δ 8.08 (s, 1H, N-H), 8.08-7.46 (m, 10H, Ar), 7.15 (d, 1H, *J* 1.2 Hz, H-6'), 6.30 (d, 1H, *J* 8.4 Hz, H-1'), 5.68 (dd, 1H, *J* 2.4 Hz, *J* 6.0 Hz, H-3'), 4,79 (dd, 1H, *J* 3.2 Hz, *J* 12,00 Hz, H-5'a), 4.68 (dd, 1H, *J* 3.2 Hz, *J* 12,00 Hz, H-5'b), 4.53 (1 H, m, H-4'), 3.59 (m, 1H, H-2'), 2.57 (m, 2H, S-CH_2), 1.63 (s, 3H, 5-CH_3), 0.73 (m, 2H, Si-CH_2), -0,07(s, 9H, Si-$(CH_3)_3$; ^{13}C NMR (100 MHz, $CDCl_3$,) δ 165.9 (COO), 165.8 (COO), 162.9 (C-2), 150.2 (C-4), 134.5(C-6), 133.8 (C-Ar), 130.0 (C-Ar), 129.5 (C-Ar), 129.4 (C-Ar), 129.0 (C-Ar), 128.6 (C-Ar), 112.1 (C-5), 88.7 (C-1'), 81.5 (C-4'), 74.6 (C-3'), 64.1 (C-5'), 50.5 (C-2'), 29.0 (S-CH_2), 17.5 (Si-CH_2), 12.1 (5-CH_3), -0.0 (Si-$(CH_3)_3$); HRMS *m/z*, observed: 583.1926; $C_{29}H_{35}N_2O_7SSi$ $[M+H]^+$ requires: 583.1890.

2',3'-Didehydro-2',3'-dideoxy-5'-(*O*-benzoyl)-2'-(2"-(trimethylsilyl)ethyl)thiothymidine (**8**)

A suspension of 2'-deoxy-3',5'-di-(*O*-methanesulfonyl)-2'-(2"-(trimethylsilyl)ethyl)thiothymidine (**5**) (0.86 g, 1.62 mmol) and anhydrous sodium benzoate (0.46 g, 4.05 mmol) in dry DMF (10 mL) was stirred under argon at

90 °C for 4 h. After completion of the reaction as detected by TLC (dichloromethane:methanol, 95:5) 100 mL of dichloromethane was added. The resulting suspension was filtered and the filtrate evaporated to dryness. The residue was purified by chromatography on silica gel with hexane: ethyl acetate (1:1). The product (**8**) was obtained as a white solid (0.49 g, 65% yield).

A suspension of 2'-deoxy-3',5'-di-(*O*-benzoyl)-2'-(2"-(trimethylsilyl)ethyl)thiothymidine (**7**) (1.25 g, 2.14 mmol) and anhydrous potassium carbonate (1.48 g, 10.7 mmol) in dry DMF (60 mL) was stirred under argon at 120 °C for 4 h. After completion of the reaction, as detected by TLC (dichloromethane:ethyl acetate, 9:1) 200 mL of dichloromethane was added. The resulting suspension was filtered and the filtrate to dryness evaporated. The crude compound was purified by chromatography on silica gel in with dichloromethane:ethyl acetate (95: 5). The product (**8**) was obtained as a white solid (0.61 g, 62% yield).

$[\alpha]_D^{23,7}$-0.58 (c = 0.2, CH_2Cl_2); mp: 52-54°C; IR ν/cm^{-1} 3040, 2950, 1720, 1680, 1450, 1250, 1100, 840, 670; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9,20 (s, 1H, NH), 8,0 (dd, 2H, *J* 1.2 Hz, *J* 8.4 Hz Ar- Ha), 7.58 (m, 1H, Ar- Hc), 7.44 (t, 2H, *J* 7.6 Hz, Ar- Hb), 6.96 (d, 1H, *J* 1.2 Hz, H-6), 6.92 (dd, 1H, *J* 1.6 Hz, *J* 3.6 Hz, H-1'), 5,80 (t, 1H, *J* 1.6 Hz, H-3'), 5.16 (m, 1H, H-4'), 4,57 (dd, 1H, *J* 4.00 Hz, *J* 12.00 Hz, H-5'a), 4.51 (dd, 1H, *J* 4.00 Hz, *J* 12.00 Hz, H-5'b), 2.82 (m, 2H, S-CH_2), 1.57 (s, 3H, 5-CH_3), 0.91 (m, 2 H, Si-CH_2), 0.02 (m, 9H, Si-$(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$,) δ 166.3 (CO), 163.7 (C-2), 151.0 (C-4), 136.8 (C-2'), 135.0 (C-6), 133.5 (C-Ar), 129.6 (C-2Ar), 129.5 (C-Ar), 128.6 (C-2Ar), 121.6 (C-3'), 111.7 (C-5), 89.8 (C-1'), 84.2 (C-4'), 65.3 (C-5'), 28.6 (S-CH_2), 16.2 (Si-CH_2), 12.1 (5-CH_3), -1.9 (Si-$(CH_3)_3$); HRMS observed: 461.1562; $C_{22}H_{29}N_2O_5SSi$ $[M+H]^+$ requires: 461.1522.

2',3'-Didehydro-2',3'-dideoxy-2'-(2"-(trimethylsilyl)ethyl) thiothymidine (**9**)

To a solution of 2',3'-didehydro-2',3'-dideoxy-5'-(*O*-benzoyl)-2'-(2" (trimethylsilyl)ethyl)thiothymidine (**8**) (0.130 g, 0.28 mmol) in anhydrous methanol (10 mL), at 0 °C, was added potassium hydroxide (0.024 g, 0.42 mmol) and the resulting solution was stirred for 1 h at room temperature. The solution was neutralized with acid resin amberlist IRH-120 at pH 7.0. The resulting suspension was filtered, evaporated to dryness and the residue obtained was purified by chromatography on silica gel with dichloromethane:methanol (95:5). The product (**9**) was obtained as a white solid (0.086 g, 86% yield); mp: 59-61°C; IR ν/cm^{-1} 3420, 2950, 1680, 1610, 1250, 1100, 890; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.40 (s, 1H, N-H), 7.35 (d, 1H, *J* 0.8 Hz, H-6), 6.89 (d, 1H, *J* 2.0 Hz, H-1'), 5.78 (s, 1H, H-3'), 4.94 (d, 1H, *J* 0.8 Hz, H-4'), 3.92 (dd, 1H, *J* 2.8 Hz, *J* 12.6 Hz, H-5'a), 3.74 (dd, 1H, *J* 2.8 Hz, *J* 12.6 Hz, H-5'b), 2.84 (m, 2H, S-CH_2), 1.86 (s, 3H, 5-CH_3), 0.92 (m, 2H, Si-CH_2), 0.04 (9 H, s, Si$(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0 (C-2), 150.6 (C-4), 136.9 (C-6), 135.2 (C-2'), 123.5 (C-3'), 110.9 (C-5), 90.3 (C-1'), 87.4 (C-4'), 63.5 (C-5'), 28.5 (S-CH_2), 16.3 (Si-CH_2), 12.4 (5-CH_3), -1.8 (Si$(CH_3)_3$); HRMS observed: 395.0932; $C_{15}H_{24}N_2KO_4SSi$: $[M+K]^+$ requires: 395.0863.

Supplementary Information

Relevant spectral data, including NMR, IR and mass spectra, are available free of charge at http://jbcs.sbq.org.br, as a PDF file.

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