SYNTHESIS OF 1-(2,3-DIDEOXY-4-C-METHYL-β-D-*glycero*-PENT-2-ENOFURANOSYL)THYMINE, 1-(2,3-DIDEOXY-4-C-METHYL-β-D-*glycero*-PENTOFURANOSYL)THYMINE AND 1-(4-C-AZIDOMETHYL-2-DEOXY-β-D-*threo*-PENTOFURANOSYL)THYMINE

Hubert HŘEBABECKÝ and Antonín HOLÝ

Institute of Organic Chemistry and Biochemistry,
Academy of Sciences of the Czech Republic, 166 10 Prague 6, The Czech Republic

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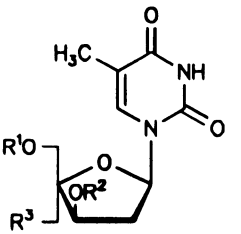
Reaction of isopropylidene derivative *I* with thionyl chloride in hexamethylphosphoric triamide afforded chloro derivative *II*. Removal of the isopropylidene group in *II* by treatment with a cation-exchanging resin (H^+ form) gave the free chloro nucleoside *III*. Reduction of the chloro derivative *II* with tributylstannane and subsequent removal of the isopropylidene group yielded deoxy derivative *V*. This was protected with tert-butyldiphenylsilyl group and converted into the mesylate *VII*. Elimination of the mesyl group followed by desilylation gave 1-(2,3-dideoxy-4-C-methyl-β-D-*glycero*-pent-2-enofuranosyl)thymine (*IX*) which was hydrogenated to afford 1-(2,3-dideoxy-4-C-methyl-β-D-*glycero*-pentofuranosyl)thymine (*X*). 1-(4-C-Azidomethyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (*XIII*) was prepared by mesylation of isopropylidene derivative *I*, nucleophilic substitution of the mesyl group with azide and removal of the isopropylidene group.

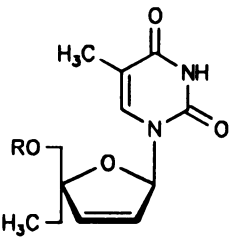
This paper concerns the synthesis of 1-(2,3-dideoxy-4-C-methyl-β-D-*glycero*-pent-2-enofuranosyl)thymine (*IX*) and 1-(2,3-dideoxy-4-C-methyl-β-D-*glycero*-pentofuranosyl)-thymine (*X*) with the aim to study the effect of introduction of methyl group into the position 4′ in 2′,3′-dideoxythymidine and 2′,3′-dideoxy-2′,3′-didehydrothymidine on the anti-HIV activity.

Recently, 2′,3′-dideoxy-2′,3′-didehydrothymidine (d4T) receives considerable attention as potentially clinically applicable compound, effective against HIV (refs[1,2]). HIV strains that are insensitive to 3′-azido-2′,3′-dideoxythymidine (AZT) do not exhibit cross-resistance against d4T (refs[3,4]) and d4T easily penetrates through the blood brain barrier[5]. Moreover, its lower toxicity and an effect almost comparable to that of AZT makes d4T a potentially effective drug in treatment of AIDS (ref.[6]).

As starting compound for the preparation of analogs *IX* and *X* we used the isopropylidene derivative *I*, obtained by isopropylidenation of 1-(2-deoxy-4-C-hydroxymethyl-α-L-*erythro*-pentofuranosyl)thymine[7]. Reaction of compound *I* with thionyl chloride in hexamethylphosphoric triamide[8] afforded in high yield the chloro derivative *II* which was reduced with tributylstannane in toluene in the presence of 2,2′-azobis-

(2-methylpropionitrile) to give 4′-C-methyl derivative *IV*. The free nucleosides *III* and *V* were prepared by heating isopropylidene derivatives *II* and *IV* with Dowex 50 (H^+ form) in 80% aqueous methanol. The nucleoside *V* was treated with chloro-tert-butyldiphenylsilane to give silyl derivative *VI* which on mesylation afforded compound *VII*. Elimination of the mesyl group by reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene in acetonitrile gave dideoxydidehydronucleoside *VIII*. The free nucleoside *IX* was obtained by desilylation with tetrabutylammonium fluoride. Hydrogenation of compound *IX* on Pd/C furnished dideoxy derivative *X*.





I, $R^1, R^2 = C(CH_3)_2$; R^3 = OH

II, $R^1, R^2 = C(CH_3)_2$; R^3 = Cl

III, $R^1 = R^2$ = H; R^3 = Cl

IV, $R^1, R^2 = C(CH_3)_2$; R^3 = H

V, $R^1 = R^2 = R^3$ = H

VI, R^1 = TBDPS; $R^2 = R^3$ = H

VII, R^1 = TBDPS; $R^2 = SO_2CH_3$; R^3 = H

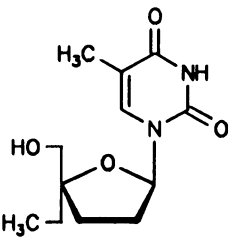
XI, $R^1, R^2 = C(CH_3)_2$; $R^3 = OSO_2CH_3$

XII, $R^1, R^2 = C(CH_3)_2$; $R^3 = N_3$

XIII, $R^1 = R^2$ = H; $R^3 = N_3$

VIII, R = TBDPS

IX, R = H



X

TBDPS = tert–butyldiphenylsilyl

Verheyden and collaborators[9] synthesized 1-(4-C-azidomethyl-2-deoxy-β-D-*erythro*-pentofuranosyl)thymine which was significantly active against HIV-1. In order to study the effect of a configurational change on the carbon atom 3′ we prepared 1-(4-C-azidomethyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (*XIII*). Mesylation of the isopropylidene derivative *I* afforded mesyl derivative *XI*, nucleophilic substitution of the mesyl group in *XI* by azide gave the azido analog *XII* which on removal of the isopropylidene group was converted into the free nucleoside *XIII*.

Structures of the synthesized compounds are in accord with the found elemental analyses and ^1H NMR spectra.

The compounds were tested in vitro on inhibitory activity against replication of HIV-1 and HIV-2 in CEM and MT-4 cells. Significant activity was found only for the dideoxydidehydro derivative *IX* (EC_{50} (μg/ml) 11.3 (HIV-1, CEM); 60 (HIV-2, CEM); 6.5 (HIV-1, MT-4); 6.8 (HIV-2, MT-4))[10].

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. ^{1}H NMR spectra (δ, ppm; *J*, Hz) were measured on a Varian XL-200 (200 MHz) instrument in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. Column chromatography was performed on silica gel (30 – 60 μm; Service Laboratories of this Institute) and thin-layer chromatography (TLC) on Silufol UV 254 sheets (Kavalier, The Czech Republic) in the following systems: S1 ethyl acetate–toluene (1 : 1); S2 ethyl acetate; S3 ethyl acetate–2-propanol (23 : 2). Solvents were evaporated at bath temperature 30 – 60 °C/2 kPa and compounds were dried at 13 Pa over phosphorus pentoxide.

1-(2-Deoxy-4-*C*-hydroxymethyl-3,5-*O*-isopropylidene-β-D-*threo*-pentofuranosyl)thymine (*I*)*

Concentrated sulfuric acid (0.08 ml) was added to a stirred mixture of 1-(2-deoxy-4-*C*-hydroxymethyl-α-L-*erythro*-pentofuranosyl)thymine[7] (5.44 g, 20 mmol), acetone (80 ml) and 2,2-dimethoxypropane (30 ml). The mixture was stirred at room temperature for 20 min and then neutralized with finely ground sodium hydrogen carbonate. The insoluble material was filtered off and washed with acetone (20 ml). The combined filtrates were concentrated and the residue was dissolved in 80% aqueous methanol (50 ml). After addition of Dowex 50X8 (H^+ form; 2 ml) the mixture was stirred at room temperature until the more mobile compound (TLC) disappeared. The ion-exchanger was filtered off and washed with methanol, the combined filtrates were evaporated and the residue was chromatographed on a column of silica gel (500 g) in ethyl acetate–2-propanol (23 : 3). Yield 5.54 g (89%) of product *I* in the form of solid foam, R_F 0.25 (S2). For $C_{14}H_{20}N_2O_6$ (312.3) calculated: 53.84% C, 6.46% H, 8.97% N; found: 53.61% C, 6.64% H, 8.75% N. ^{1}H NMR spectrum: 1.32 s and 1.41 s, 3 H and 3 H ($C(CH_3)_2$); 1.78 d, 3 H, *J* = 0.8 (5-CH_3); 1.87 dd, 1 H (*J*(2a',1') = 1.4, *J*(2a',2b') = 15.1, H-2a'); 2.84 m, 1 H (*J*(2b',1') = 8.0, *J*(2b',3') = 5.1, H-2b'); 3.15 – 3.37 m, 2 H (CH_2O); 3.78 d, 1 H (*J*(5a',5b') = 13.2, H-5a'); 4.00 d, 1 H (H-5b'); 4.43 d, 1 H (H-3'); 5.19 t, 1 H (*J*(OH, CH_2O) = 5.7, CH_2OH); 6.16 d, 1 H (H-1'); 8.00 d, 1 H (*J* = 0.9, H-6); 11.29 s, 1 H (H-3); after exchange with D_2O: 3.26 s, 2 H (CH_2O).

1-(4-*C*-Chloromethyl-2-deoxy-3,5-*O*-isopropylidene-β-D-*threo*-pentofuranosyl)thymine (*II*)

Isopropylidene derivative *I* (3.12 g, 10 mmol) was added to a stirred mixture of hexamethylphosphoric triamide (20 ml) and thionyl chloride (3 ml). The mixture was stirred to homogeneity, set aside at room temperature overnight and then added dropwise at 0 °C to a stirred mixture of water (60 ml) and sodium hydrogen carbonate (14 g). The mixture was extracted with ethyl acetate (3 × 250 ml), the combined extracts were washed with water (50 ml), dried over magnesium sulfate and the solvent was evaporated. Chromatography of the residue on a column of silica gel (350 g) in ethyl acetate–toluene (2 : 1) and subsequent crystallization from 2-propanol afforded 2.77 g (84%) of chloro derivative *II*, m.p. 180 – 182 °C,

* For the sake of formal consistence of names of all the compounds prepared, we denoted the configuration of the sugar part in compounds *I* and *XI* by symbol β-D instead of the more correct description α-L.

R_F 0.69 (S2). For $C_{14}H_{19}ClN_2O_5$ (330.8) calculated: 50.83% C, 5.79% H, 10.27% Cl, 8.47% N; found: 50.86% C, 5.78% H, 10.45% Cl, 8.53% N. ^{1}H NMR spectrum: 1.34 s and 1.44 s, 3 H and 3 H ($C(CH_3)_2$); 1.78 d, 3 H (J = 0.9, 5-CH_3); 1.93 dd, 1 H (J(2a',1') = 1.7, J(2a',2b') = 15.3, H-2a'); 2.93 m, 1 H (J(2b',1') = 8.5, J(2b',3') = 5.4, H-2b'); 3.73 d, 1 H (J(a,b) = 11.9, CH^aH–O); 3.82 d, 1 H (CH^bH–O); 3.91 d, 1 H (J(5a',5b') = 13.1, H-5a'); 4.02 d, 1 H (H-5b'); 4.40 d, 1 H (H-3'); 6.22 dd, 1 H (H-1'); 7.95 d, 1 H (J = 1.1, H-6); 11.29 s, 1 H (H-3).

1-(4-C-Chloromethyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (*III*)

Dowex 50 (H^+ form; 2 ml) was added to a solution of isopropylidene derivative *II* (165 mg, 0.5 mmol) in 80% aqueous methanol (2 ml) and the mixture was refluxed with stirring for 2 h. The ion exchanger was filtered off, washed with methanol (2 ml) and the combined filtrates were concentrated. Crystallization of the residue from 2-propanol afforded 130 mg (89%) of compound *III*, m.p. 168 – 169 °C, R_F 0.67 (S3). For $C_{11}H_{15}ClN_2O_5$ (290.7) calculated: 45.45% C, 5.20% H, 12.20% Cl, 9.64% N; found: 45.50% C, 5.28% H, 12.19% Cl, 9.80% N. ^{1}H NMR spectrum: 1.77 d, 3 H (J = 0.9, 5-CH_3); 1.94 m, 1 H (J(2a',1') = 4.0, J(2a',2b') = 14.5, J(2a',3') = 3.4, H-2a'); 2.79 m, 1 H (J(2b',1') = 7.7, J(2b',3') = 6.7, H-2b'); 3.67 m, 4 H (2 × H-5', CH_2O); 4.29 m, 1 H (J(3',OH) = 4.3, H-3'); 4.81 t, 1 H (J(OH,5') = 5.6, 5'-OH); 5.55 d, 1 H (3'-OH); 6.18 dd, 1 H (H-1'); 7.86 d, 1 H (J = 1.1, H-6); 11.27 s, 1 H (H-3).

1-(2-Deoxy-3,5-O-isopropylidene-4-C-methyl-β-D-*threo*-pentofuranosyl)thymine (*IV*)

To a stirred solution of chloronucleoside *II* (3.31 g, 10 mmol) in toluene (30 ml) was added at 100 °C 1 M solution of tributylstannane in toluene (20 ml), followed by 2,2'-azobis(2-methylpropionitrile) (200 mg). After heating at 100 °C for 40 min, the mixture was cooled and the solvent evaporated. The residue was stirred with light petroleum (100 ml), the solid was filtered and washed with light petroleum. Chromatography on a column of silica gel (300 g) in ethyl acetate–toluene (2 : 1) afforded 2.39 g (81%) of deoxy derivative *IV*, m.p. 187.5 – 188.5 °C (2-propanol), R_F 0.46 (S2). For $C_{14}H_{20}N_2O_5$ (296.3) calculated: 56.74% C, 6.80% H, 9.45% N; found: 56.67% C, 6.80% H, 9.57% N. ^{1}H NMR spectrum: 1.07 s, 3 H (4-C–CH_3); 1.31 s and 1.42 s, 3 H and 3 H ($C(CH_3)_2$); 1.77 d, 3 H (J = 0.9, 5-CH_3); 1.85 dd, 1 H (J(2a',1') = 1.6, J(2a',2b') = 15.1, H-2a'); 2.86 m, 1 H (J(2b',1') = 8.1, J(2b',3') = 4.9, H-2b'); 3.85 s, 2 H (2 × H-5'); 4.23 d, 1 H (H-3'); 6.08 dd, 1 H (H-1'); 8.00 d, 1 H (J = 0.8, H-6); 11.27 s, 1 H (H-3).

1-(2-Deoxy-4-C-methyl-β-D-*threo*-pentofuranosyl)thymine (*V*)

Using the procedure described for the chloro derivative *III*, the isopropylidene derivative *IV* (2.07 g, 7 mmol) was converted into the title deoxy compound *V* (1.54 g, 86%), m.p. 196 – 199 °C (2-propanol), R_F 0.32 (S3). For $C_{11}H_{16}N_2O_5$ (256.2) calculated: 51.55% C, 6.29% H, 10.93% N; found: 51.53% C, 6.30% H, 11.10% N. ^{1}H NMR spectrum: 1.10 s, 3 H (4-C–CH_3); 1.76 d, 3 H (J = 0.4, 5-CH_3); 1.86 m, 1 H (J(2a',1') = 3.2, J(2a',2b') = 14.4, J(2a',3') = 2.8, H-2a'); 2.74 m, 1 H (J(2b',1') = 7.8, J(2b',3') = 6.0, H-2b'); 3.57 m, 2 H (2 × H-5'); 4.01 m, 1 H (J(3',OH) = 3.8, H-3'); 4.66 t, 1 H (J(OH,5') = 5.8, 5'-OH); 5.30 d, 1 H (3'-OH); 6.09 dd, 1 H (H-1'); 7.88 d, 1 H (J = 1.0, H-6); 11.23 s, 1 H (H-3).

1-(5-O-tert-Butyldiphenylsilyl-2-deoxy-4-C-methyl-β-D-*threo*-pentofuranosyl)thymine (*VI*)

tert-Butylchlorodiphenylsilane (1.4 ml, 5.5 mmol) was added to a solution of free nucleoside *V* (1.28 g, 5 mmol) and imidazole (0.68 g, 10 mmol) in dimethylformamide (10 ml). After standing overnight at room temperature, the solvent was evaporated and the residue partitioned between water (20 ml) and ethyl acetate (100 ml). The organic layer was separated, washed with water (2 × 20 ml), dried over magnesium sulfate and the solvent was evaporated. The residue was chromatographed on a column of silica gel (200 g) in

ethyl acetate–toluene (2 : 1) to give 2.17 g (88%) of the amorphous product *VI*, R_F 0.24 (S1). For $C_{27}H_{34}N_2O_5Si$ (494.6) calculated: 65.56% C, 6.93% H, 5.66% N; found: 65.62% C, 6.92% H, 5.47% N. ^{1}H NMR spectrum: 1.00 s, 9 H ($C(CH_3)_3$); 1.24 s, 3 H (4-C–CH_3); 1.60 s, 3 H (5-CH_3); 1.86 m, 1 H (J(2a',1') = 3.0, J(2a',2b') = 14.5, J(2a',3') = 2.5, H-2a'); 2.81 m, 1 H (J(2b',1') = 7.7, J(2b',3') = 5.6, H-2b'); 3.85 s, 2 H (2 × H-5'); 4.06 m, 1 H (H-3'); 5.38 d, 1 H (J(OH,3') = 3.5, 3'-OH); 6.15 dd, 1 H (H-1'); 7.29 – 7.47 m and 7.64 – 7.70 m, 6 H and 5 H (H-6, H-arom.); 11.28 s, 1 H (H-3).

1-(5-O-tert-Butyldiphenylsilyl-2-deoxy-3-O-methanesulfonyl-4-C-methyl-β-D-*threo*-pentofuranosyl)thymine (*VII*)

Methanesulfonyl chloride (1.2 ml, 15 mmol) was added at 0 °C to a solution of compound *VI* (1.98 g, 4 mmol) in pyridine (15 ml). After standing at room temperature for 5 h, the mixture was cooled to 0 °C, water (0.5 ml) was added with stirring and the solvent was evaporated. The residue was partitioned between water (20 ml) and ethyl acetate (80 ml), the organic layer was washed successively with water (20 ml), 2% hydrochloric acid to acid reaction of the aqueous layer, water (20 ml) and 5% aqueous sodium hydrogen carbonate (20 ml). After drying with magnesium sulfate and evaporation of the solvent, the residue was chromatographed on a column of silica gel (200 g) in ethyl acetate–toluene (2 : 1). Yield 1.90 g (83%) of mesyl derivative *VII* as solid foam, R_F 0.25 (S1). For $C_{28}H_{36}N_2O_7SSi$ (572.7) calculated: 58.72% C, 6.34% H, 4.89% N, 5.60% S; found: 59.00% C, 6.44% H, 4.76% N, 5.36% S. ^{1}H NMR spectrum: 1.02 s, 9 H ($C(CH_3)_3$); 1.31 s, 3 H (4-C–CH_3); 1.55 d, 3 H (J = 1.0, 5-CH_3); 2.35 m, 1 H (J(2a',1') = 4.7, J(2a',2b') = 14.7, J(2a',3') = 3.1, H-2a'); 3.04 m, 1 H (J(2b',1') = 7.2, J(2b',3') = 5.9, H-2b'); 3.20 s, 3 H (SO_2CH_3); 3.81 d, 1 H (J(5a',5b') = 10.7, H-5a'); 3.89 d, 1 H (H-5b'); 5.16 dd, 1 H (H-3'); 6.22 dd, 1 H (H-1'); 7.32 – 7.48 m and 7.61 – 7.70 m, 7 H and 4 H (H-6, H-arom.); 11.37 s, 1 H (H-3).

1-(5-O-tert-Butyldiphenylsilyl-2,3-dideoxy-4-C-methyl-β-D-*glycero*-pent-2-enofuranosyl)thymine (*VIII*)

A solution of mesyl derivative *VII* (1.15 g, 2 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.45 ml, 3 mmol) in acetonitrile (12 ml) was heated at 70 °C for 24 h. The mixture was then diluted with ethyl acetate (100 ml), washed with water (3 × 20 ml), dried over magnesium sulfate and the solvent was evaporated. Column chromatography of the residue on silica gel (100 g) in ethyl acetate–toluene (1 : 1) afforded 760 mg (80%) of didehydro derivative *VIII* as solid foam, R_F 0.48 (S1). For $C_{27}H_{32}N_2O_4Si$ (476.6) calculated: 68.03% C, 6.77% H, 5.88% N; found: 67.82% C, 6.82% H, 5.75% N. ^{1}H NMR spectrum: 1.00 s, 9 H ($C(CH_3)_3$); 1.22 d, 3 H (J = 1.0, 5-CH_3); 1.31 s, 3 H (4-C–CH_3); 3.72 s, 2 H (2 × H-5'); 5.94 dd, 1 H (J(3',1') = 1.2, J(3',2') = 5.9, H-3'); 6.48 dd, 1 H (J(2',1') = 2.0, H-2'); 6.84 m, 1 H (H-1'); 7.09 d, 1 H (J = 1.2, H-6); 7.30 – 7.44 m and 7.58 – 7.62 m, 6 H and 4 H (H-arom.); 11.32 s, 1 H (H-3).

1-(2,3-Dideoxy-4-C-methyl-β-D-*glycero*-pent-2-enofuranosyl)thymine (*IX*)

A solution of silyl derivative *VIII* (477 mg, 1 mmol) in dioxane (5 ml) was mixed with 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (1 ml). After standing overnight at room temperature, the solution was neutralized with acetic acid to pH 7 and the solvent was evaporated. The residue was chromatographed on a column of silica gel (50 g) in ethyl acetate–2-propanol (22 : 3), affording 231 mg (97%) of didehydro derivative *IX*, R_F 0.43 (S3). For $C_{11}H_{14}N_2O_4$ (238.2) calculated: 55.45% C, 5.92% H, 11.76% N; found: 55.16% C, 6.07% H, 11.49% N. ^{1}H NMR spectrum: 1.18 s, 3 H (4-C–CH_3); 1.72 d, 3 H (J = 0.8, 5-CH_3); 3.48 m, 2 H (2 × H-5'); 5.09 t, 1 H (J(OH,5') = 5.3, 5'-OH); 5.83 dd, 1 H (J(3',1') = 1.2, J(3',2') = 5.8, H-3'); 6.33 dd, 1 H (J(2',1') = 1.8, H-2'); 6.83 dd, 1 H (H-1'); 7.75 d, 1 H (J = 1.1, H-6); 11.28 s, 1 H (H-3); after exchange with D_2O: 3.39 d, 1 H (J(5a',5b') = 11.6, H-5a'); 3.49 d, 1 H (H-5b').

1-(2,3-Dideoxy-4-C-methyl-β-D-*glycero*-pentofuranosyl)thymine (*X*)

Didehydro derivative *IX* (238 mg, 1 mmol) was hydrogenated in methanol (2.5 ml) over 10% Pd/C (25 mg) at room temperature for 12 h. The catalyst was filtered off through Celite which was then washed with methanol and the combined filtrates were taken down. The residue was dissolved in warm 2-propanol and ether was added to incipient turbidity. The product *X* which crystallized (178 mg, 74%) had m.p. 124 – 125 °C, R_F 0.44 (S3). For $C_{11}H_{16}N_2O_4$ (240.3) calculated: 54.99% C, 6.71% H, 11.66% N; found: 54.79% C, 6.74% H, 11.55% N. ^{1}H NMR spectrum: 1.11 s, 3 H (4-C–CH_3); 1.57 – 1.71 m, 1.87 – 2.18 m and 2.27 – 2.42 m, 1 H, 2 H and 1 H (2 × H-2', 2 × H-3'); 1.76 d, 1 H (*J* = 0.8, 5-CH_3); 3.32 – 3.53 m, 2 H (2 × H-5'); 5.16 t, 1 H (*J*(OH,5') = 5.2, 5'-OH); 6.02 dd, 1 H (*J*(1',2a') = 5.1, *J*(1',2b') = 6.5, H-1'); 7.86 d, 1 H (*J* = 1.2, H-6); 11.21 s, 1 H (H-3); after exchange with D_2O: 3.38 d, 1 H (*J*(5a',5b') = 11.7, H-5a'); 3.46 d, 1 H (H-5b').

1-(2-Deoxy-3,5-O-isopropylidene-4-C-methanesulfonyloxymethyl-β-D-*threo*-pentofuranosyl)thymine (*XI*)

Methanesulfonyl chloride (3 ml) was added to a cooled and stirred solution of isopropylidene derivative *I* (3.12 g, 10 mmol) in pyridine (30 ml). After standing at room temperature for 4 h, the mixture was cooled to 0 °C and water (1.5 ml) was added. The solvent was evaporated and the residue partitioned between water (30 ml) and ethyl acetate (150 ml). The organic layer was washed successively with water (30 ml), 5% hydrochloric acid to acid reaction of the aqueous layer, water (30 ml) and 10% aqueous solution of sodium hydrogen carbonate, dried over magnesium sulfate and the solvent was evaporated. Column chromatography of the residue on silica gel (300 g) in ethyl acetate afforded 3.56 g (91%) of product *II* as a solid foam, R_F 0.48 (S2). For $C_{15}H_{22}N_2O_8S$ (390.4) calculated: 46.14% C, 5.68% H, 7.18% N, 8.21% S; found: 45.99% C, 5.65% H, 6.92% N, 7.97% S. ^{1}H NMR spectrum: 1.34 s and 1.44 s, 3 H and 3 H (C(CH_3)$_2$); 1.78 d, 3 H (*J* = 1.0, 5-CH_3); 1.96 dd, 1 H (*J*(2a',1') = 1.5, *J*(2a',2b') = 15.2, H-2a'); 2.88 m, 1 H (*J*(2b',1') = 8.3, *J*(2b',3') = 5.6, H-2b'); 3.26 s, 3 H (SO_2CH_3); 3.90 d, 1 H (*J*(5a', 5b') = 13.2, H-5a'); 3.98 d, 1 H (H-5b'); 4.21 d, 1 H (*J*(a,b) = 11.0, CH^aH–O); 4.26 d, 1 H (CH^bH–O); 4.41 d, 1 H (H-3'); 6.24 dd, 1 H (H-1'); 7.94 d, 1 H (*J* = 1.2, H-6); 11.32 s, 1 H (H-3).

1-(4-C-Azidomethyl-2-deoxy-3,5-O-isopropylidene-β-D-*threo*-pentofuranosyl)thymine (*XII*)

Sodium azide (1.7 g) was added to a solution of mesyl derivative *XI* (1.95 g, 5 mmol) in dimethylformamide (15 ml) and the mixture was stirred in an argon atmosphere at 100 °C for 8 h. After cooling, the insoluble portion was filtered off, washed with acetone (10 ml) and the combined filtrates were concentrated. Column chromatography of the residue on silica gel (180 g) in ethyl acetate, followed by crystallization from 2-propanol, gave 1.63 g (97%) of azido derivative *XII*, m.p. 175 – 178 °C; R_F 0.68 (S2). For $C_{14}H_{19}N_5O_5$ (337.3) calculated: 49.84% C, 5.68% H, 20.76% N; found: 49.89% C, 5.60% H, 21.01% N. ^{1}H NMR spectrum: 1.33 s and 1.41 s, 3 H and 3 H (C(CH_3)$_2$); 1.78 d, 3 H (*J* = 0.8, 5-CH_3); 1.93 dd, 1 H (*J*(2a',1') = 1.7, *J*(2a',2b') = 15.4, H-2a'); 2.89 m, 1 H (*J*(2b',1') = 8.3, *J*(2b',3') = 5.4, H-2b'); 3.34 d, 1 H (*J*(a,b) = 12.9, CH^aH–O); 3.63 d, 1 H (CH^bH–O); 3.91 s, 2 H (2 × H-5'); 4.30 d, 1 H (H-3'); 6.24 d, 1 H (H-1'); 7.96 d, 1 H (*J* = 1.0, H-6); 11.30 s, 1 H (H-3).

1-(4-C-Azidomethyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (*XIII*)

Using the same procedure as described for the chloro derivative *III*, the isopropylidene derivative *XII* (675 mg, 2 mmol) was converted into azido derivative *XIII*; yield after crystallization from 2-propanol 576 mg (97%), m.p. 151 – 152 °C, R_F 0.56 (S3). For $C_{11}H_{15}N_5O_5$ (297.3) calculated: 44.44% C, 5.09% H, 23.56% N; found: 44.46% C, 5.06% H, 23.66% N. ^{1}H NMR spectrum: 1.77 d, 3 H (*J* = 0.8, 5-CH_3); 1.94 dt, 1 H (*J*(2a',1') = 4.2, *J*(2a',2b') = 14.4, *J*(2a',3') = 3.9, H-2a'); 2.75 m, 1 H (*J*(2b',1') = 7.6, *J*(2b',3') = 6.2,

H-2b'); 3.31 d, 1 H (J(a,b) = 12.7, CH^{a}H–O); 3.44 d, 1 H (CH^{b}H–O); 3.56 – 3.71 m, 2 H (2 × H-5'); 4.16 m, 1 H (H-3'); 4.82 t, 1 H (J(OH,5') = 5.6, 5'-OH); 5.49 d, 1 H (J(OH,3') = 4.2, 3'-OH); 6.18 dd, 1 H (H-1'); 7.86 d, 1 H (J = 1.0, H-6); 11.28 s, 1 H (H-3).

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