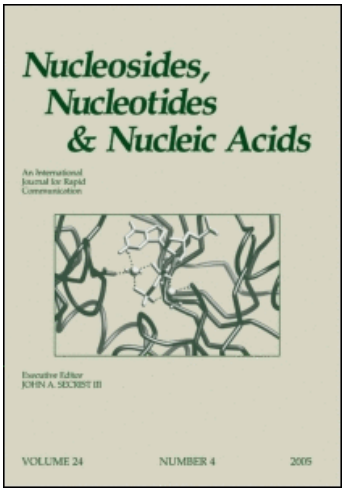

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SYNTHESIS OF 1'-DEOXYPSICOFURANOSYL-DEOXYNUCLEOSIDES AS POTENTIAL ANTI-HIV AGENTS.

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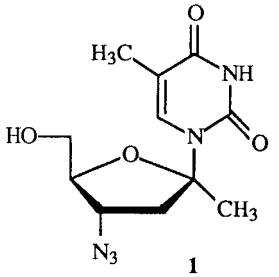
Abstract. Various routes to the targets **1, 2, 3,** 1-deoxy-psicofuranosyl nucleoside analogues related to anti-HIV agents, are reported. Two routes afforded their 6'-benzylated derivatives **9, 10** and **15**. Only the epoxide **12** and deoxynucleosides **19** and **22** were able to be deprotected leading in the first case to **16** and its ring opening derivative **17** and in the second case to **20** and to the target **3**.

Joining our efforts to study nucleosides derived from ketoses and potential inhibitors of HIV reverse transcriptase, we have focused our interest on the synthesis of the nucleosides **1, 2** and **3**, derived from 1-deoxypsicofuranose and moreover 1'-methyl analogues of the three targets : AZT, D4T and 3'-deoxythymidine.



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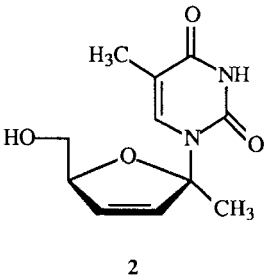

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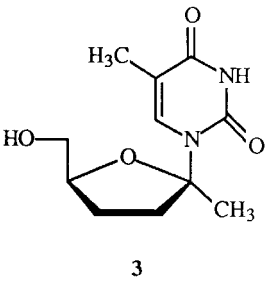


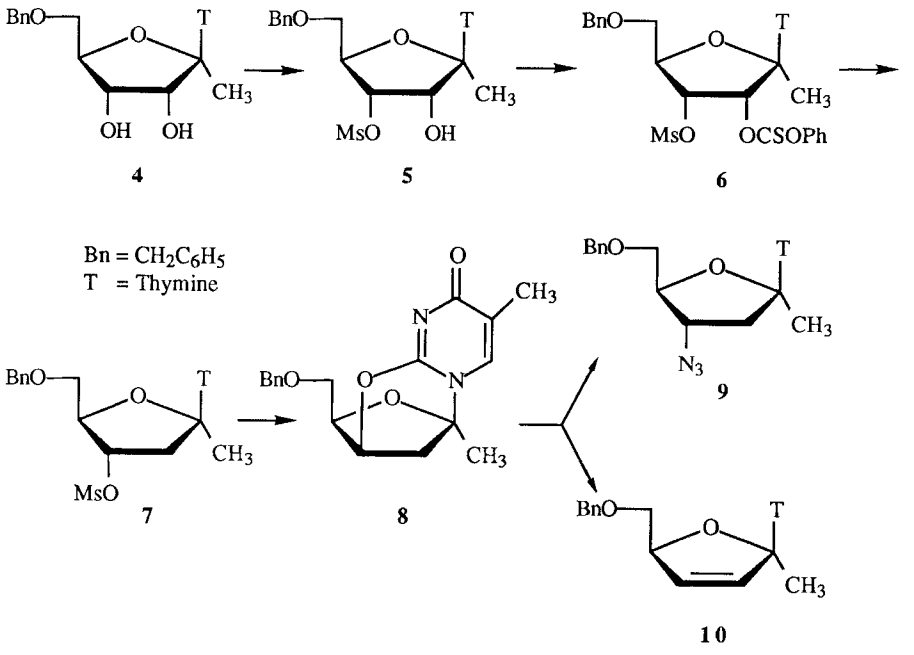
3

Two reasons have directed us to this choice :

. the naturally occuring ketosyl nucleosides psicofuranine and decoyinine are bioactive as free nucleosides without the previous phosphorylation step.[1]

. the methyl group vicinal to the potential reducing carbon of the sugar moiety may give to 1'-methyl nucleosides a stronger chemical resemblance to the biologically important 2'-deoxynucleosides.[2]

SCHEME I



In this paper, we report the different approaches that allowed access to these compounds, taking into account the important lability of their glycosidic bond.[3]

RESULTS AND DISCUSSION

The strategy adopted for the preparation of 1-(4 azido-1,3,4-trideoxy-*erythro*-β-D-hexulofuranosyl)-thymine **1** and 1-(1,3,4-trideoxy-3,4-didehydro-β-D-hexulofuranosyl)-thymine **2** is outlined in Scheme I.

Treatment of the 6'-benzylated nucleoside **4** [4] with methanesulfonyl chloride in phase-transfer catalysis conditions [5] afforded the unexpected 4'-mesylate **5** instead of the usually obtained 3'-derivative in 60 % isolated yield. Reaction of **5** with phenyl chlorothionocarbonate and 4-dimethylaminopyridine in dry acetonitrile yielded the corresponding 3'-*O*-phenoxythiocarbonyl ester **6**. Reductive deoxygenation of compound **6** in the 3'- position by tri-n-butyltin hydride, in the presence of 2',2'-azobis (2-methylpropionitrile) (AIBN) in refluxing toluene produced the 3'-deoxy nucleoside **7**. Treatment of **7** with 1,8-diazabicyclo [5.4.0] undec-7-ene in dichloromethane resulted in

a base-catalyzed elimination reaction to produce the 2,4'-anhydro derivative **8** in almost quantitative yield.

Ring opening of **8** was cleanly achieved by using a crystalline complex of potassium azide and 18-crown-6.[6] All other usual procedures did not work. **9** was obtained in only 30 % yield because of its lability and also the easy cleavage of **8** into thymine and 2-benzyloxymethyl-5-methyl-furan.

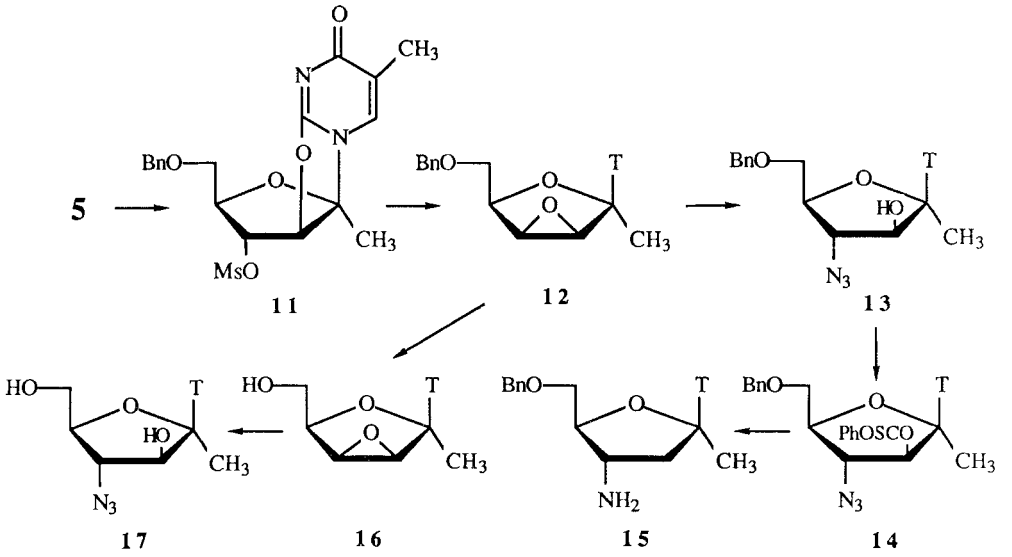
Treatment of **8** with potassium t-butoxide in DMSO resulted in a base-catalyzed elimination reaction to produce **10** in almost quantitative yield. This reaction was achieved in a NMR sample tube for following the progress and avoiding the complete cleavage of **10** during workup. All other attempts of literature methods [7,8] for the preparation of **10** failed in our hands.

The particular instability of the glycosidic bond of **9** and **10** prevented their full characterization and the deblocking of their 6'-ether function.

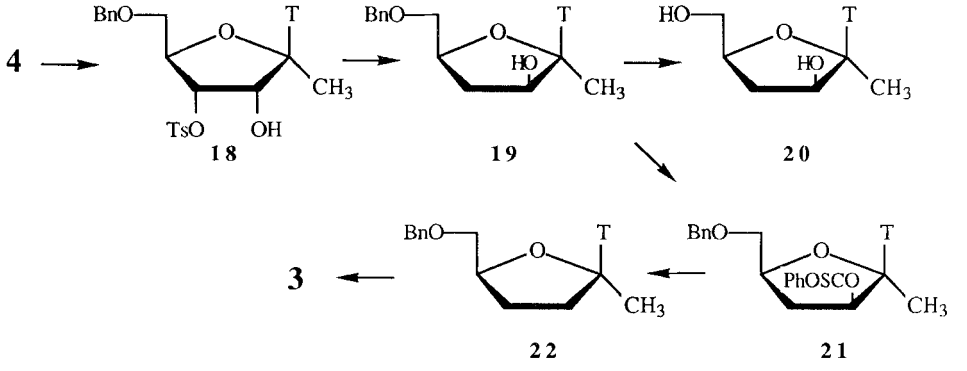
Another approach to the azido-deoxynucleoside **1** is described in Scheme II. Starting from the mesylate **5**, treatment with diethylaminosulfur trifluoride resulted in the formation of the 2,3'-anhydronucleoside **11,** which was converted into the 3',4'-anhydro derivative **12** by alkali reaction. Azidolysis of **12** with sodium azide afforded the
azido alcohol **13**, which was submitted to Barton's deoxygenation through a thiono ester intermediate [9,10] as previously described for the preparation of **7**. Unfortunately, even under these mild conditions the azido group was reduced at the same time leading to the amino-nucleoside **15**, which was shown more stable than the azido analogue **9**. On the other hand, the 6'-benzyl ether of the epoxide **12** was deprotected by hydrogenolysis and the resulting free compound **16** was submitted to azidolysis as above to produce the stable azido-nucleoside **17**.

The third target **3** was successfully prepared according to Scheme III. The starting nucleoside **4** was tosylated selectively at C-4' to **18** in the same manner as described for the preparation of mesylate **5**. One-step conversion of **18** into the 4'-deoxy-*threo*-nucleoside **19** was achieved by treatment with lithium triethylborohydride (LTBH) according to Hansske and Robins. [10] Deprotection of **19** by hydrogenolysis yielded the 1',4'-dideoxy-nucleoside **20**. Barton's deoxygenation of **19**, followed by deblocking of **22** by transfer hydrogenation [12], afforded the 1',3',4'-trideoxy-nucleoside **3**.

SCHEME II



SCHEME III



Biological studies of the compounds described in this paper have shown that none of them are active against HIV-1 in CEM cells.[13]

EXPERIMENTAL SECTION

General methods

Solvents were dried by distillation from the appropriate drying agent. Acetonitrile, toluene, dichloromethane and tetrahydrofuran were distilled from calcium hydride. Acetone was dried over calcium sulfate for 24h. and distilled after filtration.

All reactions were conducted under dry nitrogen atmosphere.

Analytical thin-layer chromatography (TLC) was performed on Kieselgel 60F-254 plates (E. Merck). Flash chromatography was conducted with Kieselgel 60 silica gel (250-400 mesh, E. Merck).

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a BRUKER MA 300 spectrometer in $CDCl_3$ unless otherwise specified. Chemical shifts were reported in parts per million (ppm) downfield from the internal standard tetramethylsilane.

Carbon magnetic resonance (^{13}C NMR) spectra were recorded on a BRUKER AM 300 spectrometer, with chemical shifts reported in ppm and proton decoupling unless otherwise specified.

Fast atom bombardment, electron impact, chemical ionization and high-resolution mass spectra were collected on a ZAB V.G. mass spectrometer.

Optical rotations were measured in 1-dm cells of 1 mL capacity with a Perkin-Elmer Model 241 polarimeter in chloroform. Concentrations are reported in grams per deciliter.

1-(6-*O*-Benzyl-1-deoxy-4-*O*-mesyl-β-D-psicofuranosyl)thymine (5). To a solution of compound **4** (547 mg, 1.5 mmol) in dry acetonitrile (40 mL) was added dibutyltin oxide (747 mg, 3 mmole), then mesyl chloride (174 µl, 2.25 mmole) and tetrahexylammonium chloride (585 mg, 1.5 mmole). The reaction mixture was stirred at room temperature overnight and evaporated to dryness. The residue (2.4 g) was applied to a silica gel column (chloroform/acetone, 5 : 1, eluent) to give 395 mg (60 %) of compound **5**. Rf 0.70 (chloroform/methanol, 90 : 10); $[\alpha]_D$ -32° (c 1.15, chloroform); UV (EtOH 95 %) : λmax 266 nm (ε 9500); ^{1}H NMR (Me_2SO-d_6) : δ 11.22 (s, 1H,

NH), 7.75 (s, 1H, H-6), 7.31 (m, 5H, H arom.), 6.02 (d, 1H, $J_{3',OH}$ = 5.4 Hz, OH-3'), 5.00 (dd, 1H, $J_{3',4'}$ = 4.4 Hz, $J_{4',5'}$ = 7.7 Hz, H-4'), 4.84 (t, 1H, H-3'), 4.54 (s, 2H, CH_2Ph), 4.35 (m, 1H, H-5'), 3.61 (dd, 1H, $J_{6'gem}$ = 11.5 Hz, $J_{6'a,5'}$ = 1.6 Hz, H-6'a), 3.57 (dd, 1H, $J_{6'gem}$ = 11.5 Hz, $J_{6'b,5'}$ =3.7 Hz, H-6'b), 1.56 (s, 3H, CH_3 base), 1.48 (s, 3H, CH_3-1'); ^{13}C NMR (Me_2SO-d_6) : δ 164.1 (C-4), 150.3 (C-2), 137.7 (C quat. benzyle), 135.7 (C-6), 128.1, 127.4, 127.2 (C arom.), 107.6 (C-5), 98.5 (C-2'), 78.9, 76.7, 72.5 (C-5', C-4', C-3'), 72.4 (CH_2Ph), 67.0 (C-6'), 37.4 (CH_3SO_2), 21.3 (C-1'), 12.0 (C-5); MS m/z : 441 (18, MH^+), 315 (57, M^+ - base), 219 (97, M^+-base-CH_3SO_3H), 127 (92, base + $2H^+$), 91 (100,CH_2Ph).

Accurate mass positive ion FAB MS m/z 440, 1284 (M^+, Calcd 440, 1253).

1-(6-*O*-Benzyl-1-deoxy-4-*O*-mesyl-3-*O*-phenylthionocarbonyl-β-*D*-psicofuranosyl)thymine (6). To a solution of compound **5** (83 mg, 0.19 mmole) in 3.8 mL of dry acetonitrile were added DMAP (138 mg, 1.14 mmole) and phenylthionocarbonate chloride (130 µl, 0.95 mmole). The reaction mixture was stirred 4 days under a nitrogen atmosphere, then diluted with 50 mL of ethyl acetate. The solution thus obtained was washed with cold water (2 x 30 mL) and dried on magnesium sulfate. Evaporation in vacuo to dryness yielded a crude product which was chromatographed on a silica gel column (chloroform/acetone, 5 : 1, eluent). 84 mg of pure **6** (77 %) was thus obtained. Rf 0.50 (chloroform/acetone, 80 : 20); $[\alpha]_D$ -31° (c 0.88, chloroform); ^1H NMR ($CDCl_3$) : δ 7.65 (s, 1H, NH), 7.62 (s, 1H,H-6), 7.5 to 7.1 (m, 10H, H arom.), 6.44 (d, 1H, $J_{3',4'}$ = 5.3 Hz), 5.50 (dd, 1H, $J_{4',5'}$ = 3.0 Hz, H-4'), 4.67 (m, 1H, H-5'), 4.56 and 4.29 (d, 2H, J_{gem} = 11.1 Hz, CH_2Ph), 3.75 (m, 2H, H-6'), 3.13 (s, 3H, CH_3SO_2), 1.79 (s, 3H, CH_3 base), 1.67 (s, 3H, CH_3-1'); MS m/z : 599 (7, MNa^+), 451 (42, M^+ - base), 355 (74, M^+-base-CH_3SO_3H), 297 (21, M^+-base-PhOCSO), 127 (47, base + $2H^+$).

Accurate mass positive ion FAB MS m/z 599, 1134 (MNa^+, Calcd. 599, 1147).

1-(6-*O*-Benzyl-1,3-dideoxy-4-*O*-mesyl-β-D-psicofuranosyl)thymine (7). To a solution of compound **6** (84 mg, 0.14 mmole) in refluxing toluene was added dropwise a solution of tri-n-butyltin hydride (196 µl) and AIBN (24 mg, 0.14 mmole) in toluene (3.6 mL). The mixture was heated at reflux for an additional 2 hours. The solution was cooled and the solvent was removed in vacuo. The residue was partitioned between 80 mL portions of petroleum ether and acetonitrile. The acetonitrile layer was separated and washed with three 50 mL portions of petroleum ether and then concentrated on a rotary evaporator.

The residual yellow oil was dissolved in EtOAc and chromatographed on silica gel. Elution with ethyl acetate afforded the titled compound **7** as a white solid (46 mg, 74 %). Rf 0.3 (ethyl acetate); $[\alpha]_D$ -10° (c 1.2, chloroform); ^1H NMR ($CDCl_3$) : δ 9.15 (s, 1H, NH), 7.67 (d, 1H, J = 1.1 Hz, H-6), 7.33 to 7.14 (m, 5H, H arom.), 5.20 (dt, 1H, $J_{4',3'a}$ = 6.1 Hz, $J_{4',5'}$ = $J_{4',3'b}$ = 1.6 Hz, H-4'), 4.64 (m, 1H, H-5'), 4.48 and 4.36 (d, 2H, J_{gem} = 11.6 Hz, CH_2Ph), 3.60 (m, 2H, H-6'), 3.05 (s, 3H, CH_3SO_2), 2.98 (dd, 1H, $J_{3'gem}$ = 15.7 Hz, H-3'a), 2.86 (dd, 1H, $J_{3'b,4'}$ = 1.6 Hz, H-3'b), 1.85 (d, 3H, CH_3 base), 1.73 (s, 3H, CH_3-1'); ^{13}C NMR ($CDCl_3$) : δ 164.3 (C-4), 149.9 (C-2), 136.9 (C quat. benzyl), 136.0 (C-6), 109.0 (C-5), 98.6 (C-2'), 85.3 and 81.6 (C-5', C-4'), 73.8 (CH_2Ph), 69.4 (C-6'), 45.6 (C-3'), 38.6 (CH_3SO_2), 27.5 (C-1'), 12.6 (CH_3 base); MS m/z : 447 (11, MNa^+), 299 (43, M^+-base), 203 (100, M^+-base-CH_3SO_3H), 127 (37, base + $2H^+$).

Accurate mass electron impact MS m/z 424,1338 (M^+, Calcd 424, 1304).

2,4'-Anhydro-1-(6-*O*-benzyl-1,3-dideoxy-β-D-hexulofuranosyl)-thymine (8). DBU (33 µl, 0.22 mmole) was added in one portion at room temperature to a magnetically stirred solution of compound **7** (85 mg, 0.2 mmole) in dry dichloromethane (2 mL). The mixture is stirred at room temperature until disappearance of the starting material (24 h). After evaporation of the solvent, the residue was chromatographed on silica gel using chloroform/methanol, 50 : 1 as eluent, to afford compound **8** (60 mg, 93 %). Rf 0.25 (chloroform/methanol, 90 : 10); $[\alpha]_D$ -47° (c 1, chloroform); ^1H NMR (C_6D_6) : δ 7.16 (m, 5H, H arom.), 6.72 (d, 1H, J = 0.8 Hz, H-6), 4.60 (s, 1H, H-4'), 4.18 (m, 2H, CH_2Ph), 3.86 (td, 1H, $J_{5',6'}$ = 7.1 Hz, $J_{5',4'}$ = 4.8 Hz, H-5'), 3.47 (m, 3H, H-6', H-3'a), 1.76 (d, 3H, J = 0.8 Hz, CH_3 base), 1.63 (s, 3H, CH_3-1'), 1.54 (dd, 1H, $J_{3'gem}$ = 12.9 Hz, $J_{3'b,4'}$ = 2.6 Hz, H-3'b); ^{13}C NMR (C_6D_6) : δ 171.5 (C-4), 154.2 (C-2), 138.4 (C quat. benzyl), 131.1 (C-6), 117.2 (C-5), 93.8 (C-2'), 84.4 and 78.2 (C-3', C-4'), 73.6 (CH_2Ph), 68.9 (C-6'), 38.7 (C-3'), 19.9 (C-1'), 14.0 (CH_3 base); MS m/z 329 (100, MH^+), 203 (13, M^+ - base), 127 (45, base + $2H^+$).

Accurate mass electron impact 328,1419 (M^+, Calcd 328,1423).

1-(4-Azido-6-*O*-benzyl-1,3,4-trideoxy-erythro-β-D-hexulofuranosyl)-thymine (9). Compound **8** (80 mg, 0.25 mmole) was dissolved in tetrahydrofuran (1.3 mL) and a dry crystalline complex of potassium azide and 18-crown-6 (170 mg) was added. After refluxing under nitrogen for 24 h, the reaction mixture was cooled in iced-water followed by the addition of diethyl ether (10 mL). The crystalline precipitate thus obtained was filtered off. The filtrate was evaporated to give a gum which was dissolved

in dichloromethane (50 mL) and washed twice with 75 % saturated KCl solution, then with water and evaporated to give a white foam. This crude product was purified by column chromatography using chloroform/methanol 95 : 5 (v/v) as eluent to afford the titled compound **9** (30 mg, 33 %).

1-(6-*O*-Benzyl-1,3,4-trideoxy-3,4-didehydro-β-D-hexulofuranosyl)-thymine (10). To a solution of compound **8** (14 mg, 0.04 mmole) in dry DMSO-d_6 (215 µl) was added t-BuOK (5 mg, 0.04 mmole) directly in the NMR-tube.

The reaction mixture, protected from moisture, was stirred magnetically at room temperature for 0.5 h and the NMR spectrum was performed. Rf 0.57 (chloroform/methanol, 90 : 10); ^{1}H NMR ($CDCl_3$) : δ 7.41 (s, 1H, H-6), 7.33 (m, 5H, H arom.), 6.78 (dd, 1H, $J_{4',3'}$ = 5.9 Hz, $J_{4',5'}$ = 1.8 Hz, H-4'), 5.92 (d, 1H, H-3'), 5.00 (m, 1H, H-5'), 4.48 (s, 2H, CH_2Ph), 3.49 (dd, 1H, J_{gem} = 10.3 Hz, $J_{6'a,5'}$ = 3.4 Hz, H-6'a), 3.26 (dd, 1H, $J_{6'b,5'}$ = 7.2 Hz, H-6'b), 1.62 and 1.61 (s, 3H, CH_3 base, CH_3-1').

Anhydro-2,3'-1-(6-O-benzyl-1-deoxy-4-O-mesyl-β-D-fructofuranosyl)-thymine (11). A solution of compound **5** (59 mg, 0.134 mmole) and diethylaminosulfur trifluoride (70 µl) in dry dichloromethane (2.7 mL) was stirred at room temperature under nitrogen for 24h. The reaction mixture was then diluted to 50 mL with dichloromethane and poured into a cold 10 % saturated sodium bicarbonate solution. The organic layer was separated and dried on magnesium sulfate. After evaporation to dryness, the obtained oil was purified by column chromatography on silica gel using chloroform/methanol 95 : 5 (v/v) as eluent. Pure compound **11** (46 mg) was thus obtained with 82 % yield. Rf 0.42 (chloroform/methanol, 90 : 10); $[\alpha]_D$ -26.1° (c 0.85, chloroform); UV (EtOH 95 %) : λ_{max} 252 nm (ε 8800); ^{1}H NMR ($CDCl_3$) : δ 7.39 to 7.21 (m, 5H, H arom.), 7.19 (d, 1H, $J_{H6,Me-5}$ = 1.3 Hz, H-6), 5.31 (dd, 1H, $J_{4',5'}$ = 1.5 Hz, $J_{4',3'}$ = 0.5 Hz, H-4'), 5.17 (br,1H, H-3'), 4.62 (tm, 1H, $J_{6'a,5'}$ = $J_{6'b,5'}$ = 4 Hz, H-5'), 4.45 and 4.36 (d, 2H, J_{gem} = 12 Hz, CH_2Ph), 3.43 (dd, 1H, J_{gem} = 11 Hz, H-6'a), 3.33 (dd, 1H, H6'b), 3.14 (s, 3H, CH_3SO_2), 2.40 (d, 3H, CH_3 base), 1.93 (s, 3H, CH_3-1'); ^{13}C NMR ($CDCl_3$) : δ 172.5 (C-4), 159 (C-2), 137, 128.8, 128.4, 128.3 (C arom.), 128 (C-6), 120 (C-5), 99.5 (C-2'), 90 (C-3'), 86.5 (C-4'), 84 (C-5'), 74 (C-6)', 68.5 (CH_2Ph), 39 (CH_3SO_2), 23.5 (C-1'), 14.8 (CH_3 base); MS (chemical ionization in NH_3) m/z 423 (100, MH^+), MS (electron impact) m/z 423 (2, MH^+), 316 (9, M^+ - $PhCH_2O$), 301 (4, M^+ - CH_2OCH_2Ph), 237 (8, 316 - CH_3SO_2), 221 (43, 316-CH_3SO_3), 91 (100, CH_2Ph).

Accurate mass electron impact MS m/z 422, 1165 (M^+, Calcd 422,1148).

1-(3,4-Anhydro-6-*O*-benzyl-1-deoxy-β-D-tagatofuranosyl)thymine (12). To a stirred solution of **11** (164 mg, 0.39 mmole) in a mixture of acetone (19.5 mL) / dioxane (3.5 mL) / water (9.5 mL) was added 2N aqueous NaOH (0.8 mL). After 3 h at room temperature, the pH of the mixture was adjusted to 7.0 by addition of Dowex 50 W-X 4 (H^+). The resin was filtered off and the filtrate was evaporated under reduced pressure. The residue was dissolved in dichloromethane (50 mL) and dried over magnesium sulfate. Removal of the solvent under reduced pressure and chromatography of the residue on silica gel using ethyl acetate/hexane 1 : 1 (v/v) as eluent afforded **12** (128 mg, 95 %). Rf 0.50 (chloroform/methanol, 85 : 15); ^1H NMR ($CDCl_3$) : δ 8.75 (s, 1H, NH), 7.47 (d, 1H, J = 1.3 Hz, H-6), 7.35 (m, 5H, H arom.), 4.61 (m, 2H, CH_2Ph), 4.52 (d, 1H, $J_{3',4'}$ = 2.8 Hz, H-3'), 4.30 (td, 1H, $J_{5',6'}$ = 6.2 Hz, $J_{5',4'}$ = 1.1 Hz, H-5'), 3.87 (dd, 1H, H-4'), 3.68 (d, 2H, H-6'), 1.89 (d, 3H, CH_3 base), 1.66 (s, 3H, CH_3-1'); ^{13}C NMR ($CDCl_3$) : δ 164.5 (C-4), 150.5 (C-5), 138 (C quat. arom.), 137 (C-6), 129.5, 128.5, 128 (C arom.), 110 (C-5), 94.5 (C-2'), 77.5 (C-5'), 74 (CH_2Ph), 69 (C-6'), 61 (C-3'), 58 (C-4'), 23 (C-1'), 13 (CH_3 base); MS (electron impact) m/z 344 (6, M^+), 219 (50, M^+-base), 91 (100, CH_2Ph^+).

Accurate mass positive ion FAB MS m/z 345,1569 (MH^+, Calcd 345,1563).

1-(4-Azido-6-*O*-benzyl-1,4-dideoxy-β-D-fructofuranosyl)thymine (13). A solution of the epoxide **12** (25 mg, 0.072 mmole) in acetone (4 mL) was treated with a solution of sodium azide (360 mg) in water (4 mL). This mixture was refluxed for 16 h. The acetone was removed under reduced pressure, and the residue was diluted with water (20 mL) and extracted with dichloromethane (40 mL). The organic layer was separated and washed with water (2 x 50 mL), dried over magnesium sulfate and concentrated. The crude product thus obtained was purified by column chromatography using ethyl acetate/hexane 1 : 1 (v/v) as eluent to afford pure **13** (14 mg, 50 %). Rf 0.42 (chloroform/methanol, 90 : 10); ^1H NMR ($CDCl_3$) : δ 9.34 (s, 1H, NH), 7.77 (d, 1H, $J_{H\text{-}6,Me\text{-}5}$ = 1.1 Hz, H-6), 7.35 (m, 5H, H arom.), 4.58 (m, 3H, CH_2Ph, H-3'), 4.18 (m, 1H, H-5'), 3.08 (m, 1H, H-4'), 3.65 (m, 2H, H-6'), 1.84 (d, 3H, CH_3 base), 1.78 (s, 3H, CH_3-1').

1(4-Azido-6-*O*-benzyl-1,4-dideoxy-3-*O*-phenylthionocarbonyl-β-D-fructofuranosyl)thymine (14). Compound **13** (66 mg, 0.170 mmole) was treated as described above for the preparation of **6** but the reaction was stopped after 16 h. The crude product was purified by column chromatography on silica gel using dichloromethane/acetone, 80 : 20 (v/v) as eluent to afford pure **14** (73 mg, 82 % yield). Rf 0.60 (chloroform/methanol, 90 : 10); ^1H NMR ($CDCl_3$: δ 8.18 (s, 1H, NH), 7.53 (d, 1H, $J_{H\text{-}6,Me\text{-}5}$ = 1.0 Hz, H-6), 7.15 (m, 10H, H arom.), 5.90 (s, 1H, H-3'), 4.63

(m, 2H, CH_2Ph), 4.33 (d, 1H, $J_{4',5'}$ = 3.5 Hz, H-4'), 4.14 (m, 1H, H-5'), 3.66 (m, 2H, H-6'), 1.86 (d, 3H, CH_3 base), 1.79 (s, 3H, CH_3-1').

Accurate mass positive ion FAB MS m/z 524,1594 (MH^+, Calcd 524,1657).

1(4-Amino-6-*O*-benzyl-1,3,4-trideoxy-*erythro*-β-D-hexulofuranosyl)-thymine (15). Compound **14** (70 mg, 0.134 mmole) was treated as described above for the preparation of **7**, but the reaction was stopped after 0.5h. The obtained oil was chromatographed on silica gel to afford pure **15** (20 mg, 43 %). Rf 0.22 (chloroform/methanol, 90 : 10); ^1H NMR (DMSO-d_6) : δ 7.78 (s, 1H, H-6), 7.32 (m, 5H, H arom.), 4.52 (s, 2H, CH_2Ph), 3.88 (m, 1H, H-5'), 3.69 (dd, 1H, $J_{6'gem}$ = 10.5 Hz, $J_{6'a,5'}$ = 3 Hz, H-6'a), 3.50 (dd, 1H, $J_{6'b,5'}$ = 5 Hz, H-6'b), 3.31 (br, NH + NH_2 + H_2O), 3.19 (m, 1H, H-4'), 2.95 (dd, 1H, $J_{3'gem}$ = 14 Hz, $J_{3'a,4'}$ = 6 Hz, H-3'a), 1.95 (dd, 1H, $J_{3'b,4'}$ = 9 Hz, H-3'b), 1.63 (s, 3H, CH_3-1'), 1.55 (s, 3H, CH_3 base); ^{13}C NMR (DMSO-d_6 + AcOD) δ : 165 (C-4), 151 (C-2), 138.5 (C quat. arom.), 136.5 (C-6), 129, 128.3, 128 (C arom.), 108 (C-5), 98 (C-1'), 83 (C-4'), 73 (C-5'), 69 (CH_2Ph), 50.5 (C-3'), 43 (C-2'), 27 (C-1'), 13 (CH_3 base); MS (chemical ionisation, NH_3) m/z 691 (36, $2MH^+$), 565 (34, $2MH^+$ -B), 363 (33, MNH_4^+), 346 (72, MH^+), 220 (100, M^+ - base); MS (FAB$^+$) m/z : 691 (6, $2MH^+$), 346 (35, MH^+), 220 (100, M^+-base).

Accurate mass positive ion FAB MS m/z 346,1781 (MH^+, Calcd 346,1793).

1-(3,4-Anhydro-β-D-tagatofuranosyl)thymine (16). To a solution of compound **12** (66 mg, 0.19 mmole) in methanol (3 mL) were added 10 % Pd/C (30 mg). The suspension was stirred under hydrogen (1 atm.) for 24 h at room temperature. Catalyst was then filtered off on celite and the filtrate was evaporated to dryness. Pure compound **16** (44 mg, 90 %) was thus obtained. Rf 0.25 (chloroform/methanol, 90 : 10); ^1H NMR ($CDCl_3$) : δ 7.51 (s, 1H, H-6), 4.55 (d, 1H, $J_{3',4'}$ = 3 Hz, H-3'), 4.23 (t, 1H, $J_{5',6'}$ = 5 Hz, H-5'), 3.93 (d, 2H, H-6'), 3.90 (d, 1H, H-4'), 3.49 (br, 2H, NH and OH), 1.91 (s, 3H, CH_3 base), 1.68 (s, 3H, CH_3-1').

Accurate mass positive ion FAB MS m/z 255,0980 (MH^+, Calcd 255,1007).

1(4-Azido-1,4-dideoxy-β-D-fructofuranosyl)thymine (17). Compound **16** (60 mg, 0.23 mmole) was treated as described above for the preparation of **13**, but the reaction mixture was directly concentrated *in vacuo* to give a residue. This crude product was purified by column chromatography on silica gel using dichloromethane/methanol, 90 : 10 (v/v) to afford pure **17** (35 mg, 50 %). Rf 0.25 (chloroform/methanol, 90 : 10); ^1H NMR (DMSO-d_6): δ 7.81 (d, 1H, $J_{H\text{-}6,Me\text{-}5}$ = 1.0 Hz, H-6), 4.27 (d, 1H, $J_{3',4'}$ =

2.3 Hz, H-3'), 4.01 (dd, 1H, $J_{4',5'}$ = 4 Hz, H-4'), 3.92 (m, 1H, H-5'), 3.57 (m, 2H, H-6'), 3.35 (br, OH + H_2O), 1.76 (d, 3H, CH_3 base), 1.69 (s, 3H, CH_3-1').

1-(6-*O*-Benzyl-1-deoxy-4-*O*-tosyl-β-D-psicofuranosyl)thymine (18). To a stirred solution of the nucleoside **4** (133 mg, 0.36 mmole) in dry acetonitrile (12 mL) was added dibutyltin oxide (183 mg, 0.73 mmole), tosyl chloride (105 mg, 0.55 mmole) and tetrahexylammonium chloride (143 mg, 0.36 mmole) at room temperature. Stirring is then continued for 16 h, after which the reaction mixture is evaporated to dryness. The residual product is purified by column chromatography on silica gel using ethyl acetate/hexane 3 : 1 (v/v) as eluent to afford compound **18** (180 mg, 95 %). Rf 0.56 (ethyl acetate/hexane, 3 : 1); $[\alpha]_D$ -36° (c 1.3, chloroform); UV (EtOH 95 %) : λ_{max} 267 nm (ε 9100); ^1H NMR ($CDCl_3$) : δ 9.52 (s, 1H, NH), 7.84, 7.28 and 7.09 (m, 2H,.5H and 2H, H arom.), 7.61 (d, 1H, $J_{H\text{-}6,Me\text{-}5}$ = 0.9 Hz, H-6), 4.98 (dd, 1H, $J_{4',3'}$ = 5.3 Hz, $J_{4',5'}$ = 1.2 Hz, H-4'), 4.64 (dd, 1H, $J_{3',OH}$ = 3.2 Hz, H-3'), 4.60 (m, 1H, H-5'), 4.46 (d, $J_{3',OH}$ = 3.2 Hz, OH-3'), 4.43 and 4.28 (d, 2H, J_{gem} = 11.1 Hz, CH_2Ph), 3.56 (m, 2H, H-6'), 2.43 (s, 3H, CH_3 arom.); 1.84 (s, 3H, CH_3 base), 1.55 (s, 3H, CH_3-1'); ^{13}C NMR ($CDCl_3$) : δ 164.2 (C-4), 151.4 (C-2), 145.0 (C-CH_3 tosyl), 136.9 (C quat. benzyl) 136.2 (C-6), 133.3 (C quat. tosyl), 129.8, 128.5, 128.1, 127.3 (C arom.), 110.0 (C-5), 1002.2 (C-2'), 83.1, 81.4, 77.5 (C-5', C-4', C-3'), 73.7 (CH_2Ph), 69.3 (C-6'), 22.7 (C-1'), 21.7 (CH_3 tosyl), 12.6 (CH_3 base).

Accurate mass positive ion FAB MS m/z 517,1638 (MH^+, Calcd 517,1671).

1-(6-*O*-Benzyl-1,4-dideoxy-β-D-*threo* -hexulofuranosyl)thymine (19). A solution of nucleoside **18** (195 mg, 0.38 mmole) in 4 mL of anhydrous tetrahydrofuran was treated under nitrogen with 1M lithium triethyl borohydride (3.8 mL). The resulting solution was stirred at room temperature for 16 h. and then cooled to 0°C. Methanol (0.4 mL) was carefully introduced to decompose the excess of hydride. The product was extracted with dichloromethane (2 x 50 mL), the organic layers were washed with water, dried on magnesium sulfate and concentrated to dryness.

The residue was chromatographed on a column of silica gel using chloroform/methanol, 95 : 5 (v/v) as eluent to afford compound **19** (120 mg, 93 %). Rf 0.68 (chloroform/methanol, 85 : 15); $[\alpha]_D$ + 36.5° (c 1.05, chloroform); UV (EtOH 95 %) : λ_{max} 268 nm (ε 9300); ^1H NMR ($CDCl_3$) : δ 8.35 (s, 1H, NH), 7.76 (d, 1H, $J_{H\text{-}6,Me\text{-}5}$ = 1.1 Hz, H-6), 7.32 (m, 5H, H arom.), 4.61 (m, 1H, H-3'), 4.58 (m, 2H, CH_2Ph), 4.47 (m, 1H, H-5'), 4.07 (d, 1H, $J_{3',OH}$ = 7.5 Hz, OH-3'), 3.70 (dd, 1H, $J_{6'gem}$ = 10.3 Hz, $J_{6'a,5'}$ = 2.7 Hz, H-6'a), 3.50 (dd, 1H, $J_{6'b,5}$ = 4.1 Hz, H-6'b), 2.56 (ddd, 1H, $J_{4'gem}$ = 14.3 Hz, $J_{4'a,5'}$ = 9.5 Hz, $J_{4'a,3'}$ = 5.8 Hz, H-4'a), 2.02 (ddd, 1H,

$J_{4'b,5'}$ = 1.8 Hz, $J_{4'b,3'}$ = 0.6 Hz, H-4'b), 1.91 (d, 3H, CH_3 base), 1.60 (s, 3H, CH_3-1').; MS (chemical ionization, NH_3) m/z : 693 (25, $2MH^+$), 584 (17, [2M-baseH]NH_4^+), 365 (54, MNH_4^+), 347 (81, MH^+), 238 (100, [M-baseH]NH_4^+), 221 (85, M^+ - base), 144 (21, [base H]NH_4^+). MS (electron impact) m/z : 346 (2, M^+), 239 (2, M^+ - base-OCH_2Ph), 221 (19, M^+ - base), 126 (9, base H^+), 107 (10, OCH_2Ph^+), 91 (100, CH_2Ph^+).

Accurate mass positive ion FAB MS m/z 347,0635 (MH^+, Calcd 347,0695).

1-(1,4-Dideoxy-β-D-hexulofuranosyl)thymine (20). Compound **19** (100 mg, 0.29 mmole) was treated as described above for the preparation of **16**, but the reaction mixture was stirred under hydrogen for 48 h. Pure compound **20** (45 mg) was thus obtained with a 61 % yield. Rf 0.70 (chloroform/methanol 85 : 15); ^1H NMR ($CDCl_3$) : δ 7.74 (s, 1H, H-6), 5.4 (s, 3H, NH, 2 OH), 4.67 (d, 1H, $J_{3',4'}$ = 5.3 Hz, H-3'), 4.38 (m, 1H, H-5'), 3.84 (dd, 1H, $J_{6'gem}$ = 12.2 Hz, $J_{6'a,5'}$ = 2.7 Hz, H-6'a), 3.58 (dd, 1H, $J_{6'gem}$ = 12.2 Hz, $J_{6'b,5'}$ = 3.0 Hz, H-6'b), 2.46 (m, 1H, H-4'a), 2.02 (d, 1H, $J_{4'gem}$ = 14.5 Hz, H-4'b), 1.81 (s, 3H, CH_3 base), 1.53 (s, 3H, CH_3-1'); ^{13}C NMR ($CDCl_3$) : δ 166.1 (C-4), 151.1 (C-2), 138.0 (C-6), 108.9 (C-5), 99.5 (C-2'), 78.4 , 74.0 (C-5', C-3'), 63.7 (CH_2O), 34.7 (C-4'), 23.6 (C-1'), 12.5 (CH_3 base); MS m/z : 279 (58, MNa^+), 131 (100, M^+ - base), 127 (53, base + $2H^+$).

Accurate mass positive ion FAB MS m/z 256, 1075 (M^+, Calcd. 256, 1059).

1-(6-*O*-Benzyl-1,4-dideoxy-3-*O*-phenylthionocarbonyl-β-D-hexulofuranosyl)thymine (21). Compound **19** (51 mg, 0.15 mmole) was treated as described for the preparation of **6**, but the reaction mixture was stirred for 5 days. The purification by chromatography afforded pure **21** (36 mg, 50 %). Rf 0.28 (chloroform/methanol, 90 : 10); $[\alpha]_D$ + 1.95° (c 1.0, chloroform), UV (EtOH 95 %), λ_{max} 264 nm (ε 8050); ^1H NMR ($CDCl_3$) : δ 8.32 (br, 1H, NH), 7.67 (s, 1H, H-6), 7.17 (m, 10H, H arom.), 5.97 (d, 1H, $J_{3',4'a}$ = 6 Hz, H-3'), 4.57 and 4.63 (d, 1H, J_{gem} = 12 Hz, CH_2Ph), 4.55 (m, 1H, H-5'), 3.58 (dd, 1H, J_{gem} = 10 Hz, $J_{6'a,5'}$ = 7.5 Hz, H-6'a), 3.50 (dd, 1H, $J_{6'b,5'}$ = 4.5 Hz, H-6'b), 2.70 (ddd, 1H, J_{gem} = 15.5 Hz, $J_{4'a,5'}$ = 9 Hz, $J_{4'a,3'}$ = 6 Hz, H-4'a), 2.27 (ddd, 1H, $J_{4'b,5'}$ = 3.5 Hz, $J_{4'b,3'}$ = 1 Hz, H-4'b), 1.88 (d, 3H, $J_{H6,Me-5}$ = 1.1 Hz, CH_3 base), 1.71 (s, 3H, CH_3-1'); MS (chemical ionization, NH_3) m/z : 500 (10, MNH_4^+), 483 (35, MH^+), 357 (100, M^+ - base), 203 (16, 357-PhOCSO).

Accurate mass positive ion FAB MS m/z 483, 161 (MH^+, Calcd. 483, 1589).

1-(6-*O*-Benzyl-1,3,4-trideoxy-β-D-hexulofuranosyl)thymine (22). Compound **21** (78 mg, 0.16 mmole) was treated as described for the preparation of **7**, but the reaction was complete after 0.5 h. The purification by chromatography on silica gel using dichloromethane/acetone 5 : 1 (v/v) as eluent afforded pure **22** (40 mg, 76 %). Rf 0.50 (chloroform/methanol, 90 : 10); $[\alpha]_D$ -3.0° (c 0.85, chloroform); UV (EtOH 95 %) : λ_{max} 268 (ε 7095); ^1H NMR (CD_2Cl_2) : δ 9.22 (s, 1H, NH), 7.84 (d, 1H, $J_{H6,Me-5}$ = 1.1 Hz, H-6), 7.32 (m, 5H, H arom.), 4.54 (s, 2H, CH_2Ph), 4.40 (m, 1H, H-4'), 3.64 (dd, 1H, $J_{6'gem}$ = 10.5 Hz, $J_{6'a,5'}$ = 3 Hz, H-6'a), 3.46 (dd, 1H, $J_{6'b,5'}$ = 6 Hz, H-6'b), 3.02 (m, 1H, H-4'a), 2.16 (m, 1H, H-4'b), 1.98 (m, 1H, H-3'a), 1.78 (m, 1H, H-3'b), 1.73 (d, 3H, CH_3 base), 1.67 (s, 3H, CH_3-1').

Accurate mass positive ion FAB MS m/z 331,1679 (MH^+, Calcd 331,1770).

1-(1,3,4-trideoxy-β-D-psicofuranosyl)thymine (3). A mixture of compound **22** (50 mg, 0.6 mmole), ammonium formate (180 mg), 10 % palladium on carbon (600 mg) and acetone (9 mL) was refluxed for 2 h. Then the same amounts of ammonium formate and 10 % palladium on carbon were added and refluxing was continued for 1 h. The catalyst was filtered off and washed with the solvent. The filtrate was evaporated to give quantitatively the pure product **3**. Rf 0.26 (chloroform/methanol, 90 : 10); $[\alpha]_D$ + 0.7° (c 1.32, acetone); UV (EtOH 95 %)q : λ_{max} 270 nm (ε 7968); ^1H NMR (acetone-d_6) : δ 8.04 (s, 1H, H-6), 4.27 (m, 1H, H-5'), 3.74 (dd, 1H J_{gem} = 11.8 Hz, $J_{6'a,5'}$ = 3.8 Hz, H-6'a), 3.64 (1H, $J_{6'b,5'}$ = 5.5 Hz, H-6'b), 3.00 (ddd, 1H, J_{gem} = 10.7 Hz, J = 7.2 and 3.4 Hz, H-4'a), 2.35 (m, 1H, H-4'b), 1.96 (m, 1H, H-3'a), 1.82 (d, 3H, CH_3 base), 1.75 (m, 1H, H-3'b), 1.66 (s, 3H, CH_3-1'); MS (electron impact) m/z : 114 (6, M^+ - base), 126 (2, base H^+); MS (chemical ionization, NH_3) m/z : 115 (100, MH^+ - base), 127 (25, base H^+).

Accurate mass positive ion FAB MS m/z 241,1207 (MH^+, Calcd 241,1188).

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