Synthesis of 3′-Deoxy-2′,3′-didehydro-3′-methylthymidine. A Potential Anti-HIV Agent

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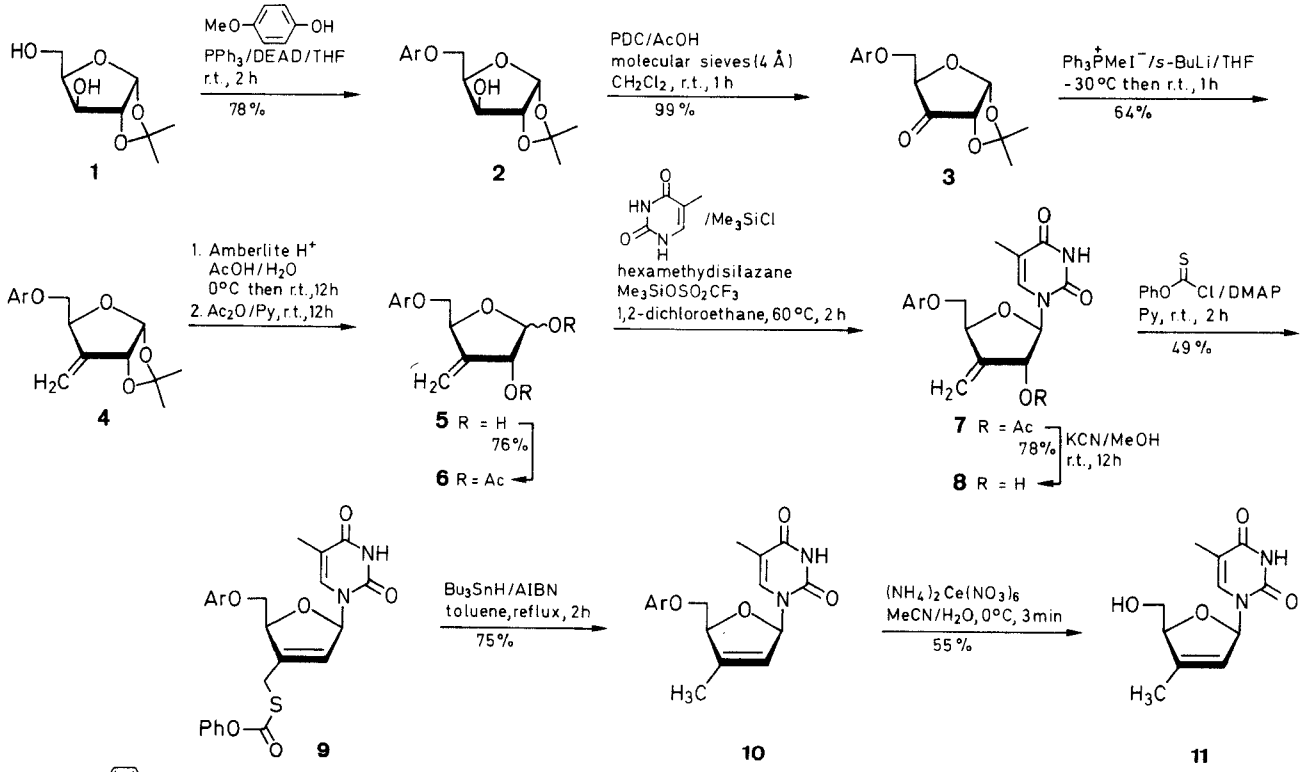
Starting from 1,2-*O*-isopropylidene-α-D-xylofuranose, a versatile method for the synthesis of branched 3′-deoxy-2′,3′-didehydro nucleosides is described and exemplified for an analogue of 3′-deoxy-2′,3′-didehydrothymidine (d4T).

Since the discovery of the human immunodeficiency virus (HIV) as the etiological agent of AIDS,[1] increasing efforts have been devoted to the synthesis and biological evaluation of compounds with potential anti-HIV activity. Several 2′,3′-dideoxy nucleoside derivatives have so far proved to be selective inhibitors of HIV replication[2,3] and one of them, 3′-azido-3′-deoxythymidine (AZT) is currently employed in the treatment of patients with AIDS. Recently, other modified nucleosides have shown comparable *in vitro* activity to AZT against HIV. Among them, 2′,3′-didehydro-2′,3′-dideoxycytidine (d4C) and its thymidine analogue (d4T) seem to be more promising.[4]

We report herein the synthesis of **11**, a slightly modified analogue of d4T.[5] Rather than following a linear route by modifying a nucleoside, we decided to develop a versatile methodology which could be employed for the synthesis of several nucleoside analogues. Thus, a suitably functionalized and protected pentofuranosyl moiety was prepared and coupled with activated thymine in the key step of the synthesis. This allows extension to other heterocyclic bases. Commercially available 1,2-*O*-isopropylidene-α-D-xylofuranose (**1**) was chosen as the starting material. Due to the variety of experimental conditions which are employed during the synthesis, the choice of the protecting group for the primary hydroxy group was of prime importance to minimize the number of steps required. A so-called permanent protective group was needed, as the benzyl group could not be used the *p*-anisyl group was chosen.[6]



Treatment of **1** under the conditions previously devised,[7] afforded the 4-O-protected derivative **2** in good yield after column chromatography on silica gel. Oxidation of **2** with pyridinium dichromate in the presence of molecular sieves (4 Å) and a catalytic amount of acetic acid[8] was nearly quantitative. The crude keto sugar **3** was pure enough for the following Wittig methylenation without further purification. The resulting 3-methylidene derivative **4** was hydrolyzed and acetylated to give **6**. The α,β-mixture was employed in the coupling with activated thymine. Due to the presence of the *p*-anisyl group, trimethylsilyl trifluoromethylsulfonate was used as catalyst[9] rather than tin tetrachloride. After classical work-up, the β-nucleoside **7** was obtained together with some nonpolar impurities. An analytical sample was obtained by column chromatography and characterized as the β-anomer by ^{1}H-NMR spectroscopic data ($J_{1',2'}$ = 5.78 Hz). Deacetylation with sodium methoxide in methanol, followed by neutralization with an acidic ion exchange resin, afforded **8**.

For synthetic purpose, the crude **7** was deacetylated with a catalytic amount of potassium cyanide in methanol. After evaporation, the crude product was dissolved in water and the nonpolar impurities extracted with toluene. The aqueous phase containing the nucleoside was neutralized (ion exchange resin) and evaporated to afford **8** in 78% yield (from **6**).

During the transformation of the 2'-OH of compound **8** into its phenoxythiocarbonyl derivative, an allylic rearrangement occurred and the 2',3'-unsaturated nucleoside **9** was obtained. Its structure was unambiguously determined by the absence of 3'-methylene group and the presence of only one vinylic proton in the ^{1}H-NMR spectrum.

The desulfurization of **9** under Barton's conditions afforded **10** which was deprotected to give the final product **11** by oxidative cleavage of the *p*-anisyl group with cerium ammonium nitrate.[6]

In conclusion, this paper presents an efficient route for the synthesis of 3'-deoxy-2',3'-didehydro-3'-methylthymidine. The approach described therein could be applied to other purines and/or pyrimidines.

Microanalyses were performed at the Service de Microanalyse of the Pierre et Marie Curie University. Melting points were determinated with a Thomas-Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 141 polarimeter. The ^{1}H-NMR spectra were recorded on Brucker AM-250 spectrometer with TMS as internal standard. Reactions were monitored by analytical TLC using 2 × 5 cm precoated alumina plates: silica gel 60 F_{254} (Merck) and detection by UV light and charring with H_2SO_4. For column chromatography, Merck silica gel 60 (230–400 Mesh) and anhydrous solvents were employed. Preparative TLC was carried out with silica gel 60 GF_{254} (0.5 mm thickness) and distilled solvents. Solvents and reagents were purified and dried by standard procedures. For synthesis of **3**, CH_2Cl_2 was redistilled over PDC. THF was distilled from Na/benzophenone.

1,2-*O*-Isopropylidene-5-*O*-(4-methoxyphenyl)-α-D-xylofuranose (2):
Under positive pressure of argon, **1** (Aldrich) (4 g, 21 mmol) and Ph_3P (7.16 g, 27.3 mmol) are dissolved in dry THF (20 mL). A solution of diethyl azodicarboxylate (4.75 g, 27.3 mmol) and 4-methoxyphenol (7.8 g, 63 mmol) in dry THF (20 mL) is slowly added (30 min) at r.t. with stirring. Stirring is continued for 2 h at r.t. and THF is evaporated under reduced pressure. To the resulting mixture, Et_2O (20 mL) is added, allowing part of the formed Ph_3PO to precipitate. After filtration, the solvent is evaporated and the resulting crude product chromatographed on a silica gel column (3.5 × 20 cm). Elution with Et_2O/petroleum ether (3:1) gives **2**; yield: 3.39 g (78%); mp 116–116.5 °C (Et_2O/petroleum ether); $[\alpha]_D^{22}$ −7.2° (*c* = 1, $CHCl_3$).

$C_{15}H_{20}O_6 \cdot 1.5H_2O$	calc.	C 55.71	H 7.16
(323.35)	found	55.55	6.61

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.45 (s, 3H, CH_3C), 1.65 (s, 3H, CH_3C), 2.78 (d, 1H, $J_{3,4}$ = 5 Hz, H-4), 3.7 (s, 3H, CH_3O), 4.25–4.45 (m, 3H, H-3, H-5a, H-5b), 4.52 (d, 1H, $J_{1,2}$ = 5.4 Hz, $J_{2,3}$ < 1 Hz, H-2), 5.93 (d, 1H, $J_{1,2}$ = 5.4 Hz, H-1), 6.77–6.81 (m, 4 H_{arom}).

1,2-*O*-Isopropylidene-5-*O*-(4-methoxyphenyl)-α-D-*erythro*-pentofuranose-3-ulose (3):
Under a positive pressure of argon, a mixture of **2** (1.23 g, 4.15 mmol), molecular sieves 4 Å (2.6 g) and pyridinium dichromate (2.53 g, 10.6 mmol) is suspended in CH_2Cl_2 (30 mL) and this suspension is cooled to 0 °C. Acetic acid (0.425 mL, 7.4 mmol) is added dropwise under stirring. Stirring is continued for 1 h at r.t., the salts are precipitated by addition of Et_2O (15 mL) and stirring (30 min) in the presence of Celite (1 g) and $MgSO_4$ (1 g). After filtration the solution is evaporated to give **3** as an oil, remaining chromium salts are removed by repeating the treatment with Et_2O. The final crude product can be used without purification in the next step; yield: 1.2 g (99%). An analytical sample is obtained by recrystallization from Et_2O/hexane; mp 102–105 °C; $[\alpha]_D^{22}$ 72.7 (*c* = 1, $CHCl_3$).

$C_{15}H_{18}O_6 \cdot 0.5\ H_2O$	calc.	C 59.40	H 6.27
(303.3)	found	59.61	6.20

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.45 (s, 3H, CH_3C), 1.49 (s, 3H, CH_3C), 3.75 (s, 3H, CH_3O), 4.24–4.39 (m, 2H, H-5_a, H-5_b), 4.45 (d, 1H, $J_{1,2}$ = 4.42 Hz, H-2), 4.61 (m, 1H, H-4), 6.19 (d, 1H, $J_{1,2}$ = 4.42 Hz, H-1), 6.8 (m, 4 H_{arom}).

3-Deoxy-1,2-*O*-isopropylidene-5-*O*-(4-methoxyphenyl)-3-methylidene-α-D-*erythro*-pentofuranose (4):
Under a positive pressure of argon, dry THF (5 mL) and Ph_3PMeI (2.6 g, 6.44 mmol) are placed in a 10 mL flask equipped with a rubber septum and cooled to −60 °C. A 1.4 M solution of *s*-BuLi in cyclohexane (2.9 mL, 4.08 mmol) is added through a syringe. The temperature is allowed to rise to −30 °C (bath temperature) and a solution of **3** (1.2 g, 4.08 mmol) in dry THF (8 mL) is added. The reaction is complete after 1 h of stirring. At 0 °C, sat. aq NH_4Cl (15 mL) is added and the solution extracted with Et_2O (2 × 20 mL). The resulting syrup is purified on a silica gel column (2 × 10 cm). Elution with Et_2O/petroleum ether (1:19) affords **4**; yield: 758 mg (64%); mp 65–67 °C (Et_2O/petroleum ether); $[\alpha]_D^{22}$ +118.5° (*c* = 1, $CHCl_3$).

$C_{16}H_{20}O_5$	calc.	C 65.76	H 6.89
(292.35)	found	65.53	6.77

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.40 (s, 3H, CH_3C), 1.54 (s, 3H, CH_3C), 3.76 (s, 3H, CH_3O), 3.98 (dd, 1H, $J_{4,5a}$ = 4.82 Hz, $J_{5a,5b}$ = 10.51 Hz, H-5a), 4.12 (dd, 1H, $J_{4,5b}$ = 3.88 Hz, H-5b), 4.97 (d, 1H, $J_{1,2}$ = 4 Hz, H-2), 5.05 (m, 1H, H-4), 5.30 (s, 1H, H_2C=), 5.49 (s, 1H, H_2C=), 5.92 (d, 1H, $J_{1,2}$ = 4 Hz, H-1), 6.80 (m, 4 H_{arom}).

1,2-Di-*O*-acetyl-3-deoxy-5-*O*-(4-methoxyphenyl)-3-methylidene-α- and -β-D-*erythro*-pentofuranose (6):
Amberlite resin IRN 77 (H^+ form, 2.5 g) is added to a cooled (0 °C) suspension of **4** (340 mg, 1.16 mmol) in H_2O/AcOH (15 mL, 1:1). The temperature is allowed to rise to r.t. and stirring is continued for 12 h. After filtration, the solvent is evaporated under reduced pressure and the residue (compound **5**) is dissolved in anhydrous pyridine (8 mL). Acetic anhyride (1.5 mL) is added to the cooled (0 °C) solution. After 12 h at r.t., the solvent is evaporated under

reduced pressure. Coevaporations with toluene (2 × 10 mL) remove traces of pyridine. The resulting mixture is partitioned between $CHCl_3$ (2 × 20 mL) and H_2O (20 mL). The $CHCl_3$ layer is separated, dried ($MgSO_4$), filtered, evaporated and applied on a silica gel column (2 × 10 cm). Elution with Et_2O/petroleum ether (3:1) gives **6** as a mixture of α- and β-anomers employed in the next step without purification; yield: 306 mg (76%).

$C_{17}H_{20}O_7 \cdot 1H_2O$	calc.	C 57.57	H 6.21	
(354.3)	found	57.40	6.23	

2'-*O*-Acetyl-3'-deoxy-5'-*O*-(4-methoxyphenyl)-3'-methylidene-5-methyluridine (7):

Under a positive pressure of argon, dry 1,2-dichloroethane (10 mL), **6** (685 mg, 2.04 mmol) and thymine (259 mg, 2.04 mmol) are placed in a 25 mL flask equipped with a rubber septum. To the resulting solution, Me_3SiCl (214 µL, 1.63 mmol), hexamethyldisilazane (350 µL, 1.63 mmol) and trimethylsilyl trifluoromethylsulfonate (454 µL, 2.45 mmol) are successively introduced through a syringe. The mixture is stirred at 60 °C for 2 h, then quenched with H_2O (2 mL) and sat. aq $NaHCO_3$ (4 mL). After decantation, the aq layer is extracted with CH_2Cl_2 (2 × 20 mL). The organic phase is dried ($MgSO_4$), filtered and evaporated. The crude mixture is directly deacetylated (*vide infra*). An analytical sample was obtained by preparative TLC. Elution with $CHCl_3$/MeOH (19:1) affords pure **7**; yield 384 mg (47%) as an oil; $[\alpha]_D^{22}$ + 10.1° (*c* = 1, $CHCl_3$).

$C_{20}H_{21}N_2O_7 \cdot 1H_2O$	calc.	C 57.14	H 5.75	N 6.66
(420.4)	found	57.56	5.58	6.58

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.8 (1, 3H, CH_3-base), 2.13 (s, 3H, CH_3CO), 3.75 (s, 3H, CH_3O), 4.06 (dd, 1H, $J_{4,5'a}$ = 2.6 Hz, $J_{5'a,5'b}$ = 10.4 Hz, H-5'a), 4.30 (dd, 1H, $J_{4',5'b}$ = 2.2 Hz, H-5'b), 4.95 (m, 1H, H-4'), 5.30 (s, 1H, H_2C=), 5.40 (s, 1H, H_2C=), 5.78 (m, 1H, $J_{1',2'}$ = 5.78 Hz, H-2'), 6.1 (d, 1H, $J_{1,2}$ = 5.78 Hz, H-1'), 6.84 (m, 4H_{arom}), 7.48 (s, 1H, H-6), 10.2 (s, 1H, H-3).

3'-Deoxy-5'-*O*-(4-methoxyphenyl)-3'-methylidene-5-methyluridine (8):

Purified **7** (370 mg, 0.92 mmol) and KCN (35 mg, 0.54 mmol) are dissolved in MeOH (5 mL) at r.t. After 3 h of stirring, Amberlite resin IRN 77 (H^+ form, 0.9 g) is added and stirring continued for 12 h. After filtration, the solvent is evaporated under reduced pressure; yield of crude **8**: 330 mg (99%); $[\alpha]_D^{22}$ 0° (*c* = 0.52, $CHCl_3$).

$C_{18}H_{20}N_2O_6$	calc.	C 59.99	H 5.59	N 7.77
(360.3)	found	59.41	5.63	7.41

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.73 (s, 3H, CH_3-base), 3.77 (s, 3H, CH_3O), 4.02 (dd, 1H, $J_{4,5'a}$ = 2.8 Hz, $J_{5'a,5'b}$ = 10.3 Hz, H-5'a), 4.30 (dd, 1H, $J_{4,5'b}$ = 1 Hz, H-5'b), 4.81 (m, 2H, H-2', OH), 4.99 (m, 1H, H-4'), 5.27 (s, 1H, H_2C=), 5.52 (s, 1H, H_2C=), 5.96 (d, 1H, $J_{1',2'}$ = 5.45 Hz, H-1'), 6.84 (m, 4H_{arom}), 7.54 (s, 1H, H-6), 10.2 (s, 1H, H-3).

Method B: preferably the crude mixture (820 mg) obtained from coupling **6** (747 mg, 2.22 mmol) with activated thymine as described above is dissolved in dry MeOH (5 mL) at r.t., KCN (79 mg, 1.22 mmol) is then added and the mixture stirred for 12 h at r.t. After evaporation, the obtained syrup (710 mg) is partitioned between H_2O (10 mL) and toluene (2 mL) and the toluene extracted with H_2O (2 × 10 mL). The aq layer is neutralized with Amberlite resin IRN 77 (H^+ form, 220 mg), filtered, evaporated and coevaporated with toluene (4 × 4 mL) to afford **8**; yield: 623 mg (78%) from **6**.

3'-Deoxy-2',3'-didehydro-5'-*O*-(4-methoxyphenyl)-3'-phenoxycarbonylthiomethylthymidine (9):

To a stirred solution of **8** (200 mg, 0.55 mmol) and 4-dimethylaminopyridine (DMAP; 139 mg, 1.14 mmol) in pyridine (5 mL) at r.t. is added *O*-phenylcarbonochloridothioate (230 µL, 1.67 mmol). Stirring is continued 2 h at r.t. and the solvent evaporated under reduced pressure. Traces of pyridine are removed by coevaporation with toluene (2 × 10 mL). The mixture is partitioned between EtOAc (2 × 20 mL) and H_2O (20 mL). The EtOAc layer is dried ($MgSO_4$), filtered and evaporated. The residue is purified by preparative TLC. Elution with EtOAc affords **9**; yield: 133 mg (49%); mp 139–142 °C (Et_2O); $[\alpha]_D^{22}$ − 65.64° (*c* = 1, $CHCl_3$).

$C_{25}h_{24}N_2O_7S \cdot 1H_2O$	calc.	C 58.36	H 5.09	N 5.44
(514.5)	found	58.96	4.91	5.24

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.75 (d, 3H, $J_{5\text{-}CH,6}$ = 1.14 Hz, CH_3-base), 3.70 (dd, 1H, $J_{5'a,5'b}$ = 12.5 Hz, $J_{5'a,4'}$ = 1.25 Hz, H-5'a), 3.75 (s, 3H, CH_3O), 3.90 (dd, 1H, $J_{5'b,4'}$ = 1.0 Hz, H-5'b), 4.24 (m, 3H, CH_2S, H-4'), 5.08 (m, 1H, H-2'), 5.86 (br s, 1H, H-1'), 6.82 (m, 4H_{arom}, 7.11–7.41 (m, 5H_{arom}, PhOCO), 7.55 (s, 1H, H-6), 8.32 (s, 1H, H-3).

3'-Deoxy-2',3'-didehydro-5'-*O*-(4-methoxyphenyl)-3'-methylthymidine (10):

Under a positive pressure of argon, **9** (80 mg, 0.16 mmol) and azobisisobutyronitrile (AIBN; 6 mg, 0.037 mmol) are dissolved in toluene (6 mL). The solution is heated to reflux and tributyltin hydride (214 µL, 0.48 mmol) is added. Heating is continued for 2 h. The solvent is evaporated under reduced pressure and the crude compound purified by preparative TLC. Elution with Et_2O/EtOAc (1:1) affords **10**; yield: 41 mg (75%); mp 138–141 °C (Et_2O/petroleum ether); $[\alpha]_D^{22}$ − 59.4° (*c* = 0.7, $CHCl_3$).

$C_{18}H_{20}N_2O_5 \cdot 3.5H_2O$	calc.	C 53.07	H 6.68	N 6.88
(407.4)	found	53.50	7.03	6.90

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.75 (s, 3H, CH_3-base), 1.81 (s, 3H, CH_3-C_3), 3.75 (s, 3H, CH_3O), 4.16 (dd, 1H, $J_{5'a,5'b}$ = 11.1 Hz, $J_{5'a,4'}$ = 1.72 Hz, H-5'a), 4.18 (dd, 1H, $J_{5'a,5'b}$ = 11.1 Hz, H-5'b), 4.30 (dd, 1H, $J_{4',5'b}$ = 2.14 Hz, H-4') 4.85 (m, 1H, H-2'), 5.5 (br s, 1H, H-1'), 6.82 (m, 4H_{arom}) 7.6 (s, 1H, H-6), 8.42 (s, 1H, H-3).

3'-Deoxy-2',3'-didehydro-3'-methylthymidine (11):

To a cooled (0 °C) solution of **10** (16 mg, 0.046 mmol) in CH_3CN/H_2O (1 mL, 4:1) cerium ammonium nitrate (51 mg, 0.092 mmol) is added. The reaction is complete after 3 min. The mixture is partitioned between $CHCl_3$ (3 × 2 mL) and sat. brine (4 mL). The $CHCl_3$ layer is washed with sat. brine (1 × 4 mL), dried ($MgSO_4$), filtered and evaporated. The resulting product is purified by preparative TLC. Elution with $CHCl_3$/MeOH (9:1) affords **11**; yield: 6 mg (55%); mp 206–209 °C (EtOAc) Lit.[5] mp 208–210 °C. ^{1}H-NMR ($CDCl_3$/TMS) is identical to that reported.[5]

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