A Convenient Route to 3′-Amino-3′-deoxythymidine

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Efficient and convenient procedures are reported for the synthesis of the title compound **9** and its α-anomer **10**. Thus, the direct condensation of phthalimide with unprotected 2-deoxy-D-ribose **(1)** using the P_4O_{10}/H_2O/n-Bu_3N reagent in $CHCl_3$ at 40 °C followed by acetylation afforded the di-*O*-acetyl-phthalimido derivatives **2** and **3** which can also be synthesized via reaction of DBU phthalimide salt with 4-acetoxy-5-hydroxy-2-pentenal **5**. Reaction of **2** with silylated thymine using the Lewis acid trimethylsilyl triflate as catalyst afforded compounds **7** and **8** which were separated by fractional crystallization, and deprotected by treatment with 33% methylamine/ethanol to give the corresponding 3-aminonucleosides **9** and **10**, respectively.

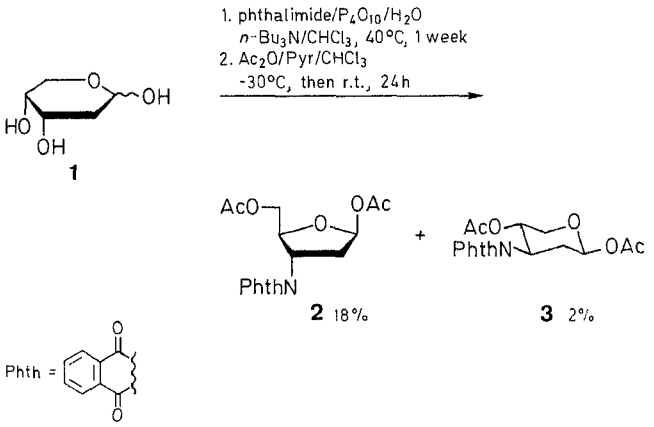
Simple methods for the synthesis of biologically important 3′-aminonucleosides are highly desirable. 3′-Amino-3′-deoxythymidine (**9**, Scheme **C**) shows potent inhibitory activity against the replication of both murine Sarcoma-180 and L1210 murine leukemia *in vitro*[1,2] and *in vivo*[3] and against P815

mouse leukemia cells.[4] Further, the platinum(II) complex of compound **9** inhibits the replication of murine L1210 cells in culture.[5] Compound **9** has been shown to exhibit moderate activity against Moloney murine leukemia (M-MULV) which is caused by a mammalian T-lymphotropic retrovirus.[6] Since retroviruses are also the causative agent of AIDS, there is a need for compounds that might be effective against these viruses. In general, inhibitors of cellular processes will often limit viral replication, but these agents usually are also quite toxic for the host. A biologically active compound like **9** can be derivatized at the 3'-amino group to give compounds which may be effective in the therapy of AIDS by blocking one or more steps of the replicative cycle[7,8] since minor structural modifications may produce marked changes in the spectrum of activity.

Compound **9** has been synthesized via two different routes:[9,10] (1) Conversion of thymidine into 3'-*O*-mesyl-5'-*O*-tritylthymidine[11] followed by treatment with the potassium salt of phthalimide, and deprotection to afford **9**,[9] the reaction proceeding via a 2,3'-anhydronucleoside intermediate;[9] (2) *O*-mesylation of 1-(2'-deoxy-5'-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine[12,13] to 1-(2'-deoxy-3'-*O*-mesyl-5'-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine, replacement of the mesyloxy group by the azido group by reaction with lithium azide, and detritylation and catalytic reduction of the 3-azido derivative to afford **9**.[10] To date, the general approach to compound **9** and analogues proceeds via the corresponding 3-azidonucleosides.[10,14-17] The main prerequisite of these routes is the availability of the nucleosides used as starting materials. An alternative synthesis of a 3'-azido-2',3'-dideoxyribofuranose derivative for nucleoside coupling reactions consists of a multistep sequence.[18,19]

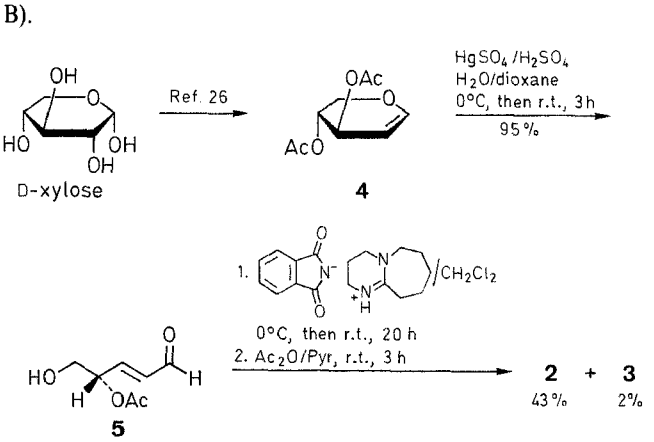
In previous papers, we reported the direct condensation of N^6-aryladenines[20] and N^6-acyladenines[21] with unprotected 2-deoxy-D-ribose using the reagent system $P_4O_{10}/H_2O/n\text{-}Bu_3N$ in chloroform at 40°C to give the corresponding 2,3-dideoxy-D-ribose derivatives via coupling at C-3 of the sugar moiety. The reaction was shown to proceed via ring cleavage of the sugar to give an aldehydo sugar which is dehydrated to an α,β-unsaturated aldehydo sugar.[21] The final steps were a Michael-type reaction of the purine with the unsaturated sugar, and ring closure. In order to find an easily available and appropriately substituted carbohydrate for the preparation of 3'-amino-2',3'-dideoxynucleosides we have utilized these findings for the direct condensation of phthalimide with 2-deoxy-D-ribose[22] as well as 2-deoxy-D-glucose[23] to give 2,3-dideoxy-3-phthalimido sugars. Since aqueous work-up was unsuccessful, the condensation products were separated from the excess phosphates by chromatography. The most interesting product was 2,3-dideoxy-3-phthalimido-D-*erythro*-pentofuranose which was isolated by repeated chromatography on a large silica column making it difficult to perform this synthesis on a preparative scale. Instead, we then used tetrabromophthalimide to obtain a mixture of isomers of analogous tetrabromophthalimido sugars as a precipitate in 73% yield which was used as its acetate for the synthesis of 3'-amino-2',3'-dideoxy-*threo*-pyranose nucleosides derived from purines[24] and 3'-amino-2',3'-dideoxyuridine.[25] Unfortunately, cleavage of the tetrabromophthalimido group to give the desired amino nucleosides proceeded with low yields only, probably due to sterical hindrance by the Br-atoms. Therefore, we turned back to the reaction of phthalimide with 2-deoxy-D-ribose using the same reaction conditions[22] which were only modified by the immediate acetylation in the reaction mixture.

In the present work, phthalimide is subjected to the condensation with 2-deoxy-D-ribose (**1**) using the $P_4O_{10}/H_2O/n\text{-}Bu_3N$ reagent system in chloroform (40°C, 1 week). The resultant products are directly acetylated by adding the reaction mixture dropwise to a mixture of acetic anhydride and pyridine in chloroform at −30°C to give 1,5-di-*O*-acetyl-2,3-dideoxy-3-phthalimido-β-D-*erythro*-pentofuranose (**2**, 18% yield) and 1,4-di-*O*-acetyl-2,3-dideoxy-3-phthalimido-β-D-*threo*-pentopyranose (**3**, 2% yield) which were isolated by fractional crystallization (Scheme **A**). This procedure (Method A) is suitable for the large-scale preparation of **2**.



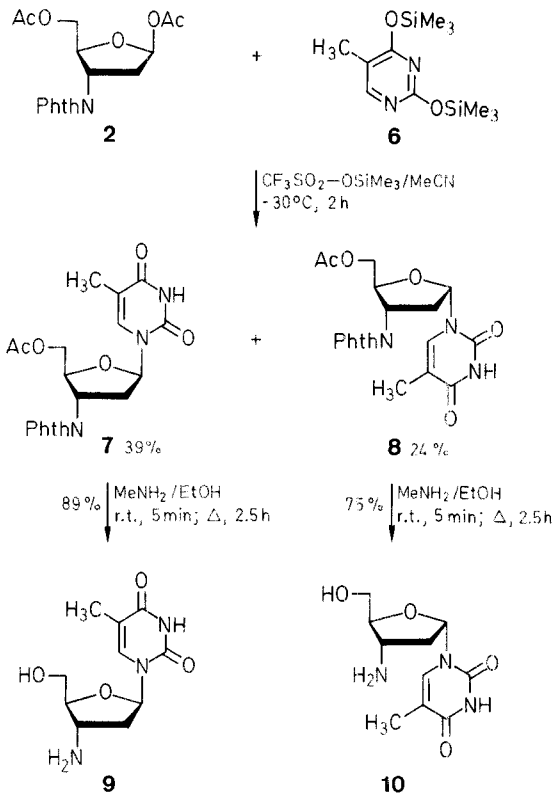
Scheme A

The reaction mechanism is probably similar to the one described above for the condensation of adenines with 2-deoxy-D-ribose. We therefore also investigated the Michael-type addition of phthalimide to α,β-unsaturated aldehydo sugars (Scheme **B**). D-Xylose was used as a cheap starting material to prepare 3,4-di-*O*-acetyl-D-xylal (**4**) as previously described[26] but compound **4** was isolated by chromatography because distillation often resulted in decomposition. Xylal **4** is easily hydrolyzed to 4-*O*-acetyl-2,3-dideoxy-aldehydo-D-glycero-*trans*-pent-2-enose (**5**) according to Ref. 27. Reaction of **5** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) phthalimide salt[23] in dichloromethane gave a syrupy product which was immediately acetylated with acetic anhydride/pyridine to give compound **2** in 43% yield and compound **3** in 2% yield (Method B).



Scheme B

By applying the reported[28] procedure for nucleoside synthesis using trimethylsilyl triflate, the reaction of **2** with silylated thymine[29] (**6**) in dry acetonitrile (2 h at −30°C) could be easily completed to give an anomer mixture of **7** and **8** (Scheme **C**).



Scheme C

Compounds **7** and **8** are separated by fractional crystallization from ethanol in 39% and 24% yield, respectively. The reaction of **7** or **8** with 33% methylamine in absolute ethanol (2.5 h at reflux temperature) results in complete deprotection of both the hydroxy and the amino groups to give 3′-amino-3′-deoxythymidine **(9)** or its α-anomer **10** in 89% and 75% yield, respectively.

The ^{1}H-NMR and ^{13}C-NMR data of compound **2** are in close agreement with the corresponding data reported[22] for β-form of the tetrabromophthalimido analogue, on which an NOE experiment has been performed; this indicates that compound **2** has the β-configuration.

P_4O_{10}/H_2O/*n*-Bu_3N Reagent in Chloroform:
Water (21.14 g, 1.173 mol) is added dropwise to P_4O_{10} (100.0 g, 0.352 mol) in $CHCl_3$ (400 mL) with stirring. Then, $CHCl_3$ (200 mL) is added and the inhomogeneous mixture is refluxed with stirring for 30 min (80°C). The mixture is then cooled to room temperature and *n*-Bu_3N (136.0 g, 0.734 mol) is cautiously added with vigorous stirring. The resultant clear solution is cooled to room temperature and $CHCl_3$ is added to a total volume of 1000 mL.

1,5-Di-*O*-acetyl-2,3-dideoxy-3-phthalimido-β-D-*erythro*-pentofuranose (2) and 1,4-Di-*O*-acetyl-2,3-dideoxy-3-phthalimido-β-D-*threo*-pentopyranose (3):

Method A: A mixture of finely powdered phthalimide (33.33 g, 0.227 mol), P_4O_{10}/H_2O/*n*-Bu_3N reagent (1000 mL), and *n*-Bu_3N (180.0 g, 0.961 mol) is refluxed for 35 min with stirring until a clear solution is obtained. The mixture is then cooled below 40°C, 2-deoxy-D-ribose (**1**; 60.0 g, 0.447 mol) is added, and stirring is continued for 1 week at 40°C. The mixture is then added dropwise to a stirred mixture of Ac_2O (365.2 g, 3.58 mol), dry pyridine (200 mL), and $CHCl_3$ (300 mL) at −30°C and stirring is continued for 24 h at room temperature. The solvents are evaporated under reduced pressure and the residue is extracted several times with Et_2O (a total of 4 L). The ether extract is washed with cold H_2O (3 × 500 mL), cold saturated aqueous $NaHCO_3$ (3 × 300 mL), and cold H_2O (3 × 250 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue is treated with dry Et_2O (200 mL). The solid product is isolated by suction (the filtrate being saved), washed well with dry Et_2O, and dried at the air to give compound **2**; yield: 27.8 g (18%, based on **1**); mp 154–156°C.

The filtrate is stored in the refrigerator for 2 days, the liquid is then decanted from a gum and again stored in the refrigerator for 3 weeks. The precipitate formed is isolated by suction, washed with cold dry Et_2O, and dried at the air to give **3**; yield: 2.4 g (2%, based on **1**); mp 143–145°C.

Method B: DBU phthalimide salt[23] (6.0 g, 0.02 mol) in CH_2Cl_2 (150 mL) is added dropwise during 1 h to a stirred solution of the (4*S*)-(*E*)-4-acetoxy-5-hydroxy-2-pentenal (**5**; 3.6 g, 0.023 mol) in CH_2Cl_2 (100 mL) at 0°C and stirring is continued for 20 h at room temperature. The solvent is then evaporated under reduced pressure. The residue is stirred with Ac_2O (200 mL) and dry pyridine (20 mL) for 3 h at room temperature. The solvents are evaporated under reduced pressure and the residue is chromatographed twice on silica gel (200 g, 0.04–0.063 mm) using CH_2Cl_2/MeOH (19:1) as eluent. The solvent is evaporated under reduced pressure and the residue is treated with dry Et_2O (30 mL). The precipitate formed is isolated by suction and dried at the air to give **2**; yield: 3.4 g (43%). The filtrate is treated as in Method A to give **3**; yield: 0.13 g (2%).

Compound **2**:

$C_{17}H_{17}NO_7$	calc.	C 58.79	H 4.93	N 4.03
(347.3)	found	58.49	4.94	4.09

MS: *m/z* (%) = 347 (M^+, 0.02); 304 (8); 288 (12); 245 (13); 227 (68); 214 (38); 202 (32); 174 (42); 130 (18); 81 (43); 43 (100); 18 (63).

^{1}H-NMR (250 MHz, $CDCl_3$/TMS): δ = 2.03 (s, 3H, CH_3CO); 2.11 (s, 3H, CH_3CO); 2.24 (dd, 1H, 2β-H); 3.11 (ddd, 1H, 2α-H); 4.16 (dd, 1H, 5a-H); 4.25 (dd, 1H, 5b-H); 4.7 (ddd, 1H, 4-H); 4.98 (dt, 1H, 3-H); 6.48 (d, 1H, 1-H); 7.75–7.89 (m, 4H_{arom}). $J_{1,2\alpha}$ = 5.16; $J_{2\alpha,2\beta}$ = 12.95; $J_{2\alpha,3}$ = 10.6; $J_{2\beta,3}$ = 7.96; $J_{3,4}$ = 7.96; $J_{4,5a}$ = 6.04, $J_{4,5b}$ = 4.95; $J_{5a,5b}$ = 11.72 Hz.

^{13}C-NMR (62.5 MHz, $CDCl_3$/TMS): δ = 20.50 ($\underline{C}H_3CO$); 21.14 ($\underline{C}H_3CO$); 34.43 (C-2); 49.59 (C-3); 64.85 (C-5); 78.15 (C-4); 97.84 (C-1); 123.35 (C-4′); 131.39 (C-3′a), 134.26 (C-5′), 167.5 (C=O), 169.66, 170.35 ($\underline{C}H_3CO$).

Compound **3**:

$C_{17}H_{17}NO_7 \cdot 0.25H_2O$	calc.	C 58.03	H 5.01	N 3.98
(351.8)	found	57.91	4.90	3.93

^{1}H-NMR (250 MHz, $CDCl_3$/TMS): δ = 1.91–2.18 (m, 7H, 2e-H, CH_3CO); 2.81 (ddd, 1H, 2a-H); 3.56 (dd, 1H, 5a-H); 4.27 (dd, 1H, 5e-H); 4.50 (m, 1H, 3-H); 5.57 (m, 1H, 4-H); 5.89 (dd, 1H, 1-H); 7.75–7.89 (m, 4H_{arom}). $J_{1,2a}$ = 9.96; $J_{1,2e}$ = 3.01; $J_{2a,2e}$ = 13; $J_{2a,3}$ = 13; $J_{3,4}$ = 9.45; $J_{4,5a}$ = 8.16; $J_{4,5e}$ = 5.13; $J_{5a,5e}$ = 11.93 Hz.

^{13}C-NMR (62.5 MHz, $CDCl_3$/TMS): δ = 20.97, 20.65 ($\underline{C}H_3CO$); 31.46 (C-2); 49.01 (C-3); 65.04 (C-5); 67.77 (C-4); 92.62 (C-1); 123.50 (C-4′); 131.56 (C-3′a); 134.29 (C-5′); 167.76 (C-1′); 169.23, 170.09 ($CH_3\underline{C}O$).

4-*O*-Acetyl-2,3-dideoxy-aldehydo-D-glycero-*trans*-pent-2-enose[(4*S*)(*E*)-4-Acetoxy-5-hydroxy-2-pentenal, 5]:
To a stirred solution of 3,4-di-*O*-acetyl-D-xylal[26] (**4**; 5 g, 0.025 mol) in 1,4-dioxane (5 mL)/5 mM H_2SO_4 (50 mL) at 0°C is added $HgSO_4$ (100 mg). Stirring is continued for 3 h at room temperature, the mixture then neutralized with $BaCO_3$ (0.1 g), and the resultant suspension filtered. The filtrate is evaporated under reduced pressure and the residue is dissolved in CH_2Cl_2 (100 mL). This solution is dried (Na_2SO_4) and evaporated to give **5** as colorless oil which can be used without further purification for the preparation of **2**; yield of **5**: 3.7 g (95%).

5′-*O*-Acetyl-3′-deoxy-3′-phthalimidothymidine (7) and 1-(5-*O*-Acetyl-2,3-dideoxy-3-phthalimido-α-D-*erythro*-pentofuranosyl)-5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (8):
A solution of trimethylsilyl triflate (4 mL, 0.022 mol) in dry MeCN (20 mL) is added to a stirred mixture of compound **2** (6.94 g, 0.02 mol) and *O,O′*-bis(trimethylsilyl)thymine[29] (**6**; 3.35 g, 0.02 mol) in dry MeCN (150 mL) at −30°C, and stirring is continued for 2 h at −30°C. The mixture is then diluted with CH_2Cl_2 (500 mL), washed with cold saturated aqueous $NaHCO_3$ (250 mL) and with cold H_2O (3 × 250 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give 8.00 g as crude product of an anomer mixture of **7** and **8**; yield: 8 g (97%); mp 208–210°C. This crude product is dissolved in the minimum amount of hot 96% EtOH (50 mL) and the solution is cooled to room temperature. The precipitate formed is isolated by filtration to give **7**; yield: 3.22 g (39%); mp 238–240°C (Lit.[9], mp 238–239°C).

The filtrate is kept at room temperature overnight. The precipitated product **8** is then isolated by suction; yield: 1.98 g (24%); mp 168–170°C.

^{1}H-NMR (250 MHz, DMSO-d_6/TMS): δ = 1.90 (s, 3H, CH_3); 2.01 (s, 3H, CH_3CO); 2.63–2.84 (m, 2H, 2′α-H, 2′-β-H); 4.08–4.27 (m, 2H, 5′a-H, 5′b-H); 4.77–4.92 (m, 2H, 3′-H, 4′-H); 6.35 (t, 1H, $J_{1,2\alpha} = J_{1,2\beta}$ = 7 Hz, 1′-H), 7.78–7.93 (m, 4H, Phth), 11.37 (br s, 1H, NH).

^{13}C-NMR (62.5 MHz, DMSO-d_6/TMS): δ = 12.38 (CH_3); 20.38 (CH_3CO); 32.58 (C-2′); 49.46 (C-3′); 63.92 (C-5′); 76.34 (C-4′); 83.54 (C-1′); 110.16 (C-5); 123.65 (C-4″); 131.41 (C-3″a); 134.42 (C-5″); 135.26 (C-6); 150.34 (C-2); 163.52 (C-4); 167.57 (C=O); 169.96 (CH_3CO).

3′-Amino-3′-deoxythymidine (9) and 1-(3-Amino-2,3-dideoxy-α-D-*erythro*-pentofuranosyl)-5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (10); General Procedure:

A 33% solution of $MeNH_2$ in absolute EtOH (60 mL) is added to a stirred suspension of compound **7** or **8** (1.5 g, 0.0036 mol) in 99.9% EtOH (30 mL) at room temperature. After 5 min, the clear solution obtained is refluxed for 2.5 h. The mixture is then cooled to room temperature and the solvent is evaporated under reduced pressure. The residue is chromatographed on silica gel (40 g, 0.04–0.063 mm) using CH_2Cl_2/MeOH (19:1) as eluent to remove all impurities, and then MeOH to elute the desired product.

Compound **9**; yield: 0.78 g (89%); mp 187–189°C (Lit.[9] mp 187–187.5°C).

Compound **10**; yield: 0.66 g (75%); mp 198–200°C.

$C_{10}H_{15}N_3O_4$	calc.	C 49.79	H 6.36	N 17.42
(241.3)	found	49.79	6.35	17.28

MS: *m/z* (%) = 241 (M^+, 5.1); 116 (100); 72 (59); 56 (40); 44 (21).

^{1}H-NMR (250 MHz, DMSO-d_6/TMS): δ = 1.81 (s, 3H, CH_3); 2.47–2.52 (m, 2H, 2′α-H, 2′β-H); 3.34–3.89 (m, 4H, 3′-H, 4′-H, 5′a-H, 5′b-H); 4.5 (br s, 2H, NH_2); 6.08 (t, 1H, $J_{1,2\alpha} = J_{1,2\beta}$ = 6.5 Hz, 1′-H); 7.91 (s, 1H, 6-H).

^{13}C-NMR (62.5 MHz, DMSO-d_6/TMS): δ = 12.16 (CH_3); 40.45 (C-2′); 52.15 (C-3′); 61.77 (C-5′); 84.17 (C-1′); 87.60 (C-4′); 109.02 (C-5); 137.04 (C-6); 150.49 (C-2); 163.61 (C-4).

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