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A novel synthesis of AZT

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Abstract—A novel synthesis of AZT has been achieved from two commercial available products acetaldehyde and D-mannitol. The originality of the synthesis consists of using the powerful monovinylogation reagent, the 2-lithio-1-trimethylsiloxyethylene, and to introduce the thymine moiety and to build the furanose ring in the same and last step.

AZT (3′-azido-3′-deoxythymidine) **1a** is one of the most active nucleoside analogue against HIV. Other nucleosides, like ddI (2′,3′-dideoxyinosine), ddC (2′,3′-dideoxycytidine), d_4T (2′,3′-didehydro-3′-deoxythymidine) and 3TC (2′,3′-dideoxy-3′-thiocytidine) also show antiviral activity. The syntheses of 2′,3′-dideoxy nucleosides, described in the literature, could be arranged according to two different approaches. They proceed either by building the furanose moiety from a sugar or a non carbohydrate compound[1] or by functionalisation of natural compounds like thymidine or other available nucleosides.[2] We report here a novel synthesis of AZT from commercial available D-mannitol and using a monovinylogation reagent, the 2-lithio-1-trimethylsiloxyethylene **2**,[3] easily obtained from acetaldehyde.

Our reaction scheme (Scheme 1), utilises a novel convergent approach to AZT **1a** by a simultaneous ring-closure base-introduction in a one step procedure.[4] It was envisaged that C_1–C_2 bond of the furanose ring could be built by condensation of the monovinylogation reagent[3] **2** with the appropriate aldehyde acetal **3**.

Protection[6] of D-mannitol, leading to D-1,2; 5,6-di-*O*-cyclohexyliden mannitol, followed by oxidative cleavage with sodium periodate,[6] afforded the protected glyceric aldehyde **3** (Scheme 1). The monovinylogation reagent **2** has been prepared, from acetaldehyde, via a bromine–lithium exchange reaction using *t*-butyllithium (*t*-BuLi) in dry diethyl ether (Et_2O) at −70°C.[3] According to usual conditions,[3] condensation of reagent **2** has been done with aldehyde **3**. But, the conditions of the sequence hydrolysis–dehydration has been modified, in the former paper,[3] to optimise the formation of the conjugated aldehyde **4**. Previously, a similar compound to **4**, (2*E*,4*S*)-4,5-*O*-isopropyliden pent-2-enal, has been described,[7] using the Tripett and Walker reagent. We have preferred to use our reagent **2** to access to compound **4** because of its usual great reactivity towards saturated, unsaturated or aromatic aldehydes and aliphatic or aromatic ketones.[3] In addition of its versatility, the ease of work-up and the high yields make this procedure attractive. Compound **4** is the key intermediate in our synthetic procedure of AZT.

The best results have been obtained by treatment of the above reaction mixture with acetyl chloride (AcCl) followed by HF–pyridine (Scheme 1).

By florisil column chromatography (pentane/Et_2O=80:20) of the obtained crude mixture, we have isolated the expected conjugated aldehyde **4** accompanied with acetylenic diacetate **5**[8] and acetylenic acetate **6**[8]. They have been formed in 60, 3 and 30% overall yields, respectively, from the starting material **3** (Scheme 1). The structure and the stereochemistry of these compounds **4**–**6** were carried out using ^{1}H NMR spectroscopy. For compound **6**, two pure diastereomers **6a** (2*R*,3*R*) and **6b** (2*R*,3*S*) have been isolated in similar ratio and identified. The configurational assignments 3*R* and 3*S* have been determined using ^{1}H NMR spectroscopy, from the J_{2-3} coupling constants values (**6a** (2*R*,3*R*): 4.0 Hz and **6b** (2*R*,3*S*): 7.5 Hz)). Isolated compound **5** seems to be a single diastereomer (same coupling constant value J_{2-3}=J_{6-7}=3.3 Hz), with the configuration 2*R*,3*R*,6*R*,7*R*, by analogy with the analysis of **6a** and **6b**. For the conjugated compound **4**, the *E* double bond configuration has been determined from the J_{2-3} coupling constant value (15.7 Hz). As in most of the cases, condensation of the reagent **2** is stereoselective.[3]

By condensation of NaN_3 in acetic medium,[1j] after 3 h, aldehyde **4** could be converted to azido aldehyde **7** in 99% yield, as a mixture of two diastereomers **7a** (60%) and **7b** (40%); percentages determined by gas chromatography and by ^{1}H NMR spectroscopy (Scheme 1). To build exclusively the furanose ring, azido aldehyde **7** was transformed to azido acetal **8** by treatment with methanol in presence of

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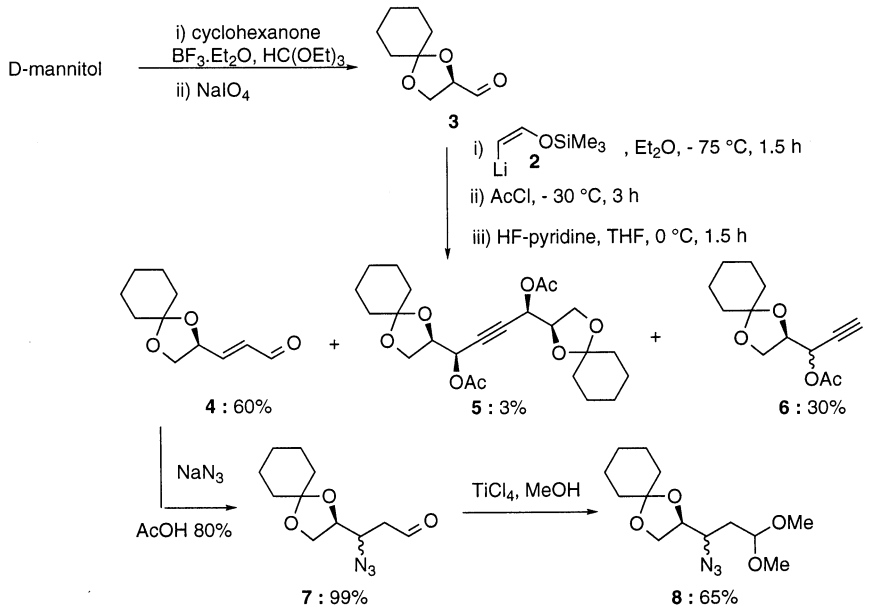
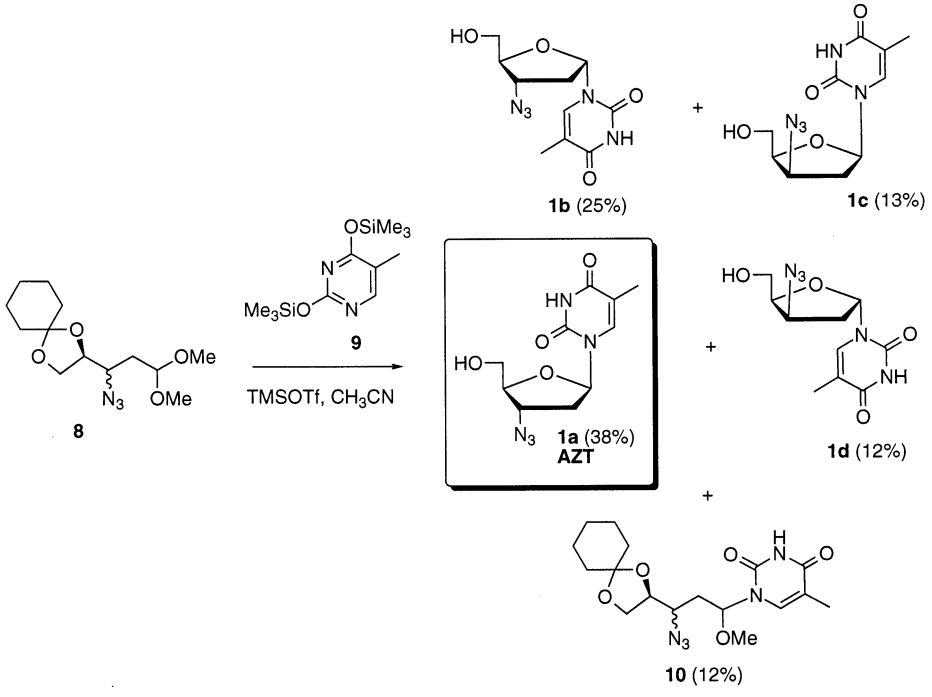


Scheme 1.

titanium chloride ($TiCl_4$).[9] The latter has been isolated as a mixture of two diastereomers **8a** and **8b** in the same ratio than the precursors **7a** and **7b** (**8a/8b**=60:40); percentages determined by gas chromatography and by ^1H NMR spectroscopy. Unfortunately, we have not succeeded to separate the diastereomers **7a**, **7b** and **8a**, **8b** using classical methods.

A coupling reaction between azido acetal **8** and silylated thymine nucleobase **9** (obtained from thymine and hexamethyldisilazane HMDS), using the Vorbrüggen et al.[10] conditions, followed in the same step by the furanose ring formation (in presence of trimethylsilyltriflate TMSOTf), has led to a mixture of AZT (**1a**) and of the diastereomers **1b–d** accompanied by the intermediate **10** (Scheme 2). We have never put in evidence the formation of a pyranose ring. The formation of **10** could be explained by the mechanism previously proposed by Pedersen et al.[11] By increasing the reaction time to 36 h at room temperature we have improved the formation of AZT and minimised the quantity of the intermediate **10** (**1a–d/10**=88:12; ratio determined by ^1H NMR spectroscopy analysis).

The condensation of the thymine group and the formation of the furanose ring, done in a one pot procedure without



Scheme 2.

addition of protic acid, have never been reported for the synthesis of AZT **1a**. The presence of a Lewis acid has been sufficient, according to our reaction conditions to permit this ring formation.[4]

From the crude product, by silica gel column chromatography ($CHCl_3$/MeOH=95:5) we have isolated and identified 38% of pure AZT **1a**, the different diastereomers **1b–d** (**1b**=25%, **1c**=13% and **1d**=12%) and 12% of the pure intermediate **10**. The analyses of AZT **1a** and of the diastereomers **1b–d** have been identical with those previously reported; moreover our AZT **1a** sample compared with a commercial one (Sigma) has been fully identical.

In summary, a novel synthesis of AZT **1a** has been achieved from two commercial available products, acetaldehyde and D-mannitol (seven steps from the starting material with an overall yield of 8%). The originality of our approach consists of using the powerful monovinylogation reagent, the 2-lithio-1-trimethylsiloxyethylene **2** and to introduce the thymine moiety and to build the furanose ring in the same and last step.

1. Experimental

1.1. General

IR spectra were recorded on a Perkin–Elmer 16 PC FT-IR spectrometer as thin films (cm^{-1}). NMR spectra were recorded on a Bruker AC 200 MHz or Bruker Avance DPX 300 MHz. $CDCl_3$ was used as solvent. No $SiMe_4$ was added; rather, shifts were referenced to the line for $CDCl_3$/$CHCl_3$ (chemical shifts δ in ppm and coupling constants J in Hz). Gas chromatography analyses were performed on a Hewlett Packard 5890 apparatus equipped with a high resolution J-W DB-1 column (30 m, 0.25 mm ID, 0.25 μm coating). GC-MS analyses (EI, 70 eV) were performed on a ATI-Unicam Automass apparatus equipped with the same column or on a JEOL JMS AX-500 spectrometer. Analytical TLC was performed on Kieselgel 60F-254-0.25 nm plates and developed with UV 250 nm or phosphomolybdic acid. Products were purified by column chromatography with Merck Kieselgel 60 (over 230–400 mesh ASTM) support or with Acros florisil (60–100 mesh) support. Observed rotations at the Na-D line were obtained using a Perkin–Elmer MC 241 polarimeter. All reactions were carried out under dry Ar. Microanalyses were carried out in IRCOF Microanalysis Laboratory of Rouen. Melting points were measured on a Reichert–Jung microscope apparatus. Solvents were purified according to standard procedures.

1.2. 4,5-*O*-Cyclohexylidene-2,3-dideoxy-aldehydo-D-glycero-*trans*-pent-2-enose (4)

To the monovinylogation reagent **2** (1.00 equiv.),[3] at −75°C and under argon, D-2,3-*O*-cyclohexylidene glyceraldehyde **3** (1.00 g, 5.88 mmol, 0.84 equiv.) in anhydrous Et_2O (2.0 mL) was added. The solution was stirred at −75°C for 30 min and warmed slowly to −30°C. The mixture was stirred for 1 h 30 min before treatment with acetyl chloride (0.42 mL, 5.88 mmol, 0.84 equiv.). The solution was stirred at −30°C for 3 h before treatment with aqueous $NaHCO_3$ (21 mL, 5%). After extraction with Et_2O, the organic layer was dried ($MgSO_4$). Evaporation has given the crude product (1.90 g, quantitative yield). Under argon, HF–pyridine (0.82 mL, 6.46 mmol, 1.10 equiv.) was added to a solution of the above crude product in anhydrous THF (6 mL), cooled to 0°C. The mixture, stirred for 1 h 30 min, was diluted with Et_2O (100 mL) before treatment with aqueous saturated $NaHCO_3$ (25 mL). The aqueous layer was extracted with Et_2O (3×50 mL). The combined extracts were washed with aqueous saturated NH_4Cl (25 mL), dried over $MgSO_4$ and concentrated to give a yellow oil. By florisil column chromatography (pentane/Et_2O=80:20) we have isolated and identified the conjugated aldehyde **4** (0.70 g) in 60% yield as a white solid (recrystallised in pentane), the acetylenic diacetate **5** (0.04 g, 3%) and the acetylenic acetate **6** (0.40 g, 30%).

1.2.1. 4,5-*O*-Cyclohexylidene-2,3-dideoxy-aldehydo-D-glycero-*trans*-pent-2-enose (4). Mp 32°C; R_f 0.21 (pentane/Et_2O=80:20); $[\alpha]_D^{20}$=+34.67 (*c* 1.50, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=1.30–1.70 (m, 10H, CH_2), 3.69 (dd, J=6.8 and 8.3 Hz, 1H, H^5), 4.19 (dd, J=6.7 and 8.4 Hz, 1H, H^5), 4.75 (m, 1H, H^4), 6.32 (ddd, J=1.3, 7.8 and 15.7 Hz, 1H, H^2), 6.74 (dd, J=5.3 and 15.7 Hz, 1H, H^3), 9.53 (d, J=7.8 Hz, 1H, H^1). ^{13}C NMR (75 MHz, $CDCl_3$): δ=23.77, 24.97, 35.10, 35.99, 68.29, 74.48, 111.15, 132.26, 153.49, 193.05; IR (KBr, neat): 3018, 2940, 2400, 1692, 1216 cm^{-1}; MS (EI, 70 eV); *m/z* (rel. int.):196 (11) [M^+], 167 (15) [M^+−CHO], 153 (74), 141 (26), 81 (52), 69 (14), 55 (100). $C_{11}H_{16}O_3$ (196.25): calcd C 67.35, H 8.16; found C 67.37, H 8.26.

1.2.2. (2*R*,3*R*,6*R*,7*R*)-1,2,7,8-di-*O*-Cyclohexylidene-3,6-diacetoxyoct-4-yne (5). Mp 104–106°C; $[\alpha]_D^{20}$=+91.94 (*c* 2.22, C_6H_6); ^1H NMR (300 MHz, $CDCl_3$): δ=1.20–1.70 (m, 20 H, CH_2), 2.05 (s, 6H), 3.88 (dd, J=5.8 and 8.6 Hz, 2H, H^1, H^8), 4.05 (dd, J=6.6 and 8.8 Hz, 2H, H^1, H^8), 4.25 (m, 2H, H^2, H^7), 5.50 (d, J=3.3 Hz, 2H, H^3, H^6); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.23, 24.10, 24.24, 25.43, 35.21, 36.18, 63.65, 65.52, 76.20, 81.45, 111.48, 169.85; IR (KBr, neat): 2976, 2934, 2860, 2802, 1756, 1443, 1381, 1347, 1120, 1075 cm^{-1}; MS (CI, CH_4); *m/z* (rel. int.): 451 (8) [M^++1], 392 (59), 391 (100) [M^+−OAc], 353 (46), 293 (46), 233 (47), 195 (40), 141 (63), 99 (50). $C_{24}H_{34}O_8$ (450.53): calcd C 64.00, H 7. 55; found C 63.82, H 7.52.

1.2.3. (2*R*,3*R*)-3-Acetoxy-1,2-*O*-cyclohexylidene pent-4-yne (6a). Colourless oil; R_f 0.47 (pentane/Et_2O=80/20); $[\alpha]_D^{20}$=+36.44 (*c* 5.96, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ=1.15–1.65 (m, 10H, CH_2), 2.10 (s, 3H), 2.40 (d, J=2.2 Hz, 1H, H^5); 3.90 (dd, J=6.0 and 8.6 Hz, 1H, H^1), 4.05 (dd, J=6.7 and 8.0 Hz, 1H, H^1), 4.30 (m, 1H, H^2), 5.42 (dd, J=2.2 and 4.0 Hz, 1H, H^3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.79, 23.67, 23.80, 24.98, 33.77, 34.78, 63.28, 65.13, 74.83, 75.81, 78.10, 111.06, 169.47; IR (KBr, neat): 2937, 2867, 2130, 1759, 1481, 1467, 1372, 1337, 1227, 1168, 1108 cm^{-1}; MS (EI, 70 eV); *m/z* (rel. int.): 238 (11) [M^+], 209 (19) [M^+−29], 195 (79) [M^+−OAc], 141 (68), 123 (31), 81 (27), 55 (100).

1.2.4. (3*S*,4*R*)-3-Acetoxy-4,5-*O*-cyclohexylidene pent-1-yne (6b). Colourless oil; R_f 0.36 (pentane/Et_2O=80:20);

$[\alpha]_D^{20}=-13.45$ (*c* 0.29, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.15–1.60$ (m, 10H, CH_2), 2.05 (s, 3H), 2.45 (d, $J=2.2$ Hz, 1H, H^5), 3.98 (dd, $J=5.3$, 9.0 Hz, 1H, H^1), 4.10 (dd, $J=6.4$ and 9.0 Hz, 1H, H^1), 4.27 (ddd, $J=5.3$, 6.4 and 7.5 Hz, 1H, H^2), 5.38 (dd, $J=2.2$ and 7.5 Hz, 1H, H^3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=23.67$, 23.80, 24.93, 29.60, 34.76, 36.05, 65.06, 65.72, 74.87, 75.71, 77.15, 111.33, 169.54; IR (KBr, neat): 2924, 2852, 1746, 1454, 1368, 1226, 1098 cm^{-1}; $C_{13}H_{18}O_4$ (238.28): calcd C 65.55, H 7.56; found C 65.49, H 7.82.

1.2.5. 4,5-*O*-Cyclohexylidene-2,3-dideoxy-3-azido-aldehydo-D-glycero-pentanose (7). According to a previously reported procedure,[1j] conjugated aldehyde **4** (0.94 g, 4.80 mmol, 1.00 equiv.) in acetic acid (10 mL, 80%) was added to NaN_3 (0.71 g, 10.92 mmol, 2.30 equiv.) in acetic acid (35 mL, 80%). The mixture, stirred for 3 h at room temperature, was treated with H_2O (60 mL) and extracted with CH_2Cl_2 (3×45 mL). The combined extracts were washed with cooled aqueous saturated $NaHCO_3$ (160 mL) and H_2O (2×45 mL), dried over $MgSO_4$ and concentrated to give azido derivative **7** (1.14 g, colourless oil) in 99% yield as a mixture of two stereomers **7a** and **7b**; the ratio was determined by GC analysis and by ^1H NMR spectroscopy (**7a/7b**=60:40); $[\alpha]_D^{20}=-25.20$ (*c* 2.52, C_6H_6); ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.30–1.70$ (m, 10H, CH_2, **7a, 7b**), 2.50–2.80 (m, 2H, H^2, **7a**, **7b**), 3.72 (dd, $J=6.1$ and 8.4 Hz, 0.4H, H^5, **7b**), 3.80 (m, 1H, H^3, **7b**, H^5, **7a**), 3.85–4.01 (m, 1.8H, H^5, **7b**, H^3, **7a**, H^4, **7a**, H^5, **7a**), 4.14 (dd, $J=6.0$ and 12.0 Hz, 0.4H, H^4, **7b**), 9.80 (m, 1H, H^1, **7a**, **7b**); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$(**7a**, **7b**): 23.58, 23.80, 23.83, 24.90, 24.93, 34.30, 34.37, 35.78, 35.98, (**7a**): 44.98 C^2, 58.06 C^3, 65.95 C^5, 76.45 C^4, 110.68 $C^{acet.}$, 198.60 C^1, (**7b**): 44.03 C^2, 57.12 C^3, 65.46 C^5, 76.78 C^4, 110.72 $C^{acet.}$, 198.46 C^1; IR (KBr, neat): 3106, 3036, 2949, 2887, 2110, 1731, 1701, 1482, 1461, 1377, 1268, 1153, 1103 cm^{-1}; MS (EI, 70 eV); *m/z* (rel. int.): 239 (9) [M^+], 205 (4), 196 (12) [M^+-HN_3], 169 (3), 152 (20), 141 (31), 81 (100), 54 (17).

1.2.6. 4,5-*O*-Cyclohexylidene-2,3-dideoxy-3-azido-1,1-dimethoxy-D-glycero-pentanose (8). Under argon, a solution of $TiCl_4$ (1.34 mL of a 1 M solution in CH_2Cl_2, 1.34 mmol, 0.17 equiv.) was added dropwise to (4*R*)-3-azido-4,5-*O*-cyclohexylidene pentanal (**7**) (1.88 g, 7.87 mmol, 1.00 equiv.) in anhydrous CH_3OH (17 mL) cooled to 0°C. The mixture was stirred at 0°C for 1 h then at room temperature for 3 h. Et_3N (0.19 mL, 1.39 mmol, 0.18 equiv.) was added and the mixture was stirred at 0°C for 10 min before treatment with H_2O (60 mL). After extraction with CH_2Cl_2, the organic layer was washed with H_2O (60 mL) dried over $MgSO_4$. Evaporation has given an oil, which was purified by florisil column chromatography (pentane/Et_2O=80:20) to afford **8** (1.46 g) in 65% yield as a mixture of two stereomers **8a** and **8b** (**8a/8b**=60:40), the ratio was determined by GC analysis and by ^1H NMR spectroscopy. ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.30–1.70$ (m, 10H, CH_2, **8a**, **8b**), 1.50–1.70 (m, 0.8H, H^2, **8b**), 1.60 (m, 0.6H, H^2, **8a**), 1.88 (ddd, $J=3.4$, 7.8 and 14.3 Hz, 0.6H, H^2, **8a**), 3.30 (s, 1.2H, CH_3, **8b**), 3.35 (s, 1.2H, CH_3, **8b**), 3.38 (s, 1.8H, CH_3, **8a**), 3.40 (s, 1.8H, CH_3, **8a**), 3.40 (m, 0.4H, H^3, **8b**), 3.65 (m, 0.6H, H^3, **8a**), 3.72 (dd, $J=6.6$ and 8.0 Hz, 0.4H, H^5, **8b**), 3.82 (dd, $J=5.5$ and 7.7 Hz, 0.6H, H^5, **8a**), 4.00 (m, 0.4H, H^5, **8b**), 4.02 (m, 1.2H, $H^{4,5}$, **8a**), 4.08 (m, 0.4H, H^4, **8b**), 4.52 (dd, $J=4.9$ and 6.4 Hz, 0.4H, H^1, **8b**), 4.55 (dd, $J=3.8$ and 7.8 Hz, 0.6H, H^1, **8a**); IR (KBr, neat): 2971, 2929, 2859, 2101, 1443, 1381, 1348, 1124, 1073 cm^{-1}; MS (EI, 70 eV); *m/z* (rel. int.): 285 (8) [M^+], 242 (7) [M^+-HN_3], 222 (2), 199 (6), 156 (8), 141 (38), 127 (80), 113 (38), 75 (90), 55 (100). $C_{13}H_{23}O_4N_3$ (285.34): calcd C 54.74, H 8.07; found C 55.06, H 8.18.

1.3. AZT: 3′α-Azido-3′-deoxy-β-thymidine (1a)

Under argon, silylated thymine nucleobase **9** (0.23 g, 0.85 mmol, 1.40 equiv.)[7] was added to (4*R*)-3-azido-1,1-dimethoxy-4,5-*O*-cyclohexylidene pentane **8** (0.17 g, 0.60 mmol, 1.00 equiv.) in anhydrous CH_3CN (5 mL). A solution of trimethylsilyltriflate (0.14 mL, 0.63 mmol, 1.05 equiv.) in CH_3CN (0.5 mL) was added dropwise to the above mixture maintained at −30°C. The mixture was stirred for 2 h 30 min at −30°C, 2 h at −20°C then 36 h at room temperature before addition of CH_2Cl_2 (20 mL) and treatment by aqueous saturated $NaHCO_3$ until basic medium. The aqueous phase was extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated to give an oil containing the four diastereomers **1a–d** and the non cyclisated derivative (4*R*)-3-azido-1-methoxy-1-thyminyl-4,5-*O*-cyclohexylidene pentane **10** (**1a–d/10**=88:12; ratios were determined by ^1H NMR spectroscopy analysis). By silica gel column chromatography ($CHCl_3/CH_3OH$=95:5) we have succeeded to isolate and identify the pure AZT (**1a**) (0.060 g) as a white solid in 38% yield, the different diastereomers **1b–d** (**1b/1c/1d**=25:13:12, respectively, 0.040, 0.021 and 0.019 g) and the (4*R*)-3-azido-1-methoxy-1-thyminyl-4,5-*O*-cyclohexylidene pentane **10** (0.030 g) in 12% yield. The analytical data of **1a** were consistent with those published and with the ones obtained from a commercial available sample.

1.3.1. 3′α-Azido-3′-desoxy-α-thymidine (1b). White solid; mp 73–74°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.55$ (s, 1H, $H^{6'}$), 1.95 (d, $J=1.1$ Hz, 3H, CH_3), 2.16 (dt, $J=4.2$ and 14.7 Hz, 1H, $H^{2'\beta}$), 2.84 (ddd, $J=6.8$, 6.9 and 14.7 Hz, 1H, $H^{2'\alpha}$), 3.65 (dd, $J=3.4$ and 12.1 Hz, 1H, $H^{5'}$), 3.71 (m, 1H, $H^{4'}$), 3.85 (dd, $J=3.0$ and 12.1 Hz, 1H, $H^{5'}$), 4.20–4.30 (m, 1H, $H^{3'}$), 6.22 (dd, $J=4.2$ and 6.9 Hz, 1H, $H^{1'}$), 7.27 (d, $J=1.1$ Hz, 1H, H^6), 8.10–8.20 (s, 1H, H^3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=12.59$ CH_3, 38.15 $C^{2'}$, 60.60 $C^{3'}$, 62.55 $C^{5'}$, 85.92 $C^{4'}$, 85.74 $C^{1'}$, 110.99 C^5, 135.04 C^6, 150.12 C^4, 163.33 C^2; IR (KBr, neat): 3390, 3197, 3062, 1694, 1472, 1270, 1100 cm^{-1}; $C_{10}H_{13}O_4N_5$ (267.24 g): calcd C 44.94, H 4.87; found: C 44.88, H 5.05.

1.3.2. 3′β-Azido-3′-desoxy-β-thymidine (1c). Colourless oil; ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.50$ (s, 1H, $H^{6'}$), 1.90 (d, $J=0.8$ Hz, 3H, CH_3), 2.50 (dt, $J=6.5$ and 14.3 Hz, 1H, $H^{2'\beta}$), 2.67 (ddd, $J=2.3$, 6.5 and 14.3 Hz, 1H, $H^{2'\alpha}$), 3.88 (m, 2H, $H^{5'}$), 4.42 (m, 1H, $H^{3'}$), 4.47 (dt, $J=4.9$ and 10.6 Hz, 1H, $H^{4'}$), 6.04 (t, $J=6.5$ Hz, 1H, $H^{1'}$), 7.07 (d, $J=0.8$ Hz, 1H, H^6); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=12.59$ CH_3, 38.25 $C^{2'}$, 61.47 $C^{5'}$, 61.90 $C^{3'}$, 83.66 $C^{4'}$, 87.43 $C^{1'}$, 111.06 C^5, 135.11 C^6, 150.28 C^4, 163.59 C^2; IR (KBr, neat): 3400, 3100, 1694, 1652, 1470, 1270, 1056.

1.3.3. 3′β-Azido-3′-desoxy-α-thymidine (1d). Colourless oil; ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.60$ (s, 1H, $H^{6'}$), 1.95

(d, J=1.1 Hz, 3H, CH_3), 2.16 (m, 1H, $H^{2'\beta}$), 2.75 (ddd, J=6.8, 7.5 and 14.7 Hz, 1H, $H^{2'\alpha}$), 3.99 (m, 2H, $H^{5'}$), 4.10 (dt, J=4.9 and 9.8 Hz, 1H, $H^{4'}$), 4.32 (ddd, J=2.6, 4.2 and 6.8 Hz, 1H, $H^{3'}$), 6.17 (dd, J=4.1 and 7.5 Hz, 1H, $H^{1'}$), 7.53 (d, J=1.1 Hz, 1H, H^6); ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.62 CH_3, 38.37 $C^{2'}$, 60.86 $C^{3'}$, 61.15 $C^{5'}$, 85.81 $C^{4'}$, 85.87 $C^{1'}$, 111.06 C^5, 135.87 C^6, 150.29 C^4, 163.54 C^2; IR (KBr, neat): 3410, 3062, 1694, 1682, 1470, 1270, 1096.

1.3.4. (4*R*)-3-Azido-1-methoxy-1-thyminyl-4,5-*O*-cyclohexylidene pentane (10). R_f 0.53 ($CHCl_3$/MeOH=95:5); ^1H NMR (300 MHz, $CDCl_3$): δ=1.30–1.70 (m, 10H, CH_2), 1.75–2.00 (m, 2H, H^2), 1.94 (s, 3H, CH_3), 3.30 (s, 3H, OCH_3), 3.40 (m, 1H, H^3), 3.70–4.20 (m, 3H, $H^{4,5}$), 5.75 (m, 1H, H^1), 7.10 (d, J=5.3 Hz, 1H), 9.10 (s, 1H); IR (KBr, neat): 2936, 2106, 1694, 1466, 1448, 1364, 1258, 1092 cm^{-1}; $C_{17}H_{25}O_5N_5$ (379.41 g): calcd C 53.83, H 6.60; found: C 53.33, H 6.76.

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