First Synthesis of 4′-Acetamido-2′-deoxythymidine

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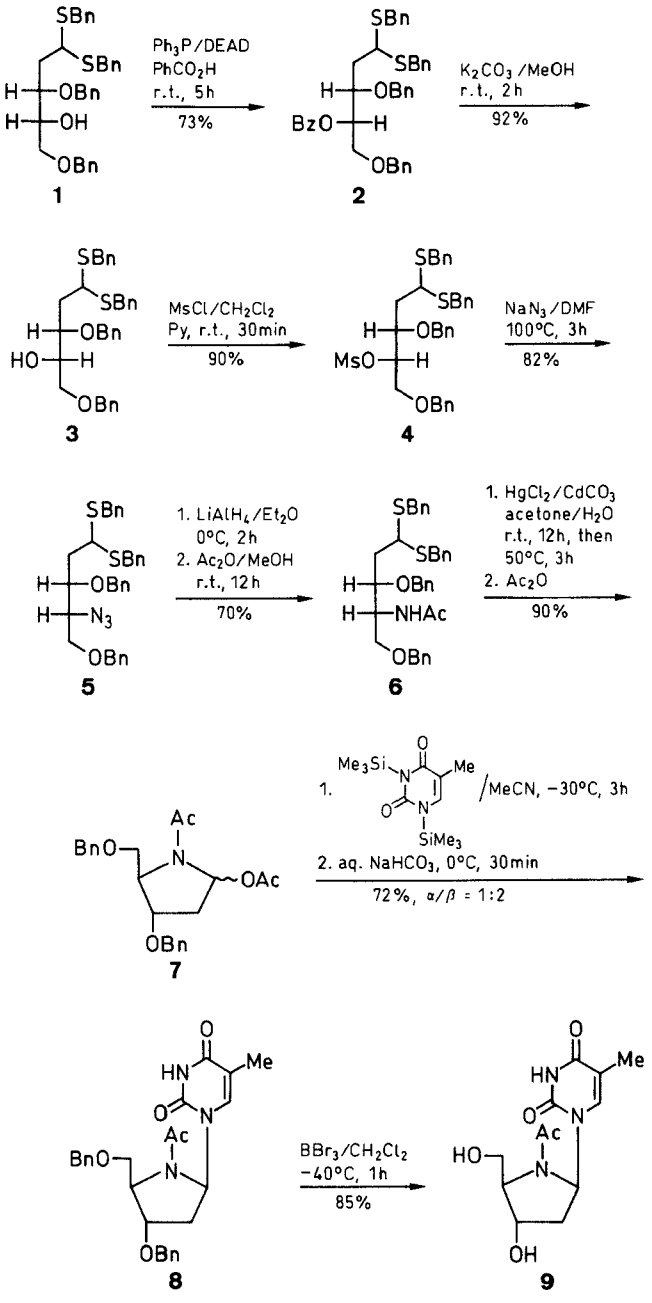
4′-Acetamido-2′-deoxythymidine was synthesized for the first time in 8 steps from 3,5-di-*O*-benzyl-2-deoxy-D-ribose dibenzyldithioacetal (**1**) derived from 2-deoxy-D-ribose.

Aminosugars, in which the pyranose or furanose ring oxygen is replaced by nitrogen, have a variety of biological activities. In most cases, these can probably be ascribed to their acting as glucosidase inhibitors.[1,2] Further studies suggested that aminosugars, which inhibited α-glucosidase I, might have anti-HIV activity. This may be attributed to the fact that the aminosugars interrupted the biosynthesis of oligosaccharides attached on the cell membrane.[3-5] All the above facts prompted us to investigate whether the 4′-aminonucleoside could also inhibit glucosidase just as aminosugar does and how it influences the biosynthesis of viral or host-cell DNA.

Previous attempts to form nucleosides containing a free-pyrrolidine sugar (4-amino-4-deoxyfuranose) have been unsuccessful due to the decomposition of the products immediately following deblocking of the amino function, presumably as a consequence of rapid elimination of the heterocyclic base, so only 4′-acetamido-4′-deoxyadenosine was synthesized.[6] Many years later, a carbon-linked nucleoside containing a 4-amino-4-deoxy-β-D-ribofuranosyl moiety was synthesized from L-lyxose in 10-steps.[7] In this paper, we wish to report the first synthesis of 4′-acetamido-2′-deoxythymidine.

During the course of our studies on the synthesis of 4′-thio-2′-deoxynucleosides,[8] we found the intermediate 3,5-di-*O*-benzyl-2-deoxy-D-ribose dibenzyldithioacetal (**1**) derived from 2-deoxy-D-ribose could be conveniently adopted for the synthesis of 4′-amino-2′-deoxynucleosides. The detailed procedure is given in the Scheme.



Scheme

The strategy of the above method is not similar to that used for the synthesis of 4′-thio-2′-deoxynucleosides.[8] In the latter case, the leaving group (I^-) at C-4 is replaced by 1-benzylthio group to form the cyclic product; however, a different approach is used in this system, including the introduction of a nucleophilic group at the 4-position and then attacking the 1-benzylthio group to form the desired product. To obtain the D-ribo-configuration product, compound **1** was first converted to the benzoyl derivative **2** with inverted configuration at C-4 by Mitsunobu method (yield, 73%).[9] Deprotection of **2** with potassium carbonate/methanol afforded **3** in 92% yield. For the introduction of an azido group at C-4, compound **3** was mesylated, and consequently treated with sodium azide in dimethylformamide to afford the key intermediate **5** in 82% yield. Catalytic reduction of the azido group in **5** was best accomplished with lithium aluminum hydride in diethyl ether at room temperature to afford the crude amine, which was then acylated with acetic anhydride in pyridine to yield **6**. Compound **6** was treated with mercury(II) chloride/cadmium carbonate in water/acetone. Under these conditions, cyclized product **7** was obtained in higher yield via intramolecular nucleophilic substitution. After acetylation, **7** was coupled with silylated thymine using trimethylsilyl triflate as catalyst to yield the 4′-acetamido-2′-deoxythymidine as the dibenzyl ether **8**. The ratio of α and β-anomer was 1:2 when acetonitrile was used as the solvent. The desired β-anomer was identified by 2D ^{1}H NMR spectroscopy and separated readily from the anomeric mixture by preparative TLC. The protective group of **8** was removed readily with boron tribromide in dichloromethane. Thus the first 4′-acetamido-2′-deoxynucleoside **9** was synthesized in 8 steps.

All (significant new) products were characterized by ^{1}H NMR, FAB-MS, IR and elemental analyses (C ± 0.35, H ± 0.23, N ± 21). The biological properties of the title compound has to be studied.

^{1}H NMR spectra were recorded on a Varian XL-200 (200 MHz) spectrometer using TMS as internal reference. FAB-MS spectra were obtained on a VG Quattro MS/MS spectrometer using samples dissolved in suitable solvent with 3-nitrobenzyl alcohol or thioglycerol as matrix. Precoated, plastic-supported silica gel TLC plates (F_{254}, 0.2 mm thickness) were supplied by E. Merck, Darmstadt. Detection was achieved under UV light (254 nm) or by spraying with 10% H_2SO_4 in MeOH and heating. Column chromatography was performed on silica gel H, 200–300 mesh, supplied by Qing Dao, China.

4-*O*-Benzoyl-3,5-di-*O*-benzyl-2-deoxy-L-lyxose Dibenzyldithioacetal (2):
To a solution of **1** (230 mg, 0.4 mmol) Ph_3P (210 mg, 0.8 mmol) and benzoic acid (98 mg, 0.8 mmol) in anhydr. THF (5 mL) was added dropwise diethyl azodicarboxylate (DEAD) (140 mg, 0.8 mmol) in anhydr. THF (1 mL). The mixture was stirred at r.t. for 5 h. After removal of the solvent, the residue was purified by chromatography; yield: 200 mg (73%).

^{1}H NMR ($CDCl_3$/TMS): δ = 2.05–2.10 (m, 2H), 3.45 (m, 2H), 3.70–3.85 (m, 8H), 4.20 (m, 1H), 4.50 (d, 1H, J = 4.6 Hz), 4.55 (s, 1H), 7.30–7.40 (m, 25H). FAB-MS: m/z = 649 (M^+ + 1), 181, 91.

3,5-Di-*O*-benzyl-2-deoxy-L-lyxose Dibenzyldithioacetal (3):
Compound **2** (4 g) was treated with K_2CO_3 (3 g) in absolute MeOH (250 mL). The mixture was stirred at r.t. overnight. After removal of the inorganic salt by filtration, the clean solution was evaporated and purified; yield: 3.1 g (92%).

^{1}H NMR ($CDCl_3$/TMS): δ = 2.05–2.10 (m, 2H), 2.40 (s, 1H), 3.46 (m, 2H), 3.73–3.90 (m, 8H), 4.20 (m, 1H), 4.40 (d, 1H, J = 5.1 Hz), 7.20–7.40 (m, 20H), 4.50 (t, 1H).

FAB-MS: m/z = 653 (M^+-matrix), 384, 279, 211.

4-Methanesulfonyl-3,5-di-*O*-benzyl-2-deoxy-L-lyxose Dibenzyldithioacetal (4):
To a solution of **3** (120 mg) in CH_2Cl_2 (5 mL) containing anhydr. pyridine (0.5 mL) was added dropwise methanesulfonyl chloride (1.5 mL). The mixture was stirred for 30 min at r.t. and then quenched by addition of MeOH (2 mL). The solvent was removed under reduced pressure and the product was purified by chromatography; yield: 123 mg (90%).

^{1}H NMR ($CDCl_3$/TMS): δ = 2.02–2.10 (m, 2H), 2.8 (s, 3H), 3.60 (m, 8H), 4.20 (m, 2H), 4.40 (s, 2H), 4.50 (d, 1H, J = 4.7 Hz), 7.10 (m, 20H).

FAB-MS: m/z = 623 (M^+ + 1), 578 (M^+ + 1 − OMs), 499 (M^+ − BnS).

4-Azido-3,5-di-*O*-benzyl-2-deoxy-D-ribose Dibenzyldithioacetal (5):
Compound **4** (1.99 g, 3.05 mmol) and NaN_3 (950 mg, 14.6 mmol) were dissolved in DMF (50 mL). The solution was stirred at 100 °C for 3 h. After removal of the solvent under reduced pressure, H_2O (75 mL) was added to the residue, and then extracted with Et_2O (3 × 100 mL). The organic layer was dried (Na_2SO_4), evaporated and purified by chromatography; yield: 1.42 g (82%); yellow syrup.

IR (film): ν = 2100 cm^{-1} (s, N≡N).

^{1}H NMR ($CDCl_3$/TMS): δ = 2.03–2.15 (m, 2H), 3.46 (m, 2H), 4.10 (m, 1H), 3.74–3.85 (m, 8H), 4.30 (d, 1H, J = 4.8 Hz), 4.45 (s, 1H), 7.2–7.4 (m, 20H).
EI-MS: m/z = 542 ($M^+ - N_2 + 1$), 434 ($M^+ - N_2$–OBn), 418 ($M^+ - N_2$–BnS).

4-Acetamido-3,5-di-*O*-benzyl-2-deoxy-D-ribose Dibenzyldithioacetal (6):
To an ice-cooled (0 °C) solution of **5** (800 mg, 1.41 mmol) in ahydr. Et_2O (50 mL) was added $LiAlH_4$ (72 mg, 1.86 mmol). After the mixture was stirred for 2 h, $Na_2SO_4 \cdot H_2O$ was introduced to stop the reaction. The inorganic salt was removed by filtration and the clean solution was evaporated to afford the crude residue, which was then dissolved in MeOH(20 mL) and Ac_2O (2 mL). The mixture was stirred overnight. After removal of the solvent, the residue was purified by chromatography to obtain the pure product in 70% yield: 576 mg (70%).

IR (KBr): ν = 3260 (NH), 1650 cm^{-1} (C=O).

^{1}H NMR (acetone-d_6): δ = 1.82 (s, 3H), 2.03–2.10 (m, 2H), 3.46 (m, 2H), 3.74–3.85 (m, 8H), 4.16 (m, 1H), 4.40 (d, 1H, J = 4.4 Hz), 7.27 (m, 20H).
EI-MS: m/z = 585 (M^+), 494 (M^+ − Bn).

1-*O*-Acetyl-4-acetamido-3,5-di-*O*-benzyl-2-deoxy-D-ribose (7):
To a solution of **6** (100 mg, 0.17 mmol) in acetone (15 mL) and H_2O (7 mL) was added $CdCO_3$ (186 mg, 1.08 mmol) and $HgCl_2$ (186 mg, 0.69 mmol). The mixture was stirred at r.t. overnight, then kept at 50 °C for 3 h. After removal of the inorganic solid, the filtrate was evaporated to yield the crude product, which was then dissolved in anhydr. pyridine (5 mL) and acetic anhydride (2 mL). The solution was stirred overnight, then poured into ice-water (20 mL), and extracted with $CHCl_3$ (3 × 10 mL). The organic layer was dried, evaporated, and purified by chromatography; yield: 61 mg (90%).

^{1}H NMR ($CDCl_3$/TMS): δ = 1.80 (s, 3H, $COCH_3$), 2.02–2.08 (m, 2H, H-2), 2.10 (s, 3H, $OCOCH_3$), 3.45 (m, 2H, H-5), 3.70–3.8 (m, 4H, CH_2Ph), 4.04–4.5 (m, 2H, H-3,4), 6.30 (d, 1H, J = 6.4 Hz, H-1), 7.2–7.3 (m, 10 H_{arom}).
FAB-MS: m/z = 397 (M = + 1), 41 (M^+ + Na).

4′-Acetamido-3′,5′-di-*O*-benzyl-2′-deoxythymidine (8):
A mixture of thymine (126 mg) and $(NH_4)_2SO_4$ (50 mg) in hexamethyldisilazane (5 mL) was refluxed at 120 °C for 5 h. The solvent was removed under reduced pressure to yield a residue, which was dissolved in MeCN (5 mL) at −30 °C and the aminosugar **7** (220 mg) was added. The mixture was stirred for 3 h at this temperature. Solid $NaHCO_3$ (0.5 g) was introduced and the mixture was warmed to 0 °C and stirred for 30 min. The mixture was filtered and the filtrate was evaporated. The product was purified by chromatography; yield: 184 mg (72%); β-anomer: 61 mg and α-anomer: 123 mg.

^{1}H NMR ($CDCl_3$/TMS): δ = 1.85 (s, 3H), 2.10 (s, 3H), 2.2–2.5 (m, 2H), 3.65 (m, 2H), 3.8 (m, 2H), 4.50 (s, 4H), 6.45 (t, 1H, J = 3.4 Hz, 5.8 Hz), 7.3–7.5 (m, 10H), 8.05 (s, 1H).
FAB-MS (m/z) = 464 (M^+ + 1), 91.

4′-Acetamido-2′-deoxythymidine (9):
To a cooled (−40 °C) solution of compound **10** (231 mg, 0.5 mmol) in anhydr. CH_2Cl_2 (10 mL) was added dropwise BBr_3 (0.8 mL). The mixture was stirred for 1 h, and then excess solid $NaHCO_3$ was added and the mixture was warmed to 0 °C and stirred for 30 min. After filtration, the clean solution was evaporated and purified by chromatography to obtain the product; yield: 120 mg (85%).

^{1}H NMR (D_2O): δ = 1.83 (s, 3H), 2.05 (s, 3H), 2.25–2.60 (m, 2H), 3.70 (m, 1H), 3.75 (m, 2H), 4.50 (m, 1H), 6.45 (t, 1H, J = 4.0 Hz, 5.6 Hz), 8.15 (s, 1H).
FAB-MS: m/z = 284 (M^+ + 1), 240 (M^+ − OAc), 43.

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