Synthesis and Antiviral Study of Acyclic Analogs of 3′-Azido, 3′-Amino, and 3′-Fluoro-3′-deoxythymidine, and of HEPT analogs

Minh-Chau Trinh,[a] Jean-Claude Florent,*[a] David S. Grierson,*[b] Claude Monneret[a]

[a] Institut Curie, Section de Biologie, URA au CNRS 1387, 26 rue d'Ulm, F-75231 Paris Cédex 05, France
[b] Institut de Chimie des Substances Naturelles, CNRS, F-91198 Gif-sur-Yvette, France

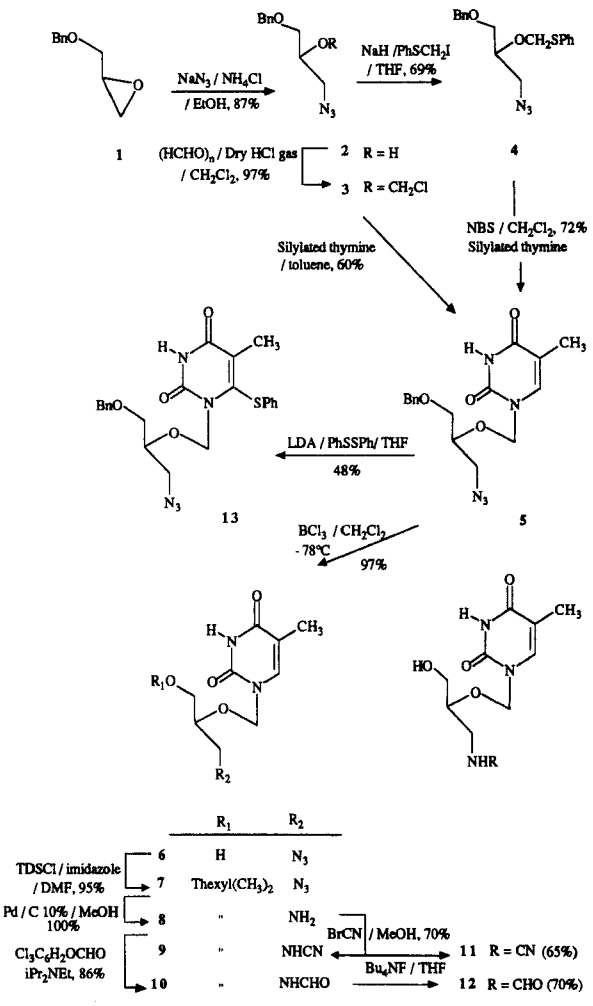
Received 3 January 1994; revised 28 March 1994

Several new acyclonucleosides have been synthesized from racemic epichlorhydrin or epifluorhydrin. This involves epoxide opening followed by chain elongation with iodomethyl phenyl sulfide and subsequent coupling of the phenylthioacetal with thymine. Deprotection afforded the title compounds **6**, **8** and **18**, whereas introduction of a phenylthio group at C-6 led to the three HEPT analogs, **13**, **19**, and **24**.

There is a continuing need for compounds that are effective in the treatment of the acquired immune deficiency syndrome (AIDS) that are superior to 3′-azido-3′-deoxythymidine (AZT)[1] or to 2′,3′-dideoxyinosine (DDI).[2] Despite the efficancy of these drugs, their prolonged use by AIDS victims is seriously limited by a number of problems, including suppression of bone-marrow cell formation (AZT)[3], peripheral neuropathy[4], and pancreatitis[5,6] (DDI). Furthermore, their short in vivo half-time in the body necessitates repeated administration[7] of large doses to maintain therapeutically effective levels. These considerations, amongst others, underline the urgency to develop new and selective antiretroviral agents.

In another area, an important advance for the treatment of Herpes infections was made by the discovery of the acyclonucleosides 9-(2-hydroethoxymethyl)guanine (acyclovir)[8] and 9-{[2-hydroxy-1-(hydroxymethyl)ethoxy]-methyl]guanine (DHPG).[9] Like AZT, the triphosphate forms of these nucleoside analogs lack the 3′-OH of deoxyribose. Thus upon incorporation into the growing DNA strand they also interupt DNA synthesis through chain termination. In view of this common mechanism of action, the synthesis of acyclonucleoside analogs related to AZT appeared highly attractive in the search for new anti-HIV drugs. Therefore, in 1989, we initiated a program to prepare different acyclic analogs of AZT and other 2′,3′-dideoxynucleosides. In a brief preliminary communication[10] the preparation of 2′,3′-seco-2′-nor-AZT **(6)** and the corresponding amine derivatives **11** and **12** from epichlorohydrin, was described. In the present report, we present the full experimental details of the synthesis of these thymine acyclonucleosides, and the results on a related synthesis of compounds **13, 19** and **24** which contain the 6-thiophenyl substituent present in the potent anti-HIV agent 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT).[11,12]

To access AZT analog **6**, 1-benzyloxypropylene oxide **1**[13,14] prepared from (±)-epichlorohydrin[15] was reacted with NaN_3 in refluxing ethanol containing NH_4Cl. The derived azide **2** was then converted into chloromethyl ether **3** through reaction with paraformaldehyde and dry HCl in 1,2-dichloroethane (84% overall yield). Subsequent condensation of **3** with bistrimethylsilylthymine gave the intermediate acyclonucleoside **5** in 60% yield after chromatography. Treatment of **5** with BCl_3 in THF at −78 °C afforded **6** in almost quantitative yield. Intermediate **5** was also used to prepare the 6-phenylthio derivative **13** by C-6 deprotonation (LDA) and reaction of the derived anion with PhSSPh.



Scheme 1

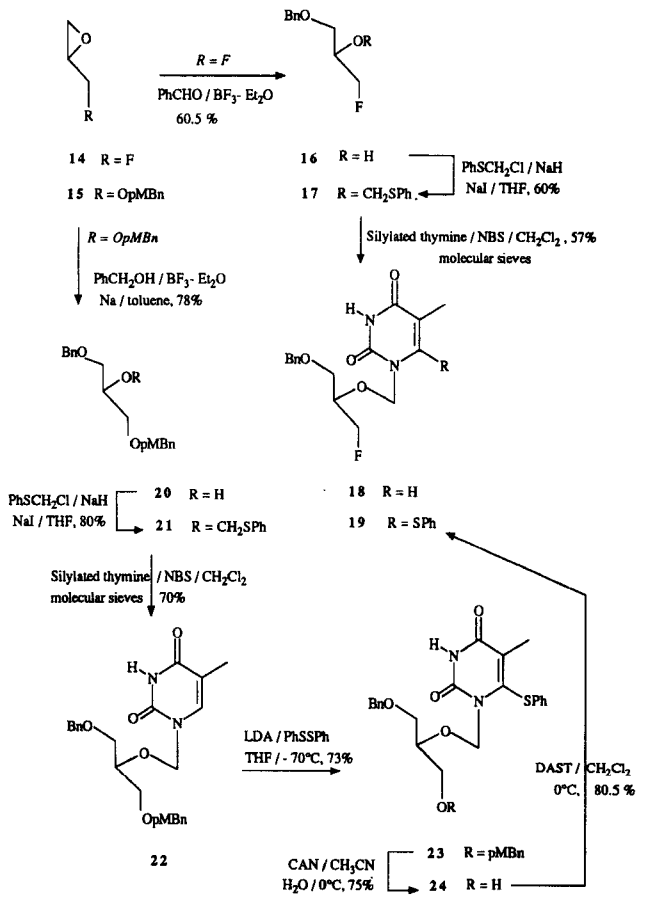
Although chloromethylation of **2** was efficient on a small scale, mediocre yields were often obtained[16] in large scale experiments. This led us to consider using an *O,S*-acetal as an alternative substrate for coupling to the pyrimidine base. Thus the sodium alkoxide of **2** was treated with iodomethyl phenyl sulfide,[17] formed in situ from commercial chloromethyl phenyl sulfide and NaI in anhydrous THF. The resultant phenylthioacetal **4** was then activated through treatment with NBS[18] and reacted with bistrimethylsilylthymine. Under these conditions compound **5** was obtained in 50% overall yield.

To prepare acyclonucleosides **11** and **12** in which the azido group is replaced by a cyanamido and formamido substituent, respectively, intermediate **5** was first converted into its 5′-*O*-dimethylthexylsilyl derivative **7** in order

to conserve solubility in common organic solvents. Catalytic hydrogenation of **7** then gave **8** in quantitative yield. Treatment of **8** with cyanogen bromide in MeOH containing NaOAc produced cyanamide **9** in 70% yield, whereas reaction with 2,4,5-trichlorophenyl formate in DMF containing ethyldiisopropylamine provided formamide **10**. Removal of the 5'-OH protecting group to give crystalline analogs **11** (65%) and **12** (75%) was then effected under standard tetrabutylammonium fluoride conditions.

Synthesis of the HEPT analogs **19** via a related route from commercial epifluorohydrin **14** involved ring opening to give the benzyloxy intermediate **16** (61%) followed by *S,O*-acetal formation (60%). Reaction of phenyl sulfide **17** with NBS and bistrimethylsilylthymine then gave the acyclonucleoside analog **18** (57%). Introduction of the SPh group at C-6 of this product was again achieved by sequential treatment with LDA and PhSSPh to afford **19**, although in rather low yield (20%).

The construction of the HEPT analog **24** was similarly initiated by opening of the *p*-methoxybenzyl (OpMBn) protected epoxide **15**, derived from epichlorohydrin with benzyl alcohol in the presence of $BF_3 \cdot Et_2O$ (78%). Conversion of **20** into the *S,O*-acetal **21** and coupling with the silylated thymine base was again followed by lithiation and introduction of the thiophenyl substituent at C-6 of **22** (40% overall for the three steps) to give **23**. Final selective OpMBn deprotection of **23** with ceric ammonium nitrate (CAN)[19] yielded compound **24** as a colourless solid (mp 135°C) after column purification



Scheme 2

(75%). Subsequent reaction of this derivative with diethylaminosulfur trifluoride (DAST) in THF at room temperature provided an alternate more efficient route to the fluoro analog **19** (80.5%).

Nucleoside analogs **6, 8, 13, 14, 19–21**, and **26** were tested for activity against the strain LAV of HIV-1 in CEM cells. The products were compared for their cytotoxicity and inhibitory effects on HIV induced cytopathogenicity. Assays were performed in the range of 0.05 to 100 μM. However no significant activity was observed compared to AZT (2 μM) used as reference. It would appear from the results for the HEPT analogs that the presence of the branching chain at C-3' abolishes activity in this series.

Melting points were determined using a Reichert Thermovar apparatus and are uncorrected. Microanalysis were performed by the Laboratoire de Microanalyse du CNRS, Lyon. Compounds **3–9, 12, 13, 23** and **24** gave C, H, N analysis ± 0.35%, **16–19, 21** and **22** gave C, H ± 0.41%. IR spectra were determined on a Perkin-Elmer Model 1710 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian EM-3930 (90 MHz) and a Bruker HX300 apparatus (300 MHz), using TMS as an internal standard. Mass spectra were recorded on a Nermag R10-10C (DCI/NH_3) spectrometer. Optical rotations were measured at 20°C on a Perkin-Elmer Model 241 polarimeter. Flash chromatography was performed on Merck silica gel 60 (Art. 9385).

(*R,S*)-1-Azido-3-benzyloxy-2-propanol (2):
To a refluxing solution of 1-benzyloxypropylene oxide (prepared from racemic epichlorhydrin **1** as reported[15]) (1.64 g, 10 mmol) in EtOH (100 mL), NaN_3 (2 g, 30 mmol) and NH_4Cl (0.7 g, 13.2 mmol) were added. After 2 h, the mixture was concentrated under reduced pressure and the residue was extracted with usual workup. Evaporation of the organic layer led to a residue which was purified by flash chromatography (hexane/acetone, 4:1) affording 1.8 g (87%) of **2** as a colorless syrup. IR and NMR spectra were identical with those reported in the literature.[14]

(*R,S*)-(1-Azido-3-benzyloxy-2-propoxy)methyl Chloride (3):
To a cooled (0°C) solution of **2** (20.7 g, 0.1 mol) in CH_2Cl_2 (100 mL), paraformaldehyde (7 g, 0.23 mol) was added and dry HCl gas was bubbled through for 2 h. The mixture was removed from the ice-bath and purged with N_2 to remove excess HCl and evaporated under reduced pressure. This yielded 24.7 g (97%) of **3** pure enough for the next step. A sample (syrup) was purified by flash chromatography (hexane/acetone, 5:1).

MS (DCI/NH_3): m/z = 273 $(M + NH_4)^+$, 256 $(M + H)^+$.

IR (film): ν = 2100 cm^{-1} (azide).

^{1}H NMR (90 MHz, $CDCl_3$): δ = 7.28 (m, 5H, Bn), 5.50 (s, 2H, CH_2Cl), 4.50 (s, 2H, CH_2Ph), 4.00 (m, 1H, CH), 3.60 (dd, 2H, $J = J'$ = 4 Hz, CH_2OBn), 3.44 (m, 2H, CH_2N_3).

(*R,S*)-(1-Azido-3-benzyloxy-2-propoxy)methyl Phenyl Sulfide (4):
NaH (80% in oil) (41.5 mg, 1.38 mmol) was added to a cooled solution (0°C) of **2** (238 mg, 1.15 mmol) in anhydr. THF (10 mL). After stirring for 0.5 h, NaI (259 mg, 1.73 mmol) and chloromethyl phenyl sulfide (275 mg, 1.74 mmol) in anhydr. THF (15 mL) were added. The mixture was stirred overnight at r.t., poured into water (50 mL) and concentrated under reduced pressure at 40°C to remove the THF. Then, extraction with EtOAc (3 × 50 mL) in the usual manner, followed by flash chromatography (cyclohexane/EtOAc, 5:1) afforded **4** (260 mg, 69%) as a syrup.

MS (DCI/NH_3): m/z = 347 $(M + NH_4)^+$, 329 $(M + H)^+$.

^{1}H NMR (90 MHz, $CDCl_3$): δ = 7.40 (m, 10H, Ph), 5.10 (s, 2H, OCH_2S), 4.00 (m, 1H, CH), 3.55 (d, 2H, J = 5 Hz, CH_2OBn), 3.40 (d, 2H, J = 5 Hz, CH_2N_3).

(*R,S*)-1-[(1-Azido-3-benzyloxy-2-propoxy)methyl]thymine (5):

(a) From **3**:

A suspension of dry thymine (600 mg, 4.8 mmol) in hexamethyldisilazane (10 mL) and dry pyridine (5 mL) was refluxed in the absence of moisture under argon for 2 h. The mixture was concentrated to dryness in vacuo and coevaporated with dry toluene (2 × 10 mL). A solution of **3** (1 g) in toluene (10 mL) was added to this residue. The reaction mixture was stirred overnight at r.t., and then under reflux for 24 h. It was subsequently poured into cold sat. aq $NaHCO_3$ and extracted with EtOAc (3 × 100 mL) in the usual manner. The crude product (1 g) was purified by flash chromatography (hexane/acetone, 3:1), furnishing 800 mg (60% yield, based on **3**) of colorless crystals of **5**; mp 68 °C (hexane).

MS (DCI/NH_3): m/z = 363 $(M + NH_4)^+$, 346 $(M + H)^+$.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 9.70 (s, 1 H, NH), 7.10 (s, 1 H, H-6), 5.32 and 5.20 (AB syst., J = 10 Hz, OCH_2N), 4.45 (s, 2 H, CH_2Ph), 4.00 (m, 1 H, CH), 3.50 (d, 2 H, J = 5 Hz, CH_2OBn), 3.33 (d, 2 H, J = 5 Hz, CH_2N_3), 1.90 (s, 1 H, CH_3-5).

(b) From **4**:

To a solution of **4** (300 mg, 0.91 mmol) and bis(trimethylsilyl)thymine (2 mmol) in dry CH_2Cl_2 (10 mL) under argon, pulverized 4 Å molecular sieves (400 mg) was added. After 10 min, *N*-bromosuccinimide (178 mg, 1 mmol) was also added. The reaction mixture was stirred at r.t. for an additional 0.5 h before quenching by addition of sat. aq sodium thiosulfate. Extraction with CH_2Cl_2 (3 × 75 mL) afforded, after usual workup, a residue which was chromatographed (silica gel; cyclohexane/EtOAc, 4:1) giving 230 mg (72% based on **4**) of **5**.

(*R,S*)-1-[(1-Azido-3-hydroxy-2-propoxy)methyl]thymine (6):

(a) From **5**:

To a solution of **5** (3.45 g, 10 mmol) in CH_2Cl_2 (50 mL) at −78 °C under Ar, was added a 1 M solution of BCl_3 in CH_2Cl_2 (40 mL, 4 mol equiv). After stirring for 5 h at −60 °C, MeOH (20 mL) was added and the reaction mixture was neutralized with 10% aq $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash chromatography (hexane/acetone, 1:1) to give 2.47 g (97%) of **6** which crystallized from hexane/EtOAc; mp 108–110 °C.

MS (DCI/NH_3) m/z = 273 $(M + NH_4)^+$, 256 $(M + H)^+$.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 9.55 (s, 1 H, NH), 7.17 (s, 1 H, H-6), 5.33 and 5.26 (AB syst., J = 10 Hz, OCH_2N), 3.88 (m, 1 H, H-4′), 3.67 (s, 2 H, H-5′), 3.44 and 3.33 (AB syst., J = 10 Hz, H-1′), 1.93 (s, 3 H, Me-5).

(b) From **9**:

Compound **9** (1 g, 2.5 mmol) in THF (50 mL) was treated at r.t. by addition of a 1 M solution of Bu_4NF in THF (7.5 mL, 7.5 mmol). After being stirred for 3 h, the reaction mixture was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/acetone, 1:1) to give 0.57 g (89%) of **6** as white crystals.

(*R,S*)-1-[(1-Azido-3-dimethylthexylsiloxy-2-propoxy)methyl]thymine (7):

To a solution of **6** (450 mg, 1.76 mmol) in DMF (5 mL) thexyldimethylsilyl chloride (350 mg, 1.95 mmol) and imidazole (240 mg, 3.52 mmol) were added. After stirring overnight at r.t. under argon, extraction with Et_2O and usual workup led to **7** (665 mg, 95% yield) which crystallized from hexane/acetone; mp 118–120 °C.

MS (DCI/NH_3): m/z = 415 $(M + NH_4)^+$, 398 $(M + H)^+$.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 9.37 (m, 1 H, NH), 7.10 (s, 1 H, H-6), 5.30 and 5.05 (AB syst., J = 6 Hz, OCH_2N), 3.75 (m, 1 H, CH), 3.55 (d, 2 H, J = 5 Hz, CH_2O), 3.25 (d, 2 H, J = 5 Hz, CH_2N_3), 1.85 (s, 3 H, CH_3-5), 1.50 (m, 1 H, CH), 0.78 (m, 12 H, 4 × CH_3), 0.00 (s, 6 H, 2 × CH_3).

(*R,S*)-1-[(1-Amino-3-dimethylthexylsiloxy-2-propoxy)methyl]thymine (8):

A solution of **7** (500 mg) in MeOH (20 mL) was stirred for 12 h under hydrogen atmosphere (1 atm) at r.t. in the presence of 10% palladium-on-charcoal as catalyst. Filtration and coevaporation of the methanolic solution afforded 480 mg (100%) of pure **8** which crystallized from hexane/acetone; mp 222–224 °C.

MS (DCI/NH_3): m/z = 372 $(M + H)^+$.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.20 (s, 1 H, H-6), 5.30 and 5.10 (AB syst., J = 10 Hz, OCH_2N), 3.75 (m, 1 H, CH), 3.75 (m, 2 H, CH_2OSi), 3.30 (m, 2 H, CH_2NH_2), 1.95 (s, 3 H, CH_3), 1.70 (m, 1 H, CH), 0.77 (m, 12 H, 4 × CH_3), 0.00 (s, 6 H, 2 × CH_3).

(*R,S*)-1-[(1-Cyanoamino-3-dimethylthexylsiloxy-2-propoxy)methyl]thymine (9):

Cyanogen bromide (16 mg, 0.15 mmol) in MeOH (2 mL) was added to **8** (50 mg, 0.13 mmol) dissolved in MeOH (8 mL). The solution was stirred overnight at r.t. and then evaporated under reduced pressure. This afforded a residue which was purified by flash chromatography (hexane/acetone, 5:1) giving 37.5 mg (70% yield) of pure **9** as crystals; mp 125 °C.

IR (Nujol): ν = 2220 (CN), 3370 cm^{-1} (NH).

MS (DCI/NH_3): m/z = 414 $(M + NH_4)^+$, 397 $(M + H)^+$.

^{1}H NMR (270 MHz, CD_3OD): δ = 9.28 (s, 1 H, NH), 7.10 (s, 1 H, H-6), 5.30 and 5.10 (AB syst., J = 10 Hz, OCH_2N), 4.62 (t, 1 H, NHCN), 3.82 (m, 1 H, H-2′), 3.65 (d, 2 H, J = 6 Hz, CH_2O), 3.20 (m, 2 H, CH_2NHCN), 1.95 (s, 3 H, CH_3), 1.70 (m, 1 H, CH), 0.80 (m, 12 H, 4 × CH_3), 0.00 (s, 6 H, 2 × CH_3).

(*R,S*)-1-[(3-Dimethylthexylsiloxy-1-formylamino-2-propoxy)methyl]thymine (10):

To a cooled solution (0–5 °C) of **8** (200 mg, 5.4 mmol) in DMF (5 mL) were added ethyldiisopropylamine (0.1 mL) and 2,4,5-trichlorophenyl formate (140 mg, 0.6 mmol). The mixture was stirred overnight at r.t. diluted with water (ca. 20 mL), extracted with EtOAc, washed with 5% aq citric acid and water, affording, after evaporation of the organic layer under reduced pressure, a residue (200 mg). Purification by flash chromatography (hexane/acetone, 2:1) gave 185 mg (86% yield) of **10** as a syrup.

IR (film): ν = 3250 (NH), 2720 (CHO), 1675 cm^{-1} (CO).

MS (DCI/NH_3): m/z = 418 $(M + NH_4)^+$, 400 $(M + H)^+$.

^{1}H NMR (270 MHz, CD_3OD): δ = 8.00 (s, 1 H, CHO), 7.40 (s, 1 H, H-6), 5.30 and 5.10 (AB syst., J = 10 Hz, OCH_2N), 3.80 (m, 1 H, CH), 3.60 (m, 2 H, CH_2O), 3.25 (m, 2 H, CH_2NH), 1.90 (s, 3 H, CH_3), 1.65 (m, 1 H, CH), 0.90 (m, 12 H, 4 × CH_3), 0.00 (s, 6 H, 2 × CH_3).

(*R,S*)-1-[(1-Cyanoamino-3-hydroxy-2-propoxy)methyl]thymine (11):

A molar solution of tetrabutylammonium fluoride (2 mL) was added to a solution of **9** (260 mg, 0.65 mmol) in anhydr. THF (10 mL). After stirring for 1 h, evaporation under reduced pressure and flash chromatography (CH_2Cl_2/methanol, 90:10), **11** was obtained (84 mg, 65%) as a crystalline compound; mp 115–117 °C (methanol).

IR (Nujol): ν = 2220 (CN), 3370 cm^{-1} (NH).

MS (DCI/NH_3): m/z = 272 $(M + NH_4)^+$, 255 $(M + H)^+$.

^{1}H NMR (270 MHz, CD_3OD): δ = 7.50 (s, 1 H, H-6), 5.30 and 5.10 (AB syst., J = 10 Hz, CH_2OH), 3.10 (m, 1 H, CH), 1.90 (s, 3 H, CH_3).

(*R,S*)-1-[(1-Formylamino-3-hydroxy-2-propoxy)methyl]thymine (12):

This compound was obtained in 70% yield from **10** according to the same procedure as for **11** and isolated as a crystalline compound from hexane/acetone: mp 108–110 °C.

IR (Nujol): ν = 3250 (NH), 2720 (CHO), 1675 cm^{-1} (CO).

MS (DCI/NH_3): m/z = 275 $(M + NH_4)^+$, 258 $(M + H)^+$.

^{1}H NMR (270 MHz, CD_3OD): δ = 8.10 (s, 1 H, CHO), 7.40 (s, 1 H, H-6), 5.30 and 5.10 (AB syst., J = 10 Hz, OCH_2N), 3.70 (m, 1 H, CH), 3.50 (m, 2 H, CH_2OH), 3.25 (m, 2 H, CH_2NH), 1.90 (s, 3 H, CH_3).

(*R,S*)-1-[(3-Azido-1-benzyloxy-2-propoxy)methyl]-6-(thiophenyl)thymine (13):
To a cooled (−70 °C) solution of LDA (2 mmol) in THF (5 mL) was added azidonucleoside **5** (280 mg, 0.7 mmol) in THF (15 mL) under nitrogen. After stirring for 0.5 h, diphenyl disulfide (308 mg, 1.4 mmol) dissolved in THF (5 mL) was added and the temperature was maintained below −70 °C with stirring for 45 min. The mixture was then allowed to reach r.t. before addition of sat. aq NH_4Cl (10 mL) and concentration in vacuo. The residue was extracted with EtOAc (3 × 30 mL), which was washed with aq $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated to dryness under reduced pressure. Purification by flash chromatography (hexane/EtOAc, 4:1 then 3:1) afforded **13** (168 mg, 48%) as a colorless syrup.

MS (DCI/NH_3): m/z = 523 $(M + NH_4)^+$, 506 $(M + H)^+$.

^1H NMR (100 MHz, $CDCl_3$): δ = 9.5 (s, 1H, NH), 7.10 (m, 5H, Ph), 5.50 (s, 2H, OCH_2N), 3.70 (m, 1H, CH), 3.50 (m, 2H, CH_2O), 3.30 (dd, 1H, J = 12, 3) and 3.15 (dd, J = 12, 6) (ABX syst., CH_2N_3), 2.00 (s, 3H, Me-5), 1.50 (m, 1H, CH), 0.80, 0.75 and 0.70 (3 s, 12H, 4 × CH_3), 0.00 (s, 6H, 2 × CH_3).

(*R,S*)-1-Benzyloxy-3-fluoro-2-propanol (16):
To a cooled solution of racemic epifluorohydrin **14** (5.32 g, 70 mmol) in anhydr. benzyl alcohol (18 mL, 174 mmol), $BF_3 \cdot Et_2O$ (8 mL, 8 mmol, 1 M in Et_2O) was added. Stirring was maintained for 2 h at 0 °C, and then the reaction mixture was allowed to reach r.t. and stirred overnight. After dilution with EtOAc (100 mL), the organic layer was washed with sat. aq $NaHCO_3$ (50 mL) and dried (Na_2SO_4). Evaporation under reduced pressure and flash chromatography (hexane/EtOAc, 3:1) led to pure **16** (7.81 g, 60.5%) as a colorless syrup.

IR (Nujol): ν = 3424 cm^{-1} (OH).

MS (DCI/NH_3): m/z = 202 $(M + NH_4)^+$.

^1H NMR (90 MHz, $CDCl_3$): δ = 7.35 (s, 5H, Ph), 4.75 and 4.20 (AB syst., J = 4.5 Hz, CH_2F), 4.57 (s, 2H, CH_2Ph), 4.00 (m, 1H, H-2), 3.58 (m, 2H, H-1), 2.40 (bs, 12H, OH).

(*R,S*)-1-Benzyloxy-3-fluoro-2-(phenylthiomethoxy)propane (17):
Compound **16** (481 mg, 2.61 mmol) in THF (10 mL) was added to a solution of NaH (60%, 130 mg, 3.25 mmol) in THF (15 mL) previously cooled in an ice-bath and under argon. After 1 h, NaI (500 mg, 3.33 mmol) in THF (5 mL) and chloromethyl phenyl sulfide (500 mg, 3.15 mmol) in THF (20 mL) were added and the mixture was allowed to reach r.t. with stirring overnight. Dilution with water (50 mL) and evaporation under reduced pressure to remove the THF were followed by extraction with EtOAc (3 × 50 mL), drying ($MgSO_4$) and concentration. Flash chromatography of the residue (cyclohexane/EtOAc, 9:1 then 5:1) afforded 480 mg (60%) of **17** as a pale yellow syrup.

MS (DCI/NH_3): m/z = 324 $(M + NH_4)^+$, 307 $(M + H)^+$.

^1H NMR (90 MHz, $CDCl_3$): δ = 7.50–7.35 (m, 10H, Ph), 5.10 (s, 2H, OCH_2S), 4.70 and 4.30 (AB syst., J = 4.5 Hz, CH_2F), 4.50 (s, 2H, CH_2Ph), 4.10 (m, 1H, H-2), 3.60 (m, 2H, CH_2O).

(*R,S*)-1-[(1-Benzyloxy-3-fluoro-2-propoxy)methylthymine (18):
Thymine (214 mg, 2 mmol) was suspended in a mixture of hexamethyldisilazane (HMDS, 5 mL) and pyridine (2 mL). The mixture was refluxed overnight and the resulting clear solution was concentrated under reduced pressure, and then in high vacuum. The residue was dissolved with stirring in dry CH_2Cl_2 (10 mL) along with the thiophenylmethyl ether **17** (280 mg, 0.91 mmol) and in the presence of 4 Å powdered molecular sieves. After 10 min, *N*-bromosuccinimide was added (178 mg, 1 mmol) and the reaction mixture was stirred for an additional 0.5 h. Sat. aq $NaHSO_3$ (10 mL) was added and the solution was filtered. The filtrate was diluted with CH_2Cl_2 and the organic layer was treated in the usual manner. Flash chromatography (hexane/EtOAc, 6:1, then 3:1) gave 167 mg (57%) of acyclonucleoside **18**.

MS (DCI/NH_3): m/z = 340 $(M + NH_4)^+$, 323 $(M + H)^+$.

^1H NMR (90 MHz, $CDCl_3$): δ = 9.15 (bs, NH), 7.20 (s, 5H, Ph), 7.10 (m, 1H, H-6), 5.20 (s, 2H, OCH_2N), 4.70 and 4.20 (AB syst., J = 4.5 Hz, CH_2F), 4.50 (s, 2H, CH_2Ph), 4.00 (m, 1H, CH), 3.50 (d, 2H, CH_2O), 1.90 (s, 3H, CH_3-5).

(*R,S*)-1-[(1-Benzyloxy-3-fluoro-2-propoxy)methyl]-6-(phenylthio)-thymine (19):
To a cooled (0 °C) solution of **24** (43 mg, 0.1 mmol) in anhydr. CH_2Cl_2 (5 mL), DAST (0.3 mL, 0.37 mmol) was added. The mixture was stirred overnight at r.t., poured into 10% aq $NaHCO_3$ and extracted with CH_2Cl_2. The organic extract was washed with 10% aq HCl, water, and then with brine. After drying ($MgSO_4$), the solvent was evaporated in vacuo and the residue was purified by flash chromatography (cyclohexane/EtOAc, 2:1), giving 33 mg (80.5%) of **19**.

MS (DCI/NH_3): m/z = 448 $(M + NH_4)^+$, 431 $(M + H)^+$.

^1H NMR (90 MHz, $CDCl_3$): δ = 9.60 (bs, 1H, NH), 7.30–7.10 (s, 5H, Ph), 7.10 (m, 10H, Ph), 5.70 (s, 2H, OCH_2N), 4.70 (m, 1H, CH), 4.50 (s, 2H, CH_2Ph), 4.30–4.00 (m, 2H, CH_2F), 3.80 (s, 3H, OCH_3), 3.60–3.40 (m, 4H, CH_2O).

(*R,S*)-1-Benzyloxy-3-(*p*-methoxybenzyloxy)-2-propanol (20):
Na (35 mg, 1.52 mmol) was added to a mixture of benzyl alcohol (156 mg, 1.45 mmol) and anhydr. toluene (8 mL). The resulting solution was heated under reflux for 2 h, added to a solution of **15** (200 mg, 1.03 mmol) in toluene (5 mL) and heated for an additional 2 h. After cooling to r.t. and neutralization by dropwise addition of aq 1 N HCl, evaporation followed by flash chromatography (hexane/acetone, 3:1) gave **20** (243 mg, 78%) as a colorless syrup.

IR: ν = 3604 (OH), 1613 cm^{-1} (Ar).

MS (DCI/NH_3): m/z = 320 $(M + NH_4)^+$.

^1H NMR (90 MHz, $CDCl_3$): δ = 7.4 (s, 5H, Ph), 7.30 (d, 2H) and 6.90 (d, 2H) (AB syst., Ph), 4.60 (s, 2H, CH_2Ar), 4.50 (s, 2H, CH_2Ph), 4.00 (m, 1H, CH), 3.80 (s, 3H, CH_3), 3.70–3.40 (m, 4H, $2CH_2$).

(*R,S*)-1-Benzyloxy-3-(*p*-methoxybenzyloxy)-2-phenylthiomethoxypropane (21):
Compound **21** was synthesized using the same method as previously described for the preparation of **4**. Alkylation of **20** (300 mg) using NaH (35 mg) and iodomethyl phenyl sulfide (159 mg) yielded 349 mg (80%) of **21** as a syrup.

MS (DCI/NH_3): m/z = 442 $(M + NH_4)^+$.

^1H NMR (90 MHz, $CDCl_3$): δ = 7.60–7.10 (m, 12H, bs, Ph), 6.70 (d, 5H, Ph), 5.13 (s, 2H, OCH_2S), 4.46 (s, 2H, OCH_2Ph), 4.40 (s, 2H, OCH_2Ph), 4.18 (m, 1H, CH), 3.76 (s, 3H, OCH_3), 3.76–3.53 (m, 4H, $2CH_2$).

(*R,S*)-1-[(1-Benzyloxy-3-(*p*-methoxybenzyloxy)-2-propoxy)methyl]-thymine (22):
This compound was synthesized using the same method as described for the preparation of **5** from **4** (compound **21**, 240 mg, 0.56 mmol; silylated thymine, 214 mg, 1.7 mmol; CH_2Cl_2, 10 mL; molecular sieves 4 A, 400 mg; NBS, 110 mg, 0.62 mmol). This afforded 175 mg (70%) of **22** after flash chromatography.

MS (DCI/NH_3): m/z = 458 $(M + NH_4)^+$.

^1H NMR (90 MHz, $CDCl_3$): δ = 7.20 (s, 5H, Ph), 7.13 and 6.76 (AB syst., J = 7.5 Hz, PhOMe), 5.20 (s, 2H, OCH_2N), 4.43 (s, 2H, OCH_2Ph), 4.36 (s, 2H, OCH_2Ph), 3.93 (m, 1H, CH), 3.70 (s, 3H, OCH_3), 3.56–3.43 (m, 4H, $2CH_2$), 1.76 (s, 3H, CH_3-5).

(*R,S*)-1-{[1-Benzyloxy-3-(*p*-methoxybenzyloxy)-2-propoxy]methyl}-6-(phenylthio)thymine (23):
To a cooled (−70 °C) solution of LDA (3.6 mmol) in THF (10 mL) was added **22** (440 mg, 1 mmol) in THF (15 mL) under nitrogen. After stirring for 0.5 h, diphenyl disulfide (784 mg, 3.6 mmol) dissolved in THF (10 mL) was added and the temperature was maintained below −70 °C with stirring for 45 min. The mixture was then allowed to reach r.t. before addition of sat. aq NH_4Cl (10 mL) and concentration in vacuo. The residue was extracted with EtOAc, which was washed with aq $NaHCO_3$ (20 mL) and brine (20 mL) to afford, after concentration to dryness under reduced pressure, a residue which was purified by flash chromatography (hexane/EtOAc, 4:1 then 3:1), to give **23** (400 mg, 73%) as a colorless syrup.

^{1}H NMR (90 MHz, $CDCl_3$): δ = 9.33 (bs, 1 H, NH), 7.26 (s, 5 H, Ph), 7.16 and 6.80 (AB, syst., J = 7.5 Hz, PhOMe), 5.66 (s, 2 H, OCH_2N), 4.46 (s, 2 H, OCH_2Ph), 4.40 (s, 2 H, OCH_2Ph), 4.10 (m, 1 H, CH), 3.76 (s, 3 H, OCH_3), 3.53–3.40 (m, 4 H, $2CH_2$), 1.86 (s, 3 H, CH_3-5).

(*R*,*S*)-1-[(1-benzyloxy-3-hydroxy-2-propoxy)methyl]-6-(phenylthio)-thymine (24):

CAN (177 mg, 0.32 mmol) was added to a cooled (0–5 °C) solution of **23** (155 mg, 0.28 mmol) in $MeCN/H_2O$ (10 mL, 4:1). After being stirred for 10 min at 0 °C and for 30 min at r.t., the reaction mixture was extracted with EtOAc in the usual manner and the residue was purified by flash chromatography (cyclohexane/EtOAc, 1:3), giving 90 mg (75%) of **24** as a colorless crystalline compound, mp 135 °C.

MS (DCI/NH_3): m/z = 446 $(M + NH_4)^+$, 429 $(M + H)^+$.

^{1}H NMR (90 MHz, $CDCl_3$): δ = 9.90 (bs, 2 H, OH and NH), 7.30 (s, 10 H, Ph), 5.76 and 5.56 (AB syst. J = 10 Hz, OCH_2N), 4.50 (s, 2 H, OCH_2Ph), 3.90 (m, 1 H, CH), 3.53–3.40 (m, 4 H, $2CH_2$), 2.03 (s, 3 H, CH_3-5).

These investigations were supported by grants from the ANRS.

(1) Horwitz, J.P.; Chua, J.; Noel, M. *J. Org. Chem.* **1964**, *29*, 2076.
(2) Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 1911.
(3) Richman, D.D.; Fischl, M.A.; Grieco, M.H.; Gottlieb, M.S.; Volberding, P.A.; Laskin, O.L.; Leedom, J.M.; Groopman, J.E.; Mildvan, D.; Hirsch, M.S.; Jackson, G.G.; Durack, T.T.; Lehrman, S.N.; and the AZT collaborative group, *N. Engl. J. Med.* **1987**, *317*, 192.
(4) Yarchoan, R.; Pluda, J.M.; Thomas, R.V.; Mitsuya, H.; Brouwers, P.; Wyvill, K.M.; Hartman, N.; Johns, D.G.; Broder, S. *Lancet* **1990**, *336*, 526.
(5) Lambert, J.S.; Seidlin, M.; Reichman, R.C.; Planck, C.S.; Laverty, M.; Morse, G.D.; Pharm, D.; Knupp, C.; McLaren, C.; Pettinelli, C.; Valentine, F.T.; Dolin, R. *N. Engl. J. Med.* **1990**, *322*, 1333.
(6) Cooley, T.P.; Kunches, L.M.; Saunders, C.A.; Ritter, J.K.; Perkins, C.J.; McLaren, C.; Path, M.R.C.; McCaffery, R.P.; Liebman, H.A. *N. Engl. J. Med.* **1990**, *322*, 1340.
(7) Klecker, R.W.; Collins, J.M.; Yarchoan, R.; Thomas, R.; Jenkins, J.F.; Broder, S.; Myers, C.E. *Clin. Pharmacol. Ther.* **1987**, *41*, 407.
(8) Schaeffer, H.J.; Beauchamp, L.; de Miranda, P.; Elion, G.; Bauer, D.J.; Collins, J.M. *Nature (London)* **1978**, *272*, 583.
(9) Martin, J.C.; Dvorak, C.A.; Smee, D.F.; Matthews, T.R.; Verheyden, J.P.H. *J. Med. Chem.* **1983**, *26*, 759.
(10) Trinh, M.C.; Florent, J.-P.; Grierson, D.S.; Monneret, C. *Tetrahedron Lett.* **1991**, *32*, 1447.
(11) Miyasaka, T.; Tanaka, H.; Baba, M.; Hayakawa, H.; Walker, R.T.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1989**, *32*, 2507.
(12) Tanaka, H.; Takashima, H.H.; Ubasawa, M.; Sekiya, K.; Nitta, I.; Baba, M.; Ghigeta, S.; Walker, R.T.; De Clercq, E.; Miyasaka, T. *J. Med. Chem.* **1992**, *35*, 4713, and references cited therein.
(13) Abushanab, E.; Sarma, M.S.P. *Synthesis* **1983**, 116.
(14) Lee, K.H.; Chen, Y.-L.; Huang, B.R.; Tzeng, C.C. *Nucleosides, Nucleotides* **1991**, 930.
(15) Bacon, J.R.; Collis, M.J., *Chem. Ind. (London)* **1971**, 930.
(16) Zakernia, M.; Davary, H.; Hakimelahi, G.H. *Helv. Chim. Acta* **1990**, *73*, 912.
(17) Matteucci, *Tetrahedron Lett.* **1990**, *31*, 2385.
(18) Sugimura, H. *Tetrahedron Lett.* **1991**, *32*, 1813; *Ibid.* **1992**, *33*, 2515.
(19) Corey, E.J.; Bock, M.G. *Tetrahedron Lett.* **1975**, 3269.