Nucleoside Analogues. Synthesis of 2',3'-Dideoxy and 2',3'-Unsaturated Ribofuranonucleosides of 5,6-Dichloro-2-mercaptobenzimidazole as Potential Antiviral Agents

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Novel benzimidazole nucleoside derivatives structurally related to 5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole (DRB) and to tetrahydroimidazobenzodiazepinethione (TIBO) compounds have been synthesized and their antiviral properties examined. The 2',3'-unsaturated nucleoside was obtained following chemical transformations of the corresponding β-D-ribofuranonucleoside, whereas the 2',3'-dideoxynucleoside was synthesized by a glycosylation reaction between a suitably protected 2,3-dideoxy-D-*glycero*-pentofuranose and silylated 5,6-dichloro-2-mercaptobenzimidazole. The prepared compounds were tested for their activity against HIV and against a variety of RNA and DNA viruses, but they did not show significant antiviral activity.

The finding that many 2',3'-dideoxynucleosides and their unsaturated derivatives show potent activity against human immunodeficiency virus (HIV)[1] has led to an increase in research in the field of this class of nucleoside analogues.[2] Today, three of these compounds, namely 3'-azido-3'-deoxythymidine (AZT),[3] 2',3'-dideoxycytidine (ddC)[4] and 2',3'-dideoxyinosine (ddI, Fig. 1)[4] have been approved for the treatment of acquired immune deficiency syndrome (AIDS). Some others, such as 2',3'-didehydro-3'-deoxythymidine (d4T, Fig. 1),[5,6] are in the late stages of clinical trials.[7,8] All these nucleoside derivatives, after cytoplasmic phosphorylation to their 5'-triphosphates, interact more or less selectively with HIV reverse transcriptase (RT) and, following their incorporation, terminate viral DNA synthesis because they lack a hydroxy group at the C'-3 position. In addition, their 5'-triphosphates, or even the terminated viral DNA chain, may act as a competitive inhibitor of HIV RT.[9,10]

On the other hand, during the past few years, several non-nucleoside RT inhibitors have been discovered.[11,12] The first reported compound of this type was a tetrahydroimidazobenzodiazepinethione (TIBO, Fig. 1).[13] Chemical modification of this prototype compound has shown that introduction of a chlorine substituent at the 8-position (R86183, Fig. 1) or at the 9-position (R82913, Fig. 1) caused a significant increase in activity.[14-16] In contrast with the above mentioned nucleoside analogues, which are equally active against HIV-1 and HIV-2 after intracellular triphosphorylation, the TIBO compounds are direct and selective inhibitors of HIV-1 RT. Their mechanism of action was found to be noncompetitive inhibition with respect to deoxynucleoside triphosphates, and uncompetitive inhibition with respect to a primer/template of HIV-1 RT.[17] However that may be, we were intrigued by a partial structural similarity between the chloro-TIBO derivatives and 5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole (commonly known as DRB, Fig. 1), a nucleoside analogue which has received much attention as a potential chemotherapeutic agent.[18] It is noteworthy that DRB has been reported to block Tat-dependent HIV RNA modification,[19] and to inhibit the multiplication of several RNA and DNA viruses in cell culture systems.[18,20]

As part of our ongoing research in the benzimidazole nucleoside field, we recently prepared the 2-mercapto derivative of DRB (**3**, Scheme 1).[21] It was therefore of interest to synthesize and to evaluate the corresponding hitherto unknown 2',3'-dideoxynucleoside (**1**, Fig. 1) and its 2',3'-unsaturated derivative (**2**, Fig. 1).

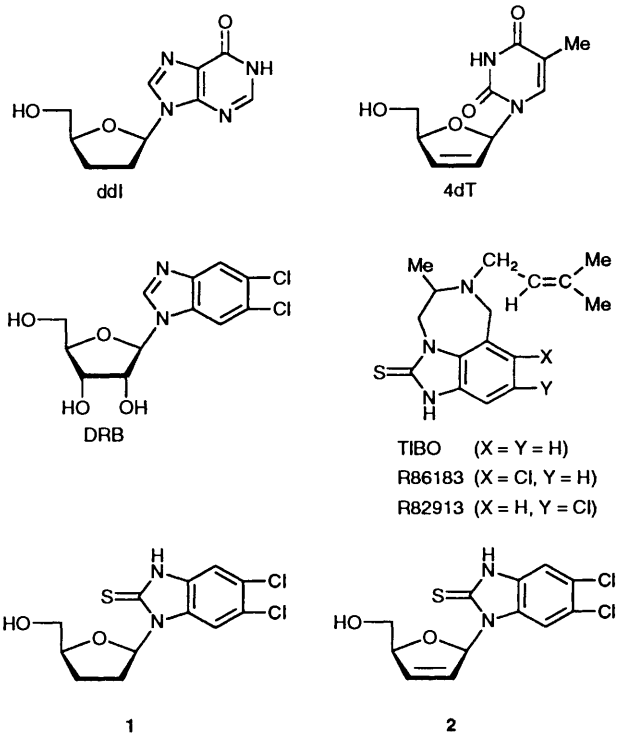
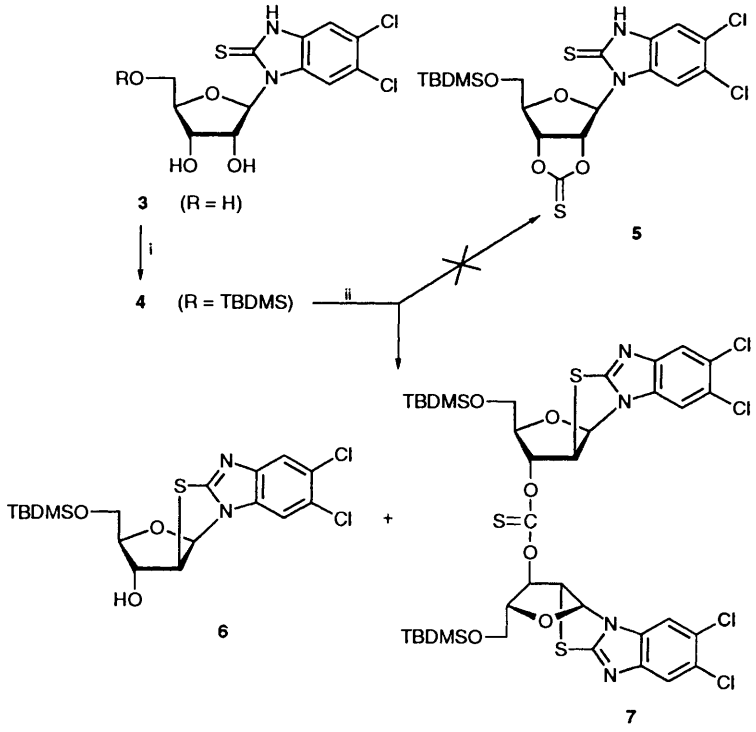


Fig. 1 Some current, and potential, drugs for the treatment of AIDS

Results and Discussion

Among the variety of reported chemical syntheses of 2',3'-dideoxy and 2',3'-unsaturated nucleosides starting from the corresponding ribofuranonucleosides,[2,22] we opted for those involving a cyclic 2',3'-thionocarbonate as a common intermediate. Such thionocarbonates, which are usually readily obtained by reaction of 5'-*O*-protected ribonucleosides with thiocarbonyldiimidazole, have been transformed under mild conditions into the corresponding 2',3'-unsaturated nucleosides by the Corey–Winter[23] reaction using a trialkyl phosphite or 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine.[24-32] The thionocarbonate nucleosides have also been transformed in several steps into the corresponding 2',3'-dideoxy nucleosides[27,33-37] by Barton deoxygenation.[38,39]



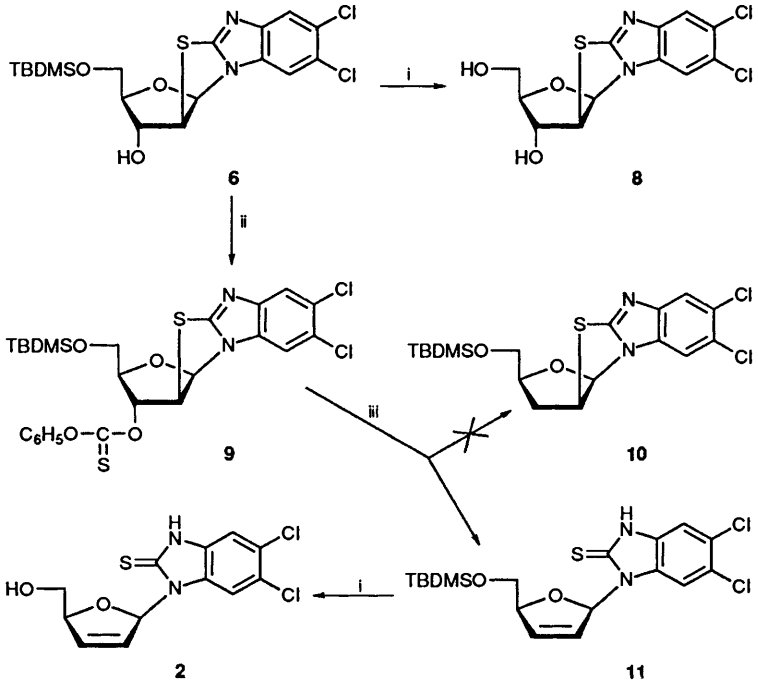
Scheme 1 *Reagents and conditions:* i, TBDMSCl, C_5H_5N; ii, 1,1'-thiocarbonyldiimidazole, MeCN–DMF

In order to prepare the key 2',3'-thionocarbonate intermediate **5**, the parent β-D-ribofuranonucleoside **3** was converted into the corresponding 5'-*O*-(*tert*-butyldimethylsilyl) derivative **4**, which was isolated as a crystalline solid in 84% yield (Scheme 1). The latter compound was then allowed to react with 1,1'-thiocarbonyldiimidazole in an acetonitrile–dimethylformamide (DMF) mixture, and the disappearance of the starting nucleoside **4** was followed by TLC. However, this reaction did not result in the formation of the expected thionocarbonate **5**. Two other products, **6** and **7**, were formed and isolated in pure form after silica gel column chromatography in 16 and 66% yield, respectively. The structures of the 2,2'-*S*-anhydronucleosides **6** and **7** were confirmed by their spectroscopic data and elemental analyses, and all attempts to obtain **5** by modifying the experimental conditions were unsuccessful.

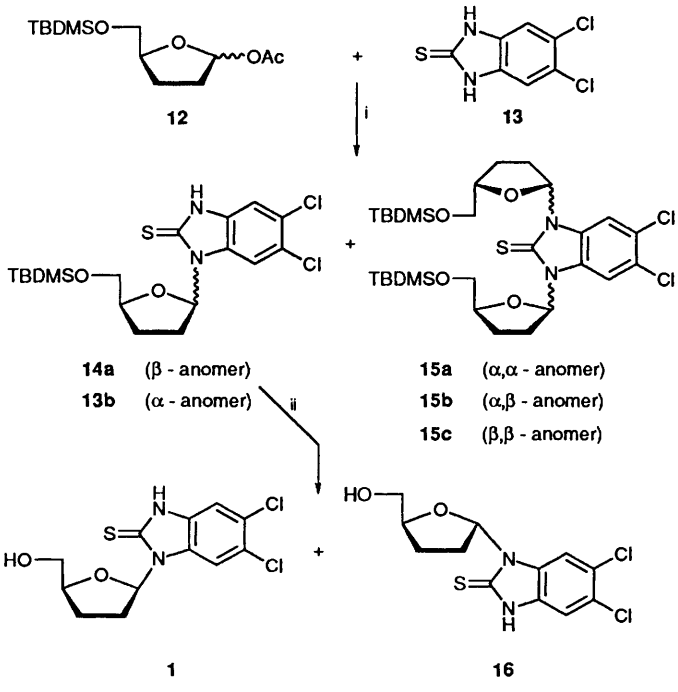
It is worth noting that 8,2'-*S*-anhydropurine and 2,2'-*S*-anhydropyrimidine nucleosides are important analogues and key intermediates in the synthesis of many biologically active derivatives of natural nucleosides. They have been prepared[40,41] by several procedures *via* the corresponding activated nucleosides, such as sulfonyl or carbonyl derivatives, but most of these methods are tedious. In our case, the propensity of diol **4** easily to form 2,2'-*S*-anhydro derivatives does not seem related to the nature of the 5'-silyl protecting group, but rather to the strong nucleophilicity of the sulfur atom at the 2-position of 5,6-dichlorobenzimidazole. Formation of 2,2'-anhydronucleosides as side-products has recently been reported during the attempted conversion of 5'-*O*-tritylated or -silylated 5-chlorouridines into 2',3'-*O*-thiocarbonyl derivatives.[30]

Desilylation of compound **6** was readily effected by treatment with 1.2 mol equiv. of tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) at room temperature for 12 h, and the unprotected 2,2'-*S*-anhydronucleoside **8** was thereby obtained as a crystalline solid in 89% yield after silica gel column chromatography (Scheme 2). On the other hand, compound **6** reacted with *O*-phenyl chloro(thio)formate and 4-(dimethylamino)pyridine (DMAP) in 1,2-dichloroethane,[42,43] to give the corresponding 3'-*O*-[phenoxy(thiocarbonyl)] derivative **9**. Deoxygenation of compound **9** with tributyltin hydride in dry toluene in the presence of 2,2'-azoisobutyronitrile (AIBN) did not afford the expected compound **10**, but instead gave the 5'-*O*-silylated 2',3'-didehydro-2',3'-dideoxynucleoside **11** in virtually quantitative yield. Structural assignment for compound **11** was based on elemental analysis and its physical properties. The formation of the double bond was clear from the ^1H NMR spectrum which showed characteristic signals at δ 6.56 and 6.35 corresponding to the olefinic protons. It is worth noting that when the symmetrical dimer **7** was treated with Bu_3SnH and AIBN under similar experimental conditions, the same unsaturated anhydronucleoside **11** and the 3'-hydroxylated nucleoside **6** were isolated in a pure state after silica gel column chromatography in 42 and 44% yield, respectively. Desilylation of compound **11** with TBAF in THF gave the desired 2',3'-didehydro-2',3'-dideoxynucleoside **2**.

Instead of attempting to reduce the 2',3'-double bond of compound **2**, we undertook an alternative synthesis of the dideoxynucleoside **1** involving glycosylation of 5,6-dichloro-2-mercaptobenzimidazole **13**[21] (Scheme 3) with 2,3-dideoxy-D-*glycero*-pentofuranose derivative **12**.[44] Reaction of the sugar **12** and the *in situ*-silylated base **13**, in acetonitrile in the presence of trimethylsilyl triflate (TMSTf) gave an inseparable mixture of β and α 1-*N*-isomers **14a** and **14b** in the ratio 2:3 (^1H NMR) in moderate yield (34%), as well as an anomeric mixture of the *N*,*N*-bis-furanoside **15** as a side-product (7%). Desilylation of compounds **14** with TBAF in THF and separation of the product mixture by silica gel column chromatography afforded the desired β-D-nucleoside **1** and the more polar α-anomer **16**. In accord with their structures, the ^1H NMR spectra of products **1** and **16** showed differences in the chemical shifts of the 1', 4' and 5' hydrogens. In particular, the chemical shift of the 4'-hydrogen of the β-anomer (δ 4.08) is ~ 0.4 ppm upfield from that of the α-isomer (δ 4.46) because of the deshielding effect of the heterocyclic base. Further confirmation of these assignments came from NOE experiments.[45]



Scheme 2 *Reagents and conditions:* i, Bu_4NF, THF; ii, DMAP, PhOC(=S)Cl, CH_2ClCH_2Cl; iii, Bu_3SnH, AIBN, toluene



Scheme 3 *Reagents and conditions:* i, BSA, TMSTf, MeCN; ii, Bu_4NF, THF

Biological Evaluation.—The unprotected nucleosides **1**, **2**, **8** and **16** were tested for their *in vitro* inhibitory effects on the replication of a number of DNA viruses (*i.e.*, human cytomegalovirus, herpes simplex virus type 1 and type 2, vaccinia virus) and RNA viruses (parainfluenza virus type III, respiratory syncytial virus, Sindbis virus, Coxsackie virus B3 and polio virus-1) in three cell systems (MRC-5, Vero and KB cells). None of these compounds showed marked antiviral effects or detectable alteration of host-cell morphology at the highest concentration tested (generally 10^{-1} or 10^{-2} mmol dm^{-3}). When evaluated in two anti-HIV assays, none of the tested compounds showed marked antiviral effect at a concentration less than 10-fold lower than the minimal concentration causing a detectable alteration of MT-4 and CEM host-cell viability.

Conclusions.—From the present work, and from our previous data on aglycone **13** and nucleoside **3** which were found to be devoid of antiviral activity,[21] it is obvious that 5,6-dichloro-2-mercaptobenzimidazole derivatives do not induce inhibition of HIV replication. If one assumes that these compounds are able to enter cells, their inactivity, and similar negative results reported for other substituted 2-mercaptobenzimidazoles,[46] indicate that an intact diazepine ring appears necessary for inhibition of HIV-1 RT by TIBO analogues. Several factors could be responsible for the inactivity of the unsaturated and dideoxy nucleosides **1** and **2**. Their inability to enter cells or to serve as substrates for intracellular enzymes catalysing triphosphorylation, as well as a lack of inhibition of viral RT by their triphosphate forms, would all account for their inactivity against HIV. Further research would be needed to test these hypotheses, but since no significant antiviral activity emerged from the present data, it does not seem worthwhile to pursue additional studies of the 5,6-dichloro-2-mercaptobenzimidazole derivatives.

Experimental

Evaporation of solvents was carried out on a rotary evaporator under reduced pressure. M.p.s were determined in open capillary tubes on a Gallenkamp MFB-595-010 M apparatus and are uncorrected. UV spectra were recorded on an Uvikon 810 (KONTRON) spectrophotometer. ^1H NMR spectra were run at ambient temperature in $(CD_3)_2SO$ with a Bruker AC 250 spectrometer. Chemical shifts are given in δ-values, $(CD_3)(CD_2H)SO$ being set at δ_H 2.49 as a reference. Deuterium exchange and decoupling experiments were performed in order to confirm proton assignments. All J values are in Hz. FAB mass spectra were recorded in the positive-ion or negative-ion mode on a JEOL DX 300 mass spectrometer operating with a JMA-DA 5000 mass data system. Xe atoms were used for the gun at 3 kV with a total discharge current of 20 mA. The matrix was 3-nitrobenzyl alcohol (NBA) or a mixture (50:50, v/v) of glycerol and thioglycerol (G-T). Only the nominal mass of ions

corresponding to the mass of the lightest chlorine isotope is given. However, the chlorine isotope peak intensity patterns were ascertained; they agreed with the formula of the ions. Specific rotations were measured on a Perkin-Elmer Model 241 spectropolarimeter (path length 1 cm), and are given in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were carried out by the Service de Microanalyses du CNRS, Division de Vernaison (France). TLC was performed on precoated aluminium sheets of Silica Gel 60 F_{254} (Merck, Art. 5554), visualization of products being accomplished by UV absorbance followed by charring with 10% ethanolic sulfuric acid and heating. Column chromatography was carried out on Silica Gel 60 (Merck, Art. 9385).

1-[5′-O-(tert-*Butyldimethylsilyl*)-β-D-*ribofuranosyl*]-5,6-*dichloro*-2-*mercaptobenzimidazole* **4**.—*tert*-Butyldimethylsilyl chloride (TBDMSCl; 0.42 g, 2.79 mmol) was added to a solution of 5,6-dichloro-2-mercapto-1-(β-D-ribofuranosyl)-benzimidazole **3**[21] (0.93 g, 2.65 mmol) in anhydrous pyridine (5.30 cm^3). The resultant solution was stirred at room temperature for 12 h. After removal of solvent under reduced pressure, the residue was dissolved in chloroform (150 cm^3), and the organic phase was washed with water (60 cm^3), dried over anhydrous sodium sulfate, and evaporated to dryness. Chromatography of the residue on a silica gel column with a stepwise gradient of methanol (0–10%) in dichloromethane afforded the *title compound* **4** (1.04 g, 84%), which was crystallized from acetonitrile, m.p. 194–196 °C (Found: C, 45.9; H, 5.5; Cl, 14.9; N, 6.1; S, 6.3; Si, 6.0. $C_{18}H_{26}Cl_2N_2O_4SSi{\cdot}1/3H_2O$ requires C, 45.85; H, 5.70; Cl, 15.04; N, 5.94; S, 6.80; Si, 5.96%); $[\alpha]_D^{20}$ −30.3 (*c* 1.0, Me_2SO); λ_{max} (95% EtOH)/nm 324 (ε 28 100), 254 (17 000) and 232 (14 200); λ_{min}/nm 282 (ε 1400) and 240 (10 200); δ_H 13.2 (1 H, br s, 3-H), 7.67 and 7.39 (1 H each, 2 s, 4- and 7-H), 6.41 (1 H, d, $J_{1',2'}$ 7.5, 1′-H), 5.28 (1 H, d, *J* 6.3, 2′-OH), 5.21 (1 H, d, *J* 4.6, 3′-OH), 4.36 (1 H, m, 2′-H), 4.07 (1 H, m, 3′-H), 3.89 (3 H, m, 4′-H and 5′-H_2), 0.90 (9 H, s, CMe_3) and 0.11 (6 H, s, $SiMe_2$); *m*/*z* (FAB > 0, G-T) 465 $(M + H)^+$ and 219 $(BH_2)^+$; *m*/*z* (FAB < 0, G-T) 463 $(M - H)^-$.

5-O-(tert-*Butyldimethylsilyl*)-6′,7′-*dichloro*-1,2-*dideoxy*-2′,3′-*dihydro*-β-D-*arabinofuranoso*[2,1-b](*thiazolo*[2,3-a]*benzimidazole*) **6** *and* 3,3-O-*Thiocarbonylbis*{5-O-(tert-*butyldimethylsilyl*)-6′,7′-*dichloro*-1,2-*dideoxy*-2′,3′-*dihydro*-β-D-*arabinofuranoso*[2,1-b](*thiazolo*[2,3-a]*benzimidazole*)} **7**.—1,1′-Thiocarbonyldiimidazole (0.59 g, 3.31 mmol) was added to a stirred solution of the nucleoside **4** (0.96 g, 2.06 mmol) in an acetonitrile–DMF mixture (4:1; 15 cm^3) at 0 °C under N_2, and the mixture was stirred for 15 min at 0 °C and 4 h at room temperature. The resulting suspension was evaporated under reduced pressure. Column chromatography of the residue on silica gel with as eluent a stepwise gradient of methanol (0–2%) in dichloromethane afforded successively the *title compounds* **7** and **6**.

Compound **6** (0.15 g, 16%), m.p. 154–156 °C (from cyclohexane) (Found: C, 48.3; H, 5.35; Cl, 15.5; S, 7.4; Si, 6.2. $C_{18}H_{24}Cl_2N_2O_3SSi$ requires C, 48.31; H, 5.41; Cl, 15.85; S, 7.17; Si, 6.28%); $[\alpha]_D^{20}$ −247.1 (*c* 1.0, Me_2SO); λ_{max} (95% EtOH)/nm 306 (ε 14 500), 296 (12 700), 263 (9800) and 256 (10 100); λ_{min}/nm 302 (ε 11 500), 272 (2600), 260 (8900) and 243 (6800); δ_H 7.75 and 7.74 (1 H each, 2 s, 4′- and 7′-H), 6.64 (1 H, d, $J_{1,2}$ 6.7, 1-H), 5.96 (1 H, br s, 3-OH), 4.83 (1 H, dd, *J* 3.4 and 6.7, 2-H), 4.38 (1 H, m, 3-H), 4.19 (1 H, m, 4-H), 3.61 (1 H, dd, *J* 4.2 and 11.4, 5-H), 3.46 (1 H, dd, *J* 5.6 and 11.4, 5-H′), 0.63 (9 H, s, CMe_3) and −0.20 and −0.25 (3 H each, 2 s, $SiMe_2$); *m*/*z* (FAB > 0, G-T) 447 $(M + H)^+$ and 219 $(BH_2)^+$; *m*/*z* (FAB < 0, G-T) 445 $(M - H)^-$.

Compound **7** (0.64 g, 66%), m.p. 274–275 °C (from ethyl acetate) (Found: C, 47.6; H, 4.9; Cl, 15.1; S, 10.0; Si, 6.1. $C_{37}H_{46}Cl_4N_4O_6S_3Si_2$ requires C, 47.38; H, 5.05; Cl, 15.12; S, 10.26; Si, 5.99%); $[\alpha]_D^{20}$ −143.0 (*c* 1.0, Me_2SO); λ_{max} (95% EtOH)/nm 327 sh (ε 9000), 304 (32 800), 295 (31 000), 261 (21 600), 254 (22 700) and 224 (81 200); λ_{min}/nm 300 (ε 29 200), 270 (13 700), 258 (20 600) and 248 (19 800); δ_H 7.83 and 7.80 (1 H each, 2 s, 4′- and 7′-H), 6.77 (1 H, d, $J_{1,2}$ 6.9, 1-H), 5.72 (1 H, m, 3-H), 5.40 (1 H, m, 2-H), 4.55 (1 H, m, 4-H), 3.63 (1 H, dd, *J* 4.5 and 11.4, 5-H), 3.52 (1 H, dd, *J* 6.1 and 11.3, 5-H′), 0.67 (9 H, s, CMe_3) and −0.23 and −0.24 (3 H each, 2 s, $SiMe_2$); *m*/*z* (FAB > 0, NBA) 935 $(M + H)^+$.

6′,7′-*Dichloro*-1,2-*dideoxy*-2′,3′-*dihydro*-β-D-*arabinofuranoso*-[2,1-b](*thiazolo*[2,3-a]*benzimidazole*) **8**.—To a solution of the silylated nucleoside **6** (0.45 g, 1.01 mmol) in dry THF (2.50 cm^3) was added a 1.1 mol dm^{-3} solution of TBAF in THF (1.15 cm^3, 1.26 mmol). The solution was stirred for 12 h at ambient temperature, and was then evaporated to dryness. Ethyl acetate (100 cm^3) and water (50 cm^3) were added. The organic phase was dried over sodium sulfate, filtered, and evaporated to dryness. The residue was subjected to silica gel column chromatography, with a stepwise gradient of methanol (0–7%) in dichloromethane to afford the *title compound* **8** (0.30 g, 89%), which was crystallized from ethyl acetate, m.p. 240–242 °C (Found: C, 41.6; H, 3.0; Cl, 20.0; N, 7.8; S, 8.5. $C_{12}H_{10}Cl_2N_2O_3S{\cdot}3/4\,H_2O$ requires C, 41.57; H, 3.34; Cl, 20.45; N, 8.08; S, 9.25%); $[\alpha]_D^{20}$ −25.6 (*c* 0.8, Me_2SO); λ_{max} (95% EtOH)/nm 306 (ε 17 300), 296 (16 300), 262 (11 100) and 255 (11 700); λ_{min}/nm 302 (ε 15 300), 272 (6100), 260 (10 400) and 243 (9600); δ_H 7.80 and 7.76 (1 H each, 2 s, 4′- and 7′-H), 6.63 (1 H, d, $J_{1,2}$ 6.7, 1-H), 5.91 (1 H, d, *J* 4.3, 3-OH), 4.86 [2 H, m, 5- and 2-OH; δ 4.82 (1 H, dd, $J_{1,2}$ 6.7, $J_{2,3}$ 2.6, 2-H) after D_2O exchange], 4.39 [1 H, m, 3-H; δ 4.36 (1 H, t, *J* 3.2, 3-H) after D_2O exchange], 3.99 (1 H, m, 4-H) and 3.28 (2 H, m, 5-H_2, partially obscured by water); *m*/*z* (FAB > 0, NBA) 333 $(M + H)^+$.

5-O-(tert-*Butyldimethylsilyl*)-6′,7′-*dichloro*-1,2-*dideoxy*-2′,3′-*dihydro*-3-O-*phenoxy*(*thiocarbonyl*)-β-D-*arabinofuranoso*-[2,1-b](*thiazolo*[2,3-a]*benzimidazole*) **9**.—To a solution of nucleoside **6** (0.40 g, 0.89 mmol) in anhydrous 1,2-dichloroethane (23.0 cm^3) were added *O*-phenyl chloro(thio)formate (0.30 cm^3, 2.17 mmol) and DMAP (0.55 g, 4.50 mmol). The solution was stirred during 24 h at room temperature, and then the solvent was removed under reduced pressure. Dichloromethane (100 cm^3) and water (50 cm^3) were added. The organic phase was dried over sodium sulfate, filtered, and evaporated to dryness. The residue was subjected to silica gel column chromatography with a stepwise gradient of methanol (0–5%) in dichloromethane to afford the *title compound* **9** (0.38 g, 73%), which was crystallized from toluene, m.p. 102–104 °C (Found: C, 52.9; H, 5.0; Cl, 11.4; N, 4.65; S, 10.1; Si, 4.6. $C_{25}H_{28}Cl_2N_2O_4S_2Si{\cdot}1/4\,C_6H_5CH_3$ requires C, 52.96; H, 4.98; Cl, 11.69; N, 4.62; S, 10.57; Si, 4.63%); m.p. 102–104 °C; $[\alpha]_D^{20}$ −131.0 (*c* 1.0, Me_2SO); λ_{max} (95% EtOH)/nm 306 (ε 11 400), 295 (10 300), 262 (10 200) and 255 (11 100); λ_{min}/nm 302 (ε 9200), 272 (3400), 260 (9700) and 250 (9500); δ_H 7.84 and 7.80 (1 H each, 2 s, 4′- and 7′-H), 7.53–7.13 (5 H, m, Ph), 6.80 (1 H, d, $J_{1,2}$ 6.8, 1-H), 5.73 (1 H, br s, 3-H), 5.48 (1 H, dd, $J_{1,2}$ 6.8, $J_{2,3}$ 1.2, 2-H), 4.58 (1 H, m, 4-H), 3.67–3.50 (2 H, m, 5-H_2), 0.67 (9 H, s, CMe_3) and −0.21 and −0.22 (3 H each, 2 s, $SiMe_2$); *m*/*z* (FAB > 0, NBA) 583 $(M + H)^+$.

1-[5′-O-(tert-*Butyldimethylsilyl*)-2′,3′-*dideoxy*-β-D-*glycero*-*pent*-2′-*enofuranosyl*]-5,6-*dichloro*-2-*mercaptobenzimidazole* **11**.—To a solution of the thiocarbonate **9** (0.47 g, 0.80 mmol) in dry toluene (8.0 cm^3) were added successively tributyltin hydride (0.53 cm^3, 1.97 mmol) and AIBN (40 mg, 0.24 mmol). The resulting solution was heated and stirred at 80 °C for

45 min under argon. The solvent was evaporated off under reduced pressure, and to the residue were added dichloromethane (50 cm^3) and water (20 cm^3). The organic phase was separated, dried over sodium sulfate, and evaporated to dryness. Column chromatography of the residue on silica gel with a stepwise gradient of methanol (0–5%) in dichloromethane afforded the *title compound* **11** (0.30 g, 86%), which was crystallized from methanol, m.p. 143–144 °C (Found: C, 50.7; H, 5.8; N, 6.2. $C_{18}H_{24}Cl_2N_2O_2SSi$ requires C, 50.10; H, 5.61; N, 6.49); $[\alpha]_D^{20}$ +132.6 (*c* 0.9, Me_2SO); λ_{max} (95% EtOH)/nm 324 (ε 31 900), 254 (18 800) and 232 (19 100); λ_{min}/nm 283 (ε 3500) and 242 (13 100); δ_H 13.3 (1 H, br s, 3-H), 7.52 and 7.39 (1 H each, 2 s, 4- and 7-H), 7.33 (1 H, m, 1′-H), 6.56 (1 H, m, 2′-H), 6.35 (1 H, m, 3′-H), 4.87 (1 H, m, 4′-H), 3.83–3.69 (2 H, m, 5′-H_2), 0.78 (9 H, s, CMe_3) and −0.05 and −0.09 (3 H each, 2 s, $SiMe_2$); *m/z* (FAB > 0, NBA) 431 $(M + H)^+$ and 219 $(BH_2)^+$; *m/z* (FAB < 0, NBA) 429 $(M - H)^-$ and 217 $(B)^-$.

5,6-*Dichloro*-1-(2′,3′-*dideoxy*-β-D-glycero-*pent*-2′-*enofuranosyl*)-2-*mercaptobenzimidazole* **2**.—To a solution of the silylated nucleoside **11** (0.38 g, 0.88 mmol) in dry THF (2.20 cm^3) was added a 1.1 mol dm^{-3} solution of TBAF in THF (1.00 cm^3, 1.10 mmol), and the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated off under reduced pressure, and to the residue were added chloroform (100 cm^3) and water (50 cm^3). The organic phase was separated, dried over sodium sulfate, and evaporated to dryness. Column chromatography of the residue on silica gel with a stepwise gradient of methanol (0–3%) in dichloromethane afforded the title compound **2** (0.25 g, 89%), which was crystallized from dichloromethane, m.p. > 280 °C; $[\alpha]_D^{20}$ +88.0 (*c* 1.0, Me_2SO); λ_{max} (95% EtOH)/nm 324 (ε 33 400), 255 (21 400) and 230 (18 100); λ_{min}/nm 282 (ε 1500) and 242 (13 000); δ_H 13.2 (1 H, br s, 3-H), 8.00 (1 H, s, 4- or 7-H), 7.35 [2 H, br s, 4- or 7-H and 1′-H; δ 7.42 (1 H, s, 4- or 7-H), 7.32 (1 H, br s, 1′-H) after D_2O exchange], 6.55 [1 H, m, 2′-H; δ 6.51 (1 H, d, $J_{2',3'}$ 5.6, 2′-H) after D_2O exchange], 6.20 [1 H, m, 3′-H; δ 6.13 (1 H, d, $J_{2',3'}$ 5.7, 3′-H) after D_2O exchange], 5.07 (1 H, br s, 5′-OH), 4.83 (1 H, br s, 4′-H) and 3.66 (2 H, br s, 5′-H_2); *m/z* (FAB > 0, G-T) 317 $(M + H)^+$ and 219 $(BH_2)^+$; *m/z* (FAB < 0, G-T) 315 $(M - H)^-$.

1-[5′-O-(tert-*Butyldimethylsilyl*)-2′,3′-*dideoxy*-D-glycero-*pentofuranosyl*]-5,6-*dichloro*-2-*mercaptobenzimidazole* **14** *and* 1,3-*Bis*-[5′-O-(tert-*butyldimethylsilyl*)-2′,3′-*dideoxy*-D-glycero-*pentofuranosyl*]-5,6-*dichlorobenzimidazoline*-2-*thione* **15**.—A suspension of 5,6-dichloro-2-mercaptobenzimidazole **13**[21] (1.09 g, 4.98 mmol) in anhydrous acetonitrile (26.0 cm^3) was treated with bis(trimethylsilyl)acetamide (BSA) (3.65 cm^3, 14.77 mmol) during 3 h under reflux. To the resulting solution was added 1-*O*-acetyl-5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-D-*glycero*-pentofuranose **12** [1.30 g, 4.74 mmol; synthesized from commercial (*S*)-γ-(hydroxymethyl)-γ-butyrolactone (Aldrich No. 34.890-2) as previously described[44]] in acetonitrile (26.0 cm^3), followed by addition of TMSTf (1.28 cm^3, 7.05 mmol). The solution was heated under reflux for 45 min. After cooling to room temperature, the reaction mixture was evaporated to dryness, and to the residue were added chloroform (700 cm^3) and aq. 10% sodium hydrogen carbonate (300 cm^3). The organic phase was separated, dried over sodium sulfate, and evaporated to dryness under reduced pressure. Column chromatography of the residue on silica gel with as eluent a stepwise gradient of ethyl acetate (0–4%) in toluene afforded successively the title compounds **14** and **15**.

Compound **14** (0.70 g, 34%) consisted of an anomeric mixture (ratio α/β ≃ 3:2 as determined from its ^1H NMR spectrum) which formed a foam upon evaporation of the solvents and which could not be crystallized; δ_H 13.1 (1 H, br s, 3-H for α- and β-anomer), 7.69 (s, 4- or 7-H β-anomer), 7.50 (s, 4- or 7-H α-anomer), 7.37 (1 H, s, 7- or 4-H α- and β-anomer), 6.62 (t, *J* 6.6, 1′-H α-anomer), 6.49 (m, 1′-H β-anomer), 4.54 (m, 4′-H α-anomer), 4.11 (m, 4′-H β-anomer), 3.93–3.53 (2 H total sum, m 2 × 5′-H_2 for α- and β-anomer), 2.40–1.90 (4 H total sum, m, 2′- and 3′-H_2 for α- and β-anomer), 0.88 (s, CMe_3 α-anomer), 0.87 (s, CMe_3 β-anomer), 0.08 (s, $SiMe_2$ β-anomer) and 0.07 and 0.05 (2 s, $SiMe_2$ α-anomer); *m/z* (FAB > 0, G-T) 433 $(M + H)^+$ and 215 $(S)^+$; *m/z* (FAB < 0, G-T) 431 $(M - H)^-$.

Compound **15** (0.22 g, 7%) consisted of a mixture of the three (α,α), (α,β) and (β,β) anomeric nucleosides [ratio (α,α)/(α,β)/(β,β) ≃ 2:2:1 as determined from its ^1H NMR spectrum]. The (α,β) anomer nucleoside **15b** could be crystallized from acetonitrile, m.p. 119–120 °C (Found: C, 53.8; H, 7.3; Cl, 11.3; N, 4.4; S, 4.95; Si, 8.2. $C_{29}H_{48}Cl_2N_2O_4SSi_2$ requires C, 53.76; H, 7.47; Cl, 10.95; N, 4.33; S, 4.95; Si, 8.67%); $[\alpha]_D^{20}$ −5.0 (*c* 1.0, Me_2SO); λ_{max} (95% EtOH)/nm 324 (ε 17 000), 256 (13 300) and 236 (12 300); λ_{min}/nm 284 (ε 3600) and 243 (9500); δ_H 7.79 and 7.58 (1 H each, 2 s, 4- and 7-H), 6.72 (1 H, t, *J* 6.5, 1′-H α-anomer), 6.59 (1 H, m, 1′-H β-anomer), 4.58 (1 H, m, 4′-H α-anomer), 4.13 (1 H, m, 4′-H β-anomer), 3.94–3.59 (4 H, m, 5′-H_2 for α- and β-anomer), 2.43–1.92 (8 H, m, 2′- and 3′-H_2 for α-and β-anomer), 0.88 and 0.87 (9 H each, 2 s, CMe_3 for α- and β-anomer), 0.08 (6 H, s, $SiMe_2$ for α- or β-anomer) and 0.07 and 0.05 (3 H each, 2 s, $SiMe_2$ for α- or β-anomer); *m/z* (FAB > 0, NBA) 647 $(M + H)^+$ and 215 $(S)^+$.

5,6-*Dichloro*-1-(2′,3′-*dideoxy*-β-D-glycero-*pentofuranosyl*)-2-*mercaptobenzimidazole* **1** *and* 5,6-*Dichloro*-1-(2′,3′-*dideoxy*-α-D-glycero-*pentofuranosyl*)-2-*mercaptobenzimidazole* **16**.—To a solution of the anomeric mixture **14** (0.69 g, 1.59 mmol) in anhydrous THF (4.0 cm^3) was added a 1.1 mol dm^{-3} solution of TBAF in THF (1.80 cm^3, 1.98 mmol). The solution was stirred for 12 h at ambient temperature, and was then evaporated to dryness. Chloroform (250 cm^3) and water (150 cm^3) were added. The organic phase was separated, dried over sodium sulfate, filtered, and evaporated to dryness. The residue was subjected to silica gel column chromatography, with a stepwise gradient of ethyl acetate (0–25%) in dichloromethane to afford successively the *title compounds* **1** and **16**.

Compound **1** (0.15 g, 10% overall yield from **12**), m.p. 180–181 °C (from dichloromethane) (Found: C, 44.6; H, 3.7; Cl, 22.6; N, 8.5; S, 9.5. $C_{12}H_{12}Cl_2N_2O_2S·1/7\,H_2O$ requires C, 44.79; H, 3.85; Cl, 22.04; N, 8.71; S, 9.97%); $[\alpha]_D^{20}$ −46.0 (*c* 1.0, Me_2SO); λ_{max} (95% EtOH)/nm 322 (ε 29 000), 252 (19 600) and 230 (16 600); λ_{min}/nm 280 (ε 1800) and 240 (12 300); δ_H 13.1 (1 H, br s, 3-H), 8.20 and 7.35 (1 H each, 2 s, 4- and 7-H), 6.53 (1 H, m, 1′-H), 5.18 (1 H, br s, 5′-OH), 4.08 (1 H, m, 4′-H), 3.72 (1 H, m, 5′-H), 3.57 (1 H, m, 5′-H′) and 2.28–2.00 (4 H, m, 2′- and 3′-H); *m/z* (FAB > 0, G-T) 319 $(M + H)^+$ and 219 $(BH_2)^+$; *m/z* (FAB < 0, G-T) 317 $(M - H)^-$.

Compound **16** (0.23 g, 15% overall yield from **12**), m.p. 110–112 °C (from toluene) (Found: C, 44.6; H, 3.9; Cl, 21.4; N, 8.5; S, 9.3. $C_{12}H_{12}Cl_2N_2O_2S·1/3\,H_2O$ requires C, 44.31; H, 3.93; Cl, 21.80; N, 8.62; S, 9.86%); $[\alpha]_D^{20}$ +47.6 (*c* 1.0, Me_2SO); λ_{max} (95% EtOH)/nm 323 (ε 28 500), 252 (21 000) and 232 (16 600); λ_{min}/nm 280 (ε 3700) and 240 (13 400); δ_H 13.1 (1 H, br s, 3-H), 7.51 and 7.38 (1 H each, 2 s, 4- and 7-H), 6.59 (1 H, t, *J* 6.7, 1′-H), 4.89 (1 H, br s, 5′-OH), 4.46 (1 H, m, 4′-H), 3.46 [2 H, m, 5′-H_2, partially obscured by water; δ 3.53 (2 H, m, 5′-H_2) after D_2O exchange], 2.35–2.12 (3 H, m, 2′-H_2 and 3′-H) and 1.91 (1 H, m, 3′-H); *m/z* (FAB > 0, G-T) 319 $(M + H)^+$ and 219 $(BH_2)^+$; *m/z* (FAB < 0, G-T) 317 $(M - H)^-$ and 217 $(B)^-$.

Biological Methods.—The broad antiviral assays on cell culture and the anti-HIV assays were performed by following previously established procedures as described in refs. 47 and 48.

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