Stereospecific synthesis of unnatural β-L-enantiomers of 2-chloroadenine pentofuranonucleoside derivatives

Arnaud Marchand, Thierry Lioux, Christophe Mathé,* Jean-Louis Imbach and Gilles Gosselin

Laboratoire de Chimie Organique Biomoléculaire de Synthèse, U.M.R. CNRS 5625, Université Montpellier II, Sciences et Techniques du Languedoc, 34095 Montpellier Cedex 5, France

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2′,3′-Dideoxy- (**1**), 2′,3′-unsaturated- (**2**), 2′,3′-dideoxy-3′-fluoro- (**3**), 3′-azido-2′,3′-dideoxy- (**4**) and 2′-deoxy- (**5**) β-L-ribofuranonucleosides of 2-chloroadenine have been synthesised and their antiviral properties examined. All these derivatives were stereospecifically prepared by glycosylation of 2,6-dichloropurine with a suitable peracylated L-*xylo*-furanose (**6**). Treatment of the resulting protected β-L-nucleoside with methanolic ammonia followed by appropriate chemical modifications gave the 2-chloro-9-(2-deoxy-β-L-*threo*-pentofuranosyl)adenine **11**. Its 5′-*O*-benzoyl derivative **12** was then converted to nucleosides **1** and **2** *via* radical deoxygenation reaction or base-promoted β-elimination of the corresponding mesyl ester. Additionally, compounds **3**–**5** were obtained from **12** either by reaction with (diethylamino)sulfur trifluoride or *via* Mitsunobu reactions using diphenylphosphoryl azide or benzoic acid as incoming nucleophiles. The prepared compounds were tested for their activity against HIV and HBV viruses, but they did not show significant antiviral activity nor cytotoxicity.

Introduction

Since the discovery of the human immunodeficiency virus (HIV) as the causative agent[1,2] of the acquired immunodeficiency syndrome (AIDS), there has been a considerable effort in the search of new compounds which could inhibit the replication of HIV. Among them, nucleoside analogues have gained a decisive place. To date, six nucleoside reverse transcriptase inhibitors, namely, 3′-azido-3′-deoxythymidine (AZT), 2′,3′-dideoxyinosine (ddI), 2′,3′-dideoxycytidine (ddC), 2′,3′-didehydro-3′-deoxythymidine (d_4T), 2′,3′-dideoxy-3′-thia-β-L-cytidine (3TC) and (1*S*,4*R*)-4-(2-amino-6-cyclopropyl-9*H*-purin-9-yl)cyclopent-2-enemethanol (Abacavir) have been approved by the Food and Drug Administration (FDA) for the treatment of HIV infection. All these nucleoside derivatives share the same features, *i.e.*, they are converted to their 5′-triphosphate by cellular kinases, which then exerts its biological effect as a virus-specific reverse transcriptase inhibitor or a chain terminator because it lacks a hydroxy group at the C-3′ position.[3] However, inherent drug resistance[4] and toxicity[5] of the currently used anti-HIV drugs have prompted the development of new agents possessing potent and broad antiviral activities. In recent years, several L-enantiomer nucleoside analogues, the mirror images of the natural D-nucleosides, have emerged as powerful antiviral agents,[6] and in this regard it is noteworthy that 3TC[7,8] was also recently approved by the FDA for use in hepatitis B virus (HBV) therapy. Their potent antiviral effect lies in the fact that L-nucleosides are phosphorylated by cellular kinases to their triphosphate form, which interacts selectively with viral polymerases while having minimal interactions with cellular polymerases. For our part, we have shown recently that various purine β-L-2′,3′-dideoxynucleoside analogues, namely β-L-2′,3′-dideoxyadenosine (β-L-ddA) and β-L-2′,3′-didehydro-2′,3′-dideoxyadenosine (β-L-d_4A)[9] as well as β-L-2′,3′-dideoxy-3′-fluoroadenosine (3′-fluoro-β-L-ddA) and β-L-3′-azido-2′,3′-dideoxyadenosine[10] (3′-azido-β-L-ddA) (X = H) were potent and selective anti-HIV and -HBV agents (Chart 1). On the basis of these findings and owing to the fact that 2-chloro substitution on the adenine aglycone (X = Cl) might be expected to increase biological activity,[11] it was of interest to synthesise in a stereospecific manner and to evaluate the corresponding 2′,3′-dideoxy- (**1**), 2′,3′-didehydro-2′,3′-dideoxy- (**2**), 3′-fluoro-2′,3′-dideoxy- (**3**) and 3′-azido-2′,3′-dideoxy- (**4**) β-L-ribofuranonucleosides of 2-chloroadenine, all of them hitherto unknown except for **1**.[12] Furthermore, we have also undertaken the synthesis and the antiviral evaluation of the 2′-deoxy derivative **5**, the enantiomer of 2-chloro-2′-deoxyadenosine,[13] a potent antitumoural agent (Chart 1).

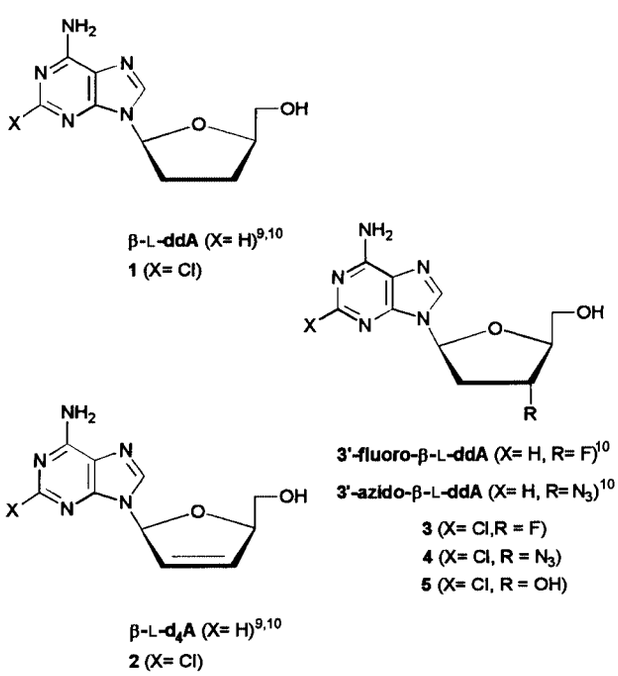
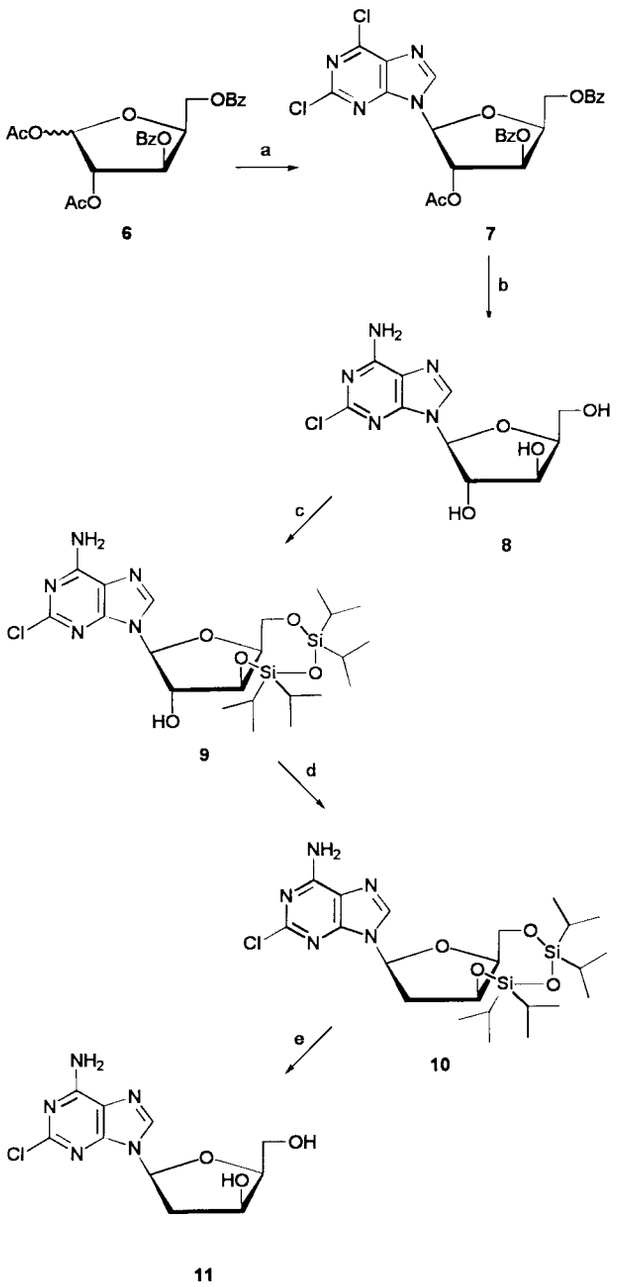


Chart 1

Results and discussion

A number of synthetic strategies have been described in the

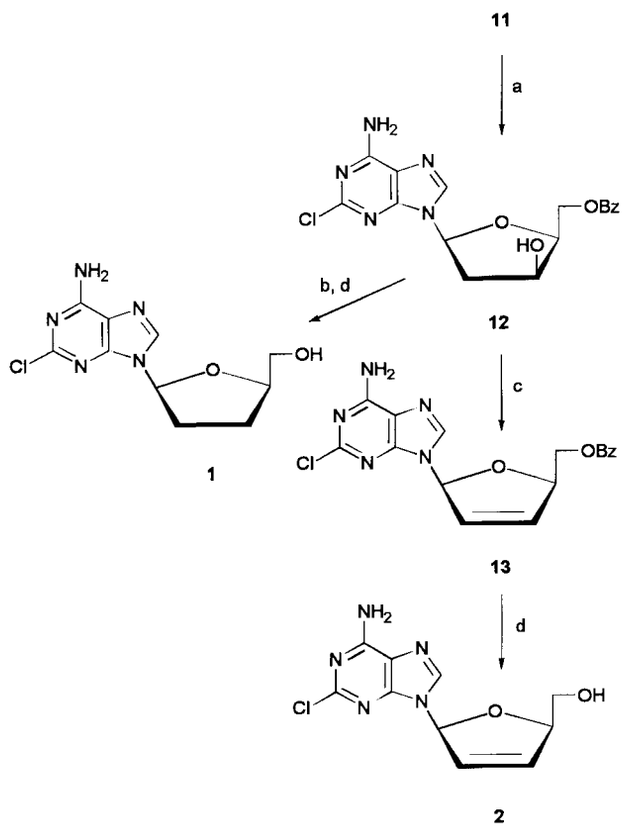
literature for the preparation of various dideoxynucleosides and analogues from nucleosides.[14–16] For our purpose, we decided for the synthesis of the target molecules **1**–**5** to condense a suitable protected L-*xylo*-furanose with the commercially available 2,6-dichloropurine. In accord with Baker's rule,[17] and owing to 2-*O*-acyl participation during the condensation, we selected as starting sugar 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-L-*xylo*-furanose **6** (Scheme 1). This sugar was prepared



Scheme 1 *Reagents and conditions*: (a) 2,6-dichloropurine, $SnCl_4$, CH_3CN, rt, 2 h; (b) MeOH–NH_3, rt, 20 h; (c) TIPSCl, DMAP, pyridine, rt, 72 h; (d) (i) DMAP, PhO(C=S)Cl, CH_3CN, rt, 1 h; (ii) $(Me_3Si)_3SiH$, AIBN, toluene, reflux, 3 h; (e) TBAF on silica gel, THF, rt, 30 min.

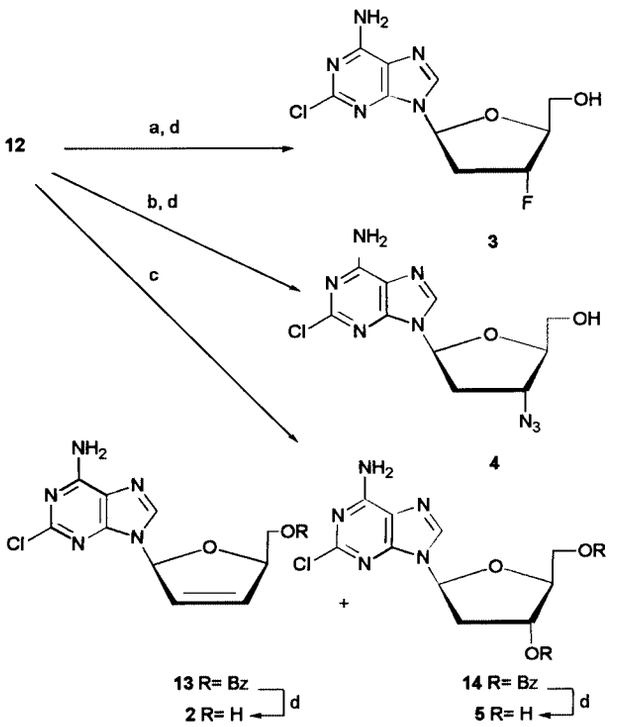
from commercial L-xylose following a synthetic pathway previously described.[18] The glycosylation reaction was carried out using stannic [tin(IV)] chloride as a catalyst[19] and afforded 9-(2-*O*-acetyl-3,5-di-*O*-benzoyl-β-L-*xylo*-furanosyl)-2,6-dichloropurine **7** in 86% yield after silica gel column chromatography. The structure of **7** was fully established from ^1H, ^{13}C NMR and UV spectra.[20] Treatment of compound **7** with methanolic ammonia removed the sugar protecting groups with concomitant amination of the 6-position to give 2-chloro-9-(β-L-*xylo*-furanosyl)adenine **8**. Simultaneous protection of the hydroxy groups in the 3′ and 5′ positions was achieved by treatment of **8** with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TIPSCl).[21] The resulting protected nucleoside **9** was treated with *O*-phenyl chloro(thio)formate [PhOC(=S)Cl] and 4-(dimethylamino)pyridine (DMAP) in acetonitrile to give the corresponding 2′-*O*-[phenoxy(thiocarbonyl)] intermediate, which was subsequently deoxygenated with tris(trimethylsilyl)silane[22] in dry toluene in the presence of α,α′-azoisobutyronitrile (AIBN) to afford the 2′-deoxy-β-L-*threo* derivative **10** in 93% overall yield. Desilylation of compound **10** was readily effected by treatment with tetrabutylammonium fluoride (TBAF) on silica gel[23,24] in tetrahydrofuran (THF) at room temperature for 30 min, and the unprotected 2′-deoxynucleoside **11** was thereby obtained as a crystalline solid in 76% yield after silica gel column chromatography.

In order to prepare the target compounds **1**–**5**, the 2′-deoxy-β-L-*threo*-pentofuranonucleoside **11** was selectively converted into the 5′-*O*-benzoyl key derivative **12** (Scheme 2). The latter



Scheme 2 *Reagents and conditions*: (a) BzCl, pyridine–DMF, 0 °C, 20 min; (b) (i) DMAP, PhO(C=S)Cl, CH_3CN, rt, 68 h; (ii) $(Me_3Si)_3SiH$, AIBN, 1,4-dioxane, reflux, 2 h; (c) (i) MsCl, pyridine, rt, 18 h; (ii) TBAF, THF, rt, 1 h; (d) MeOH–NH_3, rt, 18 h.

was then subject to a deoxygenation reaction to yield the protected 2′,3′-dideoxynucleoside intermediate. Removal of the benzoyl group with methanolic ammonia afforded the desired dideoxynucleoside derivative **1**.[12] Introduction of a double bound between the 2′- and 3′-position from **12** was achieved *via* a base-promoted β-elimination. The first step involved the preparation of the corresponding 3′-*O*-mesyl ester by treatment with mesyl chloride in pyridine, which upon reaction with TBAF in THF[25] gave the derivative **13**. Deprotection of **13** with methanolic ammonia provided the 2′,3′-didehydro-2′,3′-dideoxynucleoside **2** obtained as a crystalline solid in 67% yield after silica gel column chromatography. Additionally, the syntheses of 2′,3′-dideoxy-3′-fluoro- (**3**), 3′-azido-2′,3′-dideoxy- (**4**) and 2′-deoxy- (**5**) β-L-ribofuranonucleoside derivatives were accomplished from the key 5′-*O*-benzoyl compound **12** *via* nucleophilic substitutions with inversion of configuration at the 3′-position (Scheme 3). Several methodologies for the synthesis



Scheme 3 *Reagents and conditions*: (a) DAST, CH_2Cl_2, 0 °C, 15 min; (b) DEAD, DPPA, PPh_3, THF, 0 °C, 20 min; (c) DEAD, benzoic acid, PPh_3, THF, 0 °C, 15 min; (d) MeOH–NH_3, rt, 18 h.

of nucleosides fluorinated in the carbohydrate moiety have been extensively described in the literature.[26] For our purpose, we selected as fluorinating agent (diethylamino)sulfur trifluoride (DAST). This reagent has been widely used for the preparation of various 3′α-fluorodideoxynucleosides under mild conditions and with satisfactory yields.[27,28] Thus, reaction of DAST with **12** in dry dichloromethane at 0 °C, followed by methanolic ammonia treatment afforded, after silica gel column chromatography, the 2′,3′-dideoxy-3′-fluoro-β-L-ribofuranonucleoside **3** as a crystalline solid in 38% overall yield. Introduction of the azido group and inversion of the hydroxy group at C-3′ were achieved *via* Mitsunobu reactions[29] using as incoming nucleophiles diphenylphosphoryl azide (DPPA) or benzoic acid, respectively. Hence, reaction of **12** with diethyl azodicarboxylate (DEAD), DPPA and triphenylphosphine in dry THF at 0 °C, followed by debenzoylation with methanolic ammonia provided, after purification on silica gel column, the 3′-azido-2′,3′-dideoxy-β-L-ribofuranonucleoside **4** as the sole product in 68% yield from **12**. On the other hand, treatment of **12** with DEAD, benzoic acid and triphenylphosphine in dry THF at 0 °C gave an inseparable mixture of compounds **13** and **14**. Therefore, deprotection with methanolic ammonia and separation of the product mixture by silica gel column chromatography afforded the 2′,3′-unsaturated nucleoside **2** and the desired 2′-deoxy-β-L-ribofuranonucleoside **5** in 17 and 47% yield, respectively. Formation of the 2′,3′-unsaturated nucleoside as a side-product is probably due to a β-elimination of the transperiplanar H-2′ α proton from the 3′-*O*-[oxyphosphonium salt] intermediate, resulting from the OH-3′ activation step.[30]

Biological evaluation

The unprotected nucleosides **1**–**5**, **8** and **11** were tested for their *in vitro* inhibitory effects on the replication of HIV-1 in CEM-SS and MT-4 cell systems. None of these compounds showed marked antiviral effects or detectable alteration of host-cell morphology at the highest concentration tested (generally 10^{-1} mmol dm^{-3}). When evaluated in anti-HBV assays in HepG2 cells, none of the tested compounds showed any antiviral effect (up to a concentration of 0.1×10^{-1} mmol dm^{-3}) nor cytotoxicity (up to a concentration of 2×10^{-1} mmol dm^{-3}).

Conclusions

From the present work, it appears that β-L-nucleoside analogues of 2-chloroadenine do not induce inhibition of HIV and HBV replication, in contrast to their unchlorinated counterparts.[9,10] Several factors could be responsible for the inactivity of these nucleoside derivatives. Their inability to enter cells or to serve as substrates for intracellular enzymes catalysing triphosphorylation, as well as a lack of inhibition of viral polymerases by their triphosphate forms, would all account for their inactivity against HIV and HBV. Further research would be needed to support these hypotheses, but since no significant antiviral activity emerged from the present data, it does not seem worthwhile to pursue additional studies of the β-L-nucleoside analogues of 2-chloroadenine.

Experimental

Evaporation of solvents was carried out on a rotary evaporator under reduced pressure. Mps were determined in open capillary tubes on a Gallenkamp MFB-595-010 M apparatus and are uncorrected. UV spectra were recorded on an Uvikon 931 (Kontron) spectrophotometer. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz in $(CD_3)_2SO$ at ambient temperature with a Bruker DRX 400. Chemical shifts are given in δ-values, $(CD_3)(CD_2H)SO$ being set at δ_H 2.49 and δ_C 39.5 as a reference. Deuterium exchange and COSY experiments were performed in order to confirm proton assignments. Coupling constants, J, are reported in Hz. 2D ^{1}H–^{13}C heteronuclear COSY spectra were recorded for the attribution of ^{13}C signals. FAB mass spectra were recorded in the positive-ion or negative-ion mode on a JEOL SX 102. The matrix was 3-nitrobenzyl alcohol (NBA) or a mixture (50:50, v/v) of glycerol and 1-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 $[a]_D$-values 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). Thin-layer chromatography was performed on precoated aluminium sheets of Silica Gel 60 F_{254} (Merck, Art. 5554), visualisation 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).

9-(2-*O*-Acetyl-3,5-di-*O*-benzoyl-β-L-*xylo*-furanosyl)-2,6-dichloropurine 7

Stannic chloride (3.45 cm^3, 29.4 mmol) was added cautiously under argon to a stirred solution of 2,6-dichloropurine (4.62 g, 24.5 mmol) and 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-L-*xylo*-furanose **6** (9.00 g, 20.4 mmol) in dry acetonitrile (450 cm^3) at room temperature. After 2 h, the resulting solution was concentrated under reduced pressure to a small volume (approximately 50 cm^3) and sodium hydrogen carbonate (20 g) and water (20 cm^3) were added carefully. When the vigorous evolution of carbon dioxide had ceased, the mixture was filtered through a sintered funnel covered with Celite. The Celite was then triturated and washed several times with boiling chloroform (1000 cm^3). The combined filtrates were concentrated to approximately 150 cm^3, washed with water, dried over sodium sulfate and evaporated. Column chromatography of the residue on silica gel using a stepwise gradient of ethyl acetate (0–12%) in dichloromethane afforded the *title compound* **7** as a white foam (10.03 g, 86%), which was crystallised from 95% ethanol, mp 91 °C (Found: C, 54.85; H, 3.58; N, 9.59. $C_{26}H_{20}Cl_2N_4O_7$ requires C, 54.65; H, 3.53; N, 9.80%); $[a]_D^{20}$ −44.0 (*c* 1.02 in Me_2SO); λ_{max} (95% EtOH)/nm 274 (ε 5600), 231 (15 500); δ_H[$(CD_3)_2SO$] 2.13 (3H, s,

CH_3CO), 4.69 (2H, m, 5′-H and 5″-H), 4.95 (1H, m, 4′-H), 5.88 (1H, dd, $J_{3',2'}$ 2.1, $J_{3',4'}$ 6.8, 3′-H), 6.10 (1H, m, 2′-H), 6.40 (1H, d, $J_{1',2'}$ 3.3, 1′-H), 7.5–7.9 (10H, m, *Ph*CO), 8.96 (1H, s, 8-H); δ_C[$(CD_3)_2SO$] 21.4 (CH_3CO), 62.9 (5′-C), 76.2 (3′-C), 79.0 (2′-C), 79.3 (4′-C), 88.3 (1′-C), 129.4–134.7 (*Ph*CO and 5-C), 147.4 (8-C), 150.9 (6-C), 152.2 (4-C), 153.7 (2-C), 165.4 (CO), 166.2 (CO), 170.2 (CO); *m*/*z* (FAB > 0, GT) 571 $(M + H)^+$, 383 $(S)^+$, 189 $(BH_2)^+$; *m*/*z* (FAB < 0, GT) 569 $(M - H)^-$, 187 $(B)^-$.

2-Chloro-9-(β-L-*xylo*-furanosyl)adenine 8

A solution of **7** (10.03 g, 17.5 mmol) in methanolic ammonia (previously saturated at −10 °C and tightly stoppered) (450 cm^3) was stirred for 20 h at room temperature, then evaporated to dryness. The crude material obtained was dissolved in water (100 cm^3) and the resulting solution was washed with dichloromethane (2 × 100 cm^3). The aqueous layer was evaporated under reduced pressure and the residue was subjected to silica gel column chromatography, with a stepwise gradient of methanol (0–10%) in dichloromethane to afford the *title compound* **8** (3.52 g, 67%), which was crystallised from acetonitrile, mp 178 °C (Found: C, 39.25; H, 4.25; N, 22.33. $C_{10}H_{12}ClN_5O_4 \cdot 2/5H_2O$ requires C, 38.88; H, 4.18; N, 22.67%); $[\alpha]_D^{20}$ +66.0 (*c* 1.06 in Me_2SO); λ_{max} (95% EtOH)/nm 264 (ε 15 400); δ_H[$(CD_3)_2SO$] 3.46 (1H, m, 5′-H), 3.54 (1H, m, 5″-H), 3.84 (1H, br s, 3′-H), 3.97 (1H, br s, 4′-H), 4.08 (1H, br s, 2′-H), 4.56 (1H, t, *J* 5.6, 5′-OH), 5.36 (1H, br s, 3′-OH), 5.59 (1H, d, $J_{1',2'}$ 1.3, 1′-H), 5.71 (1H, br s, 2′-OH), 7.63 (2H, br s, NH_2), 8.04 (1H, s, 8-H); δ_C[$(CD_3)_2SO$] 58.3 (5′-C), 73.7 (3′-C), 79.5 (2′-C), 82.7 (4′-C), 88.0 (1′-C), 116.5 (5-C), 138.8 (8-C), 148.9 (4-C), 151.8 (2-C), 155.6 (6-C); *m*/*z* (FAB > 0, GT) 302 $(M + H)^+$, 170 $(BH_2)^+$; *m*/*z* (FAB < 0, GT) 300 $(M - H)^-$, 168 $(B)^-$.

2-Chloro-9-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-L-*xylo*-furanosyl]adenine 9

1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (2.30 cm^3, 7.30 mmol) was added to a solution of **8** (2.01 g, 6.63 mmol) and DMAP (0.40 g, 3.32 mmol) in dry pyridine (21 cm^3). The resulting suspension was stirred at room temperature for 72 h then evaporated under reduced pressure. Chromatography of the residue on a silica gel column using as eluent a stepwise gradient of methanol (0–3%) in dichloromethane led to the *title compound* **9** (3.03 g, 84%) which was crystallised from acetonitrile, mp 219 °C (Found: C, 48.37; H, 7.30; N, 12.74. $C_{22}H_{38}ClN_5O_5Si_2$ requires C, 48.55; H, 7.04; N, 12.87%); $[\alpha]_D^{20}$ +49.5 (*c* 1.06 in Me_2SO); λ_{max} (95% EtOH)/nm 264 (ε 15 000); δ_H[$(CD_3)_2SO$] 0.88–1.12 (28H, m, CH_3 and *CH* TIPS), 3.89–3.98 (2H, m, 5′-H and 5″-H), 4.25 (1H, d, $J_{3',2'}$ 2.7, 3′-H), 4.31 (1H, m, 4′-H), 4.47 (1H, d, $J_{2',1'}$ 3.5, 2′-H), 5.86 (1H, br s, 1′-H), 6.23 (1H, d, *J* 3.6, 2′-OH), 7.84 (2H, br s, NH_2), 8.08 (1H, s, 8-H); δ_C[$(CD_3)_2SO$] 12.6–13.6 (*C*H TIPS), 17.7–18.2 (CH_3 TIPS), 58.9 (5′-C), 76.2 (3′-C), 81.3 (2′-C), 83.0 (4′-C), 90.7 (1′-C), 118.5 (5-C), 139.8 (8-C), 150.8 (4-C), 154.0 (2-C), 157.6 (6-C); *m*/*z* (FAB > 0, NBA) 544 $(M + H)^+$, 170 $(BH_2)^+$; *m*/*z* (FAB < 0, NBA) 1085 $(2M - H)^-$, 542 $(M - H)^-$, 168 $(B)^-$.

2-Chloro-9-[2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-L-*threo*-pentofuranosyl]adenine 10

To a stirred solution of **9** (3.00 g, 5.51 mmol) in dry acetonitrile (100 cm^3) were added DMAP (2.02 g, 16.5 mmol) and phenoxy(thiocarbonyl) chloride (1.14 cm^3, 8.26 mmol) successively. After 1 h, the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (100 cm^3) and the organic layer was washed with 0.5 mol dm^{-3} hydrochloric acid (2 × 100 cm^3), dried over sodium sulfate and evaporated to dryness. The resulting crude material was coevaporated with dry toluene, then dissolved in the same solvent (85 cm^3) and α,α′-azoisobutyronitrile (0.362 g, 2.20 mmol) and tris(trimethylsilyl)silane (2.21 cm^3, 7.16 mmol) were added. The resultant solution was heated under reflux for 3 h. After cooling to room temperature, the solvent was removed under reduced pressure. Chromatography of the residue on a silica gel column using as eluent a stepwise gradient of methanol (0–3%) in dichloromethane afforded the *title compound* **10** (2.71 g, 93%) which was crystallised from acetonitrile, mp 158 °C (Found: C, 49.69, H, 7.27, N, 13.45. $C_{22}H_{38}ClN_5O_4Si_2$ requires C, 50.02; H, 7.25; N, 13.26%); $[\alpha]_D^{20}$ +65.0 (*c* 1.12 in Me_2SO); λ_{max} (95% EtOH)/nm 264 (ε 14 000); δ_H[$(CD_3)_2SO$] 0.90–1.16 (28H, m, CH_3 and *CH* TIPS), 2.47 (1H, m, 2′-H), 2.93 (1H, septuplet, $J_{2'',3'}$ 5.0, $J_{2'',1'}$ 8.3, $J_{2'',2'}$ 14.5, 2″-H), 3.82–3.91 (2H, m, 5′-H and 5″-H), 4.06 (1H, m, 4′-H), 4.61 (1H, br s, 3′-H), 6.27 (1H, d, 1′-H), 7.83 (2H, br s, NH_2), 8.24 (1H, s, 8-H); δ_C[$(CD_3)_2SO$] 12.7–13.6 (*C*H TIPS), 17.8–18.2 (CH_3 TIPS), 41.1 (2′-C), 59.4 (5′-C), 70.7 (3′-C), 83.2 (1′-C), 84.1 (4′-C), 118.4 (5-C), 140.2 (8-C), 151.1 (4-C), 154.0 (2-C), 157.6 (6-C); *m*/*z* (FAB > 0, NBA) 528 $(M + H)^+$, 170 $(BH_2)^+$; *m*/*z* (FAB < 0, NBA) 526 $(M - H)^-$, 168 $(B)^-$.

2-Chloro-9-(2-deoxy-β-L-*threo*-pentofuranosyl)adenine 11

To a stirred solution of **10** (2.70 g, 5.11 mmol) in anhydrous THF (100 cm^3) was added 1.1 mmol F^- g^{-1} TBAF on silica gel (9.30 g, 10.2 mmol). The resulting suspension was stirred for 30 min at room temperature, then filtered. The resin was washed several times with methanol and the combined filtrates were evaporated to dryness. The residue was subjected to silica gel column chromatography, with a stepwise gradient of methanol (0–10%) in dichloromethane to afford the title compound **11** (1.10 g, 76%), which was crystallised from acetonitrile, mp 194 °C; $[\alpha]_D^{20}$ +81.0 (*c* 1.01 in Me_2SO); λ_{max} (95% EtOH)/nm 264 (ε 14 500); δ_H[$(CD_3)_2SO$] 2.24 (1H, dd, $J_{2',1'}$ 8.4, $J_{2',2'}$ 14.3, 2′-H), 2.73 (1H, septuplet, $J_{2'',1'}$ 1.9, $J_{2'',3'}$ 5.4, 2′-H), 3.58 (1H, m, 5′-H), 3.72 (1H, m, 5″-H), 3.91 (1H, m, 4′-H), 4.33 (1H, m, 3′-H), 4.66 (1H, t, *J* 5.6, 5′-OH), 5.44 (1H, d, *J* 4.5, 3′-OH), 6.18 (1H, dd, 1′-H), 7.78 (2H, br s, NH_2), 8.34 (1H, s, 8-H); δ_C[$(CD_3)_2SO$] 41.6 (2′-C), 60.7 (5′-C), 69.8 (3′-C), 83.2 (1′-C), 86.3 (4′-C), 118.6 (5-C), 141.0 (8-C), 150.8 (4-C), 153.7 (2-C), 157.6 (6-C); *m*/*z* (FAB > 0, GT) 286 $(M + H)^+$, 170 $(BH_2)^+$; *m*/*z* (FAB < 0, GT) 284 $(M - H)^-$, 168 $(B)^-$.

9-(5-*O*-Benzoyl-2-deoxy-β-L-*threo*-pentofuranosyl)-2-chloroadenine 12

Benzoyl chloride (0.47 cm^3, 4.08 mmol) in dry pyridine (6.5 cm^3) was added to a stirred solution of **11** (0.775 g, 2.72 mmol) in a pyridine–DMF mixture (4:1; 37 cm^3) at 0 °C under argon. After 20 min, water was added (5 cm^3) and the solvents were removed under reduced pressure. Chloroform (100 cm^3) was added and the organic phase was washed successively with saturated aqueous sodium hydrogen carbonate (2 × 100 cm^3) and water (100 cm^3), dried over sodium sulfate and evaporated to dryness. Column chromatography of the residue on silica gel with as eluent a stepwise gradient of methanol (0–5%) in dichloromethane afforded the *title compound* **12** (0.93 g, 88%), which was crystallised from ethanol, mp 179–181 °C (Found: C, 52.09; H, 4.29; N, 17.65. $C_{17}H_{16}ClN_5O_4$ requires C, 52.38; H, 4.14; N, 17.97%); $[\alpha]_D^{20}$ +1 (*c* 0.97 in Me_2SO); λ_{max} (95% EtOH)/nm 265 (ε 16 800); λ_{min} 245 (ε 10 100); δ_H[$(CD_3)_2SO$] 2.28 (1H, m, 2′-H), 2.81 (1H, septuplet, $J_{2'',3'}$ 5.6, $J_{2'',1'}$ 8.6, $J_{2'',2'}$ 14.2, 2″-H), 4.29 (1H, m, 4′-H), 4.43–4.51 (2H, m, 3′-H and 5′-H), 4.61 (1H, dd, $J_{5'',4'}$ 3.7, $J_{5',5''}$ 11.8, 5″-H), 5.80 (1H, d, *J* 4.6, 3′-OH), 6.25 (1H, dd, $J_{1',2'}$ 2.0, 1′-H), 7.49–7.96 (7H, m, NH_2 and *Ph*CO), 8.38 (1H, s, 8-H); δ_C[$(CD_3)_2SO$] 41.4 (2′-C), 65.0 (5′-C), 70.2 (3′-C), 82.8 (4′-C), 83.6 (1′-C), 118.6 (5-C), 129.1–134.3 (*Ph*CO), 141.0 (8-C), 150.8 (4-C), 153.8 (2-C), 157.6 (6-C), 166.5 (Ph*C*O); *m*/*z* (FAB > 0, GT) 390 $(M + H)^+$, 170 $(BH_2)^+$; *m*/*z* (FAB < 0, GT) 388 $(M - H)^-$, 168 $(B)^-$.

2-Chloro-9-(2,3-dideoxy-β-L-*glycero*-pentofuranosyl)adenine 1

To a stirred solution of **12** (0.290 g, 0.74 mmol) in dry

acetonitrile (10 cm^3) were added DMAP (0.904 g, 7.40 mmol) and phenoxy(thiocarbonyl) chloride (0.207 cm^3, 1.48 mmol) successively. Stirring was pursued for 68 h, and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (40 cm^3) and the organic layer was washed with 0.5 mol dm^{-3} hydrochloric acid (2 × 50 cm^3) and dried over sodium sulfate. The resulting crude material was coevaporated with dry 1,4-dioxane, then dissolved in the same solvent (10 cm^3) and α,α′-azoisobutyronitrile (0.048 g, 0.30 mmol) and tris(trimethylsilyl)silane (0.456 cm^3, 1.48 mmol) were added. The solution was heated under reflux for 2 h. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using a stepwise gradient of methanol (0–3%) in dichloromethane. The appropriate fractions were pooled and directly treated with methanolic ammonia (17 cm^3). After 18 h, solvent was removed and the residue was purified by silica gel column chromatography using a stepwise gradient of methanol (0–3%) in chloroform to afford the title compound **1** (0.135 g, 75%), which was crystallised from ethanol, mp 238 °C (lit.,[12] 240 °C) (Found: C, 44.23; H, 4.63; N, 25.68. Calc. for $C_{10}H_{12}ClN_5O_2$: C, 44.54; H, 4.49; N, 25.97%); $[\alpha]_D^{20}$ +21.0 (*c* 1.12 in Me_2SO) [lit.,[12] +4.2 (*c* 0.15 in MeOH)]; λ_{max} (95% EtOH)/nm 265 (ε 15 500) [lit.,[12] (MeOH) 266 (ε 18 000)]; $\delta_H[(CD_3)_2SO]$ 1.98–2.08 (2H, m, 3′-H_2), 2.30–2.47 (2H, m, 2′-H_2), 3.48 (1H, m, 5″-H), 3.51 (1H, m, 5′-H), 4.09 (1H, m, 4′-H), 4.94 (1H, br s, 5′-OH), 6.13 (1H, dd, $J_{1',2'}$ 3.5, $J_{1',2'}$ 6.7, 1′-H), 7.77 (2H, br s, NH_2), 8.36 (1H, s, 8-H); $\delta_C[(CD_3)_2SO]$ 26.3 (3′-C), 32.7 (2′-C), 63.5 (5′-C), 82.8 (4′-C), 85.2 (1′-C), 118.9 (5-C), 140.3 (8-C), 150.7 (4-C), 153.7 (2-C), 157.6 (6-C); *m/z* (FAB > 0, GT) 270 $(M + H)^+$, 170 $(BH_2)^+$; *m/z* (FAB < 0, GT) 268 $(M - H)^-$, 168 $(B)^-$.

9-(5-*O*-Benzoyl-2,3-dideoxy-β-L-*glycero*-pent-2-enofuranosyl)-2-chloroadenine 13

Methanesulfonyl chloride (0.36 cm^3, 4.62 mmol) was added to a solution of nucleoside **12** (0.60 g, 1.54 mmol) in dry pyridine (23 cm^3) at 0 °C under argon. The resultant solution was stirred at room temperature for 18 h, and water was added (3 cm^3). After removal of solvents under reduced pressure, the residue was dissolved in dichloromethane (100 cm^3) and the organic phase was washed successively with saturated aqueous sodium hydrogen carbonate (100 cm^3) and water (2 × 100 cm^3). The organic layer was dried over sodium sulfate and evaporated to dryness. The crude material was dissolved in anhydrous THF (7 cm^3) and a 1.1 mol dm^{-3} solution of TBAF in THF (14 cm^3, 13.6 mmol) was added. The mixture was stirred for 1 h at ambient temperature, then evaporated to dryness. Dichloromethane (150 cm^3) and water (50 cm^3) were added. The organic phase was separated, dried and evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, with a stepwise gradient of methanol (0–3%) in dichloromethane to afford the *title compound* **13** (0.485 g, 91% overall yield from **12**), mp 173–174 °C (from MeOH) (Found: C, 53.57; H, 3.93; N, 18.56. $C_{17}H_{14}ClN_5O_3 \cdot 1/2H_2O$ requires C, 53.62; H, 3.97; N, 18.39%); $[\alpha]_D^{20}$ +77 (*c* 0.88 in Me_2SO); λ_{max} (95% EtOH)/nm 265 (ε 17 000), 225 (15 500); λ_{min} 245 (ε 10 700); $\delta_H[(CD_3)_2SO]$ 4.46 (1H, dd, $J_{5',4'}$ 5.4, $J_{5',5''}$ 12.0, 5′-H), 4.52 (1H, dd, $J_{5'',4'}$ 3.2, 5″-H), 5.23 (1H, m, 4′-H), 6.28 (1H, ddd, $J_{3',1'}$ 1.6, $J_{3',4'}$ 2.3, $J_{3',2'}$ 6.0, 3′-H), 6.59 (1H, td, $J_{2',1'}$ 2.1, 2′-H), 6.89 (1H, m, 1′-H), 7.48–7.89 (7H, m, NH_2 and *Ph*CO), 8.02 (1H, s, 8-H); $\delta_C[(CD_3)_2SO]$ 66.5 (5′-C), 85.6 (4′-C), 89.1 (1′-C), 118.8 (5-C), 126.9 (3′-C), 129.1–130.1 (*Ph*CO), 134.0 (2′-C), 134.4 (*Ph*CO), 139.9 (8-C), 151.1 (4-C), 154.1 (2-C), 157.7 (6-C); *m/z* (FAB > 0, GT) 268 (M − PhCO + 2H)$^+$, 170 $(BH_2)^+$; *m/z* (FAB < 0, GT) 370 $(M - H)^-$, 168 $(B)^-$.

2-Chloro-9-(2,3-dideoxy-β-L-*glycero*-pent-2-enofuranosyl)-adenine 2

A solution of **13** (0.383 g, 1.00 mmol) in methanolic ammonia (previously saturated at −10 °C and tightly stoppered) (20 cm^3) was stirred at ambient temperature for 18 h. After evaporation to dryness under reduced pressure, the residue was purified by silica gel column chromatography using a stepwise gradient of methanol (0–5%) in chloroform to afford the *title compound* **2** (0.179 g, 67%), which was crystallised from methanol, mp 200–203 °C (lit.,[31] 200–205 °C for the D-enantiomer) (Found: C, 44.29; H, 3.86; N, 25.50. $C_{10}H_{10}ClN_5O_2 \cdot 1/5H_2O$ requires C, 44.28; H, 3.86; N, 25.82%); $[\alpha]_D^{20}$ +29 (*c* 1.02 in Me_2SO); λ_{max} (95% EtOH)/nm 265 (ε 14 700); $\delta_H[(CD_3)_2SO]$ 3.58 (2H, m, 5′-H and 5″-H), 4.89 (1H, m, 4′-H), 4.96 (1H, t, *J* 5.6, 5′-OH), 6.14 (1H, ddd, $J_{3',1'}$ 1.5, $J_{3',4'}$ 2.2, $J_{3',2'}$ 6.0, 3′-H), 6.48 (1H, td, $J_{2',1'}$ 1.7, 2′-H), 6.86 (1H, m, 1′-H), 7.83 (1H, br s, NH_2), 8.18 (1H, s, 8-H); $\delta_C[(CD_3)_2SO]$ 63.4 (5′-C), 88.7 (1′-C), 89.1 (4′-C), 118.6 (5-C), 126.0 (3′-C), 135.5 (2′-C), 140.5 (8-C), 151.1 (4-C), 154.0 (2-C), 157.7 (6-C); *m/z* (FAB > 0, NBA) 268 $(M + H)^+$, 170 $(BH_2)^+$; *m/z* (FAB < 0, NBA) 266 $(M - H)^-$, 168 $(B)^-$.

2-Chloro-9-(2,3-dideoxy-3-fluoro-β-L-*erythro*-pentofuranosyl)-adenine 3

DAST (0.200 cm^3, 1.50 mmol) was added to a solution of nucleoside **12** (0.390 g, 1.00 mmol) in dry dichloromethane (25 cm^3) at 0 °C under argon and the mixture was stirred for 15 minutes before being poured into saturated aqueous sodium hydrogen carbonate (50 cm^3) at 0 °C. The organic phase was washed with water (2 × 50 cm^3), dried over sodium sulfate and evaporated to dryness. The residue was purified on a silica gel column with a stepwise gradient of methanol (0–4%) in dichloromethane. The appropriate fractions were pooled, and directly treated with methanolic ammonia for 18 h. After evaporation to dryness under reduced pressure, the residue was purified by silica gel column chromatography using a stepwise gradient of methanol (0–4%) in chloroform to afford the *title compound* **3** (0.110 g, 38% overall yield from **12**), which was crystallised from ethanol, mp 204–205 °C (Found: C, 41.48; H, 3.92; N, 24.35. $C_{10}H_{11}ClFN_5O_2$ requires C, 41.75; H, 3.85; N, 24.34%); $[\alpha]_D^{20}$ +42 (*c* 1.06 in Me_2SO); λ_{max} (95% EtOH)/nm 265 (ε 14 000); $\delta_H[(CD_3)_2SO]$ 2.66 (1H, m, 2′-H), 2.92 (1H, m, 2′-H), 3.58 (2H, m, 5′-H and 5″-H), 4.21 (1H, td, $J_{4',3'}$ 4.8, $J_{4',F}$ 26.7, 4′-H), 5.17 (1H, t, *J* 5.6, 5′-OH), 5.42 (1H, dd, $J_{3',2'}$ 4.8, $J_{3',F}$ 53.6, 3′-H), 6.30 (1H, dd, $J_{1',2'}$ 5.7 , $J_{1',2''}$ 9.1, 1′-H), 7.88 (2H, br s, NH_2), 8.37 (1H, s, 8-H); $\delta_C[(CD_3)_2SO]$ 37.5 (d, $J_{2'\text{-}C,F}$ 20.6, 2′-C), 61.8 (d, $J_{5'\text{-}C,F}$ 11.0, 5′-C), 84.6 (1′-C), 86.4 (d, $J_{4'\text{-}C,F}$ 22.0, 4′-C), 174.3 (d, $J_{3'\text{-}C,F}$ 20.6, 3′-C), 119.1 (5-C), 140.8 (8-C), 151.0 (4-C), 153.8 (2-C), 157.7 (6-C); *m/z* (FAB > 0, GT) 575 $(2M + H)^+$, 288 $(M + H)^+$, 170 $(BH_2)^+$; *m/z* (FAB < 0, GT) 573 $(2M - H)^-$, 286 $(M - H)^-$, 168 $(B)^-$.

9-(3-Azido-2,3-dideoxy-β-L-*erythro*-pentofuranosyl)-2-chloro-adenine 4

DEAD (0.472 cm^3, 3.00 mmol) and DPPA (0.642 cm^3, 3.00 mmol) in dry THF (18 cm^3) were added to a solution of nucleoside **12** (0.390 g, 1.00 mmol) and triphenylphosphine (0.787 g, 3.00 mmol) in dry THF (12 cm^3) at 0 °C under argon. The resulting solution was stirred for 20 min at 0 °C. Solvent was removed and the residue was subjected to silica gel column chromatography with a stepwise gradient of methanol (0–3%) in dichloromethane. The appropriate fractions were pooled and directly treated with methanolic ammonia for 18 h. Evaporation to dryness and column chromatography on silica gel using a stepwise gradient of methanol (0–4%) in chloroform afforded the title compound **4** (0.213 g, 68% overall yield from **12**), mp 169–171 °C (from ethanol); $[\alpha]_D^{20}$ +8.0 (*c* 1.00 in Me_2SO); λ_{max} (95% EtOH)/nm 265 (ε 17 100); $\delta_H[(CD_3)_2SO]$ 2.49 (1H, m, 2′-H), 2.88 (1H, m, 2′-H), 3.52–3.63 (2H, m, 5′-H and 5″-H),

3.90 (1H, m, 4′-H), 4.58 (1H, dd, $J_{3',4'}$ 5.2, $J_{3',2'}$ 11.6, 3′-H), 5.13 (1H, t, *J* 5.6, 5′-OH), 6.22 (1H, t, $J_{1',2'}$ 6.3, 1′-H), 7.84 (2H, br s, NH_2), 8.37 (1H, s, 8-H); δ_C[$(CD_3)_2SO$] 37.0 (2′-C), 61.6 (3′-C), 61.9 (5′-C), 83.8 (1′-C), 85.5 (4′-C), 119.0 (5-C), 140.6 (8-C), 150.9 (4-C), 153.9 (2-C), 157.6 (6-C); *m/z* (FAB > 0, GT) 311 $(M + H)^+$, 170 $(BH_2)^+$; *m/z* (FAB < 0, GT) 309 $(M - H)^-$, 168 $(B)^-$.

2-Chloro-9-(2-deoxy-β-L-*erythro*-pentofuranosyl)adenine 5

DEAD (0.364 cm^3, 2.31 mmol) in dry THF (20 cm^3) was added to a stirred solution of nucleoside **12** (0.300 g, 0.77 mmol), triphenylphosphine (0.605 g, 2.31 mmol) and benzoic acid (0.282 g, 2.31 mmol) in dry THF (20 cm^3) at 0 °C under argon. The resulting solution was stirred for 15 min at 0 °C. Solvent was removed and the residue was subjected to silica gel column chromatography with a stepwise gradient of methanol (0–3%) in dichloromethane to afford a mixture of compounds **13** and **14**. The mixture was treated with methanolic ammonia for 18 h. Evaporation to dryness and column chromatography (on silica gel) of the residue using a stepwise gradient of methanol (0–9%) in dichloromethane afforded successively the nucleoside derivative **2** and the *title compound* **5**.

Compound **2** (0.035 g, 17% overall yield from **12**). The physicochemical properties of **2** were identical with those previously described.

Compound **5** (0.103 g, 47% overall yield from **12**), mp 212–214 °C (from ethanol) (lit.,[13] 210–215 °C for the D-enantiomer) (Found: C, 41.57; H, 4.26; N, 23.55. $C_{10}H_{12}ClN_5O_3 \cdot 1/3H_2O$ requires C, 41.18; H, 4.38; N, 24.01%); $[\alpha]_D^{20}$ +20.0 (*c* 1.00 in Me_2SO) {lit.,[13] for the D-enantiomer, $[\alpha]_D^{26}$ −18.8 (*c* 1.00 in DMF)}; λ_{max}(95% EtOH)/nm 265 (ε 12 300); δ_H[$(CD_3)_2SO$] 2.26 (1H, m, 2′-H), 2.73 (1H, septuplet, $J_{2',1'}$ 1.9, $J_{2',3'}$ 5.4, $J_{2',2'}$ 13.3, 2′-H), 3.49 (1H, m, 5′-H), 3.59 (1H, m, 5″-H), 3.84 (1H, m, 4′-H), 4.37 (1H, m, 3′-H), 4.97 (1H, t, *J* 5.4, 5′-OH), 5.32 (1H, d, *J* 3.2, 3′-OH), 6.24 (1H, t, $J_{1',2'}$ 6.5, 1′-H), 7.82 (2H, br s, NH_2), 8.34 (1H, s, 8-H); δ_C[$(CD_3)_2SO$] 40.1 (2′-C), 62.5 (5′-C), 71.5 (3′-C), 84.4 (1′-C), 88.8 (4′-C), 119.0 (5-C), 140.7 (8-C), 150.9 (4-C), 153.8 (2-C), 157.6 (6-C); *m/z* (FAB > 0, GT) 286 $(M + H)^+$, 170 $(BH_2)^+$; *m/z* (FAB < 0, GT) 284 $(M - H)^-$, 168 $(B)^-$.

Biological methods

The anti-HIV and anti-HBV assays on cell culture were performed by following previously established procedures as described in ref. 32.

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