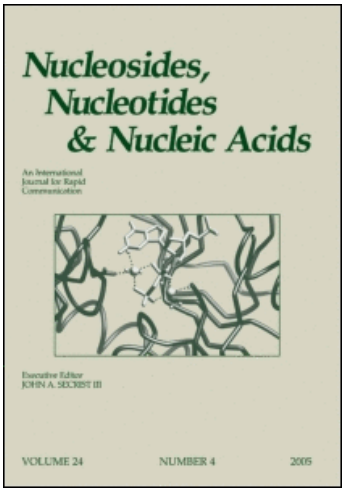

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Tai-Shun Lin[a]; Mei-Zhen Luo[a]; Ju-Liang Zhu[a]; Mao-Chin Liu[a]; Yong-Lian Zhu[a]; Ginger E. Dutschman[a]; Yung-Chi Cheng[a]
[a] Department of Pharmacology and The Comprehensive Cancer Center, Yale University School of Medicine, New Haven, Connecticut, USA

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SYNTHESIS OF A SERIES OF PURINE 2',3'-DIDEOXY-L-NUCLEOSIDE ANALOGUES AS POTENTIAL ANTIVIRAL AGENTS

Tai-Shun Lin, Mei-Zhen Luo, Ju-Liang Zhu, Mao-Chin Liu,* Yong-Lian Zhu, Ginger E. Dutschman, and Yung-Chi Cheng

Department of Pharmacology and The Comprehensive Cancer Center, Yale University School of Medicine, New Haven, Connecticut 06520-8066, *USA*

Abstract: Various 2',3'-dideoxy-L-nucleoside analogues, 6-amino-9-(2,3-dideoxy-β-L-ribofuranosyl)purine (**19**), 2-chloro-6-amino-9-(2,3-dideoxy-β-L-ribofuranosyl)-purine (**20**), 2-chloro-6-amino-9-(2,3-dideoxy-4-thio-β-L-ribofuranosyl)purine (**21**), 2,6-diamino-9-(2,3-dideoxy-β-L-ribofuranosyl)purine (**26**), 2,6-diamino-9-(2,3-dideoxy-4-thio-β-L-ribofuranosyl)-purine (**27**), 2-amino-6-chloro-9-(2,3-dideoxy-β-L-ribofuranosyl)purine (**28**), 6-chloro-9-(2,3-dideoxy-4-thio-β-L-ribofuranosyl)purine (**29**), and 6-amino-9-(2,3-dideoxy-4-thio-β-L-ribofuran-osyl)purine (**30**) have been synthesized by coupling of the sodium salt of 2-amino-6-chloropurine (**1**), 6-chloropurine (**2**), and 2,6-dichloropurine (**3**) with 1-*O*-acetyl-5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-L-ribofuranose (**4**) or 1-*O*-acetyl-5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-4-thio-L-ribofuranose (**5**) in anhydrous MeCN in the presence of either $EtAlCl_2$ or Et_2AlCl followed by separation of the α/β-anomers and deprotection of the blocking groups. However, the synthesis of 9-(2,3-dideoxy-β-L-ribofuranosyl)guanine (**57**, β-L-ddG) was not straightforward. Coupling of the silylated N^2-palmitoylguanine (**48**) with sugar **4** in anhydrous MeCN, using trimethylsilyl trifluoromethanesulfonate as a catalyst yielded *N*-9-β- and *N*-9-α-; *N*-7-β- and *N*-7-α-isomers, compounds **49-52**, which were separated by silica gel column chromatography with two appropriate eluting solvent systems. Removal of the protecting groups gave compound **57** (β-L-ddG) and the other 3 related isomers (**58-60**). The 2',3'-dideoxy-L-nucleoside analogues were tested *in vitro* against HIV-1, HBV, L1210, P388, S-180, and CCRF-CEM. 6-Amino-9-(2,3-dideoxy-β-L-ribofuranosyl)purine (**19**, β-L-ddA) was found to have antiviral activity against HBV with an ED_{50} value of 6 μM.

Considerable effort has been directed in the search for novel nucleoside analogues for use as antiviral agents. Most of these analogues are synthesized by modification of the naturally occurring nucleosides and, therefore, possess the β-D-configuration. In the past, little attention has been given to the synthesis and study of the biological activity of L-nucleosides, the enantiomers of natural D-nucleosides. However, it has been discovered

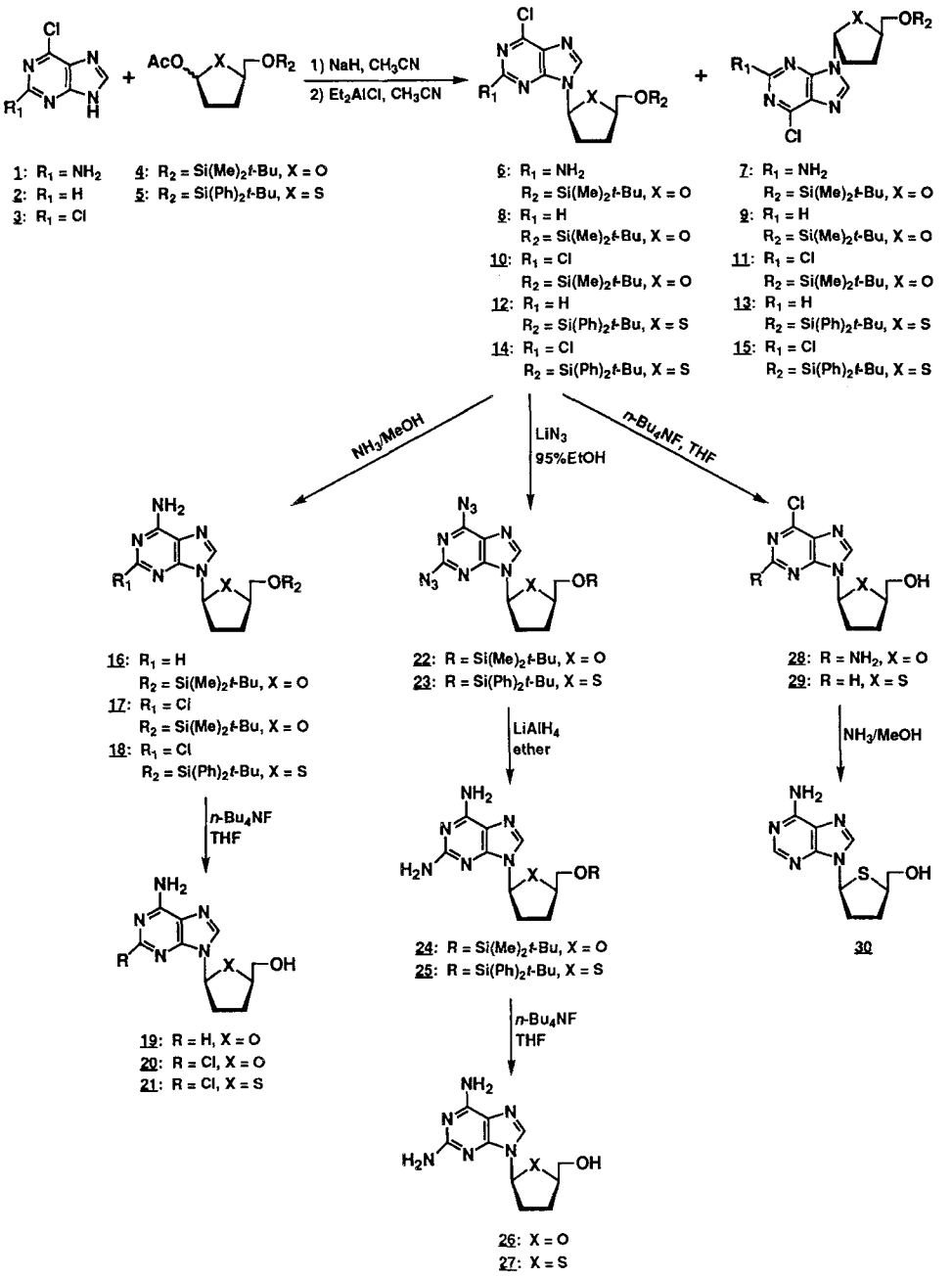
that some β-L-nucleoside derivatives also have biological activity, such as L-adenosine diphosphate (L-ADP) which interacts with bacterial polynucleotide phosphorylase.[1] A study of the metabolism of L-nucleosides demonstrated that they are not or are very poorly metabolized in mice, the reason for which may be due to the result that the L-nucleosides are not recognized by normal cellular enzymes.[2] Recently, Spadari *et al.*[3] reported that L-thymidine is not recognized by human thymidine kinase, but functions as a specific substrate for the herpes simplex virus type 1 (HSV-1) viral enzyme thereby reducing HSV-1 multiplication in HeLa cells. Belleau *et al.*[4,5] first described the synthesis and anti-human immunodeficiency virus (HIV) activity of an unusual nucleoside analogue, (±)-2',3'-dideoxy-3'-thiacytidine (BCH-189), in which the ribose is replaced by a 1,3-oxathiolane ring. Subsequently, it was found that the L-configuration isomer of BCH-189 [(−)-3TC, (−)-SddC, (−)-BCH-189], was as equally potent as the D-configuration isomer [(+)-BCH-189] against HIV-1 and HIV-2 *in vitro*. However, the L-isomer was found to be significantly less toxic to cultured human lymphocytes than the D-form and is now undergoing clinical trial in patients with AIDS and AIDS-related complex.[6,7] (−)-3TC [(−)-SddC] was also found to exhibit the most potent anti-hepatitis B virus (HBV) activity with the least toxic effect among its four possible stereoisomers.[8,9] In addition, the 5-fluoro derivative of (−)-3TC [(−)-SddC], (−)-β-L-5-fluoro-2',3'-dideoxy-3'-thiacytidine (β-L-FTC), was also synthesized and found to exhibit potent anti-HIV and anti-HBV activities *in vitro*.[10,11]

Recently, the synthesis and anti-HIV and anti-HBV activities of a series of L-configuration2',3'-dideoxypyrimidine nucleoside analogues have been reported by our laboratory.[12-17] Among these compounds, 2',3'-dideoxy-β-L-5-fluorocytidine (β-L-FddC) was found to demonstrate more potent activity against both HIV and HBV; and 2',3'-dideoxy-β-L-cytidine (β-L-ddC) was found to show more potent antiviral activity against HBV but less activity against HIV *in vitro* than 2',3'-dideoxy-β-D-cytidine (ddC), with much less host toxicity.[12,13] ddC is currently used as a drug to treat HIV infection. Similar results concerning the anti-HIV activity of β-L-ddC and β-L-FddC have also been reported by Gosselin *et al.*[18,19] and subsequently, their anti-HBV activity has also been confirmed by Schinazi *et al.*[20] Since some β-D-2',3'-dideoxypurine nucleosides, such as 2',3'-dideoxyadenosine (ddA) and 2',3'-dideoxyguanosine (ddG) are active against HIV,[21] and ddG is also active against HBV,[22] it was of interest to synthesize the enantiomers of these purine nucleosides, the unnatural L-configuration nucleoside analogues, as potential antiviral agents, as well as to study their structure-activity relationships. In addition, thionucleosides, in which the oxygen of the sugar ring has been replaced by sulfur, have shown interesting biological activities.[23-25] Thus, a series of

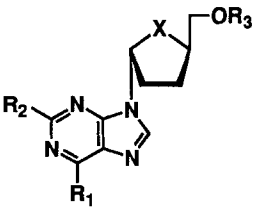
4'-thio derivatives of purine 2',3'-dideoxy-β-L-nucleosides has also been synthesized and evaluated for their antiviral activities.

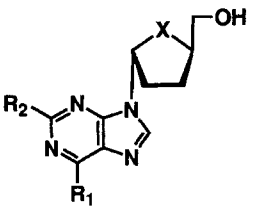
SYNTHESIS

The syntheses of 6-aminopurine dideoxynucleosides **19-21** and **30**, 2,4-diaminopurine dideoxynucleosides **26** and **27**, and 2-aminopurine dideoxynucleoside **28** are described in **SCHEME 1**. Coupling[25,26] of the sodium salts of 2-amino-6-chloropurine (**1**), 6-chloropurine (**2**), and 2,6-dichloropurine (**3**) with 1-*O*-acetyl-5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-L-ribofuranose (**4**)[13] or 1-*O*-acetyl-5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-4-thio-L-ribofuranose (**5**)[27] in anhydrous acetonitrile in the presence of either ethylaluminum dichloride ($EtAlCl_2$) or diethylaluminum chloride (Et_2AlCl) yielded the respective protected purine nucleosides **6-15** as a mixture of α/β-anomers. Most of the α/β-anomeric mixtures could be separated on a silica gel column by repeated chromatography using the appropriate solvent systems except for the mixture of 6-chloro-9-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-4-thio-β-L-ribofuranosyl]purine (**12**) and its α-anomer (**13**). However, after removal of *tert*-butyldiphenylsilyl protecting group of compounds **12** and **13**, the chromatographic separation was more readily effected to furnish the pure β-anomer, 6-chloro-9-(2,3-dideoxy-4-thio-β-L-ribofuranosyl)purine (**29**), and its α-anomer **44** in moderate yields. Nucleophilic displacement reactions of the 6-chloropurine nucleosides **8**, **10**, and **14** with saturated NH_3/MeOH solution gave the corresponding 6-aminopurine nucleosides **16-18**. Treatment of compounds **16-18** with tetra-*n*-butylammonium fluoride in tetrahydrofuran (THF) afforded the target compounds **19-21**. The β-2,6-dichloropurine nucleosides **10** and **14** were treated with lithium azide in ethanol to afford the respective diazidopurine nucleosides **22** and **23**, which were further reduced with lithium aluminum hydride ($LiAlH_4$) to produce the diamino derivatives **24** and **25**. Treatment of compounds **24** and **25** with tetra-*n*-butylammonium fluoride in THF gave the final products **26** and **27**. Deprotection of compound **6** was carried out in the usual manner to yield compound **28**. Compound **29** was refluxed in a saturated methanolic ammonia solution for 3 days to give compound **30**. The α-anomers, compounds **38-45** (**FIGURE 1**) were synthesized by a similar methodology as described for the corresponding β-anomers. 6-Amino-9-(2,3-dideoxy-β-L-ribofuranosyl)purine (**19**, β-L-ddA) was also independently synthesized by Mansuri *et al.*,[28] however, no physical properties, spectroscopic data, and experimental details were reported. The synthesis of 6-amino-9-(2,3-dideoxy-α-L-ribofuranosyl)purine (**38**, α-L-ddG) and 2,6-diamino-9-(2,3-dideoxy-α-L-ribofuranosyl)purine (**40**) by an enzymatic method was recently reported by Van Draanen and Koszalka.[29]



SCHEME 1





31: $R_1 = NH_2$, $R_2 = H$, $R_3 = Si(Me)_2t\text{-}Bu$, X = O

32: $R_1 = NH_2$, $R_2 = Cl$, $R_3 = Si(Me)_2t\text{-}Bu$, X = O

33: $R_1 = N_3$, $R_2 = N_3$, $R_3 = Si(Me)_2t\text{-}Bu$, X = O

34: $R_1 = NH_2$, $R_2 = NH_2$, $R_3 = Si(Me)_2t\text{-}Bu$, X = O

35: $R_1 = NH_2$, $R_2 = Cl$, $R_3 = Si(Ph)_2t\text{-}Bu$, X = S

36: $R_1 = N_3$, $R_2 = N_3$, $R_3 = Si(Ph)_2t\text{-}Bu$, X = S

37: $R_1 = NH_2$, $R_2 = NH_2$, $R_3 = Si(Ph)_2t\text{-}Bu$, X = S

38: $R_1 = NH_2$, $R_2 = H$, X = O

39: $R_1 = NH_2$, $R_2 = Cl$, X = O

40: $R_1 = NH_2$, $R_2 = NH_2$, X = O

41: $R_1 = Cl$, $R_2 = NH_2$, X = O

42: $R_1 = NH_2$, $R_2 = Cl$, X = S

43: $R_1 = NH_2$, $R_2 = NH_2$, X = S

44: $R_1 = Cl$, $R_2 = H$, X = S

45: $R_1 = NH_2$, $R_2 = H$, X = S

FIGURE 1

The synthesis of 9-(2,3-dideoxy-β-L-ribofuranosyl)guanine (**57**, β-L-ddG) was not straightforward. Coupling of silylated N^2-palmitoylguanine (**48**) with sugar **4** in anhydrous acetonitrile in the presence of either $EtAlCl_2$ or Et_2AlCl formed a complex mixture of products, mainly containing the 7-β- and 7-α-isomers (compounds **51** and **52**), a small amount of the 9-α-isomer, and a trace amount of the 9-β-isomer (compounds **50** and **49**). Therefore, it was difficult to isolate, especially the target 9-β-isomer (**49**). Recently, Van Draanen and Koszalka[29] also reported that because the coupling reaction was plagued by a low yield and the formation of four isomers, as an alternative synthetic approach, a phosphorylase enzymatic trans-ribosylation methodology was used to synthesize 9-(2,3-dideoxy-α-L-ribofuranosyl)guanine (**58**, α-L-ddG) from α-L-dideoxyuridine (α-L-ddU). However, in their report, the synthesis of the 9-β-isomer, 9-(2,3-dideoxy-β-L-ribofuranosyl)guanine (**57**, β-L-ddG), was not described. After careful comparison of the effects of various catalysts on the proportion of the formation of the four isomers and the efficiency of different compositions of the eluting solvent systems, we were finally able to produce and separate the four isomers (compounds **49-52**) in reasonable yields by using trimethylsilyl trifluoromethanesulfonate as a catalyst and two appropriate eluting solvent systems, as described in the Experimental Section. Deprotection of compounds **49-52** with tetra-*n*-butylammonium fluoride in THF gave the

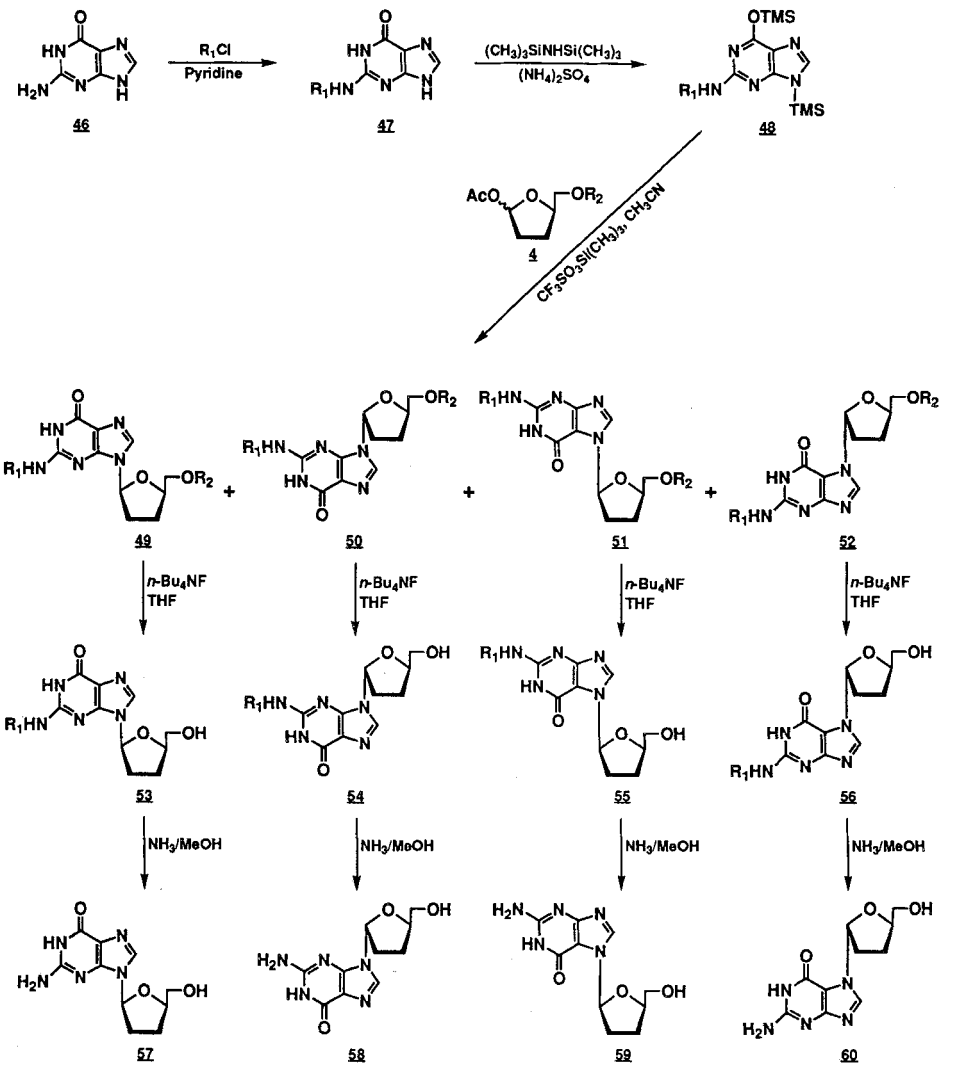
corresponding N^2-palmitoylguanine nucleoside derivatives **53-56**, followed by treatment with saturated methanolic ammonia solution, furnished the target compounds, 9-β- and 9-α-; 7-β- and 7-α-L-isomers of ddG (**57-60**) as shown in **SCHEME 2**.

The assignment of the *N*-glycosidic linkage of the *N*-7 and *N*-9 isomers is based on the characteristic UV spectra of these derivatives. The UV spectra of *N*-9 guanine nucleoside isomers showed a maximum peak at around 256 nm while the *N*-7 isomers showed a maximum peak at 282 nm. Furthermore, as shown in **TABLE 1**, the NMR spectra of the 8-H and 1'-H protons of *N*-7 isomers are both downfield than those of the corresponding *N*-9 isomers. For example, the chemical shifts of the 8-H and 1'-H protons of the *N*-7-β-isomer (**59**) appear at 8.27 and 6.30 ppm, and the *N*-9-β-isomer (**57**) chemical shifts appear at 7.42 and 5.96 ppm, respectively.

The assignment of the anomeric configuration of these nucleosides was made on the basis of characteristic proton NMR spectra. The 4'-H protons of the α-anomers appear at a lower field than those of the β-anomers. Conversely, the 5'-H protons of the α-anomers appear at a higher field than those of the β-anomers (**TABLE 2**). These shifts are attributed to the effect that protons at a syn-position relative to the base are more deshielded than those in anti-position to the base. The 4'-H protons of the α-anomers and the bases are on the same side of the sugar ring, and those of β-anomers are on the opposite of the sugar ring with the bases. On the contrary, the 5'-H protons of the α-anomers and the bases are on the opposite side of the sugar ring, and those of β-anomers are on the same side of the sugar ring with the bases. These results are consistent with those obtained from other nucleoside derivatives in both pyrimidine and purine series by us[13] and other laboratories.[30-32]

BIOLOGICAL EVALUATION

The synthesized 2',3'-dideoxy-L-nucleoside analogues were tested for their antiviral activities *in vitro* against HIV-1 and HBV by the previously reported methodology.[13] Only 6-amino-9-(2,3-dideoxy-β-L-ribofuranosyl)purine (**19**, β-L-ddA) demonstrated activity against HBV with an ED_{50} value of 6 μM. The rest of the compounds were found not to be active up to a concentration of 10 μM. All of the compounds were inactive against HIV-1 up to a concentration of 100 μM. Furthermore, the compounds were screened for their cytotoxicity against L1210, P388, Sarcoma-180 (S-180), and CCRF-CEM (CEM) neoplastic cell lines.[13] Except for compounds 2-amino-6-chloro-9-(2,3-dideoxy-β-L-ribofuranosyl)purine (**28**) and 9-(2,3-dideoxy-β-L-ribofuranosyl)guanine (**57**, β-L-ddG), which showed modest activity against CEM cells



SCHEME 2

TABLE 1. Proton NMR chemical shifts δ (ppm) for *N*-9 and *N*-7 isomers of 2',3'-dideoxy-L-α,β-guanosine derivatives.

Compd	8-H	Δ δ	1'-H	Δ δ
49 (9-β)	8.05	-0.35	5.97	-0.53
51 (7-β)	8.40		6.50	
50 (9-α)	7.70	-0.25	6.08	-0.37
52 (7-β)	7.95		6.45	
53 (9-β)	7.95	-0.65	5.95	-0.50
55 (7-β)	8.60		6.45	
54 (9-α)	7.85	-0.15	6.23	-0.30
56 (7-α)	8.00		6.53	
57 (9-β)	7.92	-0.35	5.96	-0.34
59 (7-β)	8.27		6.30	
58 (9-α)	7.81	-0.25	6.03	-0.31
60 (7-α)	8.06		6.34	

Table 2. Proton NMR chemical shifts δ (ppm) for various 2',3'-dideoxy-L-α,β-purine nucleoside derivatives.

Compd	4'-H	Δ δ	5'-H	Compd	4'-H	Δ δ	5'-H
6 (β)	4.20	-0.25	3.78	**24** (β)	4.15	-0.30	3.80
7 (α)	4.45		3.65	**34** (α)	4.45		3.65
8 (β)	4.25	-0.25	3.90	**25** (β)	3.71	-0.19	3.90
9 (α)	4.50		3.70	**37** (α)	3.90		3.62
10 (β)	4.25	-0.30	3.90	**26** (β)	4.04	-0.25	3.53
11 (α)	4.55		3.75	**40** (α)	4.29		3.40
14 (β)	3.84	-0.13	3.95	**27** (β)	3.58	-0.23	3.73
15 (α)	3.97		3.67	**43** (α)	3.81		3.41
16 (β)	4.30	-0.22	3.85	**28** (β)	4.07	-0.30	3.53
31 (α)	4.52		3.70	**41** (α)	4.37		3.45
17 (β)	4.20	-0.28	3.90	**29** (β)	3.93	-0.09	3.85
32 (α)	4.48		3.70	**44** (α)	4.02		3.73
18 (β)	3.70	-0.18	3.75	**30** (β)	3.61	-0.25	3.76
35 (α)	3.88		3.66	**45** (α)	3.86		3.43
19 (β)	4.12	-0.26	3.59	**57** (β)	4.03	-0.26	3.53
38 (α)	4.38		3.47	**58** (α)	4.29		3.39
20 (β)	4.09	-0.24	3.55	**21** (β)	3.74	-0.10	3.62
39 (α)	4.33		3.42	**42** (α)	3.84		3.42

with the respective ED_{50} values of 20 and 30 μM and compounds **20** (S-180), **28** (P388), **42** (S-180; L1210), **45** (L1210), **57** (P388), and **59** (L1210), which had ED_{50} values of 100 μM for the given cell lines, all other compounds showed no activity at 100 μM for the various cell lines. These results suggest that most of the compounds in this series were not substrates of the relevant enzyme which is responsible for the activation.

It is noteworthy that in the pyrimidine 2',3'-dideoxy-L-nucleoside series, 2',3'-dideoxy-β-L-5-fluorocytidine (β-L-FddC) is more active against both HIV-1 and HBV *in vitro* than its D-enantiomer, 2',3'-dideoxy-β-D-5-fluorocytidine (β-D-FddC).[13] On the contrary, in the purine 2',3'-dideoxy-L-nucleoside series, 9-(2,3-dideoxy-β-L-ribofuranosyl)guanine (**57**, β-L-ddG) did not show any activity against neither HIV-1 nor HBV, and its D-nucleoside counterpart, 9-(2,3-dideoxy-β-D-ribofuranosyl)guanine (ddG), demonstrates antiviral activity against both HIV-1 and HBV. In addition, 6-amino-9-(2,3-dideoxy-β-L-ribofuranosyl)purine (**19**, β-L-ddA) was found to show activity against HBV with an ED_{50} value of 6 μM. However, 6-amino-9-(2,3-dideoxy-β-D-ribofuranosyl)purine (ddA), which is known to have antiviral activity against HIV-1, was found not to be active against HBV at the tested concentration. The findings are summarized in **TABLE 3**.

EXPERIMENTAL SECTION

Melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian EM-390 (90 MHz) NMR spectrometer or a Bruker WM-250 (250 MHz) spectrometer with Me_4Si as the internal reference. Optical rotations were measured in a 1-dm cell with a Perkin-Elmer Model 241 polarimeter at 25 °C. The UV spectra were recorded on a Beckman-25 spectrophotometer. TLC was performed on EM precoated silica gel sheets containing a fluorescent indicator. Elemental analyses were carried out by the Baron Consulting Co., Orange, CT, U.S.A.

2-Amino-6-chloro-9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-β-L-ribofuranosyl]purine (6) and its α-anomer (7). A mixture of 2-amino-6-chloropurine (**1**, 5.0 g, 29 mmol) and sodium hydride (80% in mineral oil, 1.1 g, 37 mmol) in anhydrous acetonitrile (250 mL) was stirred at 60-75 °C for 2 h under nitrogen. The reaction mixture was then cooled to room temperature, followed by addition of 1-*O*-acetyl-5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-L-ribofuranose (**4**, 8.3 g, 30 mmol) and 1.8 M solution of ethylaluminum dichloride ($EtAlCl_2$) in toluene (16.6 mL, 30 mmol) over a period of 1 h at room temperature. The mixture was stirred at room temperature overnight and then slowly poured into an ice-cooled mixture of methylene

TABLE 3. Evaluation of 2',3'-dideoxy-L-nucleoside analogues against human immunodeficiency virus (HIV), hepatitis B virus (HBV), and L1210, S-180, P388, and CCRF-CEM neoplastic cell lines *in vitro*.

	ED_{50} (μM)[a]					
Compd	HIV-1[b]	HBV[c]	L1210[d]	S-180[d]	P388[d]	CCRF-CEM[d]
ddG	10		-	-	-	-
ddA	-	>10	-	-	-	-
19 (β)	>100	6	>100	>100	>100	>100
38 (α)	>100	>10	>100	>100	>100	>100
20 (β)	>100	>10	>100	100	>100	>100
39 (α)	>100	>10	>100	>100	>100	>100
21 (β)	>100	>10	>100	>100	>100	>100
42 (α)	>100	>10	100	100	>100	>100
26 (β)	>100	>10	>100	>100	>100	>100
40 (α)	>100	>10	>100	>100	>100	>100
27 (β)	>100	>10	>100	>100	>100	>100
43 (α)	>100	>10	>100	>100	>100	>100
28 (β)	>100	>10	>100	>100	100	20
41 (α)	>100	>10	>100	>100	>100	>100
30 (β)	>100	>10	>100	>100	>100	>100
45 (α)	>100	>10	100	>100	>100	>100
57 (β)	>100	>10	>100	>100	100	30
58 (α)	>100	>10	>100	>100	>100	>100
59 (β)	>100	>10	100	>100	>100	>100
60 (α)	>100	>10	>100	>100	>100	>100

[a]ED_{50} values represent the drug concentration (μM) required to inhibit 50% of viral or cancer cell replication. [b]The HIV-1 assays were performed using a viral multiplicity of 0.1 $TCID_{50}$/cell and the compounds were tested up to a concentration of 100 μM. [c]The compounds were tested up to a concentration of 10 μM. [d]The compounds were tested up to a concentration of 100 μM.

chloride and saturated sodium bicarbonate solution with stirring. The mixture was stirred for 10 min and filtered. The organic layer was washed with saturated sodium bicarbonate solution, brine, and water, then dried over anhydrous $MgSO_4$. After filtration, the solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOAc, 3:1, v/v) to give 3.8 g (33.6%) of a mixture of β-anomer (**6**) and α-anomer (**7**) with a ratio of 3:5 (estimated by ^1H NMR spectrum for the integration values of 8-H at δ 8.10 and 7.85 ppm, respectively for the β- and α-anomers). The mixture was further separated by silica gel column chromatography (EtOAc/hexane, 2:1, v/v) to afford 0.76 g (6.8%) of compound **6** (β-anomer) and 1.1 g (9.8%) of compound **7** (α-anomer).

Compound **6** was isolated as a foam: TLC, R_f 0.66 (EtOAc/hexane, 2:1, v/v); ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H, $SiMe_2$), 0.90 (s, 9 H, Si*t*-Bu), 2.00-2.55 (m, 4 H, 2'-H and 3'-H), 3.70-3.85 (d, 2 H, 5'-H), 4.10-4.30 (m, 1 H, 4'-H), 5.10-5.20 (s, 2 H, 2-NH_2, D_2O exchangeable), 6.05-6.20 (t, 1 H, 1'-H), 8.10 (s, 1 H, 8-H). Anal. Calcd. for $C_{16}H_{26}N_5O_2ClSi{\cdot}0.25\ CH_3COOC_2H_5$: C, 50.29; H, 6.95; N, 17.25. Found: C, 50.84; H, 7.17; N, 17.65.

Compound **7** was isolated as a foam: TLC, R_f 0.68 (EtOAc/hexane, 2:1, v/v); ^1H NMR ($CDCl_3$) δ 0.09 (s, 6 H, $SiMe_2$), 0.90 (s, 9 H, Si*t*-Bu), 2.00-2.60 (m, 4 H, 2'-H and 3'-H), 3.60-3.70 (d, 2 H, 5'-H), 4.35-4.55 (m, 1 H, 4'-H), 5.20-5.30 (s, 2 H, 2-NH_2, D_2O exchangeable), 6.10-6.25 (t, 1 H, 1'-H), 7.85 (s, 1 H, 8-H). Anal. Calcd. for $C_{16}H_{26}N_5O_2ClSi$: C, 50.05; H, 6.83; N, 18.24. Found: C, 50.33; H, 7.16; N, 17.93.

Compounds **8-15** were synthesized by a similar methodology as described for the preparation of compounds **6** and **7**.

6-Chloro-9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-β-L-ribofuranosyl]purine (8). Isolated as a foam (18%): TLC, R_f 0.58 (hexane/EtOAc, 4:1, v/v); ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H, $SiMe_2$), 0.90 (s, 9 H, Si*t*-Bu), 2.05-2.60 (m, 4 H, 2'-H and 3'-H), 3.65-4.10 (m, 2 H, 5'-H), 4.15-4.35 (m, 1 H, 4'-H), 6.25-6.40 (t, 1 H, 1'-H), 8.60 (s, 1 H, 8-H), 8.70 (s, 1 H, 2-H). Anal. Calcd. for $C_{16}H_{25}N_4O_2ClSi{\cdot}0.25\ CH_3COOC_2H_5$: C, 52.22; H, 6.96; N, 14.33. Found: C, 51.98; H, 7.28; N, 14.52.

6-Chloro-9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-L-ribofuranosyl]purine (9). Isolated as a foam (22%): TLC, R_f 0.70 (hexane/EtOAc, 4:1, v/v); ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H, $SiMe_2$), 0.92 (s, 9 H, Si*t*-Bu), 2.05-2.75 (m, 4 H, 2'-H and 3'-H), 3.65-3.75 (m, 2 H, 5'-H), 4.40-4.60 (m, 1 H, 4'-H), 6.25-6.40 (t, 1 H, 1'-H), 8.20 (s, 1 H, 8-H), 8.70 (s, 1 H, 2-H). Anal. Calcd. for $C_{16}H_{25}N_4O_2ClSi$: C, 52.08; H, 6.83; N, 15.19. Found: C, 52.40; H, 7.11; N, 14.93.

2,6-Dichloro-9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-β-L-ribofuranosyl]purine (10). Isolated as a glass (26%): TLC, R_f 0.51 (CH_2Cl_2/EtOAc, 10:1, v/v); ^1H NMR ($CDCl_3$) δ 0.12 (s, 6 H, $SiMe_2$), 0.92 (s, 9 H, Si*t*-Bu), 1.90-2.55 (m, 4 H, 2'-H and 3'-H), 3.75-4.05 (m, 2 H, 5'-H), 4.15-4.35 (m, 1 H, 4'-H), 6.20-6.35 (t, 1 H, 1'-H), 8.60 (s, 1 H, 8-H). Anal. Calcd. for $C_{16}H_{24}Cl_2N_4O_2Si \cdot 0.4\ CH_3COOC_2H_5 \cdot 0.1\ CH_2Cl_2$: C, 47.54; H, 6.17; N, 12.53. Found: C, 47.69; H, 5.98; N, 12.25.

2,6-Dichloro-9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-L-ribofuranosyl]purine (11). Isolated as a glass (21%): TLC, R_f 0.70 (CH_2Cl_2/EtOAc, 10:1, v/v); ^1H NMR ($CDCl_3$) δ 0.12 (s, 6 H, $SiMe_2$), 0.95 (s, 9 H, Si*t*-Bu), 2.05-2.70 (m, 4 H, 2'-H and 3'-H), 3.70-3.80 (m, 2 H, 5'-H), 4.45-4.65 (m, 1 H, 4'-H), 6.30-6.40 (t, 1 H, 1'-H), 8.25 (s, 1 H, 8-H). Anal. Calcd. for $C_{16}H_{24}Cl_2N_4O_2Si \cdot 0.4\ CH_3COOC_2H_5$: C, 48.19; H, 6.24; N, 12.77. Found: C, 48.02; H, 5.97; N, 12.71.

6-Chloro-9-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-4-thio-β-L-ribofuranosyl]purine (12) and its α-anomer (13). Isolated as a glass containing a 1:1 α/β-anomeric mixture (67%): TLC, R_f 0.20 (hexane/EtOAc, 6:1, v/v); ^1H NMR ($CDCl_3$) δ 1.10 (s, 9 H, *t*-Bu), 1.80-2.34 (m, 2 H, 3'-H), 2.34-2.63 (m, 2 H, 2'-H), 3.85-4.10 (m, 3 H, 4'-H and 5'-H), 6.18-6.35 (m, 1 H, 1'-H), 7.25-7.55 (m, 6 H, ArH), 7.55-7.80 (m, 4 H, ArH), 8.48 (d, 1 H, 1/2 α-8-H, 1/2 β-8-H), 8.70 (d, 1 H, 1/2 α-2-H, 1/2 β-2-H). Anal. Calcd. for $C_{26}H_{29}N_4ClOSSi \cdot 0.5\ H_2O$: C, 60.27; H, 5.84; N, 10.81. Found: C, 60.14; H, 5.69; N, 10.38.

2,6-Dichloro-9-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-4-thio-β-L-ribofuranosyl]purine (14) and its α-anomer (15). The mixture of β- and α-anomers was separated by silica gel column chromatography, eluting first with hexane/EtOAc (8:1, v/v), then with toluene/EtOAc (10:1, v/v) to give 3.77 g (36%) of the β-anomer **14** and 2.57 g (25%) of the α-anomer **15**.

Compound **14** was isolated as a glass: TLC, R_f 0.20 (hexane/EtOAc, 5:1, v/v); ^1H NMR ($CDCl_3$) δ 1.10 (s, 9 H, *t*-Bu), 1.78-1.92 (m, 1 H, 3'-H), 2.20-2.28 (m, 1 H, 3'-H), 2.35-2.49 (m, 2 H, 2'-H), 3.79-3.88 (m, 2 H, 4'-H and 5'-H), 3.92-3.97 (m, 1 H, 5'-H), 6.23 (dd, 1 H, 1'-H), 7.37-7.50 (m, 6 H, ArH), 7.66-7.73 (m, 4 H, ArH), 8.47 (s, 1 H, 8-H). Anal. Calcd. for $C_{26}H_{28}N_4Cl_2OSSi$: C, 57.45; H, 5.19; N, 10.31. Found: C, 57.15; H, 5.41; N, 10.37.

Compound **15** was isolated as a glass: TLC, R_f 0.19 (hexane/EtOAc, 5:1, v/v); ^1H NMR ($CDCl_3$) δ 1.08 (s, 9 H, *t*-Bu), 2.04-2.23 (m, 2 H, 3'-H), 2.33-2.45 (m, 2 H, 2'-H), 3.67 (d, 2 H, 5'-CH_2), 3.94-4.01 (m, 1 H, 4'-H), 6.20 (dd, 1 H, 1'-H), 7.37-7.51 (m, 6 H, ArH), 7.66-7.73 (m, 4 H, ArH), 8.51 (s, 1 H, 8-H). Anal. Calcd. for $C_{26}H_{28}N_4Cl_2OSSi$: C, 57.45; H, 5.19; N, 10.31. Found: C, 57.11; H, 5.44; N, 10.28.

6-Amino-9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-β-L-ribofuranosyl]purine (16). A mixture of compound **8** (0.80 g, 2.20 mmol) and 100 mL of saturated NH_3/MeOH solution was heated at 80 °C with stirring for 3 d. The cooled mixture was evaporated *in vacuo* to dryness and the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 20:1, v/v) to afford 0.54 g (71%) of product as a white solid: mp 140-143 °C; TLC, R_f 0.26 (CH_2Cl_2/MeOH, 15:1, v/v); ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H, $SiMe_2$), 0.95 (s, 9 H, Si*t*-Bu), 2.05-2.65 (m, 4 H, 2'-H and 3'-H), 3.70-4.00 (m, 2 H, 5'-H), 4.20-4.40 (m, 1 H, 4'-H), 6.10 (s, 2 H, 6-NH_2, D_2O exchangeable), 6.30-6.40 (t, 1 H, 1'-H), 8.15 (s, 1 H, 8-H), 8.25 (s, 1 H, 2-H). Anal. Calcd. for $C_{26}H_{27}N_5O_2Si{\cdot}0.1\ CH_3COOC_2H_5$: C, 54.97; H, 7.82; N, 19.54. Found: C, 55.29; H, 7.93; N, 19.29.

Compounds **17** and **18** were synthesized by a similar methodology as described for the preparation of compound **16** from respective compounds **10** and **14**.

2-Chloro-6-amino-9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-β-L-ribofuranosyl]purine (17). Isolated as a white solid (97%): mp 180-182 °C; TLC, R_f 0.50 (CH_2Cl_2/EtOH, 20:1, v/v); ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H, $SiMe_2$), 0.93 (s, 9 H, Si*t*-Bu), 1.95-2.55 (m, 4 H, 2'-H and 3'-H), 3.75-4.05 (m, 2 H, 5'-H), 4.15-4.25 (m, 1 H, 4'-H), 6.15-6.30 (t, 1 H, 1'-H), 6.35 (s, 2 H, 6-NH_2, D_2O exchangeable), 8.25 (s, 1 H, 8-H). Anal. Calcd. for $C_{16}H_{26}ClN_5O_2Si{\cdot}0.2\ CH_3COOC_2H_5$: C, 50.25; H, 6.93; N, 17.44. Found: C, 50.65; H, 7.33; N, 17.82.

2-Chloro-6-amino-9-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-4-thio-β-L-ribofuranosyl]purine (18). Isolated as a white foam (77%): TLC, R_f 0.36 (CH_2Cl_2/MeOH, 20:1, v/v); ^1H NMR (Me_2SO-d_6) δ 1.10 (s, 9 H, *t*-Bu), 1.68-2.00 (m, 1 H, 3'-H_A), 2.00-2.26 (m, 1 H, 3'-H_B), 2.26-2.57 (m, 2 H, 2'-H), 3.65-3.75 (m, 1 H, 4'-H), 3.75-4.12 (m, 2 H, 5'-H), 6.13 (t, 1 H, 1'-H), 6.80 (s, 2 H, NH_2, D_2O exchangeable), 7.30-7.53 (m, 6 H, ArH), 7.56-7.82 (m, 4 H, ArH), 8.10 (s, 1 H, 8-H). Anal. Calcd. for $C_{26}H_{30}ClN_5OSSi$: C, 59.58; H, 5.77; N, 13.36. Found: C, 59.38; H, 6.01; N, 13.21.

6-Amino-9-(2,3-dideoxy-β-L-ribofuranosyl)purine (19). To a stirred solution of compound **16** (0.48 g, 1.37 mmol) in THF (30 mL) was added dropwise 5.3 mL of tetra-*n*-butylammonium fluoride (1 M solution in THF, 5.3 mmol) at ambient temperature. The reaction was completed within 1 h, and the solvent was removed *in vacuo*. The residue was dissolved in 15 mL of water and extracted with methylene chloride (2 x 10 mL). The water layer was evaporated with 5 g of silica gel to dryness and the residue was chromatographed on a silica gel column (EtOAc/MeOH, 6:1, v/v) to afford 0.28 g (87%) of product as a white solid: mp 158-160 °C; TLC, R_f 0.46 (CH_2Cl_2/MeOH, 6:1, v/v); $[\alpha]_D$ +15.7° (*c* = 0.11, MeOH); UV (MeOH) λ_{max} 262 nm (ε 14400), λ_{min} 230

nm; UV (0.01 N HCl) λ_{max} 260 nm (ε 13600), λ_{min} 230 nm; UV (0.01 N NaOH) λ_{max} 262 nm (ε 14200), λ_{min} 228 nm; ^{1}H NMR (Me_2SO-d_6) δ 2.01-2.52 (m, 4 H, 2'-H and 3'-H), 3.48-3.66 (m, 2 H, 5'-H), 4.09-4.15 (m, 1 H, 4'-H), 5.05-5.09 (t, 1 H, 5'-OH, D_2O exchangeable), 6.20-6.24 (t, 1 H, 1'-H), 7.27 (s, 2 H, 6-NH_2, D_2O exchangeable), 8.14 (s, 1 H, 8-H), 8.36 (s, 1 H, 2-H). Anal. Calcd. for $C_{10}H_{13}N_5O_2 \cdot 0.2\ CH_3OH$: C, 50.69; H, 5.75; N, 28.98. Found: C, 50.67; H, 5.34; N, 28.61.

Compounds **20** and **21** were synthesized by a similar methodology as described for the preparation of compound **19** from respective compounds **17** and **18**.

2-Chloro-6-amino-9-(2,3-dideoxy-β-L-ribofuranosyl)purine (20). Isolated as a white solid (87%): mp 240 °C (dec.); TLC, R_f 0.56 (CH_2Cl_2/MeOH, 6:1, v/v); $[\alpha]_D$ +4.2° (*c* = 0.15, MeOH); UV (MeOH) λ_{max} 266 nm (ε 18000), λ_{min} 232 nm; UV (0.01 N HCl) λ_{max} 264 nm (ε 16100), λ_{min} 230 nm; UV (0.01 N NaOH) λ_{max} 266 nm (ε 14000), λ_{min} 232 nm; ^{1}H NMR (Me_2SO-d_6) δ 1.97-2.49 (m, 4 H, 2'-H and 3'-H), 3.46-3.63 (m, 2 H, 5'-H), 4.06-4.11 (m, 1 H, 4'-H), 4.91-4.95 (t, 1 H, 5'-OH, D_2O exchangeable), 6.13-6.15 (t, 1 H, 1'-H), 7.78 (s, 2 H, 6-NH_2, D_2O exchangeable), 8.36 (s, 1 H, 8-H). Anal. Calcd. for $C_{10}H_{12}ClN_5O_2 \cdot 0.5\ C_2H_5OH$: C, 45.13; H, 5.16; N, 23.93. Found: C, 45.32; H, 5.38; N, 23.74.

2-Chloro-6-amino-9-(2,3-dideoxy-4-thio-β-L-ribofuranosyl)purine (21). Isolated as white crystals (80%): mp 168-169 °C; TLC, R_f 0.34 (CH_2Cl_2/MeOH, 10:1, v/v); $[\alpha]_D^{25}$ -21.3° (*c* = 0.18, MeOH); UV (MeOH) λ_{max} 267 (ε 16200), λ_{min} 233 nm; UV (0.01 N HCl) λ_{max} 263 nm (ε 17500), λ_{min} 230 nm; UV (0.01 N NaOH) λ_{max} 264 nm (ε 18400), λ_{min} 230 nm; ^{1}H NMR (Me_2SO-d_6) δ 1.90-2.02 (m, 1 H, 3'-H), 2.10-2.25 (m, 1 H, 3'-H), 2.30-2.53 (m, 2 H, 2'-H), 3.56-3.68 (m, 2 H, 5'-H), 3.71-3.76 (m, 1 H, 4'-H), 5.12 (t, 1 H, 5'-OH, D_2O exchangeable), 6.07 (dd, 1 H, 1'-H), 7.81 (s, 2 H, NH_2, D_2O exchangeable), 8.44 (s, 1 H, 8-H). Anal. Calcd. for $C_{10}H_{12}ClN_5OS$: C, 42.03; H, 4.23; N, 24.51. Found: C, 42.38; H, 4.23; N, 24.13.

2,6-Diamino-9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-β-L-ribofuranosyl]purine (24). A mixture of compound **10** (0.96 g, 2.38 mmol) and lithium azide (0.60 g, 12 mmol) in 120 mL of 95% ethanol was refluxed with stirring for 2 h. The solvent was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 (30 mL) and water (10 mL). The organic layer was washed with water (10 mL) and dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the crude 2,6-diazido derivative (**22**) was redissolved in 150 mL of ether. The ethereal solution was stirred with $LiAlH_4$ (1.2 g, 30 mmol) for 30 min at room temperature. The excess $LiAlH_4$ was decomposed by the careful addition of a 20% H_2O/THF solution followed by filtration through celite. The filtrate was evaporated *in vacuo* to give the crude diamino derivative, which was then purified on a silica gel column (CH_2Cl_2/MeOH, 15:1, v/v) to afford 0.29 g

(33.4%, two reaction steps) of product as a white solid: mp 138-140 °C (dec.); TLC, R_f 0.28 (CH_2Cl_2/MeOH, 15:1, v/v); ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H, $SiMe_2$), 0.90 (s, 9 H, Si*t*-Bu), 1.90-2.50 (m, 4 H, 2'-H and 3'-H), 3.60-4.00 (m, 2 H, 5'-H), 4.05-4.25 (m, 1 H, 4'-H), 4.80-4.90 (br s, 2 H, NH_2, D_2O exchangeable), 5.70-5.80 (br s, 2 H, NH_2, D_2O exchangeable), 6.05-6.20 (t, 1 H, 1'-H), 7.90 (s, 1 H, 8-H). Anal. Calcd. for $C_{16}H_{28}N_6O_2Si$: C, 52.72; H, 7.74; N, 23.06. Found: C, 52.56; H, 8.00; N, 22.69.

2,6-Diamino-9-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-4-thio-β-L-ribofuranosyl]purine (25). The title compound was synthesized from compound **14** by the same methodology as mentioned for the preparation of compound **24** and was isolated as a foam (68%): TLC, R_f 0.46 (CH_2Cl_2/MeOH, 10:1, v/v); ^1H NMR ($CDCl_3$) δ 1.10 (s, 9 H, *t*-Bu), 1.60-2.20 (m, 2 H, 3'-H), 2.22-2.48 (m, 2 H, 2'-H), 3.60-3.82 (m, 1 H, 4'-H), 3.82-3.97 (m, 2 H, 5'-H), 4.79 (br s, 2 H, NH_2, D_2O exchangeable), 5.57 (br s, 2 H, NH_2, D_2O exchangeable), 5.97 (t, 1 H, 1'-H), 7.20-7.45 (m, 6 H, ArH), 7.50-7.72 (m, 4 H, ArH), 7.72 (s, 1 H, 8-H). Anal. Calcd. for $C_{26}H_{32}N_6OSSi$: C, 61.87; H, 6.39; N, 16.65. Found: C, 61.81; H, 6.27; N, 16.34.

2,6-Diamino-9-(2,3-dideoxy-β-L-ribofuranosyl)purine (26). Compound **26** was prepared by a similar procedure as described for the synthesis of compound **19** and isolated as a white solid (89%): mp 164-166 °C (dec.); TLC, R_f 0.51 (CH_2Cl_2/MeOH, 6:1, v/v); $[\alpha]_D$ +11° (*c* = 0.10, MeOH); UV (MeOH) λ_{max} 283 nm (ε 10700), λ_{min} 268 nm; UV (0.01 N HCl) λ_{max} 290 nm (ε 9000), λ_{min} 271 nm; UV (0.01 N NaOH) λ_{max} 282 nm (ε 9600), λ_{min} 267 nm; ^1H NMR (Me_2SO-d_6) δ 1.95-2.04 (m, 2 H, 3'-H), 2.26-2.32 (m, 2 H, 2'-H), 3.48-3.58 (m, 2 H, 5'-H), 4.02-4.05 (m, 1 H, 4'-H), 5.06 (t, 1 H, 5'-OH, D_2O exchangeable), 5.76 (s, 2 H, 6-NH_2, D_2O exchangeable), 5.97-6.02 (t, 1 H, 1'-H), 6.70 (s, 2 H, 6-NH_2, D_2O exchangeable), 7.90 (s, 1 H, 8-H). Anal. Calcd. for $C_{10}H_{14}N_6O_2 \cdot CH_3OH \cdot 0.1\ H_2O$: C, 46.50; H, 6.45; N, 29.58. Found: C, 46.78; H, 6.36; N, 29.18.

2,6-Diamino-9-(2,3-dideoxy-4-thio-β-L-ribofuranosyl)purine (27). Isolated as white crystals (66%): mp 213-215 °C; TLC, R_f 0.18 (CH_2Cl_2/MeOH, 10:1, v/v); $[\alpha]_D^{25}$ -7.3° (*c* = 0.22, MeOH); UV (MeOH) λ_{max} 279 (ε 11000), λ_{min} 236 nm; UV (0.01 N HCl) λ_{max} 288 nm (ε 12200), λ_{min} 234 nm; UV (0.01 N NaOH) λ_{max} 279 nm (ε 12000), λ_{min} 237 nm; ^1H NMR (Me_2SO-d_6) δ 1.94-2.02 (m, 1 H, 3'-H_A), 2.08-2.18 (m, 1 H, 3'-H_B), 2.27-2.44 (m, 2 H, 2'-H), 3.53-3.63 (m, 2 H, 4'-H and 5'-H), 3.65-3.80 (m, 1 H, 5'-H), 5.13 (t, 1 H, 5'-OH, D_2O exchangeable), 5.83 (br s, NH_2, D_2O exchangeable), 5.93 (t, 1 H, 1'-H), 6.71 (s, 2 H, NH_2, D_2O exchangeable), 8.00 (s, 1 H, 8-H). Anal. Calcd. for $C_{10}H_{14}N_6OS$: C, 45.10; H, 5.30; N, 31.56. Found: C, 44.85; H, 5.49; N, 31.27.

Compounds **28** and **29** were prepared by a similar procedure as described for the synthesis of compound **19** from the respective compounds **6** and **12**.

2-Amino-6-chloro-9-(2,3-dideoxy-β-L-ribofuranosyl)purine (28). Isolated as a white solid (54%): mp 135-137 °C (dec.); TLC, R_f 0.60 (CH_2Cl_2/MeOH, 6:1, v/v); $[\alpha]_D$ +0.3° (*c* = 0.11, MeOH); UV (MeOH) λ_{max} 310 nm (ε 5200), λ_{min} 268 nm; UV (0.01 N HCl) λ_{max} 308 nm (ε 3700), λ_{min} 266 nm; UV (0.01 N NaOH) λ_{max} 306 nm (ε 3800), λ_{min} 266 nm; ^1H NMR (Me_2SO-d_6) δ 1.95-2.02 (m, 2 H, 3'-H), 2.33-2.39 (m, 2 H, 2'-H), 3.46-3.60 (m, 2 H, 5'-H), 4.05-4.09 (m, 1 H, 4'-H), 4.93-4.97 (t, 1 H, 5'-OH, D_2O exchangeable), 6.09-6.10 (m, 1 H, 1'-H), 6.94 (s, 2 H, 6-NH_2, D_2O exchangeable), 8.36 (s, 1 H, 8-H). Anal. Calcd. for $C_{10}H_{12}ClN_5O_2 \cdot 0.5\ C_2H_5OH$: C, 45.13; H, 5.15; N, 23.93. Found: C, 45.10; H, 5.17; N, 23.69.

6-Chloro-9-(2,3-dideoxy-4-thio-β-L-ribofuranosyl)purine (29). Isolated as white crystals (28%): mp 138-139 °C; TLC, R_f 0.45 (EtOAc/CH_3COCH_3, 10:1, v/v); ^1H NMR ($CDCl_3$) δ 2.10-2.34 (m, 2 H, 3'-H), 2.42-2.70 (m, 2 H, 2'-H), 3.56 (t, 1 H, 5'-OH, D_2O exchangeable), 3.80-3.90 (m, 1 H, 5'-H), 3.90-4.08 (m, 2 H, 4'-H and 5'-H), 6.29 (t, 1 H, 1'-H), 8.70 (s, 1 H, 8-H), 8.88 (s, 1 H, 2-H). Anal. Calcd. for $C_{10}H_{11}ClN_4OS$: C, 44.36; H, 4.10; N, 20.70. Found: C, 44.67; H, 3.99; N, 20.42.

6-Amino-9-(2,3-dideoxy-4-thio-β-L-ribofuranosyl)purine (30). A solution of compound **29** (0.40 g, 1.48 mmol) in saturated methanolic ammonia (80 mL) was heated at 80 °C for 3 d. The solvent was removed *in vacuo*, and the residue was purified on a silica gel column (CH_2Cl_2/MeOH, 10:1, v/v) to afford 0.28 g (76%) of product as white crystals: mp 199-201 °C; TLC, R_f 0.29 (CH_2Cl_2/MeOH, 10:1, v/v); $[\alpha]_D^{25}$ -8.1° (*c* = 0.20, MeOH); UV (MeOH) λ_{max} 260 (ε 13700), λ_{min} 230 nm; UV (0.01 N HCl) λ_{max} 262 nm (ε 12300), λ_{min} 231 nm; UV (0.01 N NaOH) λ_{max} 259 nm (ε 13800), λ_{min} 228 nm; ^1H NMR (Me_2SO-d_6) δ 1.93-2.08 (m, 1 H, 3'-H_A), 2.10-2.24 (m, 1 H, 3'-H_B), 2.38-2.43 (m, 1 H, 2'-H_A), 2.45-2.60 (m, 1 H, 2'-H_B), 3.54-3.68 (m, 2 H, 5'-H and 4'-H), 3.70-3.82 (m, 1 H, 5'-H), 5.15 (t, 1 H, 5'-OH, D_2O exchangeable), 6.16 (t, 1 H, 1'-H), 7.27 (s, 2 H, NH_2, D_2O exchangeable), 8.13 (s, 1 H, 8-H), 8.42 (d, 1 H, 2-H). Anal. Calcd. for $C_{10}H_{13}N_5OS$: C, 47.79; H, 5.21; N, 27.87. Found: C, 47.77; H, 5.40; N, 27.98.

6-Amino-9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-L-ribofuranosyl]purine (31). Isolated as a white solid (77%): mp 142-144 °C; TLC, R_f 0.24 (CH_2Cl_2/MeOH, 20:1, v/v); ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H, $SiMe_2$), 0.95 (s, 9 H, Si*t*-Bu), 2.05-2.75 (m, 4 H, 2'-H and 3'-H), 3.65-3.75 (m, 2 H, 5'-H), 4.40-4.65 (m, 1 H, 4'-H), 6.15-6.25 (s, 2 H, 6-NH_2, D_2O exchangeable), 6.20-6.35 (t, 1 H,

1'-H), 7.85 (s, 1 H, 8-H), 8.35 (s, 1 H, 2-H). Anal. Calcd. for $C_{26}H_{27}N_5O_2Si$: C, 54.98; H, 7.79; N, 20.04. Found: C, 54.97; H, 7.81; N, 19.79.

2-Chloro-6-amino-9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-L-ribofuranosyl]purine (32). Isolated as a white solid (79%): mp 158-160 °C; R_f 0.46 (CH_2Cl_2/EtOH, 20:1, v/v); ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H, $SiMe_2$), 0.93 (s, 9 H, Si*t*-Bu), 2.00-2.60 (m, 4 H, 2'-H and 3'-H), 3.65-3.75 (m, 2 H, 5'-H), 4.40-4.55 (m, 1 H, 4'-H), 6.20-6.35 (t, 1 H, 1'-H), 6.55 (s, 2 H, 6-NH_2, D_2O exchangeable), 7.85 (s, 1 H, 8-H). Anal. Calcd. for $C_{16}H_{26}ClN_5O_2Si$: C, 50.05; H, 6.83; N, 18.24. Found: C, 50.33; H, 7.02; N, 17.97.

2,6-Diamino-9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-L-ribofuranosyl]purine (34). Isolated as a white solid (47%): mp 157-159 °C (dec.); TLC, R_f 0.31 (CH_2Cl_2/MeOH, 15:1, v/v); ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H, $SiMe_2$), 0.90 (s, 9 H, Si*t*-Bu), 1.95-2.65 (m, 4 H, 2'-H and 3'-H), 3.60-3.70 (m, 2 H, 5'-H), 4.35-4.55 (m, 1 H, 4'-H), 4.75-4.85 (br s, 2 H, NH_2, D_2O exchangeable), 5.65-5.75 (br s, 2 H, NH_2, D_2O exchangeable), 6.05-6.20 (t, 1 H, 1'-H), 7.60 (s, 1 H, 8-H). Anal. Calcd. for $C_{16}H_{28}N_6O_2Si$: C, 52.72; H, 7.74; N, 23.06. Found: C, 53.11; H, 7.47; N, 22.69.

2-Chloro-6-amino-9-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-4-thio-α-L-ribofuranosyl]purine (35). Isolated as a white solid (87%): mp 186-187 °C; TLC, R_f 0.43 (CH_2Cl_2/MeOH, 20:1, v/v); ^1H NMR (Me_2SO-d_6) δ 1.10 (s, 9 H, *t*-Bu), 2.00-2.18 (m, 2 H, 3'-H), 2.20-2.45 (m, 2 H, 2'-H), 3.60-3.72 (m, 2 H, 5'-H), 3.75-4.02 (m, 1 H, 4'-H), 6.06 (t, 1 H, 1'-H), 6.90 (s, 2 H, NH_2, D_2O exchangeable), 7.20-7.42 (m, 6 H, ArH), 7.45-7.70 (m, 4 H, ArH), 8.05 (s, 1 H, 8-H). Anal. Calcd. for $C_{26}H_{30}ClN_5OSSi$: C, 59.58; H, 5.77; N, 13.36. Found: C, 59.57; H, 6.02; N, 13.08.

2,6-Diamino-9-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-4-thio-α-L-ribofuranosyl]purine (37). Isolated as a foam (46%): TLC, R_f 0.54 (CH_2Cl_2/MeOH, 10:4, v/v); ^1H NMR ($CDCl_3$) δ 1.10 (s, 9 H, *t*-Bu), 2.00-2.43 (m, 4 H, 3'-H and 2'-H), 3.54-3.70 (m, 2 H, 5'-H), 3.80-4.00 (m, 1 H, 4'-H), 4.79 (br s, 2 H, NH_2, D_2O exchangeable), 5.57 (br s, 2 H, NH_2, D_2O exchangeable), 5.93 (t, 1 H, 1'-H), 7.24-7.47 (m, 6 H, ArH), 7.54-7.72 (m, 4 H, ArH), 7.80 (s, 1 H, 8-H). Anal. Calcd. for $C_{26}H_{32}N_6OSSi$: C, 61.87; H, 6.39; N, 16.65. Found: C, 62.15; H, 6.66; N, 16.81.

6-Amino-9-(2,3-dideoxy-α-L-ribofuranosyl)purine (38). Isolated as white solid (90%): mp 150-152 °C; TLC, R_f 0.47 (CH_2Cl_2/MeOH, 6:1, v/v); $[\alpha]_D$ -43.7° (*c* = 0.16, MeOH); UV (MeOH) λ_{max} 262 nm (ε 9600), λ_{min} 230 nm; UV (0.01 N HCl) λ_{max} 260 nm (ε 9100), λ_{min} 230 nm; UV (0.01 N NaOH) λ_{max} 262 nm (ε 9600), λ_{min} 230 nm; ^1H NMR (Me_2SO-d_6) δ 1.80-2.60 (m, 4 H, 2'-H and 3'-H), 3.40-3.55 (dd, 2 H,

5'-H), 4.30-4.45 (m, 1 H, 4'-H), 4.65-4.80 (t, 1 H, 5'-OH, D_2O exchangeable), 6.20-6.35 (t, 1 H, 1'-H), 7.15 (s, 2 H, 6-NH_2, D_2O exchangeable), 8.10 (s, 1 H, 8-H), 8.20 (s, 1 H, 2-H). Anal. Calcd. for $C_{10}H_{13}N_5O_2 \cdot 0.1\ C_2H_5OH$: C, 51.07; H, 5.71; N, 29.20. Found: C, 50.97; H, 5.56; N, 29.28.

2-Chloro-6-amino-9-(2,3-dideoxy-α-L-ribofuranosyl)purine (39). Isolated as a white solid (90%): mp 136-138 °C (dec.); TLC, R_f 0.64 (CH_2Cl_2/MeOH, 6:1, v/v); $[\alpha]_D$ -22.2° (*c* = 0.15, MeOH); UV (MeOH) λ_{max} 266 nm (ε 18300), λ_{min} 232 nm; UV (0.01 N HCl) λ_{max} 267 nm (ε 11900), λ_{min} 232 nm; UV (0.01 N NaOH) λ_{max} 267 nm (ε 15000), λ_{min} 232 nm; ^1H NMR (Me_2SO-d_6) δ 1.76-1.90 (m, 1 H, 3'-H_A), 2.13-2.27 (m, 1 H, 3'-H_B), 2.38-2.45 (m, 2 H, 2'-H), 3.38-3.47 (m, 2 H, 5'-H), 4.28-4.38 (m, 1 H, 4'-H), 4.77-4.82 (t, 1 H, 5'-OH, D_2O exchangeable), 6.18-6.23 (t, 1 H, 1'-H), 7.79 (s, 2 H, 6-NH_2, D_2O exchangeable), 8.29 (s, 1 H, 8-H). Anal. Calcd. for $C_{10}H_{12}ClN_5O_2 \cdot 0.1\ C_2H_5OH$: C, 44.66; H, 4.63; N, 25.53. Found: C, 44.31; H, 4.56; N, 25.49.

2,6-Diamino-9-(2,3-dideoxy-α-L-ribofuranosyl)purine (40). Isolated as a white solid (87%): mp 156-158 °C (dec.); TLC, R_f 0.40 (CH_2Cl_2/MeOH, 6:1, v/v); $[\alpha]_D$ -5.9° (*c* = 0.12, MeOH); UV (MeOH) λ_{max} 278 nm (ε 11900), λ_{min} 264 nm; UV (0.01 N HCl) λ_{max} 288 nm (ε 9300), λ_{min} 270 nm; UV (0.01 N NaOH) λ_{max} 282 nm (ε 10300), λ_{min} 267 nm; ^1H NMR (Me_2SO-d_6) δ 1.75-1.83 (m, 1 H, 3'-H_A), 2.14-2.22 (m, 1 H, 3'-H_B), 2.33-2.41 (m, 2 H, 2'-H), 3.37-3.44 (m, 2 H, 5'-H), 4.27-4.32 (m, 1 H, 4'-H), 4.74-4.79 (t, 1 H, 5'-OH, D_2O exchangeable), 5.76 (s, 2 H, 6-NH_2, D_2O exchangeable), 6.05-6.09 (t, 1 H, 1'-H), 6.67 (s, 2 H, 6-NH_2, D_2O exchangeable), 7.82 (s, 1 H, 8-H). Anal. Calcd. for $C_{10}H_{14}N_6O_2 \cdot 0.1\ C_2H_5OH \cdot CH_2Cl_2$: C, 45.94; H, 5.48; N, 30.91. Found: C, 46.23; H, 5.60; N, 30.72.

2-Amino-6-chloro-9-(2,3-dideoxy-α-L-ribofuranosyl)purine (41). Isolated as a white solid (78%): mp 136-138 °C; TLC, R_f 0.45 (EtOAc/EtOH, 6:1, v/v); $[\alpha]_D$ -11.9° (c = 0.05, MeOH); UV (MeOH) λ_{max} 304 nm (ε 6500), λ_{min} 262 nm; UV (0.01 N HCl) λ_{max} 308 nm (ε 6300), λ_{min} 266 nm; UV (0.01 N NaOH) λ_{max} 306 nm (ε 6200), λ_{min} 264 nm; ^1H NMR (Me_2SO-d_6) δ 1.95-2.50 (m, 4 H, 2'-H and 3'-H), 3.40-3.50 (m, 2 H, 5'-H), 4.25-4.50 (m, 1 H, 4'-H), 4.70-4.85 (t, 1 H, 5'-OH, D_2O exchangeable), 6.15-6.30 (m, 1 H, 1'-H), 6.85-6.90 (s, 2 H, 6-NH_2, D_2O exchangeable), 8.20 (s, 1 H, 8-H). Anal. Calcd. for $C_{10}H_{12}ClN_5O_2$: C, 44.53; H, 4.49; N, 25.97. Found: C, 44.36; H, 4.32; N, 25.61.

2-Chloro-6-amino-9-(2,3-dideoxy-4-thio-α-L-ribofuranosyl)purine (42). Isolated as white crystals (64%): mp 153-155 °C; TLC, R_f 0.33 (CH_2Cl_2:MeOH, 10:1, v/v); $[\alpha]_D$ -69.4° (*c* = 0.16, MeOH); UV (MeOH) λ_{max} 263 (ε 10900), λ_{min} 229

nm; UV (0.01 N HCl) λ_{max} 263 nm (ε 13100), λ_{min} 230 nm; UV (0.01 N NaOH) λ_{max} 262 nm (ε 12300), λ_{min} 230 nm; ^{1}H NMR (Me_2SO-d_6) δ 1.94-2.04 (m, 1 H, 3'-H_A), 2.13-2.27 (m, 1 H, 3'-H_B), 2.33-2.49 (m, 2 H, 2'-H), 3.33-3.52 (m, 2 H, 5'-H), 3.78-3.89 (m, 1 H, 4'-H), 5.05 (t, 1 H, 5'-OH, D_2O exchangeable), 6.09 (dd, 1 H, 1'-H), 7.80 (s, 2 H, NH_2, D_2O exchangeable), 8.38 (s, 1 H, 8-H). Anal. Calcd. for $C_{10}H_{12}ClN_5OS$: C, 42.03; H, 4.23; N, 24.51. Found: C, 42.30; H, 4.20; N, 24.22

2,6-Diamino-9-(2,3-dideoxy-4-thio-α-L-ribofuranosyl)purine (43). Isolated as white crystals (64%): mp 218-220 °C; TLC, R_f 0.17 (CH_2Cl_2/MeOH, 10:1, v/v); $[\alpha]_D$ -22.6° (*c* = 0.21, MeOH); UV (MeOH) λ_{max} 284 (ε 8900), λ_{min} 241 nm; UV (0.01 N HCl) λ_{max} 292 nm (ε 9300), λ_{min} 238 nm; UV (0.01 N NaOH) λ_{max} 280 nm (ε 8800), λ_{min} 238 nm; ^{1}H NMR (Me_2SO-d_6) δ 1.88-2.00 (m, 1 H, 3'-H_A), 2.12-2.28 (m, 1 H, 3'-H_B), 2.29-2.42 (m, 2 H, 2'-H), 3.32-3.50 (m, 2 H, 5'-H), 3.76-3.86 (m, 1 H, 4'-H), 5.02 (t, 1 H, 5'-OH, D_2O exchangeable), 5.83 (br s, NH_2, D_2O exchangeable), 5.95 (t, 1 H, 1'-H), 6.70 (s, 2 H, NH_2, D_2O exchangeable), 7.94 (s, 1 H, 8-H). Anal. Calcd. for $C_{10}H_{14}N_6OS$: C, 45.10; H, 5.30; N, 31.56. Found: C, 44.78; H, 5.48; N, 31.41.

6-Chloro-9-(2,3-dideoxy-4-thio-α-L-ribofuranosyl)purine (44). Isolated as a white solid (23%): mp 138-140 °C; TLC, R_f 0.38 (EtOAc/CH_3COCH_3, 10:1, v/v); ^{1}H NMR ($CDCl_3$) δ 1.95-2.06 (m, 1 H, 3'-H_A), 2.06-2.32 (m, 2 H, 3'-H_B and 2'-H_A), 2.36-2.62 (m, 1 H, 2'-H_B), 3.66-3.80 (m, 2 H, 5'-H), 3.86-4.05 (m, 1 H, 4'-H), 4.45 (t, 1 H, 5'-OH, D_2O exchangeable), 6.30 (t, 1 H, 1'-H), 8.42 (s, 1 H, 8-H), 8.70 (s, 1 H, 2-H). Anal. Calcd. for $C_{10}H_{11}ClN_4OS$: C, 44.36; H, 4.10; N, 20.70. Found: C, 44.41; H, 3.85; N, 20.34.

6-Amino-9-(2,3-dideoxy-4-thio-α-L-ribofuranosyl)purine (45). Isolated as white crystals (69%): mp 185-187 °C; TLC, R_f 0.32 (CH_2Cl_2/MeOH, 10:1, v/v); $[\alpha]_D$ -92° (*c* = 0.22, MeOH); UV (MeOH) λ_{max} 261 (ε 17100), λ_{min} 230 nm; UV (0.01 N HCl) λ_{max} 262 nm (ε 17100), λ_{min} 232 nm; UV (0.01 N NaOH) λ_{max} 262 nm (ε 16000), λ_{min} 230 nm; ^{1}H NMR (Me_2SO-d_6) δ 1.91-2.05 (m, 1 H, 3'-H_A), 2.14-2.32 (m, 1 H, 3'-H_B), 2.38-2.49 (m, 2 H, 2'-H), 3.31-3.55 (m, 2 H, 5'-H), 3.80-3.92 (m, 1 H, 4'-H), 5.03 (t, 1 H, 5'-OH, D_2O exchangeable), 6.17 (t, 1 H, 1'-H), 7.25 (s, 2 H, NH_2, D_2O exchangeable), 8.13 (s, 1 H, 8-H), 8.35 (d, 1 H, 2-H). Anal. Calcd. for $C_{10}H_{13}N_5OS$: C, 47.79; H, 5.21; N, 27.87. Found: C, 47.93; H, 5.44; N, 27.94.

9-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-β-L-ribofuranosyl]-2-palmitoylguanine (49), 9-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-α-L-ribofuranosyl]-2-palmitoylguanine (50), 7-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-β-L-ribofuranosyl]-2-palmitoylguanine (51), and 7-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-α-L-ribofuranosyl]-2-palmitoylguanine

(52). A suspension of N^2-palmitoylguanine (**47**, 3.90 g, 10.0 mmol) and 0.80 g of ammonium sulfate in 28 mL of hexamethyldisilazane was refluxed for 2 h to form a clear solution. The reaction mixture was evaporated *in vacuo* to dryness and the residue was treated with compound **4** (7.00 g, 25.0 mmol) in acetonitrile (80 mL) with stirring, followed by addition of trimethylsilyl trifluoromethanesulfonate (1.5 mL, 8.8 mmol). The reaction mixture was stirred at room temperature for 2 h, then poured with stirring into a 300 mL mixture (1:1, v/v) of 10% aqueous sodium bicarbonate solution and ethyl acetate. The two phases were separated and the water phase was extracted with ethyl acetate (2 x 100 mL). The combined ethyl acetate phase was dried over anhydrous $MgSO_4$, then filtered. After removal of the solvent by evaporation *in vacuo*, the residue was separated on a silica gel column (CH_2Cl_2/dioxane/MeCN/MeOH, 84:7:7:2, v/v) to give three fractions: Fraction 1 (R_f 0.75) yielded the 7-β-isomer, compound **51** after evaporation; Fraction 2 (R_f 0.49) gave a mixture of 9-β- and 7-α-isomers (compounds **49** and **52**, respectively) as showed by ^1H NMR spectrum; Fraction 3 (R_f 0.34) afforded the 9-α-isomer, compound **50**. The mixture of compounds **49** and **52** was further separated on a silica gel column by eluting with CH_2Cl_2/hexane/dioxane/MeCN/MeOH (51:40:4:4:1, v/v) to provide 9-β-isomer, **49** (R_f 0.19) and 7-α-isomer, **52** (R_f 0.25).

Compound **49** was isolated as a foam (0.60 g, 10%): ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H, $SiMe_2$), 0.90 (s, 9 H, Si*t*-Bu), 1.20-1.30 [s, 29 H, $(CH_2)_{13}CH_3$], 1.95-2.15 (m, 2 H, 3'-H), 2.25-2.65 [m, 4 H, 2'-H and -C(O)CH_2], 3.60-3.85 (m, 2 H, 5'-H), 4.05-4.25 (m, 1 H, 4'-H), 5.90-6.05 (m, 1 H, 1'-H), 8.05 (s, 1 H, 8-H), 10.3-10.5 (br s, 1 H, 1-NH, D_2O exchangeable), 12.1-12.3 (br s, 1 H, CONH, D_2O exchangeable).

Compound **50** was isolated as a foam (1.2 g, 20%): ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H, $SiMe_2$), 0.92 (s, 9 H, Si*t*-Bu), 1.20-1.30 [s, 29 H, $(CH_2)_{13}CH_3$], 2.00-2.20 (m, 2 H, 3'-H), 2.35-2.65 [m, 4 H, 2'-H and -C(O)CH_2], 3.40-3.60 (m, 2 H, 5'-H), 4.35-4.55 (m, 1 H, 4'-H), 6.00-6.15 (m, 1 H, 1'-H), 7.70 (s, 1 H, 8-H), 9.70-10.1 (br s, 1 H, 1-NH, D_2O exchangeable), 12.0-12.3 (br s, 1 H, CONH, D_2O exchangeable).

Compound **51** was isolated as a foam (0.40 g, 6.6%): ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H, $SiMe_2$), 0.95 (s, 9 H, Si*t*-Bu), 1.20-1.30 [s, 29 H, $(CH_2)_{13}CH_3$], 1.90-2.40 (m, 4 H, 2'-H and 3'-H), 2.55-2.75 [m, 2 H, -C(O)CH_2], 3.65-4.15 (m, 2 H, 5'-H), 4.10-4.30 (m, 1 H, 4'-H), 6.45-6.55 (m, 1 H, 1'-H), 8.40 (s, 1 H, 8-H), 10.5-10.7 (br s, 1 H, 1-NH, D_2O exchangeable), 12.2-12.4 (br s, 1 H, CONH, D_2O exchangeable).

Compound **52** was isolated as a foam (0.80 g, 13%): ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H, $SiMe_2$), 0.95 (s, 9 H, Si*t*-Bu), 1.20-1.30 [s, 29 H, $(CH_2)_{13}CH_3$], 1.60-2.20 (m, 4 H, 2'-H and 3'-H), 2.45-2.65 [m, 2 H, -C(O)CH_2], 3.60-3.70 (m, 2 H, 5'-H), 4.45-4.60 (m, 1 H, 4'-H), 6.40-6.50 (m, 1 H, 1'-H), 7.95 (s, 1 H, 8-H), 10.2-10.4 (br s, 1 H, 1-NH, D_2O exchangeable), 12.1-12.3 (br s, 1 H, CONH, D_2O exchangeable).

Compounds **49-52** were used directly for the next step reaction without further purification.

9-(2,3-Dideoxy-β-L-ribofuranosyl)-2-palmitoylguanine (53). Isolated as a white solid (90%): mp 240 °C (dec.); TLC, R_f 0.24 (EtOAc/EtOH, 6:1, v/v); ^1H NMR ($CDCl_3$) δ 1.15-1.25 [s, 29 H, $(CH_2)_{13}CH_3$], 1.85-2.15 (m, 2 H, 3'-H), 2.20-2.60 [m, 4 H, 2'-H and -C(O)CH_2], 3.50-3.80 (m, 2 H, 5'-H), 4.00-4.30 (m, 2 H, 4'-H and 5'-OH, D_2O exchangeable), 5.90-6.00 (m, 1 H, 1'-H), 7.95 (s, 1 H, 8-H), 10.3-10.6 (br s, 1 H, 1-NH, D_2O exchangeable), 11.9-12.3 (br s, 1 H, CONH, D_2O exchangeable). Anal. Calcd. for $C_{26}H_{43}N_5O_4 \cdot 0.5\ H_2O$: C, 62.62; H, 8.89; N, 14.04. Found: C, 62.91; H, 8.99; N, 13.77.

9-(2,3-Dideoxy-α-L-ribofuranosyl)-2-palmitoylguanine (54). Isolated as a white solid (91%): mp 250 °C (dec.); TLC, R_f 0.22 (EtOAc/EtOH, 6:1, v/v); ^1H NMR ($CDCl_3$) δ 1.20-1.30 [s, 29 H, $(CH_2)_{13}CH_3$], 2.35-2.65 [m, 6 H, 2'-H, 3'-H and -C(O)CH_2], 3.65-3.75 (m, 2 H, 5'-H), 4.35-4.45 (m, 2 H, 4'-H and 5'-OH, D_2O exchangeable), 6.15-6.30 (m, 1 H, 1'-H), 7.85 (s, 1 H, 8-H), 10.5-10.9 (br s, 1 H, 1-NH, D_2O exchangeable), 11.5-12.0 (br s, 1 H, CONH, D_2O exchangeable). Anal. Calcd. for $C_{26}H_{43}N_5O_4 \cdot 0.5\ H_2O$: C, 62.62; H, 8.89; N, 14.04. Found: C, 62.25; H, 8.93; N, 13.88.

7-(2,3-Dideoxy-β-L-ribofuranosyl)-2-palmitoylguanine (55). Isolated as a white solid (88%): mp 290 °C (dec.); TLC, R_f 0.57 (EtOAc/EtOH, 6:1, v/v); ^1H NMR ($CDCl_3$) δ 1.20-1.30 [s, 29 H, $(CH_2)_{13}CH_3$], 1.95-2.15 (m, 2 H, 3'-H), 2.35-2.70 [m, 4 H, 2'-H and -C(O)CH_2], 3.65-4.05 (m, 2 H, 5'-H), 4.20-4.45 (m, 2 H, 4'-H and 5'-OH, D_2O exchangeable), 6.40-6.50 (m, 1 H, 1'-H), 8.60 (s, 1 H, 8-H), 10.5-10.8 (br s, 1 H, 1-NH, D_2O exchangeable), 12.1-12.3 (br s, 1 H, CONH, D_2O exchangeable). Anal. Calcd. for $C_{26}H_{43}N_5O_4 \cdot 0.5\ H_2O$: C, 62.62; H, 8.89; N, 14.04. Found: C, 62.35; H, 8.66; N, 13.78.

7-(2,3-Dideoxy-α-L-ribofuranosyl)-2-palmitoylguanine (56). Isolated as a white solid (85%): mp 290 °C (dec.); TLC, R_f 0.44 (EtOAc/EtOH, 6:1, v/v); ^1H NMR ($CDCl_3$) δ 1.20-1.30 [s, 29 H, $(CH_2)_{13}CH_3$], 1.95-2.25 (m, 2 H, 3'-H), 2.45-2.65 [m, 4 H, 2'-H and -C(O)CH_2], 3.55-3.70 (m, 2 H, 5'-H), 4.30-4.55 (m, 2 H, 4'-H and 5'-OH, D_2O exchangeable), 6.45-6.60 (m, 1 H, 1'-H), 8.00 (s, 1 H, 8-H), 11.2-11.4 (br s, 1 H, 1-NH, D_2O exchangeable), 12.2-12.3 (br s, 1 H, CONH, D_2O exchangeable). Anal. Calcd. for $C_{26}H_{43}N_5O_4 \cdot 0.5\ H_2O$: C, 62.62; H, 8.89; N, 14.04. Found: C, 62.48; H, 9.29; N, 13.86.

9-(2,3-Dideoxy-β-L-ribofuranosyl)guanine (57). Compound **53** (0.30 g, 0.61 mmol) was treated with 80 mL of saturated methanolic ammonia at 0° C. The reaction mixture was stirred in a Wheaton pressure bottle at room temperature overnight, then

evaporated to dryness. The residue was washed thoroughly with ether to remove a trace amount of palmitamide followed by recrystallization from ethanol to furnish the target compound as white crystals (0.14 g, 92%): mp 256 °C (dec); TLC, R_f 0.44 (CH_2Cl_2/MeOH, 3:1, v/v); $[\alpha]_D$ +6.5° (*c* = 0.10, MeOH); UV (MeOH) λ_{max} 256 nm (ε 12500), λ_{min} 225 nm; UV (0.01 N HCl) λ_{max} 256 nm (ε 12200), λ_{min} 228 nm; UV (0.01 N NaOH) λ_{max} 265 nm (ε 10700), λ_{min} 233 nm; ^{1}H NMR (Me_2SO-d_6) δ 1.92-2.01 (m, 2 H, 3'-H), 2.20-2.28 (m, 2 H, 2'-H), 3.45-3.60 (m, 2 H, 5'-H), 4.00-4.06 (m, 1 H, 4'-H), 4.91-4.96 (t, 1 H, 5'-OH, D_2O exchangeable), 5.94-5.98 (m, 1 H, 1'-H), 6.49 (br s, 2 H, 2-NH_2, D_2O exchangeable), 7.92 (s, 1 H, 8-H), 10.0-10.3 (br s, 1 H, 1-NH, D_2O exchangeable). Anal. Calcd. for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.21; N, 27.28. Found: C, 47.70; H, 5.50; N, 27.58.

Compounds **58-60** were obtained by a similar procedure as described for the synthesis of compound **57**.

9-(2,3-Dideoxy-α-L-ribofuranosyl)guanine (58). Isolated as a white solid (97%): mp 230 °C; TLC, R_f 0.32 (CH_2Cl_2/MeOH, 3:1, v/v); $[\alpha]_D$ -34.8° (*c* = 0.07, MeOH); UV (MeOH) λ_{max} 256 nm (ε 10800), λ_{min} 229 nm; UV (0.01 N HCl) λ_{max} 256 nm (ε 9600), λ_{min} 229 nm; UV (0.01 N NaOH) λ_{max} 266 nm (ε 8700), λ_{min} 234 nm; ^{1}H NMR (Me_2SO-d_6) δ 2.12-2.20 (m, 2 H, 3'-H), 2.31-2.40 (m, 2 H, 2'-H), 3.36-3.42 (m, 2 H, 5'-H), 4.27-4.31 (m, 1 H, 4'-H), 4.77 (t, 1 H, 5'-OH, D_2O exchangeable), 6.01-6.06 (m, 1 H, 1'-H), 6.49 (br s, 2 H, 2-NH_2, D_2O exchangeable), 7.81 (s, 1 H, 8-H), 10.5-10.7 (br s, 1 H, 1-NH, D_2O exchangeable). Anal. Calcd. for $C_{10}H_{13}N_5O_3 \cdot 0.5\ H_2O$: C, 46.14; H, 5.42; N, 26.91. Found: C, 46.11; H, 5.58; N, 26.74.

7-(2,3-Dideoxy-β-L-ribofuranosyl)guanine (59). Isolated as white solid (85%): mp 260 °C; TLC, R_f 0.56 (CH_2Cl_2/MeOH, 2:1, v/v); $[\alpha]_D$ -10.9° (*c* = 0.06, Me_2SO); UV (MeOH) λ_{max} 282 nm (ε 7400), λ_{min} 259 nm; UV (0.01 N HCl) λ_{max} 251 nm (shoulder, ε 13200), λ_{min} 230 nm; UV (0.01 N NaOH) λ_{max} 283 nm (ε 7300), λ_{min} 260 nm; ^{1}H NMR (Me_2SO-d_6) δ 1.84-1.93 (m, 2 H, 3'-H), 2.14-2.19 (m, 1 H, 2'-H_A), 2.32-2.35 (m, 1 H, 2'-H_B), 3.49-3.55 (m, 1 H, 5'-H_A), 3.62-3.68 (m, 1 H, 5'-H_B), 4.03-4.09 (m, 1 H, 4'-H), 5.00-5.02 (t, 1 H, 5'-OH, D_2O exchangeable), 6.15 (br s, 2 H, 2-NH_2, D_2O exchangeable), 6.28-6.32 (m, 1 H, 1'-H), 8.27 (s, 1 H, 8-H), 10.8 (s, 1 H, 1-NH, D_2O exchangeable). Anal. Calcd. for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.21; N, 27.28. Found: C, 47.97; H, 5.30; N, 27.60.

7-(2,3-Dideoxy-α-L-ribofuranosyl)guanine (60). Isolated as white solid (86%): mp 280 °C; TLC, R_f 0.55 (CH_2Cl_2/MeOH, 2:1, v/v); $[\alpha]_D$ -21.4° (*c* = 0.08, Me_2SO); UV (MeOH) λ_{max} 286 nm (ε 7400), λ_{min} 262 nm; UV (0.01 N HCl) λ_{max} 250 nm (shoulder, ε 10500), λ_{min} 235 nm; UV (0.01 N NaOH) λ_{max} 282 nm (ε 9100), λ_{min}

260 nm; ^{1}H NMR (Me_2SO-d_6) δ 1.74-1.83 (m, 2 H, 3'-H_A), 1.99-2.07 (m, 1 H, 3'-H_B), 2.24-2.43 (m, 2 H, 2'-H), 3.37-3.42 (m, 2 H, 5'-H), 4.36-4.41 (m, 1 H, 4'-H), 4.75-4.80 (t, 1 H, 5'-OH, D_2O exchangeable), 6.14 (br s, 2 H, 2-NH_2, D_2O exchangeable), 6.32-6.36 (m, 1 H, 1'-H), 8.06 (s, 1 H, 8-H), 10.8 (s, 1 H, 1-NH, D_2O exchangeable). Anal. Calcd. for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.21; N, 27.28. Found: C, 47.85; H, 5.25; N, 27.64.

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