Monocyclic L-Nucleosides with Type 1 Cytokine-Inducing Activity

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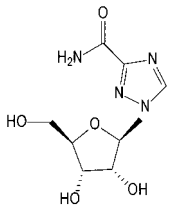
A series of 1,2,4-triazole L-nucleosides were synthesized and evaluated for their ability to stimulate type 1 cytokine production by activated human T cells in direct comparison to the known active agent ribavirin. Among the compounds prepared, 1-β-L-ribofuranosyl-1,2,4-triazole-3-carboxamide (**5**, ICN 17261) was found to be the most uniformly potent compound. Conversion of the 3-carboxamide group of **5** to a carboxamidine functionality resulted in 1-β-L-ribofuranosyl-1,2,4-triazole-3-carboxamidine hydrochloride (**10**), which induced cytokine levels comparable to **5** for two of the three type 1 cytokines examined. Modification of the carbohydrate moiety of **5** provided compounds of reduced activity. Significantly, ICN 17261 offers interesting immunomodulatory potential for the treatment of diseases where type 1 cytokines play an important role.

Introduction

Selective modulation of the immune system offers an important opportunity to control many diseases. The balance between immune protection from offending agents versus the pathologic effects of immune dysfunction can be altered by changes in the levels of two major types of cytokines secreted by subsets of T-helper cells.[1,2] Type 1 cytokines such as interleukin 2 (IL-2), interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α) generally enhance cell-mediated immunity, whereas the type 2 cytokines such as IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 are primarily involved in enhancing humoral immune responses.[3] Appropriately balanced type 1 and type 2 responses are essential in host defense, but inappropriate levels of response occur. Such inappropriate responses reduce host defense capability and can promote a wide range of immunopathological reactions.[4−13] Thus, the ability to selectively modulate the cytokine profile could be of therapeutic benefit in a wide variety of disease states.

Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide; Chart 1) is a nucleoside analogue that has demonstrated efficacy in treating viral diseases both as monotherapy (respiratory syncytial virus)[14] and in combination therapy with interferon alpha (hepatitis C virus).[15] Recently reported studies indicate that the in vivo utility of ribavirin can result not only from direct inhibition of viral replication but also from its ability to enhance T cell-mediated immunity.[16−18] This immunomodulatory effect of ribavirin is demonstrable in vitro by measuring the levels of type 1 cytokines produced by activated T cells from both humans and mice[19] and by other measures. The induction of a type 1 cytokine bias by ribavirin is functionally significant in vivo in murine systems.[20]

Chart 1. Structure of Ribavirin



Our interest in both synthesizing novel L-nucleoside analogues and ascertaining whether the interesting immunomodulatory properties of ribavirin are limited to nucleosides of D-configuration led us to examine the L-nucleoside derivatives of ribavirin. A number of investigators have reported that certain β-L-nucleosides have antiviral activity and may differ from their β-D-congeners in a variety of other biologic properties including toxicity.[21−23] However, the immunologic properties of β-L-nucleosides have not been previously reported. Also, in the majority of the studies reported, the investigators focused on compounds having biologic nucleobase moieties with altered sugars. We report here the synthesis of a series of L-nucleosides structurally related to ribavirin, a D-nucleoside in which the heterocycle is a triazole rather than a purine or pyrimidine. Our studies show that the L-enantiomer of ribavirin, **5** (ICN 17261), has type 1 cytokine-enhancing activity that is similar to that of ribavirin. In addition, other structurally related L-nucleosides such as **23** and **10** also show immunologic activity. Additional studies are underway to further evaluate the therapeutic potential of these compounds.

Chemistry

Our synthetic approach for the preparation of triazole L-ribofuranosyl nucleosides is shown in Scheme 1. The key intermediate sugar, viz. 1,2,3,5-tetra-*O*-acetyl-L-ribose (**1**), was prepared from commercially available L-ribose according to a similar procedure used for the synthesis of 1,2,3,5-tetra-*O*-acetyl-D-ribose.[24] Condensa-

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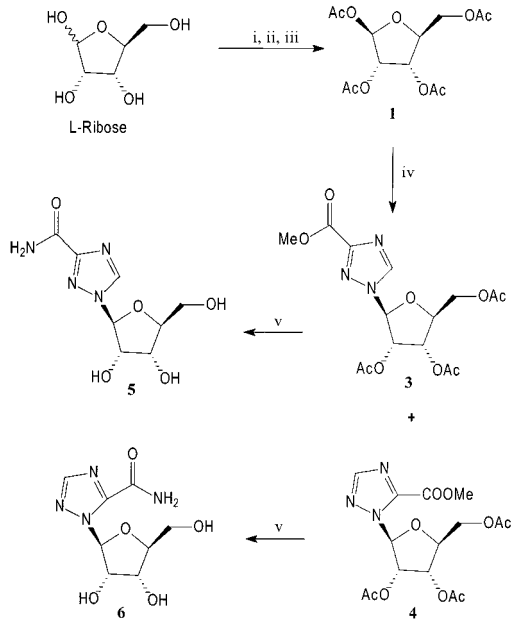
Scheme 1[a]

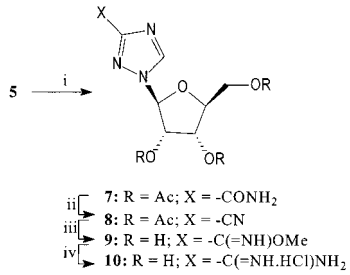


[a] Reagents: (i) MeOH, HCl; (ii) Ac_2O, Py; (iii) AcOH, Ac_2O, H_2SO_4; (iv) methyl 1,2,4-triazole-3-carboxylate (**2**), bis(*p*-nitrophenyl)phosphate, 165−175 °C; (v) $MeOH/NH_3$.

tion of **1** with methyl 1,2,4-triazole-3-carboxylate (**2**)[25] in the presence of a catalytic amount of bis(*p*-nitrophenyl)phosphate[26] at 165−70 °C for 25 min under vacuum followed by aqueous workup provided the fully protected nucleosides **3** and **4** in 78% and 11% yields, respectively. Stirring a solution of **3** in methanolic ammonia in a steel bomb at room temperature for 12 h gave 1-*β*-L-ribofuranosyl-1,2,4-triazole-3-carboxamide (**5**) in 90% yield. Similarly, compound **4** was treated with methanolic ammonia to provide 1-*β*-L-ribofuranosyl-1,2,4-triazole-5-carboxamide (**6**). The structures of **3** and **4** are based on the ^1H NMR spectra of **5** and **6** that were obtained respectively from **3** and **4**. The positions of the signals for H_5, H_3, and $H_{1'}$ are in close agreement with those reported[26] for the corresponding D-nucleosides. The chemical shift of $H_{1'}$ in **6** is δ 6.78, a downfield shift of 0.98 ppm, comparing with that of $H_{1'}$ of **5** (δ 5.80). This can be explained by a stronger inductive effect on the $H_{1'}$ induced by the presence of a closer C_5-H amide group. On the other hand, the electronegative anomeric center has less inductive effect on the further C_3-H in **6**, which is reflected in the chemical shift of C_3-H (δ 8.16), an upfield shift of 0.71 ppm in comparison with that of C_5-H in **5** (δ 8.87).

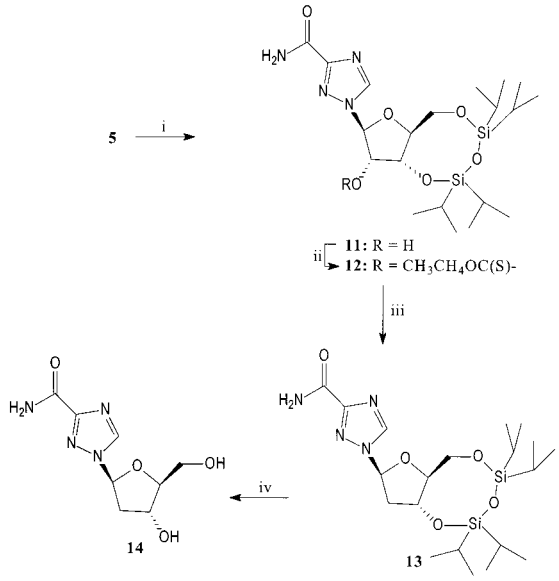
To investigate the qualitative structure−activity relationships with respect to immunological properties, we converted the 3-carboxamide functionality of **5** to an amidine hydrochloride group (Scheme 2). Thus, treatment of **5** with acetic anhydride in pyridine/dimethylformamide mixture for 12 h at room temperature under argon atmosphere afforded triacetyl derivative **7** as an amorphous solid. Dehydration of the carboxamide group in **7** was achieved by exposure of **7** to 20% phosgene in toluene at 0 °C for a 2-h period under argon atmosphere and afforded a clean product **8** in 73% yield. Reaction of **8** with freshly prepared 1 N sodium methoxide solution furnished the corresponding methyl imidate **9** in good yield. The imidate **9** on treatment with methanolic ammonia containing 1 equiv of ammonium chloride for 16 h at room temperature gave the target 1-*β*-L-ribofuranosyl-1,2,4-triazole-3-carboxamidine hydrochloride (**10**).

Scheme 2[a]



[a] Reagents: (i) Ac_2O, Py, DMF; (ii) 20% phosgene/toluene, Py, CH_2Cl_2; (iii) 1 N NaOMe, MeOH; (iv) $MeOH/NH_3$, NH_4Cl.

Scheme 3[a]

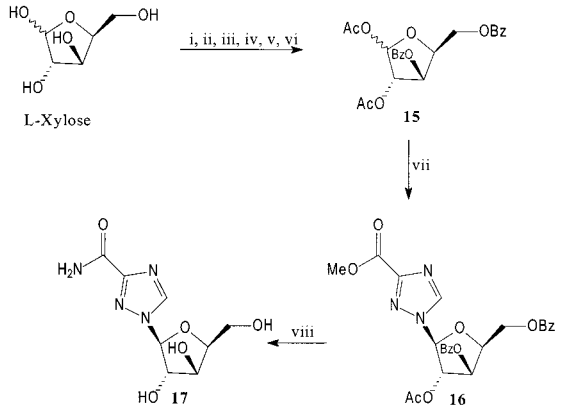


[a] Reagents: (i) 1,3-dichloro-1,1,3,3-tetraisopropyl-1,3-*O*-disiloxane, TEA, Py, DMF; (ii) phenyl chlorothionoformate, TEA, CH_2Cl_2; (iii) diphenylsilane, AIBN, dioxane; (iv) $Et_3N{\cdot}HF$, CH_2Cl_2.

2′-Deoxy nucleosides are an important class of medicinal agents, chiefly because of their pronounced antiviral activity. We explored this type of structural modification in our series as well. The 2′-deoxy derivative of **5** was prepared from **5** as shown in Scheme 3. The 3′- and 5′-hydroxyl groups in **5** were selectively protected with Markiewicz reagent ($TIPSiCl_2$)[27] to provide silyl derivative **11**. The silyl derivative **11** on further reaction with phenyl chlorothionoformate afforded **12** in 62% yield. Radical-mediated deoxygenation[28] of **12** with diphenylsilane in the presence of AIBN in dioxane under reflux furnished **13**. Deprotection of the silyl group of **13** with $Et_3N{\cdot}HF$, followed by purification of the crude product on a silica gel column, yielded the 2′-deoxy nucleoside **14**.

In an effort to study the immunomodulatory properties of other L-nucleosides, the synthesis of L-xylofuranosyl nucleosides was designed. For the synthesis of L-xylofuranosyl nucleosides, we utilized the reported[29] 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-L-xylofuranose (**15**) as a chiral starting material, which was prepared from L-xylose. Using the acid-catalyzed fusion procedure (Scheme 4), condensation of **15** with **2** provided **16**,

Scheme 4[a]



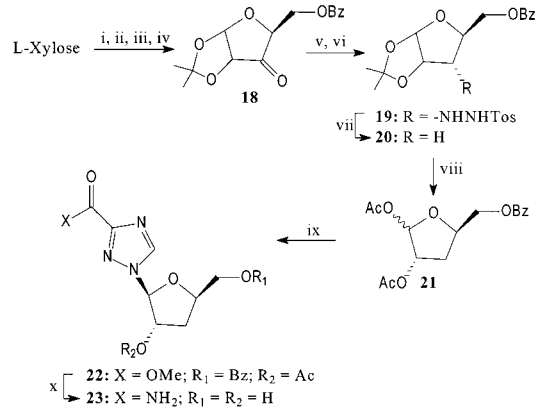
[a] Reagents: (i) Me_2CO, H_2SO_4, $CuSO_4$; (ii) NH_4OH; (iii) HCl/H_2O; (iv) $NaHCO_3$, H_2O; (v) C_6H_5COCl, TEA, $CHCl_3$; (vi) AcOH, Ac_2O, H_2SO_4; (vii) methyl 1,2,4-triazole-3-carboxylate, bis(*p*-nitrophenyl)phosphate, 165−175 °C; (viii) MeOH/NH_3.

which on treatment with methanolic ammonia afforded 1-β-L-xylofuranosyl-1,2,4-triazole-3-carboxamide (**17**) in 89% yield.

In addition to the ribose, 2′-deoxy, and xylose nucleosides described above, we also prepared 3′-deoxy analogues. To synthesize 3′-deoxy L-nucleosides, we turned our attention to a different sugar, viz. 1,2-di-*O*-acetyl-5-*O*-benzoyl-L-ribose (**21**). Even though the intermediate **21** was reported in a communication,[30] no detailed procedure was given. We elected to synthesize **21** from L-xylose. L-Xylose was transformed into a known intermediate **18** by following the literature report.[31] Compound **18** was heated with *p*-toluenesulfonylhydrazine to give the corresponding hydrazide intermediate, which on reduction with sodium cyanoborohydride in the presence of HCl afforded **19** as a crystalline product. Treatment of **19** with sodium acetate in ethanol at reflux temperature provided the protected 3-deoxy sugar **20**[30] in good yield.[32] Stirring of **20** with AcOH and acetic anhydride in the presence of concentrated H_2SO_4 at room temperature gave the required sugar **21**. Acid-catalyzed[26] fusion of **21** and **2** gave **22** in 77% yield (Scheme 5), which on subsequent treatment with methanolic ammonia yielded the target 3′-deoxy-L-nucleoside **23** as a colorless solid.

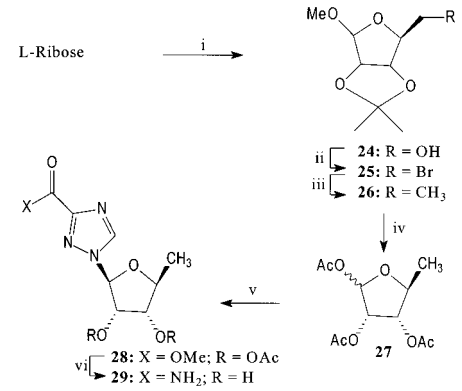
Finally, the synthesis of 5′-deoxy L-nucleoside **29** was pursued. The required intermediate sugar **27** was prepared as depicted in Scheme 6. Reaction of L-ribose with methanolic HCl solution in acetone in the presence of 2,2′-dimethoxypropane gave oil **24**. Treatment of **24** with bromine and Ph_3P provided 5-bromo derivative **25**. Hydrogenation of **25** with 10% Pd/C in the presence of potassium hydroxide afforded the protected 5-deoxy sugar **26** in excellent yield. Compound **26** was transformed to the key intermediate **27** by stirring **26** with acetic anhydride and concentrated H_2SO_4 in glacial AcOH for 12 h. Glycosylation of **2** with **27** was accomplished using Vorbrüggen conditions.[33] Accordingly, **2** was persilylated with hexamethyldisilazane under reflux to give the corresponding silylated derivative which on treatment with **27** in the presence of $SnCl_4$ at 0 °C gave **28**. Exposure of **28** to methanolic ammonia afforded 1-(5-deoxy-β-L-ribofuranosyl)-1,2,4-triazole-3-carboxmide (**29**) in 72% yield.

Scheme 5[a]



[a] Reagents: (i) Me_2CO, H_2SO_4; (ii) 0.2% HCl/H_2O; (iii) C_6H_5COCl, Py, CH_2Cl_2; (iv) PDC, Ac_2O, CH_2Cl_2; (v) *p*-toluenesulfonylhydrazine, EtOH; (vi) $NaCNBH_3$, HCl, MeOH, THF; (vii) $NaOAc{\cdot}3H_2O$, EtOH; (viii) AcOH, Ac_2O, H_2SO_4; (ix) methyl 1,2,4-triazole-3-carboxylate, bis(*p*-nitrophenyl)phosphate, 165−175 °C; (x) MeOH/NH_3.

Scheme 6[a]



[a] Reagents: (i) Me_2CO, 2,2-dimethoxypropane, HCl; (ii) Ph_3P, Br_2, CH_2Cl_2; (iii) Pd/C, KOH/H_2O, MeOH; (iv) AcOH, Ac_2O, H_2SO_4; (v) methyl 1,2,4-triazole-3-carboxylate, HMDS, $SnCl_4$, CH_3CN; (vi) MeOH/NH_3.

The β-L-configuration of the synthesized nucleosides was confirmed by comparison of the ^1H NMR spectra with those of the corresponding D-isomers.[26,34] In addition, the optical rotation of the L-compounds was found to have a specific rotation opposite to that of the D-compounds.

Results and Discussion

Recently we showed that ribavirin can enhance antiviral type 1 cytokines and suppress type 2 cytokine expression in human T cells.[19] These results prompted us to synthesize the L-isomer (**5**) of ribavirin and evaluate its impact on cytokine production. This would allow us to predict the influence of the sugar configuration on cytokine profile as well as to design and synthesize nucleosides with a specific cytokine profile. Interestingly, compound **5** had the same cytokine pattern as ribavirin (see Table 1 and Figure 1).

On the basis of the above result, compound **5** was selected as a lead upon which further structure−activity relationship studies were conducted. As shown in Schemes 1−6, L-nucleoside analogues of ribavirin were synthesized in which the carboxamide group as well as the sugar portions were modified while retaining the

Table 1. Effect of L-Nucleosides of Ribavirin on SEB-Stimulated T Cell Expression of the Type 1 Cytokines IL-2, IFN-γ, and TNF-α

	% of activated control[b]		
treatment[a]	IL-2[c]	IFN-γ[c]	TNF-α[c]
SEB	100	100	100
SEB + ribavirin	143 ± 18	131 ± 6	124 ± 4
SEB + **5**	131 ± 12	122 ± 3	144 ± 7
SEB + **14**	108 ± 9	110 ± 10	119 ± 11
SEB + **17**	100 ± 14	119 ± 7	132 ± 6
SEB + **23**	115 ± 5	114 ± 15	109 ± 11
SEB + **29**	102 ± 12	102 ± 12	125 ± 16
SEB + **6**	99 ± 7	111 ± 10	128 ± 7
SEB + **10**	133 ± 6	128 ± 7	120 ± 6

[a] T cell-derived cytokine levels from five individual human donors were determined in cell-free supernatants by ELISA. Compound numbers are shown in bold. [b] Data are shown collectively as mean percentage of activated control (±standard deviation) for all cytokines. Percentage of activated control is calculated as the ratio of activated T cell cytokine level in the presence of test nucleoside over the cytokine level of untreated activated T cells × 100%. Zero effect on cytokine levels by test nucleosides would give a percentage of activated control value of 100%. [c] The absolute level (pg/mL ± standard deviation) of SEB-induced type 1 cytokine secretion was for IL-2, 640 ± 36; for IFN-γ, 462 ± 37; and for TNF-α, 223 ± 27. Resting levels were <30 pg/mL for all cytokines.

glycosylation site and pentose sugar moiety. All the compounds were evaluated for the type 1 cytokine-enhancing activity in activated human T cells in comparison with ribavirin (used as positive control). The influence of the L-nucleosides on the cytokine pattern induced by the bacterial superantigen staphylococcal enterotoxin B (SEB) was examined in human T cells from five normal donors using protocols previously described elsewhere.[19] The secreted levels of the type 1 cytokines IL-2, TNF-α, and IFN-γ were determined in the cell-free supernatants by ELISA. The effects of these L-nucleosides on IL-2 levels are shown in Table 1. These data showed that **5**, **10**, and ribavirin, at 5 μM, significantly increased IL-2 above activated control levels with a mean percentage increase of 31%, 33%, and 43%, respectively. Table 1 also shows the effect on IFN-γ levels. Here, **5**, **10**, **17**, and ribavirin, at 5 μM, significantly enhanced IFN-γ above activated control levels with a mean percentage increase of 25%, 28%, 19%, and 31%, respectively. Finally TNF-α levels were increased substantially above activated control levels by all L-nucleosides except **23** (Table 1). However **5** and **17** appeared to be more potent enhancers of TNF-α, augmenting activated control levels by 44% and 32%, respectively (ribavirin 24%).

Previously we showed that the induction of activated type 1 cytokine levels by ribavirin exhibits a bell-shaped dose-versus-response curve, with a peak at 5 μM.[19] We evaluated the dose−response profiles of this series of L-nucleosides from 1.25 to 10 μM with respect to type 1 cytokine induction (Figure 1). In general, the dose−response profiles reveal three categories of type 1 cytokine-inducing activity: active, partially active, and inactive L-nucleosides. The active and partially active nucleosides all have a similar bell-shaped profile as ribavirin.

Collectively these data demonstrate that several structural modifications can affect this immunologic activity. Introduction of L-ribose for the D-ribose of ribavirin allowed retention of type 1 cytokine activity; indeed, compound **5** was the most potent of the L-nucleosides tested with respect to type 1 cytokine induction and was the only L-nucleoside that strongly enhanced production of all three type 1 cytokines. The furanose 2′-OH appears to be important for full activity, since conversion of the 2′-OH of **5** to hydrogen, generating the 2′-deoxy compound **14**, resulted in total loss of activity. Also, manipulation of the 3′-OH (**5** to **17**, **23**) resulted in retention of IFN-γ activity, partial loss of TNF-α activity, and total loss of IL-2-enhancing activity. This result indicates that there is considerable flexibility with respect to allowable modifications at the 3′-position of the sugar portion of the molecule. Transformation of the 5′-hydroxyl to a hydrogen (**29**) resulted in the loss of IFN-γ- and IL-2-inducing activity with retention of TNF-α-inducing activity. It is clear from the results of this study that free hydroxyls in the 2′- and 5′-positions are essential. Substitutions on the heterocycle also are important. Switching from a 3-carboxamide to a 5-carboxamide (**5** to **6**) exerted a strongly negative influence on bioactivity for all three type 1 cytokines, whereas conversion of the amide group in compound **5** to a amidine functionality (**10**) did not reduce activity. These results show that the substitution position in the triazole ring is critical for activity.

The results presented here show that the type 1 cytokine-enhancing activity is retained in an analogue in which the D-ribose moiety of ribavirin is replaced by L-ribose (**5**). However, these two compounds differ markedly with respect to other biologic properties.[35] Additional structural changes can have a significant effect on this biologic activity. To our knowledge, this report is the first demonstration that selected L-nucleosides possess immunomodulatory activity. The effect on type 1 cytokines by these L-nucleosides offers significant potential for the treatment of those diseases in which type 1 cytokines play a critical role.

Experimental Section

Melting points were measured on a Haake Büchler capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on Varian mercury 300 MHz spectrometer. The chemical shifts are expressed in δ values (ppm) relative to tetramethylsilane as internal standard. Optical rotations were performed on a JASCO DIP-370 digital polarimeter. Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ. Thin-layer chromatography (TLC) was performed on plates of silica gel 60F_{254} coated on aluminum sheets (5 × 10 cm; EM Science) using different solvents prepared freshly. ICN silica gel 18−32 (60 Å) was used for flash column chromatography. All solvents used were reagent grade. Most of the dry solvents were purchased from Fluka and used as such without further purification. Most of the reactions were conducted under argon atmosphere. Evaporations were carried out under reduced pressure with the bath temperature below 35 °C.

1,2,3,5-Tetra-*O*-acetyl-*β*-L-ribofuranose (1). To a stirred solution of L-ribose (50.0 g, 333.33 mmol) in anhydrous methanol (500 mL) at room temperature was added a freshly prepared dry methanlic HCl (40 mL, prepared by bubbling dry HCl gas into methanol at 0 °C to a weight increase of 4 g) via syringe during 15-min period under argon atmosphere. After the addition of methanolic HCl, the reaction mixture was allowed to stir at room temperature for 3−4 h. Dry pyridine (100 mL) was added and evaporated to dryness. The residue was dissolved in dry pyridine (100 mL) and evaporated to dryness under high vacuum below 40 °C. The process was repeated second time with additional dry pyridine (100 mL). The residue was dissolved in dry pyridine (250 mL) and cooled

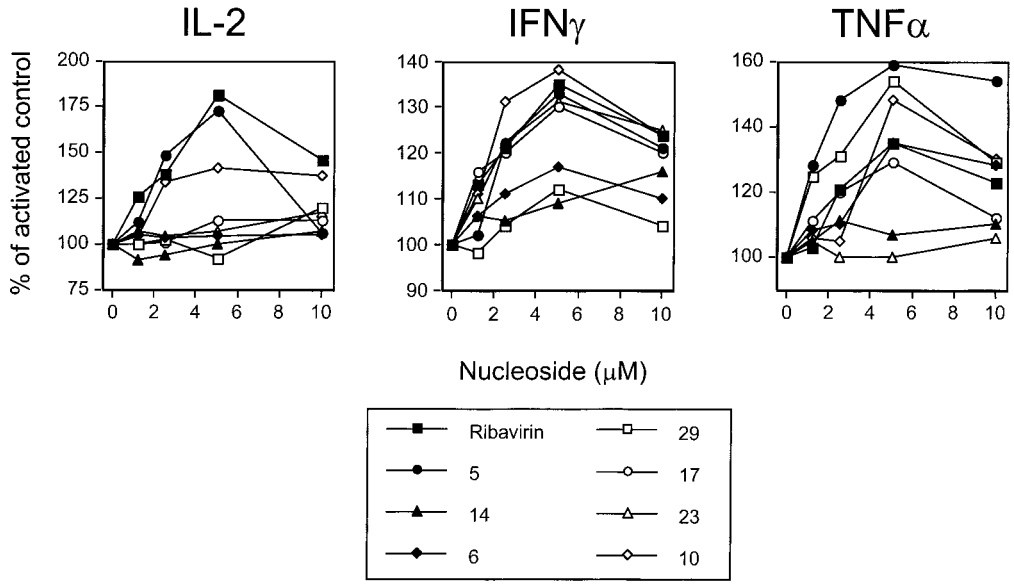


Figure 1. Dose-dependent modulation of SEB-induced type 1 cytokine responses following treatment with L-nucleoside analogues of ribavirin in human T cells. Comparison of the dose-dependent (1.25−10 μM) augmentation by L-nucleoside analogues of ribavirin of IL-2 (left panel), IFN-γ (middle panel), and TNF-α (right panel) levels in SEB-stimulated T cells from five individual human donors. Cytokine levels were determined in cell-free supernatants by ELISA. Human donors, A−E, were determined in cell-free supernatants by ELISA. Data are shown as percentage of activated control for all cytokines. Percentage of activated control is calculated as the ratio of activated T cell cytokine level in the presence of test nucleoside over the cytokine level of untreated activated T cells × 100%. Zero effect on cytokine levels by test nucleosides would give a percentage of activated control value of 100%. The absolute level (pg/mL ± standard deviation) of SEB-induced type 1 cytokine secretion was as shown in Table 1.

in an ice bath to 0 °C under argon atmosphere. To this cold stirred solution was added acetic anhydride (100 mL) via a dropping funnel during a 15-min period. After the addition of acetic anhydride, the reaction was allowed to stir at room temperature under exclusion of moisture for 24 h. The reaction mixture was evaporated to dryness. The residue was partitioned between ethyl acetate (400 mL) and water (400 mL) and extracted in ethyl acetate. The aqueous layer was extracted again with ethyl acetate (100 mL). The combined ethyl acetate extract was washed with water (400 mL), saturated $NaHCO_3$ (2 × 300 mL), water (300 mL) and brine (200 mL). The organic extract was dried over anhydrous sodium sulfate and filtered and the filtrate evaporated to dryness. The residue was coevaporated with dry toluene (2 × 150 mL) at high vacuum. The dried oily residue (92 g, 95%) was used as such for the following reaction without further characterization.

The syrup (92 g) from the above reaction was dissolved in glacial acetic acid (300 mL) and treated with acetic anhydride (75 mL) at room temperature. The solution was cooled to 0 to 5 °C in an ice bath under argon atmosphere. Concentrated H_2SO_4 (21 mL) was added slowly during 15-min period. After the addition of H_2SO_4, the reaction mixture was stirred at room temperature for 14 h and poured on crushed ice (500 g), and stirred until ice melts. Water (500 mL) was added and extracted with chloroform (2 × 300 mL). The chloroform extract was washed with water (3 × 400 mL), saturated $NaHCO_3$ (2 × 300 mL), water (200 mL) and brine (200 mL). The washed organic extract was dried over anhydrous sodium sulfate, filtered and evaporated to dryness to give an oily residue (99 g). The residue was coevaporated with dry toluene (200 mL) and dissolved in ethyl ether (200 mL) which on cooling at −10 °C for a day provided colorless crystals. The crystalline solid was filtered, washed with hexanes:ether (2:1, 50 mL) and dried to give 60.5 g (60%) of **1**: mp 57−59 °C; $[\alpha]^{20}_D$ +12.1 (*c* 2.47, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3H, COCH_3), 2.09 (s, 3H, COCH_3), 2.10 (s, 3H, COCH_3), 2.13 (s, 3H, COCH_3), 4.14 (m, 1H), 4.36 (m, 2H), 5.34 (m, 2H, $C_{2'}H$ & $C_{3'}H$), 6.16 (s, 1H, $C_{1'}H$).

Methyl 1-(2,3,5-Tri-*O*-acetyl-*β*-L-ribofuranosyl)-1,2,4-triazole-3-carboxylate (3) and Methyl 1-(2,3,5-Tri-*O*-acetyl-*β*-L-ribofuranosyl)-1,2,4-triazole-5-carboxylate (4). A mixture of methyl 1,2,4-triazole-3-carboxylate (25.4 g, 200 mmol), 1,2,3,5-tetra-*O*-acetyl-*β*-L-ribofuranose (63.66 g, 200 mmol) and bis(*p*-nitrophenyl)phosphate (1 g) was placed in a RB flask (500 mL). The flask was placed in a preheated oil bath at 165−175 °C under water aspirator vacuum with stirring for 25 min. The acetic acid displaced was collected in an ice-cold trap that is placed between aspirator and the RB flask. The flask was removed from the oil bath and allowed to cool. When the temperature of the flask reached roughly to 60−70 °C, ethyl acetate (300 mL) and saturated $NaHCO_3$ (150 mL) were introduced and extracted in ethyl acetate. The aqueous layer was extracted again with ethyl acetate (200 mL). The combined ethyl acetate extract was washed with saturated $NaHCO_3$ (300 mL), water (200 mL) and brine (150 mL). The organic extract was dried over anhydrous sodium sulfate and filtered and the filtrate evaporated to dryness. The residue was dissolved in ethanol (100 mL) and diluted with methanol (60 mL) which on cooling at 0 °C for 12 h provided colorless crystals. The solid was filtered, washed with minimum cold ethanol (20 mL) and dried at high vacuum over solid sodium hydroxide to give 60 g (78%). The filtrate was evaporated to dryness and purified on silica column using $CHCl_3$ → EtOAc (9:1) as the eluent. Two products were isolated from the filtrate: fast moving product 8.5 g (11%) and slow moving product 5 g (6.5%). The slow moving product matched with crystallized product. The fast moving product was found to be **4** and obtained as a foam. The combined yield of **3** was 65 g (84%): mp 108−110 °C; ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H, COCH_3), 2.12 (s, 3H, COCH_3), 2.13 (s, 3H, OCH_3), 3.99 (s, 3H, COCH_3), 4.22 (dd, 1H), 4.46 (m, 2H), 5.55 (t, 1H, J = 6.0 Hz), 5.75 (m, 1H), 6.05 (d, 1H, $C_{1'}H$ J = 3.6 Hz), 8.41 (s, 1H, C_5H). Anal. ($C_{15}H_{19}N_3O_9$) C, H, N. **4:** ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3H, COCH_3), 2.10 (s, 3H, COCH_3), 2.12 (s, 3H, OCH_3), 4.00 (s, 3H, COCH_3), 4.14 (m, 1H), 4.42 (m, 2H), 5.76 (t, 1H), 5.81 (m, 1H), 6.94 (d, 1H, $C_{1'}H$ J = 2.1 Hz), 8.03 (s, 1H, C_3H). Anal. ($C_{15}H_{19}N_3O_9$) C, H, N.

1-*β*-L-Ribofuranosyl-1,2,4-triazole-3-carboxamide (5). Methyl 1-(2,3,5-tri-*O*-acetyl-*β*-L-ribofuranosyl)-1,2,4-triazole-3-carboxylate (62 g, 161 mmol) was placed in a steel bomb and treated with freshly prepared methanolic ammonia (350 mL, prepared by passing dry ammonia gas into dry methanol at 0 °C until saturation) at 0 °C. The steel bomb was closed and stirred at room temperature for 18 h. The steel bomb was

cooled to 0 °C and opened and the content evaporated to dryness. The residue was treated with dry ethanol (100 mL) and evaporated to dryness. The residue obtained was triturated with acetone to give a solid, which was filtered and washed with acetone. The solid was dried overnight at room temperature and dissolved in hot ethanol (600 mL) and water (10 mL) mixture. The volume of the ethanol solution was reduced to 150 mL by heating and stirring on a hot plate. The hot ethanol solution on cooling provided colorless crystals, which was filtered, washed with acetone and dried under vacuum. Further concentration of the filtrate gave additional material: total yield 35 g (89%); mp 177−179 °C; $[\alpha]^{20}_D$ +35.3 (*c* 10, H_2O); ^{1}H NMR (Me_2SO-d_6) δ 3.46 (m, 1H, $C_{5'}H$), 3.60 (m, 1H, $C_{5'}H$), 3.94 (m, 1H, $C_{4'}H$), 4.12 (m, 1H), 4.34 (m, 1H), 4.95 (t, 1H, $C_{5'}OH$), 5.22 (d, 1H), 5.60 (d, 1H), 5.80 (d, 1H, J = 3.9 Hz, $C_{1'}H$), 7.64 (bs, 1H, NH_2), 7.84 (bs, 1H, NH_2), 8.87 (s, 1H, C_5H); ^{13}C NMR (Me_2SO-d_6) δ 61.8, 70.2, 74.4, 86.0, 91.6, 144.9, 157.4, 160.6. Anal. ($C_8H_{12}N_4O_5$) C, H, N.

1-β-L-Ribofuranosyl-1,2,4-triazole-5-carboxamide (6). Methyl 1-(2,3,5-tri-*O*-acetyl-β-L-ribofuranosyl)-1,2,4-triazole-5-carboxylate (9.63 g, 25.0 mmol) was treated with freshly prepared methanolic ammonia at 0 °C as described for compound **5**. The residue was treated with dry ethanol (100 mL) and evaporated to dryness. The residue obtained was triturated with acetone and filtered. The residue was dissolved in ethanol (100 mL). The volume of the ethanol solution was reduced to 50 mL by heating and stirring on a hot plate. The hot ethanol solution on cooling provided colorless crystals, which was filtered, washed with acetone and dried under vacuum over P_2O_5. The solid was found to be moisture sensitive and on exposure to atmosphere became a viscous material: yield 4.7 g (77%); mp becomes viscous > 75 °C and melts at 122−125 °C; $[\alpha]^{20}_D$ +40.6 (*c* 1.33, H_2O); ^{1}H NMR (Me_2SO-d_6) δ 3.40 (m, 1H, $C_{5'}H$), 3.54 (m, 1H, $C_{5'}H$), 3.86 (m, 1H, $C_{4'}H$), 4.20 (m, 1H), 4.38 (m, 1H), 4.78 (t, 1H, $C_{5'}OH$), 5.18 (d, 1H), 5.44 (d, 1H), 6.78 (d, 1H, J = 3.9 Hz, $C_{1'}H$), 8.14 (bs, 1H, NH_2), 8.16 (s, 1H, C_3H), 8.28 (bs, 1H, NH_2); ^{13}C NMR (Me_2SO-d_6) δ 62.2, 70.3, 74.2, 85.7, 90.8, 147.8, 149.4, 158.7. Anal. ($C_8H_{12}N_4O_5$) C, H, N.

1-(2,3,5-Tri-*O*-acetyl-β-L-ribofuranosyl)-1,2,4-triazole-3-carboxamide (7). A mixture of **5** (14.0 g, 57.38 mmol), acetic anhydride (23.46 g, 230.0 mmol) and triethylamine (25.25 g, 250.0 mmol) was allowed to stir at room temperature in dry pyridine:dimethylformamide mixture (1:1, 100 mL) for 12 h. The reaction mixture was evaporated too dryness to give an oily residue. The residue was partitioned between ethyl acetate (500 mL) and saturated $NaHCO_3$ (150 mL) and extracted in ethyl acetate. The organic extract was washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified on silica column using CH_2Cl_2 → EtOAc as the eluent. The pure product was pooled and evaporated to dryness to provide 17 g (80%) of **7**: ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H, $COCH_3$), 2.12 (s, 3H, $COCH_3$), 2.14 (s, 3H, OCH_3), 4.22 (m, 1H), 4.49 (m, 2H), 5.56 (m, 1H), 5.60 (m, 1H), 6.06 (d, 1H, J = 3.3 Hz), 6.24 (bs, 1H, NH_2), 7.04 (bs, 1H, NH_2), 8.38 (s, 1H, C_5H). Anal. ($C_{14}H_{18}N_4O_8$) C, H, N.

1-(2,3,5-Tri-*O*-acetyl-β-L-ribofuranosyl)-1,2,4-triazole-3-carbonitrile (8). To an ice-cold solution of **7** (12.95 g, 35.0 mmol) in dry dichloromethane (250 mL) and dry pyridine (50 mL) under argon atmosphere was added 20% phosgene in toluene (50 mL) during 30 min period. After the addition, the reaction mixture was allowed to stir at 0− 10 °C during a 2-h period. The reaction mixture was poured onto crushed ice (500 g) and extracted with dichloromethane (2 × 250 mL). The combined organic extract was washed with water (3 × 100 mL) and brine (100 mL), dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified on silica column using CH_2Cl_2 → EtOAc as the eluent. The pure product was pooled and evaporated to dryness to provide 9.0 g (73%) of **8**: ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H, $COCH_3$), 2.13 (s, 3H, $COCH_3$), 2.15 (s, 3H, OCH_3), 4.22 (dd, 1H), 4.40−4.50 (m, 2H), 5.56 (m, 1H), 5.66 (m, 1H), 6.02 (d, 1H, J = 3.3 Hz), 8.39 (s, 1H, C_5H). Anal. ($C_{14}H_{16}N_4O_7$) C, H, N.

Methyl 1-(β-L-Ribofuranosyl)-1,2,4-triazole-3-carboximidate (9). To a stirred suspension of **8** (5.6 g, 15.91 mmol) in dry methanol (60 mL) at room temperature was added 1 N sodium methoxide (10 mL) and the mixture was stirred at room temperature overnight. The clear solution was treated with Dowex H^+ resin (washed with dry methanol before use) till the pH of the solution was 4. The resin was filtered and the filtrate evaporated to dryness. The residue was purified on silica column using CH_2Cl_2 → MeOH as the eluent. The pure product was pooled and evaporated to dryness to afford 2.5 g (61%) of **9**: ^{1}H NMR (Me_2SO-d_6) δ 3.46 (m, 1H, $C_{5'}H$), 3.62 (m, 1H, $C_{5'}H$), 3.85 (s, 3H, OCH_3), 3.94 (m, 1H), 4.12 (m, 1H), 4.34 (m, 1H), 4.98 (t, 1H, $C_{5'}OH$), 5.24 (d, 1H), 5.62 (d, 1H), 5.84 (d, 1H, J = 4.2 Hz, $C_{1'}H$), 8.96 (s, 1H, C_5H). Anal. ($C_9H_{14}N_4O_5$) C, H, N.

1-(β-L-Ribofuranosyl)-1,2,4-triazole-3-carboxamidine Hydrochloride (10). To a mixture of **9** (0.6 g, 2.33 mmol) and ammonium chloride (0.13 g, 2.35 mmol) in a steel bomb was added a solution of methanol saturated at 0 °C with dry ammonia gas. The bomb was closed and the reaction mixture was allowed to stir at room temperature overnight. The steel bomb was cooled to 0 °C and opened carefully and the content was evaporated to dryness. The residue was crystallized from acetonitrile−ethanol to yield 0.5 g (77%) of **10**: mp >180 °C dec; $[\alpha]^{20}_D$ +31.4 (*c* 1.91, H_2O); ^{1}H NMR (Me_2SO-d_6) δ 3.50 (m, 1H, $C_{5'}H$), 3.60 (m, 1H, $C_{5'}H$), 3.94 (m, 1H), 4.13 (m, 1H), 4.35 (m, 1H), 5.00 (bs, 1H), 5.26 (bs, 1H), 5.64 (bs, 1H), 5.81 (d, 1H, J = 3.9 Hz, $C_{1'}H$), 7.34 (bs, 2H), 8.92 (s, 1H, C_5H); ^{13}C NMR (Me_2SO-d_6) δ 61.6, 70.4, 74.3, 86.0, 91.6, 144.8, 157.2, 160.6. Anal. ($C_8H_{14}N_5O_4Cl$) C, H, N.

1-[3,5-*O*-(1,1,3,3-Tetraisopropyl-1,3-*O*-disiloxanyl)-β-L-ribofuranosyl]-1,2,4-triazole-3-carboxamide (11). To a stirred solution of compound **5** (4.88 g, 20 mmol) in dry pyridine (40 mL) and dry dimethylformamide (40 mL) at 0 °C under argon atmosphere was added triethylamine (5.05 g, 50 mmol) followed by 1,3-dichloro-1,1,3,3-tetraisopropyl-1,3-*O*-disiloxane ($TIPSiCl_2$; 7.88 g, 25 mmol) during a 30-min period. After the addition of $TIPSiCl_2$, the reaction was allowed to stir at room temperature for 12 h and evaporated to dryness. The residue was partitioned between saturated $NaHCO_3$ (100 mL) and dichloromethane (150 mL) and extracted in dichloromethane. The organic extract was washed with water (100 mL) and brine (50 mL), dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography over silica gel using $CHCl_3$ → acetone as the eluent. The pure fractions were pooled and concentrated to give 7.0 g (72%) of **11** as a foam: ^{1}H NMR ($CDCl_3$) δ 1.02−1.08 (m, 24H, 4 × isopropyl-*H*), 3.98−4.20 (m, 3H, $C_{4'}$ & $C_{5'}H$), 4.48 (d, 1H), 4.62 (m, 1H), 5.95 (s, 1H, $C_{1'}H$), 6.16 (bs, 1H, NH_2), 6.98 (bs, 1H, NH_2), 8.41 (s, 1H, C_5H). Anal. ($C_{20}H_{38}N_4O_6Si_2$) C, H, N.

1-[2-*O*-Phenylthioformate-3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-*O*-disiloxanyl)-β-L-ribofuranosyl]-1,2,4-triazole-3-carboxamide (12). To a stirred solution of compound **11** (4.0 g, 8.23 mmol) in dry pyridine (20 mL) and dry dichloromethane (50 mL) at 0 °C under argon atmosphere was added triethylamine (2.53 g, 25 mmol) followed by phenyl chlorothionoformate (4.25 g, 24.7 mmol) during a 15-min period. The reaction was stirred at 0 °C for 1 h and at room temperature for 12 h and evaporated to dryness. The residue was partitioned between saturated $NaHCO_3$ (100 mL) and ethyl acetate (150 mL) and extracted in ethyl acetate. The organic extract was washed with water (100 mL) and brine (50 mL), dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography over silica gel using CH_2Cl_2 → EtOAc as the eluent. The pure fractions were pooled and concentrated to give 3.17 g (62%) of the pure compound as a foam: ^{1}H NMR ($CDCl_3$) δ 1.08−1.19 (m, 24H, 4 × isopropyl-*H*), 4.00−4.22 (m, 3H, $C_{4'}$ & $C_{5'}H$), 4.82 (m, 1H), 6.0 (bs, 1H, NH_2), 6.14 (d, 1H), 6.17 (s, 1H, $C_{1'}H$), 6.96 (bs, 1H, NH_2), 7.11−7.45 (m, 5H, Ph*H*), 8.47 (s, 1H, C_5H). Anal. ($C_{27}H_{42}N_4O_7SSi_2$) C, H, N.

1-[2-Deoxy-3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-*O*-disiloxanyl)-β-L-ribofuranosyl]-1,2,4-triazole-3-carboxamide (13).

Compound **12** (3.17 g, 5.09 mmol) was dissolved in dry dioxane (60 mL) and bubbled with dry argon for 15 min. To this solution were added 2,2′-azobis(isobutyronitrile) (0.82 g, 5 mmol) and diphenylsilane (1.84 g, 10 mmol) and heated at reflux for 12 h. The reaction was cooled and evaporated to dryness and the residue was purified by flash chromatography over silica gel using $CH_2Cl_2 \rightarrow$ EtOAc as the eluent. The pure fractions were pooled and concentrated to give 1.2 g (50%) of the pure compound as a foam: ^{1}H NMR ($CDCl_3$) δ 1.02−1.08 (m, 24H, 4 × isopropyl-*H*), 2.60 & 2.78 (2m, 2H, $C_{2'}H$), 3.92 (m, 1H, $C_{4'}H$), 4.02 (m, 2H, $C_{5'}H$), 4.62 (m, 1H, $C_{3'}H$), 5.74 (bs, 1H, NH_2), 6.12 (d, 1H, $C_{1'}H$), 7.0 (bs, 1H, NH_2), 8.43 (s, 1H, C_5H). Anal. ($C_{20}H_{38}N_4O_5Si_2$) C, H, N.

1-(2-Deoxy-β-L-ribofuranosyl)-1,2,4-triazole-3-carboxamide (14). Compound **13** (1.1 g, 2.34 mmol) was dissolved in dry dichloromethane (10 mL) and treated with triethylamine trihydrofluoride (10 mL). The reaction was stirred at room temperature for 3 h and evaporated to dryness. The residue was purified by flash chromatography over silica gel using $CH_2Cl_2 \rightarrow$ MeOH as the eluent. The pure fractions were pooled and concentrated to give 0.25 g (47%) of the pure compound as a foam: $[\alpha]^{20}_D$ −12 (*c* 1.33, H_2O); ^{1}H NMR ($CDCl_3$) δ 2.32 & 2.58 (2m, 2H, $C_{2'}H$), 3.40−3.60 (m, 2H, $C_{5'}H$), 3.82 (m, 1H, $C_{4'}H$), 4.38 (m, 1H, $C_{3'}H$), 4.86 (t, 1H, $C_{5'}OH$), 5.28 (d, 1H, $C_{3'}OH$), 6.22 (t, 1H, $C_{1'}H$), 7.62 (bs, 1H, NH_2), 7.84 (bs, 1H, NH_2), 8.81 (s, 1H, C_5H); ^{13}C NMR (Me_2SO-d_6) δ 62.5, 70.9, 71.9, 85.4, 88.3, 147.3, 151.0, 158.7. Anal. ($C_8H_{12}N_4O_4$) C, H, N.

1,2-Di-*O*-acetyl-3,5-di-*O*-benzoyl-L-xylofuranose (15). Compound **15** was prepared from L-xylose without purification of the intermediates in 50% (overall) yield by the method reported:[29] $[\alpha]^{20}_D$ −16.9 (*c* 0.96, acetone); ^{1}H NMR ($CDCl_3$) δ 2.06 & 2.08 (2s, 6H, 2 × $COCH_3$), 4.40−4.60 (m, 2H), 5.50−5.62 (m, 2H), 5.90 (t, 1H, 6.96 (d, 1H), 7.00−7.60 (m, 6H, Ph*H*), 8.03 (m, 4H, Ph*H*).

Methyl 1-(2-*O*-Acetyl-3,5-di-*O*-benzoyl-β-L-xylofuranosyl)-1,2,4-triazole-3-carboxylate (16). A mixture of methyl 1,2,4-triazole-3-carboxylate (1.27 g, 10.0 mmol), compound **15** (4.42 g, 10.0 mmol) and bis(*p*-nitrophenyl)phosphate (20.0 mg) was placed in a pear-shaped flask (50 mL). The flask was placed in a preheated oil bath at 165−175 °C under water aspirator vacuum with stirring for 25 min. The acetic acid displaced was collected in an ice-cold trap that is placed between aspirator and the pear-shaped flask. The flask was removed from the oil bath and allowed to cool. When the temperature of the flask reached roughly to 60−70 °C, ethyl acetate (100 mL) and saturated $NaHCO_3$ (50 mL) were introduced and extracted in ethyl acetate. The aqueous layer was extracted again with ethyl acetate (50 mL). The combined ethyl acetate extract was washed with saturated $NaHCO_3$ (50 mL), water (50 mL) and brine (50 mL). The organic extract was dried over anhydrous sodium sulfate and filtered and the filtrate evaporated to dryness. The residue was purified by flash chromatography over silica gel using hexane → EtOAc as the eluent. The pure product was pooled together and evaporated to give 4.0 g (79%) of **16**: ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 3H, $COCH_3$), 3.96 (s, 3H, OCH_3), 4.72 (m, 2H), 4.98 (m, 1H), 5.79 (t, 2H), 6.15 (s, 1H), 7.43 (m, 4H, Ph*H*), 7.59 (m, 2H, Ph*H*), 7.81 (d, 2H, Ph*H*), 8.00 (d, 2H, Ph*H*), 8.61 (s, 1H, C_5H). Anal. ($C_{25}H_{23}N_3O_9$) C, H, N.

1-(β-L-Xylofuranosyl)-1,2,4-triazole-3-carboxamide (17). Compound **16** (3.5 g, 6.88 mmol) was placed in a steel bomb and treated with freshly prepared methanolic ammonia (100 mL, prepared by passing dry ammonia gas into dry methanol at 0 °C until saturation) at 0 °C. The steel bomb was closed and stirred at room temperature for 18 h. The steel bomb was cooled to 0 °C and opened and the content evaporated to dryness. The residue was treated with dry ethanol (100 mL) and evaporated to dryness. The residue obtained was triturated with acetone and the acetone was decanted. This was repeated for two more times to remove acetamide. The residue was dissolved in minimum amount of ethanol, which on cooling inside refrigerator gave crystals: yield 1.5 g (89%); mp 172−175 °C; $[\alpha]^{20}_D$ +22 (*c* 0.49, H_2O); ^{1}H NMR (Me_2SO-d_6) δ 3.72 (m, 2H, $C_{5'}H$), 4.02 (m, 1H, $C_{4'}H$), 4.24 (m, 2H), 4.76 (t, 1H, $C_{5'}OH$), 5.32 (d, 1H), 5.75 (s, 1H), 5.97 (d, 1H, J = 4.2 Hz, $C_{1'}H$), 7.61 (bs, 1H, NH_2), 7.84 (bs, 1H, NH_2), 8.62 (s, 1H, C_5H); ^{13}C NMR (Me_2SO-d_6) δ 60.0, 74.7, 80.4, 85.2, 94.4, 144.3, 156.3, 160.6. Anal. ($C_8H_{12}N_4O_5$) C, H, N.

1,2-*O*-Isopropylidene-5-*O*-benzoyl-α-L-*erythro*-pentofuranos-3-ulose (18). Compound **18** was prepared from L-xylose in 65% yield (overall) by the method reported:[31] ^{1}H NMR ($CDCl_3$) δ 1.44 & 1.52 (2s, 2 CH_3), 4.42 (m, 1H, $C_{5'}H$), 4.50 (m, 1H, $C_{5'}H$), 4.60−4.72 (m, 2H, $C_{2'}$ & $C_{4'}H$), 6.14 (d, 1H, J = 4.4 Hz, $C_{1'}H$), 7.0.42−7.97 (m, 5H, Ph*H*).

1,2-*O*-Isopropylidene-3-deoxy-3-(*p*-toluenesulfonylhydrazino)-5-*O*-benzoyl-α-L-ribofuranose (19). A mixture of **18** (60 g, 205.5 mmol) and *p*-toluenesulfonyl hydrazide (40.92 g, 220 mmol) in dry ethanol (500 mL) was heated at reflux for 4 h. The reaction mixture was cooled and the precipitate was filtered, washed with ether and dried to give 45 g (48%) of white solid: mp 178−181 °C.

To a stirred solution of the above solid (10 g, 21.74 mmol) in tetrahydrofuran (40 mL) and methanol (40 mL) was added a trace of methyl orange (indicator) at room temperature. To this stirred solution was added sodium cyanoborohydride (0.63 g, 10 mmol) followed by methanolic HCl (saturated) drop by drop keeping the color of the solution at red−yellow transition point. The mixture was stirred at room temperature for 1 h. A second portion of sodium cyanoborohydride (0.63 g, 10 mmol) was added followed by dropwise addition of methanolic HCl during a 1-h period to maintain the pH of the reaction mixture between 2.5 and 4.0. The reaction was stirred for an additional 1 h, neutralized with saturated $NaHCO_3$ solution and evaporated to dryness. The residue was partitioned between water (100 mL) and dichloromethane (200 mL) and extracted in dichloromethane. The organic extract was washed with brine (100 mL), dried and evaporated to dryness to give 10 g (99%) of a white solid: mp 152−154 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 and 1.45 (2s, 6H, isopropyl-CH_3), 2.32 (s, 3H, Ph-CH_3), 3.28 (m, 1H), 3.75 (m, 2H), 3.84 (m, 1H), 4.20 (m, 1H), 4.67 (m, 1H), 5.82 (d, 1H), 7.24−8.02 (m, 9H, Ph*H*). Anal. ($C_{22}H_{26}N_2O_7S$) C, H, N.

1,2-Isopropylidene-3-deoxy-5-*O*-benzoyl-α-L-*erythro*-pentofuranose (20). A mixture of **19** (10 g, 21.65 mmol) and sodium acetate trihydrate (12.0 g, 88.1 mmol) in ethanol (200 mL) was heated at reflux for 2 h and cooled. The reaction was filtered and the solid was washed with ethanol and dichloromethane. The combined filtrate was evaporated and extracted in ethyl acetate (200 mL) upon partition with water (100 mL). The organic extract was washed with brine (100 mL), dried and evaporated to dryness to give 5.25 g (87%) of **20** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.32 and 1.53 (2s, 6H, isopropyl-CH_3), 1.74 (m, 1H, $C_{2'}H$), 2.15 (dd, 1H, $C_{2'}H$), 4.34 (m, 1H, $C_{5'}H$), 4.52 (m, 2H, $C_{4'}$ & $C_{5'}H$), 4.76 (m, 1H, $C_{2'}H$), 5.86 (d, 1H, $C_{1'}H$), 7.40 (m, 2H, Ph*H*), 7.53 (m, 1H, Ph*H*), 8.04 (m, 2H, Ph*H*). Anal. ($C_{15}H_{18}O_5$) C, H.

1,2-Di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-L-ribofuranose (21). A solution of **20** (21 g, 75.54 mmol) was coevaporated with dry toluene (100 mL), dissolved in glacial acetic acid (200 mL) and acetic anhydride (40 mL), and cooled to 0 °C in an ice bath under argon atmosphere. To this cold stirred solution was added concentrated H_2SO_4 (15 mL) during 30 min. After the addition of H_2SO_4, the reaction mixture was stirred at room temperature for 24 h, poured into crushed ice (1000 g) and stirred for 30 min. The aqueous solution was extracted with chloroform (3 × 300 mL). The organic extract was washed with water (3 × 300 mL), saturated $NaHCO_3$ (2 × 400 mL) and brine (100 mL), dried and evaporated to dryness to afford 24.33 g (100%) of **21** as an oil: $[\alpha]^{20}_D$ −1.9 (*c* 0.98, acetone); ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 6H, 2 × $COCH_3$), 2.04−2.30 (m, 2H, $C_{2'}H$), 4.32−4.76 (m, 3H, $C_{4'}$ & $C_{5'}H$), 5.20−5.32 (m, 1H, $C_{2'}H$), 6.20 (s, 1/3H, $C_{1'}H$), 6.85 (d, 2/3H, $C_{1'}H$), 7.40−7.60 (m, 3H, Ph*H*), 8.14 (m, 2H, Ph*H*).

Methyl 1-(2-*O*-Acetyl-5-*O*-benzoyl-3-deoxy-β-L-ribofuranosyl)-1,2,4-triazole-3-carboxylate (22). The procedure was the same as that described for compound **16**. Materials used: methyl 1,2,4-triazole-3-carboxylate (1.27 g, 10.0 mmol), compound **21** (3.54 g, 11.0 mmol) and bis(*p*-nitrophenyl)phosphate

(20.0 mg). The crude product was purified by flash chromatography over silica gel using $CHCl_3 \rightarrow$ EtOAc as the eluent. The pure product was pooled together and evaporated to give 3.0 g (77%) of **22**: ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 6H, 2 × COCH_3), 2.32 (m, 1H, C$_{2'}H$), 2.62 (m, 1H, C$_{2'}H$), 3.99 (s, 3H, OCH_3), 4.42−4.68 (m, 2H, C$_{5'}H$), 4.82 (m, 1H, C$_{4'}H$), 5.62 (d, 1H, C$_{2'}H$), 6.04 (s, 1H, C$_{1'}H$), 7.40−7.60 (m, 3H, PhH), 8.00 (m, 2H, PhH), 8.40 (s, 1H, C$_5H$). Anal. ($C_{18}H_{19}N_3O_7$) C, H, N.

1-(3-Deoxy-β-L-ribofuranosyl)-1,2,4-triazole-3-carboxamide (23). Compound **23** was prepared by following the procedure used for the preparation of **17**. Materials used: **23** (0.9 g, 2.31 mmol) and methanolic ammonia (70 mL, prepared by passing dry ammonia gas into dry methanol at 0 °C until saturation) at 0 °C. The crude product was dissolved in minimum amount of ethanol, which on cooling inside refrigerator gave 0.4 g (76%) of crystals: mp 128−131 °C; $[\alpha]^{20}_D$ +11.4 (*c* 0.56, H_2O); ^{1}H NMR (Me_2SO-d_6) δ 1.84 (m, 1H, C$_{3'}H$), 2.10 (m, 1H, C$_{3''}H$), 3.52−3.64 (m, 2H, C$_{5'}H$), 4.38−4.58 (m, 2H, C$_{2'}$ & C$_{4'}H$), 4.97 (t, 1H, C$_{5'}$OH), 5.72 (d, 1H), 5.84 (s, 1H), 7.62 (bs, 1H, NH_2), 7.82 (bs, 1H, NH_2), 8.84 (s, 1H, C$_5H$); ^{13}C NMR (Me_2SO-d_6) δ 24.2, 63.4, 75.8, 82.3, 94.9, 144.5, 157.8, 161.1. Anal. ($C_8H_{12}N_4O_4$) C, H, N.

1-Methoxy-2,3-*O*-isopropylidene-L-ribofuranose (24). L-Ribose was suspended in dry methanol (200 mL) and 2,2-dimethoxypropane (100 mL) and mixed with dry acetone (700 mL). To this stirred suspension was added methanolic HCl (20 mL, saturated at 0 °C) during a 15-min period. After the addition, the reaction mixture was allowed to stir at room temperature overnight. Pyridine (100 mL) was added and evaporated to dryness. The residue was partitioned water (500 mL) and ether (400 mL) and extracted in ether. The aqueous layer was extracted with ether (2 × 200 mL). The combined ether layer was dried and concentrated to give 62 g (92%) of crude product. The crude product was used as such for the next reaction: ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H, isopropylidene-CH_3), 1.50 (s, 3H, isopropylidene-CH_3), 3.30 (dd, 1H), 3.45 (s, 3H, OCH_3), 3.58−3.74 (m, 2H, C$_{5'}H$), 4.42 (m, 1H, C$_{5'}$OH), 4.61 (d, 1H), 4.84 (d, 1H), 4.99 (s, 1H, C$_{1'}H$). Anal. ($C_9H_{16}O_5$) C, H.

1-Methoxy-2,3-*O*-isopropylidene-5-bromo-L-ribofuranose (25). Compound **24** (55.0 g, 269 mmol) was dissolved in dry dichloromethane (900 mL) and cooled to 0 °C under argon atmosphere. To this cold solution was added Ph_3P (141.5 g, 540 mmol) followed by bromine (85.86 g, 540 mmol). The reaction mixture was refluxed for 4 h, cooled, and added to methanol (50 mL). The dichloromethane layer was washed with water (2 × 500 mL), saturated $NaHCO_3$ (2 × 500 mL), water (2 × 500 mL) and brine (200 mL), dried and evaporated to dryness. The residue was triturated with hexane:ethyl acetate (8:2, 1000 mL) and filtered. The precipitate was washed with hexane:ethyl acetate (8:2, 500 mL). The combined filtrate was evaporated to give 79 g of crude product. The crude product was placed on top of silica column packed in hexane and eluted with hexane:ethyl acetate (9:1, 1000 mL). The pure fractions were collected and evaporated to give 62.8 g (87%) of **25** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H, isopropylidene-CH_3), 1.49 (s, 3H, isopropylidene-CH_3), 3.32−3.46 (m, 5H, C$_{5'}H$ & OCH_3), 4.42 (m, 1H), 4.62 (d, 1H), 4.77 (d, 1H), 5.02 (s, 1H). Anal. ($C_9H_{15}O_4Br$) C, H, N, Br.

1-Methoxy-2,3-*O*-isopropylidene-5-deoxy-L-ribofuranose (26). Compound **25** (41.0 g, 153.6 mmol) was dissolved in dry methanol (200 mL) and treated with potassium hydroxide (8.96 g, 160 mmol) dissolved in water (10 mL). To this solution was added Pd/C (10%, 3.0 g) and hydrogenated at 45 psi for 12 h. The reaction mixture was filtered and washed with methanol (100 mL) and the filtrate evaporated to dryness. The residue was partitioned between water (100 mL) and dichloromethane (200 mL) and extracted in dichloromethane. The organic layer was washed with brine (100 mL), dried and evaporated to dryness to give 27.0 g (94%) of pure product as an oil: ^{1}H NMR ($CDCl_3$) δ 1.22−1.30 (m, 6H, isopropylidene-CH_3 & C$_{5'}$CH_3), 1.45 (s, 3H, isopropylidene-CH_3), 3.30 (s, 3H, OCH_3), 4.32 (m, 1H), 4.49 (d, 1H), 4.60 (d, 1H), 4.91 (1, 1H). Anal. ($C_9H_{16}O_4$) C, H.

1,2,3-Tri-*O*-acetyl-5-deoxy-L-ribofuranose (27). Compound **26** (13.3 g, 71.0 mmol) was dissolved in glacial acetic acid (100 mL) and acetic anhydride (40 g, 392 mmol) and cooled to 5 °C. To this cold stirred solution was added concentrated H_2SO_4 (7 mL) during 30 min. After the addition, the reaction mixture was stirred at room temperature for 12 h, poured on ice (200 g) and stirred for 1 h. The aqueous layer was extracted with ethyl acetate (2 × 150 mL). The organic layer was washed with saturated $NaHCO_3$ (200 mL), water (200 mL) and brine (100 mL), dried and evaporated to dryness to give 9.0 g (49%) of **27** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.24−1.40 (m, 3H, C$_{5'}$CH_3), 2.04−2.20 (m, 9H, 3 × COCH_3), 4.18−4.40 (m, 2H), 5.00−5.40 (m, 3H), 6.99 (d, 1H).

Methyl (2,3-Di-*O*-acetyl-5-deoxy-β-L-ribofuranosyl)-1,2,4-triazole-3-carboxylate (28). 1,2,4-Triazole-3-carboxylate (2.54 g, 20.0 mmol) in hexamethyldisilazane (100 mL) was heated at reflux for 4 h and evaporated to dryness. The residue was dissolved in dry acetonitrile (100 mL) and cooled to 0 °C under argon atmosphere. To this cold stirred solution was added 1,2,3-tri-*O*-acetyl-5-deoxy-L-ribofuranose (5.20 g, 20 mmol) followed by $SnCl_4$ (5.2 g, 20 mmol) during a 15-min period. The reaction mixture was allowed to stir at room temperature for 12 h, cooled to 0 °C, quenched with saturated $NaHCO_3$ solution and filtered, and the precipitate was washed with acetonitrile (100 mL). The combined filtrate was evaporated to dryness. The residue was partitioned between ethyl acetate (200 mL) and saturated $NaHCO_3$ (50 mL) and extracted in ethyl acetate. The aqueous layer was extracted again with ethyl acetate (100 mL). The combined ethyl acetate extract was washed with saturated $NaHCO_3$ (150 mL), water (100 mL) and brine (50 mL). The organic extract was dried over anhydrous sodium sulfate and filtered and the filtrate evaporated to dryness. The residue was purified by flash chromatography over silica gel using hexane → EtOAc as the eluent. The pure product was pooled together and evaporated to give 3.5 g (53%) of **28**: ^{1}H NMR ($CDCl_3$) δ 1.44 (d, 3H, C$_{5'}$CH_3), 2.10 (s, 6H, 2 × COCH_3), 3.99 (s, 3H, OCH_3), 4.40 (m, 1H), 5.24 (m, 1H), 5.72 (m, 1H), 5.99 (d, 1H, C$_{1'}H$), 8.38 (s, 1H, C$_5H$). Anal. ($C_{13}H_{17}N_3O_7$) C, H, N.

1-(5-Deoxy-β-L-ribofuranosyl)-1,2,4-triazole-3-carboxamide (29). Compound **28** (0.9 g, 2.75 mmol) was treated with freshly prepared methanolic ammonia (50 mL) as described for the preparation of compound **23**. The residue was dissolved in minimum amount of ethanol, which on cooling inside refrigerator gave crystals: yield 0.45 g (72%); mp 178−180 °C; $[\alpha]^{20}_D$ −70 (*c* 1.1, H_2O); ^{1}H NMR (Me_2SO-d_6) δ 1.22 (d, 3H, C$_{5'}$CH_3), 3.62 (m, 1H, C$_{4'}H$), 4.16 (m, 1H), 4.44 (m, 1H), 5.54 (d, 1H), 5.77 (d, 1H), 5.86 (d, 1H, J = 5.4 Hz, C$_{1'}H$), 7.64 (bs, 1H, NH_2), 7.84 (bs, 1H, NH_2), 8.80 (s, 1H, C$_5H$); ^{13}C NMR (Me_2SO-d_6) δ 18.4, 79.9, 80.9, 81.7, 91.8, 145.1, 157.8, 160.6. Anal. ($C_8H_{12}N_4O_4$) C, H, N.

Biological Tests. 1. Preparation of Human T Cells and Activation in Vitro. Peripheral blood mononuclear cells were isolated from healthy donors by density gradient centrifugation followed by T cell enrichment using Lymphokwik (One Lambda, Canoga Park, CA). Contaminating monocytes were removed by adherence to plastic. Purified T cells were >99% $CD2^+$, <1% HLA-DR^+, and <5% $CD25^+$ and were maintained in RPMI-AP5 (RPMI-1640 medium containing 5% autologous plasma, 1% L-glutamine, 1% penicillin/streptomycin, and 0.05% 2-mercaptoethanol). For determination of cytokine protein levels, T cells (0.2×10^6 cells in a volume of 0.2 mL) were activated by the addition of 80 ng of staphyloccocal enterotoxin B (SEB; Sigma, St. Louis, MO) and incubated in 96-well plates in the presence of 0−10 μM of various L-nucleosides or ribavirin for 48 h at 37 °C. Following activation, supernatants were analyzed for cell-derived cytokine production.

2. Extracellular Cytokine Analyses. Human cytokine levels were determined in cell supernatants, following appropriate dilution, using ELISA kits specific for IL-2, IFN-γ, and TNF-α (Biosource, Camarillo, CA). All ELISA results were expressed as pg/mL. Data are shown as percentage of activated control calculated as the ratio of activated T cell cytokine level in the presence of test nucleoside over the cytokine level of

untreated activated T cells × 100%. Zero effect on cytokine levels by test nucleosides would give a percentage of activated control value of 100%.

References

(1) (a) Aulitzky, W. E.; Huber, C.; Peschel, C. Cytokine therapy of neoplastic and inflammatory disease. *Int. Arch. Allergy Immunol.* **1993**, *101*, 221−226. (b) Kroemer, G.; Hirsch, F.; Gonzalez-Garcia, A.; Martinez, C. Differential involvement of Th1 and Th2 cytokines in autoimmune diseases. *Autoimmunity* **1996**, *24*, 25−33.

(2) Simon, A. K.; Seipelt, E.; Sieper, J. Divergent T-cell cytokine patterns in inflammatory arthritis. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *30*, 8562−8566.

(3) Mosmann, T. R.; Coffman, R. L. Th1 and Th2 Cells: Different Patterns of Lymphokine Secretion Lead to Different Functional Properties. *Annu. Rev. Immunol.* **1989**, *7*, 145−173.

(4) Dubey, C.; Bellon, B.; Druet, P. Th1 and Th2 Dependent Cytokines in Experimental Autoimmunity and Immune Reactions Induce by Chemicals. *Eur. Cytokine Network* **1991**, *2*, 147−152.

(5) Beraud, E.; Lorberboun-Galski, H.; Chan, C. C.; FitzGerald, D.; Pastan, I.; Nussenblatt, R. B. Immunospecific suppression of encephalitogenic-activated T lymphocytes by chimeric cytotoxin IL-2-PE40. *Cell Immunol.* **1991**, *133*, 379−389.

(6) Hahn, H. J.; Gerdes, J.; Lucke, S.; Liepe, L.; Kauert, C.; Volk, H. D.; Wacker, H. H.; Brocke, S.; Stein, H.; Diamantstein, T. Phenotypical characterization of the cells invading pancreatic islets of diabetic BB/OK rats: Effect of interleukin 2 receptor-targeted immunotherapy. *Eur. J. Immunol.* **1988**, *18*, 2037−2042.

(7) Kapsenberg, M. L.; Wierenga, E. A.; Bos, J. D.; Jansen, H. M. Functional subsets of allergen-reactive human CD4+ T cells. *Immunol. Today* **1991**, *12*, 392−395.

(8) (a) Walker, C.; Bode, E.; Boer, L.; Hansel, T. T.; Blaser, K.; Virchow, J. C., Jr. Allergic and nonallergic asthmatics have distinct patterns of T-cell activation and cytokine production in peripheral blood and bronchoalveolar lavage. *Am. Rev. Respir. Dis.* **1992**, *146*, 109−115. (b) van der Heijden, F. L.; Wierenga, E. A.; Bos, J. D.; Kapsenberg, M. L. High frequency of IL-4-producing CD4+ allergen-specific T lymphocytes in atopic dermatitis lesional skin. *J. Invest. Dermatol.* **1991**, *97*, 389−394.

(9) Finkelman, F. D.; Pearce, E. J.; Urban, J. F., Jr.; Sher, A. Regulation and biological function of helminth-induced cytokine responses. *Immunol. Today* **1991**, *12*, A62−66.

(10) Caceres-Dittmar, G.; Tapia, F. J.; Sanchez, M. A.; Yamamura, M.; Uyemura, K.; Modlin, R. L.; Bloom, B. R.; Convit, J. Determination of the cytokine profile in American cutaneous leishmaniasis using the polymerase chain reaction. *Clin. Exp. Immunol.* **1993**, *91*, 500−505.

(11) Del Prete, G.; Tiri, A.; Maggi, E.; De Carli, M.; Macchia, D.; Parronchi, P.; Rossi, M. E.; Pietrogrande, M. C.; Ricci, M.; Romagnani, S. Defective in vitro production of gamma-interferon and tumor necrosis factor-alpha by circulating T cells from patents with the hyper-immunoglobulin E syndrome. *J. Clin. Invest.* **1989**, *84*, 1830−1835.

(12) Schandene, L.; Ferster, A.; Mascart-Lemone, F.; Crusiaux, A.; Gerard, C.; Marchant, A.; Lybin, M.; Velu, T.; Sariban, E.; Goldman, M. T helper type 2-like cells and therapeutic effects of interferon-gamma in combined immunodeficiency with hypereosinophilia (Omenn's syndrome). *Eur. J. Immunol.* **1993**, *23*, 56−60.

(13) Barker, E.; Mackewicz, C. E.; Levy, J. A. Effects of Th1 and Th2 cytokines on $CD8^+$ cell response against human immunodeficiency virus: Implications for long-term survival. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 11135−11139.

(14) Hall, C. B.; McBride, J. T.; Walsh, E. E.; Bell, D. M.; Gala, C. L.; Hildreth, S.; Ten Eyck, L. G.; W. J. Hall. Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection. *N. Engl. J. Med.* **1983**, *308*, 1443−1447.

(15) Reichard, O.; Norkrans, G.; Fryden, A.; Braconier, J.-H.; Sonnerborg, A.; Weiland, O. Randomized, double blind, placebo controlled trial of interferon alpha 2B with and without ribavirin for chronic hepatitis C. *Lancet* **1998**, *351*, 83−87.

(16) Hultgren, C.; Milich, D. R.; Weiland, O.; Sällberg, M. The antiviral compound ribavirin modulates the T helper (Th)1/Th2 subset balance in hepatitis B and C virus-specific immune responses. *J. Gen. Virol.* **1998**, *79*, 2381−2391.

(17) Ning, Q.; Brown, D.; Parodo, J.; Cattral, M.; Fung, L.; Gorczynski, R.; Cole, E., Fung, L.; Ding, J. W.; Liu, M. F.; Rotstein, O.; Phillips, M. J.; Levy, G. Ribavirin inhibits viral-induced macrophage production of tumor necrosis factor, interleukin-1, procoagulant activity fgl2 prothrombinase and preserves Th1 cytokine production but inhibits Th2 cytokine response. *J. Immunol.* **1998**, *160*, 3487−3493.

(18) Martin, M. J.; Navas, S.; Quiroga, J. A.; Pardo, M.; Carreno, V. Effects of the ribavirin-interferon alpha combination on cultured peripheral blood mononuclear cells from chronic hepatitis C patients. *Cytokine* **1998**, *79*, 2381−2391.

(19) Tam, R. C.; Pai, B.; Bard, J.; Lim, C.; Averett, D. R.; Phan, U. T.; Milovanovic, T. Ribavirin polarizes human T cell responses towards a Type 1 cytokine profile. *J. Hepatol.* **1999**, *30*, 376−382.

(20) Tam, R. C.; Lim, C.; Bard, J.; Pai, B. Contact hypersensitivity responses following ribavirin treatment in vivo are influenced by Type 1 cytokine polarization, regulation of IL-10 expression and costimulatory signaling. *J. Immunol.* **1999**, *163*, 3709−3717.

(21) Wilson, J. E.; Martin, J. L.; Borroto-Esoda, K.; Hopkins, S.; Painter, G.; Liotta, D. C.; Furman, P. A. The 5-triphosphates of the (−) and (+) enantiomers of *cis*-5-fluoro-1-[2-hydroxymethyl)-1,3-oxathiolane-5-yl cytosine equally inhibit human immunodeficiency virus type 1 reverse transcriptase. *Antimicrob. Agents Chemother.* **1993**, *37*, 1720−1722.

(22) Skalski, V.; Chang, C. N.; Dutschman, G.; Cheng, Y. C. The biochemical basis for the differential anti-human immunodeficiency virus activity of two cis enantiomers of 2′,3′-dideoxy-3′-thiacytidine. *J. Biol. Chem.* **1993**, *268*, 23234−23238.

(23) (a) Zhu, Y. L.; Dutschman, D. E.; Liu, S. H.; Bridges, E. G.; Cheng, Y. C. Anti-hepatitis B virus and metabolism of 2′,3′-dideoxy-2′,3′-dihydro-beta-L(−)-5-fluorocytidine. *J. Biol. Chem.* **1993**, *268*, 23234−23238. (b) Furman, P. A.; Davis, M.; Liotta, D. C.; Paff, M.; Frick, L.; Nelson, D.; Dornsife, R.; Wurster, J. A.; Wilson, L. J.; Fyfe, J.; Tuttle, J.; Condreay, L.; Averett, D. R.; Schinazi, R.; Painter, G. The Anti-Hepatitis B Virus Activity, Cytotoxicity, and Anabolic Profile of the (−) and (+) Enantiomers of Cis-5-fluoro-1-{2-(hydroxymethyl)-1,3-oxythiolane-5-yl}cytosine. *Antimicrob. Agents Chemother.* **1992**, *36*, 2686−2692. (c) Paff, M. T.; Averett, D. R.; Prus, K. L.; Nelson, D. J. Intracellular Metabolism of (−) and (+) Cis-5-fluoro-1-{2-(hydroxymethyl)-1,3-oxathiolane-5-yl}cytosine in HepG2(2.2.15/P5A) Cells. *Antimicrob. Agents Chemother.* **1994**, *38*, 1230−1238. (d) Van Draanen, N. A.; Tisdale, M.; Parry, M.; Jansen, R.; Dornsife, R.; Tuttle, J. V.; Averett, D. R.; Koszalka, G. W. The Influence of Stereochemistry on the Antiviral Activities and Resistance Profiles of Dideoxycytidine Nucleosides. *Antimicrob. Agents Chemother.* **1994**, *38*, 868−871. (e) Pelicano, H.; Pierra, C.; Ericksson, S.; Gosselin, G.; Imbach, J. L.; Maury, G. *J. Med. Chem.* **1997**, *40*, 3969−7393. (f) Miller, W. H.; Daluge, S. M.; Garvey, E. P.; Hopkins, S.; Reardon, J. E.; Boyd, F. L.; Miller, R. L. *J. Biol. Chem.* **1992**, *267*, 21220−21224.

(24) Guthrie, R. D.; Smith, S. C. An Improved Preparation of 1,2,3,5-Tetra-*O*-acetyl-β-D-ribofuranose. *Chem. Ind.* **1968**, 547−548.

(25) Chipen, G. I.; Grinshtein, V. Ya. *Chem. Heterocycl. Compd. (USSR)* **1965**, *1*, 420.

(26) Witkowski, J. T.; Robins, R. K.; Sidwell, R. W.; Simon, L. N. Design, Synthesis, and Broad Spectrum Antiviral Activity of 1-β-D-ribofuranosyl-1,2,4-triaole-3-carboxamide and Related Nucleosides. *J. Med. Chem.* **1972**, *15*, 1150−1154.

(27) Markiewicz, W. T. Tetraisopropyldisiloxane-1,3-diyl, a group for simultaneous protection of 3′- and 5′-hydroxy functions of nucleosides. *J. Chem. Res. (S)* **1979**, 24−25.

(28) (a) Barton, D. H. R.; McCombie, S. W. A New Method for the Deoxygenation of Secondary Alcohols. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585. (b) Barton, D. H. R.; Subramanian, R. Reactions of Relevance to the Chemistry of Aminoglycoside Antibiotics. Part 7. Conversion of Thiocarbonates into Deoxysugars. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1718−1723.

(29) Gosselin, G.; Bergogne, M.-C.; Imbach, J.-L. Synthesis and Antiviral Evaluation of β-L-Xylo-furanosyl Nucleosides of the Five Naturally Occurring Nucleic Acid Bases. *J. Heterocycl. Chem.* **1993**, *30*, 1229−1233.

(30) Gosselin, G.; Mathé, C.; Bergogne, M.-C.; Aubertin, A.-M.; Kirn, A.; Sommadossi, J.-P.; Schinazi, R.; Imbach, J.-L. 2′- And/Or 3′-Deoxy-β-L-Pentofuranosyl Nucleoside Derivatives: Stereospecific Synthesis and Antiviral Activities. *Nucleosides Nucleotides* **1995**, *14*, 611−617.

(31) Ma, T.; Pai, S. B.; Zhu, Y. L.; Lin, J. S.; Shanmuganathan, K.; Du, J.; Wang, C.; Kim, H.; Newton, M. G.; Cheng, Y. C.; Chu, C. K. Structure−Activity Relationships of 1-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)pyrimidine Nucleosides as Anti-Hepatitis B Virus Agents. *J. Med. Chem.* **1996**, *39*, 2835−2843.

(32) (a) Misra, S.; Jain, S.; Avasthi, K.; Bhakuni, D. S. Studies on Nucleosides: Part XXVIII. Synthesis of 4-Amino (or Hydroxy)-6-methylthio-1-(3′-Deoxy-β-D-ribofuranosyl)-1-H−Pyrazolo[3,4-d]pyrimidines. *Nucleosides Nucleotides* **1990**, *9*, 837−846. (b) Nair, V.; Sinhababu, A. K. Selective Transformations of Sugar Tosylhydrazones to Deoxy and Unsaturated Sugars. *J. Org. Chem.* **1978**, *43*, 5013−5017.

(33) Vorbrüggen, H. Adventures in Silicon-Organic Chemistry. *Acc. Chem. Res.* **1995**, *28*, 509−520.

(34) Witkowski, J. T.; Fuertes, M.; Cook, P. D.; Robins, R. K. Nucleosides of 1,2,4-Triazole-3-carboxamide: Synthesis of Certain Pentofuranosyl, Deoxypentofuranosyl and Pentopyranosyl 1,2,4-Triazoles. *J. Carbohydr. Nucleosides Nucleotides* **1975**, *2*, 1−36.

(35) Tam, R. C.; Ramasamy, K. S.; Bard, J.; Pai, B.; Lim, C.; Averett, D. R. The ribavirin analogue ICN 17261 demonstrates reduced toxicity and antiviral effects with retention of both immunomodulatory activity and reduction of hepatitis-induced serum alanine aminotransferase levels. *Antimicrob. Agents Chemother.* **1999**, submitted for publication.

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