Pergamon

Tetrahedron 55 (1999) 9073–9088

TETRAHEDRON

Asymmetric Synthesis of (2'*R*,4'*R*) and (2'*S*,4'*S*)-1,3-Dioxolanyl Triazole *C*-Nucleosides

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Received 8 April 1999; accepted 21 May 1999

Abstract: In view of biological activities of both 1,3-dioxolanyl nucleosides and *C*-nucleosides, D- and L-1,3-dioxolanyl *C*-nucleosides have been synthesized as potential antiviral and/or anticancer agents. Asymmetric synthesis of four new optically pure D- and L-1,3-dioxolanyl triazole *C*-nucleosides has been accomplished *via* key intermediate **5a** and **5b** starting from D- and L-2,3-*O*-isopropylidene glyceraldehyde. The stereochemical assignments of synthesized compounds were unambiguously made based on NMR studies as well as X-ray crystallographic studies. The synthesized nucleosides have been evaluated against HIV and hepatitis B virus, however, no significant antiviral activity was observed.

Key words: 1,3-dioxolanyl nucleosides; *C*-nucleosides; selenazofurin; tiazofurin; triazole.

C-Nucleosides have been of interest as an unique class of compounds that contain a C-C bond instead of the C-N bond between the carbohydrate and heterocyclic moiety, which stabilizes the glycosyl bond of nucleosides. The naturally occurring, as well as some synthetic, *C*-nucleosides exhibit interesting biological activities. Among them, tiazofurin,[1] selenazofurin,[2] and 1,2,3-triazole *C*-nucleoside[3] have drawn significant attention as potent anticancer agents. A number of structural modifications of the ribosyl moiety of tiazofurin have been also reported.[4,5,6]

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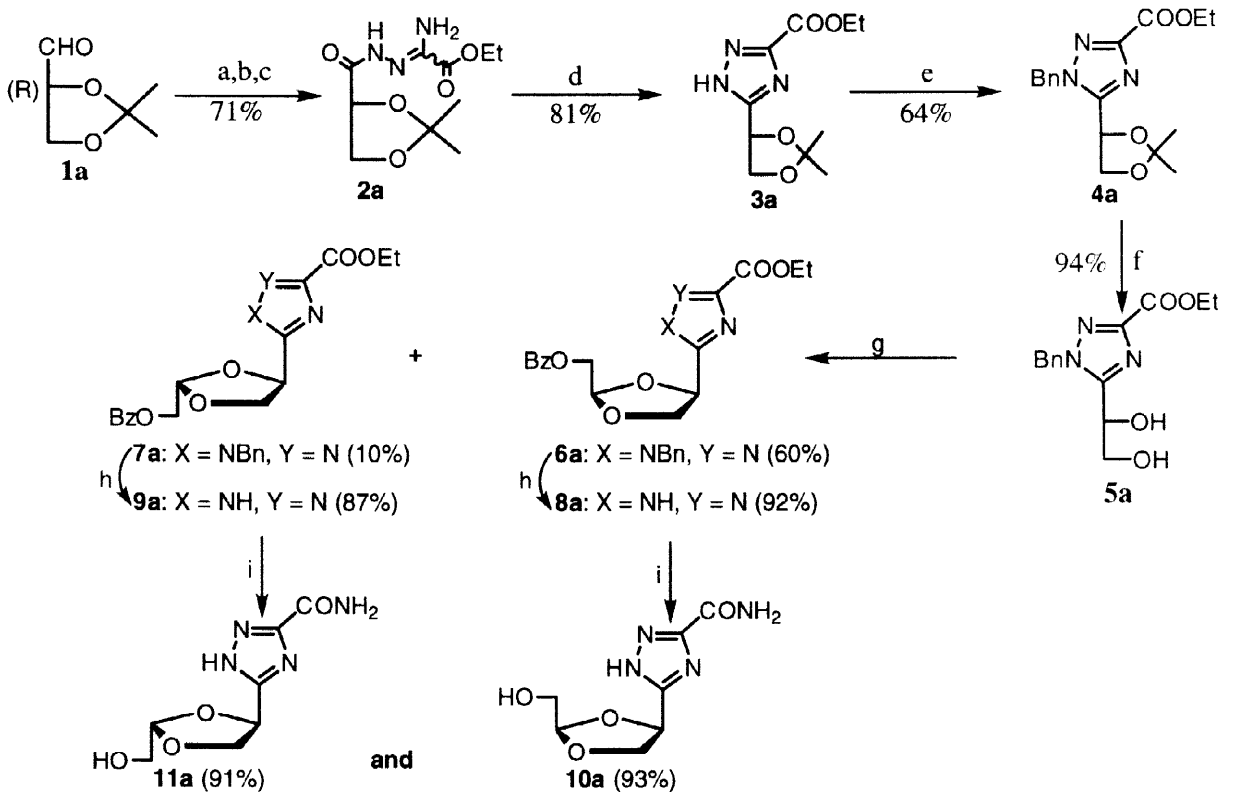
0040-4020/99/$ - see front matter
PII: S0040-4020(99)00499-8

1,3-Dioxolane nucleosides are an interesting class of sugar-modified nucleosides, in which the 3'-carbon is replaced by an oxygen atom. The first example of this class of compounds, (±)-dioxolanyl thymine, was found to exhibit moderately potent anti-HIV activity *in vitro*.[7,8,9] Subsequently, extensive structure-activity relationship studies have been carried out by several groups, including our own.[10] From the studies, a number of dioxolane nucleosides have been discovered as potent antiviral agents. Among them, (2*R*,4*R*)-9-[2-(hydroxymethyl)-1,3 dioxolan-4-yl]-2,6-diamino-purine (DAPD)[11] and (−)-(2*S*,4*S*)-1-[2-(hydroxymethyl)-1,3-dioxolan 4-yl]-cytosine [(−)-L-OddC][12] are the most promising compounds. Currently, (−)-L-OddC is undergoing phase I clinical trials as an anticancer agent. [13,14] DAPD is a prodrug of the corresponding guanine derivative, which is converted to dioxolane-guanine (DXG) by adenosine deaminase.[15] DAPD is currently undergoing phase I clinical studies as an anti-HIV and an anti-HBV agent.

In view of these interesting biological activities of 1,3-dioxolanyl nucleosides as well as *C*-nucleosides, it was of interest to synthesize hybrid nucleosides, 1,3-dioxolanyl *C*-nucleosides as potential antiviral and/or anticancer agents. We have previously published thiazole nucleosides as a communication.[16] In this paper, we wish to report the full account of 1,3-dioxolanyl *C*-nucleosides of triazole.

Synthesis of *C*-nucleosides usually starts from an appropriate sugar moiety with a proper substituent at the C-1 carbon. However, unique structural features of 1,3-dioxolanyl *C*-nucleosides require a different approach. The required 1,3-dioxolanyl moiety is an acetal, therefore, it can be constructed by reacting an aldehyde with a diol using a Lewis acid as a catalyst. Examining the stereochemical requirement at the anomeric position (4') of the 1,3-dioxolane *C*-nucleoside suggested that the β-D-form could be synthesized from a diol with *R*-configuration, while the β-L-form from a diol with *S*-configuration is required. Required diol intermediates **5a** and **5b** were synthesized from protected D-2,3-*O*-isopropylidene glyceraldehyde (**1a**) and L-2,3-*O*-isopropylidene glyceraldehyde (**1b**), respectively.

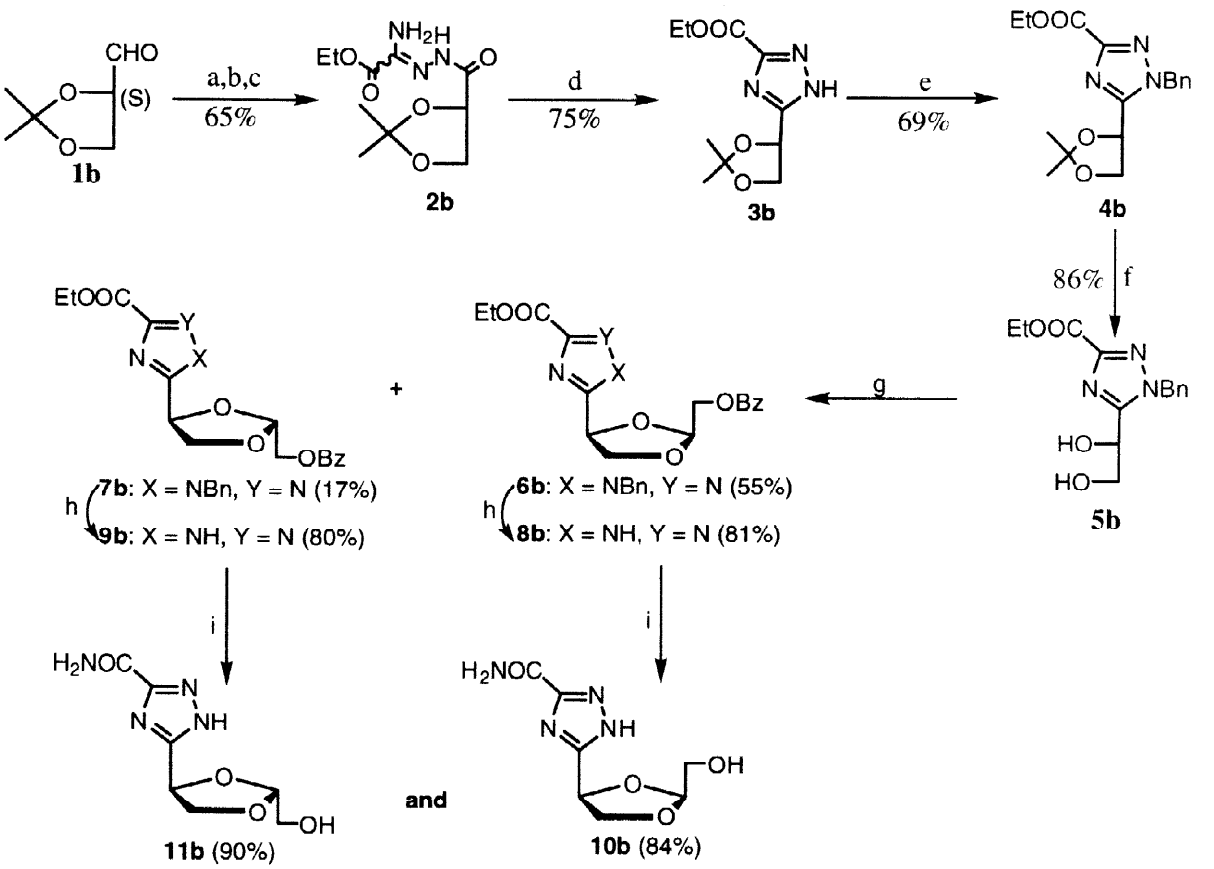
Synthesis of β-D- and α-L-1,3-dioxolanyl triazole *C*–nucleosides is illustrated in Scheme 1. In order to construct the key intermediate **5a**, (2*R*)-2,3-*O* isopropylidene glyceraldehyde



Scheme 1. a) (1) $KMnO_4$, KOH. (2) 0.5 N H_2SO_4. b) (1) ClCOOEt, Et_3N. (2) c-NH_4OH. c) amidrazonate, [H_2N-N=$C(NH_2)$-CO_2Et]. d) reflux in xylene, 4 h. e) BnBr, NaH, DMF. f) CF_3CO_2H, THF/H_2O (2:1), 50 °C, 8 h. g) $BzOCH_2CH(OMe)_2$, *p*-TsOH, benzene, reflux. h) H_2, $PdCl_2$, EtOH, 50 psi, 6 h. i) NH_3/CH_3OH, steel bomb, 110 °C, 24 h.

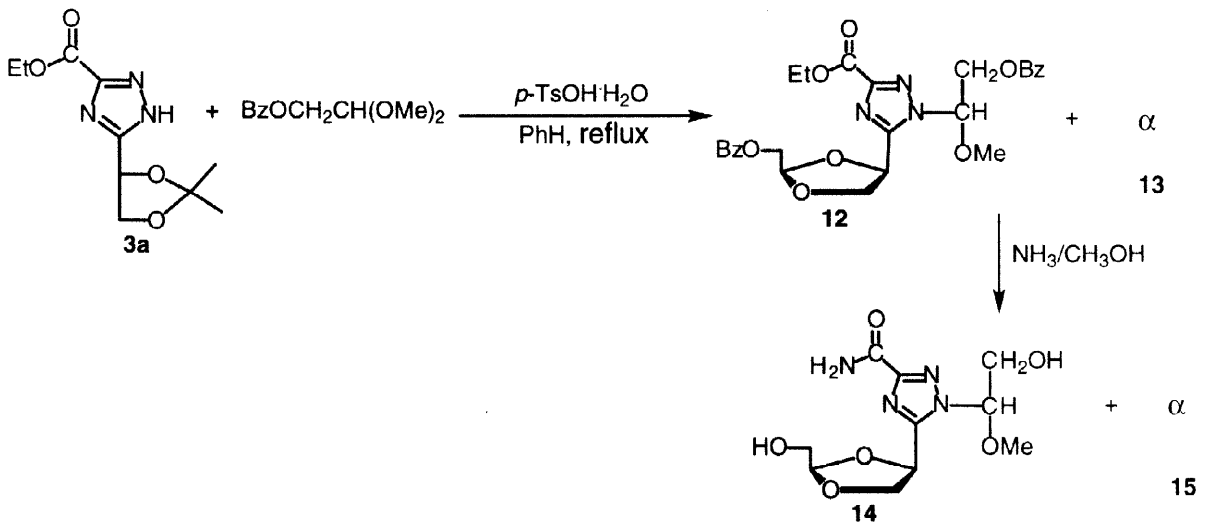
(**1a**) was chosen as the starting material. It was oxidized by potassium permanganate followed by acidification to give an acid, which in turn, was reacted with ethyl chloroformate to give an anhydride. The anhydride was treated *in situ* with amidrazonate [H_2N-N=$C(NH_2)$-COOEt][17] in THF to give the hydrazine derivative **2a** as a pale yellow precipitate. The hydrazine derivative **2a** was dehydrated to form the triazole derivative **3a** in 81% yield by heating **2a** in xylene at 180 °C in the Dean-Stark apparatus to remove water generated in the reaction.[18]

Initially, without protection of the NH group of the triazole, compound **3a** was condensed directly with 2-benzoyloxyacetaldehyde-dimethyl acetal (Scheme 3). TLC showed two spots, which could be easily separated by silica gel column chromatography. ^1H NMR data showed that the upper spot corresponded to 2-benzoyloxy-acetaldehyde, while the



Scheme 2. a) (1) $KMnO_4$, KOH. (2) 0.5 N H_2SO_4. b) (1) ClCOOEt, Et_3N. (2) c-NH_4OH. c) amidrazonate, [H_2N-N=$C(NH_2)$-CO_2Et]. d) reflux in xylene, 4 h. e) BnBr, NaH, DMF. f) CF_3CO_2H, THF/H_2O (2:1), 50 °C, 8 h. g) $BzOCH_2CH(OMe)_2$, *p*-TsOH, benzene, reflux. h) H_2, $PdCl_2$, EtOH, 50 psi, 6 h. i) NH_3/CH_3OH, steel bomb, 110 °C, 24 h.

lower spot was a mixture of dioxolane nucleosides **12** and **13**. The mixture was *O*-debenzylated and converted to the carboxamide derivative by treatment with methanolic ammonia at room temperature to give two compounds **14** and **15**, which were separated by silica gel column chromatography. The tentative assignment of the *cis* and *trans* structures of **14** and **15** was made based on chemical shifts of 2'-H (the chemical shift of 2'-H of α-isomer is downfield compared to that of the β-isomer due to the deshielding effect of the heterocyclic base to the 2'-H in the α-isomer). ^{1}H NMR spectra showed extra signals of each of OCH_3, CH_2, CH, and OH compared to the desired target nucleosides (Table 1), which suggested that an aminal moiety was formed on the N-1 of the triazole ring.



Scheme 3. Direct condensation of **3a** with 2-benzoyloxy acetaldehyde-dimethyl acetal.

Table 1.

Chemical shifts of 2'-H of **14** and **15** and comparison of other signals.

Signals	Chemical Shifts δ (ppm) (**14**)	Chemical Shifts δ (ppm) (**15**)
Aminal CH	6.43	6.50
CH_2	3.77	3.80
OCH_3	3.20	3.26
OH	4.94	5.02
2'-H	5.13	5.23

As the free NH group was reactive with 2-benzoyloxyacetaldehyde-dimethyl acetal, it needed to be protected before the condensation reaction. Different protection approaches have been tried, in which attempts to protect NH by amides or carbamates with acetyl chloride, benzoyl chloride, or ethyl chloroformate failed. Protection of sterically and electronically favorable N-1 position with a benzyl group succeeded when **3a** was treated with

sodium hydride and benzyl bromide in dry DMF to give **4a** in 64% yield without N-4 benzylated isomer. Deprotection of the isopropylidene group of **4a** was conducted by treating **4a** with trifluoroacetic acid in THF and H_2O (2:1) to give the key intermediate **5a** in 94% yield. Construction of the 1,3-dioxolane triazole *C*-nucleosides was carried out similar to 1,3-dioxolanyl selenazole *C*-nucleosides by condensing **5a** with 2-benzoyloxyacetaldehyde dimethyl acetal. Two products **6a** and **7a** were obtained after separation by silica gel column chromatography in 60% and 10% yield, respectively. Hydrogenolysis to remove N-benzyl protecting groups of **6a** and **7a** was carried out in the presence of H_2 (50 psi), catalyst (20-30% $PdCl_2$), and solvent (EtOH) to give **8a** and **9a** in 92% and 87% yield, respectively. Catalytic hydrogenolysis did not work when Et_3N was added in advance to neutralize the HCl generated in the reaction. Deprotection of **8a** and **9a** with methanolic ammonia at room temperature failed to transform the ethoxycarbonyl to a carboxamide group, while deprotection of the mixture of **12** and **13** was successfully converted an ethoxycarbonyl group to a carboxamide group at room temperature (Scheme 3). Therefore, deprotection of **8a** and **9a** and carboxamide formation was carried out with methanolic ammonia in a steel bomb at 110 °C to afford the desired β-D-and α-L-1,3-dioxolanyl triazole *C*-nucleosides: 5-[(2*R*,4*R*)-2-(hydroxymethyl)-1,3-dioxolan-4-yl]-1,2,4-triazole-3-carboxamide (**10a**) and 5-[(2*S*,4*R*)-2-(hydroxymethyl)-1,3-dioxolan-4-yl]-1,2,4-triazole-3-carboxamide (**11a**), in 93% and 91% yield, respectively.

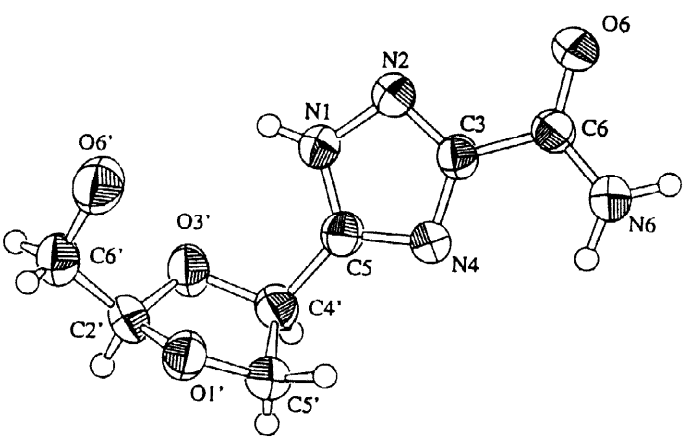


Figure 1. ORTEP drawing of compound **10a**.

Using the same procedure, β-L-and α-D-1,3-dioxolanyl triazole *C*-nucleosides, 5-[(2*S*,4*S*)-2-(hydroxymethyl)-1,3-dioxolan-4-yl]-1,2,4-triazole-3-carboxamide (**10b**) and 5 [(2*R*,4*S*)-2-(hydroxymethyl)-1,3-dioxolan-4-yl]-1,2,4-triazole-3-carboxamide (**11b**) were synthesized (Scheme 2). The structures of **10a**, **11a**, **10b**, and **11b** were characterized by optical rotation, UV absorption, elemental analysis, and NMR studies. The stereochemical assignment of the *cis* and *trans* (α and β) nucleosides was made based on the comparison of the physical data to those of thiazole[16] and selenazole[19] *C*-nucleosides as well as X-ray crystallographic studies of **10a** (Figure 1). Analysis of the X-ray structure[20] of compound **10a** shows a sugar puckering with the pseudorotation phase angle P = 27.6° and ν_{max} =34.8°, the hydroxyl methyl group orientation γ = 61.6°, (O1'-C2'-C6'-O6'), and base orientation, χ = 177.8°, (C4-C5-C4'-O3').

The synthesized nucleosides were evaluated against HIV and hepatitis B virus in peripheral blood mononuclear and 2.2.15 cells, respectively. None of the synthesized nucleosides showed any significant anti-HIV activity or anti-HBV activity.

In summary, we have developed a convenient synthetic method of optically pure, both D- and L-1,3-dioxolanyl triazole *C*-nucleosides.

Experimental Section

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. NMR spectra were recorded on a Brucker AMX 400 Fourier transform spectrometer; chemical shifts are reported in parts per million (δ), and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), and pseudo t (two overlapping doublet). UV spectra were obtained on a Beckman DU-7 or DU-650 spectrophotometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Dry triethylamine and 1,4-dioxane, benzene were obtained by distillation from CaH_2 prior to use. Dry THF was obtained by distillation from Na and benzophenone when the solution became

purple.

1-(Ethoxyoxalimidyl)-2-[(2*R*)-2,3-*O*-isopropylidene-2,3-dihydroxy-propanoyl]hydrazine (2a). To a solution of (2*R*)-2,3-*O*-isopropylidene glyceradehyde (**1a**) (5 g, 38.5 mmol) in H_2O (250 mL), a solution of KOH (6.25 g, 110 mmol) and $KMnO_4$ (9.5 g, 60.0 mmol) in H_2O (250 mL) wsa added dropwise. The reaction mixture was stirred at room temperature for 3 h. The resulting solid was filtered off. The filtrate was evaporated to a reduced volume (150 mL) and acidified with aq. H_2SO_4 (1 N) to pH 2-3. The mixture was extracted with EtOAc (3 x 100 mL). The combined organic layer was dried ($MgSO_4$) for 3 h. Evaporation of the solvent gave crude acid (4.6 g, 82%), which was directly used for the next step without further purification. The acid derivative (3.5 g, 23.9 mmol) dissolved in dry THF (60 mL), Et_3N (2.76 mL, 28.76 mmol) was added to the solution. The reaction mixture was cooled to -5 °C and ethyl chloroformate (2.76 mL, 28.76 mmol) was added dropwise. After the mixture was stirred for 40 min at 0 °C, the white salt was filtered off. A solution of amidrazonate (2 g, 15.3 mmol) in THF (30 mL) (amidrazonate was made in one step from ethyl thioxamate and hydrazine) was added to the filtrate. The mixture was stirred at room temperature for 5 h, during which time the product precipitated out. The product was collected as a pale yellow solid after filtration. The filtrate was evaporated to 1/2 volume and further stirred at room temperature overnight. Another batch of product was collected in the same manner. A total 2.8 g of product **2a** was obtained (yield 71%, based on the amidrazonate) as a mixture of *cis* and *trans* isomers. mp 160-162 °C; UV (CH_3OH): λ_{max} = 278.5 nm; ^{1}H NMR (DMSO-d_6): δ 10.14, 10.02 (2s, 1H, D_2O exchangeable), 6.80, 6.50 (2s, 2H, D_2O exchangeable), 5.01, 4.59 (2t, J = 6.8 Hz, 1H), 4.34 (pseudo t, J = 8.0 Hz, 0.4 H), 4.24 (q, J = 7.1 Hz, 2H), 4.15 (pseudo t, J = 7.8 Hz, 0.6 H), 3.98 (dd, J = 5.7, 8.2 Hz, 0.4H), 3.83 (dd, J = 6.8, 8.0 Hz, 0.6H), 1.39, 1.35 (2s, 6H), 1.25 (m, 3H); ^{13}C NMR (DMSO-d_6): δ 171.6, 166.6, 162.4, 161.9, 141.1, 136.5, 110.4, 109.9, 74.3, 73.5, 67.4, 67.0, 62.1, 61.9, 26.1, 26.0, 14.3, 14.3; Anal. Calcd for $C_{10}H_{17}N_3O_5$: C, 46.33; H, 6.56; N, 16.22. Found: C, 46.05; H, 6.64; N, 16.25.

5-[(1*R*)-1,2-*O*-Isopropylideneglycol-1-yl]-3-ethoxycarbonyl-1,2,4-triazole (3a). The hydrazine derivative **2a** (1.4 g, 5.4 mmol) was dissolved in xylene (250 mL) which was

refluxed at 180 °C (oil bath) in the Dean-Stark apparatus to remove the water generated in the reaction. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography ($CH_3OH/CHCl_3$, 1-5%) to afford the product **3a** (1.05 g, 81%). mp 88-90 °C; $[\alpha]^{25}_D$ = +38.10° (c 0.92, CH_3OH); UV (CH_3OH): λ_{max} = 242.0 nm; ^1H NMR (DMSO-d_6): δ 14.74 (br s, 1H, D_2O exchangeable), 5.27 (pseudo t, J = 6.2 Hz, 1H), 4.34 (m, 3H), 4.13 (dd, J = 6.0, 8.3 Hz, 1H), 1.39 (s, 6H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 159.7, 156.7, 154.1, 110.1, 69.7, 67.9, 61.1, 26.1, 14.1; Anal. Calcd for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.22; N, 17.43. Found: C, 49.84; H, 6.20; N, 17.37.

5-[(1*R*)-1,2-*O*-Isopropylideneglycol-1-yl]-3-ethoxycarbonyl-1-benzyl-1*H*-1,2,4 triazole (4a). To a solution of triazole **3a** (800 mg, 3.32 mmol) in dry DMF (20 mL), NaH (100 mg, 3.98 mmol) was added portionwise at room temperature. The mixture was stirred at room temperature until there was no further evolution of hydrogen gas (ca 25 min). The reaction mixture benzyl bromide (472 μl, 3.98 mmol) was added dropwise. The mixture was heated at 60 °C until completion of the reaction, and the solvent was evaporated to give a residue, which was purified by silica gel column chromatography to give product **4a** as a syrup (704 mg, 64%). $[\alpha]^{25}_D$ = +7.99° (c 0.90, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 246.0 nm; ^1H NMR ($CDCl_3$): δ 7.30 7.32 (m, 5H), 5.78 (q, J = 14.3 Hz, 2H), 5.24 (pseudo t, J = 6.7 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 4.35 (pseudo t, J = 7.1 Hz, 1H), 4.26 (dd, J = 6.9, 8.3 Hz, 1H), 1.53, 1.46 (2s, 6H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 161.6, 157.8, 144.6, 135.2, 128.7, 128.5, 128.3, 128.1, 110.6, 71.8, 68.6, 62.6, 54.5, 26.3, 25.9, 14.1; Anal. Calcd for $C_{17}H_{21}N_3O_4$: C, 61.63; H, 6.84; N, 12.69. Found: C, 61.53; H, 6.40; N, 12.59.

5-[(1*R*)-Glycol-1-yl]-3-ethoxycarbonyl-1-benzyl-1*H*-1,2,4-triazole (5a). To a solution of triazole compound **4a** (700 mg, 2.1 mmol) in a mixture of THF (20 mL) and H_2O (10 mL), trifluoroacetic acid (194 μl, 2.52 mmol) was added dropwise. The reaction mixture was then stirred at 50 °C for 8 h. The mixture was neutralized with Et_3N and evaporated to give a syrupy residue. The residue was purified by silica gel column chromatography to afford product **5a** (580 mg, 94%) as a white solid. Compound **5a**: mp 76-77 °C; $[\alpha]^{25}_D$ = +20.51 (c 0.72, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 244.0 nm; ^1H NMR ($CDCl_3$): δ 7.31 (m, 5H), 5.75 (s, 2H), 4.95 (dd, J = 4.8, 9.4 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 3.97 (m, 2H), 3.87 (d, J

= 5.7 Hz, 1H, D_2O exchangeable), 3.11 (br s, 1H, exchangeable); 1.39 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 163.0, 157.7, 144.4, 135.0, 128.8, 128.4, 128.1, 68.6, 65.5, 62.8, 54.5, 14.1; Anal. Calcd for $C_{14}H_{17}N_3O_4$: C, 57.73; H, 5.84; N, 14.43. Found: C, 57.74; H, 5.83; N, 14.36.

5-[(2*R*,4*R*)-2-(Benzoyloxymethyl)-1,3-dioxolan-4-yl]-3-ethoxycarbonyl-1 benzyl-1*H*-1,2,4-triazole (6a) and 5-[(2*S*,4*R*)-2-(benzoyloxymethyl)-1,3 dioxolan-4-yl]-3-ethoxycarbonyl-1-benzyl-1*H*-1,2,4-triazole (7a). To a solution of diol derivative **5a** (580 mg, 1.98 mmol) in dry benzene (100 mL), 2-benzoyloxyacetaldehyde dimethyl acetal (625 mg, 2.98 mmol) and *p*-TsOH·H_2O (128 mg) were added sequentially. The mixture was refluxed gently in the Dean-Stark apparatus to remove water. The reaction mixture was cooled down to room temperature and neutralized with Et_3N. Evaporation of the solvent afforded a syrup, which was purified by silica gel column chromatography to give β-isomer **6a** (520 mg, 60%) and α-isomer **7a** (86 mg, 10%). Compound **6a**: Rf = 0.40 (EtOAc/hexane, 1:1); $[\alpha]^{25}_D$ = +6.24° (c 0.75, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 242.0 nm; ^1H NMR ($CDCl_3$): δ 7.87 (d, J = 7.3 Hz, 2H), 7.23-7.40 (m, 8H), 5.56 (q, J = 15.2 Hz, 2H), 5.42 (pseudo t, J = 3.1 Hz, 1H), 5.11 (dd, J = 4.8, 6.6 Hz, 1H), 4.82 (dd, J = 4.8, 8.6 Hz, 1H), 4.46 (q, J = 7.1 Hz, 2H), 4.35 (m, 1H), 4.27 (m, 1H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 165.9, 159.7, 153.8, 153.1, 134.4, 133.3, 129.7, 128.9, 128.5, 128.4, 127.6, 103.3, 70.2, 68.8, 63.3, 62.0, 53.7, 14.3; Anal. Calcd for $C_{23}H_{23}N_3O_6$: C, 63.16; H, 5.26; N, 9.61. Found: C, 62.99; H, 5.29; N, 9.56.

Compound **7a**: Rf = 0.53 (EtOAc/hexane, 1:1); $[\alpha]^{25}_D$ = +18.23° (c 0.64, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 243.5 nm; ^1H NMR ($CDCl_3$): δ 7.23-8.07 (m, 10H), 5.58 (q, J = 15.2 Hz, 2H), 5.34 (m, 1H), 5.16 (m, 1H), 4.43-4.53 (m, 5H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 166.4, 160.1, 154.0, 153.8, 134.8, 133.7, 130.1, 129.4, 128.9, 128.9, 128.0, 102.9, 69.8, 69.3, 64.1, 62.5, 54.2, 14.3; Anal. Calcd for $C_{23}H_{23}N_3O_6$: C, 63.16; H, 5.26; N, 9.61. Found: C, 62.91; H, 5.34; N, 9.52.

5-[(2*R*,4*R*)-2-(Benzoyloxymethyl)-1,3-dioxolan-4-yl]-3-ethoxycarbonyl-1,2,4 triazole (8a) and 5-[(2*S*,4*R*)-2-(benzoyloxymethyl)-1,3-dioxolan-4-yl]-3 ethoxycarbonyl-1,2,4-triazole (9a). To a solution of fully protected dioxolanyl triazole

nucleoside **6a** (423 mg, 0.96 mmol) in ethanol (20 mL), catalyst $PdCl_2$ (34 mg, 0.19 mmol) was added carefully. The reaction mixture was hydrogenated in a hydrogenation apparatus (Parr shaker) at 50 psi until completion of the reaction. The reaction mixture was neutralized with Et_3N and filtered. The filtrate was evaporated to give a syrupy residue. The residue was purified by silica gel column chromatography to give debenzylated product **8a** (309 mg, 92%) as a syrup. The same procedure was applied to prepare **9a** (yield 87%).

Compound **8a**: $[\alpha]^{25}_D$ = +112.44° (c 0.86, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 244.5 nm; ^1H NMR ($CDCl_3$): δ 13.09 (br s, 1H), 8.03 (d, *J* = 8.0 Hz, 2H), 7.42-7.59 (m, 3H, Ar-H), 5.42 (m, 2H), 4.75 (dd, *J* = 6.0, 12.0 Hz, 1H), 4.47 (q, *J* = 7.0 Hz, 2H), 4.30-4.39 (m, 3H), 1.42 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 167.7, 160.0, 158.7, 134.1, 130.3, 129.4, 128.9, 103.3, 71.9, 71.3, 64.8, 62.5, 14.6; Anal. Calcd for $C_{16}H_{17}N_3O_6 \cdot 0.9\ H_2O$: C, 52.86; H, 5.17; N, 11.56. Found: C, 52.52; H, 4.82; N, 11.20.

Compound **9a**: $[\alpha]^{25}_D$ = +46.55° (c 0.72, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 242.0 nm; ^1H NMR ($CDCl_3$): δ 13.55 (br s, 1H); 7.41-8.01 (m, 5H), 5.58 (pseudo t, *J* = 3.4 Hz, 1H), 5.44 (dd, *J* = 6.2, 12.0 Hz, 1H), 4.40-4.54 (m, 5H), 4.24 (dd, *J* = 6.1, 8.4 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 167.2, 166.3, 159.2, 158.3, 133.4, 129.9, 129.7, 128.6, 128.5, 102.6, 71.7, 69.9, 64.0, 62.4, 14.1; Anal. Calcd for $C_{16}H_{17}N_3O_6 \cdot 0.6\ H_2O$: C, 53.66; H, 5.08; N, 11.74. Found: C, 53.88; H, 4.99; N, 11.65.

5-[(2*R*,4*R*)-2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-1,2,4-triazole-3-carboxamide (10a) and 5-[(2*S*,4*R*)-2-(hydroxymethyl)-1,3-dioxolan-4-yl]-1,2,4-triazole-3 carboxamide (11a). The protected triazole nucleoside **18a** (310 mg, 0.89 mmol) was treated with methanolic ammonia (15 mL) in a steel bomb at 110 °C for 24 h. After completion of the reaction, the solvent was evaporated to give a residue, which was purified by reverse phase HPLC. Conditions for HPLC purification are: reverse phase C-18 column (PrepPak®, 55-105 μm); mobile phase; 10% CH_3OH / H_2O; flow rate; 50 mL/min; UV detector; at 240 nm. The appropriate fractions were collected and evaporated to dryness to afford the product **10a** as a white solid (178 mg, 93%). Compound **10a** could be recrystallized from methanol-ether. Compound **11a** was prepared by the same procedure from **9a** (yield 91%).

Compound **10a**: mp 141-142 °C; $[\alpha]^{25}_{D}$ = +40.69° (c 0.50, CH_3OH); ^1H NMR (DMSO-d_6): δ 7.98, 7.52 (2s, D_2O exchangeable), 5.20 (pseudo t, J = 5.7 Hz, 1H), 5.03 (t, J = 3.8 Hz, 1H), 4.16 (m, 2H), 3.50 (m, 2H), 3.34 (br s, 1H, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 159.6, 153.3, 105.5, 70.9, 68.8, 62.4; FAB HRMS: Calcd for $C_7H_{10}N_4O_4H$+ (MH+): 215.0780. Found: 215.0781. Anal. Calcd for $C_7H_{10}N_4O_4$: C, 39.25; H, 4.67; N, 26.17. Found: C, 39.29; H, 4.75; N, 25.89.

Compound **11a**: mp 69-71 °C; $[\alpha]^{25}_{D}$ = +34.14° (c 0.29, CH_3OH); ^1H NMR (DMSO-d_6): δ 8.03, 7.77 (2s, D_2O exchangeable), 5.21 (t, J = 6.5 Hz, 1H), 5.12 (t, J = 3.7 Hz, 1H), 4.97 (pseudo t, J = 3.9 Hz, 1H, D_2O exchangeable), 4.28 (dd, J = 6.7, 8.0 Hz, 1H), 3.99 (dd, J = 6.5, 8.1 Hz, 1H), 3.40 (d, J = 3.7 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 159.5, 153.2, 104.9, 70.7, 69.0, 62.4; FAB HRMS: Calcd for $C_7H_{10}N_4O_4H$+ (MH+): 215.0780. Found: 215.0807. Anal. Calcd for $C_7H_{10}N_4O_4 \cdot 0.25\ H_2O$: C, 38.44; H, 4.80; N, 25.63. Found: C, 38.55; H, 4.80; N, 25.38.

Using the same procedure as the D-series, the *L*-series of compounds were synthesized.

1-(Ethoxyoxalimidyl)-2-[(2*S*)-2,3-*O*-isopropylidene-2,3 dihydroxy-propanoyl]hydrazine (2b). mp 161-162 °C; ^1H NMR (DMSO-d_6): δ 10.12, 9.86 (2s, 1H, D_2O exchangeable), 6.74, 6.49 (2s, 2H, D_2O exchangeable), 4.86, 4.38 (2t, J = 6.8 Hz, 1H), 4.34 (pseudo t, J = 8.0 Hz, 0.5 H), 4.24 (q, J = 7.1 Hz, 2H), 4.15 (dd, J = 3.4, 8.2 Hz, 0.5 H), 3.96 (dd, J = 5.6, 8.0 Hz, 0.5H), 3.84 (dd, J = 6.9, 8.2 Hz, 0.5H), 1.38, 1.34 (2s, 6H), 1.26 (m, 3H); ^{13}C NMR (DMSO-d_6): δ 171.6, 166.6, 162.4, 161.9, 141.1, 136.5, 110.4, 109.9, 74.3, 73.5, 67.4, 67.0, 62.1, 61.9, 26.1, 26.0, 14.3, 14.3; Anal. Calcd for $C_{10}H_{17}N_3O_5$: C, 46.33; H, 6.56; N, 16.22. Found: C, 46.20; H, 6.57; N, 16.26.

5-[(1*S*)-1,2-*O*-Isopropylideneglycol-1-yl]-3-ethoxycarbonyl-1,2,4-triazole (3b). mp 89-91 °C; $[\alpha]^{25}_{D}$ = -39.04° (c 0.73, CH_3OH); UV (CH_3OH): λ_{max} = 242.5 nm; ^1H NMR (DMSO-d_6): δ 14.69 (br s, 1H, D_2O exchangeable), 5.31 (pseudo t, J = 5.5 Hz, 1H), 4.28 (m, 3H), 4.13 (dd, J = 5.8, 8.5 Hz, 1H), 1.38 (s, 6H), 1.30 (t, J = 6.5 Hz, 3H); ^{13}C NMR (DMSO d_6): δ 159.7 156.7, 154.2, 110.2, 69.7, 67.9, 61.1, 26.2, 14.2; Anal. Calcd for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.22; N, 17.43. Found: C, 49.94; H, 6.31; N, 17.26.

5-[(1*S*)-1,2-*O*-Isopropylideneglycol-1-yl]-3-ethoxycarbonyl-1-benzyl-1*H*-1,2,4

triazole (4b). $[\alpha]^{25}_{D}$ = -8.12° (c 1.0, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 246.0 nm; ^{1}H NMR ($CDCl_3$): δ 7.32-7.35 (m, 5H), 5.75 (q, *J* = 12.7 Hz, 2H), 5.20 (pseudo t, *J* = 6.5 Hz, 1H), 1H), 4.48 (q, *J* = 6.5 Hz, 2H), 4.28 (pseudo t, *J* = 6.5 Hz, 1H), 4.23 (dd, *J* = 5.5, 7.9 Hz, 1H), 1.50, 1.43 (s, s, 6H), 1.33 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 161.7, 157.9, 144.7, 135.3, 128.8, 128.6, 128.4, 128.2, 110.7, 71.8, 68.7, 62.7, 54.6, 26.4, 25.9, 14.2; Anal. Calcd for $C_{17}H_{21}N_3O_4$: C, 61.63; H, 6.34; N, 12.69. Found: C, 61.66; H, 6.39; N, 12.60.

5-[(1*S*)-Glycol-1-yl]-3-ethoxycarbonyl-1-benzyl-1*H*-1,2,4-triazole (5b). mp 73-74 °C; $[\alpha]^{25}_{D}$ = -19.61° (c 0.63, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 244.5 nm; ^{1}H NMR ($CDCl_3$): δ 7.43 (m, 5H), 5.86 (s, 2H), 5.04 (dd, *J* = 4.5, 8.1 Hz, 1H), 4.53 (q, *J* = 6.5 Hz, 2H), 4.08 (m, 2H), 3.99 (d, *J* = 4.9 Hz, 1H, D_2O exchangeable), 3.21 (br s, 1H, D_2O exchangeable); 1.45 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 162.9, 157.6, 144.3, 134.9, 128.7, 128.3, 127.9, 68.5, 65.4, 62.8, 54.5, 13.9; Anal. Calcd for $C_{14}H_{17}N_3O_4$: C, 57.73; H, 5.84; N, 14.43. Found: C, 57.91; H, 5.83; N, 14.45.

5-[(2*S*,4*S*)-2-(Benzoyloxymethyl)-1,3-dioxolan-4-yl]-3-ethoxycarbonyl-1 benzyl-1*H*-1,2,4-triazole (6b). $[\alpha]^{25}_{D}$ = -6.34° (c 0.82, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 241.5 nm; ^{1}H NMR ($CDCl_3$): δ 7.91 (d, *J* = 7.3 Hz, 2H), 7.26-7.43 (m, 8H), 5.59 (q, *J* = 13.8 Hz, 2H), 5.38 (pseudo t, *J* = 3.5 Hz, 1H), 5.11 (dd, *J* = 4.8, 7.0 Hz, 1H), 4.77 (dd, *J* = 5.4, 7.9 Hz, 1H), 4.42 (q, *J* = 7.0, 2H), 4.41 (m, 1H), 4.32 (m, 1H), 1.28 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 166.0, 159.7, 153.8, 153.1, 134.4, 133.3, 129.7, 128.9, 128.5, 128.4, 127.6, 103.3, 70.2, 68.4, 63.4, 62.1, 53.8, 14.4; Anal. Calcd for $C_{23}H_{23}N_3O_6$·0.2EtOAc: C, 62.82; H, 5.45; N, 9.23. Found: C, 62.53; H, 5.21; N, 9.39.

5-[(2*R*,4*S*)-2-(Benzoyloxymethyl)-1,3-dioxolan-4-yl]-3-ethoxycarbonyl-1-benzyl 1*H*-1,2,4-triazole (7b). $[\alpha]^{25}_{D}$ = -19.18° (c 0.78, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 243.5 nm; ^{1}H NMR ($CDCl_3$): δ 7.18-8.00 (m, 10H), 5.62 (q, *J* = 14.2 Hz, 2H), 5.31 (m, 1H), 5.17 (m, 1H), 4.42-4.55 (m, 5H), 1.42 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 166.4, 160.1, 154.0, 153.8, 134.8, 133.7, 130.1, 129.4, 128.9, 128.9, 128.0, 102.9, 69.8, 69.3, 64.1, 62.5, 54.2, 14.3; Anal. Calcd for $C_{23}H_{23}N_3O_6$·0.1EtOAc: C, 62.98; H, 5.34; N, 9.42. Found: C, 63.36; H, 5.58; N, 9.08.

5-[(2*S*,4*S*)-2-(Benzoyloxymethyl)-1,3-dioxolan-4-yl]-3-ethoxycarbonyl-1,2,4

triazole (8b). $[\alpha]^{25}_{D}$ = -113.08° (c 0.91, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 244.0 nm; ^1H NMR ($CDCl_3$): δ 12.88 (br s, 1H), 7.95 (d, *J* = 7.2 Hz, 2H), 7.53 (m, 3H, Ar-H), 5.45 (m, 2H), 4.78 (dd, *J* = 5.5, 11.0 Hz, 1H), 4.33 (q, *J* =6.2 Hz, 2H), 4.32-4.40 (m, 3H), 1.39 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 167.5, 159.9, 158.6, 134.1, 130.2, 129.4, 128.9, 103.2, 71.9, 71.3, 64.8, 62.5, 14.6; Anal. Calcd for $C_{16}H_{17}N_3O_6 \cdot 0.7\ H_2O$: C, 53.39; H, 5.11; N, 11.67. Found: C, 53.06; H, 4.90; N, 11.32.

5-[(2*R*,4*S*)-2-(Benzoyloxymethyl)-1,3-dioxolan-4-yl]-3-ethoxycarbonyl-1,2,4 triazole (9b). $[\alpha]^{25}_{D}$ = -45.27° (c 0.44, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 242.5 nm; ^1H NMR ($CDCl_3$): δ 12.98 (br s, 1H);, 7.41-8.12 (m, 5H), 5.50 (pseudo t, *J* = 3.1 Hz, 1H), 5.38 (dd, *J* = 6.7, 11.5 Hz, 1H), 4.47-4.55 (m, 5H), 4.28 (dd, *J* = 5.8, 7.9 Hz, 1H), 1.32 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 167.3, 166.4, 159.3, 158.4, 133.5, 130.7, 129.7, 127.9, 127.5, 102.6, 71.8, 69.9, 63.8, 62.3, 14.0; Anal. Calcd for $C_{16}H_{17}N_3O_6 \cdot 0.5\ H_2O$: C, 53.93; H, 5.05; N, 11.79. Found: C, 54.02; H, 5.08; N, 11.70.

5-[(2*S*,4*S*)-2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-1,2,4-triazole-3-carboxamide (10b). mp 139-141 °C; $[\alpha]^{25}_{D}$ = -40.68° (c 0.54, CH_3OH); ^1H NMR (DMSO-d_6): δ 7.88, 7.42 (s, D_2O exchangeable), 5.12 (pseudo t, *J* = 5.3 Hz, 1H), 5.13 (t, *J* = 3.8 Hz, 1H), 4.25 (m, 2H), 3.59 (m, 2H), 3.41 (br s, 1H, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 159.8, 153.4, 105.6, 71.1, 68.8, 62.5; FAB HRMS: Calcd for $C_7H_{10}N_4O_4H$+ (MH+): 215.0780. Found: 215.0779. Anal. Calcd for $C_7H_{10}N_4O_4$: C, 39.25; H, 4.67; N, 26.17. Found: C, 39.09; H, 4.66; N, 26.03.

5-[(2*R*,4*S*)-2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-1,2,4-triazole-3-carboxamide (11b). mp 70-72 °C; $[\alpha]^{25}_{D}$ = -34.92° (c 0.29, CH_3OH); ^1H NMR (DMSO-d_6): δ 7.96, 7.62 (2s, D_2O exchangeable), 5.15 (t, *J* = 5.8 Hz, 1H), 5.06 (t, *J* = 3.2 Hz, 1H), 4.87 (pseudo t, *J* = 4.6 Hz, 1H, D_2O exchangeable), 4.15 (dd, *J* = 6.9, 8.0 Hz, 1H), 3.86 (dd, *J* = 6.4, 8.0 Hz, 1H), 3.32 (d, *J* = 3.9 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 159.7, 153.3, 104.9, 70.7, 80.0, 62.5; FAB HRMS: Calcd for $C_7H_{10}N_4O_4H$+ (MH+): 215.0780. Found: 215.0788. Anal. Calcd for $C_7H_{10}N_4O_4 \cdot 0.25\ H_2O$: C, 38.44; H, 4.80; N, 25.63. Found: C, 38.24; H, 4.79; N, 25.38.

Acknowledgements: This research was supported by U.S. Public Health Service Research

Grant (AI 32351) from the National Institutes of Health. We thank Dr. R. F. Schinazi of Emory University / V.A Medical Center and Dr. Y.-C. Cheng of Yale University for anti-HIV and anti-HBV activity, respectively. We also thank Dr. Mike Bartlett of the University of Georgia for performing the high resolution mass spectral data.

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