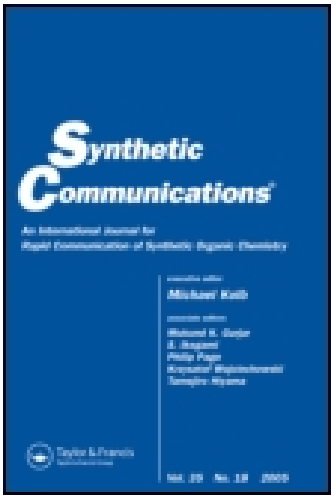

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Synthesis and Biological Evaluation of Novel Isonucleosides with 1,2,4-Triazole-3-Carboxamide

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Synthesis and Biological Evaluation of Novel Isonucleosides with 1,2,4-Triazole-3-Carboxamide

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Abstract: Novel 1,2,4-triazole isonucleosides (**1** and **2**) were efficiently synthesized starting from D-ribose and D-xylose, respectively. The key steps were condensation of cyclic sulfate **8** with methyl-1,2,4-triazole-3-carboxylate and nucleophilic displacement of the tosylate **15** with methyl-1,2,4-triazole-3-carboxylate, respectively.

Keywords: Antiviral agent, IMPDH, isonucleoside, 1,2,4-trizole

INTRODUCTION

Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) is a synthetic purine nucleoside analog that is structurally similar to guanine and inosine. It shows broad-spectrum antiviral activity against a variety of both DNA and RNA viruses[1–3] and is currently clinically used in combination with interferon-α (IFN-α) to treat hepatitis C virus[4] infection and as monotherapy for Lassa fever virus infection[5] and severe respiratory syncytial virus infection.[6] It has been suggested that ribavirin monophosphate (RMP), the

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active form of ribavirin, inhibits inosine monophosphate dehydrogenase (IMPDH) activity in vitro and in vivo.[7] IMPDH catalyzes the NAD^+-dependent oxidation of inosine 5′-monophosphate (IMP) to xanthine 5′-monophosphte (XMP), the rate limiting step in de novo biosynthesis of guanine nucleotides. Therefore, inhibition of IMPDH results in a decrease in the intracellular concentration of guanine nucleotide,[8] blocking DNA and RNA synthesis. An alternative mechanism of action for ribavirin is inhibition of viral-encoded polymerase and genomic RNA capping.

In antiviral chemotherapy, toxicity and emerging drug-resistant virus strains are major problems.[9] To overcome these drawbacks, a number of structurally modified nucleosides have been synthesized. Among them, isonucleosides in which the base is transposed from the natural 1′-position to isomeric 2′-position have been reported to have antiviral activities.[10] This class of nucleosides has attracted much attention because of the stabilization of the glycosyl bond and metabolic resistance to adenosine deaminase.[10a,11,12]

Based on these findings, it was very interesting to design and synthesize 1,2,4-triazole isonucleosides. Here we report the synthesis of novel (2S,4S)-isonucleosides with triazole base moiety (Figure 1).

RESULTS AND DISCUSSION

Our synthetic strategies to the target 1,2,4-triazole isonucleosides are to condense cyclic sulfate and alkylate 1,4-anhydro-D-ribitol derivative with methyl-1,2,4-triazole-3-carboxylate, respectively.

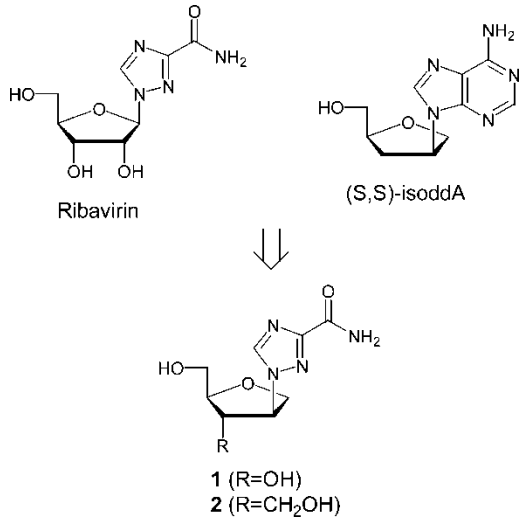
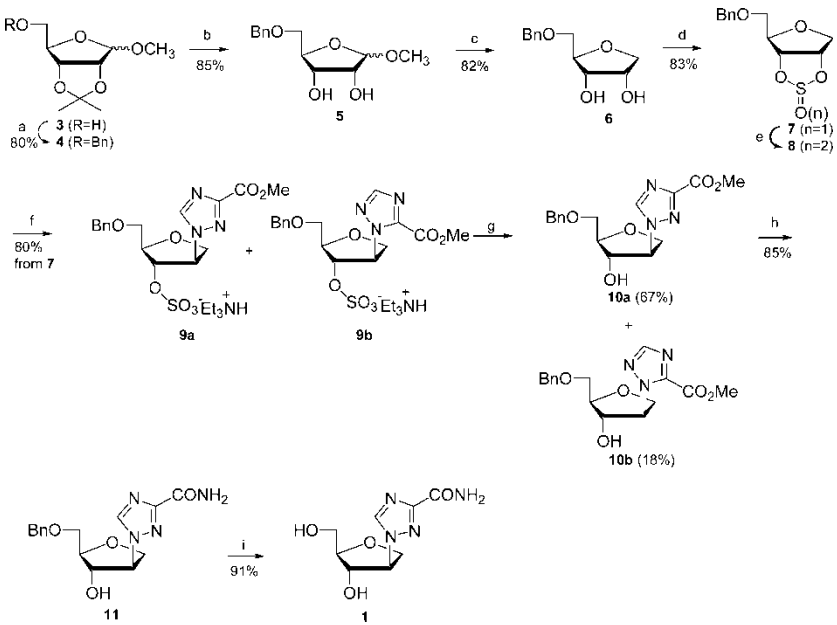


Figure 1. Rationale to the target nucleosides.

Synthesis of cyclic sulfate derivative **8**, a key intermediate for 3-carboxamido-1-(3-hydroxy-2-hydroxymethyl-tetrahydrofuran-4-yl)-1,2,4-triazole **1**, could be achieved starting from 2,3-isopropylidene-1-methyl-D-furanoside **3**, which could be easily synthesized from D-ribose and is shown in Scheme 1.

The 5-hydroxy group of **3** was protected with a benzyl group to give the benzylate **4**, in which the 2,3-isopropylidene group was removed by treatment of Dowex $50H^+$ resin in MeOH to afford the diol **5**. To remove the methoxy group at the anomeric position, two hydroxy groups of compound **5** were protected in situ as trimethylsilyl (TMS) ether on reflux with hexamethyldisilazane (HMDS), and then this intermediate was treated with trimethylsilyl triflate (TMSOTf) and triethylsilane to give the 1,4-anhydro ribitol derivative **6**.[13] Compound **6** reacted with thionyl chloride to afford the cyclic sulfite **7**, which was oxidized with $RuCl_3/NaIO_4$ to give the cyclic sulfate **8** as a key intermediate.

Cyclic sulfate **8** was condensed with methyl-1,2,4-triazole-3-carboxylate by the procedure described by Nair[14] to give a mixture of two isomeric

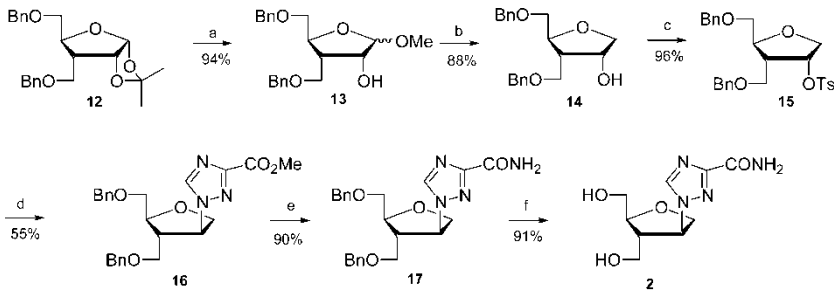


Scheme 1. Reagents and conditions: (a) BnBr, NaH, TBAI, THF, rt, 18 h; (b) Dowex$50H^+$, MeOH, rt, 3 day; (c) (1) HMDS, $(NH_4)_2SO_4$, reflux, 2 h; (2) Et_3SiH, TMSOTf, CH_2Cl_2, rt, 3 h; (d) $SOCl_2$, pyridine, rt, 3 h; (e) $NaIO_4/RuCl_3$, $CCl_4/CH_3CN/H_2O$, rt, 30 min; (f) methyl-1,2,4-triazole-3-carboxylate, DBU, CH_3CN, 75°C, 2 h; (g) 2% HCl, MeOH, 45°C, 18 h; (h) NH_3/MeOH, rt, 16 h; (i) Pd/C, EtOH, H_2, rt, 18 h.

products **9a** and **9b**, which could not be separated by silica-gel column chromatography. The mixture was treated with 2% aqueous HCl in MeOH to afford the 3-substituted N_1-β-nucleoside **10a** and 5-substituted N_1-β-nucleoside **10b** in ratio of 3.7/1, respectively. The structural assignments of the regioisomers, **10a** and **10b**, were readily made by the comparison of their ^{1}H NMR data. The signals for 3-H of minor isomer **10b** (δ5.59) appeared at a lower field than did the signal for the major isomer **10a** (δ4.88) because of the deshielding effect of carbonyl group. Ammonolysis of **10a** using methanolic ammonia gave the amide **11**, which was deprotected by catalytic dehydrogenation to provide the desired 1,2,4-triazole isonucleoside **1**.

The synthesis of 3-carboxamido-1-(2,3-di-hydroxymethyl-tetrahydrofuran-4-yl)-1,2,4-triazol **2** is outlined in Scheme 2. 5-*O*-Benzyl-3-benzyloxymethyl-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose **12** was easily prepared from D-xylose,[15] which was treated with 1% HCl in MeOH to afford the methyl riboside **13**. The methoxy group at the anomeric position was removed as described for compound **5** to afford the 1,4-anhydro-D-ribitol **14**. To introduce the triazole base moiety into the sugar ring, the hydroxy group of **14** was converted into the tosylate and triflate, respectively. Attempted nucleophilic displacements of the tosylate and triflate derivative with the sodium salt of methyl-1,2,4-triazole-3-carboxylate in DMF provided the desired product **16** in low yield (<10%). However, the triazole anion derived from deprotonation of methyl-1,2,4-triazole-3-carboxylate with DBU in acetonitrile reacted with the tosylate **15** to afford the desired triazole-isonucleoside **16** in 55% yield. Compound **16** was treated with methanolic ammonia to give the amide **17**, of which the benzyl group was deprotected using catalytic hydrogenation to yield the 1,2,4-triazole isonucleoside **2**.

In summary, we have efficiently synthesized 1,2,4-triazole isonucleosides **1** and **2** by condensation of cyclic sulfate **8** with methyl-1,2,4-triazole-3-carboxylate and nucleophilic displacement of the tosylate **15** with methyl-1,2,4-triazole-3-carboxylate, respectively.



Scheme 2. Reagents and conditions: (a) 1% HCl in MeOH, rt, 3h; (b) (1) HMDS, $(NH_4)_2SO_4$, reflux, 2 h; (2) Et_3SiH, TMSOTf, CH_2Cl_2, rt, 3 h; (c) TsCl, CH_2Cl_2, DMAP, rt, 18 h; (d) methyl-1,2,4-triazole-3-carboxylate, DBU, CH_3CN, 75°C, 18 h; (e) NH_3/MeOH, rt, 14 h; (f) H_2, Pd/C, EtOH, rt, 20 h.

EXPERIMENTAL

General Methods

NMR spectra were recorded in a 300-MHz apparatus using tetramethylsilane (TMS) as an internal standard, and the chemical shifts are reported in ppm (δ). Coupling constants are reported in hertz (Hz). Infrared spectra were recorded in a Perkin-Elmer 1710 FTIR spectrophotometer. Mass spectra recorded by FAB (fast atom bombardment) on a VG Tro-2, GC-MS. TLC were carried out on Merck silica-gel 60 F_{254} precoated plates, and silica-gel column chromatography was performed on silica-gel 60, 230–400 mesh, Merck. All anhydrous solvents were distilled over CaH_2 or Na/benzophenone prior to use.

1-*O*-Methyl-5-*O*-benzyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (4)

A solution of **3** (4.26 g, 20.9 mmol) in anhydrous THF (15 mL) was added to a stirred solution of 60% suspension of NaH in mineral oil (1.24 g, 31.3 mmol) and n-Bu_4NI (2.31 g, 6.26 mmol) in anhydrous THF (40 mL). The mixture was stirred for 30 min at rt and cooled to 0°C. BnBr (3.7 mL, 31.3 mmol) was added to this solution. After being stirred for 18 h at rt, the reaction mixture was quenched with ice water and poured into EtOAc. The organic layer was washed with sat. $NaHCO_3$ solution and brine, dried ($MgSO_4$), filtrated, and evaporated. The residue was purified by silica-gel column chromatography (Hex : EtOAc = 6 : 1) to give **4** (4.91 g, 16.7 mmol, 80%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.27–7.35 (m, 5H), 4.96 (s, 1H), 4.69 (dd, 1H, $J = 0.8$, 5.9 Hz), 4.51–4.59 (m, 3H), 4.35–4.40 (m, 1H), 3.39–3.55 (m, 2H), 3.29 (s, 3H), 1.48, 1.31 (2s, 6H); FAB-MS m/z: 295 $[M + H]^+$. Anal. calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.08; H, 7.69.

1-*O*-Methyl-5-*O*-benzyl-β-D-ribofuranoside (5)

A suspension of **4** (2.05 g, 6.96 mmol) and Dowex 50 H^+ in MeOH (20 mL) was stirred for 3 days at rt and filtered through a silica-gel pad (washed with CH_2Cl_2). The filtrate was evaporated. The residue was purified by silica-gel column chromatography (Hex : EtOAc = 1 : 2) to give **5** (1.5 g, 5.9 mmol, 85%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.27–7.48 (m, 5H), 4.81 (s, 1H), 4.53–4.62 (m, 2H), 4.05–4.15 (m, 2H), 3.97 (d, 1H, $J = 4.6$ Hz), 3.59 (d, 2H, $J = 5.5$ Hz), 3.32 (s, 3H), 3.12, 2.05 (2s, 2H); FAB-MS m/z: 255$[M + H]^+$. Anal. calcd. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.28; H, 7.22.

1,4-Anhydro-5-*O*-benzyl-D-ribitol (6)

A solution of **5** (1.4 g, 5.51 mmol) and ammonium sulfate (catalytic amount, 73 mg, 0.6 mmol) in HMDS (15 mL) was refluxed for 2 h and evaporated under anhydrous conditions. The residue was dissolved in CH_2Cl_2 (15 mL), and then Et_3SiH (4.4 mL, 27.6 mmol) and TMSOTf (5.3 mL, 27.6 mmol) were added to this solution. The mixture was stirred for 1.5 h at rt, quenched with sat. $NaHCO_3$ solution, and extracted with CH_2Cl_2 ($\times 3$). The combined organic layers were washed with brine, dried ($MgSO_4$), filtrated, and evaporated. The residue was purified by silica-gel column chromatography (Hex : EtOAc = 1 : 3) to give **6** (1.01 g, 4.5 mmol, 82%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.37 (10H, m), 4.60–4.52 (m, 4H), 4.18 (m, 1H), 4.06 (dd, 1H, $J = 4.8$, 10.0 Hz), 3.96–4.01 (m, 1H), 3.85–3.91 (m, 1H), 3.75(dd, 1H, $J = 3.5$, 9.9 Hz), 3.63 (dd, 1H, $J = 4.0$, 10.7 Hz), 3.56 (dd, 1H, $J = 5.0$, 10.7 Hz), 3.17–3.19 (m, 2H); FAB-MS m/z: 225$[M + H]^+$. Anal. calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.04; H, 7.16.

1,4-Anhydro-5-*O*-benzyl-2,3-cyclicsulfate-D-ribitol (7)

Thionyl chloride (1.65 mL, 22.5 mmol) was added to a stirred solution of **6** (1.01 g, 4.5 mmol) in pyridine (20 mL) at 0°C. The reaction mixture was stirred for 3 h at rt and evaporated. The residue was partitioned between CH_2Cl_2 and water. The organic layer was washed with brine, dried ($MgSO_4$), filtrated, and evaporated. The residue was purified by silica-gel column chromatography (Hex : EtOAc = 2 : 1) to give **7** (1.01 g, 3.74 mmol, 83%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.39 (m, 10H), 5.31–5.36 (m, 1H), 5.27 (dd, 1H, dd, $J = 2.0$, 5.8 Hz), 4.59–4.47 (2H, m, 2 × Bn), 4.35 (dd, 1H, $J = 4.9$, 10.6 Hz), 4.26 (dd, 1H, $J = 2.4$, 10.6 Hz), 3.70 (m, 2H); FAB-MS m/z: 271$[M + H]^+$. Anal. calcd. for $C_{12}H_{14}O_5S$: C, 53.32; H, 5.22; S, 11.86. Found: C, 53.14; H, 5.34; S, 11.78.

(3′R,4′R)-1-(2′-Benzyloxymethyl-3′-hydroxytetrahydrofuran-4′-yl)-3-methoxycarbonyl-1,2,4-triazole(10a) and (3′R,4′R)-1-(2′-Benzyloxymethyl-3′-hydroxytetrahydrofuran-4′-yl)-5-carboxamido-1,2,4-triazole (10b)

$NaIO_4$ (580 mg, 2.7 mmol) and $RuCl_3 \cdot H_2O$ (catalytic amount, 10 mg) were added to a stirred solution of **7** (488 mg, 1.8 mmol) in $CCl_4/CH_3CN/H_2O$ (1/1/1.5, 17.5 mL). The reaction mixture was stirred for 30 min at rt and filtered through a silica-gel pad (washed with EtOAc). The filtrate was washed with brine, dried ($MgSO_4$), filtrated, and evaporated to give crude **8**.

DBU (0.28 mL, 3.8 mmol) was added to a suspension of methyl-1,2,4-triazole-3-carboxylate (459 mg, 3.62 mmol) in anhydrous CH_3CN (40 mL).

The suspension was stirred for 30 min at rt. A solution of sulfate (**8**) in CH_3CN (18 mL) was added to this resulting clear solution and the reaction mixture was heated at 70°C for 2 h. The solvent was removed under reduced pressure and the residue was purified by silica-gel column chromatography (CH_2Cl_2 : MeOH = 10 : 1) to give **9a** and **9b** as mixture (740 mg, 1.44 mmol, 80%).

A solution of **9a** and **9b** (740 mg, 1.44 mmol) in 2% HCl in MeOH(20 mL) was stirred at 45°C for 18 h and evaporated. The residue was purified by silica-gel column chromatography (Hex : EtOAc = 1 : 2) to give **10a** (320 mg, 0.96 mmol, 67%) and **10b** (85 mg, 0.25 mmol, 18%)

10a: ^{1}H NMR ($CDCl_3$, 300 MHz):): δ 8.37 (s, 1H), 7.19–7.46 (m, 5H), 4.88 (dd, 1H, $J = 4.6$, 8.8 Hz), 4.52–4.62 (m, 2H), 4.31 (d, 2H, $J = 5.3$ Hz), 3.96–4.01 (m, 4H), 3.67 (m, 2H), 2.97 (d, 1H, $J = 3.3$ Hz); IR (KBr): 3394, 2870, 1738, 1467, 1231, 1170, 1087 cm^{-1}; FAB-MS m/z: 356 $[M + Na]^+$, 334 $[M + H]^+$. Anal. calcd. for $C_{16}H_{19}N_3O_5$: C, 57.65; H, 5.75; N, 12.61. Found: C, 57.54; H, 5.84; N, 12.42.

10b: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.98 (s, 1H), 7.25–7.34 (m, 5H), 5.59 (dd, 1H, $J = 4.2$, 8.0 Hz), 4.49–4.60 (m, 3H), 4.31–4.46 (m, 2H), 4.00–4.06 (m, 4H), 3.68–3.76 (m, 2H), 2.89 (brs, 1H); IR (KBr): 3332, 2868, 1733, 1273, 1094 cm^{-1}; FAB-MS m/z: 334 $[M + H]^+$.

(3′R,4′R)-1-(2′-Benzyloxymethyl-3′-hydroxytetrahydrofuran-4′-yl)-3-carboxamido-1,2,4-triazole (11)

A solution of **10a** (223 mg, 0.67 mmol) in methanolic ammonia (15 mL) was stirred for 16 h at rt and evaporated. The residue was purified by silica-gel column chromatography (Hex : EtOAc = 1 : 4) to give **11** (181.4 mg, 0.57 mmol, 85%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.36 (s, 1H), 7.25–7.31 (m, 10H), 7.15, 6.29 (2brs, 2H), 6.29 (s, 1H), 4.52–4.56 (m, 3H), 4.26–4.29 (m, 2H), 3.99 (m, 1H), 3.63–3.73 (m, 2H); IR (KBr): 3327, 2870, 1685, 1292, 1085 cm^{-1}; FAB-MS m/z: 319 $[M + H]^+$, 341$[M + Na]^+$. Anal. calcd. for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60. Found: C, 57.58; H, 5.80; N, 17.52.

(3′R,4′R)-3-Carboxamido-1-(3′-hydroxy-2′-hydroxymethyl-tetrahydrofuran-4′-yl)-1,2,4-triazole (1)

A suspension of **11** (181 mg, 0.57 mmol) and Pd/C (80 mg) in EtOH (10 mL) was degassed and hydrogenated under hydrogen atmosphere for 18 h at rt. The reaction mixture was filtered through silica-gel pad (washed with MeOH) and the filtrate was evaporated. The residue was purified by silica-gel column chromatography (CH_2Cl_2 : MeOH = 7 : 1) to give **1** (118 mg, 0.52 mmol, 91%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.65 (s, 1H), 7.77, 7.56 (2s, 2H), 5.76 (d, 1H, $J = 5.5$ Hz), 4.81–4.88 (m, 2H), 4.26 (dd, 1H, $J = 5.1$, 11.6 Hz), 4.12 (dd, 1H, $J = 6.7$, 9.7 Hz), 4.04 (dd, 1H, $J = 5.3$, 9.8 Hz), 3.42–3.68 (m, 3H); IR (KBr): 3399, 1686, 1296, 1079 cm^{-1}; FAB-MS m/z: 229 $[M + H]^+$, 251 $[M + Na]^+$. Anal. calcd. for $C_8H_{12}N_4O_4$: C, 42.10; H, 5.30; N, 24.55. Found: C, 41.95; H, 5.54; N, 24.12.

5-*O*-Benzyl-3-*C*-benzyloxymethyl-3-deoxy-1-*O*-methyl-α,β-D-ribofuranoside (13)

A solution of **12** (3.39 g, 8.82 mmol) in 1% HCl in MeOH (25 mL) was stirred for 1.5 h at rt, and then neutralized with pyridine and evaporated. The residue was purified by silica-gel column chromatography (Hex : EtOAc = 2 : 1) to give **13** (2.97 g, 8.29 mmol, 94%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.34 (m, 10H), 4.81 (s, 1H), 4.57–4.62 (m, 4H), 4.31–4.38 (m, 1H), 4.23 (t, 1H, $J = 4.4$ Hz), 3.72–3.80 (m, 2H), 3.54–3.56 (m, 2H), 3.32 (s, 3H), 2.94 (d, 1H, $J = 3.90$ Hz), 2.37–2.44 (m, 1H); FAB-MS m/z: 381$[M + Na]^+$. Anal. calcd. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.24; H, 7.40.

1,4-Anhydro-5-*O*-benzyl-3-*C*-benzyloxymethyl-3-deoxy-D-ribitol (14)

A solution of **13** (2.97 g, 8.29 mmol) and ammonium sulfate (catalytic amount) in HMDS (20 mL) was refluxed for 2 h, cooled to rt, and evaporated to dryness. The residue was dissolved in CH_2Cl_2 (20 mL), and then Et_3SiH (6.63 mL, 41.5 mmol) and TMSOTf (8.02 mL, 41.5 mmol) were added to this solution. The mixture was stirred for 1.5 h at rt, quenched with sat. $NaHCO_3$ solution, and extracted with CH_2Cl_2 (×3). The combined organic layers were dried ($MgSO_4$), filtrated, and evaporated. The residue was purified by silica-gel column chromatography (Hex : EtOAc = 1 : 1) to give **14** (2.4 g, 7.3 mmol, 88%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.36 (m, 10H), 4.46–4.61 (m, 5H), 4.08 (m, 1H), 4.03 (dd, 1H, $J = 9.8$, 4.1 Hz), 3.78 (dd, 1H, $J = 2.2$, 9.8 Hz), 3.70 (d, 2H, $J = 6.3$ Hz), 3.51–3.60 (m, 2H), 2.60 (s, 1H), 2.33 (m, 1H); FAB-MS m/z: 329$[M + H]^+$, 351$[M + Na]^+$. Anal. calcd. for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 72.98; H, 7.52.

1,4-Anhydro-5-*O*-benzyl-3-*C*-benzyloxymethyl-3-deoxy-2-*O*-*p*-toluenesulfonyl-D-ribitol (15)

A solution of **14** (528 mg, 7.3 mmol), DMAP (3.93 mg, 3.22 mmol), and TsCl (460 mg, 2.41 mmol) in anhydrous CH_2Cl_2 (8 mL) was stirred for 18 h at rt.

The mixure was quenched with ice water and extracted with CH_2Cl_2 ($\times 3$). The combined organic layers were washed with brine, dried ($MgSO_4$), filtrated, and evaporated. The residue was purified by silica-gel column chromatography (Hex : EtOAc = 3 : 1) to give **15a** (740 mg, 1.54 mmol, 96%)

^{1}H NMR ($CDCl_3$, 300 MHz): 7.22–7.77 (m, 12H), 5.14 (m, 1H), 4.43–4.58 (m, 2H), 4.32–4.39 (m, 2H), 3.89–4.09 (m, 3H), 3.44–3.70 (m, 4H), 2.56 (m, 1H); FAB-MS m/z: 505 $[M + Na]^+$. Anal. calcd. for $C_{27}H_{30}O_6S$: C, 67.20; H, 6.27; S, 6.64. Found: C, 67.04; H, 6.44; S, 6.42.

(3′R,4′R)-1-(2′,3′-Di-benzyloxymethyl-tetrahydrofuran-4′-yl)-3-methoxycarbonyl-1,2,4-triazole (16)

A mixture of methyl-1,2,4-triazole-3-carboxylate (342 mg, 1.68 mmol) and NaH (80 mg, 2.01 mmol) in DMF (10 mL) was stirred for 30 min at rt. A solution of **15** (647 mg, 1.44 mmol) in DMF (5 mL) was added. The reaction mixture was stirred at 75°C for 18 h, quenched with ice water, and extracted with EtOAc ($\times 2$). The combined organic layers were dried ($MgSO_4$), filtrated, and evaporated. The residue was purified by silica-gel column chromatography (Hex : EtOAc = 1 : 1) to give **16** (346 mg, 0.79 mmol, 55%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.43 (s, 1H), 7.25–7.37 (m, 10H), 4.91 (1H, m, H-4′), 4.46–4.63 (m, 4H), 4.02–4.19 (m, 3H), 3.99 (s, 3H) 3.52–3.77 (m, 4H), 2.75 (1H, m, H-3′); IR (KBr): 2862, 1738, 1225, 1097 cm^{-1}; FAB-MS m/z: 438$[M + H]^+$, 460$[M + Na]^+$. Anal. calcd. for $C_{24}H_{22}N_3O_5$: C, 65.89; H, 6.22; N, 9.60. Found: C, 65.72; H, 6.30; N, 9.48.

(3′R,4′R)-1-(2′,3′-Di-benzyloxymethyl-tetrahydrofuran-4′-yl)-3-carboxamido-1,2,4-triazole (17)

A solution of **16** (340 mg, 0.78 mmol) in methanolic ammonia (15 mL) was stirred for 14 h at rt and evaporated to dryness. The residue was purified by silica-gel column chromatography (Hex : EtOAc = 1 : 2) to give **17** (295 mg, 0.70 mmol, 90%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.32 (s, 1H), 7.25–7.38 (m, 10H), 6.99, 5.97 (2 × brs, 2H), 5.01–4.96 (m, 1H), 4.46–4.63 (m, 4H), 4.03–4.21 (m, 3H), 3.48–3.77 (m, 4H), 2.74, (m, 1H); IR (KBr): 3323, 2863, 1692, 1097 cm^{-1}; FAB-MS m/z: 423$[M + H]^+$, 445$[M + Na]^+$. Anal. calcd. for $C_{23}H_{26}N_4O_4$: C, 65.39; H, 6.20; N, 13.26. Found: C, 65.24; H, 6.28; N, 13.19.

(3′R,4′R)-3-Carboxamido-1-(2′,3′-di-hydroxymethyl-tetrahydrofuran-4′-yl)-1,2,4-triazole (2)

A suspension of **17** (290 mg, 0.69 mmol) Pd/C (100 mg) in EtOH (10 mL) was degassed and hydrogenated under a hydrogen atmosphere for 20 h at rt.

The reaction mixture was filtered through a silica-gel pad (washed with MeOH) and the filtrate was evaporated. The residue was purified by silica-gel column chromatography (CH_2Cl_2 : MeOH = 7 : 1) to give **2** (151 mg, 0.62 mmol, 91%).

^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.67 (s, 1H), 7.75, 7.56 (2s, 2H), 4.92–4.98 (m, 3H), 3.99 (d, 2H, J = 5.9 Hz), 3.70 (m, 1H), 3.47–3.62 (m, 4H), 2.49 (m, 1H); FAB-MS m/z: 243 $[M+H]^+$, 265 $[M+Na]^+$. Anal. calcd. for $C_9H_{14}N_4O_4$: C, 44.63; H, 5.83; N, 23.13. Found: C, 44.38; H, 5.96; N, 22.98.

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