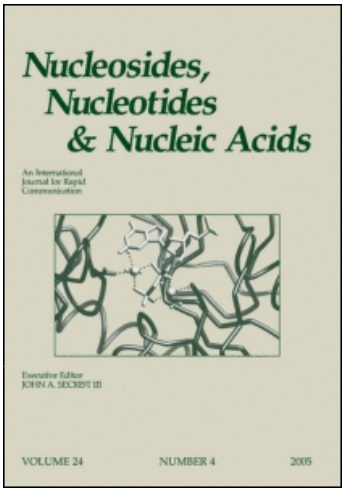

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Synthesis and Biological Evaluation of Novel Apio Nucleosides with Thiazole-4-carboxamide and 1,2,4-Triazole-3-carboxamide

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ABSTRACT

In view of biological activities of azole nucleosides and apio-dideoxynucleoside, novel apio nucleoside analogues (**1** and **2**) with thiazole and triazole base moiety were synthesized using 2,3-*O*-isopropylidene-apio-β-D-furanose (**3**), which was prepared from D-mannose.

Key Words: Apionucleosides; Thiazole; Triazole; Inosine monophosphate dehydrogenase.

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INTRODUCTION

Inosine 5′-monophosphate dehydrogenase (IMPDH) catalyses the oxidation of inosine 5′-monophosphate (IMP) to xanthine 5′-monophosphate (XMP) with the concomitant reduction of NAD^+ to NADH,[1,2] which is the committed and rate-limiting reaction in de novo guanine nucleotide biosynthesis and provides necessary precursors for DNA and RNA biosynthesis. Therefore, inhibition of IMPDH results in a decrease in the intracellular concentration of guanine nucleotide, leading to interrupt DNA and RNA synthesis.[3] IMPDH inhibitors have clinical utility as antiviral,[4] anticancer[5] or immunosuppressive agents[6,7] and IMPDH may be an attractive target for the development of antimicrobial agents because bacterial IMPDH enzymes show biochemical and kinetic characteristics that are different than the mammalian IMPDH enzymes.[8]

Several classes of IMPDH inhibitors have been described[9] and among them, nucleoside analogs are phosphorylated to their monophosphates and which then inhibit IMPDH competitively. For example, ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide)[10] is a broad spectrum antiviral agent and tiazofurin (2-β-D-ribofuranosylthiazole-4-carboxamide)[11] is a C-nucleoside with potent inhibitory activity against IMPDH[3] and is currently undergoing clinical trials as an antitumor agent.[4]

Apionucleosides[12–14] are a novel class of nucleosides in that hydroxymethyl side chain is moved from the 4′ position to the 3′ position. This class of nucleosides has attracted much attention owing to stabilization of glycosyl bond and metabolic resistance to adenosine deaminase.[14]

On the basis of these interesting biological activity of apionucleosides as well as thiazole and triazole nucleosides, it was of great interest to design and synthesize apionucleosides with thiazole and 1,2,4-triazole heterocycles (Fig. 1). Here we report the synthesis of novel thiazole and 1,2,4-triazole apionucleosides (**1** and **2**), starting from D-mannose.

RESULTS AND DISCUSSION

Our synthetic strategy to the target thiazole apionucleoside **1** is to synthesize apiofuranosyl cyanide **10** as a key intermediate from D-mannose and then to cyclocondense with L-cysteine ethyl ester hydrochloride. Apiofuranosyl cyanide **10** could be easily synthesized from glycosyl donor **9**. Synthesis of **9** is illustrated in Scheme 1. 2,3-*O*-Isopropylidene-apio-β-D-furanose (**3**) was prepared from D-mannose by modified Ho's method.[15] Primary hydroxy group of **3** was selectively protected with benzoyl group to give the benzoate **4**. We tried to synthesize 3′-*O*-benzoyl-1-*O*-methyl-D-apiofuranose (**7**) directly by treating **4** with 1% methanolic HCl, but under this reaction conditions, 3′-*O*-debenzolylated methyl glycoside **5** with 2,3-*O*-isopropylidene group intact was instead obtained as a major compound. Treatment of **5** with benzoyl chloride gave the benzoate **6**, in which 2,3-*O*-isopropylidene group was smoothly removed by treatment of Dowex $50H^+$ resin in MeOH at 60°C to afford the diol **7**. Treatment of **7** with benzoyl chloride in pyridine in the presence of catalytic amounts of DMAP at 50°C yielded the tribenzoate **8**. However, when the reaction was carried out in absence

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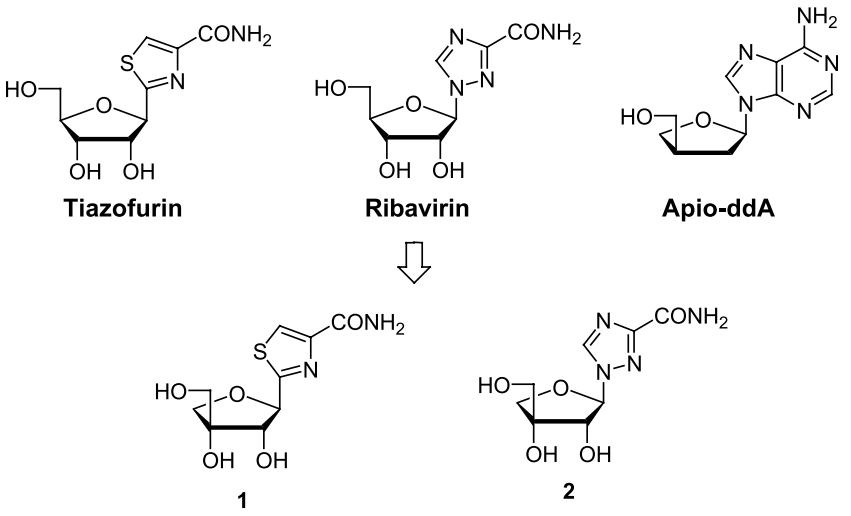
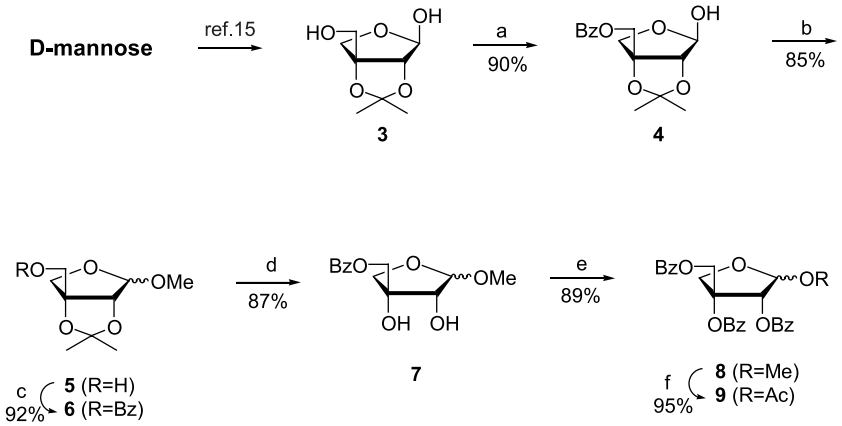


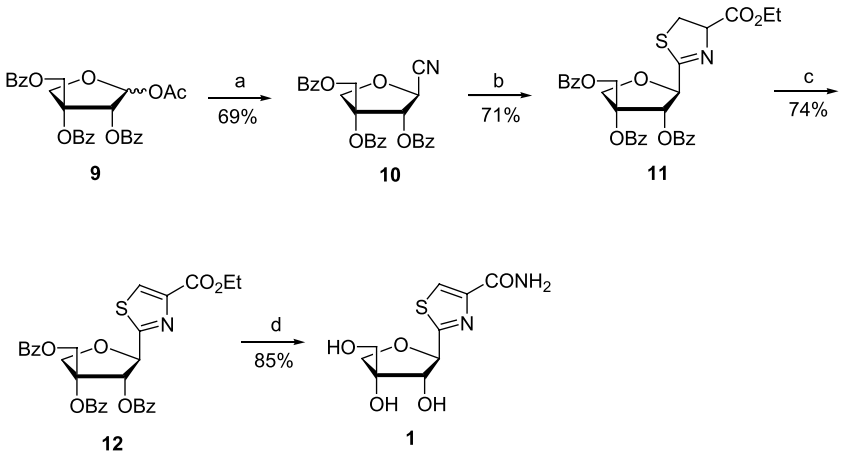
Figure 1. The rationale to the target nucleosides.

of DMAP, a mixture of dibenzoate and tribenzoate was obtained in 1:1 ratio. Compound **8** was treated with $Ac_2O/AcOH/H_2SO_4$ to give the glycosyl donor **9**.

For the synthesis of 2-(apio-β-D-furanosyl)thiazole-4-carboxamide (**1**), acetate **9** was treated with trimethysilyl cyanide in dichloromethane in presence of stannic chloride as a Lewis acid catalyst to give apiosyl cyanide **10** as shown in Scheme 2. Using the reported procedure,[16] cyanide **10** was converted to thiazoline **11** by treating with L-cysteine ethyl ester hydrochloride in the presence of triethylamine and then



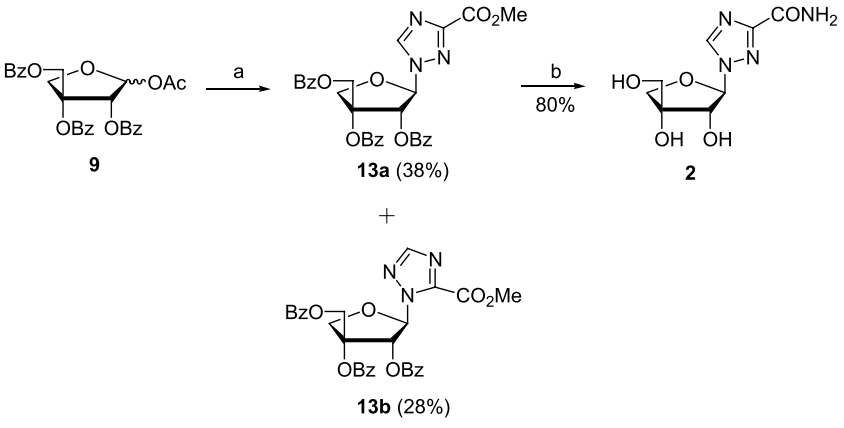
Scheme 1. Reagents and Conditions: (a) BzCl, pyridine, CH_2Cl_2,0°C, 2 hr; (b) 1% HCL in MeOH, RT, 5 hr; (c) BzCl, pyridine. RT, 5 hr; (d) Dowex $50H^+$, 60°C, 2 day; (e) BzCl, DMAP, pyridine, 50°C, overnight; (f) $AcOH/Ac_2O/c\text{-}H_2SO_4$, RT, 30 min.



Scheme 2. Reagents and Conditions: (a) TMSCN, $SnCl_4$, CH_2Cl_2, reflux, 3 hr; (b) L-cysteine ethyl ester hydrocholoride, Et_3N, MeOH, RT, 2 hr; (c) DBU, $BrCCl_3$, Ch_2Cl_2, 0°C, 16 hr; (d) NH_3/MeOH, RT, 24 hr.

dehydrogenation of **11** by treatment with bromotrichloromethane[17] in combination with DBU at 0°C gave the thiazole **12**. Aminolysis of ester **12** followed by debenzoylation using methanolic ammonia afforded 2-(apio-β-D-furanosyl)thiazole-4-carboxamide (**1**).

Synthesis of 1,2,4-triazole apionucleoside **2** is outlined in Scheme 3. Condensation of glycosyl donor **9** with silylated methyl-1,2,4-triazole-3-carboxylate, prepared by refluxing methyl-1,2,4-triazole-3-carboxylate with hexamethyldisilazane (HMDS), in the presence of stannic chloride in acetonitrile afforded the 3-substituted N_1-β-nucleoside **13a** and 5-substituted N_1-β-nucleoside **13b** in 3.7:1 ratio. When



Scheme 3. Reagents and Conditions: (a) silylated methyl-1,2,4-triazole-3-carboxylate, $SnCl_4$, CH_3CN, RT, 18 hr; (b) NH_3/MeOH, RT, 24 hr.

trimethylsilyl trifluoromethanesulfonate (TMSOTf) and 1,2-dichloroethane were used as a Lewis acid and solvent, respectively, the reaction yield was very poor. The structural assignments of the regioisomers, **13a** and **13b** were readily made by the comparison of their ^{1}H-NMR spectra. The signals for 1′-H and 2′-H of minor isomer 13b (δ 7.20 and 6.54) appeared at lower field than that of major isomer **13a** (δ 6.42 and 6.35) due to the deshielding effect of carbonyl group.[18] Compound 13a was treated with methanolic ammonia to provide 1-(apio-β-D-furanosyl)-1,2,4-triazole-3-carboxamide (**2**).

The final nucleosides **1** and **2** were assayed against several viruses such as HIV-1, HSV-1, HSV-2 and HBV as well as cancer cells such as colon and stomach cancer cells. These compounds were found to be inactive against cancer cells and viruses tested up to 100 μg/mL.

In summary, we have accomplished the synthesis of thiazole and triazole containing apionucleosides **1** and **2**, starting from D-mannose via cyclocondensation of glycosyl cyanide **10** with L-cysteine ethyl ester hydrochloride and condensation of glycosyl donor **9** with methyl-1,2,4-triazole-3-carboxylate, respectively. Unfortunately, the final nucleosides did not show any significant biological activity.

EXPERIMENTAL

General Methods. Melting points were determined on a Melting Point Büchi B-540 apparatus and are uncorrected. 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.

3′-*O*-Benzoyl-2,3-*O*-isopropylidene-β-D-apiofuranoside (4). To a stirred solution of **3** (1.69 g, 8.9 mmol) and pyridine (2.16 mL, 26.7 mmol) in anhydrous CH_2Cl_2 (20 ml) was added BzCl (1.24 mL, 10.7 mmol) dropwise at 0°C and the mixture was stirred at 0°C for 2 h and partitioned between CH_2Cl_2/H_2O. The organic layer was washed with brine, dried ($MgSO_4$), filtrated and evaporated. The residue was purified by silica gel column chromatography (Hex/EtOAc = 4/1) to give **4** (2.35 g, 90%) as a foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.98 (m, 5 H, Bz), 6.47 (s, 1 H, H-1), 4.66 (s, 1 H, H-2), 4.52 (d, 1 H, J = 12.6 Hz, H_a-3′), 4.42 (d, 1 H, J = 12.6 Hz, H_b-3′), 4.18 (d, 1 H, J = 10.3 Hz, H_a-4), 4.05 (d, 1 H, J = 10.3 Hz, H_b-4), 1.55 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3); IR (KBr): 2991, 1728, 1252, 1135, 1097, 936, 714 cm^{-1}; FAB-MS *m/z*: 317 $[M + Na]^+$.

Methyl 2,3-*O*-Isopropylidene-β-D-apiofuranoside (5). To a stirred solution of **4** (2.35 g, 7.99 mmol) in MeOH (15 mL) was added AcCl (0.2 mL) at room temperature and the mixture was stirred at room temperature for 5 h, neutralized with pyridine, and evaporated. The residue was purified by silica gel column chromatography (Hex/

EtOAc = 2/1) to give **5** (1.39 g, 85%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.96 (s, 1 H, H-1), 4.31 (s, 1 H, H-2), 3.95 (d, 1 H, J = 10.1 Hz, H_a-3′), 3.80 (d, 1 H, J = 10.2 Hz, H_b-3′), 3.76 (d, 2 H, J = 1.7, H-4), 3.33 (s, 3 H, OCH_3), 1.50 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3); IR (KBr): 3477, 2990, 2937, 1456, 1375, 1247, 1096, 1021, 995, 931 cm^{-1}; FAB-MS *m/z*: 227 $[M + Na]^+$, 205$[M + H]^+$.

Methyl 3′-*O*-Benzoyl-2,3-*O*-isoprpylidene-β-D-apiofuranoside (6). To a stirred solution of **5** (1.39 g, 3.81 mmol) in pyridine (15 mL) was added BzCl (1.19 mL, 10.21 mmol) at room temperature and the mixture was stirred at room temperature for 5 h and evaporated. The residue was dissolved in EtOAc and 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 = 5/1) to give **6** (1.93 g, 92%) as a foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.71 (m, 5 H, Bz), 4.99 (s, 1 H, H-1), 4.68 (d, 1 H, J = 11.7 Hz, H_a-3′), 4.58(s, 1 H, H-2), 4.55 (d, 1 H, J = 11.8 Hz, H_b-3′), 4.05 (d, 1 H, J = 9.9 Hz, H-4a), 3.95 (d, 1 H, J = 9.9 Hz, H_b-4), 3.33 (s, 3 H, OCH_3), 1.51 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3); IR (KBr): 2990, 1725, 1272, 1102, 1020, 709 cm^{-1}; FAB-MS *m/z*: 277 $[M- OCH_3]^+$.

Methyl 3′-*O*-Benzoyl-β-D-apiofuranoside (7). To a stirred solution of **6** (1 g, 3.24 mmol) in MeOH (20 mL) was added Dowex $50H^+$ resin (3 g) and the reaction mixture was stirred at 60°C for 2 d, cooled to room temperature and filtrated. The filtrate was evaporated and the residue was purified by silica gel column chromatography (Hex/EtOAc = 1/1) to give **7** (759 mg, 87%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42–8.02 (m, 5 H, Bz), 4.92 (d, 1 H, J = 1.8 Hz, H-1), 4.47 (s, 2 H, H-3′), 4.04 (d, 1 H, J = 10.1 Hz, H_a-4), 4.00 (d, 1 H, J = 1.8 Hz, H-2), 3.95 (d, 1 H, J = 10.1 Hz, H_b-4), 3.38 (s, 3 H, OCH_3); IR (KBr): 3434, 2942, 1720, 1277, 1110, 1023, 713 cm^{-1}; FAB-MS *m/z*: 291 $[M + Na]^+$, 269 $[M + H]^+$.

Methyl 2,3,3′-Tri-*O*-benzoyl-β-D-apiofuranoside (8). To a stirred solution of **7** (759 mg, 2.83 mmol) and DMAP (150 mg) in pyridine (15 mL) was added BzCl (0.99 mL, 8.53 mmol) at room temperature and the reaction mixture was stirred at 50°C overnight, cooled to room temperature and evaporated. The residue was dissolved in EtOAc and 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 = 5/1) to give **8** (1.2 g, 89%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23–8.17 (m, 15 H, 3 × Bz), 5.86 (s, 1 H, H-1), 5.16 (m, 2 H, H-2, H_a-3′), 4.96 (d, 1 H, J = 12.3 Hz, H_b-3′), 4.54 (d, 2 H, J = 2.0 Hz, H-4), 3.46 (s, 3 H, OCH_3); IR (KBr): 2938, 1727, 1275, 1107, 710 cm^{-1}; FAB-MS *m/z*: 499 $[M + Na]^+$, 445 $[M- OCH_3]^+$.

Acetyl 2,3,3′-Tri-*O*-benzoyl-β-D-apiofuranoside (9). A solution of **8** (946 mg, 1.99 mmol) in $AcOH/Ac_2O/c\text{-}H_2SO_4$ (8 mL/2 mL/0.56 mL) was stirred at room temperature for 30 min. The reaction mixture was poured into sat. $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), filtrated and evaporated. The residue was purified by silica gel column chromatography (Hex/EtOAc = 4/1) to give **9** (950 mg, 95%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ

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7.25–8.10 (m, 15 H, 3 × Bz), 6.42 (s, 1 H, H-1), 5.99 (s, 1 H, H-2), 5.16 (d, 1 H, J = 12.5 Hz, H_a-3′), 4.99 (d, 1 H, J = 12.5 Hz, H_b-3′), 4.68 (d, 1 H, J = 10.6 Hz, H_a-4), 4.55 (d, 1 H, J = 10.6 Hz, H_b-4), 2.14 (s, 3 H, OAc); IR (KBr): 3066, 1728, 1267, 1109, 710 cm^{-1}; FAB-MS *m/z*: 527 $[M + Na]^+$, 445 $[M- OAc]^+$.

2,3,3′-Tri-*O*-benzoyl-β-D-apiofuranosyl cyanide (10). To a stirred solution of **9** (789 mg, 1.56 mmol) in anhydrous CH_2Cl_2 (10 mL) were added TMSCN (0.83 mL, 6.22 mmol) and $SnCl_4$ (1 M solution in CH_2Cl_2, 0.31 mL) and the reaction mixture was refluxed for 3 h, cooled to room temperature and patitioned between CH_2Cl_2/H_2O. The organic layer was washed with brine, dried ($MgSO_4$), filtrated and evaporated. The residue was purified by silica gel column chromatography (Hex/EtOAc = 4/1) to give **10** (512 mg, 69%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–8.14 (m, 15 H, 3 × Bz), 6.12 (d, 1 H, J = 4.2 Hz, H-1), 5.08 (d, 1 H, J = 12.3 Hz, H_a-3′), 4.93 (d, 1 H, J = 12.3 Hz, H_b-3′), 4.92 (d, 1 H, J = 4.1 Hz, H-2), 4.69 (d, 1 H, J = 10.7 Hz, H_a-4), 4.46 (d, 1 H, J = 10.7 Hz, H_b-4); IR (KBr): 3067, 1729, 1280, 1104, 710 cm^{-1}; FAB-MS *m/z*: 494 $[M + Na]^+$, 445 $[M- CN]^+$.

Ethyl 2-(2′,3′,3″-Tri-*O*-benzoyl–apio-β-D-furanosyl)thiazoline-4-carboxylate (11). To a stirred solution of **10** (512 mg, 1.09 mmol) in anhydrous MeOH (15 mL) was added L-cysteine ethyl ester hydrochloride (302 mg, 1.63 mmol) followed by TEA (0.23 mL, 1.66 mmol) at room temperature. The reaction mixture was stirred for 2 h and evaporated. The residue was dissolved in CH_2Cl_2 and the organic layer was washed with water, sat. $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$), filtrated and evaporated. The residue was purified by silica gel column chromatography (Hex/EtOAc = 3/1) to give **11** (459 mg, 71%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24–8.06 (m, 15 H, 3 × Bz), 6.14 (d, 1 H, J = 5.0 Hz, H-1′), 5.15(m, 1 H, H-4), 5.08 (dd, 1 H, J = 1.5, 5.0 Hz, H-2′), 5.07 (d, 1 H, J = 12.3 Hz, H_a-3″), 4.81 (d, 1 H, J = 12.3 Hz, H_b-3″), 4.77 (d, 1 H, J = 10.6 Hz, H_a-4′), 4.43 (d, 1 H, J = 10.6 Hz, H_b-4′), 4.01–4.17 (m, 2 H, OCH_2CH_3), 3.50–3.64 (m, 2 H, H-5), 1.13 (t, 3 H, J = 7.1 Hz, OCH_2CH_3); IR (KBr): 2984, 1720, 1273, 1107, 711 cm^{-1}; FAB-MS *m/z*: 626 $[M + Na]^+$, 604 $[M + H]^+$; Anal calcd for $C_{32}H_{29}NO_9S$: C, 63.67; H, 4.84; N, 2.32; S,5.31. Found: C, 63.42; H, 5.02; N, 2.44; S, 5.53.

Ethyl 2-(2′,3′,3″-Tri-*O*-benzoyl-apio-β-D-furanosyl)thiazole-4-carboxylate (12). To a stirred solution of **11** (459 mg, 0.76 mmol) in anhydrous CH_2Cl_2 (20 mL) was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (0.23 mL, 1.54 mmol). The solution was cooled to 0°C and bromotrichloromethane (0.09 mL, 0.91 mmol) was added dropwise. The reaction mixture was stirred at 0°C for 16 h and evaporated. The residue was dissolved in EtOAc and washed with sat. aqueous NH_4Cl solution (×3). The organic layer was dried ($MgSO_4$), filtrated and evaporated. The residue was purified by silica gel column chromatography (Hex/EtOAc = 2/1) to give **12** (340 mg, 74%) as a solid. mp:129 ∼ 131°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (s, 1 H, H-5), 7.25–8.09 (m, 15 H, 3 × Bz), 6.01 (d, 1 H, J = 5.0 Hz, H-1′), 5.60 (d, 1 H, J = 5.0 Hz, H-2′), 5.06 (d, 1 H, J = 12.1Hz, H_a-3″), 4.89 (d, 1 H, J = 10.7 Hz, H_a-4′), 4.74 (d, 1 H, J = 12.1 Hz, H_b-3″), 4.50 (d, 1 H, J = 10.8 Hz, H_b-4′), 4.32 (q, 2 H, J = 7.2 Hz, OCH_2CH_3), 1.31 (t, 3 H, J = 7.1 Hz, OCH_2CH_3); IR (KBr): 2921, 1727, 1601, 1267,

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1100, 711 cm^{-1}; FAB-MS *m/z*: 624 $[M + Na]^+$, 602 $[M + H]^+$; Anal calcd for $C_{32}H_{27},NO_9S$: C, 63.88; H, 4.52; N, 2.33; S, 5.33. Found: C, 63.59; H, 4.66; N, 2.30; S, 5.36.

2-(Apio-β-D-furanosyl)thiazole-4-carboxamide (1). A mixture of **12** (340 mg, 0.57 mmol) in saturated methanolic ammonia (20 mL) was stirred at room temperature for 24 h and evaporated. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 5/1) to give **1** (125 mg, 85%) as a solid. Mp 159 ∼ 161°C; ^1H NMR (300 MHz, DMSO-d_6): δ 8.13 (s, 1 H, H-5), 7.67–7.56 (br d, 2 H, NH_2), 5.38 (d, 1 H, *J* = 7.0 Hz, OH), 4.86 (m, 2 H, H-1′ and OH), 4.71 (s, 1 H, OH), 4.11 (d, 1 H, *J* = 9.3 Hz, H_a-3″), 3.95 (dd, 1 H, *J* = 7.0, 7.5 Hz, H-2′), 3.70 (d, 1 H, *J* = 9.3 Hz, H_b-3″), 3.26 (m, 2 H, H-4′); IR (KBr): 3413, 1683, 1604, 1389, 1113, 1064, 630 cm^{-1}; FAB-MS *m/z*: 283 $[M + Na]^+$, 261 $[M + H]^+$; Anal calcd for C_9H_{12},N_2O_5S: C, 41.53; H, 4.65; N, 10.76; S, 12.32. Found: C, 41.23; H, 4.79; N, 10.59; S, 12.07.

Methyl 1-(2′,3′,3″-Tri-*O*-benzoyl–apio-β-D-furanosyl)triazole-3-carboxylate (13a) and methyl 1-(2′,3′,3″-tri-*O*-benzoyl–apio-β-D-furanosyl)triazole-5-carboxylate (13b). A suspension of methyl-1,2,3-triazole-3-carboxylate (367 mg, 2.89 mmol) and ammonium sulfate (40 mg) in anhydrous HMDS (10 mL) was refluxed for 16 h and concentrated under anhydrous conditions. The residue was dissolved in acetonitrile (10 mL) and a solution of **9** (730 mg, 1.48 mmol) in acetonitrile (10 mL) was added to this solution followed by addition of $SnCl_4$ (1 M solution in CH_2Cl_2, 1.48 mL) at 0°C and the reaction mixture was stirred at room temperature for 18 h, quenched by addition of sat. $NaHCO_3$ solution and filtered through a Celite pad. The filtrate was extracted with CH_2Cl_2 (×3) and 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 = 2/1) to give **13a** (317 mg, 38%) and **13b** (234 mg, 28%).

13a: R_f = 0.17 (Hex/EtOAc = 2/1); ^1H NMR (300 MHz, $CDCl_3$): δ 8.44 (s, 1 H, H-5), 7.92–7.32 (m, 15 H, 3 × Bz), 6.42 (d, 1 H, *J* = 4.2 Hz, H-1′). 6.35 (d, 1 H, *J* = 4.2 Hz, H-2′), 5.12 (d, 1 H, *J* = 12.1 Hz, H_a-3″), 5.05 (d, 1 H, *J* = 12.1 Hz, H_b-3″), 4.85 (d, 1 H, *J* = 11.0 Hz, H_a-4′), 4.78 (d, 1 H, *J* = 10.9 Hz, H_b-4′), 3.97 (s, 3 H, OCH_3); IR (KBr): 3010, 1730, 1267, 1109, 1027, 711 cm^{-1}; FAB-MS *m/z*: 594 $[M + Na]^+$; Anal calcd for $C_{30}H_{25},N_3O_9$: C, 63.04; H, 4.41; N, 7.35. Found: C, 62.78; H, 4.33; N, 7.08.

13b: R_f = 0.31 (Hex/EtOAc = 2/1); ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (s, 1 H, H-3), 7.95–7.31 (m, 15 H, 3 × Bz), 7.20 (d, 1 H, *J* = 3.7 Hz, H-1′). 6.54 (d, 1 H, *J* = 3.6 Hz, H-2′), 5.23 (s, 2 H, H-3″), 4.83 (d, 1 H, *J* = 10.6 Hz, H_a-4′), 4.74 (d, 1 H, *J* = 10.6 Hz, H_b-4′), 3.99 (s, 3 H, OCH_3); IR (KBr): 3009, 1729, 1273, 1107, 1068, 711 cm^{-1}; FAB-MS *m/z*: 594 $[M + Na]^+$.

1-(Apio-β-D-furanosyl)triazole-3-carboamide (2). A mixture of **13a** (317 mg, 0.55 mmol) in saturated methanolic ammonia (20 mL) was stirred at room temperature for 24 h and evaporated. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 5/1) to give **2** (108 mg, 80%) as a solid. ^1H NMR (300 MHz,

DMSO-d_6): δ 8.88 (s, 1 H, H-5), 7.84–7.62 (br d, 2 H, NH_2), 5.78 (d, 1 H, J = 7.1Hz, H-1′), 5.50 (d, 1 H, J = 6.8, OH), 4.95 (dd, 1 H, J = 5.3, 5.5 Hz, OH), 4.89 (s, 1 H, OH), 4.59 (dd, 1 H, J = 6.7, 7.0 Hz, H-2′) 4.21 (d, 1 H, J = 9.3 Hz, H_a-4′), 3.73 (d, 1 H, J = 9.4 Hz, H_b-4′), 3.40 (dd, 1 H, J = 5.5, 11.0 Hz, H_a-3″), 3.32 (dd, 1 H, J = 5.2, 11.0 Hz, H_b-3″); IR (KBr): 3428, 1685, 1107, 808, 702 cm^{-1}; FAB-MS *m/z*: 267 $[M + Na]^+$; Anal calcd for C_8H_{12},N_4O_5: C, 39.35; H, 4.95; N, 22.94. Found: C, 39.12; H, 5.04; N, 22.74.

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