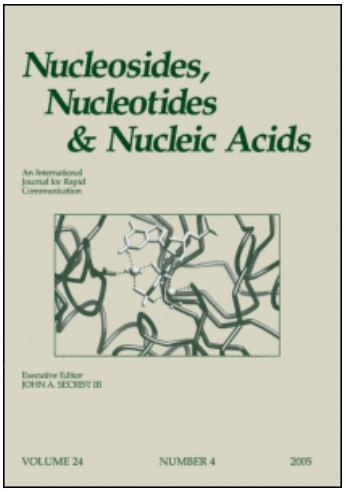


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of Triazole Nucleoside Derivatives

Zicheng Li[a]; Shuhua Chen[a]; Ning Jiang[b]; Gang Cui[a]
[a] Faculty of Chemistry, Sichuan University, Chengdu Sichuan, P. R. China [b] Sichuan Industrial Institute of Antibiotics, Chengdu Sichuan, P. R. China

Online publication date: 06 September 2003

To cite this Article Li, Zicheng , Chen, Shuhua , Jiang, Ning and Cui, Gang(2003) 'Synthesis of Triazole Nucleoside Derivatives', Nucleosides, Nucleotides and Nucleic Acids, 22: 4, 419 — 435
To link to this Article: DOI: 10.1081/NCN-120022032
URL: http://dx.doi.org/10.1081/NCN-120022032

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, No. 4, pp. 419–435, 2003

Synthesis of Triazole Nucleoside Derivatives

Zicheng Li,[1] Shuhua Chen,[1,*] Ning Jiang,[2] and Gang Cui[1]

[1]Faculty of Chemistry, Sichuan University, Chengdu
Sichuan, P. R. China
[2]Sichuan Industrial Institute of Antibiotics, Chengdu
Sichuan, P. R. China

ABSTRACT

5′-*O*-Mesyl-2′,3′-*O*-isopropylidene ribonucleosides (**4** and **12**) were converted to their 5′-substituted nucleosides in good yields by reacted with NaN_3 or KI. 2′,3′-*O*-Isopropylidene ribonucleosides (**3** and **11**) were prepared in good yields from ribonucleosides **1** and **2** with a reaction mixture of acetone and triethyl orthoformate instead of using acetone diethyl acetal. Compound **1** or **2** was treated with 2-acetoxyisobutyryl halide (Cl or Br) to give 1-[2-*O*-acetyl-3-halo-3-deoxy-5-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]-1,2,4-triazole-3-carboxamide (**19**, **22**, and **23**) in high yields. Instead of using 2-acetoxyisobutyryl bromide, the mixture of 2-acetoxyisobutyryl chloride and NaBr was employed in the synthesis of **22** and **23**. Treatment of **19** with an activated Zn/Cu couple and deprotection gave 2′,3′-anhydro nucleoside (**21**), and treatment of **22** and **23** with an activated Zn/Cu couple and a little of HOAc and deprotection gave corresponding 2′,3′-unsaturated triazole nucleosides (**24** and **25**), respectively. The biological activity of the compounds (**7**∼**10**, **15**∼**18**, and **24**) was examined in human liver cancer cells (A-549), lung cancer cells (BEL-7402), and Flu-A cells.

Key Words: Ribavirin derivative; Triazole nucleoside derivative; Antiviral activity; Synthesis.

*Correspondence: Shuhua Chen, Faculty of Chemistry, Sichuan University, No. 15 Road Wangjiang, Chengdu Sichuan 610064, P. R. China; Fax: ++86-28-85412285; E-mail: chemchensh@sina.com.

DOI: 10.1081/NCN-120022032
1525-7770 (Print); 1532-2335 (Online)

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Virazole (**1**) exhibits a broad spectrum of activity against both DNA and RNA viruses in vitro and in vivo.[1] Various derivatives modified on the triazole ring have been widely researched, but none has exhibited better activity than the parent compound. We speculated that the triazole-3-carboxamide ring was essential for the activity of the derivatives of **1**. 5′-Amino-2′,5′-dideoxy-5-iodouridine (AIDU) has a broad spectrum of activity against HSV-1, HSV-2, guinea-pig like virus, and murine leukemia viruses.[2] Several 2′,3′-dideoxy and 2′,3′-unsaturated nucleosides, including 1-(2,3-dideoxy-β- D-*glycero*-pent-2-enofuranosyl)thymine(d4T), 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl) cytosine (d4C), 2′,3′-dideoxyinosine (ddI) and 2′,3′-dideoxycytidine (ddC), have activity against HIV in vitro and in vivo, among them, d4T, ddC and ddI have been approved for the treatment of AIDS. Our interest in nucleosides as antiviral and anticancer agents prompted us to synthesize some triazole nucleoside derivatives. The present study describes the synthesis of a series of such kinds of nucleoside analogs.

RESULTS AND DISCUSSION

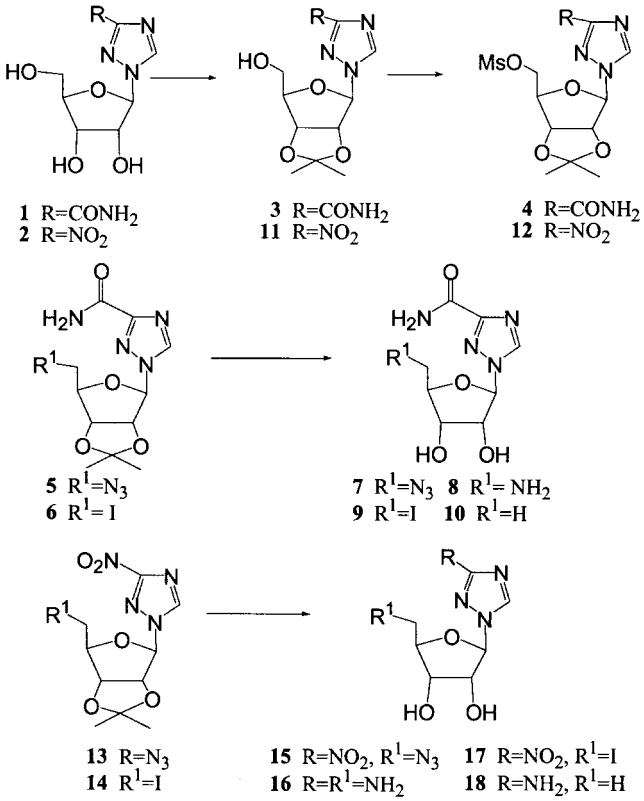
5′-Substituted derivatives of 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamides (**7-10**) and 5′-substituted derivatives of 3-nitro or amino-1-(β-D-ribofuranosyl)-1,2,4-triazoles (**15-18**) were synthesized by using the following general method. Compounds **1** and **2** were protected on the 2′ and 3′ positions with an isopropylidene group using a reaction mixture of triethyl orthoformate and acetone with TsOH·H_2O as a catalyst. Because both nucleosides have low solubility in acetone or acetone diethyl acetal, low yields were obtained in the formation of the isopropylidene moiety using only acetone or acetone diethyl acetal as reagent and solvent catalyzed by concentrated sulfuric acid or TsOH·H_2O (approx. 20% yield). We found that when triethyl orthoformate was added to acetone using TsOH·H_2O as a catalyst, and the solution was stirred overnight, followed by addition to a suspension of virazole in a little of DMF and stirring continued for 24 h at 50°C, the yield was raised to 85%, which was the same as or higher than that had been reported using the acetone diethyl acetal method.[3]

5′-Mesyl nucleosides were obtained by treatment of the isopropylidene-blocked nucleosides with methanesulfonyl chloride in dry pyridine. The mesyl group was replaced by either iodo or azido, and the isopropylidene was then removed to give 5′-substituted nucleosides. The iodo, azido and nitro groups were hydrogenated to hydrogen and amino (Sch. 1).

Compound **1** reacted with 2-acetoxyisobutyryl chloride to give **19** and **20** via an intermediate acetoxonium ion, in the absence of participation by the triazole ring, the intermediate acetoxonium ion will be opened by chloride ion from the β face of the sugar at either C3′ or C2′ giving **19** and **20**, respectively. Attack at C3′ is preferred based on the steric effect.[4] Tlc and products separated by silica gel column chromatography showed a 3:1 ratio of **19**:**20**. Compounds **19** and **20** were treated with an activated Zn/Cu couple in dry acetonitrile, then treated with NaOMe in MeOH to give 2′,3′-anhydro compound **21**.

For the synthesis of 2′,3′-unsaturated nucleosides, 2-acetoxyisobutyryl chloride was prepared from 2-hydroxyisobutyric acid by reacted with acetic chloride and then

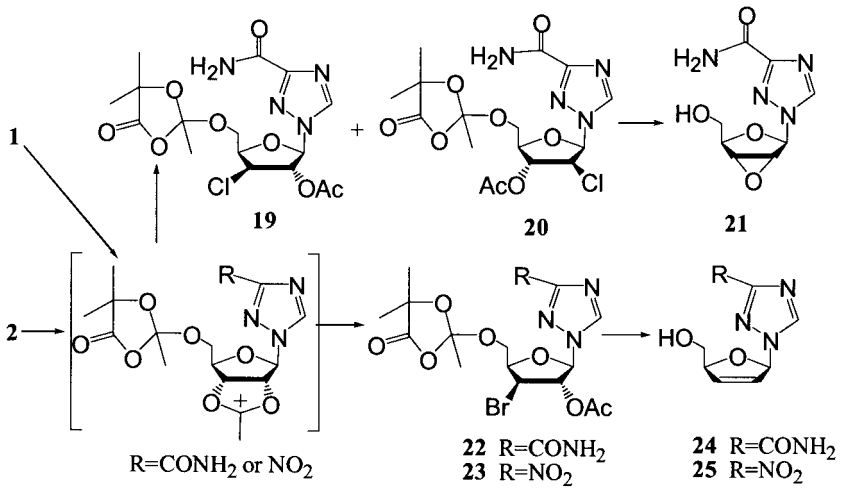
Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016



Scheme 1.

with $SOCl_2$ in a 82% yield,[5] 2-acetoxyisobutyryl bromide was prepared from 2-acetoxyisobutyric acid and PBr_3 in a low yield,[6] or prepared from 2-acetoxyisobutyryl chloride and LiBr in 45% yield.[7] The latter method must be performed under inert gas to avoid moisture, especially in the process of the filtration removing insoluble salt. Herein we adopted an improved method, 2-acetoxyisobutyryl bromide was prepared from the reaction mixture of 2-acetoxyisobutyryl chloride and NaBr in dry acetonitrile, the product acid bromide was directly used in the next reaction without further purification. It has been found that some of the chloro compounds were also present by nucleosides reacted with 2-acetoxyisobutyryl chloride in the presence of a large excess of bromide ions. In our case, no chloro compounds were detected by mass spectrum.

Compounds **1** and **2** reacted with the mixture of 2-acetoxyisobutyryl chloride and NaBr in refluxing dry acetonitrile to give **22** and **23**, and the yields of **22** and **23** were the same as or higher than those reported in references. The same intermediate was produced in the formation of **22** and **23** as in the case of **19** and **20**, though the larger bromine atom more selectively attacked the 3′-position, there by forming the 3′-bromoxylo isomer as the major product. Compounds **22** and **23** were treated



Scheme 2.

with an activated Zn/Cu couple, and then with NaOMe in MeOH to give the anticipated 2′,3′-unsaturated nucleosides **24** and **25**, respectively[8,9] (Sch. 2).

Antitumor and antiviral activity of the compounds (**7**∼**10**, **15**∼**18**, and **24**) in A-549 cells, BEL-7402 cells, and Flu-A cells revealed that only compound **9** provided a weak level of protection against viral infection, $IC_{25} = 0.4\,\mu mol/mL$, no cytotoxicity was evidenced at that concentration.

From the present work, the modification on sugar moiety of nucleosides with unnatural bases does not lead to inhibition of virus and tumor multiplication, the relation of structure and activity need further study.

EXPERIMENTAL

Melting points were determined on a capillary apparatus and are uncorrected. TLC was performed on microscope slides coated with silica gel GF_{254} purchased from Qingdao Haiyang Chemical factory, and column chromatography was performed on silica gel (10–40 μM, Qingdao). Elemental analyses were performed on a Carlo-Elmer instrument. ^1H NMR spectra were recorded on a Varian A-200 MHz or 400 MHz instrument, and tetramethylsilane was the external standard; chemical shifts are reported in p.p.m. (δ) and signals are quoted as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), m (complex multiplet), and br (broad). Mass spectra were recorded on a PE2400-2 instrument.

1-β-D-Ribofuranosyl-1,2,4-triazole-3-carboxamide (1). According to Ref. 1, 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose was fused with methyl 1,2,4-triazole-3-carboxylate in the presence of bis (*p*-nitrophenyl) phosphate as a catalyst at 165–170°C, followed by treatment with NH_3 in methanol to give compound **1**: mp 169–170°C (lit.1 mp 165–170°C).

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (3). Triethyl orthoformate (3 mL, 18 mmol) and $TsOH \cdot H_2O$ (35 mg) were added to acetone (20 mL) and the solution was stirred overnight at room temperature. The solution was then added to **1** (2 g, 8.2 mmol) dissolved in dry DMF (5 mL), and the mixture was stirred overnight at 50°C. The solvent was evaporated under vacuum, and the residual yellow syrup was purified by flash chromatography on silica gel (CH_2Cl_2-MeOH, 8:2) to afford **3** as a colorless foam (1.63 g, yield 85%). mp: 116–118°C; ^{1}H NMR (DMSO-d_6): δ 8.87 (s, 1H, H-5), 7.86 and 7.66 (2s, 2H, $CONH_2$), 6.20 (d, 1H, $J = 1.2$ Hz, H-1′), 5.18 (dd, $J = 1.2$ Hz and 5.9 Hz, H-2′), 4.97 (t, 1H, $J = 5.4$ Hz, H-3′), 4.91(dd, 1H, $J = 1.8$ Hz and 6 Hz, OH-5′), 4.23 (dd, 1H, $J = 1.7$ Hz and 5.8 Hz, H-4′), 3.45 (m, 2H, H-5′), 1.50 (s, 3H, CH_3), 1.32 (s, 3H, CH_3).

1-(2,3-*O*-Isopropylidene-5-*O*-mesyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (4). Mesyl chloride (1.2 mL, 15.4 mmol) was slowly added to a solution of **3** (1.5 g, 5.28 mmol) dissolved in 10 mL of dry pyridine and cooled in ice-water bath, and the mixture was stirred overnight at r.t. The solution was filtered and washed with CH_2Cl_2, the filtrate was evaporated, and the residue was dissolved in CH_2Cl_2, which was washed with brine and dried with anhydrous $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (CH_2Cl_2 : MeOH = 95 : 5) to give **4** as a colorless foam(1.85 g, yield 87%). mp: 79–81°C; ^{1}H NMR (DMSO-d_6): δ 8.84 (s, 1H, H-5), 7.89 and 7.69 (2s, 2H, $CONH_2$), 6.39 (s, 1H, H-1′), 5.18 (d, 1H, $J = 5.7$ Hz, H-2′), 5.03 (d, 1H, $J = 5.7$ Hz, H-3′), 4.25–4.49 (m, 3H, H-4′, H-5′), 3.14 (s, 3H, Ms), 1.52 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); mass spectrum (EI) m/e 361 ($M^+ - 1$, 65).

1-(5-Azido-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (5). To a solution of **4** (1 g, 2.76 mmol) dissolved in 5 mL of dry DMF was added sodium azide (350 mg, 5.4 mmol), and the suspension was then heated at 120°C for 0.75 h until tlc showed that the reaction had been completed. The reaction solution was poured into 10 g of crushed ice and extracted with CH_2Cl_2 (3×20 mL). The organic phases were washed with water, dried with anhydrous $NaSO_4$, evaporated, and purified by silica gel column chromatography (CH_2Cl_2-MeOH, 95:5) to afford **5** as a colorless foam (0.82 g, 96% yield). mp: 97–99°C; ^{1}H NMR (DMSO-d_6): δ 8.85 (s, 1H, H-5), 7.90 and 7.68 (2s, 2H, $CONH_2$), 6.37 (s, 1H, H-1′), 5.22 (d, 1H, $J = 5.5$ Hz, H-2′), 4.94 (d, 1H, $J = 5.6$ Hz, H-3′), 4.38 (m, 1H, H-4′), 3.65 (pseudo t, 2H, H-5′), 1.52 (s, 3H, CH_3), 1.33 (s, 3H, CH_3).

1-(5-Azido-5-deoxy-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (7). To a solution of **5** (800 mg, 2.59 mmol) in 10 mL of methanol was added 0.5 mL of concentrated HCl at r. t. and the solution was stirred for 5 h. Solid $NaHCO_3$ was used to adjust the solution to pH 7 and the solvent was removed under reduced pressure. The residual solid was purified by silica gel column chromatography (CH_2Cl_2: MeOH = 8 : 2) to give a colorless solid (660 mg, 95%). mp: 124–125°C; ^{1}H NMR (DMSO-d_6) : δ 8.86 (s, 1H, H-5), 7.84 and 7.64 (2s, 2H, $CONH_2$), 5.92 (d, 1H, $J = 2.7$ Hz, H-1′), 5.70 (d, 1H, $J = 5.2$ Hz, OH-2′), 5.38 (d, 1H, $J = 5.7$ Hz, OH-3′), 4.39 (dd, 1H, $J = 2.8$ Hz and 5.3 Hz, H-2′), 4.20 (dd, 1H, $J = 5.4$ Hz and 5.6 Hz, H-3′), 4.06 (dd, 1H, $J = 5.8$ Hz and 9.3 Hz, H-4′), 3.54 (m, 2H, H-5′); mass spectrum

(EI) m/e 270 ($M^+ + 1$, 87); Anal. for $C_8H_{11}N_7O_4$: C, 35.69; H, 4.12; N, 36.42; found: C, 35.66; H, 4.00; N, 36.52.

1-(5-Amino-5-deoxy-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (8). A solution of **7** (500 mg, 1.86 mmol) in 25 mL of methanol was hydrogenated in the presence of 0.5 g of 10% Pd/C for 6 h at 1 atmosphere, the mixture was filtered through a celite pad, and the filtrate was concentrated and purified by silica gel column chromatography to afford a pale-yellow solid (370 mg, 82%). mp: 142–143°C; ^{1}H NMR (DMSO-d_6): δ 8.88 (s, 1H, 5-H), 7.84 and 7.64 (2s, 2H, $CONH_2$), 5.96 (s, 1H, H-1′), 5.85 (d, 2H, $J = 3.6$ Hz, OH-2′, OH-3′), 4.34 (br s, 1H, H-2′), 4.20 (br s, 1H, H-3′), 3.95 (dd, 1H, $J = 5.4$ Hz and 11.5 Hz, H-4′), 3.2–3.4 (m, 2H, H-5′); mass spectrum (EI) m/e 266 ($M^+ + Na$, 10); Anal. for $C_8H_{13}N_5O_4$: C, 39.51; H, 5.39; N, 28.79; found: C, 39.60; H, 5.41; N, 28.65.

1-(5-Iodo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (6). Dry potassium iodide (730 mg, 4.4 mmol) was added into a solution of **4** (800 mg, 2.21 mmol) in 5 mL of dry DMF and the suspension was heated for 0.5 h at 125°C. The reaction mixture was then poured into 20 g of crushed ice, which was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with 10% aqueous $Na_2S_2O_3$ (2 × 10 mL) and brine, dried with anhydrous Na_2SO_4, filtered, and evaporated to give a brown oil that was purified by silica gel column chromatography (CH_2Cl_2 : MeOH = 95 : 5) to give a colorless solid (810 mg, yield 93%). mp: 136–138°C; ^{1}H NMR (DMSO-d_6): δ 8.89 (s, 1H, H-5), 7.84 and 7.64 (2s, 2H, $CONH_2$), 6.27 (d, 1H, $J = 2.8$ Hz, H-1′), 5.36 (d, 1H, $J = 5.4$ Hz, H-2′), 4.95 (d, 1H, $J = 5.5$ Hz, H-3′), 4.34 (dd, 1H, $J = 5.8$ Hz and 9.3 Hz, H-4′), 3.54 (m, 2H, H-5′). 1.53 (s, 3H, CH_3), 1.34 (s, 3H, CH_3).

1-(5-Iodo-5-deoxy-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (9). Compound **9** was prepared from **6** using the procedure of the synthesis of **7** in 83% yield. mp: 164–165°C; ^{1}H NMR (DMSO-d_6): δ 8.87 (s, 1H, 5-H), 7.87 and 7.64 (2s, 2H, $CONH_2$), 5.88 (d, 1H, $J = 3.7$ Hz, H-1′), 5.70 (d, 1H, $J = 5.1$ Hz, OH-2′), 5.47 (d, 1H, $J = 4.9$ Hz, OH-3′), 4.48 (d, 1H, $J = 3.9$ Hz, H-2′), 4.19 (d, 1H, $J = 4.4$ Hz, H-3′), 4.04 (dd, 1H, $J = 5.2$ Hz and 11.5 Hz, H-4′), 3.3–3.57 (m, 2H, H-5′); Anal. for $C_8H_{11}IN_4O_4$, C, 27.14; H, 3.13; N, 15.82; found: C, 27.10; H, 3.17; N, 15.64.

1-(5-Deoxy-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (10). Compound **9** was hydrogenated according to the procedure for **7** to give **10**, mp: 126–127°C; ^{1}H NMR (DMSO-d_6): δ 8.89 (s, 1H, 5-H), 7.86 and 7.66 (2s, 2H, $CONH_2$), 5.91 (d, 1H, $J = 2.8$ Hz, H-1′), 5.68 (d, 1H, $J = 5.3$ Hz, OH-2′), 5.37 (d, 1H, $J = 5.6$ Hz, OH-3′), 4.38 (dd, 1H, $J = 2.8$ Hz and 5.3 Hz, H-2′), 4.21 (dd, 1H, $J = 5.4$ Hz and 5.6 Hz, H-3′), 4.01 (dd, 1H, $J = 5.8$ Hz and 9.3 Hz, H-4′), 1.33 (m, 3H, H-5′); mass spectrum (EI) m/e 229 ($M^+ + 1$, 100); Anal. for $C_8H_{12}N_4O_4$: C, 42.10; H, 5.30; N, 24.55; found: C, 42.25; H, 5.25; N, 24.38.

3-Nitro-1-(β-D-ribofuranosyl)-1,2,4-triazole (2). Compound **2** was prepared according to a previously reported procedure.[10] mp: 138.5–140°C (lit.10 138–140°C).

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

3-Nitro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,4-triazole (11). Compound **11** was prepared from **2** according to the procedure for **3** in 82% yield, mp 105–106°C; ^{1}H NMR (DMSO-d_6): δ 9.01 (s, 1H, H-5), 6.25 (s, 1H, H-1′), 5.21 (d, 1H, $J = 4.4$ Hz, H-2′), 4.99 (dd, 1H, $J = 4.4$ Hz and 7.8 Hz, H-3′), 4.90 (t, 1H, $J = 5.2$ Hz, OH-5′), 4.36 (dd, 1H, $J = 5.2$ Hz and 5.2 Hz, H-4′), 3.5 (m, 2H, H-5′), 1.50 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); mass spectrum (EI) m/e 287 ($M^+ + 1$, 100).

3-Nitro-1-(2,3-*O*-isopropylidene-5-*O*-mesyl-β-D-ribofuranosyl)-1,2,4-triazole (12). Compound **12** was prepared from **11** according to the procedure for **4** in 88% yield, mp: 87–88°C; ^{1}H NMR (DMSO-d_6): δ 9.04 (s, 1H, H-5), 6.43 (s, 1H, H-1′), 5.28 (dd, 1H, $J = 1.4$ Hz and 5.8 Hz, H-2′), 4.99 (dd, 1H, $J = 1.6$ Hz and 6.0 Hz, H-3′), 4.59 (m, 1H, H-4′), 4.39 (dd, 1H, $J = 4.8$Hz and 10.5 Hz, H-5′a), 4.32 (dd, 1H, $J = 7.0$ Hz and 10.5 Hz, H-5′b), 3.13 (s, 3H, MsO), 1.52 (s, 3H, CH_3), 1.35 (s, 1H, CH_3); mass spectrum (EI) m/e 365 ($M^+ + 1$, 20).

3-Nitro-1-(5-azido-5-deoxy-β-D-ribofuranosyl)-1,2,4-triazole (15). Compound **15** was prepared from **12** according to the procedure for **7** in 92% yield. mp: 136.5–138°C; ^{1}H NMR (DMSO-d_6): δ 9.10 (s, 1H, H-5), 6.02 (d, 1H, $J = 2.8$ Hz, H-1′), 5.84 (d, 1H, $J = 2.8$ Hz, OH-2′), 5.50 (d, 1H, $J = 6$ Hz, OH-3′), 4.40 (m, 1H, H-2′), 4.27 (dd, 1H, H-3′), 4.12 (ddd, 1H, $J = 3.2$ Hz, 6 Hz and 3 Hz, H-4′), 3.62 (dd, 1H, $J = 3.2$ Hz and 13.6 Hz, H-5′a), 3.45 (dd, 1H, $J = 6$ Hz and 13.6 Hz, H-5′b); mass spectrum (EI) m/e 272 ($M^+ + 1$, 25); Anal. for $C_7H_9N_7O_5$: C, 31.00; H, 3.35; N, 36.15; found: C, 30.85; H, 3.36; N, 35.96.

3-Amino-1-(5-amino-5-deoxy-β-D-ribofuranosyl)-1,2,4-triazole (16). Compound **16** was prepared from **13** according to the procedure for **8** in 87% yield as a pale yellow oil. ^{1}H NMR (DMSO-d_6): δ 8.2 (s, 1H, H-5), 5.50 (d, 1H, $J = 4$ Hz, H-1′), 5.37 (s, 2H, OH-2′, OH-3′), 4.28 (m, 1H, H-2′), 4.08 (m, 1H, H-3′), 3.80 (m, 1H, H-4′), 3.50 (m, 2H, NH_2), 2.75 (dd, 1H, $J = 4.4$ Hz and 13.2 Hz, H-5′a), 2.66 (dd, 1H, $J = 6$ Hz and 13.2 Hz, H-5′b); mass spectrum (EI) m/e 216 ($M^+ + 1$, 10); Anal. for $C_7H_{13}N_5O_3$: C, 39.07; H, 6.09; N, 32.54; found: C, 39.13; H, 6.15; N, 32.42.

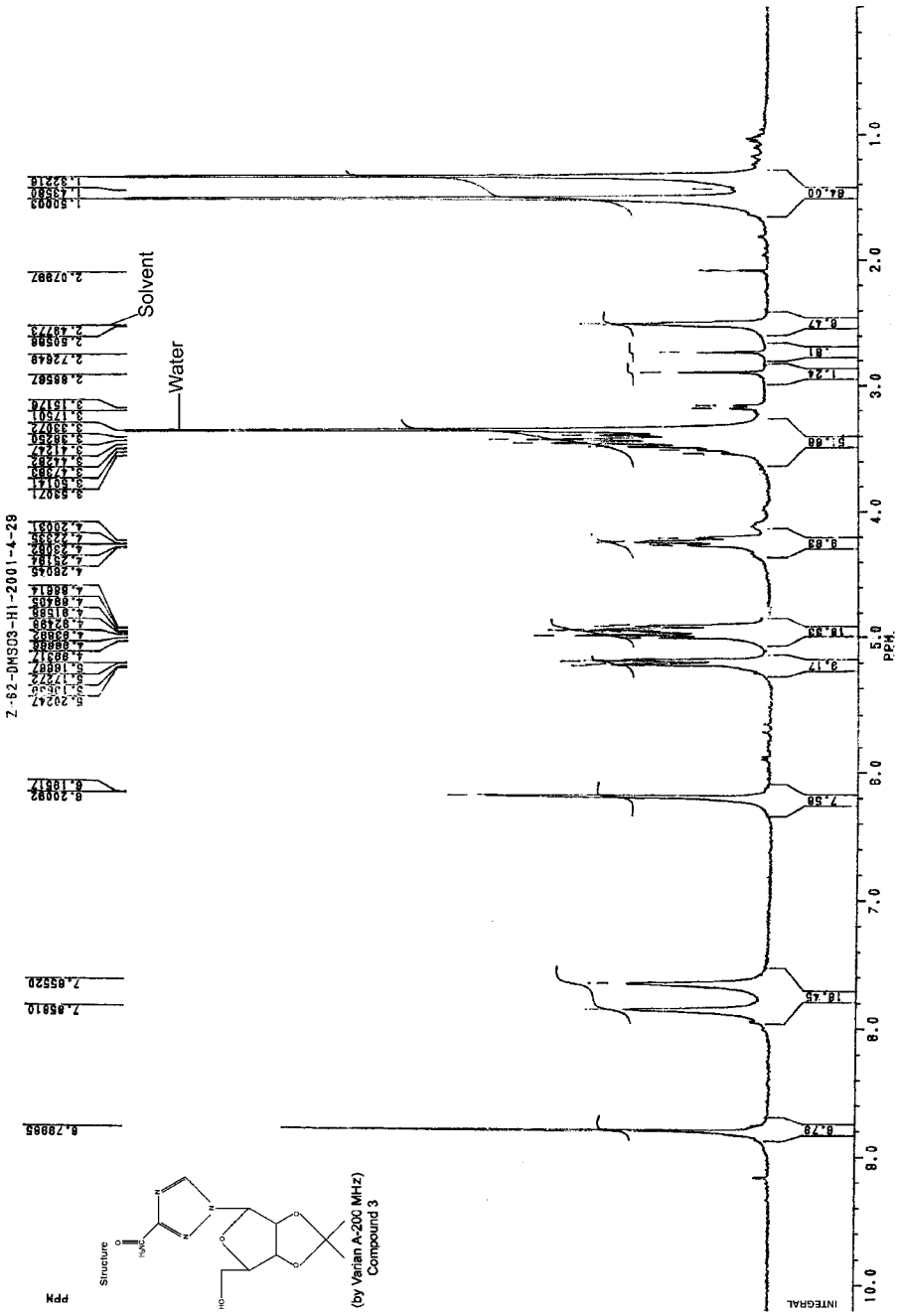
3-Nitro-1-(5-iodo-5-deoxy-β-D-ribofuranosyl)-1,2,4-triazole (17). Compound **17** was prepared from **12** according to the procedure for **9** in 89% yield as a colorless solid, mp: 107–109°C; ^{1}H NMR (DMSO-d_6): 9.10 (s, 1H, H-5), 5.99 (d, 1H, $J = 3.2$ Hz, H-1′), 5.79 (br s, 1H, OH-2′), 5.53 (br s, 1H, OH-3′), 4.48 (s, 1H, H-2′), 4.22–4.03 (m, 2H, H-3′, H-4′), 3.56–3.33 (m, 2H, H-5′); mass spectrum (EI) m/e 357 ($M^+ + 1$, 20); Anal. for $C_7H_9IN_4O_5$: C, 23.61; H, 2.55; N, 15.73; found: C, 23.50; H, 2.43; N, 15.45.

3-Amino-1-(5-deoxy-β-D-ribofuranosyl)-1,2,4-triazole (18). Compound **18** was prepared from **17** according to the procedure for **10** in 85% yield as a colorless solid, mp: 101–103°C; ^{1}H NMR (DMSO-d_6): δ 8.22 (s, 1H, H-5), 5.65 (d, 1H, $J = 3.8$ Hz, H-1′), 5.67 (d, 1H, $J = 3.2$ Hz, OH-2′), 5.49 (d, 1H, $J = 3.3$ Hz, OH-3′), 4.38 (d, 1H, $J = 4.0$ Hz, H-2′), 4.14 (t, 1H, $J = 5$ Hz, H-3′), 3.9 (m, 1H, H-4′), 1.21(dd, 3H, $J = 3.2$ Hz and 5.8 Hz, H-5′); mass spectrum (EI) m/e 199 ($M^+ - 1$, 14); Anal. for $C_7H_{12}N_4O_3$: C, 42.00; H, 6.04; N, 27.99; found: C, 41.92; H, 6.15; N, 27.75.

1-[2-*O*-Acetyl-3-chloro-3-deoxy-5-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]-1,2,4-triazole-3-carboxamide (19) and 1-[3-*O*-acetyl-2-chloro-2-deoxy-5-*O*-(2,5,5-trimethyl-1,3- dioxolan-4-on-2-yl)-β-D-arabinofuranosyl]-1,2,4-triazole-3-carboxamide (20). Compound **1** (230 mg, 0.9 mmol) was suspended in dry acetonitrile (20 mL). To this solution was slowly added 2-acetoxyisobutyryl chloride (540 mg, 2.7 mmol) in 10 mL of anhydrous acetonitrile with stirring at r.t.. After a clear solution was attained for about 20 min, stirring was continued for 4 h at 60°C. The solution was then cooled to room temperature, and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (100 mL), washed with satur. aqueous $NaHCO_3$ (2×30 mL), water (50 mL) and dried with anhydrous $MgSO_4$. The solvent was removed giving a pale yellow oily product (387 mg, 94% yield). The oily product was purified by silica gel column chromatography (CH_2Cl_2:MeOH = 97:3), a colorless foam was obtained (292 mg), which showed a 3 : 1 mixture of compounds **19**: **20**. ^{1}H NMR (DMSO-d_6) of **19**: δ 8.82 (s, 1H, H-5), 7.82 and 7.68 (2s, 2H, $CONH_2$), 6.20 (d, 1H, $J = 3.9$ Hz, H-1′), 5.76 (dd, 1H, $J = 4.2$ Hz and 3.3 Hz, H-2′), 4.86 (dd, 1H, $J = 3.3$ Hz and 6.6 Hz, H-3′), 4.38 (m, 1H, H-4′), 3.88 (dd, 1H, $J = 4.8$ Hz and 12.9 Hz, H-5′a), 3.59 (dd, 1H, $J = 6.2$ Hz and 12.9 Hz, H-5′b), 2.08 (s, 3H, OAc), 1.73 (s, 3H, CH_3CO_3), 1.49, 1.45 (2s, 6H, $(CH_3)_2C$); mass spectrum (EI) m/e 433 (M^+, 100).

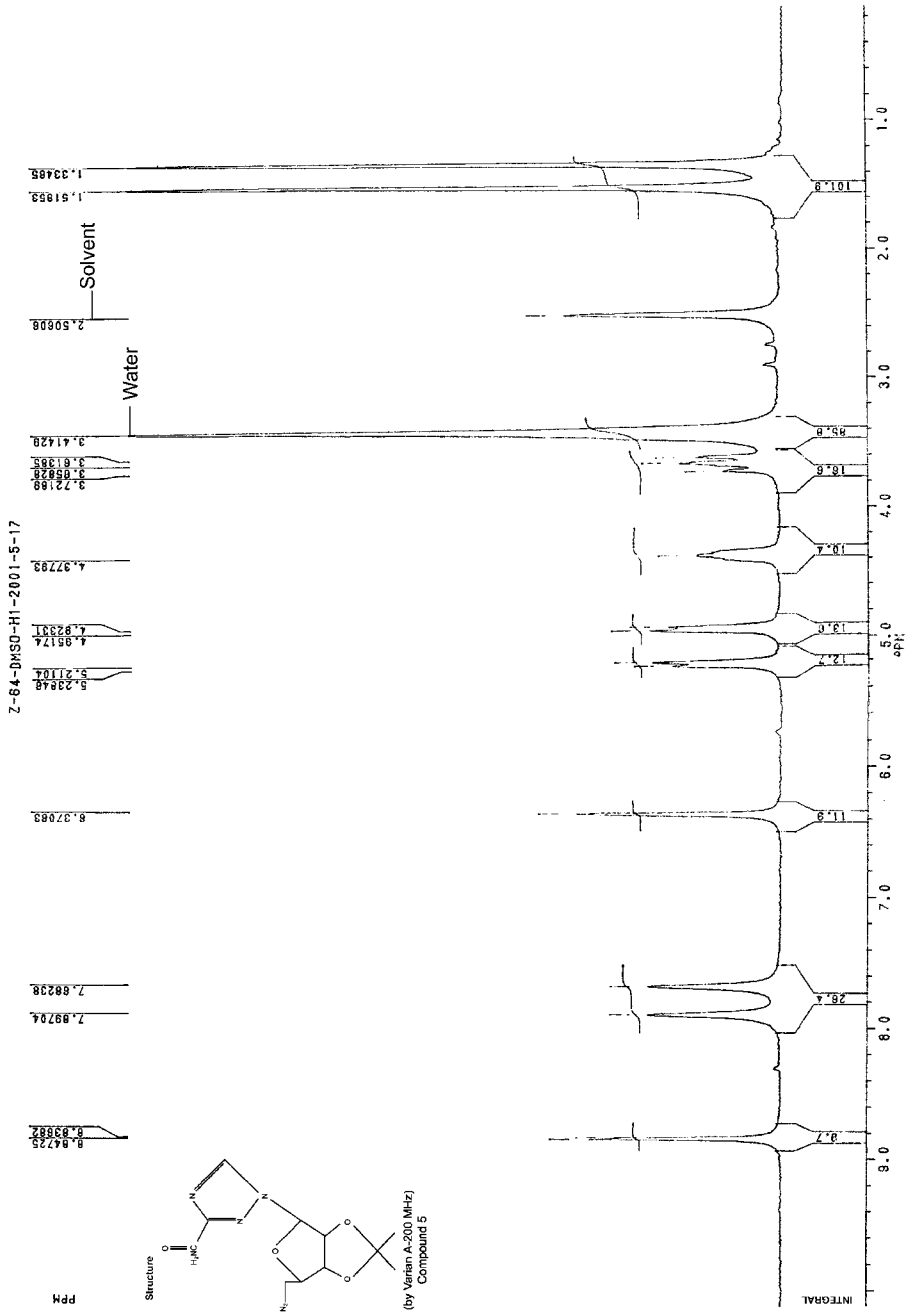
1-(2,3-Anhydro-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (21). Compound **19** (156 mg, 0.33 mmol) was dissolved in 15 mL of anhydrous MeCN, Zn/Cu (0.8 g) was added, the mixture was stirred overnight at r. t., the mixture was filtered through a celite pad, and the filtrate was evaporated under vacuum. The residue was dissolved in 0.5 g NaOMe in 20 mL of dry methanol, and the solution was stirred overnight at r. t. The solvent was removed, and the residue was purified by silica column chromatography (CH_2Cl_2:MeOH = 20:1) to give a colorless foam. ^{1}H NMR (DMSO-d_6): δ 8.77 (s, 1H, H-5), 7.91 and 7.69 (2s, 2H, $CONH_2$), 5.82 (d, 1H, $J = 2.6$ Hz, H-1′), 4.70 (s, 1H, H-2′), 4.48 (d, 1H, $J = 4.3$ Hz, H-3′), 3.73 (m, 1H, H-4′), 3.5 (m, 2H, H-5′); mass spectrum (EI) m/e 227 ($M^+ + 1$, 100); Anal. for $C_8H_{10}N_4O_4$: C, 42.48; H, 4.46; N, 24.77; found: C, 42.79; H, 4.76; N, 24.39.

1-[2-*O*-Acetyl-3-bromo-3-deoxy-5-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]-1,2,4-triazole-3-carboxamide (22). 2-Acetoxyisobutyryl chloride (10.29 g, 62.5 mmol) was added in a suspension solution of NaBr (24.4 g, 237 mmol) in 100 mL of anhydrous MeCN, and the mixture was stirred for 0.5 h at room temperature under N_2. Compound **1** (5 g, 20.5 mmol) was then added, and the resulting mixture was heated for 3 h at 70°C. The reaction solution was cooled to r. t., filtered, and most of the solvent was removed under vacuum with maintaining the temperature at lower than 40°C. Water (50 mL) was added into the residue, it was extracted with ethyl acetate (2×50 mL). The organic phases were washed with satur. aqueous $NaHCO_3$ (2×30 mL), water (2×30 mL), and dried with anhydrous $MgSO_4$. The solvent was removed to give a brown oily product (7.3 g, 74.8% yield). ^{1}H NMR (DMSO-d_6): δ 8.82 (s, 1H, H-5), 7.82 and 7.66 (2s, 2H, $CONH_2$), 6.20 (d, 1H, $J =$ 3.9 Hz, H-1′), 5.16 (dd, 1H, $J = 4.2$ Hz, H-2′), 4.86 (dd, 1H, $J = 3.3$ Hz and 6.6 Hz, H-3′), 4.38 (m, 1H, H-4′), 3.88 (dd, 1H, $J = 4.8$ Hz and 12.9 Hz, H-5′a), 3.61(dd, 1H, $J = 5.6$ Hz and 12.8 Hz, H-5′b), 2.09 (s, 3H, OAc), 1.73 (s, 3H, CH_3CO_3), 1.49



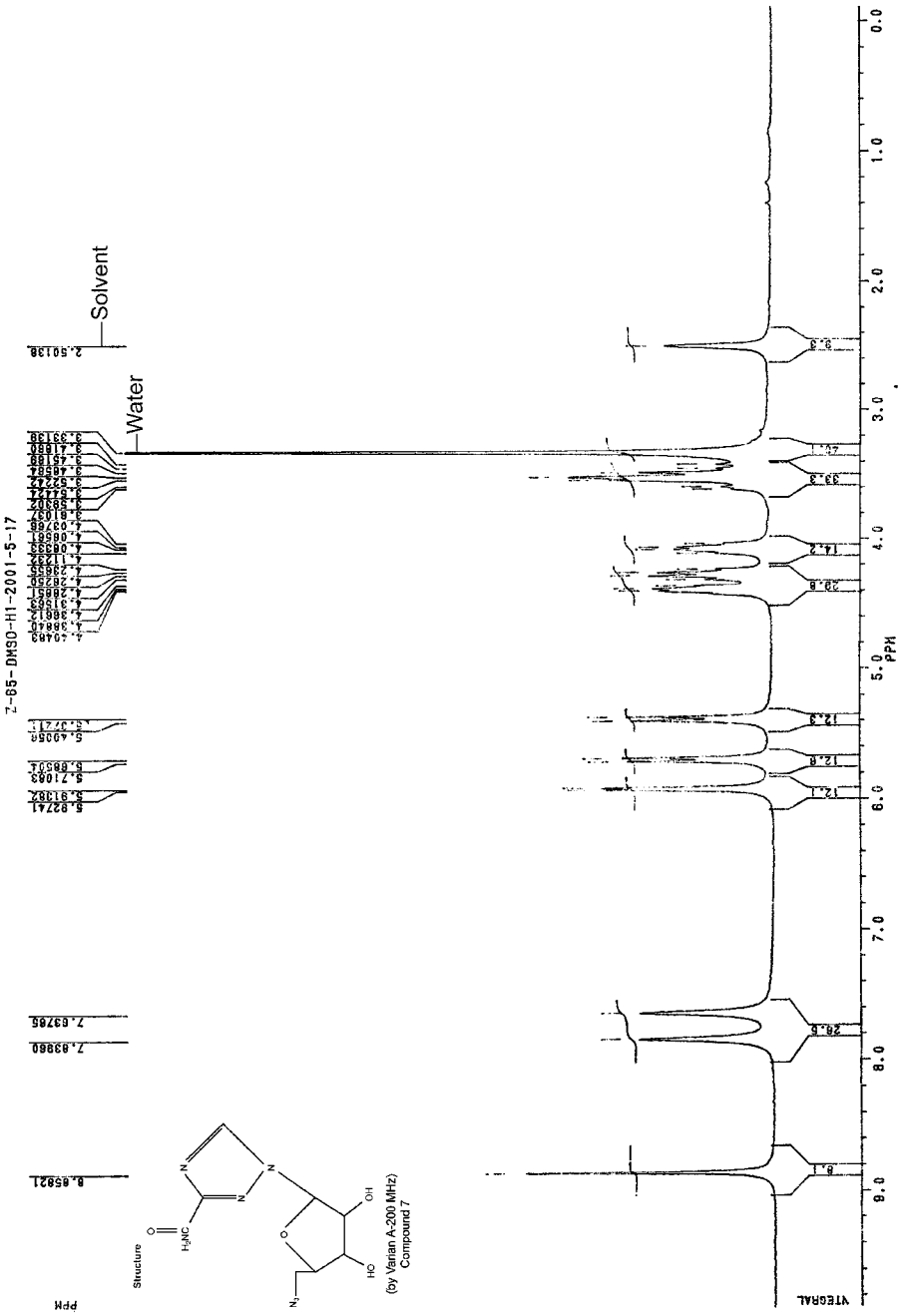
Compound 3.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016



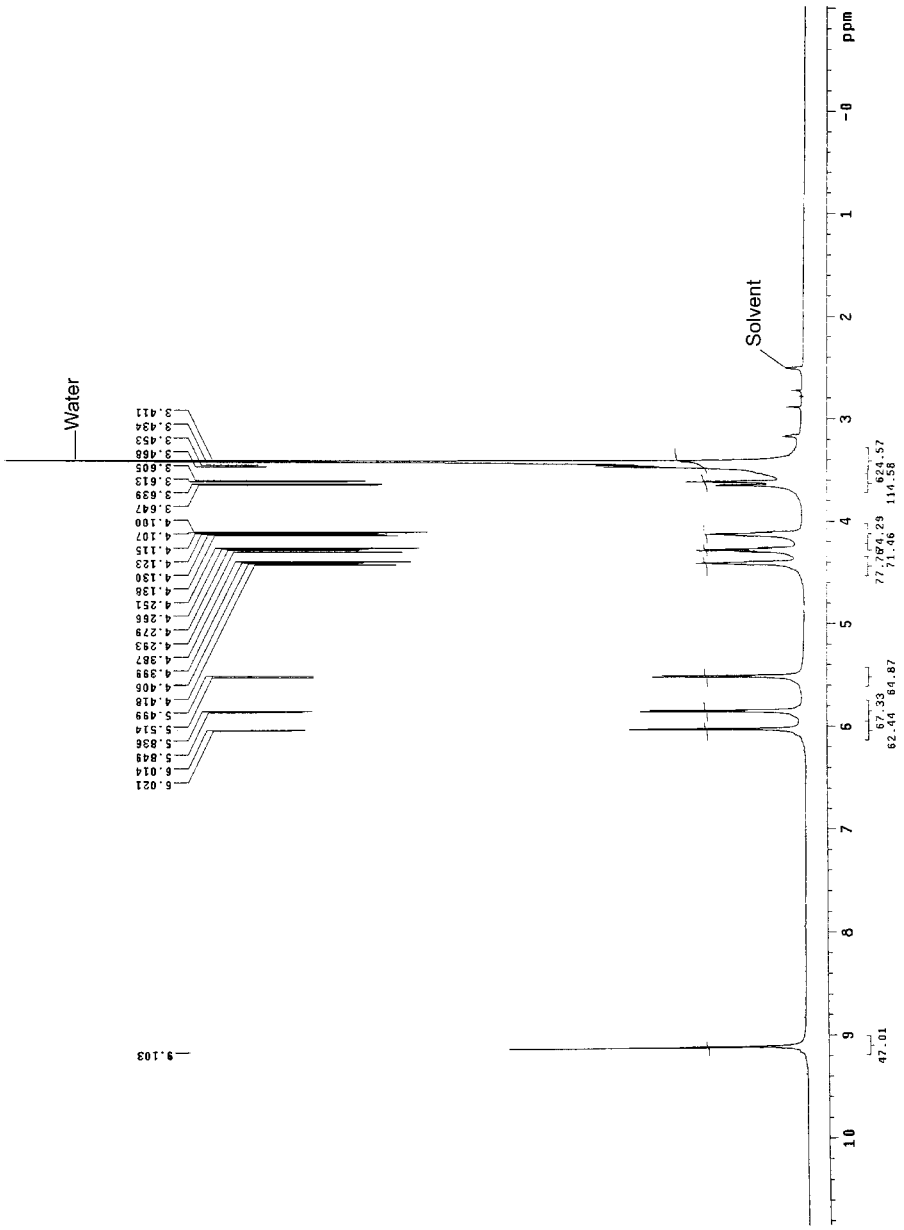
Compound 5.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016



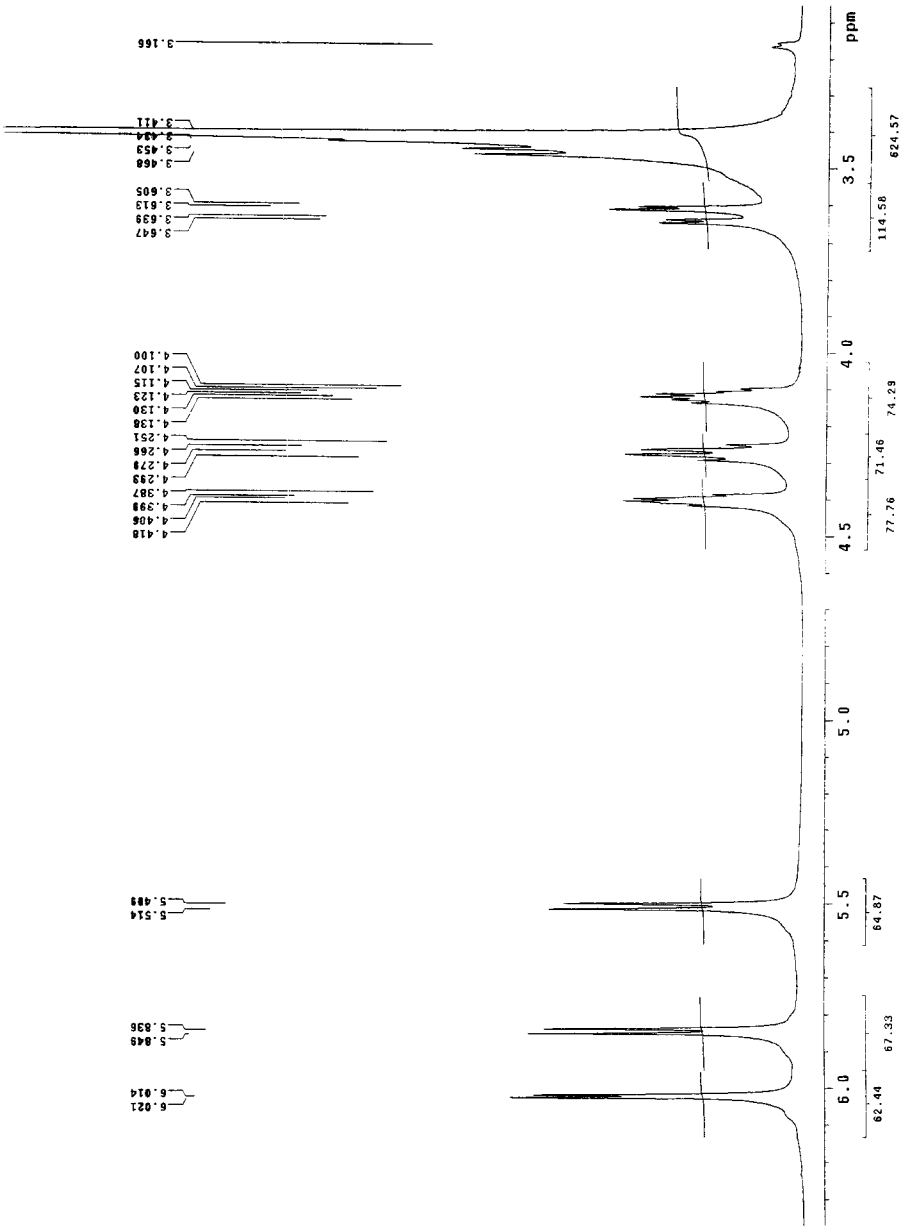
Compound 7.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016



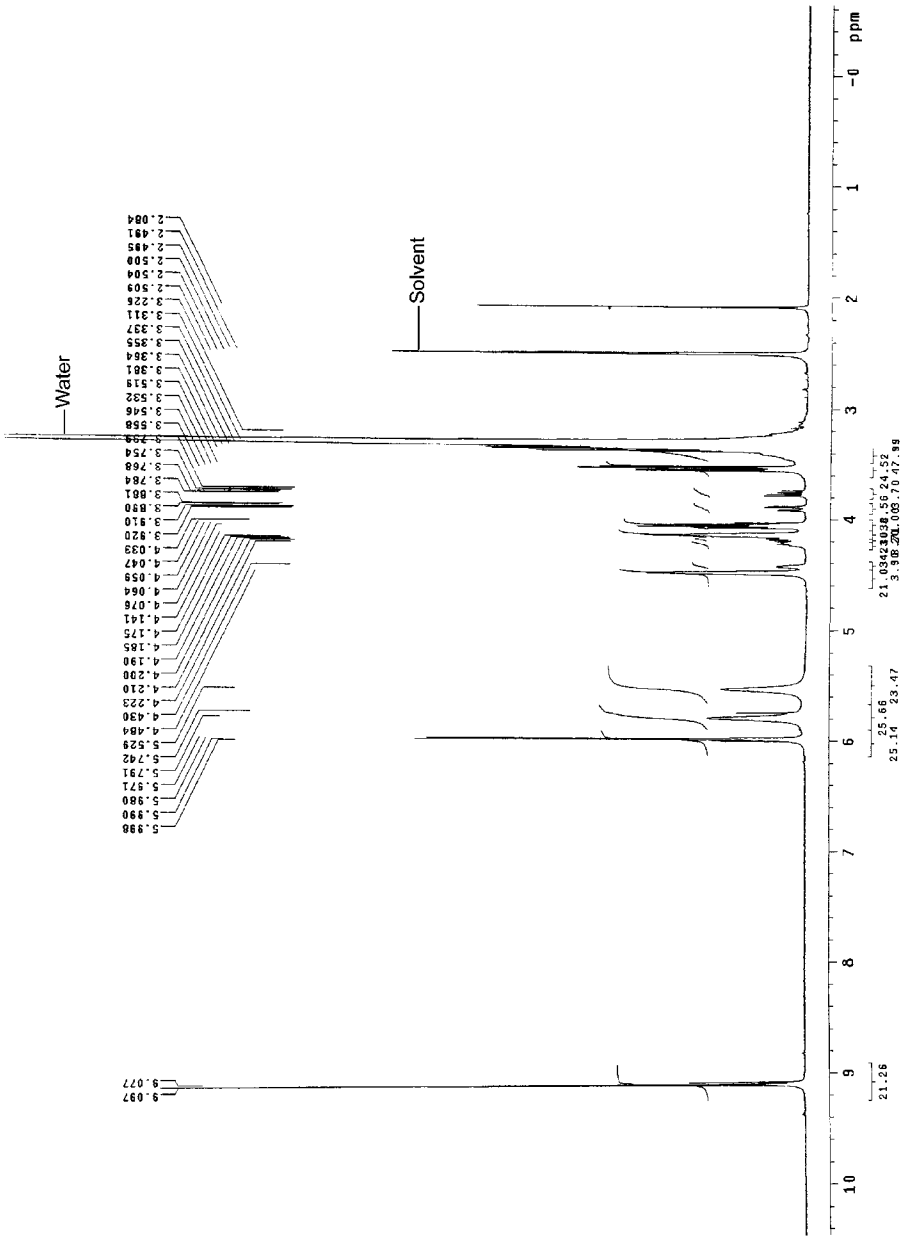
Compound 15.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

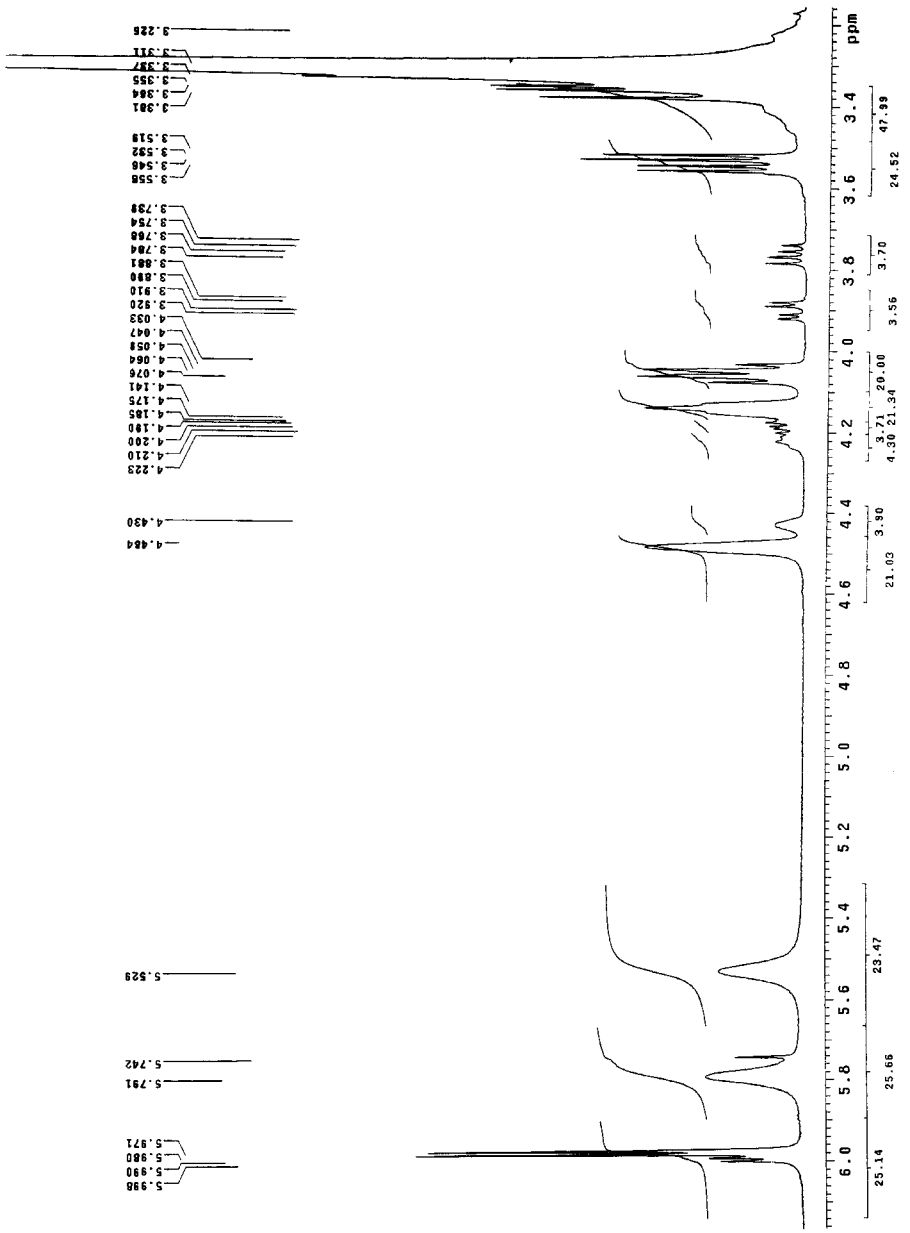


Compound 2.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016



Compound 17.



Compound 1.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

and 1.45 (2s, 6H, $(CH_3)_2C$); mass spectrum (EI) m/e 477 ($M^+ + 1$, 95), 479 ($M^+ + 3$, 100%).

1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-1,2,4-triazole-3-carboxamide (24). Compound **22** (7.2 g) was dissolved in 30 mL of anhydrous MeCN, to which was added 3.5 g of Zn/Cu and 1.5 mL of HOAc. The mixture was stirred for 5 h at r. t. filtered through a celite pad, and the filtrate was removed under vacuum. The residue was dissolved in 100 mL of ethyl acetate, organic phase was washed with 5% aqueous EDTA (2×50 mL), water (2×50 mL), and dried with anhydrous $MgSO_4$. The solvent was removed, and the residue was dissolved in 20 mL of methanol containing 0.3 g of NaOMe. The solution was stirred for 4 h at r. t., the solvent was removed, and the residue was purified by silica column chromatography to give a colorless foam (350 mg, 16% yield). ^{1}H NMR (acetone-d_6): δ 8.86 (s, 1H, H-5), 7.87 and 7.64 (2s, 2H, $CONH_2$), 7.29 (br s, 1H, H-1′), 6.67 (br s, 1H, H-3′), 5.91 (d, 1H, $J = 3.3$ Hz, H-2′), 4.18 (m, 1H, H-4′), 3.3–3.6 (m, 2H, H-5′); mass spectrum (EI) m/e 211 ($M^+ + 1$, 24%); Anal. for $C_8H_{10}N_4O_3$: C, 45.71; H, 4.80; N, 26.66; found: C, 45.92; H, 4.65; N, 26.79.

3-Nitro-1-[2-*O*-acetyl-3-bromo-3-deoxy-5-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]-1,2,4-triazole (23). Compound **23** was prepared according to procedure for **22** in 89% yield. mass spectrum (EI) m/e 481 ($M^+ + 1$, 5), 365 ($M^+ - 114$, 100).

3-Nitro-1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-1,2,4-triazole (25). Compound **25** was prepared from **23** according to the procedures for **24** to give a pale yellow foam in 21% yield. ^{1}H NMR (acetone-d_6): δ 8.99 (s, 1H, H-5), 7.21 (s, 1H, H-1′), 6.78 (s, 1H, H-3′), 5.94 (s, 1H, H-2′), 4.96 (m, 1H, H-4′), 3.52 (m, 2H, H-5′); mass spectrum (EI) m/e 212 (M^+, 7); Anal. for $C_7H_8N_4O_4$: C, 39.63; H, 3.80; N, 26.41; found: C, 39.51; H, 3.66; N, 26.75.

ACKNOWLEDGMENTS

This paper was supported by funding from Chengdu Molecule Laboratory, Hengdian Group, Zhejiang, P. R. China. The authors also thank the National Center for Drug Screening of China for biological activity test.

REFERENCES

1. 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-triazole-3-carboxamide and related nucleosides. J. Med. Chem. **1972**, *15* (11), 1150–1154.
2. AIDU. Drugs of the future **1982**, *7* (6), 375–377.
3. Hampton, A. Nucleosides. II. A new prepareation for the conversion of ribonucleosides to 2′,3′-*O*-isopropylidene derivatives. J. Chem. Soc. **1961**, *83*, 3640–3645.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

4. Jain, T.C.; Jenkins, I.D.; Russell, A.F.; Verheyden, J.P.H.; Moffatt, J.G. Reactions of 2-acyloxyisobutyryl halides with nucleosides. IV. A facile synthesis of 2′,3′-unsaturated nucleosides using chromous acetate. J. Org. Chem. **1974**, *39* (1), 30–38.
5. Greenberg, S.; Moffatt, J.G. Reactions of 2-acyloxyisobutyryl halides with nucleosides. I. Reactions of model diols and of uridine. J. Am. Chem. Soc. **1973**, *95* (12), 4016–4025.
6. Mattocks, A.R. Novel reactions of some α-acyloxy-acid halides. Part II. Some further examples. J. Chem. Soc. **1964**, 4840–4845.
7. Russell, A.F.; Greenberg, S.; Moffatt, J.G. Reactions of 2-acyloxyisobutyryl halides with nucleosides. II. Reactions of adenosine. J. Am. Chem. Soc. **1973**, *95* (12), 4025–4030.
8. Bhat, V.; Stocker, E.; Ugarkar, B.G. A new synthesis of 2′,3′-dideoxyinosine. Synth. Commun. **1992**, *22* (10), 1481–1486.
9. Mansuri, M.M.; Starrett, J.E.; Wos, J.A., Jr.; Tortolani, D.R.; Brodfuehrer, P.R.; Howell, H.G.; Martin, J.C. Preparation of 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (d4T) and 2′,3′-dideoxyadenosine (ddA): General methods for the synthesis of 2′,3′-olefinic and 2′,3′-dideoxy nucleoside anaolues active against HIV. J. Org. Chem. **1989**, *54*, 4780–4785.
10. Witkowski, J.T.; Robins, R.K. The chemical synthesis of the 1,2,4-triazole nucleosides related to uridine, 2′-deoxyuridine, thymidine, and cytidine. J. Org. Chem. **1970**, *35* (8), 2635–2641.

Received May 22, 2002
Accepted February 10, 2003

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016