Heteroatom Chemistry
Volume 15, Number 5, 2004

N- and *C*-Acyclic Thionuleoside Analogues of 1,2,3-Triazole

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Received 11 March 2004

ABSTRACT: *Cycloaddition of the azide derivative* **5** *with 1,4-dihydroxybutyne afforded the N-thio-acyclic nucleoside* **6**, *which prepared alternatively from coupling of the bromo derivative* **8** *with 2-acetoxyethylmercaptan. Deblocking of* **6** *gave the free nucleoside* **7**. *Mesylation of* **6** *furnished the dimesylate* **9**, *which gave three rearranged products* **14–16** *on treatment with chloride anion. These compounds might be obtained via the episulfonium ion* **10**, *which is subjected to nucleophilic displacement and further sulfur participation. Deblocking of* **14–16** *afforded the free nucleoside analogues* **17–19**, *and their structures were confirmed by COSY, ROESY, HMQC, and HMBC NMR techniques. Compound* **16** *was prepared alternatively from chlorination of alcohol* **6** *with* Ph_3P-CCl_4. *Carbomoylation of* **6** *led to the carbamate* **20**, *which gave the free nucleoside analogue* **21** *on deblocking.* © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:380–387, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20030

INTRODUCTION

The use of acyclonucleoside analogues as potent antiviral agents, such as the antiherpetic drug ACV (Acyclovir, Zovirax®), HBG, DHPG, PMEA, and HPMPA derivatives, has stimulated extensive research in the synthesis of this class of compound [1–6]. The importance of a polyhydroxyalkyl other or a polyhydroxyalkyl chain conformation in the interaction of acyclic nucleosides with enzymes has been witnessed [7], and the effectiveness and affinities for the viral thymidine kinase are varied because of the conformational factor. Tanaka et al. [8] prepared 1-[2-hydroxyethoxy)methyl]-6-(phenylthio)-thymine (HEPT) as an active compound against HIV-1, since other nucleoside analogues exhibited different activity such as benzyacyclouridine [9] as a potent inhibitor of uridinephosphorylase [10], as-triazine acyclonucleosides as inhibitor of ortidylatephosphoribosyltransferase [11], as well as 4-substituted 1-[(2-hydroxy-ethoxy)methyl]-1,2,3-triazol-(4,5)-ylmethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidines [12]. In last decade, a considerable interest by replacement of the oxygen atom of the side chain by sulfur atom has been reported [13]. Keller et al. [2] prepared a series of acyclic nucleosides including the thio analogues in an enzymatic phosphorylation study and correlations with antiherpetic and anti-HIV activities such as **1**, in addition to its activity aganist HIV (0.5 μg). Moreover, Yokoyama et al. [14] have synthesized a variety of 1,2,3-triazole derivatives bearing acyclic sugar moieties including compound **2** as promising anti-HSV-1 agents. The thio analogue of *C*-tiazofurins, **3** [15], is another example of this series. A review of acyclonucleosides

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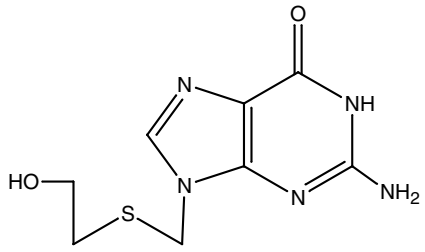

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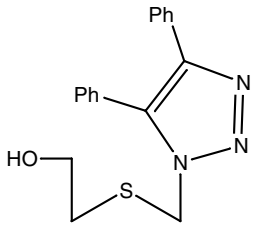

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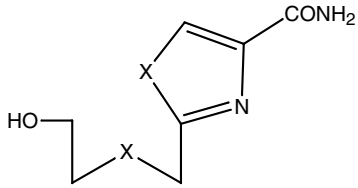

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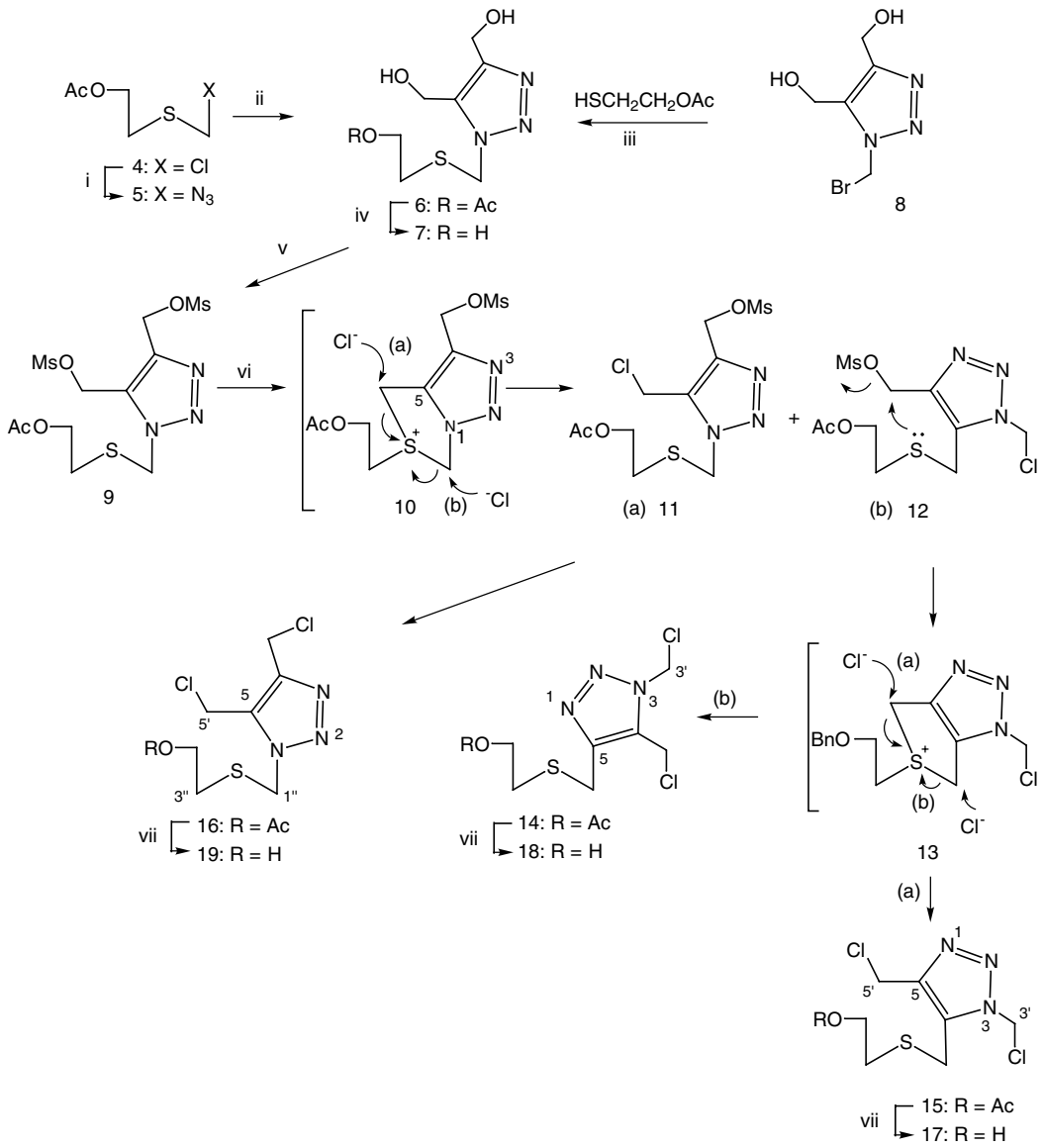
appeared recently [16]. In connection with our synthetic approaches on the synthesis of acyclic *N*- and *C*-nucleosides [17–20] and the 1,2,3-triazoles [21] and their carbamate analogues [22], we herein report on the synthesis of novel acyclic 1,2,3-triazole *N*-thionucleoside analogues bearing 1,2,3-triazole ring carrying potential halomethyl and carbamate groups in addition to their rearrangement to the *C*-thio acyclic analogues via the sulfur participation, as promising antiviral or antineoplastic agents. A few halomethyl nucleoside derivatives have been described with potential cytostatic activity [23,24], such as *N*-glycosyl(halomethyl)-1,2,3-triazoles [25] and 3-substituted-thymidine analogues [26] as alkylating and antiviral agents, respectively.

RESULTS AND DISCUSSION

One of the most fruitful approaches for the synthesis of 1,2,3-triazole rings is the 1,3-dipolar cycloaddition [27–29] between substituted acetylene and dipolarophiles and alkyl azide derivatives. The azide derivative **5** was prepared from the treatment of 4-acetoxyethylthio)methyl chloride (**4**) [13] with LiN_3 under nitrogen at 23°C (should store at low temperature) and allowed to react with 1,4-dihydroxybutyne in toluene–pyridine (10:1) under nitrogen at boiling temperature to give, after chromatography, the corresponding N-1-isomer **6** in 27%. The low yield of **6** might be explained in terms of the decomposition of the thioether moiety at high temperature. In an alternative method [30], the bromo derivative **8** [31] was boiled, under nitrogen, in THF with 2-mercaptoethylacetate in the presence of K_2CO_3 to afford **6** in a better yield (56%). Deacetylation of **6** was carried out with NH_3/MeOH at 23°C to yield **7** (72%). Treatment of the alcohol **6** with methanesulfonyl chloride in the presence of Et_3N as a catalyst and CH_2Cl_2 as a solvent at low temperature afforded, after purification by chromatography, the dimesylate derivative **9** (75%). The structures of compounds **5–9** were proven by ^{1}H NMR and mass spectra. The ^{1}H NMR of **5** showed a singlet at δ 4.07 and was attributed to CH_2N_3, since the two triplets at δ 3.62 and 2.76 with J coupling of 5.9 Hz were assigned to CH_2OAc and SCH_2, respectively. The IR of **5** showed a strong absorption at 2100 cm^{-1} that was attributed to the azide group. The ^{1}H NMR of **6**, **7**, and **9** showed similar signal patterns. CH_2-1″ appeared as singlets at δ 5.30, 5.35, and 5.38, respectively. The lower field triplets at δ 2.83, 2.78, and 2.89 were attributed to CH_2-3″, because of the influence of sulfur atom in comparison to those of the oxygen analogues [17,18]. The triplets (J 6.0 Hz) at δ 3.89, 3.75, and 3.91 were assigned to CH_2-4″, respectively. The two doublets at the region 4.01–4.67 were identified as CH_2-OH groups at C-4 and C-5 of the triazole ring, which concluded from comparison to the alcohol analogues prepared by de la Heras et al. [25], while the hydroxyl groups were identified by D_2O exchange. The mesylate groups of **9** appeared as two singlets at δ 3.12 and 3.01.

Next, our attempt was to study the displacement of the mesylate group of **9** by different potential active groups such as halogens. Thus, treatment of **9** with tetrabutylammoium chloride in a mixture of MeOH–CH_2Cl_2 as a solvent at 23°C gave three interesting minor rearranged products as oil, separated by chromatography. These products are tentatively identified as the 3,4-bis(chloromethyl)-*C*-nucleoside **14** (20%) (FABMS m/z 298/300 $[M+H]^+$), the 3,5-bis(chloromethyl)-*C*-analogue **15** (9%) [FABMS m/z (320/322 $[M+Na]^+$), and the 4,5-bis(chloromethyl)-*N*-nucleoside **16** (41%) (FABMS m/z 298/300 $[M+H]^+$). Deblocking of **14–16** with K_2CO_3 in MeOH at 23°C afforded chromatographically the pure free nucleoside analogues **17–19** in 80, 75 and 83% yield (Scheme 1). The structures of **14–19** were secured by homo- and heteronuclear NMR spectroscopic methods and by mass spectra. The *C*-nucleoside analogues **14**, **15**, **17**, and **18** showed similar pattern of spectra, where CH_2-1′ and CH_2-4″ appeared as multiplets in the region δ 3.34–3.48, while CH_2-3″ appeared as triplets in the region δ 2.56–2.62 ($J \sim 6.0$ Hz). The variation in the chemical shifts between *N*-CH_2Cl and *C*-CH_2Cl is clear, since the former protons appeared at higher field in the region δ 5.97–6.11, while the latter protons



SCHEME 1 Reagents and conditions: (i) LiN_3, DMF. 23°C; (ii) HO–CH_2–C≡C=CH_2OH; toluene/pyridine 10:1, reflux, 16 h; (iii) K_2CO_3, THF, reflux, 2 h; (iv) NH_3/MeOH, 23°C, 4 h; (v) MsCl, Et_3N, CH_2Cl_2, 0°C, 1 h; (vi) $BnEt_3N^+Cl^-$, MeOH/CH_2Cl_2, 23°C, 16 h; (vii) MeOH, K_2CO_3, 23°C, 7 h.

appeared at δ 4.91–4.91, both groups as singlets. The rotating frame nuclear Overhauser enhancement spectroscopy (ROESY) [32] suggested a small distance between CH_2-1″ and CH_2-4″ of **17** and **18**, and also confirmed the linkage of the thioether precursor to the triazole ring. The *C*-site attachment of C-1″ to C-4 and C-5 of the triazole ring of **17** and **18** was concluded from the COSY, HMQC [33], and HMBC [34] spectra, via the $^2J_{C,H}$ and $^3J_{C,H}$ correlations. Gradient selected HMBC spectrum of **17** showed $^2J_{C,H}$ correlations between CH_2-1″ (δ 3.34 and 3.38) and C-4 and C-5 (δ 133.5 and 133.7), respectively, confirming the *C*-alkylation in **17** and **18** as well as **14** and **15**. The $^3J_{C,H}$ correlations between CH_2-1″ and C-5 and C-3, respectively, is an additional proof for the *C*-alkylation. Furthermore, the long-range coupling between CH_2-4″ and C-4 and C-5 of the triazole ring of **17** and **18**, respectively, is an additional proof of the *C*-alkylation rather than *N*-alkylation. The ROESY spectrum of **17** showed cross signals of CH_2-1″ (δ 3.34) to N^3-CH_2Cl (δ 6.15) and to C_5-CH_2Cl (δ 4.98) protons; meanwhile, the same spectrum of **18** showed only one cross signal of CH_2-1″ at (δ 3.38) to C_4-CH_2Cl (δ 6.09), confirming the position of the CH_2Cl groups in the triazole ring.

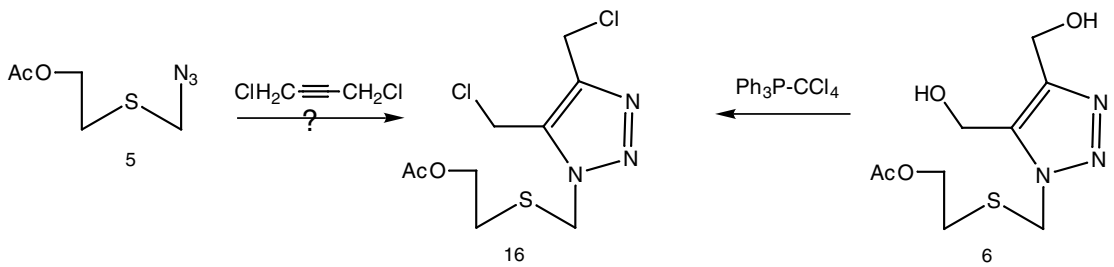
The structure of **19** was concluded from the ROESY and HMBC spectra as well as from the comparison of the ^{1}H NMR spectrum with those of 1-[2-(hydroxy)ethylthio]methyl-4,5-diphenyl-1,2,5-triazole [14], and was found to be consistent with the assigned structure, especially of the thioether group. As expected, the S-(CH_2-1″)-N group (δ 5.37) appeared at higher field in comparison to S-(CH_2-1″)-C groups of **17** and **18** (δ 3.34 and 3.38, respectively), confirming the *N*-site of the triazole ring of **19**. Furthermore, the gradient selected ^{1}H-^{13}C HSQC [35] spectrum of **19** made possible assignments of the carbon resonance, since CH_2-1″ at δ 5.20 is coupled to C-1″ at δ 69.1. Furthermore, the structures of **19** were determined from the ^{1}H NMR spectrum. The triplet resonance of CH_2-3″ and CH_2-4″ at δ 2.78 and 2.79 are coupled to C-3″ and C-4″ at δ 29.1 and 55.9, respectively. The HMBC spectrum revealed two $^2J_{C,H}$ couplings between both methylene (CH_2Cl) groups (δ 4.87, 5.11) and C-4 (δ 37.0) and C-5 (δ 32.1), respectively. The same spectral analysis for the acetate analogue **16** was observed.

With respect to our earlier and recent work on thiosugars, we investigated [36,37] the nucleophilic displacement reactions of the sulfonate esters to obtain products either with retention of configuration or ring contraction. The mechanistic pathway of such reactions was suggested [38] to proceed via the reactive intermediate episulfonium ions such as **10**, formed by sulfur participation. This intermediate was attacked spontaneously by the chloride ion at C-5′ to give **11** or C-1″ furnished **12**. A similar mesylate group displacement of **12** by chlorine via sulfur participation would lead to both compounds **14** and **15**; meanwhile, displacement of the mesylate group of **11** by chlorine via SN_2 reaction would furnish the *N*-nucleoside **16**, as shown in Scheme 1.

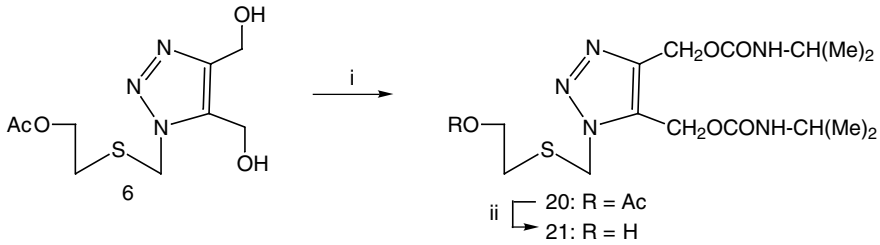
The synthesis of **16** was investigated by an alternative route to improve the yield percentage. Thus, 1,3-dipolar cycloaddition of **4** with 1,4-dichlorobutyne gave a complex mixture, which could not be separated by chromatography. However, conversion of the hydroxyl groups of **6** by treatment with triphenyl phosphite-CCl_4 in CH_3CN at 23°C under nitrogen for 72 h gave after chromatography a better yield of **16** (67%), in comparison to the above experiments (Scheme 2). The ^{1}H NMR of **16** showed identical chemical shifts, while the molecular ion was detected by FABMS *m/z* 298/300 $[M+H]^+$.

Recent studies showed that some carbamates [39,40] exhibited in vitro potential antineoplastic activity against HL-60 human leukaemia and HT-29 human colon carcinoma cells. These findings prompted us to use the alcohol **6** to synthesize new, promising potential carbamates. Thus, treatment of **6** with isopropyl isocyanate in the presence of $Sn(Bu)_2(OAc)_2$ as a catalyst in CH_2Cl_2 under nitrogen at 23°C for 5 h afforded chromatographically **20** (60%) as a syrup. Deblocking of **20** with K_2CO_3 in MeOH at 23°C for 5 h gave, after chromatographic purification, the free carbamate analogue **21** (76%) as a foam (Scheme 3). The structures of **20** and **21** were deduced from the ^{1}H NMR and mass spectra as well as from comparison to those of **16** and the carbamate derivative prepared previously [22]. CH_2-1″ appeared as singlets at δ 5.37 and 5.39, respectively, while the triplets at δ 3.90 and 3.71 (J 6.0 Hz) were attributed to CH_2-3″. The triplet and multiplet at δ 2.82 and 2.76 were assigned to CH_2-4″, respectively. The two methylene protons of the carbamate group at C-4 and C-5 resonated for **20** and **21** as two singlets at δ 5.17 and 5.17, respectively, while the $CH(Me)_2$ protons appeared as multiplets at δ 3.65 and 3.67, respectively. The two doublets of $CH(Me)_2$ groups of each compound were resonated at δ 1.17, 0.91 and 1.19, 9.95, respectively.

In conclusion, the 1,3-dipolar cycloaddition of the acyclic thioether azide with 1,4-dihydroxybutyne furnished the triazole nucleoside analogues in a good yield, while cyclization with 1,4-dichlorobutyne was unsuccessful. The nucleophilic displacement of the triazole ring bears CH_2-sulphonate ester groups by chlorine anion gave *N*- and *C*-nucleoside analogues via spontaneous sulfur participation. Direct conversion of the CH_2-hydroxy groups of the triazole ring



SCHEME 2



SCHEME 3 Reagents and conditions: (i) Me_2CHNCO, $Sn(Bu)_2(OAc)_2$; (ii) K_2CO_3–MeOH, 23°C, 5 h.

by Ph_3PCCl_4 afforded the dichloro derivative with retention of the *N*-site of the nucleoside.

EXPERIMENTAL

*4-Acetoxyethylthiomethylazide (**5**)*

To a solution of NaN_3 (0.31 g, 4.67 mmol) in 20 mL of anhydr DMF was added 1.0 g (4.67 mmol) of freshly prepared distilled compound **4** and the resulting mixture was heated at 80°C under nitrogen, with stirring for 4 h. The solid was filtered and washed with DMF (3 × 7 mL), and the combined filtrate was partitioned between water (70 mL) and ether (4 × 30 mL). After drying over anhydrous Na_2SO_4, the solvent was evaporated and the oil obtained was purified by column of chromatography (SiO_2, hexane) to give **5** (0.67 g, 82%) as a pale yellow oil. IR (CCl_4): 2100 cm^{-1} (N_3), 1731 cm^{-1} (COMe); ^1H NMR ($CDCl_3$): δ 4.07 (s, 2H, N_3—CH_2), 3.62 (t, 2H, $J = 5.9$ Hz, CH_2OAc), 2.76 (t, 2H, $J = 5.9$ Hz, S-CH_2), 1.96 (s, 3H, OAc); MS (FAB) *m/z* (%): 176 (77) $[M + H]^+$. Exact mass ($C_5H_9N_3O_2S$) calculated: 176.2189 $[M + H]^+$; found: 175.2181.

*1-[(2-Acetoxyethylthio)methyl]-4,5-bis(hydroxymethyl)-1,2,3-triazole (**6**)*

Method A. A solution of **5** (700 mg, 4.00 mmol) and 2-butyne-1,4-diol (21.6 mmol) in 30 mL of a mixture of toluene–pyridine (10:1) was refluxed under nitrogen for 16 h. The solvents were evaporated to dryness, and the residue was partitioned between water (30 mL) and CH_2Cl_2 (4 × 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was chromatographed onto a silica gel column, using, in gradient, MeOH (0–1%) and CH_2Cl_2 as eluent to give **6** (280 mg, 27%) as an oil. ^1H NMR (DMSO-d_6): δ 5.35 (m, 2H, $2CH_2OH$), 5.30 (s, 2H, CH_2-1″), 4.60, 4.51 (2d, 4H, 2 × CH_2OH), 3.89 (t, 2H, $J = 6.0$ Hz, CH_2-4″), 2.83 (t, 2H, $J = 6.0$ Hz, CH_2-3″), 2.02 (s, 3H, OAc); MS (FAB) *m/z* (%): 284 (92) $[M + Na]^+$. Exact mass ($C_9H_{15}N_3O_4S$) calculated: 284.2910 $[M + Na]^+$; found: 284.2902.

Method B. A mixture of **8** (200 mg, 0.90 mmol), 2-mercaptoethylacetate (460 mg, 3.83 mmol), and K_2CO_3 (595 mg, 4.30 mmol) in dry THF (30 mL) was heated and refluxed under nitrogen for 2 h. After cooling, the solution was evaporated to dryness and the residue was partitioned between CH_2Cl_2 (2 × 20 mL) and water (25 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was purified on a column of silica gel (7 g) using, in gradient, MeOH (0–1%) and CH_2Cl_2 to give **6** (560 mg, 56%), as a colorless oil, which has identical ^1H NMR and mass data in comparison with those of the authentic sample prepared in method A.

*1-[(2-Hydroxyethylthio)methyl]-4,5-bis(hydroxymethyl)-1,2,3-triazole (**7**)*

A solution of **6** (200 mg, 0.77 mmol) in 16% NH_3/MeOH solution (7 mL) was stirred at 2°C for 3 h. The solution was evaporated to dryness and the residue was purified on SiO_2 column (5 g), using, in gradient, MeOH (0–2%) and CH_2Cl_2 to give **7** (121 mg, 72%) as an oil. ^1H NMR (DMSO-d_6): δ 5.39 (m, 2H, $2CH_2OH$), 5.35 (s, 2H, CH_2-1″), 4.67, 4.55 (2d, 4H, 2 × CH_2OH), 3.75 (t, 2H, $J = 6.0$ Hz, CH_2-4″), 2.78 (t, 2H, $J = 6.0$ Hz, CH_2-3″); MS (FAB) *m/z* (%): 220 (89) $[M + H]^+$. Exact mass ($C_7H_{13}N_3O_3S$) calculated: 220.2720 $[M + H]^+$; found: 220.2713.

*1-[(2-Acetoxyethylthio)methyl]-4,5-bis(methanesulfonylmethyl)-1,2,3-triazole (**9**)*

The diol **6** (500 mg, 2.28 mmol) in dry CH_2Cl_2 (15 mL) containing Et_3N (1.7 mL) and the solution was stirred and cooled to 0°C. A cold solution of methanesulfonyl chloride (0.70 mL) in dry CH_2Cl_2 (15 mL) was added slowly, under nitrogen, to the above stirred solution. After about 1 h, water (30 mL)

was added and the mixture was separated. The organic extract was washed with ice-cold dil. aqueous $NaHCO_3$ (30 mL), dried (Na_2SO_4), filtered and evaporated to dryness to give an amorphous product. The residue was purified on a SiO_2 column (10 g) using ethyl acetate- hexane (1:3) as eluent to give **9** (714 mg, 75%); as an amorphous product. ^{1}H NMR ($CDCl_3$): δ 5.38 (s, 2H, CH_2-1″), 5.21, 5.03 (2d, 4H, 2 × CH_2O-), 3.91 (t, 2H, $J = 5.8$ Hz, CH_2-4″), 3.12, 3.01 (2s, 6H, 2 × SO_2Me), 2.89 (t, 2H, $J = 5.8$ Hz, CH_2-3″); MS (FAB) *m/z* (%): 440 (89) $[M + Na]^+$. For $C_{11}H_{19}N_3O_8S_3$ (417.5) calculated: 31.65% C, 4.59% H, 10.07% N; found: 31.46% C, 4.09 H, 9.78% N.

Reaction of the Dimesylate **9** *with Chloro Nucleophile*

A mixture of **9** (500 mg, 2.27 mmol) and benzylammonium chloride (850 mg, mmol) in a mixture of MeOH (30 mL) and CH_2Cl_2 (10 mL) was stirred for 16 h at 23°C. The solution was evaporated to dryness and the residue was partitioned between water (30 mL) and CH_2Cl_2 (3 × 20 mL), and evaporation of the combined organic extracts yielded a mixture of three products (monitored by TLC). The mixture was chromatographed on SiO_2 column (12 g) and eluted, in gradient, with MeOH (0–1%) and CH_2Cl_2 to give first a pure syrup, tentatively identified as 5-[(2-acetoxyethylthio)methyl]-3,4-bis(chloromethyl)-1,2,3-triazole **14** (135 mg, 20%) as a syrup. ^{1}H NMR ($CDCl_3$): δ 6.11 (s, 2H, $ClCH_2$-3′), 4.95 (s, 2H, $ClCH_2$-4′), 3.88 (t, 2H, $J = 5.5$ Hz, CH_2-4″), 3.43 (s, 2H, CH_2-1″), 2.79 (t, 2H, $J = 5.5$ Hz, CH_2-3″), 2.02 (s, 3H, OAc); MS (FAB) *m/z* (%): 298/300 (78) $[M + H]^+$. Exact mass ($C_9H_{13}Cl_2N_3O_2S$) calculated: 299.2006 $[M + H]^+$. Found: 299.1981.

The second fraction was characterized as 4-[(2-acetoxyethylthio)methyl]-3,5-bis(chloromethyl)-1,2,3-triazole **15** (72 mg, 9%), as a syrupy product. ^{1}H NMR (CDCl3): δ 5.97 (s, 2H, $ClCH_2$-3′), 4.91 (s, 2H, $ClCH_2$-5′), 3.85 (t, 2H, $J = 5.6$ Hz, CH_2-4″), 3.48 (s, 2H, CH_2-1″), 2.77 (t, 2H, $J = 5.6$ Hz, CH_2-3″), 1.98 (s, 3H, OAc); MS (FAB) *m/z* (%): 320/322 (70) $[M + Na]^+$. Exact mass ($C_9H_{13}Cl_2N_3O_2S$) calculated: 299.2006 $[M + H]^+$; found: 299.1989.

The third fraction was identified as 1-[(2-acetoxyethylthio)methyl]-4,5-bis-(chloromethyl)-1,2,3-triazole **16** (278 mg, 41 %). ^{1}H NMR ($CDCl_3$): δ 5.37 (s, 2H, CH_2-1″), 5.04 (s, 2H, $ClCH_2$-5′), 4.82 (s, 2H, $ClCH_2$-4′), 3.87 (t, 2H, $J = 6.0$ Hz, CH_2-4″), 2.84 (t, 2H, $J = 6.0$ Hz, CH_2-3″), 1.98 (s, 3H, OAc); MS (FAB) *m/z* (%): 298/300 (90) $[M + H]^+$. Exact mass ($C_9H_{13}Cl_2N_3O_2S$) calculated: 299.2006 $[M + H]^+$. Found: 299.1984.

Deprotection of the Acylated Nucleoside Analogues **14–16**

General Procedure. A solution of the protected nucleoside analogues **14–16** (300 mg, 1.00 mmol) in dry MeOH (10 mL) containing K_2CO_3 (167 mg, 1.21 mmol) was stirred at 23°C for 7 h. The solvent was evaporated to dryness and the residue was purified on SiO_2 column (7 g) using ethyl acetate–petroleum ether (1:1), which yielded the pure free nucleoside analogues **17–19**, as oil.

*3,4-Bis(chloromethyl)-5-[(2-hydroxyethylthio)-methyl]-1,2,3-triazole (***17***)*

Yield 205 mg (80%); ^{1}H NMR (DMSO-d_6/D_2O, 600 MHz, HMBC): δ 6.15 (s, 2H, $ClCH_2$-3′), 4.98 (s, 2H, $ClCH_2$-4′), 3.71 (t, 2H, $J = 6.5$ Hz, CH_2-4″), 3.34 (s, 2H, CH_2-1″), 2.78 (t, 2H, $J = 6.5$ Hz, CH_2-3″); ^{13}C NMR (DMSO-d_6): 133.5 (C-4), 132.7 (C-5), 65.0 ($ClCH_2$-3′), 54.7 (C-4″), 43.9 (C-1″), 36.0 ($ClCH_2$-4′), 28.9 (C-3″); MS (FAB) *m/z* (%): 278/280 (85) $[M + Na]^+$. Exact mass ($C_7H_{11}Cl_2N_3OS$) calculated: 279.1453 $[M + Na]^+$; found: 279.1432.

*3,5-Bis(chloromethyl)-4-[(2-hydroxyethylthio)-methyl]-1,2,3-triazole (***18***)*

Yield 192 mg (75%); ^{1}H NMR (DMSO-d_6/D_2O, 600 MHz, HMBC): δ 6.09 (s, 2H, $ClCH_2$-4′), 4.91 (s, 2H, $ClCH_2$-5′), 3.70 (t, 2H, $J = 6.2$ Hz, CH_2-4″), 3.38 (s, 2H, CH_2-1″), 2.75 (t, 2H, $J = 6.2$ Hz, CH_2-3″); ^{13}C NMR (DMSO-d_6): 133.7 (C-5), 132.9 (C-4), 65.2 ($ClCH_2$-3′), 54.8 (C-4″), 43.0 (C-1″), 36.1 ($ClCH_2$-3′), 28.8 (C-3″); MS (FAB) *m/z* (%): 257/259 (90) $[M + H]^+$. Exact mass ($C_7H_{11}Cl_2N_3OS$) calculated: 257.1633 $[M + H]^+$. Found: 257.1623.

*4,5-Bis(chloromethyl)-1-[(2-hydroxyethylthio)-methyl]-1,2,3-triazole (***19***)*

Yield 213 mg (83%); ^{1}H NMR (DMSO-d_6/D_2O, 600 MHz, HMBC): δ 5.20 (s, 2H, CH_2-1″), 5.11 (s, 2H, $ClCH_2$-5′), 4.87 (s, 2H, $ClCH_2$-4′), 3.79 (t, 2H, $J = 6.2$ Hz, CH-4″), 2.78 (t, 2H, $J = 6.2$ Hz, CH-3″); ^{13}C NMR (DMSO-d_6): δ 134.7 (C-4), 134.3 (C-5), 69.1 (C-1″), 55.9 (C-4″), 37.0 ($ClCH_2$-4′), 32.1 ($ClCH_2$-5′), 29.1 (C-3″); MS (FAB) *m/z* (%): 278/280 (88) $[M + Na]^+$. Exact mass ($C_7H_{11}Cl_2N_3OS$) calculated: 279.1453 $[M + Na]^+$; found: 279.1438.

Reaction of **5** *with 1,4-Dichlorobutyne*

A solution of **5** (100 mg, 0.57 mmol) in anhydrous toluene (10 mL) and 1,4-dichloroacetylene (283 mg,

2.30 mmol) was refluxed for 4.5 h. After cooling, the solution was evaporated to dryness and the residue was partitioned between CH_2Cl_2 (3 × 15 mL) and water (15 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness to give a brown residue (TLC showed a complex mixture), which was difficult to separate by chromatography.

Reaction of **6** *with Triphenylphosphine and* CCl_4

To a solution of **6** (100 mg, 0.38 mmol) in dry CH_3CN (5 mL) were added Ph_3P (105 mg, 0.40 mmol) and CCl_4 (1 mL) and the solution was stirred at 23°C. After 16 h, an additional amount of Ph_3P (105 m) and CCl_4 (1 mL) was added. The reaction was completed after 72 h. Evaporation of the mixture afforded a crude oil which was worked up as in the previous experiment, and the residue was purified on a SiO_2 column (5 g). Elution with ethyl acetate–petroleum ether (1.1) gave **16** (76 mg, 67%) as a syrup, which had physical properties identical with those of the authentic sample prepared previously from the dimesylate **9**.

*1-[(2-Acetoxyethylthio)methyl]-4,5-dimethaol-4,5-bis(isopropylcarbamate)-1,2,3-triazole (***20***)*

A mixture of **6** (230 mg, 0.81 mmol), isopropyl isocyanate (755 mg, 2.20 mmol), and $Sn(Bu)_2(OAc)_2$ (105 mg, 0.30 mmol) in CH_2Cl_2 (20 mL) was stirred under nitrogen at 23°C for 5 h. The solution was evaporated and the residue was partitioned between CH_2Cl_2 (3 × 15 mL) and water (15 mL). The combined organic extracts were dried (Na_2SO4), filtered, and evaporated to dryness. The residue was purified on a SiO_2 column (10 g) using, in gradient, MeOH (0–2%) and CH_2Cl_2 to give **20** (210 mg, 60%) as a syrup. ^{1}H NMR ($CDCl_3$): MS (FAB) *m/z* (%): 432 (90) $[M + H]^+$. For $C_{17}H_{29}Cl_2N_5O_6S$ (431.5) calculated: 47.32% C, 6.77% H, 16.23% N; found: 47.02% C, 6.67 H, 15.92% N. ^{1}H NMR ($CDCl_3$): δ 7.33 (br s, 1H, NH), 5.37 (s, 2H, CH_2-1″), 5.22 (s, 4H, CH_2-4′, CH_2-5′), 3.90 (t, 2H, $J = 6.0$ Hz, CH_2-4″), 2.82 (t, 2H, $J = 6.0$ Hz, CH_2-3″), 3.65 (m, 2H, $CHMe_2$), 1.98 (s, 3H, OAc), 1.02 (d, 6H, $CHMe_2$), 0.89 (d, 6H, $CHMe_2$); MS (FAB) *m/z* (%): 454 (82) $[M + Na]^+$. Exact mass ($C_{17}H_{29}N_5O_6S$) calculated: 432.5200 $[M+H]^+$; found: 432.5189.

*1-[(2-Hydroxyethylthio)methyl]-4,5-dimethaol-4,5-bis(isopropylcarbamate)-1,2,3-triazole (***21***)*

A solution of **20** (150 mg, 0.35 mmol) in anhydrous MeOH (5 mL) containing K_2CO_3 (57 mg, 0.42 mmol) was stirred at 23°C for 16 h. The reaction mixture was worked up as in **17** to give **20** (103 mg, 76%) as a foam. ^{1}H NMR (DMSO-d_6/D_2O): δ 5.39 (s, 2H, CH_2-1″), 5.17 (s, 4H, CH_2-4′, CH_2-5′), 3.71 (m, 2H, CH_2-4″), 2.76 (t, 2H, $J = 6.0$ Hz, CH_2-3″), 3.67 (m, 2H, $CHMe_2$), 1.19 (d, 6H, $CHMe_2$), 0.95 (d, 6H, $CHMe_2$); MS (FAB) *m/z* (%): 390 (95) $[M + H]^+$. For $C_{15}H_{27}N_5O_5S.H_2O$ (423.5) calculated: 42.54% C, 6.90% H, 16.54% N; found: 42.31% C, 6.79%H, 16.21% N.

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