Efficient Synthesis of Fused Isothiazole C-Nucleosides. 2. Synthesis of 8-Aza-7,9-deaza-7-thiaguanosine and 8-Aza-7,9-deaza-7-thiaadenosine

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Recently we have reported the synthesis of the purine-like isothiazolo[4,5-*d*]pyrimidine C-nucleoside **1** and the corresponding α-isomer from the 4-amino-3-β-D-ribofuranosylisothiazole-5-carboxylates **2β** and **2α**.[1] Now, we want to describe the preparation of the guanosine and adenosine related C-nucleosides **3** and **4**.

Synthesis of **3** was carried out by a procedure starting from isothiazole C-nucleoside **2β** reported with some modifications for the conversion of blocked 3-amino-4-β-D-ribofuranosyl-1*H*-pyrrole-2-carboxylate into 9-deazaguanosine.[2] The original procedure for guanosine starting with the 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICAR)[3] and benzoyl isothiocyanate could not be applied for **2β**, as the carbethoxy group of **2β** did not undergo ammonolysis.

Thus, **2β** was treated with benzoyl isothiocyanate in dry dichloromethane at 25 °C for 48 h to afford after chromatographic separation the 4-[(*N*-benzoylthiocarbamoyl)amino]isothiazole derivative **5β** in 93% yield. Deprotonation of **5β** with sodium hydride in dichloromethane and subsequent addition of methyl iodide gave after 3 h at rt and chromatographic purification the protected 4-[(*N*-benzoyl-*S*-methylthiocarbamoyl)amino]-isothiazole C-nucleoside **6β** with no trace of the other anomer. A methyl signal at δ 2.41 in the ^{1}H NMR spectrum of **6β** confirmed the exclusive S-methylation of **5β**. **5β** and **6β** were obtained as crystalline compounds. Cyclization of **6β** was effected with methanolic NH_3 in a sealed vessel. After 16 h heating at 90–100 °C the reaction was completed and thin-layer chromatography of the reaction mixture showed the formation of two products.

After chromatographic separation, spectroscopic data confirmed that the less-polar product was the 5-(methylthio)-3-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)isothiazolo[4,5-*d*]pyrimidin-7(6*H*)-one (**7β**) (51% yield). The more-polar compound turned out to be the desired, fully blocked 5-aminoisothiazolo[4,5-*d*]pyrimidin-7(6*H*)-one C-nucleoside **8β** (47% yield).

7β and **8β** were characterized by their elemental analysis and ^{1}H/^{13}C NMR, IR, and mass spectra. In the ^{1}H NMR spectrum **7β** revealed a broad NH signal at δ 13.19 and a singlet signal (SCH_3 group) at δ 2.48, whereas **8β** showed a broad NH_2 signal at δ 6.74. The β-configuration of both compounds was confirmed by the 4′-H signals appearing as multiplets in accordance with empirical studies of several 2,3-O-isopropylidenated N- and C-nucleosides.[4]

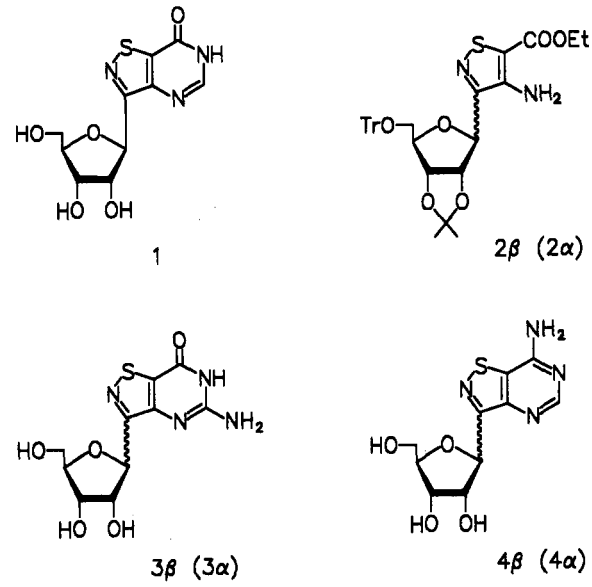

Figure 1.

As in the conversion of 3-amino-4-β-D-ribofuranosyl-1*H*-pyrrole-2-carboxylate into 9-deazaguanosine[2] and of 4-amino-3-β-D-ribofuranosylpyrazole-5-carboxamide into 5-aminoformycin B[5] by using the benzoyl isothiocyanate method, the formation of corresponding 5-methylthio analogs to **7β** was also reported.

Upon applying this procedure to α-isomeric isothiazole **2α**, the α-C-nucleosides **7α** and **8α** were accessible, too. Thus, treatment of **2α** with benzoyl isothiocyanate followed by methylation of the resulting thioureido α-derivative **5α** (93% yield) gave protected *S*-methylthioureido derivative **6α** in 91% yield, which was cyclized to the 5-(methylthio)-3-(2,3-*O*-isopropylidene-5-*O*-trityl-α-D-ribofuranosyl)isothiazolo[4,5-*d*]pyrimidine (**7α**) (31% yield) and the more-polar 5-amino α-C-nucleoside **8α** (67% yield), respectively, by heating in MeOH/NH_3 (Scheme 1). Compound **7α** was characterized by its NH signal in the ^{1}H NMR spectrum at δ 11.48 and the methyl singlet at δ 2.52, and **8α** by the broad NH_2 signal at δ 6.66. The 4′-H signals of **7α** and **8α** appearing as pseudotriplets confirmed their α-configuration.[4] Other spectroscopic data indicated as well that no anomerization occurred during the conversion of **2β** into **7β** and **8β** and **2α** into **7α** and **8α**.

All attempts to convert 5-methylthio C-nucleosides **7β** or **7α** to the 5-amino derivatives **8β** (**8α**) by treatment with methanolic NH_3 were unsuccessful. Thus, formation of **8α,β** from **7α,β** as intermediates could be excluded. Further mechanistic investigations showed that although compound **2β** and the α-isomer were resistant to ammonolysis upon treatment **6β** (**6α**) with MeOH/NH_3 at 25 °C an unexpected ammonolysis of the carbethoxy group was observed and the corresponding amides **6β′** (**6α′**) were obtained in 91 and 90% yield, respectively. Only by raising the reaction temperature did these amides then undergo ring closure to **7β** and **8β** (**7α** and **8α**). The ratio of the β- and α-5-amino *vs* the 5-methylthio derivatives was,

(1) Wamhoff, H.; Berressem, R.; Nieger, M. *J. Org. Chem.* **1993**, *58*, 5181.
(2) Lim, M.-I.; Ren, W.-Y.; Otter, B. A.; Klein, R. S. *J. Org. Chem.* **1983**, *48*, 780.
(3) Yamazaki, A.; Okutzu, M. *J. Heterocycl. Chem.* **1978**, *15*, 353.
(4) (a) Ohrui, H.; Jones, G. H.; Moffat, J. G.; Maddox, M. L.; Christensen, A. T.; Byram, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4602. (b) Cousineau, T. J.; Secrist, J. A., III. *J. Org. Chem.* **1979**, *44*, 4351. (c) Poonian, M. S.; Nawoswiat, E. F. *Ibid.* **1980**, *45*, 203. (d) Logue, M. S.; Sarangan, S. *Nucleosides Nucleotides* **1982**, *1*, 89.
(5) Lewis, A. F.; Townsend, L. B. *J. Am. Chem. Soc.* **1982**, *104*, 1073.

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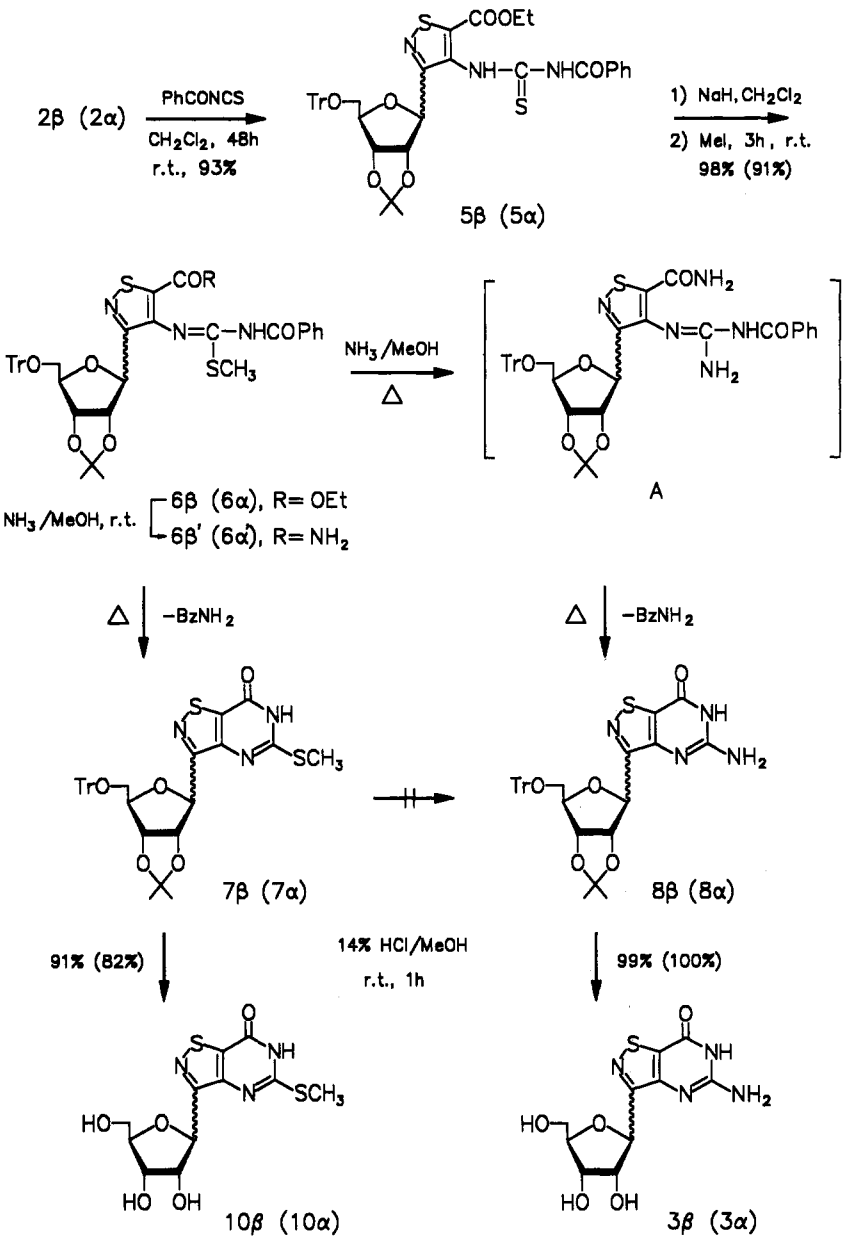
Scheme 1



regardless of the configuration at C-1′, about 2:1 to 1:1. Experiments with different ammonia concentrations showed that lower ammonia concentrations led to a lower yield of the 5-amino nucleosides and favored the formation of the 5-methylthio derivatives 7β and 7α. Thus, as shown in Scheme 1 a direct nucleophilic attack of the amide NH_2 group of 6β′ (6α′) at the carbamoyl C atom with loss of benzamide was expected to lead to the 5-methylthio nucleosides. Higher ammonia concentrations favor the substitution of the methylthio group by NH_2 and subsequent ring closure of the resulting guanidine intermediates A yields the 5-amino derivatives 8β and 8α, respectively.

Deprotection of blocked C-nucleosides 8β and 8α with 14% methanolic HCl at 25 °C for 1 h afforded the 8-aza-7,9-deaza-7-thiaguanosine (3β) and the α-isomer 3α, respectively, as monohydrochloride salts in nearly quantitative yields. The free 5-(methylthio)-3-β-D-ribofuranosylisothiazolo[4,5-*d*]pyrimidin-7(6*H*)-one (10β) and the α-epimer 10α were obtained from 7β and 7α in 91 and 82% yield (Scheme 1).

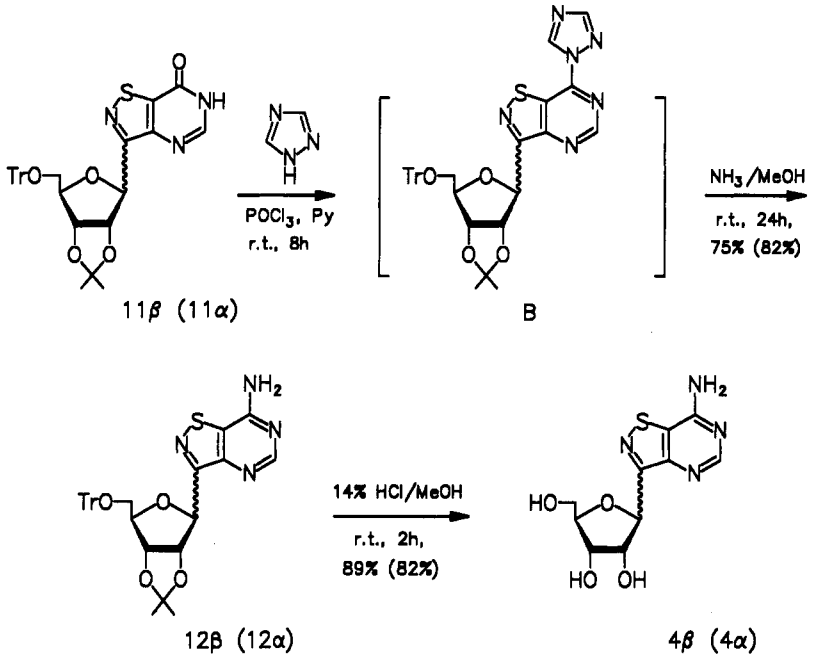
Adenosine-like nucleosides are accessible by standard cyclization procedures from heterocyclic enamino nitriles.[6] As the preparation of a C-glycosidic 4-aminoisothiazole-5-carbonitrile by treatment of the corresponding tosyloximino nitrile precursor[1] with 2-mercaptoacetonitrile or by transformation of C-nucleoside 2β failed, an alternative approach to the 8-aza-7,9-deaza-7-thiaadenosine 4β was developed.

Synthesis of 4β was accomplished starting from protected isothiazolo[4,5-*d*]pyrimidin-7(6*H*)-one C-nucleoside[1] 11β using a modified procedure originally reported by Divakar and Reese[7] to convert uracil nucleosides into corresponding 4-amino- and 4-(*N*,*N*-dialkylamino)pyrimidine derivatives. To our knowledge, there exist no other examples, in which this method has been specifically applied to a heterocondensed ring system. Other methods

(6) (a) Taylor, E. C.; McKillop, A. The Chemistry of Cyclic Enaminonitriles and o-Aminonitriles. In *Advanced Organic Chemistry*; Wiley-Interscience: New York, 1970; Vol. 7, Chapter VIII, p 243. (b) Lim, M.-I.; Klein, R. S. *Tetrahedron Lett.* **1981**, *22*, 25. (c) Bhattacharya, B. K.; Lim, M.-I.; Otter, B. A.; Klein, R. S. *Tetrahedron Lett.* **1986**, *27*, 815.

(7) Divakar, K. J.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1171.

Scheme 2



to convert inosine and related nucleosides into 6-aminopurines,[8] in the case of 11β, turned out to be much less efficient.

Thus, as shown in Scheme 2, treatment of 11β with tris(1,2,4-1*H*-triazolyl)phosphine oxide[7] in pyridine at 25 °C for 8 h gave the 7-triazolyl intermediate **B**, which was not isolated, but directly converted into the 7-amino nucleoside 12β by addition of methanolic ammonia to the reaction mixture. After chromatographic separation the 7-amino-3-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)isothiazolo[4,5-*d*]pyrimidine (12β) could be isolated in 75% yield as the only product. It was identified by the broad singlet signal of the NH_2 group at δ 5.72 in the ^1H NMR spectrum and the multiplet of the 4′-H signal typically for β-configured 2,3-*O*-isopropylidenated nucleosides.[4] The mass spectrum revealed a molecular ion at *m/z* 566 (M^+). Analogously, 7-amino α-nucleoside 12α was obtained from 11α in 82% yield. The spectroscopic data indicated the α-configuration (4′-H: pseudotriplet at δ 4.60). Comparison of the ^1H NMR data of 12β and 12α additionally confirmed the stereochemical assignment at C-1′.[9] Thus, the 1′-H signal for 12β (δ 5.58) appeared at higher field than that for 12α (δ 6.02) and the smaller difference between the Me-shifts (Δδ) of the isopropylidene group of 12α provided its α-configuration (7.2 Hz for 12α vs 46.0 Hz for 12β).

Deprotection of 12β and 12α with 14% HCl/MeOH for 2 h at 25 °C gave the 8-aza-7,9-deaza-7-thiaadenosine 4β and the α-C-nucleoside 4α as monohydrochloride salts in 89 and 82% yield, respectively (Scheme 2).

(8) (a) Fox, J. J.; Wempen, I.; Hampton, A.; Doerr, I. L. *J. Am. Chem. Soc.* **1958**, *80*, 1669. (b) Zemlicka, J.; Šorm, F. *Collect. Czech. Chem. Commun.* **1965**, *30*, 1880. (c) Long, R. A.; Lewis, A. F.; Robins, R. K.; Townsend, L. B. *J. Chem. Soc.* **1971**, 2443. (d) Reese, C. B.; Ubasawa, A. *Tetrahedron Lett.* **1980**, *21*, 2265. (e) Sung, W. L. *J. Chem. Soc., Chem. Commun.* **1981**, 1089. (f) Robins, M. J.; Uznanski, B. *Can. J. Chem.* **1981**, *59*, 2601. (g) Matsuda, A.; Obi, K.; Miyasaka, T. *Chem. Pharm. Bull.* **1985**, *33*, 2575. (h) Zhou, X. X.; Welch, C. J.; Chattopadhyaya, J. *Acta Chem. Scand.* **1986**, *B40*, 806. (i) Adamiak, R. W.; Biala, E.; Gdaniec, Z.; Mielewczyk, S.; Skalski, B. *Chem. Scr.* **1986**, *26*, 7. (j) Herdewijn, P.; Van Aerschot, A. *Nucleosides Nucleotides* **1989**, *8*, 933.

(9) See ref 1 and refs cited therein.

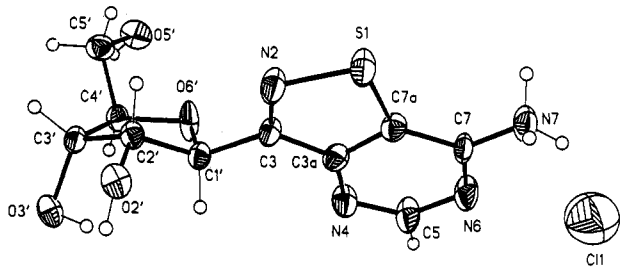


Figure 2. Perspective view and atom labeling of the crystal structure of 7-amino-3-β-D-ribofuranosylisothiazolo[4,5-*d*]pyrimidine 4β (50% probability thermal ellipsoids).

Primary screening of the 8-aza-7,9-deaza-7-thiapurine C-nucleosides described above and those in ref 1 up to 100 μM showed no antiviral properties against HIV, HCMV, HSV, and rhinoviruses. However, in cell culture the 7-amino nucleoside 4β and the α-isomer 4α exhibited cytotoxic effects in concentrations of 0.1 and 1 μM, respectively. Detailed investigations of the biological activities are in progress, and the results will be published elsewhere.

X-ray Crystallographic Analysis. The configuration of 4β was confirmed by X-ray crystallography. As shown in Figure 2, the ribofuranosyl-ring exhibits the C-1′-exo-C-2′-endo conformation. The molecule is in the anti conformation.

Crystal data: $C_{10}H_{13}ClN_4O_4S$, M_r = 320.8, colorless blocks, crystal dimensions 0.5 × 0.9 × 1.0 mm, crystallized from EtOH; orthorhombic, space group $P2_12_12_1$, a = 7.408(1), b = 9.824(2), c = 17.258(4) Å, V = 1255.9(1) Å^3, Z = 4, d_{calc} = 1.696 g/cm^3, λ(Mo Kα) = 0.71073 Å, μ(Mo Kα) = 0.49 mm^{-1}, F(000) = 664.2206 symmetry-independent reflections measured on an Siemens R3m/V diffractometer at 25 °C ($2\Theta_{max}$ = 50°, ω-scans, scan range 1.20°), 2113 reflections with $|F| > 3\sigma(F)$ used for structure solution (direct methods) and refinement (full-matrix least-squares, 192 parameters), non-hydrogen atoms refined anisotropically, H atoms localized by difference electron density determination and refined by means of a "riding" model; R = 0.077 (R_w = 0.082, $w^{-1} = \sigma^2(F) + 0.0010F^2$), the absolute

configuration was confirmed by η-refinement (η = 0.9(3)), largest peak in final difference Fourier map 1.13 e Å^{-3}. Structure solved and refined with SHELXTL-Plus.

Experimental Section

Melting points were not corrected. Microanalyses were carried out by the analytical laboratory of the Institute. The yields refer to analytically pure compounds. TLC was performed with Merck silica gel plates 60 F_{254} and column chromatography by standard techniques on Merck silica gel 60 (70–230 mesh). Light petroleum ether (bp 40–60 °C) was used whenever this solvent was required. The following instruments were used for spectroscopic measurements. UV: Cary-17; IR: Perkin-Elmer 157-G; MS: A.E.I. (Kratos) MS-50, 70 eV; ^{1}H NMR and ^{13}C NMR: Bruker WH-90, AC-200, and AM-400.

The NMR spectra were measured at 90, 200, and 400 MHz. TMS at 0.0 ppm was used as the internal standard for the ^{1}H NMR spectra, and the central line of either $CDCl_3$ (δ 77.0) or DMSO-d_6 (δ 39.5) was referenced in ^{13}C NMR spectra. Marked (*) intensities of molecular ion peaks indicate that the mass spectra were measured by the fast atom bombardment technique.

Ethyl 4-[(Benzoylthiocarbamoyl)amino]-3-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)isothiazole-5-carboxylates (5β and 5α). A solution of isothiazole C-nucleoside 2β (2α) and benzoyl isothiocyanate in dichloromethane (20 mL) was stirred at 25 °C for 48 h under anhydrous conditions. After evaporation of the reaction mixture, the syrup obtained was chromatographed on silica gel (petroleum ether–ethyl acetate, 2:1) to afford 5β (5α) after crystallization from petroleum ether/ethyl acetate, as white precipitates.

β-Isomer 5β (1.4 g, 93%) was obtained from 2β (1.2 g, 2.05 mmol) and 0.3 mL (2.25 mmol) of benzoyl isothiocyanate: mp 85 °C (2-propanol); IR (KBr) 3390, 3130 (NH), 1715, 1670 (C=O), 1590 cm^{-1} (C=C, C=N); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.41 (dd, 1 H, J = 6.4, 3.6 Hz, 2'-H), 5.35 (d, 1 H, J = 3.8 Hz, 1'-H), 4.69 (dd, 1 H, J = 6.4, 2.8 Hz, 3'-H), 4.39 (t, 1 H, J = 3.2 Hz, 4'-H), 3.04 (d, 2 H, J = 5.2 Hz, 5'a,b-H), 4.37 (q, 2 H, J = 7.6 Hz, CH_2), 1.37 (t, 3 H, J = 7.2 Hz, CH_3), 1.57 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 7.88–7.46 (m, benzoyl), 7.40–7.12 (m, trityl), 12.36 (br s, 1 H, NH) 9.20 (br s, 1 H, NH); ^{13}C NMR (200 MHz, $CDCl_3$) δ 180.30 (C=S), 166.52, 165.27 (C=O), 159.00 (C-4), 148.96 (C-3), 134.27 (C-5), 133.75, 131.33, 129.11, 127.69 (benzoyl), 143.72, 128.60, 127.78, 126.94, 86.60 (trityl), 85.10 (C-1'), 83.56 (C-4'), 82.82 (C-2'), 82.31 (C-3'), 63.97 (C-5'), 113.54, 27.30, 25.45 ($C(CH_3)_2$), 62.23, 14.11 (OCH_2CH_3); MS m/z 749 (M^+, 0.3*). Anal. Calcd for $C_{41}H_{39}N_3O_7S_2$: C, 65.69; H, 5.21; N, 5.62. Found: C, 65.45; H, 5.40; N, 5.55.

2α (1 g, 1.71 mmol) and 0.25 mL (1.88 mmol) of benzoyl isothiocyanate gave 1.2 g (93%) of **α-epimer 5α**: mp 105 °C (EtOH); IR (KBr) 3410, 3140 (NH), 1720, 1675 (C=O), 1595 cm^{-1} (C=C, C=N); ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.25 (t, 1 H, J = 6.0 Hz, 2'-H), 5.81 (d, 1 H, J = 4.8 Hz, 1'-H), 4.80 (d, 1 H, J = 6.2 Hz, 3'-H), 4.48 (m, 1 H, 4'-H), 3.54 (dd, 1 H, J = 10.1, 3.0 Hz, 5'a-H), 3.17 (dd, 1 H, J = 10.1, 3.8 Hz, 5'b-H), 4.39 (q, 2 H, J = 7.6 Hz), 1.38 (t, 3 H, J = 7.2 Hz, CH_3), 1.23 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 7.89–7.45 (m, 5 H, benzoyl), 7.33–7.11 (m, 15 H, trityl), 12.26 (br s, 1 H, NH), 9.14 (br s, 1 H, NH); ^{13}C NMR (200 MHz, $CDCl_3$) δ 180.31 (C=S), 166.49, 163.46 (C=O), 159.18 (C-4), 148.34 (C-3), 133.48 (C-5), 133.71, 131.23, 129.02, 127.62 (benzoyl), 143.43, 128.55, 127.89, 127.02, 87.37 (trityl), 83.41 (C-1'), 83.27 (C-4'), 82.14 (C-3'), 82.04 (C-2'), 65.42 (C-5'), 112.93, 25.96, 24.90 ($C(CH_3)_2$), 62.07, 14.05 (OCH_2CH_3); MS m/z 749 (M^+, 11.6*). Anal. Calcd for $C_{41}H_{39}N_3O_7S_2$: C, 65.69; H, 5.21; N, 5.62. Found: C, 65.25; H, 5.30; N, 5.90.

Ethyl 4-[(*N*-Benzoyl-*S*-methylthiocarbamoyl)amino]-3-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)isothiazole-5-carboxylates (6β and 6α). To a solution of the thioureido derivatives 5β (5α) in dry dichloromethane (50 mL) was added NaH. After the H_2 evolution was finished, methyl iodide was added and the reaction mixture was stirred at 25 °C for 3 h with exclusion from moisture. After evaporation the residue was treated with ethyl acetate and filtered, and the filtrate was flash-chromatographed on silica gel (20 g). After evaporation the colorless syrup obtained was crystallized from petroleum ether/ethyl acetate to afford 6β (6α) as white solid.

Compound 6β (2.2 g, 98%) was obtained from 5β (2.2 g, 3.0 mmol), 0.09 g (3.0 mmol) NaH, and 0.7 mL (11.8 mmol) methyl iodide: mp 132 °C (ether/ethyl acetate); IR (KBr) 3280 (NH), 1695, 1675 (C=O), 1630 cm^{-1} (C=N); ^{1}H NMR (200 MHz, DMSO-d_6) δ 5.09 (dd, 1 H, J = 5.8, 2.7 Hz, 2'-H), 5.04 (d, 1 H, J = 3.2 Hz, 1'-H), 4.51 (dd, 1 H, J = 6.4, 3.4 Hz, 3'-H), 4.17 (m, 1 H, 4'-H), 3.03 (m, 2 H, 5'a,b-H), 4.25 (q, 2 H, J = 7.1 Hz, CH_2), 2.41 (s, 3 H, SCH_3), 1.48 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.26 (t, 3 H, CH_3), 7.61–7.16 (m, 20 H, trityl and benzoyl), 10.74 (br s, 1 H, NH); ^{13}C NMR (200 MHz, DMSO-d_6) δ 165.29, 163.25 (C=O), 159.61 (C-4), 157.49 (C=N), 145.43 (C-3), 134.12 (C-5), 132.88, 132.53, 128.36, 128.12 (benzoyl), 143.60, 128.24, 127.86, 126.97, 86.05 (trityl), 84.54 (C-1'), 83.34 (C-4'), 82.39 (C-2'), 80.84 (C-3'), 64.33 (C-5'), 112.72, 27.14, 25.22 ($C(CH_3)_2$), 61.26, 13.96 (OCH_2CH_3), 14.52 (SCH_3); MS m/z 764 (M^+ + H, 19.6*). Anal. Calcd for $C_{42}H_{41}N_3O_7S_2$: C, 66.06; H, 5.37; N, 5.51. Found: C, 65.85; H, 5.35; N, 5.60.

5α (2.6 g, 3.5 mmol), 0.1 g (3.5 mmol) of NaH, and 0.85 mL (13.9 mmol) of methyl iodide gave **α-derivative 6α** (2.4 g, 91%): mp 95 °C (PE/ethyl acetate); IR (KBr) 3350 (NH), 1700 (C=O), 1600 cm^{-1} (C=C, C=N); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.03 (t, 1 H, J = 5.9 Hz, 2'-H), 5.56 (d, 1 H, J = 5.0 Hz, 1'-H), 4.67 (d, 1 H, J = 6.3 Hz, 3'-H), 4.48 (t, 1 H, J = 2.5 Hz, 4'-H), 3.57 (dd, 1 H, J = 11.1, 3.8 Hz, 5'a-H), 3.11 (dd, 1 H, J = 11.1, 2.9 Hz, 5'b-H), 4.48 (qd, 2 H, J = 7.9, 1.7 Hz, CH_2), 2.43 (s, 3 H, SCH_3), 1.04 (s, 3 H, CH_3), 0.71 (s, 3 H, CH_3), 1.31 (t, 3 H, J = 7.2 Hz, CH_3), 7.61–7.10 (m, 20 H, trityl and benzoyl), 8.51 (br s, 1 H, NH); ^{13}C NMR (200 MHz, $CDCl_3$) δ 164.06, 161.72 (C=O), 159.95 (C-4), 157.94 (C=N), 142.62 (C-3), 136.55 (C-5), 133.06, 132.60, 128.94, 127.30 (benzoyl), 143.39, 128.50, 127.99, 127.20, 87.60 (trityl), 83.55 (C-1'), 83.55 (C-4'), 82.65 (C-2'), 82.65 (C-3'), 65.68 (C-5'), 112.86, 25.69, 24.48 ($C(CH_3)_2$), 61.68, 14.12 (OCH_2CH_3), 14.97 (SCH_3); MS m/z 764 (M^+ + H, 9.8*). Anal. Calcd for $C_{42}H_{41}N_3O_7S_2$: C, 66.06; H, 5.37; N, 5.51. Found: C, 65.95; H, 5.50; N, 5.45.

4-[(*N*-Benzoyl-*S*-methylthiocarbamoyl)amino]-3-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)isothiazole-5-carboxamide (6β' and 6α'). *S*-Methylthioureido derivative 6β (6α) was dissolved in 10 mL of methanolic NH_3 (saturated at 0 °C) and stirred at 25 °C for 72 h. After evaporation the syrup obtained was crystallized from petroleum ether/ether.

An amount of 0.16 g (0.21 mmol) of 6β gave 0.14 g (91%) of carboxamide 6β': mp 134 °C (2-propanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.11 (dd, 1 H, J = 6.2, 3.1 Hz, 2'-H), 4.90 (d, 1 H, J = 2.4 Hz, 1'-H), 4.64 (dd, 1H, J = 6.3, 3.2 Hz, 3'-H), 4.14 (m, 1 H, 4'-H), 3.05 (dd, 1 H, J = 9.8, 5.6 Hz, 5'a-H), 2.98 (dd, 1 H, J = 9.8, 6.0 Hz, 5'b-H), 2.50 (s, 3 H, SCH_3), 1.48 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 7.98–7.33 (m, 7H, benzoyl and NH_2), 7.31–7.21 (m, 15 H, trityl), 10.92 (br s, 1 H, NH); MS m/z 735 (M^+ + H, 100*).

Amide 6α' (0.6 g, 90%) was obtained from 0.7 g (0.9 mmol) of 6α: mp 122 °C (2-propanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.22 (d, 1 H, J = 4.4 Hz, 1'-H), 5.07 (m, 1 H, 2'-H), 4.69 (d, 1 H, J = 6.0 Hz, 3'-H), 4.28 (m, 1 H, 4'-H), 3.20 (dd, 1 H, J = 10.3, 3.4 Hz, 5'a-H), 3.12 (dd, 1 H, J = 10.3, 4.8 Hz, 5'b-H), 2.41 (s, 3 H, SCH_3), 1.17 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 7.92–7.46 (m, 7 H, benzoyl and NH_2), 7.39–7.17 (m, 15 H, trityl), 10.55 (br s, 1 H, NH), 7.71 (br s, 2 H, NH_2). Anal. Calcd for $C_{40}H_{38}N_4O_6S_2$: C, 65.38; H, 5.21; N, 7.62. Found: C, 64.97; H, 5.29; N, 7.51.

5-Amino-3-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)isothiazolo[4,5-*d*]pyrimidin-7(6*H*)-one (8β and 8α) and 5-(Methylthio)-3-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)isothiazolo[4,5-*d*]pyrimidin-7(6*H*)-one (7β and 7α). A solution of *S*-methylthioureido derivative 6β (6α) in 40 mL of methanolic NH_3 (saturated at 0 °C) was stirred at 90–100 °C in a sealed steel vessel for 16 h. The reaction mixture was allowed to cool to room temperature and evaporated to dryness. The residue obtained firstly was chromatographed with cyclohexane/ethyl acetate (2:1) to afford the less-polar 5-methylthio derivatives 7β (7α). Then chromatography was continued with ethyl acetate to afford the more-polar 5-amino C-nucleoside 8β (8α) as a colorless syrup.

5-Methylthio β-Nucleoside 7β (0.9 g, 51%) was obtained from 2.2 g (2.9 mmol) of 6β after crystallization from petroleum

ether/ether as a white solid: mp 129 °C (MeOH); IR (KBr) 1670 (C=O), 1545 cm^{-1} (C=N); ^{1}H NMR (90 MHz, DMSO-d_6) δ 5.34 (m, 1 H, 2′-H), 5.33 (d, 1 H, J = 5.8 Hz, 1′-H), 4.76 (dd, 1 H, J = 5.2, 3.8 Hz, 3′-H), 4.33 (m, 1 H, 4′-H), 3.07 (m, 2 H, 5′a,b-H), 2.48 (s, 3 H, SCH_3), 1.54 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 7.48–7.16 (m, 15 H, trityl), 13.19 (br s, 1 H, NH); ^{13}C NMR (200 MHz, DMSO-d_6) δ 163.05 (C=O), 160.32 (C-5), 156.01 (C-3a), 150.24 (C-3), 138.01 (C-7a), 143.47, 128.16, 127.78, 126.97, 86.01 (trityl), 84.42 (C-1′), 83.00 (C-4′), 82.57 (C-2′), 81.01 (C-3′), 64.25 (C-5′), 113.19, 27.16, 25.23 ($C(CH_3)_2$), 13.05 (SCH_3); MS m/z 613 (M^+, 0.1). Anal. Calcd for $C_{33}H_{31}N_3O_5S_2$: C, 64.60; H, 5.06; N, 6.85. Found: C, 64.70; H, 5.55; N, 6.90.

After crystallization from PE/ether/ethyl acetate **5-amino C-nucleoside 8β** (0.8 g) was obtained in 47% yield: mp 159 °C (2-propanol); IR (KBr) 3415, 3315, 3150 (NH), 1670 (C=O)), 1630 (NH_2), 1590 cm^{-1} (C=C, C=N); ^{1}H NMR (90 MHz, DMSO-d_6) δ 5.33–5.16 (m, 2 H, 1′/2′-H), 4.76 (dd, 1 H, J = 5.8, 3.4 Hz, 3′-H), 4.25 (m, 1 H, 4′-H), 3.08 (d, 2 H, J = 6.0 Hz, 5′a,b-H), 1.52 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 7.51–7.16 (m, 15 H, trityl), 6.74 (br s, 2 H, NH_2); ^{13}C NMR (90 MHz, DMSO-d_6) δ 162.17 (C=O), 156.67 (C-5), 155.09 (C-3a), 153.14 (C-3), 130.71 (C-7a), 143.56, 128.22, 127.77, 126.93, 85.95 (trityl), 84.82 (C-1′), 82.94 (C-4′), 82.58 (C-2′), 80.28 (C-3′), 64.29 (C-5′), 112.85, 27.20, 25.32 ($C(CH_3)_2$); MS m/z 162 (M^+, 1.1). Anal. Calcd for $C_{32}H_{30}N_4O_5S$: C, 65.98; H, 5.16; N, 9.62. Found: C, 65.85; H, 5.05; N, 9.60.

An amount of 2.0 g (2.6 mmol) of α-isomer **6α** gave 0.5 g (31%) of **α-C-nucleoside 7α** after crystallization from petroleum ether/ether: mp 234 °C (MeOH); IR (KBr) 1675 (C=O), 1545 cm^{-1} (C=N); ^{1}H NMR (200 MHz, DMSO-d_6) δ 5.97 (d, 1 H, J = 4.6 Hz, 1′-H), 5.46 (dd, 1 H, J = 5.7, 4.2 Hz, 2′-H), 4.91 (d, 1 H, J = 6.4 Hz, 3′-H), 4.54 (t, 1 H, J = 3.0 Hz, 4′-H), 3.60 (dd, 1 H, J = 10.6, 3.0 Hz, 5′a-H), 3.24 (dd, 1 H, J = 10.6, 3.4 Hz, 5′b-H), 2.52 (s, 3 H, SCH_3), 1.32 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 7.50–7.18 (m, 15 H, trityl), 11.48 (br s, 1 H, NH); ^{13}C NMR (200 MHz, DMSO-d_6) δ 161.55 (C=O), 159.27 (C-5), 158.26 (C-3a), 150.35 (C-3), 136.84 (C-7a), 143.47, 128.62, 127.93, 127.18, 87.51 (trityl), 83.72 (C-1′), 83.61 (C-4′), 82.70 (C-3′), 82.52 (C-2′), 65.60 (C-5′), 113.04, 26.07, 25.37 ($C(CH_3)_2$), 13.68 (SCH_3); MS m/z 613 (M^+, 0.3). Anal. Calcd for $C_{33}H_{31}N_3O_5S_2 \cdot 0.5CH_3OH$: C, 63.91; H, 5.24; N, 6.67. Found: C, 64.00; H, 5.25; N, 6.80.

More polar **C-nucleoside 8α** (1.0 g) was obtained in 67% yield after crystallization from petroleum ether/ether: mp 162 °C (2-propanol); IR (KBr) 3320, 3160 (NH), 1670 (C=O), 1620 (NH_2), 1595 cm^{-1} (C=C, C=N); ^{1}H NMR (200 MHz, DMSO-d_6) δ 5.40 (d, 1 H, J = 4.0 Hz, 1′-H), 5.20 (dd, 1 H, J = 6.0, 4.4 Hz, 2′-H), 4.76 (d, 1 H, J = 6.8 Hz, 3′-H), 4.40 (t, 1 H, J = 4.0 Hz, 4′-H), 3.16 (d, 2 H, J = 4.4 Hz, 5′a,b-H), 1.18 (s, 6 H, 2 CH_3), 7.46–7.17 (m, 15 H, trityl), 11.33 (br s, 1 H, NH), 6.66 (br s, 2 H, NH_2); ^{13}C NMR (200 MHz, DMSO-d_6) δ 160.41 (C=O), 156.80 (C-5), 155.06 (C-3a), 155.06 (C-3), 129.73 (C-7a), 143.48, 128.26, 128.08, 127.18, 86.58 (trityl), 82.61 (C-1′), 82.61 (C-4′), 81.65 (C-3′), 80.84 (C-2′), 63.58 (C-5′), 112.22, 25.96, 25.11 ($C(CH_3)_2$); MS m/z 162 (M^+, 1.3). Anal. Calcd for $C_{32}H_{30}N_4O_5S$: C, 65.98; H, 5.16; N, 9.62. Found: C, 65.55; H, 5.50; N, 9.70.

5-Amino-3-D-ribofuranosylisothiazolo[4,5-*d*]pyrimidin-7-(6*H*)-one (3β and 3α) and 5-(Methylthio)-3-D-ribofuranosylisothiazolo[4,5-*d*]pyrimidin-7(6*H*)-one (10β and 10α). A solution of the corresponding C-nucleoside in 14% methanolic HCl (15–20 mL) was stirred at 25 °C for 1 h. After evaporation, the residue obtained was crystallized from ether. The resulting white precipitate was treated several times with ether and decanted and then filtered and washed with ether. After recrystallization from MeOH, the free C-nucleosides were obtained as crystalline solids. **3β and 3α** were obtained as monohydrochloride salts.

8β (0.8 g, 1.4 mmol) gave 0.46 g (99%) of **8-aza-7,9-deaza-7-thiaguanosine 3β**: mp 196 °C (MeOH); IR (KBr) 3600–3100 (NH, OH), 1720 (C=O), 1660 (NH_2), 1605, 1505 cm^{-1} (C=C, C=N); ^{1}H NMR (90 MHz, DMSO-d_6) δ 5.03 (d, 1 H, J = 6.4 Hz, 1′-H), 4.40 (dd, 1 H, J = 6.0, 5.2 Hz, 2′-H), 4.18–3.87 (m, 2 H, 3′/4′-H), 3.66 (m, 2 H, 5′a,b-H), 7.40 (br s, 1 H, NH); ^{13}C NMR (90 MHz, DMSO-d_6) δ 160.98 (C=O), 155.18 (C-5), 153.76 (C-3a), 144.70 (C-3), 133.37 (C-7a), 85.43 (C-1′), 80.38 (C-4′), 74.23 (C-2′), 71.71 (C-3′), 61.64 (C-5′); MS m/z 301 (M^+ + H, 100*). Anal. Calcd for $C_{10}H_{12}N_4O_5S \cdot HCl$: C, 35.66; H, 3.86; N, 16.64. Found: C, 35.66; H, 3.85; N, 16.80.

8α (1.0 g, 1.7 mmol) afforded 0.58 g (100%) of **α-isomer 3α**: mp 214 °C (MeOH); IR (KBr) 3600–3000 (NH, OH), 1720 (C=O), 1660 (NH_2), 1580, 1500 cm^{-1} (C=C, C=N); ^{1}H NMR (200 MHz, DMSO-d_6) δ 5.28 (d, 1 H, J = 3.6 Hz, 1′-H), 4.34 (t, 1 H, J = 4.2 Hz, 2′-H), 4.16 (dd, 1 H, J = 7.3, 4.4 Hz, 3′-H), 4.08 (m, 1 H, 4′-H), 3.68 (dd, 1 H, J = 12.7, 2.2 Hz, 5′a-H), 3.48 (dd, 1 H, J = 12.7, 4.2 Hz, 5′b-H), 7.66 (br s, 1 H, NH); ^{13}C NMR (90 MHz, DMSO-d_6) δ 159.36 (C=O), 154.83 (C-5), 153.40 (C-3a), 142.75 (C-3), 133.33 (C-7a), 83.03 (C-1′), 80.90 (C-4′), 73.65 (C-3′), 71.97 (C-2′), 61.32 (C-5′); MS m/z 301 (M^+ + H, 12.6*). Anal. Calcd for $C_{10}H_{12}N_4O_5S \cdot HCl$: C, 35.66; H, 3.86; N, 16.64. Found: C, 35.90; H, 4.00; N, 16.65.

Free 5-methylthio β-C-nucleoside 10β (0.44 g, 91%) was obtained from **7β** (0.9 g, 1.5 mmol): mp 269 °C (MeOH); IR (KBr) 3430, 3290 (NH, OH), 1705 (C=O), 1540 cm^{-1} (C=C, C=N); ^{1}H NMR (200 MHz, DMSO-d_6) δ 5.10 (d, 1 H, J = 5.7 Hz, 1′-H), 4.52 (q, 1 H, J = 5.3 Hz, 2′-H), 4.07 (q, 1 H, J = 5.3 Hz, 3′-H), 3.83 (q, 1 H, J = 4.6 Hz, 4′-H), 3.52 (m, 2 H, 5′a,b-H), 5.14 (d, 1 H, J = 6.9 Hz, 2′-OH), 5.01 (d, 1 H, J = 5.7 Hz, 3′-OH), 4.69 (br s, 1 H, 5′-OH), 2.60 (s, 3 H, SCH_3), 13.17 (br s, 1 H, NH); ^{13}C NMR (90 MHz, DMSO-d_6) δ 164.34 (C=O), 160.23 (C-5), 156.19 (C-3a), 150.65 (C-3), 137.90 (C-7a), 85.04 (C-1′), 79.64 (C-4′), 73.49 (C-2′), 71.58 (C-3′), 62.22 (C-5′), 13.12 (SCH_3); MS m/z 332 (M^+ + H, 100*). Anal. Calcd for $C_{11}H_{13}N_3O_5S_2$: C, 39.88; H, 3.93; N, 12.69. Found: C, 40.10; H, 3.90; N, 12.90.

7α (0.5 g, 0.82 mmol) gave **α-nucleoside 11α** (0.22 g, 82%): mp 234 °C (MeOH); IR (KBr) 3480, 3430, 3200 (NH, OH), 1675 (C=O), 1555 cm^{-1} (C=C, C=N); ^{1}H NMR (200 MHz, DMSO-d_6) δ 5.42 (d, 1 H, J = 3.4 Hz, 1′-H), 4.93 (m, 1 H, 2′-H), 4.51 (m, 1 H, 3′-H), 3.95 (m, 1 H, 4′-H), 3.69 (m, 1 H, 5′a-H), 3.47 (m, 1 H, 5′b-H), 4.74 (d, 1 H, J = 5.0 Hz, 2′-OH), 4.71 (d, 1 H, J = 4.2 Hz, 3′-OH), 2.57 (s, 3 H, SCH_3), 13.13 (br s, 1 H, NH); ^{13}C NMR (400 MHz, DMSO-d_6) δ 164.19 (C=O), 159.77 (C-5), 156.32 (C-3a), 150.07 (C-3), 136.44 (C-7a), 82.20 (C-1′), 80.45 (C-4′), 72.45 (C-3′), 71.90 (C-2′), 61.33 (C-5′), 13.22 (SCH_3); MS m/z 332 (M^+ + H, 6.0*). Anal. Calcd for $C_{11}H_{13}N_3O_5S_2$: C, 39.88; H, 3.93; N, 12.69. Found: C, 40.20; H, 3.65; N, 12.80.

7-Amino-3-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)-isothiazolo[4,5-*d*]pyrimidine (12β and 12α). To a solution of 1,2,4-1*H*-triazole (1.0 g, 7.2 mmol) in dry pyridine (30 mL) was added phosphoryl chloride (0.36 mL, 3.6 mmol). After being stirred for 15 min, C-nucleoside **11β** was added and the resulting dark-blue solution was stirred at 25 °C with exclusion from moisture. After 8 h the 7-triazolyl intermediate **B** had formed, and methanolic NH_3 (saturated at 0 °C) was added and the resulting brown reaction mixture was stirred for additional 18 h at rt. After evaporation to dryness, the residue obtained initially was flash-chromatographed on 20 g of silica gel (chloroform–MeOH, 9:1) and then chromatographed with ethyl acetate, and the colorless syrup obtained was crystallized from petroleum ether/ethyl acetate to afford after recrystallization, **12β** (0.45 g, 75%) as a white solid: mp 94 °C (PE/ethyl acetate); IR (KBr) 3320, 3170 (NH), 1630 (δ_{NH}), 1555, 1530 cm^{-1} (C=C, C=N); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.58 (d, 1 H, J = 5.4 Hz, 1′-H), 5.58 (q, 1 H, J = 3.7 Hz, 2′-H), 4.86 (dd, 1 H, J = 5.6, 2.8 Hz, 3′-H), 4.48 (m, 1 H, 4′-H), 3.17 (m, 2 H, 5′a,b-H), 1.62 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 8.62 (s, 1 H, 5-H), 7.40–7.10 (m, 15 H, trityl), 5.72 (br s, 2 H, NH_2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 164.14 (C-7), 156.43 (C-3a), 155.75 (C-5), 154.01 (C-3), 130.38 (C-7a), 143.88, 128.76, 127.79, 127.01, 86.75 (trityl), 85.13 (C-1′), 83.38 (C-4′), 83.19 (C-2′), 81.99 (C-3′), 64.15 (C-5′), 114.10, 27.54, 25.80 ($C(CH_3)_2$); MS m/z 566 (M^+, 0.1). Anal. Calcd for $C_{32}H_{30}N_4O_4S$: C, 67.85; H, 5.30; N, 9.89. Found: C, 68.10; H, 5.15; N, 9.65.

The same procedure with **11α** (0.6 g, 1.1 mmol) gave **12α** (0.5 g, 82%) after crystallization from *n*-hexane/EtOH: mp 109 °C (*n*-hexane/EtOH); IR (KBr) 3310, 3180 (NH), 1635 (δ_{NH}), 1555, 1525 cm^{-1} (C=C, C=N); ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.02 (d, 1 H, J = 5.0 Hz, 1′-H), 5.50 (m, 1 H, 2′-H), 4.84 (d, 1 H, J = 5.4 Hz, 3′-H), 4.60 (t, 1 H, J = 3.6 Hz, 4′-H), 3.51 (dd, 1 H, J = 10.0, 4.2 Hz, 5′a-H), 3.24 (dd, 1 H, J = 10.0, 4.2 Hz, 5′b-H), 1.29 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3), 8.67 (s, 1 H, 5-H), 7.60–7.11 (m, 15 H, trityl), 5.46 (br s, 2 H, NH_2); ^{13}C NMR (200 MHz, $CDCl_3$) δ 162.62 (C-7), 156.53 (C-3a), 155.73 (C-5), 153.07 (C-3), 129.56 (C-7a), 143.45, 128.64, 127.99, 127.20, 87.52 (trityl), 83.51 (C-1′), 83.51 (C-4′), 82.46 (C-3′), 82.34 (C-2′), 64.52 (C-5′), 113.02, 26.09, 25.22 ($C(CH_3)_2$); MS m/z 566 (M^+, 8.4). Anal. Calcd for

$C_{32}H_{30}N_4O_4S \cdot CH_3CH_2OH$: C, 66.67; H, 5.88; N, 9.15. Found: C, 66.50; H, 5.50; N, 9.30.

7-Amino-3-D-ribofuranosylisothiazolo[4,5-*d*]pyrimidine (4β and 4α). **12β** (**12α**) was dissolved in 14% methanolic HCl (10 mL) and stirred for 2 h at 25 °C. The same workup procedure as described for nucleosides **3–10** gave free 8-aza-7,9-deaza-7-thiaadenosine **4β** and α-isomer **4α** as crystalline monohydrochloride salts.

β-Isomer 4β (0.23 g, 89%) was obtained from 0.45 g (0.8 mmol) of **12β** after recrystallization from EtOH: mp 209 °C (EtOH); IR (KBr) 3450, 3240, 3060 (NH, OH), 1660 (δ_{NH}), 1595 cm^{-1} (C=C, C=N); ^1H NMR (200 MHz, DMSO-d_6) δ 5.13 (d, 1 H, J = 6.7 Hz, 1′-H), 4.40 (dd, 1 H, J = 7.0, 4.8 Hz, 2′-H), 4.08 (dd, 1 H, J = 5.3, 3.4 Hz, 3′-H), 4.01 (q, 1 H, J = 3.6 Hz), 3.65 (m, 2 H, 5′a,b-H), 8.65 (s, 1 H, 5-H), 9.50 (br s, 2 H, NH_2); ^{13}C NMR (200 MHz, DMSO-d_6) δ 160.65 (C-7), 159.31 (C-3a), 150.85 (C-5), 141.60 (C-3), 134.65 (C-7a), 86.83 (C-1′), 82.45 (C-4′), 76.22 (C-2′), 72.99 (C-3′), 62.63 (C-5′); MS m/z 285 (M^+ + H, 23.2). Anal. Calcd for $C_{10}H_{12}N_4O_4S \cdot HCl$: C, 37.44; H, 4.06; N, 17.47. Found: C, 37.40; H, 4.05; N, 17.25.

12α (0.5 g, 0.88 mmol) gave 0.23 g (82%) of **α-isomer 4α**, mp 229 °C (EtOH); IR (KBr) 3340, 3160, 3020 (NH, OH), 1675 (δ_{NH}), 1595 cm^{-1} (C=C, C=N); ^1H NMR (200 MHz, DMSO-d_6) δ 5.47 (d, 1 H, J = 3.9 Hz, 1′-H), 4.41 (t, 1 H, J = 4.8 Hz, 2′-H), 4.22 (dd, 1 H, J = 8.3, 3.9 Hz, 3′-H), 4.13 (m, 1 H, 4′-H), 3.69 (dd, 1 H, J = 11.3, 2.9 Hz, 5′a-H), 3.51 (dd, 1 H, J = 11.3, 3.6 Hz), 8.64 (s, 1 H, 5-H), 9.46 (br s, 2 H, NH_2); ^{13}C NMR (200 MHz, DMSO-d_6) δ 160.94 (C-7), 159.90 (C-3a), 152.17 (C-5), 144.03 (C-3), 135.48 (C-7a), 84.85 (C-1′), 83.43 (C-4′), 76.26 (C-3′), 74.20 (C-2′), 63.86 (C-5′); MS m/z 285 (M^+ + H, 22.5). Anal. Calcd for $C_{10}H_{12}N_4O_4S \cdot HCl$: C, 37.44; H, 4.06; N, 17.47. Found: C, 37.70; H, 4.10; N, 17.45.

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