Efficient Synthesis of Fused Isothiazole C-Nucleosides. 1. Synthesis of a 3-β-D-Ribofuranosylisothiazolo[4,5-*d*]pyrimidin-7(6*H*)-one Isostere of Inosine

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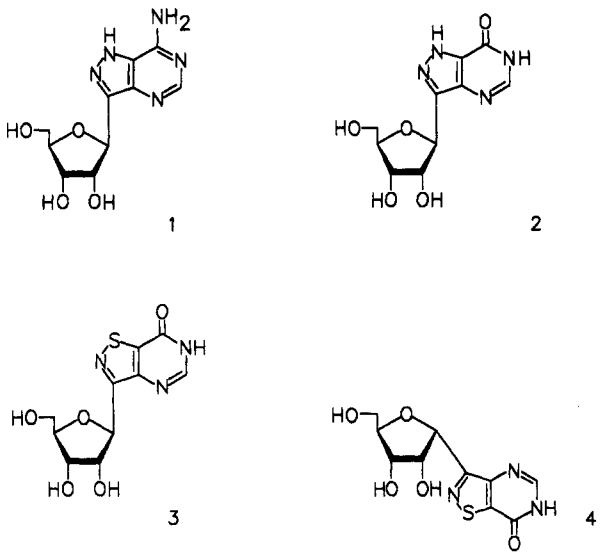
The reaction of 2-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)acetonitrile (**6**) with isopentyl nitrite/NaH and subsequent tosylation of Na–oximino nitrile **7** gave protected 2-D-ribofuranosyl-2-(tosyloximino)acetonitriles **9α,β** as novel C-nucleoside precursors. Treatment of **9α,β** with ethyl 2-mercaptoacetate under basic conditions afforded epimeric ethyl 4-aminoisothiazole-5-carboxylate C-nucleosides **10α,β**. Cyclization of **10α,β** to the desired 3-D-ribofuranosylisothiazolo[4,5-*d*]pyrimidin-7(6*H*)-ones **14α,β** was accomplished by the reaction of **10α,β** with triethyl orthoformate and subsequent amminolysis. Deprotection of **14β** and **14α** in 7% HCl/MeOH gave the title compound **3** and α-isomeric C-nucleoside **4** as monohydrochloride salt, respectively. The configuration of C-glycoside **9α** was established by X-ray crystallography.

Natural C-nucleosides,[1,2] such as formycin (**1**) and formycin B (**2**), display significant antiviral and antitumor activities.[3] In the search for new chemotherapeutic drugs in the last few years, a number of these unusual nucleosides with fused ring systems have been synthesized by replacing the natural purine bases with isosteric purine-like systems.[4–9]

We wish to report on a novel synthetic approach to purine-like C-nucleosides via C-glycosidic tosyloximino nitrile precursors. We used this approach to synthesize 3-β-D-ribofuranosylisothiazolo[4,5-*d*]pyrimidin-7(6*H*)-one (**3**), an isostere of inosine, and α-isomer **4**.

It has been reported in the literature that tosyloximino nitriles[10] **5** are versatile compounds for heterocyclic synthesis. Their reactivity toward various nucleophiles allows nucleophilic displacement of the tosylate group and subsequent cyclization of the resulting acyclic intermediates.[11–15]

Scheme I



For our work on C-nucleoside synthesis, we first required a simple approach to a new tosyloximino nitrile precursor derived from 2-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)acetonitrile (**6**).[16] Regioselective C-nitrosation in the position α to the CN group was accomplished by treatment of **6** with isopentyl nitrite in dimethoxyethane in the presence of NaH for 12–24 h at 25 °C. This procedure afforded the sodium salt of the desired 2-(2,3-*O*-isopropylidene-5′-*O*-trityl-D-ribofuranosyl)-2-oximinoacetonitrile (**7**).[17]

The yield of **7** depended strongly on the volume of the solvent and the stoichiometry of the starting materials. Other oximino nitriles have been prepared by direct α-nitrosation of aliphatic nitriles,[18] but in the case of β-C-(cyanomethyl) glycoside **6**, this approach turned out to be

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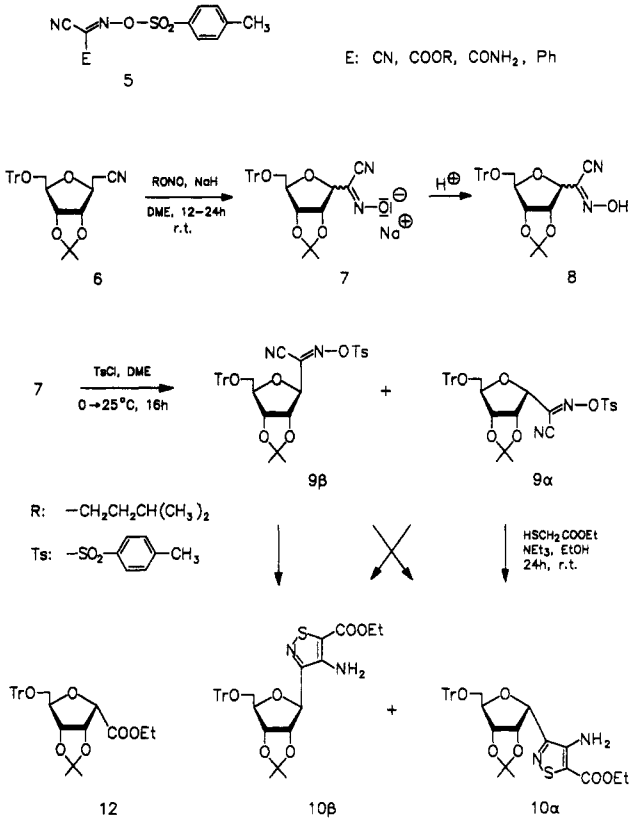
Scheme II



unsuccessful. Treatment of **6** with an alkyl nitrite in the presence of strong bases, such as NaOR or KOR, resulted only in epimerization of **6** to the thermodynamically more stable α-isomer.[16] Na–oximino nitrile **7**, isolable as a hygroscopic, white powder, could be used in the following tosylation step without further purification. Acidification of an aqueous solution of **7** with diluted mineralic acid afforded oximino nitrile **8** as an amorphous, hygroscopic brown precipitate that darkened in the air. Compound **8** was characterized by high-resolution mass spectrometry (HRMS).

Tosylation of **7** was achieved with TsCl. After chromatographic separation, isomeric 2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)-2-(tosyloximino)acetonitriles (**9β** and **9α**) were obtained in overall yields of 65% and 21%, respectively.

The C-1′ stereochemistry of C-glycosides **9β** and **9α** was determined from their ^{1}H NMR spectra according to the rules given for α/β-epimeric pairs of C-nucleosides[19] and 2,3-*O*-isopropylidenated C-nucleosides,[16,20] respectively. Thus, the 1′-H signal of the β-isomer appeared at δ 4.95 ppm[20] at higher field than that of **9α** (δ 5.42). Furthermore, **9β** exhibited a definitively larger difference ($\Delta\delta$) between the Me shifts of the isopropylidene groups[16,20] (22.5 Hz for **9β** vs 16.2 Hz for **9α**).

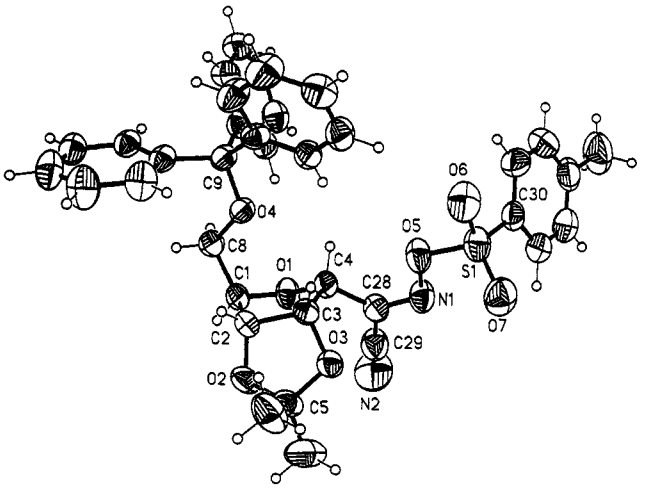


Figure 1. Perspective view and atom labeling of the crystal structure of 2-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-α-D-ribofuranosyl)-2-(tosyloximino)-acetonitrile (**11**) (50% probability thermal ellipsoids).

The assignment of the stereochemistry of the C=N bond of **9** was made arbitrarily. For the cyclization reaction described below, the stereochemistry seemed of minor interest because of the small rotational barrier of the C=N-double bond.[15b] The X-ray analysis of C-glycoside **9α** revealed, however, that at least in the solid state the thermodynamically more stable *E*-configuration is preferred.

In contrast to tosyloximino nitriles **5** the C-glycosides **9β** and **9α** possess only one electron-withdrawing group at the oxime C-atom. The other group is replaced by the sterically-hindered sugar moiety. Because of the positive polarization of the oxime N-atom, its reactivity toward nucleophiles is strongly decreased. As a consequence, when **9β** and **9α** were treated with malonodinitrile and derivatives in the presence of a base, either no reaction was observed or an undesired nucleophilic attack on the sulfoxyl S-atom took place, yielding oximino nitrile **8**.

However, treating a mixture of **9β** and **9α** (3:1) with ethyl 2-mercaptoacetate gave, after 24 h at 25 °C, a mixture of the expected ethyl 4-amino-3-D-ribofuranosylisothiazole-5-carboxylates **10β** and **10α**. Chromatographic separation afforded the two isomers in a ratio of 2:5. Thus, the formation of the thermodynamically more stable α-isomer seems to be favored.

The epimerization observed at C-1′ can be explained in terms of common acyclic intermediate **A**. Expulsion of the tosylate group from **A** leads to unisolable epimeric [(carbethoxymethyl)thio]imino nitriles **11β** and **11α**, which, in the presence of triethylamine, cyclize spontaneously to give **10β** and **10α**.

The configurations at C-1′ of **10α** and **10β** were again determined by comparison of ^{1}H NMR data.[16,19,20] The 1′-H signal of **10β** appeared at higher field (δ 4.95) compared to that of **10α** (δ 5.43). The larger difference ($\Delta\delta$) between the Me shifts of the isopropylidene groups (17.1 Hz for **10α** vs 19.8 Hz for **10β**) provided further evidence for the β-configuration of **10β**.

A small amount (3%) of altronic acid derivative **12** was isolated as a byproduct; it is obviously formed by nucleo-

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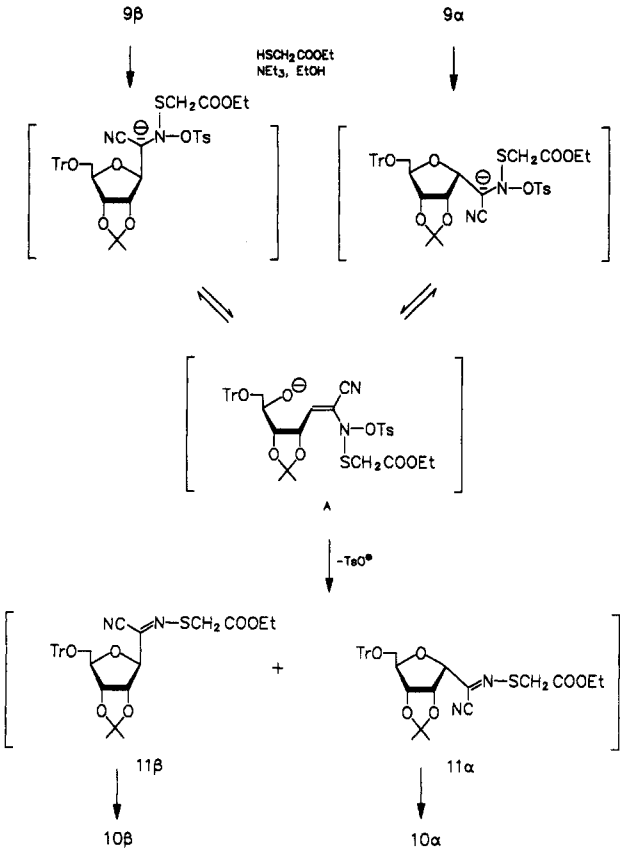
Scheme III



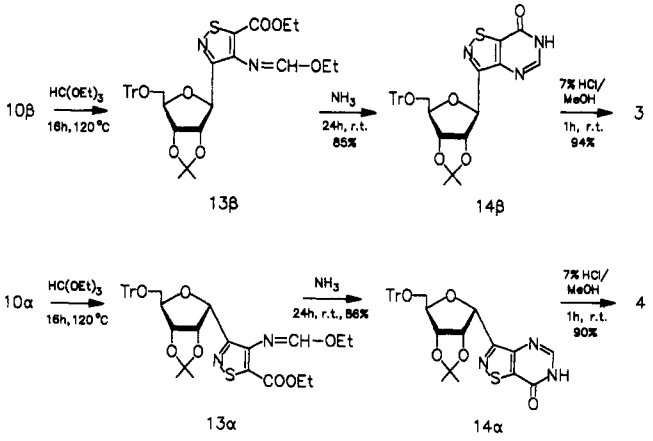
philic attack of EtOH at the oxime C-atom[12] of **9α** and subsequent hydrolysis of the resulting ethyl imidocarboxylate. This reaction is favored in the case of **9α** because of the stronger positive polarization of C-2, as indicated by the ^{13}C NMR shift of C-2 (δ 147.31 for **9α** vs δ 140.26 for **9β**). The α-configuration of **12** was confirmed by the ^{13}C NMR signals of the isopropylidene methyl groups found at 25.13 and 26.12 ppm, in excellent agreement with literature values for 2,3-*O*-isopropylidene-α-D-ribofuranose derivatives (24.9 ± 0.3 and 26.3 ± 0.2 ppm).[16,21]

Isothiazole enamino esters **10α,β** are suitable precursors[22] for the synthesis of purine-like isothiazolo[4,5-*d*]-pyrimidine C-nucleosides. Treatment of **10β** and **10α** with triethyl orthoformate at 120 °C for 16 h gave formimido derivatives **13β** and **13α** as syrupy residues, which were not isolated but were instead cyclized with EtOH/NH_3[23] to the desired fully blocked 3-β-D-ribofuranosylisothiazolo-[4,5-*d*]pyrimidin-7(6*H*)-one **14β** and α-epimer **14α** in 85% and 86% yield, respectively.

All attempts to vary the reaction conditions of the cyclization of **10α** and **10β**,[24] (e.g., treatment of **10α,β** with formamide[25] in acetic anhydride, formamidine acetate in boiling EtOH,[26] or DMF–dialkyl acetal in DMF[27]) failed.

The ^1H NMR data revealed that, upon conversion of **10β** to **14β** and of **10α** to **14α**, no epimerization occurs at C-1′. The smaller chemical shift[20] of the 1′-H of **14β** (δ 5.32 vs δ 5.76 for **14α**) confirmed its β-configuration. In agreement with the NMR data for several other 2,3-*O*-isopropylidenated C-ribonucleosides,[16,28] additional ^1H NMR spectral evidence was obtained from the observation that the 4′-H signal of **14α** appeared as a pseudotriplet, whereas that of **14β** appeared as a multiplet typical for β-C-nucleosides. The β-configuration of **14β** was definitely confirmed by NOE difference spectroscopy in DMSO-d_6. When the signal of the 1′-H at 5.32 ppm was irradiated, a 1.4% intensity enhancement of the 4′-H signal at 4.27 ppm was observed.

Scheme IV



The deprotection of **14β** and **14α** in 7% methanolic HCl at 25 °C for 1 h afforded 3-β-D-ribofuranosylisothiazolo-[4,5-*d*]pyrimidin-7(6*H*)-one (**3**) in 94% yield, and α-C-nucleoside **4** was obtained as monohydrochloride salt (90% yield).

In primary screening, **3** and **4** turned out to be inactive against rhino viruses. Detailed investigations of the biological activities of the novel isothiazolo[4,5-*d*]pyrimidine C-nucleosides are in progress, and the results will be published elsewhere.

X-ray Crystallographic Analysis. The structure of tosyloximino nitrile C-glycoside **9α** was unambiguously confirmed by X-ray crystallography. As shown in Figure 1, the ribofuranosyl ring exhibits the O-1-endo envelope conformation[16] in which the sterically hindered 5-*O*-trityl group and the oxime C-atom are positioned in less hindered pseudoaxial orientations.[29]

Crystal data: $C_{36}H_{34}N_2O_7S$, M_r = 638.7, colorless plates, crystal dimensions 0.1 × 0.4 × 0.9 mm, crystallized from CH_3OH; monoclinic, space group *C*2 (No. 5), a = 37.114-(2) Å, b = 8.288(1) Å, c = 10.983(2) Å, β = 96.35(1)°, V = 3.358(1) nm^3, Z = 4, d_{calc} = 1.26 g/cm^3, λ(Mo Kα) = 0.710 73 Å, μ(Mo Kα) = 0.14 mm^{-1}, F(000) = 1344. A total of 5915 symmetry-independent reflections were measured on an Enraf-Nonius CAD4 diffractometer at 25 °C ($2\Theta_{max}$ = 50°, scans, scan range (0.90 + 0.35 tg Θ)°), 4261 reflections with $|F| > 3\sigma(F)$ used for structure solution (direct methods) and refinement (full-matrix least-squares, 415 parameters), non-hydrogen atoms refined anisotropically, H atoms localized by difference electron density determination and refined by means of a "riding" model; R = 0.044 (R_w =

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(29) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

0.040, $w^{-1} = \sigma^2(F) + 0.0005F^2$), the absolute configuration was confirmed by n-refinement (n = 1.2(2)), largest peak in final difference Fourier map 0.28 e Å^{-3}. The structure was solved and refined with SHELXTL-Plus.

Experimental Section

Melting points are 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.

2-(2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranosyl)-2-oximinoacetonitrile Sodium Azaenolate (7). To a mixture of **6** (10 g, 22 mmol) and isopentyl nitrite (9 mL, 66 mmol) in dry DME (50 mL) was added NaH (2.11 g, 88 mmol), and the resulting suspension was stirred at 25 °C under anhydrous conditions for 12–24 h. After the reaction was completed (monitored by TLC), the resulting light-brown reaction mixture containing **7** was used without workup for the next step: HRMS of the corresponding oximino nitrile **8** calcd for $C_{29}H_{28}N_2O_4$ 484.1998, found 484.1995; MS m/z 484 (M^+, 1.5).

2-(2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranosyl)-2-(tosyloximino)acetonitriles (9β and 9α). After addition of dry DME (250 mL) and dropwise addition of glacial acetic acid (2.52 mL, 44 mmol) to the reaction mixture of **7** at 0 °C, a solution of tosyl chloride (9.23 g, 48.4 mmol) in dry DME (100 mL) was added over a period of 1 h. The viscous suspension obtained was stirred for an additional 15 h at 25 °C. The NaCl/NaOAc formed was filtered over Celite and washed several times with DME. The filtrate was evaporated to dryness, and the resulting syrup was chromatographed on silica gel (petroleum ether–ethyl acetate (14:5)) to give, after crystallization from MeOH, **9β** and **9α** as pale yellow solids.

β-C-Glycoside 9β (more polar): 9.1 g (65%); mp 78–82 °C; UV (CH_2Cl_2) λ_{max} (log ϵ) 206 (4.19), 219 nm (4.38); IR (KBr) 2215 (C≡N), 1595 (C=C), 1390, 1195 cm^{-1} (S=O); ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.95 (d, 1 H, J = 4.0 Hz, 1′-H), 4.93 (t, 1 H, J = 6.2 Hz, 2′-H), 4.67 (m, 1 H, 3′-H), 4.38 (t, 1 H, J = 3.6 Hz, 4′-H), 3.37 (dd, 1 H, J = 10.9, 3.4 Hz, 5′a-H), 3.08 (dd, 1 H, J = 10.9, 3.6 Hz, 5′b-H), 2.42 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3), 7.93–7.11 (m, 19 H, trityl and AA′BB′, tosyl); ^{13}C NMR (200 MHz, $CDCl_3$) δ 146.42, 130.82, 129.96, 129.16, 21.73 (tosyl), 143.15, 128.39, 127.98, 127.29, 87.52 (trityl), 140.26 (C-2), 107.33 (C-1), 85.06 (C-1′), 83.10 (C-4′), 82.97 (C-2′), 80.10 (C-3′), 64.80 (C-5′), 114.16, 24.78, 24.15 (C(CH_3)$_2$); MS m/z 638 (M^+, 0.1). Anal. Calcd for $C_{36}H_{34}N_2O_7S \cdot CH_3OH$: C, 66.25; H, 5.71; N, 4.18. Found: C, 66.46; H, 5.70; N, 4.06..

α-Isomer 9α (less polar): 2.9 g (21%); mp 158 °C; UV (CH_2Cl_2) λ_{max} (log ϵ) 225 nm (4.34); IR (KBr) 2220 (C≡N), 1590 (C=C), 1390, 1195 cm^{-1} (S=O); ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.42 (d, 1 H, J = 4.6 Hz, 1′-H), 5.08 (t, 1 H, J = 5.4 Hz, 2′-H), 4.54 (d, 1 H, J = 6.4 Hz, 3′-H), 4.30 (t, 1 H, J = 3.0 Hz, 4′-H), 3.44 (dd, 1 H, J = 10.6, 2.4 Hz, 5′a-H), 2.98 (dd, 1 H, J = 10.6, 2.2 Hz, 5′b-H), 2.34 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 7.87–7.13 (m, 19 H, trityl and AA′BB′, tosyl); ^{13}C NMR (200 MHz, $CDCl_3$) δ 146.46, 130.93, 130.05, 129.32, 21.89 (tosyl), 143.19, 128.51, 128.24, 127.49, 88.04 (trityl), 147.31 (C-2), 110.74 (C-1), 84.59 (C-1′), 83.03 (C-4′), 81.89 (C-3′), 78.86 (C-2′), 65.52 (C-5′), 113.47, 25.59, 24.43 (C(CH_3)$_2$); MS m/z 638 (M^+, 0.4). Anal. Calcd for $C_{36}H_{34}N_2O_7S$: C, 67.70; H, 5.37; N, 4.39. Found: C, 67.72; H, 5.57; N, 4.60.

Ethyl 4-Amino-3-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)isothiazole-5-carboxylates (10β and 10α). Isomeric tosyloximino nitriles **9β** and **9α** (10 g, 15.7 mmol, 3:1), ethyl 2-mercaptoacetate (2.1 mL, 18.8 mmol), and triethylamine (3.3 mL, 23.6 mmol) were dissolved in dry EtOH (200 mL), and the reaction mixture was stirred at 25 °C for 24 h. After evaporation, the residue obtained was chromatographed (cyclohexane–ethyl acetate (7:1)) to afford epimeric isothiazoles **10β** and **10α** as white solids after crystallization from EtOH and byproduct **12** as colorless needles from MeOH.

β-Nucleoside 10β (less polar): 1.8 g (20%); mp 79–82 °C; UV (CH_2Cl_2) λ_{max} (log ϵ) 336 (3.90), 205 nm (4.35); IR (KBr) 3460, 3330 (NH), 1690 (C=O), 1595 cm^{-1} (C=C); ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.95 (d, 1 H, J = 4.4 Hz, 1′-H), 5.28 (dd, 1 H, J = 6.8, 4.8 Hz, 2′-H), 4.64 (dd, 1 H, J = 6.6, 3.0 Hz, 3′-H), 4.28 (m, 1 H, 4′-H), 3.04 (m, 2 H, 5′a,b-H), 4.22 (q, 2 H, J = 7.4 Hz, CH_2), 1.23 (t, 3 H, J = 6.8 Hz, CH_3), 1.48 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 7.38–7.04 (m, 15 H, trityl), 5.59 (br s, 2 H, NH_2); ^{13}C NMR (200 MHz, $CDCl_3$) δ 162.43 (C=O), 157.01 (C-4), 147.51 (C-3), 122.39 (C-5), 143.42, 128.60, 127.90, 127.19, 86.97 (trityl), 84.60 (C-1′), 84.20 (C-4′), 83.19 (C-2′), 81.85 (C-3′), 63.41 (C-5′), 114.32, 27.34, 25.43 (C(CH_3)$_2$), 60.84, 14.38 (OCH_2CH_3); MS m/z 586 (M^+, 0.4). Anal. Calcd for $C_{33}H_{34}N_2O_6S$: C, 67.56; H, 5.84; N, 4.77. Found: C, 67.30; H, 5.86; N, 5.08.

α-Isomer 10α (more polar): 4.8 g (52%); mp 80–85 °C; UV (CH_2Cl_2) λ_{max} (log ϵ) 335 (3.97), 205 nm (4.47); IR (KBr) 3490, 3370 (NH), 1685 (C=O), 1590 cm^{-1} (C=C); ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.43 (d, 1 H, J = 4.8 Hz, 1′-H), 4.99 (dd, 1 H, J = 5.6, 4.4 Hz, 2′-H), 4.67 (d, 1 H, J = 6.2 Hz, 3′-H), 4.35 (t, 1 H, J = 2.5 Hz, 4′-H), 3.22 (m, 2 H, 5′a,b-H), 4.25 (q, 2 H, J = 7.2 Hz, CH_2), 1.27 (t, 3 H, J = 6.6 Hz, CH_3), 1.39 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 7.49–7.11 (m, 15 H, trityl), 5.85 (br s, 2 H, NH_2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 162.75 (C=O), 154.91 (C-4), 149.31 (C-3), 121.19 (C-5), 143.49, 128.69, 128.11, 127.34, 87.55 (trityl), 84.42 (C-1′), 83.83 (C-3′), 83.41 (C-4′), 82.60 (C-2′), 64.15 (C-5′), 112.83, 26.02, 24.08 (C(CH_3)$_2$), 60.72, 14.44 (OCH_2CH_3); MS m/z 586 (M^+, 1.9). Anal. Calcd for $C_{33}H_{34}N_2O_6S$: C, 67.56; H, 5.84; N, 4.77. Found: C, 67.03; H, 5.63; N, 4.40.

Ethyl 2,5-anhydro-3,4-*O*-isopropylidene-6-*O*-trityl-D-altronate (12): 0.4 g (3%); mp 153 °C; UV (CH_2Cl_2) λ_{max} (log ϵ) 217 nm (4.18); IR (KBr) 1750 (C=O), 1595 cm^{-1} (C=C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.94 (d, 1 H, J = 5.1 Hz, 1′-H), 5.14 (t, 1 H, J = 5.5 Hz, 2′-H), 4.70 (dd, 1 H, J = 6.0, 1.2 Hz, 3′-H), 4.42 (t, 1 H, J = 3.4 Hz, 4′-H), 3.43 (dd, 1 H, J = 10.1, 3.4 Hz, 5′a-H), 3.10 (dd, 1 H, J = 10.1, 3.1 Hz, 5′b-H), 4.31 (m, 2 H, J = 3.6 Hz, CH_2), 1.33 (t, 3 H, J = 7.2 Hz, CH_3), 1.45 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 7.42–7.18 (m, 15 H, trityl); ^{13}C NMR (200 MHz, $CDCl_3$) δ 168.45 (C=O), 143.40, 128.55, 127.98, 127.23, 87.45 (trityl), 84.17 (C-1′), 82.75 (C-4′), 82.50 (C-2′), 82.33 (C-3′), 65.04 (C-5′), 113.07, 26.12, 25.13 (C(CH_3)$_2$), 61.14, 14.31 (OCH_2CH_3); HRMS m/z calcd 488.2199, found 488.2203; MS m/z 488 (M^+, 0.7). Anal. Calcd for $C_{30}H_{32}O_6$: C, 73.77; H, 6.56. Found: C, 73.85; H, 6.60.

3-(2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranosyl)isothiazolo[4,5-*d*]pyrimidin-7(6*H*)-ones (14β and 14α). A solution of isothiazole C-nucleoside **10β** or **10α** in dry triethyl orthoformate (20–30 mL) was heated with stirring at 120 °C for 16 h. After evaporation of the reaction mixture, the resulting residue was dissolved in dry EtOH (30–40 mL), and a stream of dry ammonia gas was passed into the solution for 24 h at 25 °C. Evaporation of the reaction mixture and crystallization of the residue from MeOH gave fully blocked C-nucleosides **14β** and **14α**, respectively, as white solids.

β-Nucleoside 14β (1.64 g, 85%) was obtained from **10β** (2 g, 3.41 mmol) as colorless needles after recrystallization from MeOH: mp 196 °C; UV (CH_2Cl_2) k_{max} (log ϵ) 304 (3.99), 230 (4.34), 217 nm (4.46); IR (KBr) 3180 (NH), 1690 (C=O), 1590, 1580 cm^{-1} (C=C, C=N); ^{1}H NMR (90 MHz, DMSO-d_6) δ 5.32 (d, 1 H, J = 4.0 Hz, 1′-H), 5.26 (m, 1 H, 2′-H), 4.75 (dd, 1 H, J = 5.6, 3.0 Hz, 3′-H), 4.27 (m, 1 H, 4′-H), 3.00 (m, 2 H, 5′a,b-H), 1.50 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 8.22 (s, 1 H, 5-H), 7.44–7.11 (m, 15 H, trityl), 3.15 (br s, 1 H, OH); ^{13}C NMR (200 MHz, DMSO-d_6) δ 164.09 (C=O), 155.76 (C-3a), 150.70 (C-3), 148.04 (C-5), 141.60 (C-7a), 143.53, 128.21, 127.80, 126.98, 86.00 (trityl), 84.62 (C-1′), 83.12 (C-4′), 82.51 (C-2′), 80.61 (C-3′), 64.02 (C-5′), 113.11, 27.20, 25.30 (C(CH_3)$_2$); MS m/z 567 (M^+-H, 6.0). Anal. Calcd for $C_{32}H_{29}N_3O_5S$: C, 67.71; H, 5.15; N, 7.40. Found: C, 67.32; H, 5.25; N, 7.28.

10α (1.5 g, 2.65 mmol) gave 1.25 g (86%) of **α-isomer 14α** as colorless plates after recrystallization from MeOH: mp 253 °C; UV (CH_2Cl_2) λ_{max} (log ϵ) 303 (3.81), 232 (4.08), 210 nm (4.50); IR (KBr) 3190 (NH), 1690 (C=O), 1580 cm^{-1} (C=C, C=N); ^{1}H

NMR (400 MHz, DMSO-d_6) δ 5.76 (d, 1 H, J = 4.6 Hz, 1′-H), 5.29 (t, 1 H, J = 6.2 Hz, 2′-H), 4.73 (d, 1 H, J = 6.9 Hz, 3′-H), 4.38 (t, 1 H, J = 4.6 Hz, 4′-H), 3.28 (dd, 1 H, J = 10.0, 3.8 Hz, 5′a-H), 3.19 (dd, 1 H, J = 10.0, 4.6 Hz, 5′b-H), 8.32 (s, 1 H, 5-H), 1.17 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 7.46–7.24 (m, 15 H, trityl), 3.35 (br s, 1 H, OH); ^{13}C NMR (400 MHz, DMSO-d_6) δ 162.72 (C=O), 155.87 (C-3a), 150.13 (C-3), 148.19 (C-5), 140.17 (C-7a), 143.43, 128.25, 128.05, 127.17, 86.76 (trityl), 82.70 (C-1′), 82.42 (C-4′), 81.94 (C-3′), 81.00 (C-2′), 64.20 (C-5′), 112.14, 25.85, 24.97 ($C(CH_3)_2$); MS m/z 567 (M^+, 0.2). Anal. Calcd for $C_{32}H_{29}N_3O_5S$: C, 67.71; H, 5.15; N, 7.40. Found: C, 67.45; H, 5.28; N, 7.39.

3-D-Ribofuranosylisothiazolo[4,5-*d*]pyrimidin-7(6*H*)-ones 3 and 4. Protected C-nucleosides 14β and 14α were dissolved separately in 7% methanolic HCl (15–20 mL) and stirred for 1 h at 25 °C. After evaporation of the solvent, the residues were crystallized from Et_2O and filtered, and the white precipitates obtained were washed several times with Et_2O.

Recrystallization of the **β-C-nucleoside 3** from 2-propanol afforded 0.16 g (94%) from 0.34 g (0.6 mmol) of 14β: mp 192 °C; UV (pH = 7) λ_{max} (log ϵ) 303 (4.06), 238 (4.13), 205 nm (4.24); IR (KBr) 3400–3100 (OH, NH), 1705 (C=O), 1590 cm^{-1} (C=N); ^{1}H NMR (200 MHz, DMSO-d_6) δ 5.10 (d, 1 H, J = 6.7 Hz, 1′-H), 4.48 (q, 1 H, J = 5.5 Hz, 2′-H), 4.06 (q, 1 H, J = 5.0 Hz, 3′-H), 3.90 (q, 1 H, J = 4.2 Hz, 4′-H), 3.53 (m, 2 H, 5′a,b-H), 8.39 (s, 1 H, 5-H), 5.16 (d, 1 H, J = 6.3 Hz, 2′-OH), 5.02 (d, 1 H, J = 5.1 Hz, 3′-OH), 4.93 (m, 1 H, 5′-OH) 12.96 (br s, 1 H, NH); ^{13}C NMR (200 MHz, DMSO-d_6) δ 165.43 (C=O), 155.88 (C-3a), 150.70 (C-3), 148.12 (C-5), 141.68 (C-7a), 85.84 (C-1′), 79.70 (C-4′), 74.16 (C-2′), 71.89 (C-3′), 62.38 (C-5′); MS m/z 285 (M^+, 14.0). Anal. Calcd for $C_{10}H_{11}N_3O_5S$: C, 42.06; H, 3.86; N, 14.72. Found: C, 41.73; H, 3.64; N, 14.34.

14α (0.45 g, 0.8 mmol) gave 0.23 g (90%) of **α-isomer 4** after recrystallization from MeOH, as a crystalline monohydrochloride salt: mp 253 °C; UV (pH = 7) λ_{max} (log ϵ) 303 (4.21), 237 (4.29), 203 nm (4.41); IR (KBr) 3450–3100 (OH, NH), 1670 (C=O), 1580 cm^{-1} (C=N); ^{1}H NMR (200 MHz, DMSO-d_6) δ 5.47 (d, 1 H, J = 4.2 Hz, 1′-H), 4.45 (t, 1 H, J = 4.3 Hz, 2′-H), 4.12 (dd, 1 H, J = 8.1, 4.7 Hz, 3′-H), 3.96 (m, 1 H, 4′-H), 3.68 (dd, 1 H, J = 11.4, 3.5 Hz, 5′a-H), 3.48 (dd, 1 H, J = 11.7, 4.4 Hz, 5′b-H), 8.26 (s, 1 H, 5-H), 5.55 (br s, 1 H, OH); ^{13}C NMR (200 MHz, DMSO-d_6) δ 164.94 (C=O), 156.00 (C-3a), 150.17 (C-3), 147.91 (C-5), 140.33 (C-7a), 82.60 (C-1′), 80.14 (C-4′), 72.69 (C-3′), 72.09 (C-2′), 61.49 (C-5′); MS m/z 285 (M^+, 5.0). Anal. Calcd for $C_{10}H_{12}N_3O_5S \cdot HCl \cdot 0.5CH_3OH$: C, 37.33; H, 4.44; N, 12.44. Found: C, 37.76; H, 4.51; N, 12.22.

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