

Asymmetric Synthesis of 1,3-Dithiolane Nucleoside Analogues

Romualdo Caputo,^[a] Annalisa Guaragna,^{*[a]} Giovanni Palumbo,^[a] and Silvana Pedatella^[a]*Dedicated to Prof. L. Mangoni on his 70th birthday***Keywords:** Nucleosides / Sulfur heterocycles / Chirality / Sulfoxides / Antiviral agents

We report the ready asymmetric synthesis of nucleoside analogues containing a 1,3-dithiolane ring that mimics the sugar moiety of natural nucleosides. The synthesis is accomplished in three main steps from benzoyloxyethanal 1,3-dithiolane, the key step being its conversion into a chiral monosulfoxide

by a modified Sharpless sulfo-oxygenation reaction. The nucleoside analogues were obtained in good overall yields and with excellent enantiomeric excesses.

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Introduction

The discovery of modified nucleosides that are effective in the treatment of Acquired Immunodeficiency Syndrome^[1] (AIDS) has aroused a great interest in the synthesis of such molecules during the last decade. Only a few nucleoside analogues, which act as reverse transcriptase inhibitors^[2] (NRTI), have been approved so far for the treatment of HIV-infected individuals, including AZT^[3] (Zidovudine), ddC^[4] (Zalcitabine), ddI^[5] (Didanosine), d4T^[6] (Stavudine), 3TC^[7] (Lamivudine), and the carbocyclic analogue ABC^[8] (Abacavir).

In general, nucleoside analogues having one or more heteroatoms replacing the ring atoms of the sugar moiety turn out to be more potent,^[9] possess improved selectivity toward mutant viruses, and show enhanced cellular uptake. The sugar configuration also seems to affect the biological activity of the NRTIs;^[10] in fact, β -L-(–)-2'-deoxy-3'-thiacytidine (lamivudine), which is the sole L-nucleoside analogue in use, is much less cytotoxic^[11] than its D-enantiomer (BCH-189), although both of them are roughly equipotent against the replication of HIV-1. All these considerations have spurred chemical research towards the synthesis of new L-sugar-based nucleoside analogues as potential reverse transcriptase inhibitors.

As a consequence, several methods are available in the recent literature for the synthesis of various nucleoside analogues,^[12] although the real challenge is the difficulty in preparing such compounds in optically pure forms.

In this paper, we report a new asymmetric synthesis of 1,3-dithiolane nucleoside analogues, a class of thioribonucleosides having a second sulfur atom replacing the 3' ribose carbon atom. Synthetic paths leading to such compounds are not very common and, to the best of our knowledge, so far only two synthetic routes have been reported,^[13,14] although both of them lead to racemic products that need resolution by HPLC on chiral columns to get enantiomerically pure compounds.

Results and Discussion

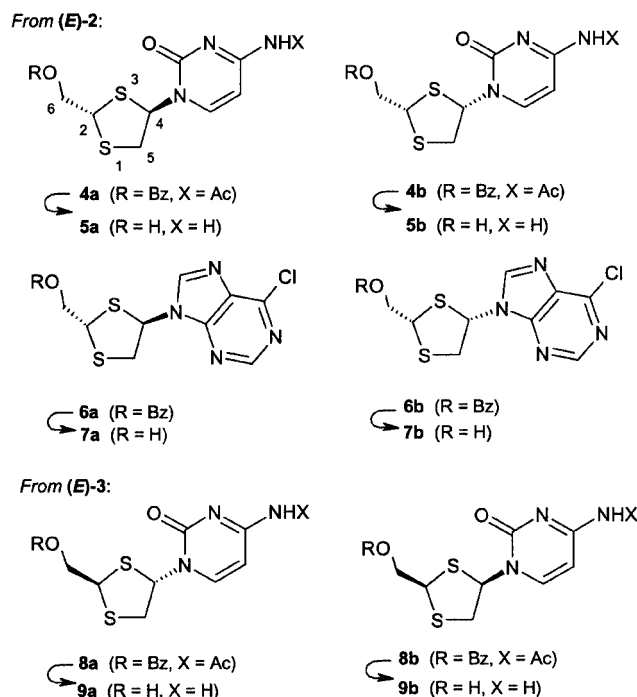
As a part of our current interest in the synthesis of modified sugars^[15] for their incorporation into nucleoside analogues, we have devised a new general approach to the asymmetric synthesis of chiral 1,3-dithiolanyl nucleosides (2,4-disubstituted 1,3-dithiolanes) with excellent enantiomeric excesses, in three main steps starting from benzoyloxyethanal 1,3-dithiolane.^[16]

The key step of our approach is the preparation of the chiral sulfoxides **2** (Scheme 1). 2-[(Phenylcarbonyloxy)methyl]-1,3-dithiolane (**1**) was obtained in very high yield (98%) by treatment of benzoyloxyethanal^[17] (from monobenzoylglycerol) with ethanedithiol in the presence of polystyryl diphenylphosphane–iodine complex, which acts as both a Lewis acid and a dehydrating agent, according to a procedure formerly developed in our laboratory^[18]. The conversion of achiral **1** into the chiral sulfoxides **2** was then performed by a Di Furia–Modena oxidation^[19] with *tert*-butyl hydroperoxide and diethyl D-tartrate in the presence of Ti^{IV} isopropoxide as catalyst.

In order to avoid the double oxidation of **1** at both the sulfur atoms (and overoxidation to the sulfone as well) we used a 5:1 molar ratio of **1** and the oxidizing system (*t*BuOOH/D-DET/Ti^{IV}). Under such conditions, the oxida-

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Scheme 1. Conversion of 1,3-dithiolane **1** into chiral sulfoxides **2** and **3**; i. D-DET/Ti(*O**i*Pr)₄/tBuOOH in CH₂Cl₂, -20 °C, 16 h; ii. same as i., but with L-DET

ferent, and their melting points differ by more than 90 °C) nor do they match our data for the same compounds.

Our new approach to the asymmetric synthesis of hetero-substituted nucleoside analogues may represent a rapid entry to optically pure materials and potentially is amenable to the preparation of multi-gram quantities of these important compounds.

Experimental Section

General: ^1H and ^{13}C NMR spectra: Varian Inova 500, Bruker DRX-400, Varian Gemini 200 spectrometers, CDCl_3 unless otherwise specified, TMS internal standard. Optical rotations: Jasco P-1010 (1.0 dm cell). Combustion analyses: Perkin–Elmer Series II 2400, CHNS analyzer. HPLC analyses: Gynkotek M480 chromatograph equipped with UVD 160S detector. Chiral columns: Cyclobond I 2000 RSP 4.6 mm ID $\times$ 250 mm (Astec) and DIACEL-chiralcel-OD-R 4.6 mm ID $\times$ 250 mm (JT Baker). TLC analyses: silica gel Merck 60 F₂₅₄ plates (0.2 mm layer thickness). Column chromatography: Merck Kieselgel 60 (70–230 mesh). Dry solvents were distilled immediately before use.

Compound 1: A solution of benzyloxyethanal (3.7 g, 22.6 mmol) in dry MeCN (25 mL) was added with a syringe in one portion to a magnetically stirred suspension of polystyryl diphenylphosphane–iodine complex (22.6 mmol, prepared in situ) in dry MeCN (150 mL), at room temperature and under an atmosphere of dry N₂. After 10 min, 1 M ethanedithiol in the same solvent (23 mL) was added in one portion. Benzyloxyethanal was fully consumed (TLC monitoring) within 2 h. Solid K₂CO₃ (excess) was added, the suspension stirred for a couple of minutes, and then filtered. The residual solid was washed with chloroform (3 × 100 mL), and then the combined filtrates were washed with 5 N aq

sodium thiosulfate (50 mL) and water until neutral. The solvents were then evaporated under reduced pressure to leave a residue consisting of practically pure **1** (5.3 g, 98%) as an oil. $C_{11}H_{12}O_2S_2$ (240.3): calcd. C 54.97, H 5.03; found C 55.13, H 5.04. 1H NMR (200 MHz): δ = 3.25 (s, 4 H, 4-H and 5-H), 4.35 (d, $J_{6,2}$ = 7.1 Hz, 2 H, 6-H), 4.79 (t, $J_{2,6}$ = 7.1 Hz, 1 H, 2-H), 7.38–7.52 (m, 3 H, *para*-H and *meta*-H), 8.03 (d, J_{ortho} = 7.9 Hz, 2 H, *ortho*-H). ^{13}C NMR (200 MHz): δ = 37.8 (C-4, C-5), 50.4 (C-2), 68.0 (C-6), 120.5 (C-arom), 128.2–132.9 (C-arom), 165.8 (C=O).

Compound 2. Typical Procedure: Diethyl D-tartrate (1.4 mL, 9.6 mmol) dissolved in dry CH_2Cl_2 (15 mL) was added under vigorous magnetic stirring at room temperature to a solution of Ti^{IV} isopropoxide (0.7 mL, 2.4 mmol) in dry CH_2Cl_2 (15 mL). After 10 min, the resulting yellow homogeneous solution was cooled to $-20^\circ C$. *tert*-Butyl hydroperoxide (1.6 mL, 5.7 mmol) was then added dropwise, followed after a few minutes by 1,3-dithiolane **1** (2.9 g, 12.1 mmol) dissolved in dry CH_2Cl_2 (20 mL). The reaction mixture was maintained at $-20^\circ C$ whilst stirring for 14 h, then quenched with cold H_2O (30 mL) and warmed up to room temperature. The resulting emulsion was cleared by filtration through Celite and the organic layer was then separated. The aqueous phase was extracted with CH_2Cl_2 (2×50 mL) and the combined organic phases were washed with 10% aq. sodium metabisulfite (100 mL), 5% aq. sodium hydroxide, and brine until neutral, then dried (Na_2SO_4) and the solvents evaporated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$) and, in addition to the unreacted starting material (1.5 g, 6.2 mmol), two diastereoisomeric sulfoxides were separated (overall yield 1.35 g, 90%). (*E*)-**2** (1.29 g, 5.03 mmol), m.p. 82–83 $^\circ C$ (from hexane). $[a]_D^{25}$ = -75.8 (c = 0.7, $CHCl_3$). $C_{11}H_{12}O_3S_2$ (256.3): calcd. C 51.54, H 4.72; found C 51.67, H 4.70. 1H NMR (400 MHz): δ = 2.80–2.94 (m, 1 H, 5- H_a), 3.48–3.62 (m, 2 H, 4-H), 3.75–3.86 (m, 1 H, 5- H_b), 4.35 (dd, $J_{6a,2}$ = 9.3, $J_{6a,6b}$ = 12.4 Hz, 1 H, 6- H_a), 4.53 (dd, $J_{6b,2}$ = 4.9, $J_{6b,6a}$ = 12.4 Hz, 1 H, 6- H_b), 4.59 (dd, $J_{2,6b}$ = 4.9, $J_{2,6a}$ = 9.3 Hz, 1 H, 2-H), 7.43–7.51 (m, 2 H, *meta*-H), 7.60 (t, J_{ortho} = 7.4 Hz, 1 H, *para*-H), 8.02 (d, J_{ortho} = 7.4 Hz, 2 H, *ortho*-H). [The signal of the 2-H proton is split by addition of $Eu(hfc)_3$ from δ = 4.59 (dd) to δ = 5.06 (br. s, 96%) and δ = 5.17 (br. s, 4%).] ^{13}C NMR (400 MHz): δ = 32.8 (C-4), 55.1 (C-5), 63.6 (C-6), 72.3 (C-2), 128.9, 129.0, 130.1, 133.9 (C-arom), 166.1 (C=O). HPLC (DIACEL, 60% MeCN plus 0.01% TFA in H_2O): R_t = 15.48 min (4%), 19.99 min (96%).

(*E*)-**3** was prepared (yield 90%) under the same conditions from **1** using diethyl L-tartrate: m.p. 71–73 $^\circ C$ (from hexane). $[a]_D^{25}$ = +74.9 (c = 0.6, $CHCl_3$). $C_{11}H_{12}O_3S_2$ (256.3): calcd. C 51.54, H 4.72; found C 51.41, H 4.73. 1H NMR and ^{13}C NMR spectra superimposable on those of (*E*)-**2**. HPLC (DIACEL, 60% MeCN plus 0.01% TFA in H_2O): R_t = 15.48 min (97%), 19.99 min (3%).

Compounds 4a and 4b. Typical Procedure: Trimethylsilyl triflate (TMSOTf) (0.9 mL, 4.8 mmol) and triethylamine (0.6 mL, 4.8 mmol) were added dropwise sequentially to a magnetically stirred suspension of *N*⁴-acetylcytosine (0.1 g, 1.2 mmol) in dry toluene (15 mL), at 0 $^\circ C$ and under nitrogen atmosphere. After 20 min a suspension of sulfoxide **2** [(*E*)-pair] (0.2 g, 0.8 mmol) in dry toluene (5 mL) was added and the resulting mixture was stirred overnight. After partial evaporation of the solvent under reduced pressure the residue was diluted with EtOAc (15 mL), washed with 5% aq $NaHCO_3$ (2×10 mL) and water until neutral, dried (Na_2SO_4), and then the solvents were evaporated under reduced pressure. After purification by column chromatography on silica gel (EtOAc/petroleum ether, 7:3) two diastereoisomeric cytosinyl dithiolanes (overall yield 0.22 g, 70%) were obtained.

Higher R_f product **4a** (*trans*) (0.12 g), m.p. 194–196 $^\circ C$ (MeOH). $[a]_D^{25}$ = +78.0 (c = 0.2, $CHCl_3$). $C_{17}H_{17}N_3O_4S_2$ (391.4): calcd. C 52.12, H 4.38; found C 52.26, H 4.37. 1H NMR (500 MHz): δ = 2.23 (s, 3 H, $COCH_3$), 3.46 (dd, $J_{5a,4}$ = 1.3, $J_{5a,5b}$ = 13.5 Hz, 1 H, 5- H_a), 3.63 (dd, $J_{5b,4}$ = 4.6, $J_{5b,5a}$ = 13.5 Hz, 1 H, 5- H_b), 4.37 (dd, $J_{6a,2}$ = 7.2, $J_{6a,6b}$ = 11.4 Hz, 1 H, 6- H_a), 4.49 (dd, $J_{6b,2}$ = 7.2, $J_{6b,6a}$ = 11.4 Hz, 1 H, 6- H_b), 5.02 (t, $J_{2,6a}$ = $J_{2,6b}$ = 7.2 Hz, 1 H, 2-H), 6.78 (dd, $J_{4,5a}$ = 1.3, $J_{4,5b}$ = 4.6 Hz, 1 H, 4-H), 7.41 (d, $J_{5',6'}$ = 7.5 Hz, 1 H, H-5'), 7.45–7.48 (m, 2 H, *meta*-H), 7.60 (t, J_{ortho} = 7.4 Hz, 1 H, *para*-H), 8.04 (d, J_{ortho} = 7.4 Hz, 2 H, *ortho*-H), 8.24 (d, $J_{6',5'}$ = 7.5 Hz, 1 H, 6'-H), 8.42 (br. s, 1 H, NH); [2-H, 4-H protons: no NOE effect]. ^{13}C NMR (200 MHz): δ = 24.7 ($COCH_3$), 43.8 (C-5), 51.6 (C-2), 67.1 (C-4), 70.2 (C-6), 96.0 (C-5'), 128.4, 129.1, 129.6, 133.3 (C-arom), 146.3 (C-6'), 155.2 (C=O), 162.9 (C=N), 165.7 (C=O), 171.1 (C=O). HPLC (Cyclobond I 2000 RSP, 50% MeOH plus 0.1 M NH_4OAc in H_2O): R_t = 25.98 min (96%), 29.09 min (4%).

Lower R_f product **4b** (*cis*) (0.1 g), m.p. 148–150 $^\circ C$ (MeOH). $[a]_D^{25}$ = -85.0 (c = 0.2, $CHCl_3$). $C_{17}H_{17}N_3O_4S_2$ (391.4): calcd. C 52.16, H 4.38; found C 52.33, H 4.41. 1H NMR (500 MHz): δ = 2.24 (s, 3 H, $COCH_3$), 3.48 (dd, $J_{5a,4}$ = 2.6, $J_{5a,5b}$ = 13.5 Hz, 1 H, 5- H_a), 3.62 (dd, $J_{5b,4}$ = 4.6, $J_{5b,5a}$ = 13.5 Hz, 1 H, 5- H_b), 4.78 (dd, $J_{6a,2}$ = 5.6, $J_{6a,6b}$ = 11.8 Hz, 1 H, 6- H_a), 4.81 (dd, $J_{6b,2}$ = 5.6, $J_{6b,6a}$ = 11.8 Hz, 1 H, 6- H_b), 5.02 (t, $J_{2,6a}$ = $J_{2,6b}$ = 5.6 Hz, 1 H, 2-H), 6.71 (dd, $J_{4,5a}$ = 2.6, $J_{4,5b}$ = 4.6 Hz, 1 H, 4-H), 7.29 (d, $J_{5',6'}$ = 7.5 Hz, 1 H, 5'-H), 7.49–7.53 (m, 2 H, *meta*-H), 7.64 (t, J_{ortho} = 7.6 Hz, 1 H, *para*-H), 8.07 (d, J_{ortho} = 7.4 Hz, 2 H, *ortho*-H), 8.51 (d, $J_{6',5'}$ = 7.5 Hz, 1 H, 6'-H); [2-H, 4-H protons: NOE effect]. ^{13}C NMR (200 MHz): δ = 24.7 (CH_3CO), 45.3 (C-5), 53.6 (C-2), 64.7 (C-4), 69.6 (C-6), 96.1 (C-5'), 128.5, 129.6, 130.8, 133.6 (C-arom), 146.3 (C-6'), 155.0 (C=O), 162.7 (C=N), 165.8 (C=O), 171.0 (C=O). HPLC (Cyclobond I 2000 RSP, 50% MeOH plus 0.1 M NH_4OAc in H_2O): R_t = 13.37 min (96%), 15.76 min (4%).

Under the same conditions the sulfoxides **3** [(*E*)-pair] afforded their enantiomeric nucleosides (**8a** and **8b**) in 72% yield, *trans/cis* = 1.1:1.0:

8a (*trans*), m.p. 193–195 $^\circ C$ (MeOH). $[a]_D^{25}$ = -80.0 (c = 0.2, $CHCl_3$). $C_{17}H_{17}N_3O_4S_2$ (391.4): calcd. C 52.16, H 4.38; found C 52.21, H 4.38. 1H NMR and ^{13}C NMR spectra superimposable on those of **4a**. HPLC (Cyclobond I 2000 RSP, 50% MeOH plus 0.1 M NH_4OAc in H_2O): R_t = 27.40 min (97%), 29.45 min (3%).

8b (*cis*), m.p. 149–151 $^\circ C$ (MeOH). $[a]_D^{25}$ = +84 (c = 0.2, $CHCl_3$). $C_{17}H_{17}N_3O_4S_2$ (391.4): calcd. C 52.16, H 4.38; found C 52.25, H 4.39. 1H NMR and ^{13}C NMR spectra superimposable on those of **4b**. HPLC (Cyclobond I 2000 RSP, 50% MeOH plus 0.1 M NH_4OAc in H_2O): R_t = 13.74 min (3%), 16.32 min (97%).

Compounds 6a and 6b: Trimethylsilyl triflate (TMSOTf) (0.44 mL, 2.4 mmol) and triethylamine (0.4 mL, 2.4 mmol) were added dropwise sequentially to a magnetically stirred suspension of 6-chloropurine (0.26 g, 1.6 mmol) in dry toluene (10 mL) at 0 $^\circ C$ under an N_2 atmosphere. After 4 h a suspension of sulfoxide **2** [(*E*)-pair] (0.2 g, 0.8 mmol) and ZnI_2 (0.08 g, 0.24 mmol) in the same solvent (5 mL) was added and the resulting mixture was stirred overnight. After partial evaporation of the solvent under reduced pressure, the residue was redissolved in EtOAc (15 mL), washed with 5% aq $NaHCO_3$ (2×10 mL) and water until neutral, dried (Na_2SO_4), and then the solvents evaporated under reduced pressure. After purification by column chromatography on silica gel (EtOAc/petroleum ether, 7:3) two diastereoisomeric purinyl dithiolanes **6a** and **6b** (0.4 g, yield 65%) were obtained.

Higher R_f product **6a** (*trans*) (0.2 g), m.p. 156–157 °C (MeOH). $[\alpha]_D^{25} = +43.3$ ($c = 0.2$, MeOH). $C_{16}H_{13}ClN_4O_2S_2$ (392.9): calcd. C 48.91, H 3.34; found C 48.80, H 3.35. 1H NMR (500 MHz): $\delta = 3.42$ (dd, $J_{5a,4} = 1.5$, $J_{5a,5b} = 13.4$ Hz, 1 H, 5- H_a), 3.79 (dd, $J_{5b,4} = 4.1$, $J_{5b,5a} = 13.4$ Hz, 1 H, 5- H_b), 4.45 (dd, $J_{6a,2} = 7.3$, $J_{6a,6b} = 11.4$ Hz, 1 H, 6- H_a), 4.56 (dd, $J_{6b,2} = 7.3$, $J_{6b,6a} = 11.4$ Hz, 1 H, 6- H_b), 5.15 (t, $J_{2,6a} = J_{2,6b} = 7.3$ Hz, 1 H, 2-H), 7.12 (dd, $J_{4,5a} = 1.5$, $J_{4,5b} = 4.1$ Hz, 1 H, 4-H), 7.50 (t, $J_{ortho} = 7.3$ Hz, 2 H, *meta*-H), 7.62 (t, $J_{ortho} = 7.3$ Hz, 1 H, *para*-H), 8.07 (d, $J = 7.3$ Hz, 2 H, *ortho*-H), 8.82 (s, 1 H, 2'-H), 8.91 (s, 1 H, 8'-H); [2-H, 4-H protons: no NOE effect]. ^{13}C NMR (200 MHz): $\delta = 45.0$ (C-5), 51.8 (C-2), 66.8 (C-4), 69.4 (C-6), 121.7 (C-5'), 128.6, 129.2, 130.8, 133.6 (C-arom), 142.4 (C-4'), 148.5 (C-8'), 152.8 (C-2'), 162.8 (C-6'), 165.9 (C=O).

Lower R_f product **6b** (*cis*) (0.2 g), amorphous. $[\alpha]_D^{25} = -34.4$ ($c = 0.2$, MeOH). $C_{16}H_{13}ClN_4O_2S_2$ (392.9): calcd. C 48.91, H 3.34; found C 48.83, H 3.33. 1H NMR (500 MHz): $\delta = 3.65$ (dd, $J_{5a,4} = 2.5$, $J_{5a,5b} = 13.4$ Hz, 1 H, 5- H_a), 3.81 (dd, $J_{5b,4} = 4.4$, $J_{5b,5a} = 13.4$ Hz, 1 H, 5- H_b), 4.73 (dd, $J_{6a,2} = 6.4$, $J_{6a,6b} = 11.7$ Hz, 1 H, 6- H_a), 4.79 (dd, $J_{6b,2} = 6.4$, $J_{6b,6a} = 11.7$ Hz, 1 H, 6- H_b), 5.17 (t, $J_{2,6a} = J_{2,6b} = 6.4$ Hz, 1 H, 2-H), 7.06 (dd, $J_{4,5a} = 2.5$, $J_{4,5b} = 4.4$ Hz, 1 H, 4-H), 7.49 (t, $J_{ortho} = 7.3$ Hz, 2 H, *meta*-H), 7.62 (t, $J_{ortho} = 7.3$ Hz, 1 H, *para*-H), 8.04 (d, $J = 7.3$ Hz, 2 H, *ortho*-H), 8.92 (s, 1 H, 2'-H), 9.02 (s, 1 H, 8'-H); [2-H, 4-H protons: NOE effect]. ^{13}C NMR (200 MHz): $\delta = 46.3$ (C-5), 53.4 (C-2), 65.5 (C-4), 68.7 (C-6), 120.5, (C-5'), 128.0, 129.1, 133.6 (C-arom), 142.1 (C-4'), 148.2 (C-8'), 152.7 (C-2'), 162.6 (C-6'), 165.8 (C=O).

Typical Deprotection Procedure. Compound **5a**: NaOMe (5.4 mg, 0.1 mmol) was added at room temperature to a stirring solution of **4a** (0.04 g, 0.1 mmol) in MeOH (5 mL) under an N_2 atmosphere. After 6 h the reaction mixture was quenched with glacial acetic acid (excess), the MeOH was removed under reduced pressure, and the crude residue chromatographed on silica gel ($CHCl_3$ /MeOH, 9:1) to give pure **5a** (0.02 g, yield 81%), m.p. 205 °C dec. (EtOAc). $[\alpha]_D^{25} = +26.5$ ($c = 0.7$, MeOH). $C_8H_{11}N_3O_2S_2$ (245.3): calcd. C 39.17, H 4.52; found C 39.06, H 4.55. 1H NMR (400 MHz, $[D_6]DMSO$): $\delta = 3.32$ –3.58 (m, 4 H, 5-H and 6-H), 4.72 (t, $J_{2,6} = 6.9$ Hz, 1 H, 2-H), 5.35 (t, $J_{OH,6} = 5.6$ Hz, 1 H, OH), 5.71 (d, $J_{5',6'} = 7.6$ Hz, 1 H, 5'-H), 6.48 (dd, $J_{4,5a} = 1.2$, $J_{4,5b} = 4.6$ Hz, 1 H, H-4), 7.22 (br. d, 2 H, NH_2), 7.88 (d, $J_{6',5'} = 7.6$ Hz, 1 H, 6'-H). ^{13}C NMR (500 MHz, $[D_6]DMSO$): $\delta = 42.6$ (C-5), 55.1 (C-2), 65.9 (C-4), 68.0 (C-6), 93.2 (C-5'), 142.5 (C-6'), 155.1 (C=O), 165.6 (C=N). HPLC (Cyclobond I 2000 RSP, 50% MeOH plus 0.1 M NH_4OAc in H_2O): $R_t = 9.68$ min (4%), 10.63 min (96%).

The followings nucleosides were also obtained under the same deprotection conditions.

Compound 5b from 4b: 83% yield, m.p. 110–112 °C (EtOAc). $[\alpha]_D^{25} = +18.5$ ($c = 0.06$, MeOH). $C_8H_{11}N_3O_2S_2$ (245.3): calcd. C 39.17, H 4.52; found C 39.26, H 4.53. 1H NMR (400 MHz, $[D_6]DMSO$): $\delta = 3.36$ (dd, $J_{5a,4} = 4.8$, $J_{5a,5b} = 12.7$ Hz, 1 H, 5- H_a), 3.46 (dd, $J_{5b,4} = 4.6$, $J_{5a,5b} = 12.7$ Hz, 1 H, 5- H_b), 3.73 (t, $J_{6,2} = 6.0$ Hz, 2 H, 6-H), 4.60 (t, $J_{2,6} = 6.0$ Hz, 1 H, 2-H), 5.49 (t, $J_{OH,6} = 5.9$ Hz, 1 H, OH), 5.74 (d, $J_{5',6'} = 7.3$ Hz, 1 H, 5'-H), 6.47 (dd, $J_{4,5a} = 4.8$, $J_{4,5b} = 4.6$ Hz, 1 H, H-4), 7.15 (bd, 2 H, NH_2), 8.04 (d, $J_{6',5'} = 7.3$ Hz, 1 H, 6'-H). ^{13}C NMR (500 MHz, $[D_6]DMSO$): $\delta = 42.3$ (C-5), 55.9 (C-2), 64.7 (C-4), 67.6 (C-6), 93.7 (C-5'), 142.1 (C-6'), 155.2 (C=O), 165.6 (C=N). HPLC (Cyclobond I 2000 RSP, 50% MeOH plus 0.1 M NH_4OAc in H_2O): $R_t = 9.76$ min (4%), 10.81 min (96%).

Compound 9a from 8a: 80% yield, m.p. 202 °C dec. (EtOAc). $[\alpha]_D^{25} = -28.5$ ($c = 0.7$, MeOH). $C_8H_{11}N_3O_2S_2$ (245.3): calcd. C 39.17, H 4.52; found C 39.29, H 4.51. 1H NMR and ^{13}C NMR spectra superimposable on those of **5a**. HPLC (50% MeOH plus 0.1 M NH_4OAc in H_2O): $R_t = 9.70$ min (97%), 10.65 min (3%).

Compound 9b from 8b: 78% yield, m.p. 108–110 °C (EtOAc). $[\alpha]_D^{25} = -20.5$ ($c = 0.1$, MeOH). $C_8H_{11}N_3O_2S_2$ (245.3): calcd. C 39.17, H 4.52; found C 39.22, H 4.52. 1H NMR and ^{13}C NMR spectra superimposable on those of **5b**. HPLC (50% MeOH plus 0.1 M NH_4OAc in H_2O): $R_t = 9.75$ min (97%), 10.79 min (3%).

Compound 7a from 6a: 94% yield, m.p. 192–194 °C (MeOH). $[\alpha]_D^{25} = +25.8$ ($c = 0.34$, MeOH). $C_9H_9ClN_4OS_2$ (288.8): calcd. C 37.43, H 3.14; found C 37.36, H 3.12. 1H NMR (500 MHz): $\delta = 3.39$ (dd, $J_{5a,4} = 1.5$, $J_{5a,5b} = 13.2$ Hz, 1 H, 5- H_a), 3.64 (dd, $J_{5b,4} = 4.2$, $J_{5b,5a} = 13.2$ Hz, 1 H, 5- H_b), 3.72–3.78 (m, 2 H, 6-H), 4.87 (t, $J_{2,6} = 6.6$ Hz, 1 H, 2-H), 6.85 (dd, $J_{4,5a} = 1.5$, $J_{4,5b} = 4.2$ Hz, 1 H, 4-H), 8.61 (s, 1 H, 2'-H), 8.64 (s, 1 H, 8'-H). ^{13}C NMR (500 MHz): $\delta = 44.5$ (C-5), 54.3 (C-2), 66.2 (C-4), 69.5 (C-6), 112.0 (C-5'), 144.9 (C-8'), 152.3 (C-8'), 156.7 (C-4'), 161.9 (C-5').

Compound 7b from 6b: 95% yield, amorphous. $[\alpha]_D^{25} = -32.7$ ($c = 0.34$, MeOH). $C_9H_9ClN_4OS_2$ (288.8): calcd. C 37.43, H 3.14; found C 37.35, H 3.15. 1H NMR (500 MHz): $\delta = 3.53$ (dd, $J_{5a,4} = 2.9$, $J_{5a,5b} = 13.1$ Hz, 1 H, 5- H_a), 3.72 (dd, $J_{5b,4} = 4.4$, $J_{5b,5a} = 13.1$ Hz, 1 H, 5- H_b), 3.74–3.81 (m, 2 H, 6-H), 4.91 (t, $J_{2,6} = 5.6$ Hz, 1 H, 2-H), 6.78 (dd, $J_{4,5a} = 2.9$, $J_{4,5b} = 4.4$ Hz, 1 H, 4-H), 8.65 (s, 1 H, 2'-H), 8.84 (s, 1 H, 8'-H). ^{13}C NMR (500 MHz): $\delta = 46.2$ (C-5), 56.9 (C-2), 65.5 (C-4), 69.1 (C-6), 111.5 (C-5'), 144.5 (C-8'), 152.3 (C-2'), 156.0 (C-4'), 160.2 (C-6').

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