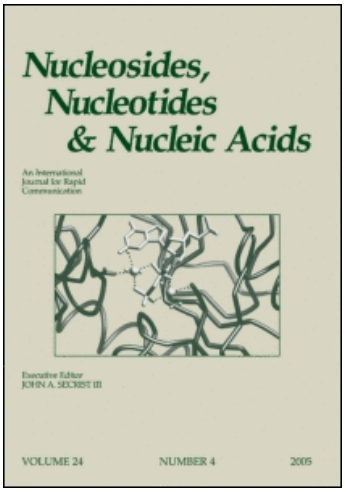

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Efficient Synthesis of 4-Thio-D-ribofuranose and Some 4'-Thioribonucleosides

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EFFICIENT SYNTHESIS OF 4- THIO-D-RIBOFURANOSE AND SOME 4'-THIORIBONUCLEOSIDES .

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ABSTRACT : A synthetic pathway to reach easily the 4-thio-D-ribofuranose is described. Some corresponding pyrimidine α and ß 4'-thioribonucleosides have been synthesized and evaluated as antiviral agents against various viruses.

Sugar-modified nucleoside analogues have attracted considerable interest, mainly as potential antiviral or antitumor agents (1, 2). Thus, since 3'-azido-3'-deoxythymidine (AZT) has been shown to be a potent antiviral agent against human immunodeficiency virus (HIV) (3) a number of reports have appeared on the synthesis of sugar-modified nucleoside analogues. Recently, several 2',3'-dideoxy and 2',3'-unsaturated-2',3'-dideoxy nucleosides have been shown promising *in vitro* activity (4). However, despite the demonstration of their *in vitro* efficiency, the clinical usefulness of these compounds is always hampered by various limiting factors, the appreciable toxic side effects being the more restrictive (5). This point justified the search for novel nucleoside analogues which appeared to be an attractive synthetic aim for the development of potential anti-HIV agents. Among all the sugar modification investigated few of them concern the replacement of the oxygen atom in the carbohydrate ring by various other atoms (6) except for the carbocyclic series. For those reasons, we were interested by the nucleosides analogues with sulfur replacing the oxygen atom in the sugar moiety.

Sugar with intracyclic sulfur were first described in 1961 (7, 8) and some of the corresponding nucleosides soon afterwards (7, 9-16). But these thionucleosides have not been completely screened for their potential antiviral activities and furthermore

they could be used as starting synthons to reach the unknown corresponding chimeric oligonucleotides.

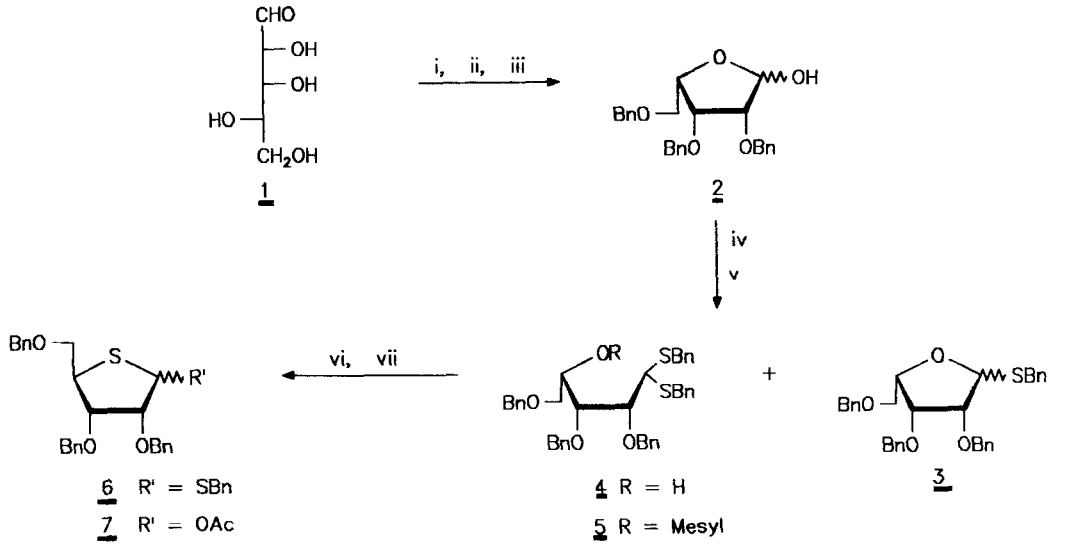
However since this work was finished, some recent publications (17-23) reported the synthesis and biological evaluation of some 4'-thionucleosides in the 2'-deoxyribofuranose and xylofuranose series but not in the 4'-thioribofuranose series and this prompted us to publish our data. In earlier publications (7, 8), the 4-thio-D-ribofuranose was obtained in six steps in a 6 % overall yield and the corresponding 4-thio-2-deoxysugar was reached after fourteen steps (8 % yield). Then the corresponding thionucleosides were synthesized through condensation of the activated nucleobase with a suitable protected thiosugar.

Therefore our initial effort was focused on the design of a strategy which could give rise to a better access to a 4-thioribofuranose sugar. In addition, we were interested on having a good leaving group on the anomeric position and a non participating protecting group on the 2-OH to afford an α / ß mixture of nucleosides. Afterwards the corresponding nucleosidic series could be explored for their potential antiviral activities and for being transformed to the oligonucleotidic constitutive synthons.

For that purpose, we looked at a strategy based on the introduction of a sulfur atom on the C-1 position followed by a nucleophilic displacement of an activated 4-hydroxyl group with inversion of configuration.

The 2,3,5-tri-O-benzyl-4-thio-1-O-acetyl-D-ribofuranose **7** is obtained from L-lyxose **1** with an overall yield of 21 % as shown on Figure 1. After synthesis in usual manner of the 2,3,5-tri-O-benzyl-L-lyxofuranose **2** (24), treatment of **2** with thiobenzyl alcohol (25) led to a mixture of dithiobenzyl acetal **4** (66 % yield) and hemithioacetal **3** (25 %). After chromatographic separation, **3** was reacted again under the same conditions to afford **4** in quantitative yield. The mesylation of **4** gave the expected compound **5** which was characterised by spectral evidence. The nucleophilic substitution can be directly achieved by warming the mesylation reaction in aqueous pyridine or heating with sodium iodide in acetone (26) or sodium iodide and baryum carbonate in acetone (19).

In order to optimize the reaction yield we used as cyclisation agent the *tetra*-butyl ammonium iodide and barium carbonate in pyridine (23). Under these conditions, **5** cyclised smoothly to give the benzyl 2,3,5-tri-O-benzyl 1,4-dithio-D-ribofuranoside **6** as a mixture of anomers in a 94 % overall yield . Treatment of **6** with mercuric acetate in acetic acid (27) gave **7** as an anomeric mixture.



(i = MeOH, HCl; ii = BnBr, KOH; iii = HCl, H_2O, dioxane; iv = BnSH, HCl, v = MesCl, pyr.; vi = NBu_4I, $BaCO_3$; vii = $Hg(OAc)_2$)

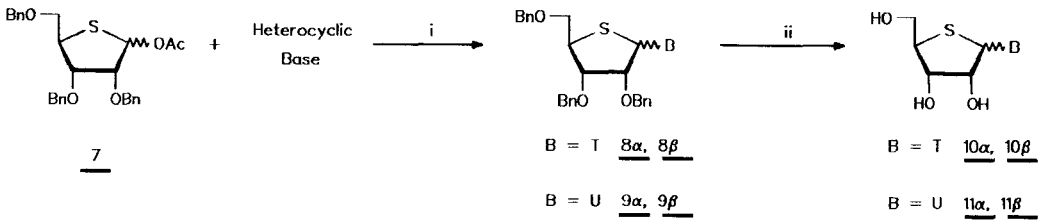
Figure 1

Thus, the 1-O-acetyl-2,3,5-tri-O-benzyl-4-thio-D-ribofuranose 7 was obtained from L-lyxose in an overall yield of 21 %.

The anomeric mixture 7 was purified by silica gel column chromatography and the α and ß anomers were separated and fully characterised independently.

We then investigated first the synthesis of the 4'-thio-D-ribofuranonucleosides corresponding to thymine and uracil in order to rapidly evaluate their antiviral behavior and also to reach the corresponding homothiooligoribonucleotides (28).

The corresponding pyrimidines were silylated with N, O-*bis* (trimethylsilyl)acetamide (BSA) and condensed with 7 (anomeric mixture) using *tri*-methylsilyltrifluoromethane sulfonate (TMSTf) as coupling reagent giving rise to the expected nucleoside derivative 8 (77 % yield, α/ß = 43/57) and 9 (74 % yield, α/ß = 47,5/53,5) (Fig.2).



(i = BSA, TMSTf, CH_3CN; ii = BBr_3, CH_2Cl_2)

Figure 2

As expected with a 2' non participating group, an anomeric mixture was obtained in both cases. Separation of the two anomers was achieved before deblocking on a silica gel column. Deprotection of each anomers were performed independently using boron tribromide (29) instead of boron trichloride (20) as only 7.5 equiv. of BBr_3 were necessary for completion of the reaction.

Anomeric configuration was ascertained using NOESY experiments on the protected nucleosides. Spectra analysis of **8 ß** and **9 ß** clearly show correlative spots corresponding to dipolar interactions between $H_{1'}$ - H_6 and $H_{2'}$ - H_6 protons, due to the spatial neighbourhood of these atoms. **8 α** and **9 α** NOESY spectra present the same $H_{1'}$ - H_6 and $H_{2'}$ - H_6 interactions plus some connectivities between H_6 - benzylic methylene and H_6 - $H_{4'}$ which are possible when taking into account the base rotation around the nucleosidic binding C-N only in the case of α anomer. Indeed only this conformation reviews the small three dimensional distances between $H_{1'}$, $H_{2'}$, CH_2 and H_6 protons.

All the prepared thionucleosides analogues were tested for their *in vitro* inhibitory effects on the replication of a number of DNA viruses (i.e. Human Cytomegalovirus, Herpes Simplex Virus type 1 and type 2, Vaccinia Virus) and RNA virus (Parainfluenza Virus type III, Respiratory Syncitial Virus, Sindbio Virus, Coxsackie Virus B3 and Polio Virus-1) in three cell system (MRC-5, Vero, and KB cells).

None of the thionucleosides analogues showed an antiviral effect at doses up to 1mM. When evaluated in two anti-human immunodeficiency virus assays, none of the tested compounds showed a marked antiviral effect at a concentration less than 10-fold lower than the minimal concentration causing a detectable alteration of MT-4 and CEM host cell viability (1mM).

CONCLUSION

The process described in this paper allows to reach the thionucleosidic series of α and ß configuration. This thioribonucleosides are now available for use in oligothionucleotide synthesis (28).

EXPERIMENTAL SECTION.

GENERAL METHODS.

Melting points were determined with a Büchi-Tottoli 510 apparatus and are uncorrected. Sample for U.V. spectra were dissolved in spectroscopic grade ethanol 95 and spectra were recorded on a UVIKON 800 spectrophotometer. ^1H NMR spectra were determined with a BRUCKER AM 300 MHz or a BRUKER AC 250 MHz with tetramethylsilane as internal standard, chemical shift are quoted in ppm (s = singlet, d = doublet, t = triplet, m = multiplet, dd = double doublet, q = quadruplet, br = broad signal) and coupling constants J in Hertz (Hz). Electron mass spectra (70 eV) were recorded on a JEOL JMS DX 300 mass spectrometer. Precoated MERCK Silica gel F_{254} plates were used for TLC. Detection was achieved under U.V. light (254 nm) or by spraying with 30 % H_2SO_4 in ethanol and heating. Column chromatography was performed on MERCK silica gel (0.063-0.200 mm). All the solvants were distilled before use and rendered anhydrous according to the procedure given by D. D. PERRIN and W. L. F. ARMAREGO, Purification of Laboratory Chemicals. Pergamon Press, London (1988).

The 2,3,5-tri-O-benzyl-L-lyxofuranose 2 was synthesized from L-lyxose according to BARKER and FLETCHER Jr. procedure (24) with 40 % yield.

2,3,5-tri-O-benzyl-1-thiobenzyl-L-lyxofuranose 3 and 2,3,5-tri-O-benzyl-L-lyxose dibenzyl dithioacetal 4.

2 (7.23 g, 17.21 mmol) was stirred at 0° C with concentrated hydrogen chloride (4.82 ml, 60.25 mmol) and thiobenzylic alcohol (7.68 ml, 65.41 mmol) without any solvent. Five minutes later, 2 could not be detected on TLC and the reaction mixture reached room temperature with continuous stirring. The hemithioacetal 3 (R_f 0.63 in CH_2Cl_2, MeOH - 99 : 1) formed initially turned into the dithiocetal 4 (R_f 0.50 in CH_2Cl_2, MeOH - 99 : 1) within 2.5 h. The reaction mixture was neutralized with a

5 % aqueous $NaHCO_3$ solution, diluted in methylene chloride, and extracted. The organic layer was dried over sodium sulfate and concentrated. The crude product applied on a silica gel column chromatography was eluted with CH_2Cl_2, MeOH (99 : 1). The appropriate fractions were combined and evaporated to give 8.27 g of pure **4** (yield = 66 %) and 2.59 g of **3** (yield = 25 %).
The remaining compound **3** was reacted again under the same conditions to afford **4** quantitatively.

2,3,5-tri-O-benzyl-L-lyxose dibenzyl dithioacetal **4**.

MS FAB > 0 GT m/z 651 $[M+H]^+$, 633 $[M+H-H_2O]^+$, 527 $[M+H-\Phi CH_2SH]^+$. ^1H NMR (300 MHz $CDCl_3$) δ 3.61, (m, 3H, H_4, H_5, $H_{5'}$), 3.80, (m, 4H, -S-CH_2-Φ), 4.06 - 4.30, (m, 3H, H_1, H_2, H_3), 4.40 - 4.90, (m, 6H, -O-CH_2-Φ), 4.80, (d, 1H, OH), 7.30, (m, 25H, -O-CH_2-Φ and -S-CH_2-Φ).

2,3,5-tri-O-benzyl-1-thiobenzyl-L-lyxofuranose **3**.

MS FAB > 0 NOBA m/z 525 $[M + H]^+$, 419 $[M + H - \Phi CH_2OH]^+$. ^1H NMR (250 MHz $CDCl_3$) δ 3.75, (m, 2H, H_5, $H_{5'}$), 3.88 (m, 2H, S-CH_2-Φ), 3.92, (m, 1H, H_2), 4.14, (t, 1H, H_3, $J_{3,2}$ = 4.6, $J_{3,4}$ = 4.6), 4.36, (m, 1H, H_4, $J_{4,3}$ = 4.6), 4.51, (m, 6H, O-CH_2-Φ), 5.26, (d, 1H, H_1, $J_{1,2}$ = 4.6), 7.30, (m, 20H, O-CH_2-Φ, S-CH_2-Φ).

Benzyl 2,3,5-tri-O-benzyl 1,4 dithio-D-ribofuranoside **6**.

A solution of the dithioacetal **4** (7.59 g, 11.67 mmol) in anhydrous pyridine (100 ml) was treated slowly at 0°C with mesyl chloride (1.74 g, 15.18 mmol). The solution was stirred for 4 h until **4** had consumed to give **5** (R_f 0.54 in CH_2Cl_2, MeOH - 99 : 0.5). To this reaction mixture was added barium carbonate (2.30 g, 11.67 mmol) and *tetra*-butylammonium iodide (4.31 g, 11.67 mmol) and the dark yellow heterogeneous solution was heated under reflux for 0.75 h to give **6** (R_f 0.61 in CH_2Cl_2, MeOH - 99 : 0.5). The solution was evaporated under reduced pressure, diluted with dichloromethane, washed with a 5 % aqueous $NaHCO_3$ solution and extracted. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was applied on a silica gel column chromatography with hexane, dichloromethane (1 : 1) as the eluant system to afford finally 5.99 g of pure **6** (yield 94 %).

Benzyl 2,3,5-tri-O-benzyl 1,4 dithio-D-ribofuranoside 6.

MS EI m/z 542 $[M]^{+\cdot}$, 451 $[M-\Phi CH_2]^{+\cdot}$, 419 $[M-\Phi CH_2 S]^{+\cdot}$. ^{1}H NMR (250 MHz $CDCl_3$) δ 3.51, (q, 1H, H_5, $J_{5,5'}$ = 9.5, $J_{5,4}$ = 6.7), 3.64, (q, 1H, $H_{5'}$, $J_{5',5}$ = 9.5, $J_{5',4}$ = 6.8), 3.75, (m, 3H, H_4, -S-$\underline{CH}_2$-Φ), 3.84, (t, 1H, H_2, $J_{2,1}$ = 3.7, $J_{2,3}$ = 3.7), 4.06, (q, 1H, H_3, $J_{3,2}$ = 3.4, $J_{3,4}$ = 6.4), 4.30, (d, 1H, H_1, $J_{1,2}$ = 4.0), 4.4 - 4.5, (m, 6H, -O-$\underline{CH}_2$-Φ), 7.30, (m, 20H, Φ-CH_2-O, Φ-CH_2-S,). ^{13}C NMR Decoupling ^{1}H δ 37.04, (s, C_2), 47.62, (s, C_3), 50.95, (s, C_5), 72.30,(q,-CH_2-Φ), 80.99, (s, C_4), 83.48, (s, C_1), 127.8, (m, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$ aromatic), 137.8, (q, $C_{1'}$ aromatic).

2,3,5-tri-O-benzyl-1-O-acetyl-4-thio-D-ribofuranose 7.

Compound 6 (5.99 g, 11.05 mmol) was stirred with acetic acid (103.5 g, 1.724 mol) and mercuric acetate (7.89 g, 24.75 mmol) at room temperature for 2.5 h. The reaction mixture was diluted in dichloromethane, washed successively with water, saturated aqueous $NaHCO_3$ and 5 % KCN aqueous solution. The methylene chloride layer was dried over Na_2SO_4 and concentrated. Chromatography of the crude product in dichloromethane as the eluant gave 86 % of pure ß anomer (R_f 0.23 in CH_2Cl_2) and 14 % of pure α compound (Rf 0.14 in CH_2Cl_2) with 86 % overall yield.

7α

MS FAB > 0 NOBA m/z 569 $[M+H+G]^+$, 477 $[M-H]^+$, 419 $[M+H-CH_3CO_2H]^+$, 371 $[M+H-\Phi CH_2OH]^+$. ^{1}H NMR (250 MHz DMSO-d_6) δ 2.04, (s, 3H, CH_3 CO), 3.4, (m, 1H, $H_{5'}$), 3.52, (q, 1H, H_5, $J_{5,5'}$ = 9.9, $J_{5,4}$ = 6.8), 3.52, (q, 1H, H_4, $J_{4,3}$ = 3.2, $J_{4,5}$ = 6.7, $J_{4,5'}$ = 6.7), 4.09, (t, 1H, H_3, $J_{3,4}$ = 3.5, $J_{3,2}$ = 3.4), 4.27, (t, 1H, H_2, $J_{2,3}$ = 4.1 , $J_{2,1}$ = 4.4), 4.6, (m, 6H, -O-$\underline{CH}_2$-Φ), 6.09, (d, 1H, H_1, $J_{1,2}$ = 4.6), 7.4, (m, 15H, O -CH_2-Φ).

7ß

MS FAB > 0 NOBA m/z 569 $[M-H+G]^+$, 477 $[M-H]^+$, 419 $[M+H-CH_3CO_2H]^+$, 371 $[M+H-\Phi CH_2OH]^+$. ^{1}H NMR (250 MHz DMSO-d_6) δ 3.5, (m, 1H, $H_{5'}$, $J_{5',5}$ = 9.2, $J_{5',4}$ = 3.8), 3.63, (m, 1H, H_4), 3.8, (q, 1H, H_5, $J_{5,5'}$ = 9.3, $J_{5,4}$ = 3.8), 3.97, (q, 1H, H_3, $J_{3,4}$ = 8.1, $J_{3,2}$ = 3.4), 4.31, (q, 1H, H_2, $J_{2,3}$ = 3.1, $J_{2,1}$ = 2.2), 4.62, (m, 6H, -$\underline{CH}_2$-Φ), 5.83, (d, 1H, H_1, $J_{1,2}$ = 1.9), 7.3, (m, 15H, O-CH_2-Φ).

1-[2',3',5'-tri-O-benzyl-4'-thio-ß-D-ribofuranosyl]Thymine **8ß** and 1-[2',3',5'-tri-O-benzyl-4'-thio-α-D-ribofuranosyl]Thymine **8α**.

Method A

To a solution of **7** (1.97 g, 4.10 mmol) and Thymine (0.52 g, 4.13 mmol) in anhydrous acetonitrile (62 ml) were added consecutively hexamethyldisilazane (HMDS) (533 mg, 3.30 mmol), trimethylsilyl chloride (TMSCl) (359 mg, 3.30 mmol) and $SnCl_4$ (1.29 g, 4.96 mmol) and the mixture was heated under reflux of acetonitrile for 20 min. When no more **7** could be detected on TLC the reaction mixture was concentrated under reduced pressure to a small volume (10 ml), diluted with dichloromethane, washed with two portions (50 ml each) of saturated aqueous sodium bicarbonate followed by water. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by chromatography over silica gel and eluted with CH_2Cl_2, MeOH - 98 : 2 to afford **8** as a mixture of anomers (39 % yield).

Method B

To a suspension of Thymine (596 mg, 4.72 mmol) in anhydrous acetonitrile (20 ml) in a round bottom flask flushed with argon was added BSA (3.84 g, 18.9 mmol). The reaction mixture was allowed to warm under reflux for 0.5 h until all the base became soluble. At this time, **7** (1.87 g, 3.92 mmol) dissolved in four portions (5 ml each) of acetonitrile and TMSTf (1.26 g, 5.67 mmol) were added and the reaction mixture stirred for 2.5 h. The solution was then cooled to 0°C and a precipitate appeared as in proportion the addition of a 5 % aqueous $NaHCO_3$ solution. The heterogenous mixture was concentrated till complete evaporation of acetonitrile and methylene chloride (40 ml) was added to the bicarbonate solution. The organic layer was washed with two portions (30 ml each) of water, dried over Na_2SO_4 and concentrated to dryness. The crude product was applied on a silica gel column chromatography and eluted with diethylether. **8ß** (R_f 0.65 in ether, 41 % yield) and **8α** (R_f 0.44 in ether, 36.5 % yield) were obtained with 77 % overall yield.

8α :

$[\alpha]_D^{20}$ +3.83° (c 3.42 $CHCl_3$). MS FAB > 0 NOBA m/z 545 $[M+H]^+$. ^{1}H NMR (300 MHz DMSO-d_6) δ 1.53, (d, 3H, CH_3, $J_{Me,6}$ = 0.7), 3.48, (q, 1H, $H_{5''}$, $J_{5'',5'}$ = 9.9, $J_{5'',4'}$ = 7.2), 3.67, (q, 1H, $H_{5'}$, $J_{5',5''}$ = 9.9, $J_{5',4'}$ = 5.7), 3.94, (m, 1H, $H_{4'}$), 4.16, (dd, 1H, $H_{3'}$, $J_{3',4'}$ = 5.1, $J_{3',2'}$ = 3.7), 4.44, (dd, 1H, $H_{2'}$, $J_{2',1'}$ = 6.0, $J_{2',3'}$ = 3.7), 4.50, (m, 6H, -O-$\underline{CH}_2$-Φ), 6.33, (d, 1H, $H_{1'}$, $J_{1',2'}$ = 6.0), 7.30, (m, 15H, -O-CH_2-Φ), 7.86, (d, 1H, H_6, $J_{6,Me}$ = 1.0), 11.29, (s, 1H, NH).

8ß :

$[\alpha]_D^{20}$ +8.49° (c 2.99 $CHCl_3$).MS FAB > 0 NOBA m/z 545 $[M+H]^+$. ^{1}H NMR (300 MHz DMSO-d_6) δ 1.47, (s, 3H, CH_3), 3.70, (m, 3H, $H_{4'}$, $H_{5'}$, $H_{5''}$), 4.17, (m, 1H, $H_{3'}$, $J_{3',2'}$ = 3.2, $J_{3',4'}$ = 3.0), 4.27, (dd, 1H, $H_{2'}$, $J_{2',3'}$ = 3.7, $J_{2',1'}$ = 7.0), 4.54, (m, 6H, -O-$\underline{CH}_2$-Φ), 6.07, (d, 1H, $H_{1'}$, $J_{1',2'}$ = 7.1), 7.27, (m, 15H, -O-CH_2-Φ), 7.52, (s, 1H, H_6), 11.33, (s, 1H, NH). ^{13}C NMR decoupling ^{1}H (DMSO-d_6) δ 11.91, (s, CH_3), 47.94, (s, $C_{5'}$), 61.03, (s, $C_{2'}$), 70.80, (s, $C_{3'}$), 71.18, (m, CH_2 benzylic), 78.00, (s, $C_{4'}$), 81.76, (s, $C_{1'}$), 109.75, (s, C_6), 128.08, (m, $C_{2'}$,$C_{3'}$,$C_{4'}$,$C_{5'}$,$C_{6'}$ aromatic), 135.72, (s, C_5), 137.89, (m, $C_{1'}$ aromatic), 150.81, (s, C_2), 163.28, (s, C_4).

1-[2',3',5'-tri-O-benzyl-4'-thio-α-D-ribofuranosyl]Uracil **9α** and 1-[2',3',5'-tri-O-benzyl-4'-thio-ß-D-ribofuranosyl]Uracil **9ß**.

9α and **9ß** were synthesized according to the method B developed for **8**. After the usual work-up the crude products were applied on a silica gel column chromatography in hexane, diethylether - 1 : 2 as the eluant system . **9α** (R_f 0.36 in ether, 31 % yield) and **9ß** (R_f 0.46 in ether, 41.7 % yield) were obtained as pure products.

9α :

$[\alpha]_D^{20}$ +3.2° (c 1.0 $CHCl_3$). MS FAB > 0 NOBA m/z 531 $[M+H]^+$. ^{1}H NMR (300 MHz DMSO-d_6) δ 3.46, (dd, 1H, $H_{5''}$, $J_{5'',5'}$ = 9.8, $J_{5'',4'}$ = 7.3), 3.66, (dd, 1H, $H_{5'}$, $J_{5',5''}$ = 9.9, $J_{5',4'}$ = 5.6), 3.91, (m, 1H, $H_{4'}$, $J_{4',5'}$ = 5.6, $J_{4',5''}$ = 7.3, $J_{4',3'}$ = 5.6), 4.12, (dd, 1H, $H_{3'}$, $J_{3',4'}$ = 5.5, $J_{3',2'}$ = 3.7), 4.42, (dd, 1H, $H_{2'}$, $J_{2',3'}$ = 3.7, $J_{2',1'}$ = 5.8), 4.53, (m, 6H, -O-$\underline{CH}_2$-Φ), 5.48 , (d, 1H, H_6, $J_{6,5}$ = 8.1), 6.30, (d, 1H, $H_{1'}$, $J_{1',2'}$ = 5.9), 7.30, m, 15H, -O-CH_2-Φ), 8.00, (d, 1H, H_5, $J_{5,6}$ = 8.1), 11.3, (s, 1H, NH).

9ß :

$[\alpha]_D^{20}$ +13.1° (c 1.0 $CHCl_3$). MS FAB > 0 NOBA m/z 531 $[M+H]^+$. ^{1}H NMR (300 MHz DMSO-d 6) δ 3.71, (m, 3H, $H_{4'}$, $H_{5'}$, $H_{5''}$), 4.09, (t, 1H, $H_{3'}$, $J_{3',2'}$ = 3.6, $J_{3',4'}$ = 3.6), 4.26, (dd, 1H, $H_{2'}$, $J_{2',1'}$ = 6.1, $J_{2',3'}$ = 3.6), 4.53, (m, 6H, -O-$\underline{CH}_2$-Φ), 5.25, (d, 1H, H_5, $J_{5,6}$ = 8.0), 6.03, (d, 1H, $H_{1'}$, $J_{1',2'}$ = 6.2), 7.30, (m, 15H, -O-CH_2-Φ), 7.85, (d, 1H, H_6, $J_{6,5}$ = 8.1), 11.34, (s, 1H, NH).

1-[4'-thio-ß-D-ribofuranosyl]Thymine **10ß.**

A solution of **8ß** (978 mg, 1.79 mmol) in dichloromethane (15 ml) was treated at -78°C under argon with a solution (1M) of boron tribromide in dichloromethane (13.42 ml). As in proportion the addition of the BBr_3 solution, the initially colourless reaction mixture turned to dark yellow. After 0.5 h with stirring at -78°C, methanol (6 ml) was added and the solution cleared, then pyridine (8 ml) neutralized the reaction mixture from pH 1 to pH 7 before evaporation to dryness. The residue was dissolved in methylene chloride and applied on a silica gel column chromatography in CH_2Cl_2, MeOH - 95 : 5 to afford pure **10ß** (R_f = 0.32 in CH_2Cl_2, MeOH - 9 : 1, 82 % yield).

10ß :
$[\alpha]_D^{20}$ -27.4° (c 2.26 H_2O). U.V. pH 12 λ_{max} = 270 nm, ϵ 8400, [lit.(13) pH 12 λ max 271 nm, ϵ 8500]. MS FAB > 0 NOBA m/z 297 $[M+H+Na]^+$, 275 $[M+H]^+$. ^1H NMR (300 MHz DMSO-d_6) δ 1.80, (d, 1H, 3H, $CH_{3'}$, $J_{Me,6}$ = 0.7), 3.18, (m, 1H, $H_{4'}$), 3.55, (m, 1H, $H_{5''}$, $J_{5'',5'}$ = 11.0, $J_{5'',4'}$ = 5.4, $J_{5'',OH}$ = 5.4), 3.67, (m, 1H, $H_{5'}$, $J_{5',5''}$ = 11.0, $J_{5',4'}$ = 6.5, $J_{5',OH}$ = 5.8), 4.05, (m, 1H, $H_{3'}$, $J_{3',4'}$ = 3.8, $J_{3',2'}$ = 3.8, $J_{3',OH}$ = 3.8), 4.19, (m, 1H, $H_{2'}$, $J_{2',3'}$ = 3.7, $J_{2',1'}$ = 7.7, $J_{2',OH}$ = 6.2), 5.20, (t, 1H, $OH_{5'}$, $J_{OH,5'}$ = 5.5, $J_{OH,5''}$ = 5.5), 5.25, (d, 1H, $OH_{3'}$, $J_{OH,3'}$ = 4.0), 5.42, (d, 1H, $OH_{2'}$, $J_{OH,2'}$ = 6.0), 5.91, (d, 1H, $H_{1'}$, $J_{1',2'}$ = 7.8), 7.83, (d, 1H, H_6, $J_{6,Me}$ = 1.0), 11.30, (s, 1H, NH).

1-[4'-thio-α-D-ribofuranosyl]Thymine **10α**.

10α was prepared from **8α** according to the same procedure as described for **10ß**. After the usual work-up, **10α** (R_f 0.36 in CH_2Cl_2, MeOH - 9 : 1) was obtained in 80 % yield.

10α :
$[\alpha]_D^{20}$ +15.96° (c 1.065 H_2O). U.V. pH 12 λ_{max} = 269 nm, ϵ 10950 [lit. (13) pH 12 λ max 270.5 nm, ϵ 11261]. MS FAB > 0 NOBA m/z 297 $[M+Na]^+$, 275 $[M+H]^+$. ^1H NMR (300 MHz DMSO-d_6) δ 1.77, (s, 3H, CH_3), 3.41, (m, 1H, $H_{5''}$, $J_{5'',5'}$ = 10.9, $J_{5'',4'}$ = 2.9, $J_{5'',OH}$ = 5.7), 3.6, (m, 1H, $H_{4'}$, $J_{4',5'}$ = 4.3, $J_{4',5''}$ = 3.4, $J_{4',3'}$ = 7.7), 3.79, (m, 1H, $H_{5'}$, $J_{5',5''}$ = 10.8, $J_{5',4'}$ = 4.3, $J_{5',OH}$ = 4.8), 3.88, (m, 1H, $H_{3'}$, $J_{3',2'}$ = 3.5, $J_{3',4'}$ = 7.6, $J_{3',OH}$ = 6.4), 4.12,(m, 1H, $H_{2'}$, $J_{2',1'}$ = 5.0, $J_{2',3'}$ = 3.5, $J_{2',OH}$ = 5.2), 4.95, (q, 1H, $OH_{5'}$, $J_{OH,5'}$ = 4.8, $J_{OH,5''}$ = 5.7), 5.24, (d, 1H, $OH_{3'}$, $J_{OH,3'}$ = 6.4), 5.58, (d, 1H,

OH $_{2'}$, J $_{OH,2'}$ = 5.2), 6.09, (d, 1H, H $_{1'}$, J $_{1',2'}$ = 5.0), 7.88, (s, 1H, H $_6$), 11.23, (s, 1H, NH).

1-[4'-thio-ß-D-ribofuranosyl]Uracil **11ß**.

11ß was synthesized as described for **10ß** and was obtained as a white solid with 79 % yield.

11ß :
mp 195-196°C (EtOH), [lit.(13) 191-192°C]. R $_f$ 0.44 in CH_2Cl_2,MeOH - 8 : 2. $[\alpha]_D^{20}$ -8.25° (c 2.06 H_2O). U.V. pH 2 λ_{max} = 264 nm, ϵ 10530, [lit. (13) pH 2 λ max 266 nm, ϵ 10291]. MS FAB > 0 GT m/z 261 $[M+H]^+$. ^{1}H NMR (250 MHz DMSO-d $_6$) δ 3.20, (m, 1H, H $_{4'}$, J$_{4',5'}$ = 5.4, J $_{4',5''}$ = 5.8, J $_{4',3'}$ = 2.5), 3.57, (m, 2H, H $_{5'}$,H $_{5''}$), 4.02, (m, 1H, H $_{3'}$, J $_{3',2'}$ = 3.2, J $_{3',4'}$ = 2.8), 4.13, (dd, 1H, H $_{2'}$, J $_{2',3'}$ = 3.5, J $_{2',1'}$ = 7.4), 5.18, (m, 1H, OH $_{5'}$), 5.28, (m, 1H, OH $_{3'}$), 5.49, (m, 1H,OH $_{2'}$), 5.70, (m, 1H, H $_5$, J $_{5,6}$ = 8.1), 5.88, (d, 1H , H $_{1'}$, J $_{1',2'}$ = 7.4), 8.00, (d, 1H, H $_6$, J $_{6,5}$ = 8.2), 11.1, (s, 1H, NH).

1-[4'-thio-α-D-ribofuranosyl]Uracil **11α**.

11α was prepared from **9α** according to the procedure of **10α** and was isolated as a white solid yielding 81 %.

11α :
mp 241-242°C (CH_2Cl_2, EtOH), [lit.(13) mp 243-244°C]. R $_f$ 0.48 in CH_2Cl_2,MeOH - 8 : 2. $[\alpha]_D^{20}$ +4.8° (c 1.25 $CHCl_3$). U.V. pH 2 λ_{max} = 265 nm, ϵ 12130, [lit.(13) pH 2 λmax 266 nm, ϵ 12228]. MS FAB > 0 NOBA m/z 283 $[M+Na]^+$, 261 $[M+H]^+$. ^{1}H NMR (300 MHz DMSO-d_6) δ 3.39, (m, 2H, H $_{5'}$, H $_{5''}$), 3.60, (m, 1H, H $_{4'}$, J $_{4',5'}$ = 7.6, J $_{4',3'}$ = 7.6, J $_{4',5''}$ = 4.1), 3.87, (m, 1H, H $_{3'}$, J $_{3',2'}$ = 3.5, J $_{3',4'}$ = 7.5), 4.12, (m, 1H, H $_{2'}$, J $_{2',3'}$ = 3.7, J $_{2',1'}$ = 4.9), 4.98, (q, 1H, $OH_{5'}$, J $_{OH,5'}$ = 4.7, J $_{OH,5''}$ = 4.6), 5.28, (d, 1H, $OH_{3'}$, J $_{OH,3'}$ = 6.3), 5.60, (d, 1H, H $_5$, J $_{5,6}$ = 8.1), 5.64, (d, 1H, $OH_{2'}$, J $_{OH,2'}$ = 5.2), 6.06, (d, 1H, H $_{1'}$, J $_{1'2'}$ = 5.1), 8.01, (d, 1H, H $_6$, J $_{6,5}$ = 8.1), 11.1, (s, 1H, NH).

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REFERENCES

1- R. T. Walker, E. De Clercq and F. Eckstein (Eds.), *Nucleoside Analogues, Chemistry, Biology and Medicinal Applications, Nato Advanced Study Institutes*, Series A, Life Sciences, **Vol. 26**, Plenum Press, New York, 1979.

2- J. L. Rideout, D. W. Henry and L. M. Beauchamp, III, (Eds.), *Nucleosides Nucleotides and Their Biological Applications*, Academic Press, New York, 1983.

3- H. Mitsuya, K. J. Weinhold, P. A. Furman, M. H. St.Clair, S. N. Lehrman, R. C. Gallo, D. Bolognesi, D. W. Barry and S. Broder, *Proc. Natl. Acad. Sci.*, USA, 1985, **82**, 7096.

4- P. Herdewijn and E. De Clercq in " *Design of Anti-AIDS Drugs* ", E. De Clercq Ed., **Vol. 14**, Elsevier, Amsterdam, 1990, pp. 141-174.

5- M. Mitsuya, T. Shirasaka and E. De Clercq in " *Design of Anti-AIDS Drugs* ", E. De Clercq Ed., **Vol. 14**, Elsevier, Amsterdam, 1990, pp. 25-61.

6- R. L. Whistler and A. K. M. Anisuzzaman in " *Synthetic Methods for Carbohydrates* ", H. S. Elkadem Ed., ACS Symposium Series, 1977, **39**, 133.

7- E. J. Reist, D. E. Gueffroy and L. Goodman, *J. Am. Chem. Soc.*, 1964, **86**, 5658.

8- Y. L. Fu and M. Bobek, *J. Org. Chem.*,1976, **41**, 3831.

9- M, Bobek, R. L. Whistler and A. Bloch, *J. Med. Chem.*, 1970, **13**, 411.

10- N. Ototani and R. L. Whistler, *J. Med. Chem.*, 1974, **17**, 535.

11-R. G. S. Ritchie and W. A. Szarek, *J. Chem. Soc. Chem. Commun.*, **1973**, 686.

12- B. Urbas and R. L. Whistler, *J. Org. Chem.*, 1966, **31**, 813.

13- E. J. Reist, L. V. Fischer and L. Goodman, *J. Org. Chem.*, 1968, **33**, 189.

14- R. L. Whistler, L. W. Doner and U. G. Nayak, *J. Org. Chem.*, 1971, **36**, 108.

15- M. Bobek, R. L. Whistler and A. Bloch, *J. Med. Chem.*, 1972, **15**, 168.

16- M. W. Pickering, J. T. Witkowski and R. K. Robins, *J. Med. Chem.*, 1976, **19**, 841.

17- J. A. Secrist III, K. N. Tiwari, J. M. Riordan and J. A. Montgomery, *J. Med. Chem.*, 1991, **34**, 2361.

18- M. R. Dyson, P. L. Coe and R. T. Walker, *J. Chem. Soc. Chem. Commun.*, **1991**, 741.

19- M. R. Dyson, P. L. Coe and R. T. Walker, *Carbohydrate Res.*, 1991, **216**, 237.

20- M. R. Dyson, P. L. Coe and R.T. Walker, *J. Med. Chem.*, 1991, **34**, 2782.

21- J. A. Secrist III, R. M. Riggs, K. N. Tiwari and J. A. Montgomery, *J. Med. Chem.*, 1992, **35**, 533.

22- M. W. Bredemkamp, C. W. Holzapfel and A. D. Swanepoel, *S. Afr. J. Chem.*,1991,**44**,31.

23- M. W. Bredemkamp, C. W. Holzapfel and A. D. Swanepoel, *Tetrahedron. Lett.*, 1990, **31**, 2759.

24- J. Barker and H. G. Fletcher, Jr., *J. Org. Chem.*, 1961, **26**, 4605.

25- T. Van Es, *Carbohydr. Res.*, 1976, **46**, 237.

26- J. Harness and N. A. Hughes, *J. Chem. Soc. Chem. Commun.*, **1971**, 811.

27- K. Blumberg, A. Fucello and T. Van Es, *Carbohydr. Res.*, 1979, **70**, 217.

28- J.-L. Barascut, L. Bellon and J.-L. Imbach, *Biochem. Biophys. Res. Comm.* 1992, accepted for publication.

29- N. G. Kundu, R. P. Hertzberg and S. J. Hannon, *Tetrahedron Lett.*, 1980, **21**, 1109.

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