Available online at www.sciencedirect.com

ScienceDirect

Carbohydrate Research 343 (2008) 1099–1103

Carbohydrate
RESEARCH

Note

A concise synthesis of 3-fluoro-5-thio-xylo- and glucopyranoses, useful precursors towards their corresponding pyranonucleoside derivatives

Evangelia Tsoukala, Stella Manta, Niki Tzioumaki, George Agelis and Dimitri Komiotis*

Department of Biochemistry and Biotechnology, Laboratory of Organic Chemistry, University of Thessaly,
26 Ploutonos Str., GR-41221 Larissa, Greece

Received 14 December 2007; received in revised form 1 February 2008; accepted 4 February 2008

Abstract—The chemical synthesis of 1,2,4-tri-*O*-acetyl-3-deoxy-3-fluoro-5-thio-D-xylopyranose, 1,2,4,6-tetra-*O*-acetyl-3-deoxy-3-fluoro-5-thio-α-D-glucopyranose and their corresponding nucleosides of thymine is described. Treatment of 3-fluoro-5-*S*-acetyl-5-thio-D-xylofuranose, obtained by hydrolysis of the isopropylidene group of 3-fluoro-1,2-*O*-isopropylidene-5-*S*-acetyl-5-thio-D-xylofuranose, with methanolic ammonia and direct acetylation, led to triacetylated 3-deoxy-3-fluoro-5-thio-D-xylopyranose. Condensation of acetylated 3-fluoro-5-thio-D-xylopyranose with silylated thymine afforded the corresponding nucleoside. Selective benzoylation and direct methanesulfonylation of 3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose gave the 6-*O*-benzoyl-5-*O*-methylsulfonyl derivative, which on treatment with sodium methoxide afforded the 5,6-anhydro derivative. Treatment of the latter with thiourea, followed by acetolysis, gave the 3-fluoro-5-*S*-acetyl-6-*O*-acetyl-1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose. 3-Fluoro-5-*S*-acetyl-6-*O*-acetyl-5-thio-D-glucofuranose, obtained after hydrolysis of 5-thiofuranose isopropylidene, was treated with ammonia in methanol and directly acetylated, giving tetraacetylated 3-deoxy-3-fluoro-5-thio-α-D-glucopyranose. Condensation of the latter with silylated thymine afforded the desired 3-deoxy-3-fluoro-5-thio-β-D-glucopyranonucleoside analogue.

Keywords: Thiosugars; Thionucleosides; 3-Fluoro-5-thioxylopyranose; 3-Fluoro-5-thio-glucopyranose; Thymine

Thiosugars and their derivatives, containing a sulfur atom in the ring, possess unique physicochemical properties and exhibit remarkable biological activities.[1–3] Thionucleosides have been studied extensively,[4–8] because of their potent biological activities,[4,5,9] and have been recognized as a novel and important class of antiviral[6,9] and antitumour candidates.[5–9]

In recent years, there has been a great deal of activity in the synthesis of fluorine-containing nucleosides and analogues due to the unique properties of the fluorine atom.[10] The promising therapeutic potential of fluoronucleosides along with the unique biological activities of 4′-thionucleosides has drawn special attention on the design and synthesis of fluorinated-4′-thionucleosides.[11,12]

Despite the ever increasing profile of 4′-thionucleosides as clinically useful agents and the interesting biological properties of 5-thiopyranoses,[13–16] very few systematic studies on 5-thiopyranosyl analogues have been reported, even though nucleosides with a six-membered carbohydrate moiety are known for their significant antiviral[17,18] and antibiotic[19] properties.

Our recent work on the synthesis of modified nucleoside analogues[20–22] indicated that fluoropyranonucleosides are efficient antitumour growth inhibitors and have a promising potential in combating rotaviral infections. As a continuation of our studies and based on the evidence that the presence of sulfur in the sugar ring of nucleosides stabilizes the *N*-glycosyl linkage, we report herein on the preparation of 3-fluoro-5-thio-xylo- and

---

* Corresponding author. Tel.: +30 2410 565285; fax: +30 2410 565290; e-mail: dkom@bio.uth.gr

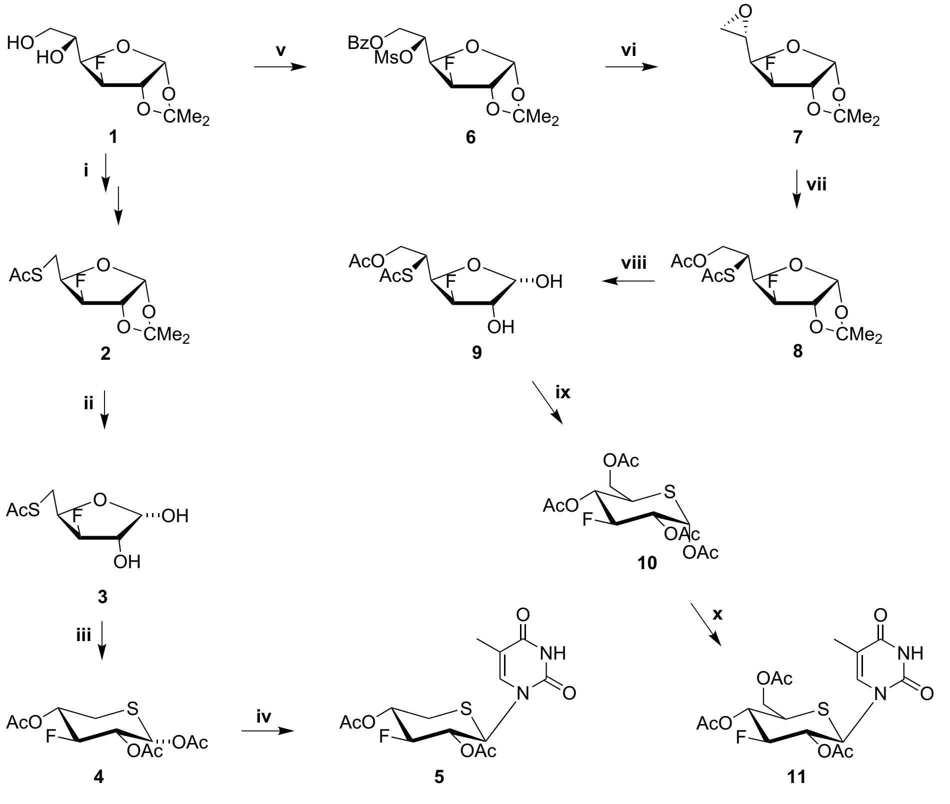
0008-6215/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2008.02.004

glucopyranoses, useful precursors for the synthesis of 3-fluoro-5-thio-xylo- and glucopyranonucleoside analogues.

3-Deoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose[22] (**1**) was chosen as starting material for the synthesis of 5-thioxylopyranose (Scheme 1). Oxidation of diol **1**, followed by reduction, sulfonylation and treatment with potassium thioacetate gave the desired thioacetate **2**.[22] Treatment of **2** with sodium methoxide[23] gave the corresponding thiol, which underwent simultaneous oxidation to the disulfide (ESIMS: *m*/*z* 415.6 [M+H$^+$]). Since deacetylation of **2** before deisopropylidenation gave a disulfide, the isopropylidene acetal group of **2** was first hydrolyzed with 90% aqueous trifluoroacetic acid at room temperature[24] to give **3**. Acetate deprotection of **3** with methanolic ammonia[25] followed by direct standard acetylation gave a mixture of the anomeric 5-thioxylopyranose triacetates **4**, in a 4:1 α/β ratio. This was corroborated by the coupling constants ($\alpha: J_{1',2'}$ 2.5 Hz, $J_{2',3'}$ 9.5 Hz, $J_{3',4'}$ 9.5 Hz; $\beta: J_{1',2'}$ 8.8 Hz, $J_{2',3'}$ 8.6 Hz, $J_{3',4'}$ 8.6 Hz) in the ^{1}H NMR spectrum of **4**. The tri-*O*-acetyl derivative showed no absorption characteristic of an *S*-acetyl group at 1697 cm^{-1}; this compound, therefore, must have a thiopyranose structure. Condensation of the anomeric mixture **4** with silylated thymine in the presence of Sn(IV) chloride afforded solely the protected β-nucleoside **5**. In the ^{1}H NMR spectrum of this nucleoside, H-1′ appeared as a doublet at δ 5.75 with a high $J_{1',2'}$ value (10.7 Hz), which indicated that the sugar moiety adopted the β-configuration.

Compound **1** was also used as a donor for the synthesis of 5-thioglucopyranose (Scheme 1). Selective benzoylation of the primary hydroxyl group at C-6 with benzoyl chloride in pyridine at −25 °C afforded the corresponding 6-benzoate; this was mesylated with methanesulfonyl chloride in pyridine to give the 6-*O*-benzoyl-5-*O*-methylsulfonyl derivative (**6**).[26]

Diester **6** in dry chloroform was treated with sodium methoxide[27] in methanol to give 5,6-epoxide **7**. Treatment of this epoxide with thiourea, followed by acetolysis,[26] gave 5-thiofuranose **8**. The IR spectrum of **8** exhibited characteristic absorptions at 1730 (*O*-acetyl group) and 1685 cm^{-1} (*S*-acetyl group). Isopropylidene **8** was then hydrolyzed over 20 min with 90% aqueous TFA at room temperature[24] to give 3-deoxy-3-fluoro-5-*S*-acetyl-6-*O*-acetyl-5-thio-D-glucofuranose (**9**). Treatment of **9** with methanolic ammonia[25] and direct standard acetylation gave the 5-thioglucopyranose tetraacetate **10**, mainly as the α-anomer showing $J_{1',2'}$ 3.2 Hz, $J_{2',3'}$ 10.0 Hz, $J_{3',4'}$ 9.5 Hz in its ^{1}H NMR spectrum.



Scheme 1. Reagents and conditions: (i) (a) NaIO$_4$/MeOH; (b) NaBH$_4$/MeOH; (c) TsCl/pyridine; (d) KSAc/DMF/100 °C; (ii) 90% TFA; (iii) (a) NH$_3$, MeOH; (b) Ac$_2$O, pyridine; (iv) silylated thymine, Sn(IV) chloride; (v) (a) BzCl/pyridine/−25 °C; (b) MsCl/pyridine; (vi) NaOMe/CHCl$_3$; (vii) (a) thiourea/MeOH; (b) KOAc/AcOH/Ac$_2$O/140 °C; (viii) 90% TFA; (ix) (a) NH$_3$, MeOH; (b) Ac$_2$O, pyridine; (x) silylated thymine, Sn(IV) chloride.

Silylated thymine was condensed with the thiopyranose tetraacetate **10** using Sn(IV) chloride as catalyst to give the protected β-nucleoside **11**. The ^{1}H NMR spectrum of **11** showed large $J_{H,H}$ coupling values of $J_{1',2'}$ 10.7 Hz, $J_{2',3'}$ 9.0 Hz, $J_{3',4'}$ 9.7 Hz, indicative for the β-configuration of the sugar moiety.

In summary, we have accomplished the synthesis of two 3-fluoro-5-thiopyranoses (**4** and **10**). Furthermore, the usefulness of those analogues was exemplified by their easy transformation to their corresponding pyranonucleoside derivatives **5** and **11**.

1. Experimental

1.1. General

Melting points were recorded in a Mel-Temp apparatus and are uncorrected. TLC was performed on Merck precoated 60F$_{254}$ plates. Reactions were monitored by TLC on silica gel, with detection by UV light (254 nm) or by charring with sulfuric acid. Flash chromatography was performed using silica gel (240–400 mesh, Merck).

NMR spectra were recorded at room temperature using a Bruker 400 MHz spectrometer. CDCl$_3$ and/or CD$_3$OD with internal tetramethylsilane (TMS) for ^{1}H and internal trifluorotoluene (TFT) for decoupled ^{19}F were used. The chemical shifts are expressed δ. Infrared spectra were obtained with a Perkin–Elmer Model 1600 FT-IR spectrophotometer. Optical rotations were measured using Autopol I polarimeter. All reactions were carried out in dry solvents. MeCN was distilled from calcium hydride and stored over 3E molecular sieves. DMF was also stored over 3E molecular sieves. Pyridine was stored over pellets of potassium hydroxide. All reactions sensitive to oxygen or moisture were carried out under nitrogen atmosphere.

1.2. 3-Deoxy-3-fluoro-5-*S*-acetyl-5-thio-D-xylofuranose (3)

A soln of thioacetate **2**[22] (4.20 mmol, 1.05 g) in 90% TFA (105 mL) was stirred for 20 min at room temperature. The mixture was extracted with EtOAc and the extract was sequentially washed with satd aq NaHCO$_3$ and brine, dried (Na$_2$SO$_4$) and concentrated under diminished pressure to leave a residue, which was purified by flash column chromatography (1:1 hexane–EtOAc, R_f 0.2) to give 0.64 g (72%) of diol **3** as a colourless syrup: $[\alpha]_D^{20}$ +8 (c 0.1, MeOH); IR (Nujol); ν 1697 cm^{-1} (SAc); ^{1}H NMR (CD$_3$OD, 400 MHz): δ 5.41 (d, 0.3H, $J_{1',2'}$ 3.6 Hz, H-1′(α)), 5.13 (s, 0.7H, H-1′(β)), 4.41–4.08 (m, 5H, H-2′, H-3′, H-4′ and H-5′$_{a,b}$(α,β)), 2.37 (s, 2.1H, SAc(β)), 2.36 (s, 0.9H, SAc(α)). Anal. Calcd for $C_7H_{11}FO_4S$: C, 39.99; H, 5.27. Found: C, 40.14; H, 5.32. ESIMS: m/z 211.3 [M+H$^+$].

1.3. 1,2,4-Tri-*O*-acetyl-3-deoxy-3-fluoro-5-thio-D-xylopyranose (4)

A soln of diol **3** (3.02 mmol, 0.64 g) in methanolic ammonia soln (67 mL) was stirred for 2 h at room temperature. The reaction mixture was concentrated under diminished pressure and crude was obtained as a colourless oil. Acetylation of the residue with Ac$_2$O-pyridine (1:2, 60.4 mL) and chromatography of the product (3:2 hexane–EtOAc, R_f 0.4) gave 0.58 g (65%) of triacetate mixture **4** as a colourless syrup (α/β 4:1, NMR): $[\alpha]_D^{20}$ +121 (c 0.1, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 6.09 (d, 0.8H, $J_{1',2'}$ 2.5 Hz, H-1′(α)), 5.81 (d, 0.2H, $J_{1',2'}$ 8.8 Hz, H-1′(β)), 5.47–5.15 (m, 2H, H-2′, H-4′(α,β)), 4.72 (dt, 0.8H, J 9.5 Hz, $J_{3',F}$ 50.9 Hz, H-3′(α)), 4.42 (dt, 0.2H, J 8.6 Hz, $J_{3',F}$ 49.1 Hz, H-3′(β)), 2.99–2.61 (m, 2H, H-5′$_{a,b}$(α,β)), 2.16, 2.12, 2.07 (3s, 7.2H, 3OAc(α)), 2.11, 2.10, 2.09 (3s, 1.8H, 3OAc(β)). Anal. Calcd for $C_{11}H_{15}FO_6S$: C, 44.89; H, 5.14. Found: C, 44.74; H, 5.27. ESIMS: m/z 295.4 [M+H$^+$].

1.4. 1-(2,4-Di-*O*-acetyl-3-deoxy-3-fluoro-5-thio-β-D-xylopyranosyl)thymine (5)

A mixture of thymine (3.33 mmol, 0.42 g), hexamethyldisilazane (HMDS) (4.12 mmol, 0.9 mL) and saccharine (0.15 mmol, 27 mg) in anhyd MeCN (10.4 mL) was refluxed for 30 min. To this were added triacetylated 3-deoxy-3-fluoro-5-thio-D-xylopyranose (**4**) (1.96 mmol, 0.58 g) and Sn(IV) chloride (3.34 mmol, 0.39 mL). The reaction mixture was refluxed for 2 h, then cooled, neutralized with satd aq NaHCO$_3$ and extracted with CH$_2$Cl$_2$ (500 mL). The organic layer was washed with water (3 × 10 mL) and dried (Na$_2$SO$_4$), evaporated to dryness, and purified by flash chromatography (7:3 hexane–EtOAc, R_f 0.4) to give 0.48 g (68%) of **5** as white crystals: mp 239–241 °C (hexane–EtOAc); $[\alpha]_D^{20}$ +42 (c 0.1, CHCl$_3$); λ_{max} (CHCl$_3$) 260 nm (ε 8400); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.28 (br s, 1H, NH), 7.26 (s, 1H, H-6), 5.75 (d, 1H, $J_{1',2'}$ 10.7 Hz, H-1′), 5.47 (q, 1H, $J_{2',3'}$ 9.1 Hz, H-2′), 5.21 (dd, 1H, $J_{3',4'}$ 9.2 Hz, $J_{4',5'a}$ 11.2 Hz, $J_{4',5'b}$ 4.9 Hz, H-4′), 4.46 (dt, 1H, $J_{3',F}$ 49.6 Hz, H-3′), 3.01–2.93 (m, 1H, H-5′$_b$), 2.82–2.74 (m, 1H, H-5′$_a$), 2.13 and 2.05 (2s, 6H, 2OAc), 1.94 (s, 3H, 5-CH$_3$); ^{19}F NMR: δ −65.42. Anal. Calcd for $C_{14}H_{17}FN_2O_6S$: C, 46.66; H, 4.75; N, 7.77. Found: C, 46.74; H, 4.57; N, 7.53. ESIMS: m/z 361.4 [M+H$^+$].

1.5. 3-Deoxy-3-fluoro-6-*O*-benzoyl-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-α-D-glucofuranose (6)

To a stirred soln of **1**[22] (9.20 mmol, 2.05 g) in pyridine (9.2 mL)–CH$_2$Cl$_2$ (18 mL) at between −30 °C and −20 °C was slowly added a soln of BzCl (1.3 mL) in CH$_2$Cl$_2$ (12 mL) during 1 h, followed by MsCl (0.9 mL). The reaction mixture was gradually warmed to room temperature, and the mixture was stirred overnight, washed several times with satd aq NaHCO$_3$ soln and evaporated. The residue was chromatographed on a column of silica gel (4:1 hexane–EtOAc, R_f 0.2) to give 2.90 g (78%) of **6** as an oil: $[\alpha]_D^{20}$ −21 (*c* 0.1, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.10–8.05 and 7.61–7.42 (m, 5H, ArH), 6.01 (d, 1H, $J_{1',2'}$ 3.6 Hz, H-1′), 5.25–5.18 (m, 1H, H-5′), 5.12 (dd, 1H, $J_{3',F}$ 49.5 Hz, $J_{3',4'}$ 2.1 Hz, H-3′), 4.89 (dd, 1H, $J_{6'a,6'b}$ 12.9 Hz, $J_{5',6'a}$ 2.1 Hz, H-6$'_a$), 4.74 (dd, 1H, $J_{2',F}$ 10.1 Hz, H-2′), 4.52 (dd, 1H, $J_{5',6'b}$ 6.1 Hz, H-6$'_b$), 4.42 (dd, 1H, $J_{4',5'}$ 8.2 Hz, H-4′), 3.06 (s, 3H, SO$_2$Me), 1.49 (s, 3H, CH$_3$), 1.34 (s, 3H, CH$_3$); ^{19}F NMR: δ −65.0. Anal. Calcd for C$_{17}$H$_{21}$FO$_8$S: C, 50.49; H, 5.23. Found: C, 50.54; H, 5.37. ESIMS: *m*/*z* 405.6 [M+H$^+$].

1.6. 3-Deoxy-3-fluoro-5,6-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose (7)

To a soln of **6** (7.17 mmol, 2.90 g) in dry CHCl$_3$ (29 mL), cooled to −15 °C, was added, with stirring, an ice-cooled soln of freshly prepared NaOMe methoxide in MeOH (0.14 g of Na in 9 mL MeOH). The mixture was stirred overnight below 0 °C, extracted with EtOAc and the extract was washed with brine, then dried (Na$_2$SO$_4$) and concentrated. The crude 5,6-anhydro compound **7** was sufficiently pure for the next reaction after chromatography (4:1 hexane–EtOAc, R_f 0.4), which gave 1.04 g (71%) of compound **7** as an oil: $[\alpha]_D^{20}$ −37 (*c* 0.1, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 6.05 (d, 1H, $J_{1',2'}$ 3.7 Hz, H-1′), 4.97 (dd, 1H, $J_{3',F}$ 50.1 Hz, $J_{3',4'}$ 2.4 Hz, H-3′) 4.72 (dd, 1H, $J_{2',F}$ 11.1 Hz, H-2′), 3.93 (dd, 1H, $J_{4',5'}$ 6.0 Hz, H-4′), 3.28–3.21 (m, 1H, H-5′), 2.90–2.87 and 2.74–2.70 (m, 2H, H-6$'_{a,b}$), 1.47 (s, 3H, CH$_3$), 1.33 (s, 3H, CH$_3$); ^{19}F NMR: δ −63.85. Anal. Calcd for C$_9$H$_{13}$FO$_4$: C, 52.94; H, 6.42. Found: C, 52.73; H, 6.37. ESIMS: *m*/*z* 205.2 [M+H$^+$].

1.7. 3-Deoxy-3-fluoro-5-*S*-acetyl-6-*O*-acetyl-1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose (8)

A mixture of epoxide **7** (5.09 mmol, 1.04 g) and thiourea (5.09 mmol, 0.39 g) in MeOH (26.5 mL) was kept at room temperature overnight and was then evaporated. CH$_2$Cl$_2$ was then added to the residue, insoluble solid was removed by filtration through Celite and the filtrate was evaporated. A mixture of the residue with potassium acetate (8.20 mmol, 0.80 g) in acetic acid (1.8 mL)–acetic anhydride (9.1 mL) was refluxed at 140 °C for 19 h. After the mixture had cooled, ice-cold water was added and the mixture was stirred for 1 h before being extracted with EtOAc and the extract was evaporated. The residue was chromatographed (4:1 hexane–EtOAc, R_f 0.35) and 1.13 g (69%) of thioacetate **8** was obtained as colourless leaflets: mp 101–103 °C (hexane–EtOAc); $[\alpha]_D^{20}$ −10 (*c* 0.1, CHCl$_3$); IR (Nujol); ν 1685 (SAc), 1730 (OAc) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 5.98 (d, 1H, $J_{1',2'}$ 3.7 Hz, H-1′), 4.96 (dd, 1H, $J_{3',F}$ 49.7 Hz, $J_{3',4'}$ 2.1 Hz, H-3′), 4.68 (dd, 1H, $J_{2',F}$ 10.3 Hz, H-2′), 4.46–4.31 (m, 3H, H-4′ and H-6$'_{a,b}$), 4.15–4.08 (m, 1H, H-5′), 2.36 (s, 3H, SAc), 2.06 (s, 3H, OAc), 1.49 (s, 3H, CH$_3$), 1.33 (s, 3H, CH$_3$). ^{19}F NMR: δ −63.87. Anal. Calcd for C$_{13}$H$_{19}$FO$_6$S: C, 48.44; H, 5.94. Found: C, 48.57; H, 5.77. ESIMS: *m*/*z* 323.4 [M+H$^+$].

1.8. 3-Deoxy-3-fluoro-5-*S*-acetyl-6-*O*-acetyl-5-thio-D-glucofuranose (9)

Thioacetate **8** (3.50 mmol, 1.13 g) in 90% TFA (87 mL) was stirred for 30 min at room temperature. The mixture was extracted with EtOAc and the extract was washed with satd NaHCO$_3$ and brine, then dried (Na$_2$SO$_4$) and concentrated. Chromatography of the residue (3:7 hexane–EtOAc, R_f 0.3) gave 0.65 g (66%) of diol **9** as white leaflets: mp 83–86 °C (hexane–EtOAc); $[\alpha]_D^{20}$ +5 (*c* 0.1, MeOH); IR (Nujol); ν 1685 (SAc), 1730 (OAc) cm^{-1}; ^{1}H NMR (CD$_3$OD, 400 MHz): δ 5.45 (d, 0.3H, $J_{1',2'}$ 3.9 Hz, H-1′(α)), 5.17 (s, 0.7H, H-1′(β)), 4.51–4.01 (m, 6H, H-2′, H-3′, H-4′, H-5′ and H-6$'_{a,b}$), 2.36 (s, 2.1H, SAc(β)), 2.35 (s, 0.9H, SAc(α)), 2.05 (s, 2.1H, OAc(β)), 2.04 (s, 0.9H, OAc(α)); ^{19}F NMR: δ −65.0. Anal. Calcd for C$_{10}$H$_{15}$FO$_6$S: C, 42.55; H, 5.36. Found: C, 42.67; H, 5.47. ESIMS: *m*/*z* 283.4 [M+H$^+$].

1.9. 1,2,4,6-Tetra-*O*-acetyl-3-deoxy-3-fluoro-5-thio-α-D-glucopyranose (10)

A soln of diol **9** (2.31 mmol, 0.65 g) in methanolic ammonia (51 mL) was stirred for 2 h at room temperature. The reaction mixture was concentrated under diminished pressure and the crude was obtained as colourless oil. Acetylation of the residue with Ac$_2$O-pyridine (1:2, 46 mL) and chromatography of the product (1:1 hexane–EtOAc, R_f 0.4) gave 0.59 g (69%) of tetraacetate **10** as a colourless syrup: $[\alpha]_D^{20}$ +230 (*c* 0.1, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 6.15 (d, 1H, $J_{1',2'}$ 3.2 Hz, H-1′), 5.45 (dd, 1H, $J_{3',4'}$ 9.5 Hz, $J_{4',5'}$ 9.4 Hz, H-4′), 5.34 (dd, 1H, $J_{2',3'}$ 10.0 Hz, H-2′), 4.71 (dt, 1H, $J_{3',F}$ 50.6 Hz, H-3′), 4.35 (dd, 1H, $J_{6'a,6'b}$ 12.1 Hz, $J_{5',6'a}$ 5.1 Hz, H-6$'_a$), 4.10 (dd, 1H, $J_{5',6'b}$ 2.8 Hz, H-6$'_b$), 3.55–3.49 (m, 1H, H-5′), 2.17, 2.13, 2.09, 2.07 (4s, 12H, 4OAc); ^{19}F NMR: δ −63.43. Anal. Calcd for C$_{14}$H$_{19}$FO$_8$S: C, 45.90; H, 5.23. Found: C, 45.77; H, 5.37. ESIMS: *m*/*z* 367.6 [M+H$^+$].

1.10. 1-(2,4,6-Tri-*O*-acetyl-3-deoxy-3-fluoro-5-thio-β-D-glucopyranosyl)thymine (11)

A mixture of thymine (2.23 mmol, 0.28 g), HMDS (2.76 mmol, 0.6 mL) and saccharine (0.10 mmol, 19 mg) in anhyd MeCN (7.4 mL) was refluxed for

30 min. To this were added tetraacetylated 3-deoxy-3-fluoro-5-thio-D-glucopyranose (**10**) (1.59 mmol, 0.59 g) and Sn(IV) chloride (2.23 mmol, 0.26 mL). The reaction mixture was refluxed for 2 h, then cooled, neutralized with aq sodium bicarbonate and extracted with CH_2Cl_2 (500 mL). The organic layer was washed with water (3 × 10 mL) and dried (Na_2SO_4), evaporated to dryness, finally purified with flash chromatography (7:3 hexane–EtOAc, R_f 0.4) to give 0.47 g (68%) of compound **11** as a white crystalline: mp 194–196 °C (hexane–EtOAc); $[\alpha]_D^{20}$ +42 (*c* 0.1, $CHCl_3$); λ_{max} ($CHCl_3$) 260 nm (ε 10,100); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.51 (br s, 1H, NH), 7.26 (s, 1H, H-6), 5.84 (d, 1H, $J_{1',2'}$ 10.7 Hz, H-1′), 5.57 (t, 1H, $J_{2',3'}$ 9.0 Hz, H-2′), 5.41 (dd, 1H, $J_{3',4'}$ 9.7 Hz, $J_{4',5'}$ 10.0 Hz, H-4′), 4.45 (dt, 1H, $J_{3',F}$ 49.3 Hz, H-3′), 4.34 (dd, 1H, $J_{6'a,6'b}$ 12.2 Hz, $J_{5',6'a}$ 5.6 Hz, H-$6'_a$), 4.16 (dd, 1H, $J_{5',6'b}$ 2.8 Hz, H-$6'_b$), 3.43–3.35 (m, 1H, H-5), 2.14, 2.10, 2.05 (3s, 9H, 3OAc), 1.95 (s, 3H, 5-CH_3); ^{19}F NMR: δ −64.3. Anal. Calcd for $C_{17}H_{21}FN_2O_8S$: C, 47.22; H, 4.89; N, 6.48. Found: C, 47.44; H, 4.67; N, 6.22. ESIMS: *m*/*z* 433.5 [M+H$^+$].

Acknowledgements

This work was supported in part by the Greek General Secretariat for Research and Technology Program No. 3245C and bilateral scientific-technology project between Greece and Slovenia. The authors are grateful to Dr. K. Antonakis (Ec. Nat. Sup. de Chimie de Paris; CNRS-FRE 2463) for encouraging this work, to Dr. T. Halmos (Ec. Nat. Sup. de Chimie de Paris) for the unstinted and fruitful aid, as well as to ELPEN pharmaceuticals for financial support.

References

1. Witczak, J. Z. *Curr. Med. Chem.* **1999**, *6*, 165–178.
2. Robina, I.; Vogel, P.; Witczak, J. Z. *Curr. Org. Chem.* **2001**, *5*, 1177–1214 and references cited therein.
3. Robina, I.; Vogel, P. *Curr. Org. Chem.* **2002**, *6*, 471–491.
4. Choo, H.; Chong, Y.; Choi, Y.; Mathew, J.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2003**, *46*, 389–398.
5. Malsen, H. J.; Hughes, D.; Hursthouse, M.; De Clercq, E.; Balzarini, J.; Simons, C. *J. Med. Chem.* **2004**, *47*, 5482–5491.
6. Zhu, W.; Chong, Y.; Choo, H.; Mathews, J.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2004**, *47*, 1631–1640.
7. Jeong, L. S.; Jin, D. Z.; Kim, H. O.; Shin, D. H.; Moon, H. R.; Hyung, R.; Gunaga, P.; Chun, M. W.; Kim, Y.-C.; Melman, N.; Gao, Z.-G.; Jacobson, K. A. *J. Med. Chem.* **2003**, *46*, 3775–3777.
8. Paquette, L. A.; Dong, S. *J. Org. Chem.* **2005**, *70*, 5655–5664.
9. Gunaga, P.; Moon, R. H.; Choi, J. W.; Shin, H. D.; Park, G. J.; Jeong, S. L. *Curr. Med. Chem.* **2004**, *11*, 2585–2637.
10. Meng, W.-D.; Qing, F.-L. *Curr. Top. Med. Chem.* **2006**, *6*, 1499–1528.
11. Machida, H.; Ashida, N.; Miura, S.; Endo, M.; Yamada, K.; Kitano, K.; Yoshimura, Y.; Sakata, S.; Ijichi, O.; Eizuru, Y. *Antiviral Res.* **1998**, *39*, 129–137.
12. Yoshimura, Y.; Kitano, K.; Yamada, K.; Sakata, S.; Miura, S.; Ashida, N.; Machida, H. *Bioorg. Med. Chem.* **2000**, *8*, 1545–1558.
13. Uenishi, J.; Ohmiya, H. *Tetrahedron* **2003**, *59*, 7011–7022.
14. Bellamy, F.; Barberousse, V.; Martin, N.; Masson, P.; Millet, J.; Samreth, S.; Sepulchre, C.; Theveniaux, J.; Horton, D. *Eur. J. Med. Chem.* **1995**, *30*, 101–115 (and ref. cited therein).
15. Al-Masoudi, N. A.; Al-Soud, Y. A.; Schuppler, T. *J. Carbohydr. Chem.* **2005**, *24*, 237–250.
16. Al-Masoudi, N. A.; Al-Soud, Y. A. *J. Carbohydr. Chem.* **2004**, *23*, 111–122.
17. Ostrowski, T.; Wroblowski, B.; Busson, R.; Rozenski, J.; De Clercq, E.; Bennet, M. S.; Champness, J. N.; Summers, W. C.; Sanderson, M. R.; Herdewijn, P. *J. Med. Chem.* **1998**, *41*, 4343–4353.
18. Maurinsh, Y.; Schraml, J.; De Winter, H.; Blaton, N.; Peeters, O.; Lescrinier, E.; Rozenski, J.; Van Aerschot, A.; De Clercq, E.; Busson, R.; Herdewijn, P. *J. Org. Chem.* **1997**, *62*, 2861–2871.
19. Haouz, A.; Vanheusden, V.; Munier-Lechman, H.; Froeyen, M.; Herdewijn, P.; Van Galenbergh, S.; Delarue, M. *J. Biol. Chem.* **2003**, *278*, 4963–4971.
20. Manta, S.; Agelis, G.; Botić, T.; Cencič, A.; Komiotis, D. *Bioorg. Med. Chem.* **2007**, *15*, 980–987.
21. Manta, S.; Agelis, G.; Botić, T.; Cencič, A.; Komiotis, D. *Eur. J. Med. Chem.* **2008**, *43*, 420–428.
22. Tsoukala, E.; Agelis, G.; Dolinsek, J.; Botić, T.; Cencič, A.; Komiotis, D. *Bioorg. Med. Chem.* **2007**, *15*, 3241–3247.
23. Bozo, E.; Boros, S.; Kuszmann, J.; Gacs-Baitz, E.; Parkanyi, L. *Carbohydr. Res.* **1998**, *308*, 297–310.
24. Tsuda, Y.; Sato, Y.; Kanemitsu, K.; Hosoi, S.; Shibayama, K.; Nakao, K.; Ichikawa, Y. *Chem. Pharm. Bull.* **1996**, *44*, 1465–1475.
25. Vanheusden, V.; Busson, R.; Herdewijn, P.; Van Calenbergh, S. *J. Org. Chem.* **2004**, *69*, 4446–4453.
26. Yuasa, H.; Tamura, J.; Hashimoto, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2763–2769.
27. Hasegawa, A.; Kawai, Y.; Kasugai, H.; Kiso, M. *Carbohydr. Res.* **1978**, *63*, 131–137.