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TETRAHEDRON: *ASYMMETRY*

Synthesis of 2-C-(4-aminocarbonyl-2-thiazoyl)-1,4-anhydro-L-xylitols and their fluoro derivatives

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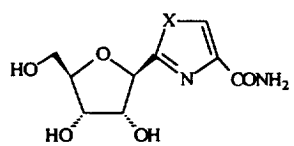
Abstract

3,5-O-Benzylidene-2-C-cyano-1,4-anhydro-L-xylitol **7** was synthesized stereoselectively from D-xylose in 7 steps. 2-C-(4-Aminocarbonyl-2-thiazoyl)-1,4-anhydro-L-xylitols and their fluoro derivatives were synthesized from the cyanohydrin **7**. Fluorination of compound **9** proceeded with retention of configuration using diethylaminosulfur trifluoride (DAST). © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

Considerable effort has been directed to the search for novel nucleoside analogues for use as antiviral and antitumor agents. The biological activity of the naturally occurring C-nucleosides has stimulated the research of this field in the last two decades. Among them, tiazofurin[1] and its selenium analogue, selenazofurin,[2] with distinguished antitumor and antiviral activity, have gained significant attention.



X = S, tiazofurin
X = Se, selenazofurin

Structural modifications of the ribofuranosyl moiety of tiazofurin have been reported including preparation of 5′-, 3′-, or 2′-substituted derivatives,[1,3,4] arabino- and xylofuranosyl,[5,6] acyclic,[7] pyranosyl,[8] carbocyclic[9] analogues. However, these substances were devoid of any significant biological activity.

Recently, a number of nucleosides with the unnatural L-configuration have been reported as potent chemotherapeutic agents against HIV, HBV and certain forms of cancer. It is interesting that these L-nucleosides have potent biological activities, while some of them show lower toxicity

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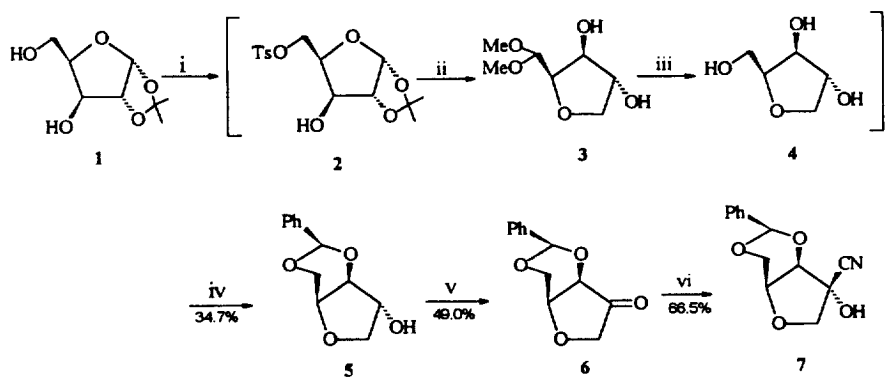
profiles than their D-counterparts.[10] We have reported the synthesis of 4′-(R)-hydroxyl-5′-(S)-hydroxymethyl-tetrahydrofuranyl purines and pyridines from D-xylose[11] and some derivatives of 4-deoxy-4-nucleobase-2,5-anhydro-L-mannitol from D-glucose.[12] In this paper, we report the synthesis of 2-C-(4-aminocarbonyl-2-thiazoyl)-1,4-anhydro-L-xylitols and their fluoro derivatives.

2. Results and discussion

1,2-O-Isopropylidene-α-D-xylose **1** was prepared from D-xylose according to the method of Moravcova et al.[13] Tosylation of **1** was completed by the reaction of **1** with toluenesulfonyl chloride in pyridine at 0°C to give compound **2**.[14] After treatment of **2** with 1% trifluoroacetic acid in methanol at 80°C, followed by reaction with sodium borohydride, 1,4-anhydro-L-xylitol **4** was obtained and the protection of **4** was completed in the presence of benzaldehyde and anhydrous zinc chloride in 34.7% yield in one pot.[11,12,14,15] The 2-OH in **5** was oxidized by using chromium trioxide/pyridine/acetic anhydride in dichloromethane to give ketone **6**. The key intermediate, cyanohydrin **7**, was formed from a stereoselective addition of potassium cyanide to **6** in ethyl acetate at room temperature. The cyano group was introduced from the upper side on C-2 in 66.5% yield (Scheme 1). If the 2-hydroxy group is 'up' on the ring, the cyanohydrin obtained may be less stable than **7** due to the stereoelectronic effect between the neighboring oxygen atoms. The stereochemistry at C-2 of cyanohydrin **7** was determined by a single crystal X-ray analysis (Fig. 1). It was shown that the cyano group on the cyanohydrin **7** was at the same side of 3,5-O-benzylidene group.

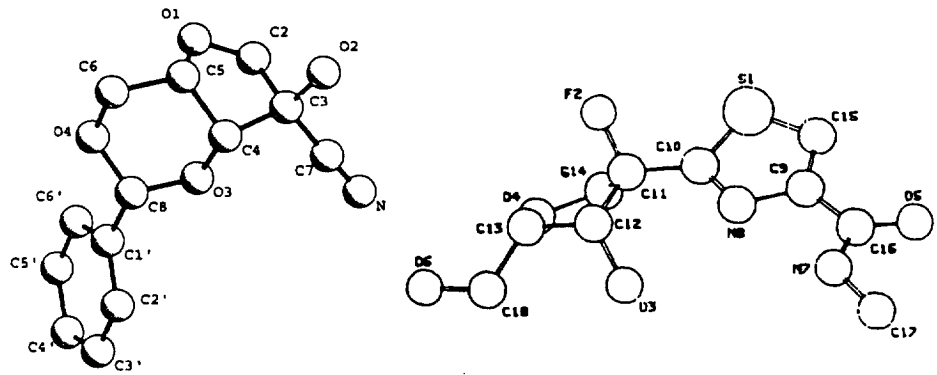


(i) TsCl, Py., r.t.; (ii)1% TFA, MeOH, 80°C; (iii) 0.3% TFA, H_2O, 80°C; $NaBH_4$, H_2O, r.t.; (iv) PhCHO, $ZnCl_2$, r.t.; (v) CrO_3, Py., Ac_2O, CH_2Cl_2, r.t.; (vi)KCN, EtOAc-H_2O, r.t.

Scheme 1.

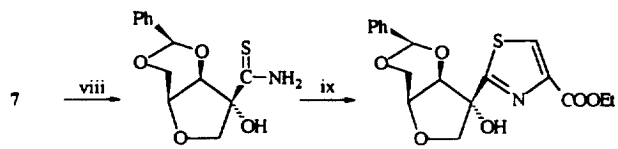
Compound **8** was obtained by the reaction of **7** and hydrogen sulphide in the presence of a catalytic amount of 4-methylaminopyridine. The thiazole **9** was synthesized by the reaction of thioamide **8** and ethyl bromopyruvate in acetonitrile at room temperature in 73.5% yield (Scheme 2).

Ammonolysis of this ester afforded the amide **10** and **11** and deblocking of the benzylidene group was completed using 0.5% aqueous trifluoroacetic acid solution at 75°C to give compounds **12** and **13** in approximately quantitative yields (Scheme 3). The fluorinated analogue **14** was obtained by fluorination of **9** with diethylaminosulfur trifluoride (DAST) in dichloromethane at room temperature in very good yield. Usually, it was assumed that DAST fluorination of the hydroxyl group would proceed with inversion of configuration.[16] However, Jeong et al.[17] reported that fluorination of hydroxyl groups at C2′ and C3′ of the 4′-thioribofuranosyl ring with DAST proceeded with exclusive retention of configuration



7 16

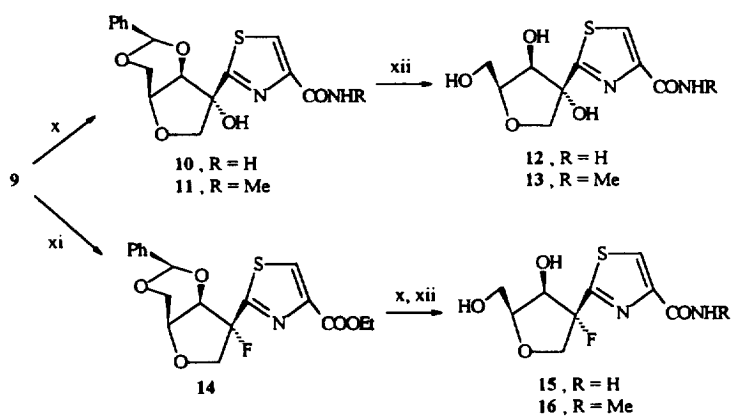
Fig. 1. Crystal X-ray structures of compounds **7** and **16**



(viii) H_2S, DMAP, EtOH-dioxane, r.t.; (ix) $BrCH_2COCO_2Et$, CH_3CN, r.t.

Scheme 2.

due to the participation of the 4′-thiofuranose sulfur via a double inversion mechanism. The structure of **16** was determined by a single crystal X-ray analysis (Fig. 1). The X-ray derived structure of **16** shows that fluorine was 'down' on the sugar ring. It appears, therefore, a double inversion mechanism during the DAST reaction of compound **9** is responsible for the retention of the configuration.



(x) NH_3-H_2O or CH_3NH_2, EtOH, r.t.; (xi) DAST, CH_2Cl_2, r.t.; (xii) 0.5%TFA, 75°C

Scheme 3.

3. Conclusion

Novel nucleosides **12**, **13**, **15** and **16** were synthesized stereoselectively by construction of a thiazole moiety from cyanohydrin **7**. The fluorination of compound **9** with DAST proceeded with the retention of the configuration.

4. Experimental section

4.1. General procedures

Melting points were determined on a Kofler melting point apparatus and were uncorrected. Optical rotations were determined with a Perkin–Elmer 243B polarimeter. IR spectra were recorded on a DE-983G spectrophotometer in KBr pellets. UV spectra were recorded on a Pharmacia LKB Biochrom 4060 spectrophotometer. Mass spectra were obtained on either ZAB-HS or KYKY-ZHP-5 mass spectrometers. NMR spectra were recorded on Varian-300, Varian-500 or Brucker DPX-400 spectrometers with TMS as an internal standard. Exchangeable protons were detected by addition of D_2O. Column chromatography was performed on silica gel (200–300 mesh) and silica gel GF_{254} was used for TLC purchased from the Qingdao Chemical Company, China.

*4.2. 3,5-O-Benzylidene-1,4-anhydro-*L*-xylitol* **5**

Toluenesulfonyl chloride (50 g, 0.26 mol) was added to a stirred solution of **1** (46.0 g, 0.24 mol) in pyridine (300 ml) at 0°C. The mixture was stirred at room temperature for 2 h. Some of the solvent was evaporated and the residue was stirred with saturated $NaHCO_3$ (100 ml) for 30 min. The mixture was extracted with $CHCl_3$, washed with 1 M H_2SO_4 and H_2O, then dried over anhydrous Na_2SO_4 to yield a yellow–white solid. The crude solid was allowed to react in 1% trifluoroacetic acid in methanol (600 ml) at 80°C for 24 h, followed by neutralization with solid $NaHCO_3$. The solvents were evaporated and the residue was extracted with acetone (300 ml). After the acetone solution was concentrated, a pale-yellow syrup, in which compound **3** was contained, was dissolved in water (300 ml) containing 0.3% trifluoroacetic acid. The solution was heated at 80°C for 6 h, then cooled to 0°C. After neutralization, the mixture was treated with $NaBH_4$ (13.0 g) at room temperature for 1.5 h, then cooled to 0°C and neutralized again. The residue was evaporated and the mixture was applied to a silica gel column and eluted with ethanol. The combined eluant was concentrated and evaporated with toluene (50 ml×2). Freshly dried zinc chloride (30 g) and 100 ml (0.98 mol) of benzaldehyde were added to the resulting syrup and the suspension was stirred vigorously for 2 days at room temperature. The mixture was poured into cold water and extracted with $CHCl_3$. The combined organic layer was dried with anhydrous Na_2SO_4. After filtration and removal of the solvent, the desired product **5** (10.2 g) was obtained as white needles. An additional compound **5** (8.3 g) was obtained from the mother liquid. The total yield was 34.7% from **1**. $[\alpha]_D^{22}$ +3.3 (c 0.060, MeOH). ^{1}H NMR ($CDCl_3$) δ ppm: 7.46 (2H, m, arom H), 7.36 (3H, m, arom H), 5.44 (1H, s, PhC*H*<), 4.43 (1H, d, $J_{5a,5b}$=13.3 Hz, H_{5a}), 4.39 (1H, d, $J_{1a,1b}$=11.1 Hz, H_{1a}), 4.38 (1H, d, $J_{3,4}$=6.0 Hz, H_3), 4.31 (1H, d, $J_{2,1b}$=2.4 Hz, H_2), 4.12 (1H, dd, $J_{5b,5a}$=13.3 Hz, $J_{5b,4}$=1.8 Hz, H_{5b}), 3.99 (1H, m, H_4), 3.82 (1H, dd, $J_{1b,1a}$=11.1 Hz, $J_{1b,2}$=2.4 Hz, H_{1b}). Calcd for $C_{12}H_{14}O_4$ (222.26): C, 64.84; H, 6.36. Found: C, 64.45; H, 6.35.

4.3. 3,5-O-Benzylidene-2-keto-1,4-anhydro-L-xylitol 6

To a stirred suspension of CrO_3 (27 g, 0.27 mol) in CH_2Cl_2 (200 ml) under an ice–water external bath were carefully added pyridine (44 ml, 0.54 mol), a solution of **5** (20 g, 0.090 mol) in CH_2Cl_2 (200 ml) and Ac_2O (25.5 ml, 0.27 mol). The mixture was stirred at room temperature for 3 h, then poured into ethyl acetate (400 ml) and stirred for more than 30 min. After filtration through a short silica gel column eluted with EtOAc, the combined eluant was concentrated and neutralized with concentrated NaOH aqueous solution. The mixture was extracted with $CHCl_3$, washed with 1 M H_2SO_4 and H_2O, dried with anhydrous Na_2SO_4 and evaporated to yield a brown solid which was recrystallized from ethanol to give **6** as a white solid (9.7 g, 49.0%). $[\alpha]_D^{22}$ −32.4 (c 0.074, MeOH). ^{1}H NMR ($CDCl_3$) δ ppm: 7.48 (2H, m, arom H), 7.36 (3H, m, arom H), 5.55 (1H, s, PhC*H*<), 4.49 (1H, d, $J_{5a,5b}$=12.6 Hz, H_{5a}), 4.48 (1H, d, $J_{1a,1b}$=18.0 Hz, H_{1a}), 4.29 (1H, d, $J_{5b,5a}$=12.6 Hz, $J_{5b,4}$=2.4 Hz, H_{5b}), 4.28 (1H, d, $J_{3,4}$=2.4 Hz, H_3), 4.01 (1H, d, $J_{1b,1a}$=18.0 Hz, H_{1b}), 4.00 (1H, m, H_4). ^{13}C NMR ($CDCl_3$) δ ppm: 206.4 (C_2), 135.3, 127.7, 126.7 (×2), 124.5 (×2) (arom C), 97.9 (Ph*C*H<), 72.2 (C_3), 71.1 (C_4), 69.4 (C_1), 65.4 (C_5). Calcd for $C_{12}H_{12}O_4$ (220.24): C, 65.43; H, 5.50. Found: C, 65.43; H, 5.39.

4.4. 3,5-O-Benzylidene-2-C-cyano-1,4-anhydro-L-xylitol 7

A mixture of **6** (8.7 g, 0.040 mmol), ethyl acetate (200 ml), water (100 ml), sodium hydrogen carbonate (7.0 g) and potassium cyanide (3.0 g, 0.046 mmol) was stirred vigorously at room temperature overnight. The organic phase was separated and dried over anhydrous Na_2SO_4. After evaporation, the residue was purified by silica gel chromatography and recrystallized from EtOH to give **7** as white crystals (6.5 g, 66.5%). m.p. >355°C. $[\alpha]_D^{22}$ −86.4 (c 0.044, MeOH). IR ν_{max}^{KBr} (cm^{-1}): 2245. EI-MS (m/z): 247[M^+]. ^{1}H NMR (DMSO-d_6) δ ppm: 7.42 (5H, m, arom H), 7.33 (1H, s, exchangeable, 2-O*H*), 5.66 (1H, s, PhC*H*<), 4.53 (1H, d, $J_{3,4}$=2.4 Hz, H_3), 4.26 (1H, d, $J_{1a,1b}$=9.2 Hz, H_{1a}), 4.20 (1H, d, $J_{5a,5b}$=13.0 Hz, H_{5a}), 4.15 (1H, d, $J_{5b,5a}$=13.0 Hz, $J_{5b,4}$=1.6 Hz, H_{5b}), 4.02 (1H, d, $J_{4,5b}$=1.6 Hz, H_4), 3.98 (1H, d, $J_{1b,1a}$=9.2 Hz, H_{1b}). ^{13}C NMR ($CDCl_3$) δ ppm: 137.7, 128.9, 128.1 (×2), 126.0 (×2) (arom C), 118.0 (*C*N), 97.7 (Ph*C*H<), 79.9 (C_2), 76.5 (C_3), 75.0 (C_1), 72.5 (C_4), 66.5 (C_5). Calcd for $C_{13}H_{13}O_4N$ (247.27): C, 63.14; H, 5.31; N, 5.67. Found: C, 63.17; H, 5.19; N, 5.65. Crystal data: empirical formula, $C_{13}H_{13}O_4N$; formula weight, 247.25; crystal system, orthorhombic; space group, $P2_12_12_1$; a=5.641(2), b=12.652(4), c=17.045(5) Å, V=1216.5(7) Å^3, Z=4, D_x=1.350 g/cm^3.

4.5. 3,5-O-Benzylidene-2-C-aminothiocarbonyl-1,4-anhydro-L-xylitol 8

Hydrogen sulphide was introduced into the vigorously stirred reaction mixture of compound **7** (7.6 g, 0.031 mmol) and 4-dimethylaminopyridine (1.4 g) in ethanol (80 ml) and dioxane (80 ml) at room temperature for 20 h. The reaction mixture was sealed and stirred for over 10 h. The solvent was evaporated and the residue was purified by silica gel chromatography (2–20% ethyl acetate–petroleum ether) to yield compound **8** as a white solid (3.5 g, 40.5%). $[\alpha]_D^{22}$ −214.7 (c 0.034, MeOH). UV λ_{max}^{MeOH} (log ε): 207.6 (4.03), 268.9 (4.08). EI–MS (m/z): 281[M^+]. ^{1}H NMR (DMSO-d_6) δ ppm: 9.83, 9.10 (each 1H, s, NH_2), 7.38 (5H, m, arom H), 6.10 (1H, s, 2-O*H*), 5.48 (1H, s, PhC*H*<), 4.73 (1H, d, $J_{1a,1b}$=9.2 Hz, H_{1a}), 4.35 (1H, d, $J_{5a,5b}$=12.0 Hz, H_{5a}), 4.19 (1H, s, H_3), 4.10 (1H, d, $J_{5b,5a}$=12.0 Hz, H_{5b}), 4.08 (1H, s, H_4), 3.80 (1H, d, $J_{1b,1a}$=9.2 Hz, H_{1b}). Calcd for $C_{13}H_{15}O_4NS$ (281.35): C, 55.49; H, 5.38; N, 4.98. Found: C, 55.42; H, 5.37; N, 4.67.

4.6. 3,5-O-Benzylidene-2-C-(4-ethoxycarbonyl-2-thiazoyl)-1,4-anhydro-L-xylitol 9

Compound **8** (3.0 g, 0.011 mol) in anhydrous acetonitrile (150 ml) was reacted with ethyl bromopyruvate (5.3 ml, 0.042 mmol) for 48 h. The reaction mixture was concentrated and stirred with saturated $NaHCO_3$ solution (50 ml) for 20 min and then extracted with diethyl ether and dried. On removal of the solvent, a brown syrup was obtained. After silica gel column chromatography ($CHCl_3$:CH_3OH, 200:1) and recrystallization from ethanol, compound **9** was obtained as a white solid (2.96 g, 73.5%). $[\alpha]_D^{22}$ −176.5 (c 0.034, MeOH). UV λ_{max}^{MeOH} (log ε): 205.1 (4.43), 233.6 (4.05). EI-MS (m/z): 377[M^+]. ^{1}H NMR (DMSO-d_6) δ ppm: 8.55 (1H, s, $H_{5'}$), 7.32 (5H, m, arom H), 6.92 (1H, s, 2-O*H*), 5.57 (1H, s, PhC*H*<), 4.69 (1H, d, $J_{1a,1b}$=9.5 Hz, H_{1a}), 4.40 (1H, d, $J_{3,4}$=2.0 Hz, H_3), 4.31 (2H, q, J=7.5 Hz, –OC*H*$_2$CH$_3$), 4.23 (1H, overlapped, H_4), 4.21 (1H, d, $J_{5a,5b}$=12.0 Hz, H_{5a}), 4.17 (1H, dd, $J_{5b,5a}$=12.0 Hz, $J_{5b,4}$=1.5 Hz, H_{5b}), 4.07 (1H, d, $J_{1b,1a}$=9.5 Hz, H_{1b}), 1.30 (3H, t, J=7.5 Hz, –OCH$_2$C*H*$_3$). ^{13}C NMR (DMSO-d_6) δ ppm: 170.6 ($C_{2'}$), 160.8 (–*C*OOEt), 145.4 ($C_{4'}$), 130.3 ($C_{5'}$), 138.1, 128.6, 127.9 (×2), 126.1 (×2) (arom C), 97.4 (Ph*C*H<), 82.8 (C_2), 81.2 (C_3), 76.3 (C_1), 73.2 (C_4), 67.1 (–O*C*H$_2$CH$_3$), 60.7 (C_5), 14.2 (–OCH$_2$*C*H$_3$). Calcd for $C_{18}H_{19}O_6NS$ (377.44): C, 57.24; H, 5.08; N, 3.71. Found: C, 57.11; H, 4.93; N, 3.64.

4.7. 3,5-O-Benzylidene-2-C-(4-aminocarbonyl-2-thiazoyl)-1,4-anhydro-L-xylitol 10

The solution of ester **9** (0.20 g, 0.53 mmol) in ethanol (4 ml) was allowed to react with 25% ammonia solution (4 ml) at room temperature until consumption of the starting material. The crude product was purified by silica gel column chromatography (petroleum ether:ethyl acetate 1:3) and recrystallization from ethanol yielded amide **10** (150 mg, 81.2%). $[\alpha]_D^{22}$ −147.8 (c 0.046, MeOH). UV λ_{max}^{MeOH} (log ε): 206.0 (4.30), 234.7 (3.84). PFAB-MS (m/z): 349 [M+1]$^+$. ^{1}H NMR (DMSO-d_6) δ ppm: 8.26 (1H, s, $H_{5'}$), 7.66, 7.62 (each 1H, N*H*$_2$), 7.32 (5H, m, arom H), 6.84 (1H, s, 2-O*H*), 5.54 (1H, s, PhC*H*<), 4.84 (1H, d, $J_{1a,1b}$=9.0 Hz, H_{1a}), 4.34 (1H, d, $J_{3,4}$=2.0 Hz, H_3), 4.22 (1H, s, H_4), 4.21 (1H, d, $J_{5a,5b}$=12.0 Hz, H_{5a}), 4.16 (1H, d, $J_{5b,5a}$=12.0 Hz, H_{5b}), 4.03 (1H, d, $J_{1b,1a}$=9.0 Hz, H_{1b}). Calcd for $C_{16}H_{16}O_5N_2S$ (348.40): C, 55.15; H, 4.64; N, 8.04. Found: C, 54.93; H, 5.10; N, 7.83.

4.8. 3,5-O-Benzylidene-2-C-(4-methylaminocarbonyl-2-thiazoyl)-1,4-anhydro-L-xylitol 11

Compound **11** (160 mg, 83.3%) was obtained by the same procedure as **10**, except using methylamine instead of ammonia. $[\alpha]_D^{22}$ −128.8 (c 0.052, MeOH). UV λ_{max}^{MeOH} (log ε): 205.7 (3.35), 232.7 (3.01). PFAB-MS (m/z): 363 [M+1]$^+$. ^{1}H NMR (DMSO-d_6) δ ppm: 8.28 (1H, q, J=5.0 Hz, –N*H*CH$_3$), 8.23 (1H, s, $H_{5'}$), 7.31 (5H, m, arom H), 6.84 (1H, s, 2-O*H*), 5.54 (1H, s, PhC*H*<), 4.88 (1H, d, $J_{1a,1b}$=9.5 Hz, H_{1a}), 4.34 (1H, d, $J_{3,4}$=2.0 Hz, H_3), 4.22 (1H, s, H_4), 4.21 (1H, d, $J_{5a,5b}$=11.0 Hz, H_{5a}), 4.16 (1H, d, $J_{5b,5a}$=11.0 Hz, H_{5b}), 4.04 (1H, d, $J_{1b,1a}$=9.5 Hz, H_{1b}), 2.81 (3H, d, J=5.0 Hz, –NHC*H*$_3$). Calcd for $C_{17}H_{18}O_5N_2S$ (362.43): C, 56.33; H, 5.02; N, 7.73. Found: C, 56.62; H, 4.91; N, 7.64.

4.9. 2-C-(4-Aminocarbonyl-2-thiazoyl)-1,4-anhydro-L-xylitol 12

Compound **10** (0.10 g, 0.29 mmol) was heated in 10 ml of 0.5% aqueous trifluoroacetic acid at 75°C to remove the benzylidene group to yield compound **12** (93.8%), $[\alpha]_D^{22}$ −52.8 (c 0.036, MeOH). UV λ_{max}^{MeOH} (log ε): 204.5 (4.15), 231.2 (3.79). PFAB-MS (m/z): 261 [M+1]$^+$. ^{1}H NMR (DMSO-d_6) δ ppm: 8.24 (1H, s, $H_{5'}$), 7.72, 7.56 (each 1H, –N*H*$_2$), 6.53 (1H, s, 2-O*H*), 5.16 (1H, d, $J_{3\text{-OH, H3}}$=6.0 Hz, 3-O*H*), 4.58 (1H, t, $J_{5\text{-OH, H5}}$=5.5 Hz, 5-OH), 4.49 (1H, d, $J_{1a,1b}$=9.0 Hz, H_{1a}), 4.22 (1H, m, $J_{4,5}$=5.5 Hz,

$J_{4,3}$=3.0 Hz, H_4), 3.92 (1H, dd, $J_{H3,3\text{-}OH}$=6.0 Hz, $J_{3,4}$=3.0 Hz, H_3), 3.83 (1H, d, $J_{1a,1b}$=9.0 Hz, H_{1b}), 3.64 (1H, m, $J_{5a,5\text{-}OH}$=5.5 Hz, $J_{5a,4}$=5.5 Hz, $J_{5a,5b}$=10.5 Hz, H_{5a}), 3.52 (1H, m, $J_{5b,5\text{-}OH}$=5.5 Hz, $J_{5b,4}$=5.5 Hz, $J_{5b,5a}$=10.5 Hz, H_{5b}). ^{13}C NMR (DMSO-d_6) δ ppm: 172.1 ($C_{2'}$), 162.4 (–*C*ONH$_2$), 149.4 ($C_{4'}$), 125.0 ($C_{5'}$), 83.4 (C_2), 82.9 (C_4), 77.9 (C_3), 75.0 (C_1), 59.6 (C_5). Calcd for $C_9H_{12}O_5N_2S$ (260.29): C, 41.52; H, 4.61; N, 10.76. Found: C, 41.25; H, 4.58; N, 10.58.

4.10. 2-C-(4-Methylaminocarbonyl-2-thiazoyl)-1,4-anhydro-L-*xylitol* **13**

After removal of the benzylidene group as above, compound **11** (0.10 g, 0.28 mmol) was converted to yield **13** (95.1%), $[\alpha]_D^{22}$ −36.8 (c 0.068, MeOH). UV λ_{max}^{MeOH} (log ε): 203.5 (4.04), 233.4 (3.81). PFAB-MS (m/z): 275 $[M+1]^+$. ^{1}H NMR (DMSO-d_6) δ ppm: 8.29 (1H, q, J=5.0 Hz, –N*H*CH$_3$), 8.20 (1H, s, $H_{5'}$), 6.54 (1H, s, 2-O*H*), 5.12 (1H, d, $J_{3\text{-}OH,\,H3}$=5.5 Hz, 3-O*H*), 4.57 (1H, t, $J_{5\text{-}OH,\,H5}$=5.5 Hz, 5-OH), 4.50 (1H, d, $J_{1a,1b}$=9.0 Hz, H_{1a}), 4.20 (1H, m, H_4), 3.91 (1H, dd, $J_{H3,3\text{-}OH}$=5.5 Hz, $J_{3,4}$=3.5 Hz, H_3), 3.82 (1H, d, $J_{1a,1b}$=9.0 Hz, H_{1b}), 3.63 (1H, m, H_{5a}), 3.50 (1H, m, H_{5b}), 2.77 (3H, d, J=5.0 Hz, –NHC*H*$_3$). Calcd for $C_{10}H_{14}O_5N_2S$ (274.32): C, 43.78; H, 5.15; N, 10.21. Found: C, 43.37; H, 5.26; N, 9.98.

4.11. 3,5-O-Benzylidene-2-C-(4-ethoxycarbonyl-2-thiazoyl)-2-deoxy-2-fluoro-1,4-anhydro-L-*xylitol* **14**

A solution of **9** (0.40 mg, 1.1 mmol) in anhydrous CH_2Cl_2 (20 ml) was treated with diethylaminosulfur trifluoride for 6 h at room temperature. The mixture was evaporated and purified by column chromatography to yield compound **14** (0.39 g, 97.0%). $[\alpha]_D^{34}$ −78.8 (c 0.035, MeOH). UV λ_{max}^{MeOH} (log ε): 207.0 (4.63), 236.0 (3.91). PFAB-MS (m/z): 380 $[M+1]^+$. ^{1}H NMR (DMSO-d_6) δ ppm: 8.71 (1H, s, $H_{5'}$), 7.32 (5H, m, arom H), 5.67 (1H, s, PhC*H*<), 4.94 (1H, dd, $J_{3,4}$=2.5 Hz, $J_{3,F}$=8.0 Hz, H_3), 4.74 (1H, dd, $J_{1a,1b}$=11.0 Hz, $J_{1a,F}$=41.0 Hz, H_{1a}), 4.44 (1H, dd, $J_{1b,1a}$=11.0 Hz, $J_{1b,F}$=26.0 Hz, H_{1b}), 4.32 (2H, q, J=7.5 Hz, –OC*H*$_2$CH$_3$), 4.29 (1H, d, $J_{5a,5b}$=12.5 Hz, H_{5a}), 4.26 (1H, overlapped, H_4), 4.24 (1H, dd, $J_{5b,5a}$=12.5 Hz, $J_{5b,4}$=1.5 Hz, H_{5b}), 1.30 (3H, t, J=7.5 Hz, –OCH$_2$C*H*$_3$). ^{13}C NMR (DMSO-d_6) δ ppm: 162.1 (d, J=24.9 Hz, $C_{2'}$), 160.4 (–*C*OOEt), 146.0 ($C_{4'}$), 131.7 ($C_{5'}$), 137.6, 128.9, 128.0 (×2), 126.0 (×2) (arom C), 102.2 (d, J=177.1 Hz, C_2), 97.8 (Ph*C*H<), 78.7 (d, J=34.5 Hz, C_3), 74.1 (d, J=22.0 Hz, C_1), 73.3 (C_4), 66.6 (–O*C*H$_2$CH$_3$), 61.0 (C_5), 14.2 (–OCH$_2$*C*H$_3$). ^{19}F NMR (DMSO-d_6, CF_3COOH as an external strandard) δ ppm: −12.58 (dddd, $J_{1a,F}$=41.0 Hz, $J_{1b,F}$=26.0 Hz, $J_{3,F}$=8.0 Hz, $J_{4,F}$=3.8 Hz). Calcd for $C_{18}H_{18}O_5NSF$ (379.43): C, 56.97; H, 4.79; N, 3.69. Found: C, 56.69; H, 4.71; N, 3.35.

4.12. 2-C-(4-Aminocarbonyl-2-thiazoyl)-2-deoxy-2-fluoro-1,4-anhydro-L-*xylitol* **15**

After ammonolysis and removal of the benzylidene group as above, compound **14** (90 mg, 0.24 mmol) was converted to yield **15** (50 mg, 80.4%). $[\alpha]_D^{34}$ −8.3 (c 0.040, MeOH). UV λ_{max}^{MeOH} (log ε): 203.4 (4.37), 232.3 (3.93, sh). PFAB-MS (m/z): 263 $[M+1]^+$. ^{1}H NMR (DMSO-d_6) δ ppm: 8.42 (1H, s, $H_{5'}$), 7.80, 7.65 (each 1H, s, –N*H*$_2$), 5.78 (1H, d, $J_{3\text{-}OH,\,H3}$=6.0 Hz, 3-O*H*), 4.73 (1H, t, $J_{5\text{-}OH,\,H5}$=6.0 Hz, 5-OH), 4.64 (1H, d, $J_{1a,1b}$=11.5 Hz, $J_{1a,F}$=42.0 Hz, H_{1a}), 4.30 (1H, m, $J_{H3,3\text{-}OH}$=6.0 Hz, $J_{3,4}$=3.5 Hz, $J_{3,F}$=9.5 Hz, H_4), 4.18 (1H, dd, $J_{1b,1a}$=11.5 Hz, $J_{1b,F}$=26.0 Hz, H_{1b}), 4.17 (1H, overlapped, H_4), 3.68 (1H, m, $J_{5a,5b}$=11.5 Hz, $J_{5a,5\text{-}OH}$=6.0 Hz, $J_{5a,4}$=5.5 Hz, H_{5a}), 3.56 (1H, m, $J_{5b,5a}$=11.5 Hz, $J_{5b,5\text{-}OH}$=6.0 Hz, $J_{5b,4}$=5.5 Hz, H_{5b}). ^{13}C NMR (DMSO-d_6) δ ppm:163.3 (d, J=26.9 Hz, $C_{2'}$), 162.0 (–*C*OONH$_2$), 149.9 ($C_{4'}$), 126.5 ($C_{5'}$), 103.8 (d, J=177.1 Hz, C_2), 82.9 (C_4), 75.5 (d, J=29.8 Hz, C_3), 72.4 (d, J=22.0 Hz, C_1), 59.1 (C_5). ^{19}F NMR (DMSO-d_6, CF_3COOH as an external standard) δ ppm: −7.37 (dddd, $J_{H1a,F}$=42.0 Hz, $J_{H1b,F}$=26.0 Hz, $J_{H3,F}$=9.5 Hz, $J_{H4,F}$=4.7 Hz). Calcd for $C_9H_{11}O_4N_2SF$ (262.28): C, 41.21; H, 4.24; N, 10.68. Found: C, 41.40; H, 4.37; N, 10.29.

4.13. 2-C-(4-Methylaminocarbonyl-2-thiazoyl)-2-deoxy-2-fluoro-1,4-anhydro-L-xylitol **16**

Compound **14** (0.25 g, 0.66 mmol) was converted as above to yield **16** (0.15 g, 82.4%). m.p. 152–153°C. $[\alpha]_D^{34}$ −2.3 (c 0.068, MeOH). UV λ_{max}^{MeOH} (log ε): 206.1 (4.16), 231.3 (3.84). PFAB-MS (m/z): 277 $[M+1]^+$. ^{1}H NMR (DMSO-d_6) δ ppm: 8.40 (1H, s, $H_{5'}$), 8.38 (1H, q, J =5.0 Hz, –N*H*CH$_3$), 5.78 (1H, d, $J_{3\text{-OH, H3}}$=6.0 Hz, 3-O*H*), 4.73 (1H, t, $J_{5\text{-OH, H5}}$=6.0 Hz, 5-O*H*), 4.65 (1H, dd, $J_{1a,1b}$=11.5 Hz, $J_{1a,F}$=42.0 Hz, H_{1a}), 4.30 (1H, m, $J_{H3,3OH}$=6.0 Hz, $J_{3,4}$=3.5 Hz, $J_{3,F}$=9.5 Hz, H_3),4.18 (1H, dd, $J_{1b,1a}$=11.5 Hz, $J_{1b,F}$=26.0 Hz, H_{1b}), 4.17 (1H, overlapped, H_4), 3.68 (1H, m, $J_{5a,5b}$=11.0 Hz, $J_{5a,5\text{-OH}}$=6.0 Hz, $J_{5a,4}$=5.5 Hz, H_{5a}), 3.57 (1H, m, $J_{5b,5a}$=11.0 Hz, $J_{5b,5\text{-OH}}$=6.0 Hz, $J_{5b,4}$=5.5 Hz, H_{5b}), 2.79 (3H, d, J=5.0 Hz, –NHC*H*$_3$). ^{13}C NMR (DMSO-d_6) δ ppm: 163.4 (d, J=26.8 Hz, $C_{2'}$), 160.7 (–*C*OONHCH$_3$), 149.7 ($C_{4'}$), 125.8 ($C_{5'}$), 103.8 (d, J=177.1 Hz, C_2), 82.9 (C_4), 75.5 (d, J=30.6 Hz, C_3), 72.4 (d, J=21.0 Hz, C_1), 59.1 (C_5), 25.8 (–NH*C*H$_3$). ^{19}F NMR (DMSO-d_6, CF_3COOH as external standard) δ ppm: −7.76 (dddd, $J_{H1a,F}$=42.0 Hz, $J_{H1b,F}$=26.0 Hz, $J_{H3,F}$=9.5 Hz, $J_{H4,F}$=5.2 Hz). Calcd for $C_{10}H_{13}O_4N_2SF$ (276.28): C, 43.47; H, 4.74; N, 10.14. Found: C, 43.57; H, 4.76; N, 10.32. Crystal data: empirical formula, $C_{13}H_{13}O_4N$; formula weight, 276.26; crystal system, monoclinic; space group, $P2_1$; a=6.889(1), b=9.677(2), c=8.982(1) Å, β=96.96(3)°, V=594.4(8) Å^3, Z=2, D_c=1.54 g/cm^3, F (000)=286.

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