Synthesis of 2-Fluoro Sugar and Its Condensation Reaction with Silylated Thymine

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2,3-Dideoxy-2-fluoro-D-*erythro*-pentofuranose was easily prepared from 3-DPA lactone. The condensation reaction between 1-*O*-acetyl derivative of this sugar and silylated thymine in the presence of TMSOTf proceeded in a poorly stereoselective manner.

It has recently been well recognized that the introduction of the fluorine atom into biologically active compounds induces some new and attractive effects. Among them, the fluorine atom at the 2-position of sugar moieties is known to affect the strength of the glycosyl bond.[1] This aspect is important in connection with the lifetime of medicines in vivo. We have developed a convenient method for preparing 3-DPA lactone (**1**),[2] known as a hunger substance. γ-Lactone can be utilized as a starting material for furanoses. Moreover, the hydroxyl group on the C-2 of **1** could be replaced by the fluorine atom with the aid of an aminosulfur trifluoride.[3] In this paper, we report the simple synthesis of 2,3-dideoxy-2-fluoro-*erythro*-pentofuranose (**2**) and its utilization for nucleoside synthesis (Scheme 1).[4]

The primary hydroxyl group of 3-DPA lactone (**1**) was protected by the *t*-butyldiphenylsilyl group (Scheme 2). The reaction of protected lactone (**3**) with (dimethylamino)sulfur trifluoride (diMeDAST) proceeded smoothly to afford the fluorinated lactone **4**. The configuration of the fluorine atom on the C-2 was determined by NOESY experiment (see Experimental section). Reduction of lactone **4** with DIBAL-H at −78 °C afforded the lactol **2** that existed as an anomeric mixture of 90 : 10 (^{1}H NMR). The major isomer is identified as the β anomer from the chemical shifts of the H-4 and H-5 experienced with 2′-deoxynucleoside syntheses.[5a] It can be obtained as a single isomer by recrystallization from hexane–diethyl ether. This isomer anomerized slowly in $CDCl_3$ (2 h; 95 : 5, 22 h; 93 : 7). Acetylation of the β anomer of **2** was carried out under standard conditions to afford the acetate **5** as an anomeric mixture of 96 : 4 (^{1}H NMR). The major isomer was the β anomer judging from the chemical shifts.

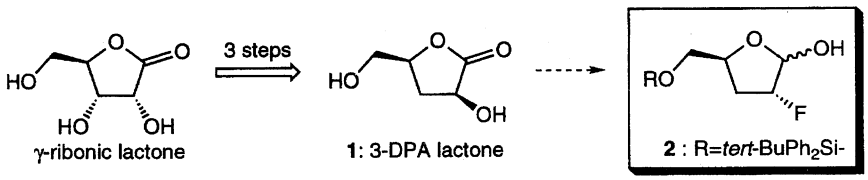
We have studied the synthesis of nucleoside derivatives utilizing the condensation reactions between sugars and nucleic bases in the presence of Lewis acids.[6] In these reactions, the role of the substituents on the C-2 of the sugars is significant[5] (Scheme 3). The acyloxy group is a well-known example.[7] We have already clarified the effect of the phenylthio group (PhS).[6,8] The condensation reactions were also reported for sugars having the phenylseleno group (PhSe)[9] and a bromine atom.[10] We were very interested in the stereoselectivity of this reaction with **5** because we anticipated that the dipole moment of the C–F bond could affect the anomeric ratio to form the β-anomer more favorably.[4]

The condensation reaction between **5** ($\alpha : \beta = 4 : 96$) and silylated thymine (**10**) was carried out in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a catalyst[7a] (Scheme 4). The product consisted of two anomers in the ratio of 67 : 33 (^{1}H NMR). This ratio revealed that the effect of the fluorine atom on the C-2 was not significant for the stereocontrol in glycosidation reaction catalyzed by TMSOTf. Deprotection of the silyl group with tetrabutylammonium fluoride followed by separation with silica-gel column chromatography afforded the β-anomer (**17**, 66% yield) and the α-anomer (**18**, 33% yield). The β-anomer **17** was identified from the reported ^{1}H and ^{13}C NMR spectra[11] and the stereochemistry of the fluorine atom was proofed. The chemical shifts of the H-4′ and H-5′ of α-anomer **18** accorded with those of the β-anomer **17**.[5a]

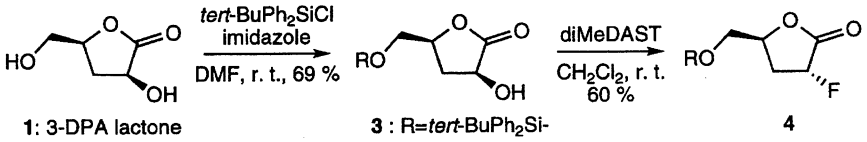
In conclusion, an easy procedure was established for preparing 2,3-dideoxy-2-fluoro-D-*erythro*-pentofuranose (**2**). This sugar was utilized for nucleoside synthesis. In this case, the effect of the fluorine atom on the C-2 of the sugar was not significant when the condensation reaction was carried out in the presence of TMSOTf. Other uses for this fluorinated sugar **2** and its precursors are now under investigation.

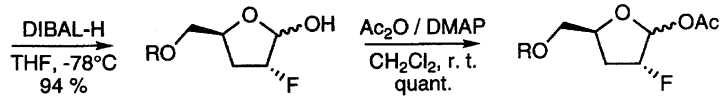
Experimental

All the melting points are uncorrected. The optical rotation was measured on a JASCO DIP-370 polarimeter. The ^{1}H NMR spectra were recorded on a Bruker AC-300P spec-



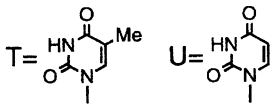
Scheme 1.



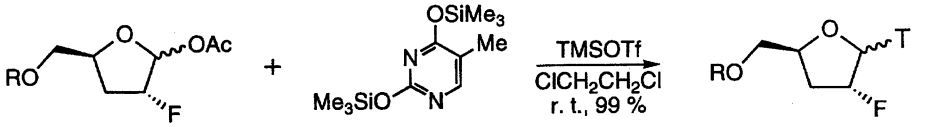


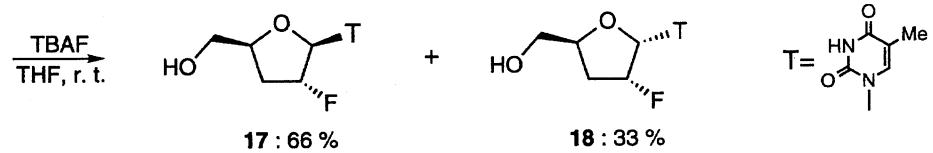
Scheme 2.

6 : R^1=*tert*-$BuPh_2Si$-, X=H, R^2=Ac	**10** : R^3=Me	$ClCH_2CH_2Cl$	**12** : B=T, β : α = 55 : 45
7 : R^1=*tert*-$BuPh_2Si$-, X=SPh, R^2=Ac	**11** : R^3=H	$ClCH_2CH_2Cl$	**13** : B=U, β : α = 79 : 21
8 : R^1=*tert*-$BuPh_2Si$-, X=SePh, R^2=Ac	**10** : R^3=Me	$ClCH_2CH_2Cl$	**14** : B=T, β : α = 99 : 1
9 : R^1=*p*-$MeC_6H_4C(O)$-, X=Br, R^2=Me	**10** : R^3=Me	MeCN	**15** : B=T, β : α = 63 : 37



Scheme 3.





Scheme 4.

trometer (300 MHz) or a Bruker DMX-500 spectrometer (500 MHz). Spectra were acquired on the AC-300P unless otherwise noted. The ^{13}C NMR spectra were recorded at 75 MHz on a Bruker AC-300P spectrometer. The chemical shifts are given in ppm (δ) relative to tetramethylsilane for ^1H NMR and relative to $CDCl_3$ (77.0 ppm) for ^{13}C NMR. The IR spectra were measured on a JASCO FT/IR-5000 spectrophotometer.

(2*S*, 4*S*)-5-(*t*-Butyldiphenylsiloxy)-2-hydroxypentan-4-olide (3). To a mixture of (2*S*, 4*S*)-2,5-dihydroxypentan-4-olide (3-DPA lactone; **1**, 4.63 g, 35.0 mmol) and imidazole (2.40 g, 35.2 mmol) in dry *N*,*N*-dimethylformamide (DMF, 30 ml) over anhydrous calcium chloride, *t*-butylchlorodiphenylsilane (10.5 ml, 41.0 mmol) was added dropwise at 0 °C and the mixture was stirred at room temperature for 2.4 h. The reaction mixture was poured into

water and extracted with diethyl ether three times. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue was purified by silica-gel column chromatography (hexane : ethyl acetate=3 : 2—1 : 1) to afford **3** (8.98 g, 69%) as a colorless oil. $[\alpha]_D^{23}$ +10.2° (*c* 1.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=7.72—7.61 (4H, m, aromatic H), 7.50—7.35 (6H, m, aromatic H), 4.57—4.46 (2H, m, H-2, H-4), 3.91 (1H, dd, *J*=11.6, 3.2 Hz, H-5), 3.73 (1H, dd, *J*=11.6, 4.0 Hz, H-5), 2.95 (1H, d, *J*=3.9 Hz, OH), 2.60 (1H, ddd, *J*=12.8, 8.6, 6.1 Hz, H-3), 2.23 (1H, dt, *J*=12.8, 9.5 Hz, H-3), 1.06 (9H, s, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ=135.64 (aromatic C), 135.55 (aromatic C), 132.47 (aromatic C), 129.97 (aromatic C), 127.86 (aromatic C), 77.19 (C-4), 68.27 (C-2), 64.41 (C-5), 32.39 (C-3), 26.71 (*t*-Bu), 19.22 (*t*-Bu); IR (KBr) 3402 (m), 1760 (s), 1197 (m), 1134 (s), 1115 (m), 1018 (m), 979 (m), 708 (s), 506 (m), 485 (w) cm^{-1}. Anal. Found: C, 68.23; H, 7.12%. Calcd for $C_{21}H_{26}O_4Si$: C, 68.07; H, 7.07%.

(2*R*, 4*S*)-5-(*t*-Butyldiphenylsiloxy)-2-fluoropentan-4-olide (4). Under an argon atmosphere, a solution of (2*S*, 4*S*)-5-(*t*-butyldiphenylsiloxy)-2-hydroxypentan-4-olide (**3**, 7.43 g, 20.0 mmol) in dry dichloromethane (30 ml) was added dropwise to a solution of (dimethylamino)sulfur trifluoride (3.56 g, 22.0 mmol) in dry dichloromethane (20 ml) at −78 °C. The mixture was stirred at room temperature for 2.5 h, then poured into saturated aqueous sodium hydrogencarbonate and extracted three times with chloroform. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue was purified by silica-gel column chromatography (hexane : ethyl acetate=7 : 1) to afford **4** (4.44 g, 60%) as a colorless crystalline solid. The configuration at the C-2 was determined by the NOESY spectrum of **4** in which the NOE was observed between H of *t*-Bu and H-2 (8.1%). The NOE was also observed between H of *t*-Bu and H-3β (2.6%). Mp 119.0—122.5 °C (hexane–dichloromethane); $[\alpha]_D^{29}$ +51.3° (*c* 1.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ=7.64—7.60 (4H, m, aromatic H), 7.48—7.40 (6H, m, aromatic H), 5.49 (1H, ddd, *J*=52.8, 8.2, 7.9 Hz, H-2), 4.71 (1H, ddd, *J*=6.9, 2.0, 1.9 Hz, H-4), 3.92 (1H, ddd, *J*=11.5, 2.1, 2.0 Hz, H-5), 3.61 (1H, dd, *J*=11.5, 1.9 Hz, H-5), 2.73—2.67 (1H, m, H-3β), 2.54 (1H, dddd, *J*=27.8, 13.5, 8.6, 8.2 Hz, H-3α), 1.05 (9H, s, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ=135.54 (aromatic C), 135.41 (aromatic C), 132.38 (aromatic C), 131.77 (aromatic C), 130.12 (aromatic C), 127.96 (aromatic C), 85.55 (d, *J*=187.9 Hz, C-2), 77.28 (d, *J*=4.9 Hz, C-4), 64.99 (C-5), 31.80 (d, *J*=20.2 Hz, C-3), 26.74 (*t*-Bu), 19.08 (*t*-Bu); IR (KBr) 1798 (s), 1193 (m), 1112 (s), 1094 (s), 1081 (m), 704 (s), 505 (m), 491 (m) cm^{-1}. Anal. Found: C, 67.67; H, 7.03; F, 5.03%. Calcd for $C_{21}H_{25}FO_3Si$: C, 67.71; H, 6.76; F, 5.10%.

5-*O*-(*t*-Butyldiphenylsilyl)-2,3-dideoxy-2-fluoro-D-*erythro*-pentofuranose (2). Under an argon atmosphere, a toluene solution[12] of di(*i*-butyl)aluminum hydride (1.0 mol dm^{-1}, 11 ml, 11 mmol) was added dropwise to a solution of (2*R*, 4*S*)-5-(*t*-butyldiphenylsiloxy)-2-fluoropentan-4-olide (**4**, 2.04 g, 5.48 mmol) in dry tetrahydrofuran (20 ml) at −78 °C. The mixture was stirred at the same temperature for 3 h, then a small quantity of water was added. After standing at room temperature for a while, anhydrous magnesium sulfate was added. The precipitate was filtered off with a Celite pad, washed with tetrahydrofuran and the solvent was removed under reduced pressure. The residue was purified by silica-gel column chromatography (hexane : ethyl acetate=6 : 1) to afford **2** (1.93 g, 94%) as a colorless crystalline solid. Mp 67.5—68.5 °C (hexane–diethyl ether); $[\alpha]_D^{29}$ −6.9° (*c* 0.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=7.72—7.64 (4H, m, aromatic H), 7.50—7.35 (6H, m, aromatic H), 5.39 (1H, t, *J*=7.6 Hz, H-1), 4.99 (1H, dd, *J*=52.6, 4.1 Hz, H-2), 4.52 (1H, tt, *J*=7.8, 2.6 Hz, H-4), 3.88 (1H, dd, *J*=11.1, 2.6 Hz, H-5), 3.63 (1H, d, *J*=7.6 Hz, OH), 3.49 (1H, dd, *J*=11.1, 2.6 Hz, H-5), 2.34 (1H, dddd, *J*=42.8, 14.7, 7.8, 4.1 Hz, H-3), 2.13 (1H, ddd, *J*=25.1, 14.7, 7.8 Hz, H-3), 1.07 (9H, s, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ=135.65 (aromatic C), 135.52 (aromatic C), 132.23 (aromatic C), 132.16 (aromatic C), 130.10 (aromatic C), 129.99 (aromatic C), 127.89 (aromatic C), 99.85 (d, *J*=30.9 Hz, C-1), 96.59 (d, *J*=179.3 Hz, C-2), 79.46 (C-4), 64.86 (C-5), 30.00 (d, *J*=20.8 Hz, C-3), 26.80 (*t*-Bu), 19.13 (*t*-Bu); IR (KBr) 3394 (w), 1429 (m), 1112 (s), 1094 (s), 1058 (m), 1044 (m), 992 (m), 704 (s), 509 (m) cm^{-1}. Anal. Found: C, 67.19; H. 7.18; F, 5.14%. Calcd for $C_{21}H_{27}FO_3Si$: C, 67.35; H, 7.27; F, 5.07%.

1-*O*-Acetyl-5-*O*-(*t*-butyldiphenylsilyl)-2,3-dideoxy-2-fluoro-D-*erythro*-pentofuranose (5). 5-*O*-(*t*-Butyldiphenylsilyl)-2,3-dideoxy-2-fluoro-D-*erythro*-pentofuranose (**2**, 315 mg, 0.84 mmol) was dissolved in dry dichloromethane (10 ml). To this solution, acetic anhydride (0.50 ml, 5.3 mmol) and 4-(dimethylamino)pyridine (10 mg) were added and the mixture was stirred overnight at room temperature. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted three times with chloroform. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue was purified by silica-gel column chromatography (hexane : ethyl acetate=8 : 1) to afford an anomeric mixture (96 : 4) of **5** (352 mg, quantitative yield) as a colorless oil. $[\alpha]_D^{25}$ −29.6° (*c* 1.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=7.72—7.65 (4H, m, aromatic H), 7.48—7.35 (6H, m, aromatic H), 6.37 (0.04H, dd, *J*=4.1, 1.7 Hz, H-1), 6.30 (0.96H, d, *J*=10.4 Hz, H-1), 5.40—4.96 (1H, m, H-2), 4.58—4.44 (1H, m, H-4), 3.84—3.68 (1+0.96H, m, H-5), 3.60 (0.04H, dd, *J*=11.3, 2.9 Hz, H-5), 2.45—2.11 (2+3×0.04H, m, H-3, Ac), 1.90 (3×0.96H, s, Ac), 1.06 (9H, s, *t*-Bu); ^{13}C NMR ($CDCl_3$) of the major anomer δ=169.44 (CH_3CO), 135.56 (aromatic C), 135.52 (aromatic C), 133.27 (aromatic C), 133.15 (aromatic C), 129.78 (aromatic C), 129.72 (aromatic C), 127.72 (aromatic C), 127.70 (aromatic C), 99.30 (d, *J*=34.3 Hz, C-1), 95.50 (d, *J*=178.8 Hz, C-2), 81.38 (C-4), 65.32 (C-5), 31.65 (d, *J*=20.6 Hz, C-3), 26.77 (*t*-Bu), 21.06 (CH_3CO), 19.28 (*t*-Bu); IR (neat) 1749 (s), 1430 (m), 1231 (m), 1136 (m), 1114 (s), 1012 (s), 960 (m), 824 (w), 743 (w), 704 (s), 505 (m) cm^{-1}. HRMS (FAB) Found: *m/z* 439.1739 $(M+Na)^+$. Calcd for $C_{23}H_{29}FO_4SiNa$: $(M+Na)^+$, 439.1717.

Anomeric Mixture of 1-[5-*O*-(*t*-Butyldiphenylsilyl)-2,3-dideoxy-2-fluoro-D-*erythro*-pentofuranosyl]-thymine (16). Under an argon atmosphere, silylated thymine (**10**, 816 mg, 3.03 mmol) and 1-*O*-acetyl-5-*O*-(*t*-butyldiphenylsilyl)-2,3-dideoxy-2-fluoro-D-*erythro*-pentofuranose (**5**, α : β=4 : 96, 252 mg, 0.605 mmol) were dissolved in dry 1,2-dichloroethane (5 ml). To this solution, 0.65 ml (3.36 mmol) of trimethylsilyl trifluoromethanesulfonate was added dropwise and the mixture was stirred under an argon atmosphere at room temperature for 5 h. This reaction

mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted three times with chloroform. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue was purified by silica-gel column chromatography (hexane : ethyl acetate=3 : 2) to afford the anomeric mixture ($\alpha:\beta$=33 : 67) of **16** (289 mg, 99% yield) as a white foam. $[\alpha]_D^{26}$ −5.2° (*c* 1.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ= 9.90 (1H, br, NH), 7.79—7.60 (4H, m, aromatic H), 7.52—7.30 (7H, m, H-6, aromatic H), 6.16 (0.33H, dd, J=20.5, 2.8 Hz, H-1′), 6.00 (0.67H, d, J=18.2 Hz, H-1′), 5.47—5.21 (0.33H, m, H-2′), 5.25 (0.67H, dd, J=51.8, 4.4 Hz, H-2′), 4.62—4.53 (0.33H, m, H-4′), 4.51—4.40 (0.67H, m, H-4′), 4.16 (0.67H, dd, J=11.9, 2.4 Hz, H-5′), 3.91 (0.33H, dd, J=11.3, 3.3 Hz, H-5′), 3.82 (0.67H, dd, J=11.9, 3.3 Hz, H-5′), 3.69 (0.33H, dd, J=11.3, 3.6 Hz, H-5′), 2.51—2.03 (2H, m, H-3′), 1.94 (0.33×3H, d, J=1.1, Hz, Me), 1.61 (0.67×3H, d, J=1.1 Hz, Me), 1.11 (0.67×9H, s, *t*-Bu), 1.08 (0.33×9H, s, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ=164.15 (C-4 of α isomer), 164.10 (C-4 of β), 150.47 (C-2 of α), 150.22 (C-2 of β), 136.36 (C-6 of α), 135.50 (C-6 of β), 135.44 (aromatic C), 135.41 (aromatic C), 135.36 (aromatic C), 135.33 (aromatic C), 135.30 (aromatic C), 135.26 (aromatic C), 135.22 (aromatic C), 132.98 (aromatic C), 132.75 (aromatic C), 132.57 (aromatic C), 130.02 (aromatic C), 129.96 (aromatic C), 129.83 (aromatic C), 127.87 (aromatic C), 127.84 (aromatic C), 127.74 (aromatic C), 110.80 (C-5 of β), 109.75 (C-5 of α), 96.35 (d, J=182.2 Hz, C-2′ of β), 92.03 (d, J=186.8 Hz, C-2′ of α), 90.74 (d, J=37.2 Hz, C-1′ of β), 86.60 (d, J=15.6 Hz, C-1′ of α), 80.88 (C-4′ of β), 79.38 (C-4′ of α), 64.87 (C-5′ of α), 63.65 (C-5′ of β), 33.39 (d, J=20.5 Hz, C-3′ of α), 31.97 (d, J=21.1 Hz, C-3′ of β), 26.95 (*t*-Bu of β), 26.75 (*t*-Bu of α), 19.35 (*t*-Bu of β), 19.16 (*t*-Bu of α), 12.52 (Me of α), 12.09 (Me of β); IR (KBr) 3164 (w), 1695 (s), 1472 (m), 1430 (w), 1268 (w), 1114 (m), 999 (w), 823 (w), 796 (w), 704 (m), 506 (m) cm^{-1}. HRMS (FAB) Found: m/z 483.2133 $(M+H)^+$. Calcd for $C_{26}H_{32}FN_2O_4Si$: $(M+H)^+$, 483.2115.

1-[2,3-Dideoxy-2-fluoro-β-D-*erythro*-pentofuranosyl]thymine (17) and 1-[2,3-Dideoxy-2-fluoro-α-D-*erythro*-pentofuranosyl]thymine (18). An anomeric mixture of 1-[5-*O*-(*t*-butyldiphenylsilyl)-2,3-dideoxy-2-fluoro-D-*erythro*-pentofuranosyl]thymine (**16**, $\alpha:\beta$=33 : 67, 77.4 mg, 0.160 mmol) was dissolved in tetrahydrofuran (5 ml). To this solution, a tetrahydrofuran solution of tetrabutylammonium fluoride (1 mol dm^{-1}, 0.18 ml, 0.18 mmol) was added and the reaction mixture was stirred for 3 h at room temperature. A portion of cation exchange resin (Amberlite IR-120B, H^+ form) was added to neutralize the reaction mixture. The resin was filtered off, washed with tetrahydrofuran, the solvent was removed under reduced pressure, and the residue was purified by silica-gel column chromatography (hexane : ethyl acetate=1 : 1) to afford products **17** (26.4 mg, 66%) and **18** (13.0 mg, 33%) as white foams. The spectral data of the major isomer **17** were identical with those reported before[11] and **17** was identified as the β anomer. The spectral data of the minor isomer **18** is shown below. $[\alpha]_D^{29}$ −93.9° (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=9.73 (1H, br.s, NH), 7.23 (1H, q, J=0.6 Hz, H-6), 6.17 (1H, dd, J=21.2, 2.7 Hz, H-1′), 5.41—5.16 (1H, dm, J=52.6 Hz, H-2′), 4.67—4.58 (1H, m, H-4′), 3.95 (1H, dd, J=12.4, 2.4 Hz, H-5′), 3.58 (1H, dd, J=12.4, 3.8 Hz, H-5′), 3.08 (1H, br.s, OH), 2.42—2.25 (2H, m, H-3′), 1.90 (3H, d, J=0.6 Hz, Me); ^{13}C NMR ($CDCl_3$) δ=164.15 (C-4), 150.61 (C-2), 136.50 (C-6), 110.07 (C-5), 92.29 (d, J=187.0 Hz, C-2′), 86.36 (d, J=15.4 Hz, C-1′), 79.84 (C-4′), 63.37 (C-5′), 32.89 (d, J=20.4 Hz, C-3′), 12.47 (Me); IR (KBr) 3440 (m), 3170 (w), 1708 (s), 1656 (s), 1484 (w), 1400 (w), 1291 (m), 1276 (m), 1109 (m), 1073 (m), 1055 (m), 814 (w), 594 (w) cm^{-1}. HRMS (FAB) Found: m/z 245.0954 $(M+H)^+$. Calcd for $C_{10}H_{14}FN_2O_4$: $(M+H)^+$, 245.0938.

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