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Synthesis of hydantoin analogues of 3′-fluoro-3′-deoxythymidine (FLT)

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Summary – Reaction of methyl 2-deoxy-5-*O*-(4-phenylbenzoyl)-β-D-*erythro*-pentofuranoside **2** with diethylaminosulfur trifluoride (DAST) in a 1:10 molar ratio in CH_2Cl_2 at room temperature for 5 d afforded methyl 2,3-dideoxy-3-fluoro-5-*O*-(4-phenylbenzoyl)-β-D-*erythro*-pentofuranoside **4** in 57% yield, while the α-anomer **3** under the same reaction conditions yielded the 3-fluoro-α-D-*erythro* derivative **10** in 14% yield together with the 5-fluoro-α-D-*threo* derivative **11** in 22% yield. (*Z*)-5-Benzylidene-, (*E*)-ethylidene- and 5,5-dimethylhydantoin nucleosides were obtained by condensation of the appropriate silylated nucleobases with **4** The protected nucleosides were in all cases deblocked by treatment with sodium methoxide in methanol. The (*Z*)-ethylidene group isomerized to the *E* configuration during the nucleoside synthesis.

hydantoin / 3′-fluoro-3′-deoxythymidine / methyl 2,3-dideoxy-3-fluoro-β-D-*erythro*-pentofuranoside

Introduction

The discovery of the human immunodeficiency virus (HIV) as the causative agent of AIDS [1-3] and the identification of HIV as a retrovirus have prompted efforts to synthesize reverse transcriptase inhibitors [4-6]. Several nucleoside analogues, including 3′-fluoro-3′-deoxythymidine (FLT) [6-8], proved to be one of the most potent anti-HIV agents. Considering that the size of an active molecule is often crucial for its activity, we thought it would be a challenge to design modifications of the nucleobase in FLT that fulfil the requirement of not increasing the size of the nucleobase. An obvious possibility is a five-membered heterocyclic ring such as imidazolidine-2,4-dione (hydantoin). When this nucleobase is substituted with ethylidene group in the 5-position of the hydantoin ring, it can be compared to thymidine. The only difference is the ring contraction of the pyrimidine ring by a *de facto* rearrangement of carbonyl from C-5 to C-6. Hydantoin nucleosides are seldomly described in the literature [9] and are unknown as FLT analogues.

FLT and a number of its analogues were synthesized by fluorination of the corresponding 2′-deoxy nucleosides [4, 10-12]. Fleet *et al* [13] synthesized 3′-deoxy-3′-fluorothymidine through condensation of thymine with a preformed 2,3-dideoxy-3-fluoro-D-*erythro*-pentofuranose derivative which was in turn prepared through the intermediate methyl 3,5-*O*-isopropylidene-D-xylofuranoside in a multistep process [13-15]. Motawia and Pedersen [16] obtained methyl 2,3-dideoxy-3-fluoro-5-*O*-(4-phenylbenzoyl)-β-D-*erythro*-pentofuranoside **4** by epimerization of C-3 in 2-deoxy-D-ribose by oxidation-reduction reactions, followed by treatment with diethylaminosulfur trifluoride (DAST). This synthesis suffered from the instability of one of the intermediates. Thus, it is highly desirable to find an easy way of introducing fluorine at the C-3 of a 2-deoxy sugar in order to provide an intermediate suitable for efficient coupling with nucleobases in order to make nucleoside analogues.

Results and discussion

Compounds **2** and **3** were synthesized as reported [17] from 2-deoxy-D-ribose **1** through ring contraction and concomittant methyl glycosidation followed by 5-OH protection with biphenyl-4-carbonyl chloride. Treatment of methyl 2-deoxy-5-*O*-(4-phenylbenzoyl)-β-D-*erythro*-pentofuranoside **2** or its α anomer **3** with DAST in dry CH_2Cl_2 at room temperature afforded different products according to the reaction conditions. The reaction time and the amount of DAST used in the reaction are important factors. When **2** was allowed to

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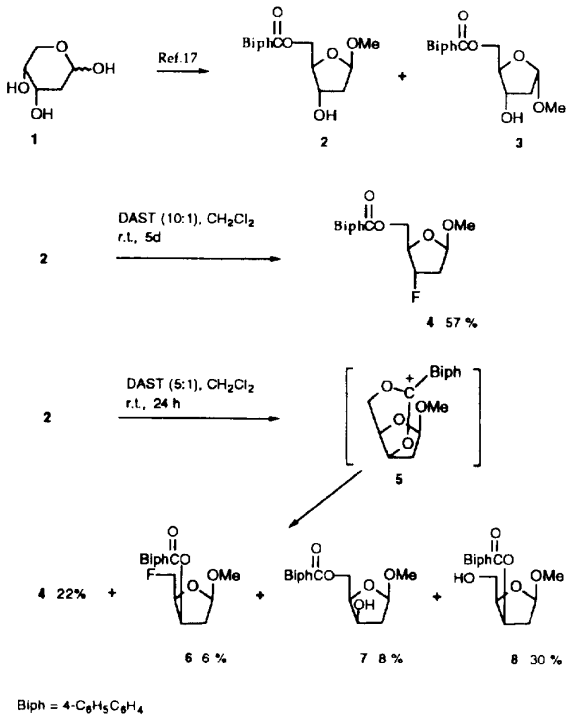
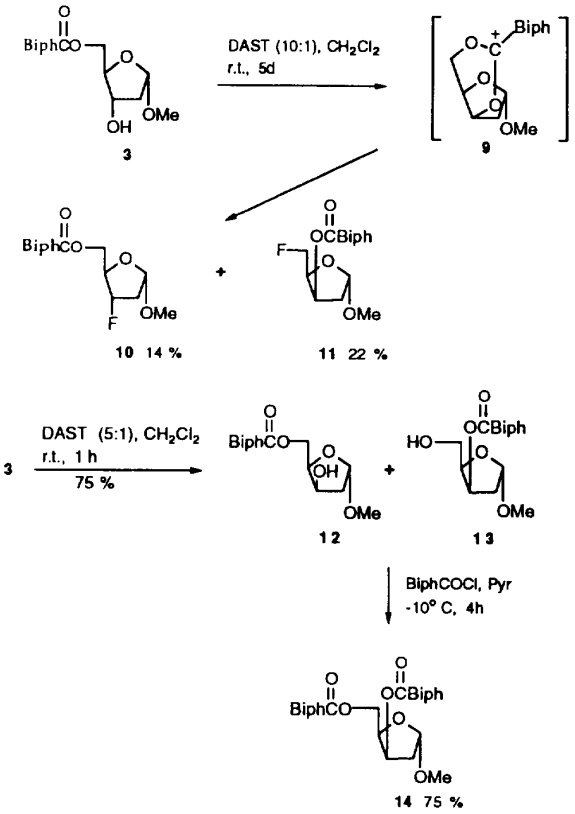
react with DAST in a 1:5 molar ratio at room temperature for 24 h, we obtained the compounds **4** and **6-8**. This is explained by a neighroring group participation of the carbonyl group from the 5-*O*-(biphenyl-4-carbonyl) protecting group resulting in a bicyclic carbonium intermediate **5** with the carbonyl oxygen attached to C-3. This allows the fluoride anion to attack either from the α face of the sugar at C-3, with formation of **4**, or at C-5 of the bicyclic intermediate **5**, to give methyl 2,5-dideoxy-3-*O*-(4-phenylbenzoyl)-5-fluoro-β-D-*threo*-pentofuranoside **6**. On the other hand, the attack of hydroxyl anion on the intermediate carbonium ion **5** during work-up afforded methyl 2-deoxy-5-*O*-(4-phenylbenzoyl)-β-D-*threo*-pentofuranoside **7** and methyl 2-deoxy-3-*O*-(4-phenylbenzoyl)-β-D-*threo*-pentofuranoside **8**. Compound **7** was identical to an authentic sample previously synthesized in our laboratory [16]. However, when compound **2** was allowed to react with DAST in a 1:10 molar ratio in dry CH_2Cl_2 at room temperature for 5 d, compound **4** was obtained in 57% yield without contamination of the 5-fluoro derivative **6**, which was an advantage in the chromatographic purification.



Scheme 1

Similarly, when the α anomer **3** was allowed to react with DAST in a 1:10 molar ratio at room temperature for 5 d, we separated both methyl 2,3-dideoxy-3-fluoro-5-*O*-(4-phenylbenzoyl)-α-D-*erythro*-pentofuranoside **10** in 14% yield and methyl 2,5-dideoxy-3-*O*-(4-phenylbenzoyl)-5-fluoro-α-D-*threo*-pentofuranoside **11** in 22% yield. The formation of these compounds is explained by the attack of fluoride anion on the intermediate carbonium ion **9** at C-3 from the α face



Scheme 2

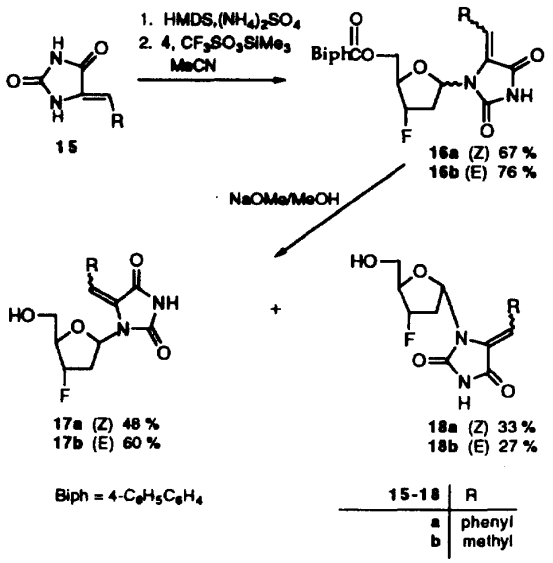
of the sugar to give **10** or at C-5 to give **11**. Starting from the α anomer **3** it was not possible to avoid formation of the 5-fluoro derivative **11** and a more careful chromatographic work-up was therefore needed to isolate **10** in a pure state. The less favorable attack by fluoride at C-3 in **9** is most likely due to increased sterical hindrance by the methoxy group when compared with **5** which has a β methoxy group. The α anomer **3** was allowed to react with DAST in a 1:5 molar ratio at room temperature for 1 h. A mixture of methyl 2-deoxy-3-*O*-(4-phenylbenzoyl)-α-D-*threo*-pentofuranoside **13** and methyl 2-deoxy-5-*O*-(4-phenylbenzoyl)-α-D-*threo*-pentofuranoside **12** was obtained in the ratio 2:1 in 75% yield. This is explained on the basis of formation of the cyclic intermediate **9**, which, on attack by the hydroxyl anion, produces either the known *threo* configuration **12** [16] with the 4-biphenylcarbonyl protecting group at 5-*O*, or **13** which also has *threo* configuration with the protecting group at 3-*O*. Reaction of a mixture of **12** and **13** with biphenyl-4-carbonyl chloride in pyridine at -10°C yielded methyl 2-deoxy-3,5-di-*O*-(4-phenylbenzoyl)-α-D-*threo*-pentofuranoside **14**, which was the only stereo isomer found in the reaction mixture. Our observation on the inversion of the configuration at the 3-position in **3** on treatment with DAST under less drastic conditions falls in line with the investigation on 2'-deoxyadenosine by Herdewijn who observed an anchimeric assistance of a 5'-*O*-carbonyl function for in-

version of configuration at the 3′-carbon atom on treatment with triflic anhydride-pyridine and water [18].

The structures of the new sugars were deduced by comparing ^1H and ^{13}C NMR spectra with those of the known compounds **4**, **7** and **12** [16]. 2D and NOE spectra were also used to confirm the structure of compounds **6**, **8**, **11** and **14**. The *cis* configuration of methoxy and acyloxy in the *β-threo* derivative **6** and **8** was deduced from irradiation of 3-H which resulted in a large NOE enhancement of 2α-H compared with that of 2β-H. The 2α-H and 2β-H were assigned by irradiation of 1-H leading to the larger NOE enhancement in the former proton. The configuration of **6** and **8** was confirmed by the apparent doublet of 2β-H in the ^1H NMR spectrum. This proton has a large geminal coupling to 2α-H and the nearly zero couplings to 1-H and 3-H indicate that these two protons are *trans* to 2β-H [19-21]. For the *erythro* anomer **10** we were unable to use NOE to confirm the *cis* relationship of the methoxy and acyloxy groups due to overlapping resonances of 2α-H and 2β-H, and 3-H and 1-H in a variety of solvents. However, in acetone-d_6 the two 2-H resonances were well separated and the 2α-H appeared as a sharp doublet of doublets with large couplings to fluorine and the geminal 2β-H. The nearly zero couplings of 2α-H to 1-H and 3-H is again taken as an evidence for a *trans* relationship of the latter two protons in relation to 2α-H [19-21]. The *trans* relationship between the methoxy and 3-acyloxy groups in **11** and **14** was easily deduced from the strong NOE effects between 1-H and 2β-H and between 2α-H and 3-H when one of the protons in each pair was irradiated.

The nucleobases (*Z*)-5-benzylidenehydantoin [22] **15a** and (*Z*)-5-ethylidenehydantoin [23] **15b**, prepared as described previously, and 5,5-dimethylhydantoin **19** were silylated by refluxing in 1,1,1,3,3,3-hexamethyldisilazane (HMDS) using ammonium sulfate as the catalyst [24]. Condensation of the protected fluoro sugar **4** with the silylated alkylidene-hydantoins **15** using trimethylsilyl trifluoromethane sulfonate (TMS triflate) as the catalyst according to the method of Vorbrüggen [25] afforded the protected nucleosides **16**. The anomeric mixture **16a** (α/β = 1:2) could easily be separated by column chromatography over silica into its α anomer (17%) and β anomer (50%). On the other hand **16b** (α/β = 1:2) was isolated as an anomeric mixture. Deprotection of (*Z*)-1-[2,3-dideoxy-3-fluoro-5-*O*-(4-phenylbenzoyl)-D-*erythro*-pentofuranosyl]-5-benzylidenehydantoin **16a** as an anomeric mixture using sodium methoxide in methanol at room temperature gave (*Z*)-1-(2,3-dideoxy-3-fluoro-β-D-*erythro*-pentofuranosyl)-5-benzylidenehydantoin **17a** in 48% yield and its α anomer **18a** in 33% yield. In a similar way, deprotection of the ethylidene derivative **16b** afforded (*E*)-1-(2,3-dideoxy-3-fluoro-β-D-*erythro* pentofuranosyl)-5-ethylidenehydantoin **17b** in 60% yield and the corresponding α anomer **18b** in 22% yield.

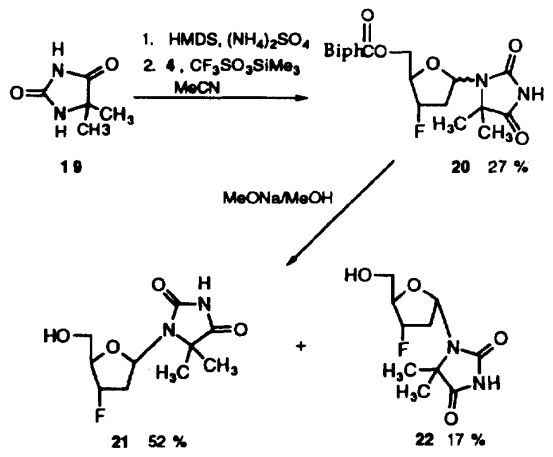
In the ^{13}C NMR spectra, we assigned lines at 114.9 and 113.86 ppm to the exocyclic vinylic carbons of compound **17a** and **18a**, respectively, which have *Z*-configuration, in agreement with the finding of Tan *et al* [26], who reported the exocyclic vinylic carbons in (*Z*)-methylenehydantoins at higher fields than those of the corresponding *E*-isomers. For compounds **17b** and



Scheme 3

18b we found the exocyclic vinylic carbons at 116.54 and 119.33 ppm, respectively. These values are typical [9] for *E*-ethylidene isomers. For the starting nucleobase **15b** with *Z* configuration, the value was 106.9 ppm. This indicates that the ethylidene group isomerized from the *Z* to *E* configuration during the nucleoside synthesis.

Under the same conditions as stated above, the silylated derivative of 5,5-dimethyl-hydantoin **19** was reacted with the fluoro sugar **4** using TMS triflate as the catalyst to give 1-[2,3-dideoxy-3-fluoro-5-*O*-(4-phenylbenzoyl)-D-*erythro*-pentofuranosyl]-5,5-dimethylhydantoin **20** (α/β = 1:3). Upon deprotection with sodium methoxide in methanol 1-(2,3-dideoxy-3-fluoro-β-D-*erythro*-pentofuranosyl)-5,5-dimethylhydantoin **21** was obtained in 52% yield together with its α anomer **22** in 17% yield.



Scheme 4

The assignment of the anomeric configuration was made by ^{1}H NMR spectra; the 4'-H of the α anomers appears downfield from that observed for the β anomers, and the 5'-H of the α anomers appear upfield from those observed for the β anomers [27, 28]. Compounds **17a,b**, **18a**, **21** and **22** were selected for ^{1}H NOE difference spectroscopy to assign the anomeric configuration, site of glycosylation on the hydantoin ring and *Z* or *E* configuration of the exocyclic double bond in the nucleobase. The protons in the ^{1}H NMR spectra were assigned by ^{1}H-^{1}H homonuclear shift correlated (COSY) 2D-NMR. A typical decisive feature for β configuration was irradiation of 2'α-H at the α-site of the aglycone which resulted in strong NOE enhancements (4, 4 and 5%) for the 1'-H proton for compounds **17a**, **17b** and **21**, respectively. Moreover notable strong NOE enhancements were found (4, 5 and 5%, respectively) in 3'-H when the same compounds were irradiated on 2'β-H at the β site of the aglycone. On the other hand, the α configuration for **18a** and **22** was assigned by strong NOE enhancements in 2'β-H (4 and 6%, respectively) when 1'-H was irradiated. Strong NOE enhancements were also found (3 and 6%, respectively) in 3'-H when 2'-β-H was irradiated. *Z* configuration of the exocyclic double bond and N^1-glycosylation of the hydantoin ring were proved by NOE enhancements in the aromatic *ortho* protons of the phenyl group of compounds **17a** and **18a** (2 and 1%), when 1'-H was irradiated. Furthermore, this NOE contact between 1'-H proton and the aromatic protons indicated a pronounced preference for *syn* conformation of the nucleobase around the glycosidic bond. Similarly, an NOE enhancement for the 2'β-H resonance (1%) upon irradiation of the vinylic proton in the ethylidene group of **17b** proved N^1-glycosylation, the *E* configuration of the exocyclic double bond of the hydantoin ring, and, more interestingly, the *anti* conformation of the nucleobase around the glycosidic bond. N^1-glycosylation and the *syn* conformation for compound **21** were proved by a strong NOE enhancement (4%) in the methyl group, when the 1'-H proton was irradiated. On the other hand, compound **22** showed NOE enhancements (1, 1% and zero) in the methyl groups upon irradiation of 2'α-H, 4'-H and 1^1-H, respectively, which confirms the N^1-glycosylation and an *anti* conformation. It was not possible to get conclusive evidence on the stereochemistry of compound **18b** from the NOE spectrum because of overlapping resonances in the ^{1}H NMR spectrum. Instead, through-space couplings to fluorine became the decisive result. A through-space coupling from fluorine to the exocyclic vinylic carbon (6.0 Hz) in the ^{13}C NMR spectrum proved N^1-glycosylation and the α configuration. These findings were confirmed by a through-space coupling of fluorine to the vinylic hydrogen (1.9 Hz) in the ^{1}H NMR spectrum. The latter also confirmed the *E* configuration of the exocyclic double bond and the *anti* conformation around the glycosidic bond to the nucleobase.

Compounds **16**, **17**, **21** and **22** were investigated for their antiviral activity, but no significant activity was found against HIV-1. A moderate activity was found against HSV-1 in Vero cells for **17b** (ED_{50} = 25 μM), and no toxicity was observed at 100 μM for this compound in Vero cells.

Experimental section

*Methyl 2,3-dideoxy-3-fluoro-5-O-(4-phenylbenzoyl)-β-D-*erythro*-pentofuranoside* **4**

DAST (4 mL, 0.03 mol) was added in one portion to a stirred solution of **2** (1.0 g, 0.003 mol) in dry CH_2Cl_2 (20 mL) at −10°C. The mixture was stirred at rt for 5 d and then 5-10 mL of the CH_2Cl_2 phase were added dropwise to a Buchner funnel containing silica gel (40 g) covered with a layer of $CHCl_3$. The organic phase was removed by suction. The silica gel was again covered with a layer of $CHCl_3$ and addition of the CH_2Cl_2 phase was repeated. The silica gel was washed well with $CHCl_3$ and the combined organic phases were evaporated *in vacuo*. The residue was chromatographed on silica gel (40 g) with petroleum ether (65-70°C)/Et_2O (9:1, v/v) to obtain pure **4**. Yield : 0.57 g (57%); mp 60°C; lit [16] mp 58-60°C.

Synthesis of **4** *and* **6-8**

Compound **2** (1.0 g, 0.003 mol) was reacted with DAST (2 mL, 0.015 mol) for 24 h as in the synthesis of **4**. The reaction mixture was washed out from the Buchner funnel with the gradient from 0-5% MeOH in $CHCl_3$. The combined organic phases were evaporated *in vacuo* and chromatographed on silica gel (40 g) with petroleum ether (65-70°C)/Et_2O gradient from 9:1 to 4:1 (v/v) to give 220 mg (22%) of **4**, 55 mg (6%) of **6**, 80 mg (7%) of **7** and 300 mg (30%) of **8**.

*Methyl 2,5-dideoxy-3-O-(4-phenylbenzoyl)-5-fluoro-β-D-*threo*-pentofuranoside* **6**

Mp 75°C.

^{1}H NMR ($CDCl_3$) : δ 2.21 (d, 1H, J = 13.9 Hz, 2 β-H), 2.48 (m, 1H, 2 α-H), 3.43 (s, 3H, OCH_3), 4.32-4.54 (2×m, 1H, $J_{F,4}$ = 27.3 Hz, 4-H), 4.62-4.80 (2×m, 2H, $J_{F,5}$ = 46.5 Hz, 5-H), 5.20 (d, 1H, J = 5.0 Hz, 1-H), 5.40 (m, 1H, 3-H), 7.46 (m, 3H, H_{arom}), 7.64 (m, 4H, H_{arom}), 8.11 (d, 2H, J = 6.6 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$) : δ 39.07 (C-2), 55.04 (OCH_3), 73.92 (C-3, $J_{F,3}$ = 6.3 Hz), 82.21 (C-4, $J_{F,4}$ = 18.2 Hz), 82.82 (C-5, $J_{F,5}$ = 172.3 Hz, 127.01, 127.19, 128.13, 128.85, 130.20, 139.87, 146.04 (C_{arom}), 166.35 (C=O).

FAB MS : m/z 331 ($M + H^+$).

Anal $C_{19}H_{19}FO_4$, calc : C 69.08, H 5.80. Found : C 69.52, H 6.30.

*Methyl 2-deoxy-5-O-(4-phenylbenzoyl)-β-D-*threo*-pentofuranoside* **7**

Mp 96°C, lit [16] mp 96-97°C.

*Methyl 2,3-dideoxy-3-O-(4-phenylbenzoyl)-β-D-*threo*-pentofuranoside* **8**

Mp 79°C.

^{1}H NMR ($CDCl_3$) : δ 2.26 (dt, 1H, J = 14.6, 2.0 Hz, 2β-H), 2.55 (m, 2H, 2 α-H, 5-OH), 3.45 (s, 3H, OCH_3), 3.84 (m, 2H, 5-H), 4.38 (q, 1H, J = 5.4 Hz, 4-H), 5.13 (dd, 1H, J = 1.4, 5.6 Hz, 1-H), 5.61 (m, 1H, 3-H), 7.46 (m, 3H, H_{arom}), 7.64 (m, 4H, H_{arom}), 8.10 (d, 2H, J = 8.37 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$) : δ 39.34 (C-2), 55.40 (OCH_3), 61.85 (C-5), 72.89 (C-3), 81.61 (C-4), 104.41 (C-1), 127.06, 127.17, 128.10, 128.31, 128.83, 130.21, 139.85, 146.02 (C_{arom}), 166.20 (C=O).

FAB MS : m/z 329 ($M + H^+$).

Anal $C_{19}H_{20}O_5$, calc : C 69.50, H 6.14. Found : C 69.27, H 6.16.

Methyl 2,3-dideoxy-3-fluoro-5-O-(4-phenylbenzoyl)-α-D-erythro-pentofuranoside **10** *and methyl 2,5-dideoxy-5-fluoro-3-O-(4-phenylbenzoyl)-α-D-threo-pentofuranoside* **11**

Compound **3** (1.0 g, 0.003 mol) and DAST (4 mL, 0.03 mol) were reacted in a similar way for 5 d as in the synthesis of **4**. Chromatography on silica gel (40 g) with petroleum ether (65-70°C)/Et_2O (9:1, v/v) afforded 140 mg (14%) of **10** and 220 mg (22%) of **11**.

• *Compound* **10**

^1H NMR (CD_3COCD_3) : δ 2.18 (dd, 1H, $J_{2\alpha,F}$ = 24.5 Hz, $J_{2\alpha,2\beta}$ = 15.0 Hz, 2α-H), 2.41 (2×m, 1H, $J_{2\beta,F}$ = 34.8 Hz, 2 β-H), 3.34 (s, 3H, OCH_3), 4.46 (d, 2H, J = 4.1 Hz, 5-H), 4.54 (m, 1H, 4-H), 5.17 (d, 1H, J = 5.0 Hz, 1-H), 5.29 (2 × m, 1H, $J_{3,F}$ = 57.6 Hz, 3-H), 7.4-8.1 (m, 9H, H_{arom}).

^{13}C NMR ($CDCl_3$) : δ 39.62 (C-2, $J_{F,2}$ = 20,7 Hz), 55.15 (OCH_3), 63.78 (C-5, $J_{F,5}$ = 8.9 Hz), 81.62 (C-4, $J_{F,4}$ = 26.7 Hz), 93.54 (C-3, $J_{F,3}$ = 181.0 Hz), 105.09 (C-1), 127.05, 127.16, 128.14, 128.22, 128.85, 130.03, 139.76, 146.0 (C_{arom}), 166.03 (C=O).

FAB MS : m/z 331 ($M + H^+$).

Anal $C_{19}H_{19}FO_4$, calc : C 69.08, H 5.80. Found : C 69.31, H 5.91.

• *Compound* **11**

Mp 55°C.

^1H NMR ($CDCl_3$) : δ 2.36 (m, 2H, 2-H), 3.41 (s, 3H, OCH_3), 4.58 (2 × m, 1H, $J_{F,4}$ = 23.3 Hz, 4-H), 4.61-4.82 (2 × m, 2H, $J_{F,5}$ = 46.6 Hz, 5-H), 5.26 (dd, 1H, J = 5.3, 2.3 Hz, 1-H), 5.73 (m, 1H, 3-H), 7.46 (m, 3H, H_{arom}), 7.67 (m, 4H, H_{arom}), 8.06 (d, 2H, J = 8.3 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$) : δ 40.36 (C-2), 55.21 (OCH_3), 73.83 (C-3, J = 5.7 Hz), 77.21 (C-4, $J_{F,4}$ = 20.9 Hz), 81.36 (C-5, $J_{F,5}$ = 170.2 Hz), 104.11 (C-1), 126.95, 127.06, 128.09, 128.16, 128.84, 130.04, 139.98, 146.00 (C_{arom}), 166.05 (C=O).

FAB MS : m/z 331 ($M + H^+$).

Anal $C_{19}H_{19}FO_4$, calc : C 69.08, H 5.80. Found : C 68.74, H 6.17.

Methyl 2-deoxy-5-O-(4-phenylbenzoyl)-α-D-threo-pentofuranoside **12** *and methyl 2-deoxy-3-O-(4-phenylbenzoyl)-α-D-threo-pentofuranoside* **13**

Compound **3** (1.0 g, 0.003 mol) was reacted with DAST (2 mL, 0.015 mol) for 1 h as described in the case of **4** and **6-8** to give 750 mg (75%) of a mixture of **12** and **13** in the ratio 1:2. Compound **12** was identified by comparing the ^{13}C NMR spectrum of the mixture with an authentic sample [16].

• *Compound* **13**

^{13}C NMR ($CDCl_3$) : δ 42.29 (C-2), 55.33 (OCH_3), 60.56 (C-5), 74.43 (C-3), 79.53 (C-4), 103.91 (C-1), 127.06, 127.15, 128.13, 128.83, 130.18, 139.71, 145.76 (C_{arom}), 166.00 (CO).

Methyl 2-deoxy-3,5-di-O-(4-phenylbenzoyl)-α-D-threo-pentofuranoside **14**

Biphenyl-4-carbonyl chloride (0.86 g, 0.004 mol) was added in small portions to a stirred solution of a mixture of **7** and **8** (1 g, 0.003 mol) in dry pyridine (10 mL) at −20°C. Stirring was continued for 4 h at −10°C. The reaction mixture was poured onto crushed ice and extracted with $CHCl_3$. The extracts were washed with sat $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was coevaporated with toluene (5 mL) three times and chromatographed on silica gel (30 g) with petroleum ether (65-70°C)/Et_2O (9:1, v/v) to obtain compound **14** as a pure white solid. Yield 1.1 g (75%); mp 97°C.

^1H NMR ($CDCl_3$) : δ 2.41 (m, 2H, 2-H), 3.42 (s, 3H, OCH_3), 4.55-4.70 (m, 3H, 4-H, 5-H), 5.28 (dd, 1H, J = 2.6, 5.3 Hz, 1-H), 5.82 (m, 1H, 3-H), 7.43 (m, 6H, H_{arom}), 7.60 (m, 8H, H_{arom}), 8.06 (d, 4H, J = 8.3 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$) : δ 40.54 (C-2), 55.29 (OCH_3), 62.60 (C-5), 73.98 (C-3), 76.68 (C-4), 104.15 (C-1), 126.94, 127.07, 127.18, 128.09, 128.30, 128.52, 128.84, 130.12, 139.67, 139.82, 145.71, 145.98 (C_{arom}), 165.62, 165.90 (2 CO).

FAB MS : m/z 509 ($M + H^+$).

Anal $C_{32}H_{28}O_6$ calc : C 75.58, H 5.55. Found : C 75.59, H 5.56.

Silylation of the hydantoins **15** *and* **19**

A mixture of the hydantoin **15** or **19** (5.3 mmol), anhydrous $(NH_4)_2SO_4$ (0.026 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (40 mL) was refluxed overnight. The clear solution obtained was cooled and the solvent was evaporated *in vacuo* to give the corresponding silylated compounds as pale-yellow oils.

(Z)-1-[2,3-Dideoxy-3-fluoro-5-O-(4-phenylbenzoyl)-D-erythro-pentofuranosyl]-5-benzylidene-hydantoin **16a**

A solution of the fluoro sugar **4** (1.0 g, 3 mmol) in anhydrous MeCN (20 mL) was added to a stirred solution of silylated **15a** (5.3 mmol) in anhydrous MeCN (30 mL) and the mixture was cooled to −50°C. A solution of $CF_3SO_3SiMe_3$ (1.08 mL, 6 mmol) in anhydrous MeCN (10 mL) was added dropwise during 5 min at −50°C. The mixture was stirred at −30°C for 3 h and then at −20°C overnight. The mixture was diluted with CH_2Cl_2 (200 mL), washed with sat aq $NaHCO_3$ (200 mL), water (2 × 100 mL) and dried over anhydrous Na_2SO_4. The mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel using $CHCl_3$ to afford the anomers of **16a**.

• *Compound* **16a** *(α anomer)*

Yield : 250 mg (17%) as a white foam.

^1H NMR ($CDCl_3$) : δ 2.51 (m, 1H, 2'-H), 3.13 (m, 1H, 2'-H), 4.34 (m, 2H, 5'-H), 4.72 (m, 1H, 4'-H), 5.0 (m, 1H, $J_{F,3'}$ = 55.8 Hz, 3'-H), 5.57 (t, 1H, J = 7.2 Hz, 1-H), 6.85 (s, 1H, =CH), 7.31, 8.13 (m, 14H, H_{arom}), 8.83 (s, 1H, NH).

^{13}C NMR ($CDCl_3$) : δ 34.89 (d, $J_{F,C-2'}$ = 21.0 Hz, C-2'), 63.94 (d, J = 3.7 Hz, C-5'), 80.81 (d, $J_{F,C-4'}$ = 25.6 Hz, C-4'), 83.74 (d, $J_{F,C-1'}$ = 6.4 Hz, C-1'), 91.86 (d, $J_{F,C-3'}$ = 186.9, C-3'), 113.86 (=CH), 127.07, 127.22, 128.27, 128.59, 128.93, 128.97, 129.08, 130.10, 132.32, 139.86, 145.98 (C-5 and C_{arom}), 153.71 (C-2), 163.24 (C-4), 165.90 (CO).

FAB MS : m/z : 487 (M + H^+).

• *Compound* **16a** *(β anomer)*

Yield : 0.75 g (50%) as a white foam.

^{1}H NMR ($CDCl_3$) : δ 2.31 (dddd, 1H, J = 2.8, 7.1, 14.3, 23.5 Hz, 2′-H), 3.26 (m, 1H, 2′-H), 4.27 (tdd, 1H, J = 2.6, 5.9 Hz, $J_{F,4'}$ = 24.3 Hz, 4′-H), 4.53 (m, 2H, 5′-H), 5.38 (2×m, 1H, $J_{F,3'}$ = 55.3 Hz, 3′-H), 5.69 (t, 1H, J = 7.1 Hz, 1′-H), 6.93 (s, 1H, =CH), 7.38-8.13 (m, 14H, H_{arom}), 8.90 (s, 1H, NH).

^{13}C NMR ($CDCl_3$) : δ 34.50 (d, $J_{F,C-2'}$ = 21.1 Hz, C-2′), 63.55 (d, $J_{F,C-5'}$ = 8.2 Hz, C-5′), 81.85 (d, $J_{F,C-4'}$ = 25.7 Hz, C-4′), 84.23 (d, $J_{F,C-1'}$ = 2.7 Hz, C-1′), 93.43 (d, $J_{F,C-3'}$ = 179.5 Hz, C-3′), 114.36 (=CH), 127.05, 127.25, 128.16, 128.42, 128.74, 128.90, 129.10, 129.17, 130.30, 132.18, 139.93, 145.89 (C-5 and C_{arom}), 153.73 (C-2), 163.31 (C-4), 166.09 (CO).

FAB MS : m/z : 487 (M + H^+).

Anal $C_{28}H_{23}FN_2O_5$, H_2O calc : C 66.64, H 4.99, N 5.55. Found : C 67.13, H 4.70, N 5.55.

*(E)-1-[2,3-Dideoxy-3-fluoro-5-O-(4-phenylbenzoyl)-*D-erythro*-pentofuranosyl]-5-ethylidene-hydantoin* **16b**

The anomeric mixture **16b** was prepared as described for **16a**. The mixture was chromatographed on silica gel with $CHCl_3$ to give 1.0 g (76%) of **16b** as a white foam (α/β = 1:2).

FAB MS : m/z 425 (M + H^+, 100).

*1-[2,3-Dideoxy-3-fluoro-5-O-(4-phenylbenzoyl)-*D-erythro*-pentofuranosyl]-5,5-dimethylhydantoin* **20**

The anomeric mixture **20** was prepared as described for **16a**. The mixture was chromatographed on silica gel with $CHCl_3$ to yield 0.35 g (27%) of **20** as a white foam (α/β = 1:3).

FAB MS : m/z 427 (M + H^+, 100).

*(Z)-5-Benzylidene-1-(2,3-dideoxy-3-fluoro-β-*D-erythro*-pentofuranosyl)hydantoin* **17a** *and its α-anomer* **18a**

To a stirred suspension of an anomeric mixture **16a** (0.4 g, 0.82 mmol) in anhydrous MeOH (10 mL) was added portionwise NaOMe (0.045 g, 0.82 mmol) in anhydrous MeOH (10 mL) at rt and the solution was stirred overnight. After evaporation of the solvent *in vacuo*, H_2O (15 mL) was added and the mixture was extracted several times with CH_2Cl_2 to remove the ester formed during the deprotection. To the resulting aqueous solution was added an ion exchange resin (Dowex 50 W×2, H^+-form), previously washed with MeOH. After stirring for 5 min, the solution was filtered, evaporated *in vacuo* and the residue chromatographed on silica gel with the gradient 0-2% MeOH in $CHCl_3$ to give **17a** and **18a**.

• *Compound* **17a**

Yield 120 mg (48%) as a white foam.

^{1}H NMR ($CDCl_3$) : δ 2.28 (m, 1H, 2′α-H), 2.92-3.08 (2×m, 1H, $J_{2',\beta,F}$ = 40.4 Hz, 2′β-H), 3.70-4.20 (m, 3H, 4′-H and 5′-H), 5.24 (dd, 1H, J = 4.7, $J_{3',F}$ = 58.9 Hz, 3′-H), 5.65 (dd, 1H, J = 5.7, 9.6 Hz, 1-H), 6.97 (s, 1H, =CH), 7.39-7.41 (m, 5H, H_{arom}), 9.02 (s, 1H, NH).

^{13}C NMR ($CDCl_3$) : δ 35.46 (d, $J_{F,C-2'}$ = 20.3 Hz, C-2′), 62.68 (d, $J_{F,C-5'}$ = 10.8 Hz, C-5′), 85.41 (d, $J_{F,C-4'}$ = 24.0 Hz, C-4′), 85.48 (C-1′), 94.51 (d, $J_{F,C-3'}$ = 175.6 Hz, C-3′), 114.90 (=CH), 128.70, 128.93, 129.31, 131.93 (C-5 and C_{arom}), 154.67 (C-2), 163.09 (C-4).

MS (EI) : m/z 306 (M^+, 11).

Anal $C_{15}H_{15}FN_2O_4$, H_2O, Calc : C 55.53, H 5.28, N 8.64. Found : C 55.83, H 5.01, N 8.48.

• *Compound* **18a**

Yield 83 mg (33%) as a white foam.

^{1}H NMR ($CDCl_3$) : δ 2.54 (m, 1H, 2′β-H), 3.15 (m, 1H, 2′α-H), 3.75 (m, 2H, 5′-H), 4.45 (2 × m, 1H, $J_{F,-4'}$ = 22.4 Hz, 4′-H), 5.01 (2×m, 1H, $J_{F,3'}$ = 56.4 Hz, 3′-H), 5.50 (t, 1H, J = 7.3 Hz, 1′-H), 6.92 (s, 1H, =CH), 7.38 (s, 5H, H_{arom}), 8.98 (s, 1H, NH).

^{13}C NMR ($CDCl_3$) : δ 34.99 (d, $J_{F,C-2'}$ = 21.6 Hz, C-2′), 61.58 (d, $J_{F,C-5'}$ = 2.6 Hz, C-5′), 83.16 (d, $J_{F,C-4'}$ = 25.5 Hz, C-4′), 83.90 (d, $J_{F,C-1'}$ = 7.5 Hz, C-1′), 90.74 (d, $J_{F,C-3'}$ = 184.5 Hz, C-3′), 113.86 (=CH), 128.58, 128.94, 129.01, 129.31, 132.52 (C-5 and C_{arom}), 154.07 (C-2), 163.33 (C-4).

MS (EI) : m/z 306 (M^+, 59). HRMS $C_{15}H_{15}FN_2O_4$, calc : 306.1025. Found : 306.1019.

*(E)-1-(2,3-Dideoxy-3-fluoro-β-*D-erythro*-pentofuranosyl)-5-ethylidenehydantoin* **17b** *and its α-anomer* **18b**

The protected nucleoside **16b** (1.0 g, 2.27 mmol) was treated as described for the treatment of **16a**. Purification by column chromatography on silica gel with the gradient 0-2% MeOH in $CHCl_3$ afforded **17b** and **18b**.

• *Compound* **17b**

Yield : 345 mg (60%) as a white foam.

^{1}H NMR ($CDCl_3$) : δ 2.21 (d, 3H, J = 7.5 Hz, CH_3), 2.34 (m, 1H, 2′α-H), 2.98-3.13 (2 × m, 1H, $J_{2'\beta,F}$ = 38.6 Hz, 2′β-H), 3.82 (m, 2H, 5′-H), 4.24 (d, 1H, $J_{F,4'}$ = 27.8 Hz, 4′-H), 5.33 (dd, 1H, $J_{F,3'}$ = 54.4 Hz, J = 4.8 Hz, 3′-H), 5.76 (dd, 1H, J = 5.8, 9.5 Hz, 1′-H), 5.92 (q, 1H, J = 7.5 Hz, =CH), 9.35 (s, 1H, NH).

^{13}C NMR ($CDCl_3$) : δ 11.87 (CH_3), 35.03 (d, $J_{F,C-2'}$ = 20.2 Hz, C-2′), 62.25 (d, $J_{F,C-5'}$ = 10.5 Hz, C-5′), 82.61 (C-1′), 84.98 (d, $J_{F,C-4'}$ = 24.0 Hz, C-4′), 94.41 (d, $J_{F,C-3'}$ = 175.8 Hz, C-3′), 116.54 (=CH), 128.61 (C-5), 152.87 (C-2), 162.62 (C-4).

MS (EI) : m/z 244 (M^+, 3). HRMS $C_{10}H_{13}FN_2O_4$, calc : 244.0859. Found : 244.0846.

• *Compound* **18b**

Yield : 155 mg (27%).

^{1}H NMR ($CDCl_3$) : δ 2.21 (d, 3H, J = 7.6 Hz, CH_3), 2.64 (m, 2H, 2′-H), 3.69 (dd, 1H, J = 3.8, 12.0 Hz, 5′-H), 3.77 (dd, 1H, J = 2.2, 12.0 Hz, 5′-H), 4.45 (d, 1H, J = 22.1 Hz, 4′-H), 5.31 (dd, 1H, $J_{F,3'}$ = 55.9 Hz, J = 6.5 Hz, 3′-H), 6.14 (dq, 1H, $J_{H,F}$ = 1.9 Hz, J = 7.6 Hz, =CH), 6.25 (t, 1H, $J_{1',2'}$ = 7.9 Hz, 1′-H), 9.33 (s, 1H, NH).

^{13}C NMR ($CDCl_3$) : δ 12.34 (CH_3), 34.96 (d, $J_{F,C-2'}$ = 21.3 Hz, C-2′), 62.48 (d, $J_{F,C-5'}$ = 9.6 Hz, C-5′), 82.22 (C-1′), 84.48 (d, $J_{F,C-4'}$ = 23.7 Hz, C-4′), 93.98 (d, $J_{F,C-3'}$ = 179.1 Hz, C-3′), 119.33 (d, $J_{C,F}$ = 6.0 Hz, =CH), 126.14 (C-5), 153.11 (C-2), 163.10 (C-4).

MS (EI) : m/z 244 (M^+, 26). HRMS $C_{10}H_{13}FN_2O_4$, calc : 244.0859. Found : 244.0851.

*1-(2,3-Dideoxy-3-fluoro-β-*D*-erythro-pentofuranosyl)-5,5-dimethylhydantoin* **21** *and its α-anomer* **22**

The protected nucleoside **20** (0.30 g, 0.7 mmol) was treated as described for **16a**. Purification by column chromatography on silica gel with the gradient 0-2% MeOH in $CHCl_3$ afforded **21** and **22**.

• *Compound* **21**

Yield : 90 mg (52%) as a white solid; mp 153-155°C.

^{1}H NMR (CD_3OD) : δ 1.38 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.28 (m, 1H, 2′α-H), 2.99 (m, 1H, 2′β-H), 3.66 (m, 2H, 5′-H), 4.08-4.19 (m, 1H, $J_{F,4'}$ = 27.0 Hz, 4′-H), 5.12-5.39 (m, 2H, 1′-H, 3′-H), 8.98 (s, 1H, NH).

^{13}C NMR (CD_3OD) δ 23.66 (CH_3), 23.73 (CH_3), 36.67 (d, $J_{F,C-2'}$ = 20.2 Hz, C-2′), 63.72 (d, $J_{F,C-5'}$ = 7.5 Hz, C-5′), 85.23 (C-1′), 86.52 (d, $J_{F,C-4'}$ = 23.3 Hz, C-4′), 96.39 (d, $J_{F,C-3'}$ = 175.1 Hz, C-3′), 156.90 (C-2), 178.50 (C-4).

MS (EI) : m/z 246 (M^+, 3). HRMS $C_{10}H_{15}FN_2O_4$, calc : 246.1016. Found : 246.0988.

• *Compound* **22**

Yield : 30 mg (17%) as a white foam.

^{1}H NMR (CD_3OD) : δ 1.27 (s, 6H, 2 CH_3), 2.57 (m, 1H, 2′β-H), 2.83 (m, 1H, 2′α-H), 3.55 (dd, 1H, J = 4.2, 12.2 Hz, 5′-H), 3.60 (dd, 1H, J = 3.2, 12.2 Hz, 5′-H), 4.27 (m, 1H, 4′-H), 4.92-5.18 (2 × m, 1H, $J_{F,3'-H}$ = 58.9, 3′-H), 5.72 (dd, 1H, J = 6.7, 7.8 Hz, 1′-H.

^{13}C NMR (CD_3OD) : δ 24.84, 24.91 (2 CH_3), 35.20 (d, $J_{F,C-2'}$ = 21.6 Hz, C-2′), 62.33 (d, $J_{F,C-5'}$ = 3.6 Hz, C-5′), 81.43 (d, $J_{F,C-1}$ = 7.1 Hz, C-1′), 85.12 (d, $J_{F,C-4'}$ = 23.9 Hz, C-4′), 93.11 (d, $J_{F,C-3'}$ = 182.2 Hz, C-3′), 156.69 (C-2), 178.99 (C-4).

MS (EI) : m/z 246 (M^+, 6). HRMS $C_{10}H_{15}FN_2O_4$, calc : 246.1016. Found : 246.1019.

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