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Synthesis of fluorocyclobutanones and their use in the synthesis of fluoronucleosides

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Abstract

Fluorocyclobutanones can be prepared from reaction of hydroxycyclobutanones with diethylaminosulfur trifluoride (DAST). Other fluorine containing cyclobutanones can be prepared by alkene/fluoroketene cycloadditions. The photochemical ring-opening of these synthetic intermediates with 6-chloropurine produces fluorinated nucleoside analogs.

Keywords: Fluoroketene; Fluoronucleosides; Fluorocyclobutanones; Photochemistry

1. Introduction

Fluorinated drugs are commonly used in the treatment of disease. Such drugs include antimalarials, antidepressants, anaesthetics, steroids and antiviral agents [1]. The synthesis and biological evaluation of acid stable 2′- and 3′-fluoronucleosides as active agents against HIV have been reported [2–8]. The replacement of a hydrogen atom for fluorine often maintains the bulk geometry of the molecule but produces significant electronic changes. The fluorine atom with a van der Waals radius of 1.35 Å compared to that of hydrogen (1.17 Å) is the most electronegative atom that can be introduced into an organic molecule. The larger bond strength of a C–F bond compared to C–H (116 kcal/mol versus 100 kcal/mol) causes changes in the substrate metabolism when such fluorinated molecules are used as drugs [9,10]. Fluorine may also serve as an isopolar mimic of a hydroxyl group since it can act as a hydrogen bond acceptor because the C–F bond length (1.35 Å) is very similar to the C–O bond length (1.43 Å). The mechanism by which fluorine prevents the oxidative catabolism of the nucleosides is thought to be via the creation of a ribo-like sugar that is sterically and electronically similar to one with a hydroxyl group, which cannot undergo decomposition.

One of the most potent anti-HIV compound that has been reported is 3′-fluoro-2′,3′-dideoxythymidine [2] (FddThd). Of the 2′-fluoronucleoside analogs, 1-(2′-dideoxy-2′-fluoro-1′-β-D-arabinofuranosyl)-5-iodouracil (FIAC) **1** has been proven to be a potent and selective *anti-herpes* virus agent [11,12]. More recently, the thymidine nucleotide derived from **2** (phosphate ester at 5′-OH of nucleoside **2**) containing a fluoromethyl group at the 3′-position exhibits potent inhibitory activity for thymidine monophosphate kinase (TMPKT) of *Mycobacterium tuberculosis* [13]. Although the nucleotide has a somewhat higher affinity for the enzyme, the parent nucleoside exhibits affinity for bacterial TMPKT in the same order of magnitude and displays a superior selectivity profile versus human TMPKT. However, both purine and pyrimidine nucleosides based on the 3′-fluoromethylriboside unit in **2** do not exhibit antiviral activity [14,15]. These and other nucleosides are prepared by classical approaches involving lengthy multi-step sequences starting from sugar precursors.

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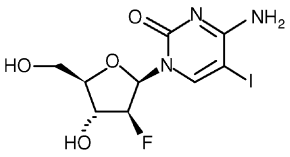

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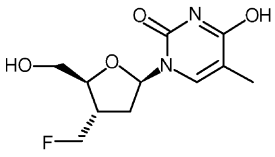

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Our interest in preparing fluorinated cyclobutanones originated with the general method we have developed for the preparation of nucleosides involving a key photochemical ring-expansion [16] of cyclobutanones. In this report, we detail extensions of this approach to fluorinated analogs of these derivatives.

2. Results and discussion

2.1. Synthesis of fluorinated cyclobutanones

The introduction of fluorine into cyclobutanone can be readily achieved with diethylaminosulfur trifluoride (DAST) a reagent known to replace a hydroxyl group with fluoride [17]. Two 3-fluorocyclobutanones **4** and **5** were chosen for this study. 3-Hydroxymethylcyclobutanone (**3**) was prepared by hydrogenolysis of 3-benzyloxycyclobutanone [18] with formic acid catalyzed by palladium. Alcohol **3** was treated with DAST giving 3-fluoromethylcyclobutanone (**4**) in 50% yield. The structure of ketone **4** was confirmed by spectral data. The ^{1}H NMR spectrum showed a doublet at δ 4.6 ppm (J = 47 Hz) for the methylene hydrogens next to the fluorine which was consistent with the ^{19}F NMR peak at δ −222.7 ppm (txd, J = 47, 23 Hz).

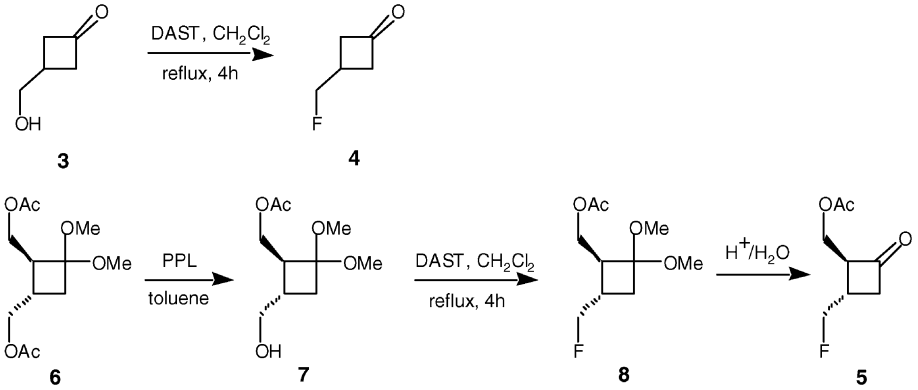
The optically active 3-floromethylcyclobutanone **5** was prepared from a sequence of reactions starting with the known ketal **6** [16b]. Selective enzymatic hydrolysis of **6** with Porcine Pancreatic Lipase (PPL) afforded mono-ester **7** in 95% yield [19]. Treatment of **7** with DAST under the same conditions as in the conversion to **4** gave fluoroketal **8** in 82% yield. The fluorinated cyclobutanone **5** was obtained from **8** by treatment with aqueous acid in 10% yield.

Fluorocyclobutanone **5** was characterized by ^{1}H NMR, ^{19}F NMR, ^{13}C NMR, FT-IR and mass spectrometry. The ^{1}H NMR spectrum of **5** showed the methylene hydrogens next to fluorine at δ 4.6 ppm (J = 47 Hz). Similarly, the ^{19}F NMR spectrum exhibited a triplet at δ −224.8 ppm (J = 47 Hz) which was further split into a doublet (J = 20.7 Hz).

Fluoroketene, obtained using a literature method [20], was employed in a [2 + 2] cycloaddition with 1,3-cyclopentadiene. The α-fluorocyclobutanone **9** was prepared in 30% yield and its spectroscopic analysis was in agreement with that of the reported data for the same compound [21]. Although the authors reported a mixture containing 12:88 (*exo*:*endo*) for the two stereoisomers, in our case a single stereoisomer was formed for which the *endo* stereochemistry was assigned. Other unsymmetrical haloketenes have also been reported to undergo the cycloaddition with cyclopentadiene in a stereospecific manner yielding only the *endo*-halo isomer [21]. The ^{1}H NMR spectrum of **9** showed a doublet at δ 5.6 ppm (J = 53.4 Hz) for the *geminal* hydrogen bonded to the carbon center bearing fluorine and the ^{19}F NMR spectrum showed a doublet at δ −185.5 ppm (J = 53.4 Hz) for the fluorine α to the carbonyl group.

2.2. Photolysis of cyclobutanones

Fluorocyclobutanone **4** was subjected to UV irradiation in acetonitrile in the presence of 6-chloropurine. A 1:1 mixture of stereoisomers of the ring-expansion product was isolated in 17% yield. The two *cis*- and *trans*-stereoisomers, **10** and **11**, were further separated by preparative TLC using repetitive elutions and their structures were ascertained from spectroscopic analysis by ^{1}H NMR and ^{19}F NMR.



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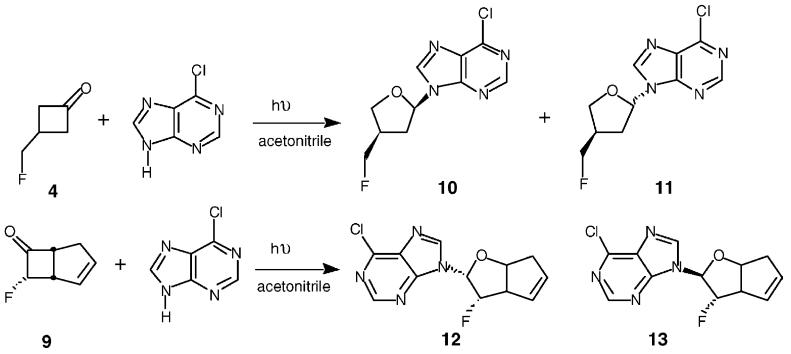

The anomeric configurations for **10** and **11** were assigned based on the splitting pattern of the acetal (1′-H) which for the β-anomer **10** appears as a triplet and for the α-anomer **11** as a quartet, a very general feature associated with conformational effects [16f] of the five-member ring. For the β-anomer (*cis*-configuration), the steric interaction between the base and the CH_2F substituent of the sugar moiety causes deformation of the five-membered ring altering the dihedral angles between C-1′ and C-2′ protons to such an extent that the *vicinal*-coupling constants are almost equal, resulting in a triplet splitting for the acetal proton. For the α-anomer (*trans*-configuration), where the base and CH_2F groups are on opposite sides of the ring, such deformation does not occur, resulting in a doublet of doublets for the acetal proton signal. The assignments are further corroborated by the difference in chemical shifts of the methylene proton signals associated with the CH_2F group for the two anomers. The β-anomer **10** shows a more deshielded signal (δ 4.6 ppm) for the CH_2F group relative to the α-anomer **11** as would be expected from the relative proximity of these protons to the aromatic base.

Photolysis of fluorocyclobutanone **9** in the presence of 6-chloropurine as the carbene quencher gave two stereoisomers **12** and **13** which were isolated and purified by preparative TLC in 15 and 8.7% yields, respectively. The stereochemistry of the pure isomers **12** and **13** was ascertained from their hydrogen–fluorine chemical shifts and coupling constants. Extensive studies have shown that the magnitude of these vicinal hydrogen–fluorine coupling constants as a function of the dihedral angle appears to follow a relationship similar to that described by Karplus for proton–proton couplings [22–26]. It is interesting to note that the photochemical ring-expansion of ketone **9** occurs by regioselective bond cleavage at the alkyl substituted carbon rather than the fluorine substituted α-carbon. Regioisomers from the latter ring-expansion pathway were not observed in the reaction mixture although cycloelimination byproducts derived from the cleavage of the α-fluorocarbon/carbonyl group were detected as byproducts.

The nucleosides derived from fluorocyclobutanone **5** as well as their biological activity will be the subject of a separate publication [27].

3. Experimental

3.1. General experimental procedures

Melting points (mp) were determined on a Reichert melting point apparatus and were uncorrected. Proton and carbon NMR spectra were recorded on a Bruker ARX 400 (400 MHz) spectrometer in $CDCl_3$ (unless otherwise noted) containing 1% tetramethylsilane (TMS) as internal standard and fluorine spectra were recorded on a Bruker AC 200 (200 MHz) using $CFCl_3$ as the internal standard. Chemical shifts are quoted in δ values in parts per million (ppm) downfield from TMS ($\delta = 0$) for proton and carbon NMR and upfield from $CFCl_3$ ($\delta = 0$) for fluorine NMR. The tabulation of NMR data follows the order: chemical shift (δ), multiplicity, integration (no. of protons), coupling constant (J). The splitting pattern of each resonance is coded: s = singlet, d = doublet, t = triplet, dd = doublet of doublets and m = multiplet.

Fourier transform infrared spectra were recorded on a Pye Unicam SP3-200 spectrometer as thin films or KBr pellets. Mass spectra (MS) were recorded at 70 eV on a Kratos profile mass spectrometer. The following code was expressed: ionization mode, mass/charge (m/e) value. Unless otherwise specified, the EI mode is assumed. Elemental analyses were performed by Guelph Chemical Laboratories.

Photolysis was carried out using a Hanovia 450 W medium-pressure mercury arc lamp in a water-cooled quartz immersion well. Pyrex tubes containing the samples were strapped around this well and the assembly immersed in an ice-water bath. The samples were purged with Ar for 30 min prior to irradiation. All solvents used in these reactions were dried and distilled.

Analytical thin layer chromatography (TLC) was done on commercially prepared silica gel 60F 254 plastic sheets (Merck & Co.). Preparative TLC was done on Aldrich silica gel 60F 254 precoated glass plates. These sheets were visualized by examination with ultraviolet light (254 nm), iodine or by exposing the glass to the 20% phosphomolybdic acid in ethanol solution followed by heating the glass sheet. For column chromatography, silica gel obtained from Silicycle (flash chromatography grade, 20–45 μm) was used.

Porcine Pancreatic Lipase (containing 160 U/mg solid, using olive oil as substrate) was purchased from Sigma and used as received.

3.1.1. 3-Fluoromethylcyclobutanone (**4**)

A two neck round bottom flask equipped with a condenser, magnetic stirrer and argon inlet was charged with a solution of hydroxy ketone **3** (0.3 g, 3.0 mmol) in dry methylene chloride (30 mL). To this mixture was added a solution of DAST (1.5 eq) in methylene chloride (5 mL) dropwise at the refluxing temperature. The mixture was allowed to stir for 4 h. After this time, the mixture was washed three times with a saturated solution of $NaHCO_3$ and the organic layer was extracted in methylene chloride and dried over $MgSO_4$. Compound **4** was purified in 60% yield as an oil by flash silica gel chromatography using methylene chloride: petroleum ether (3:4) solvent mixture as the eluent. ^{1}H NMR: δ 4.65–4.50 (m, 2H), 3.22–3.15 (m, 2H), 3.01–2.95 (m, 2H), 2.81–2.75 (m, 1H); ^{19}F NMR ($CFCl_3$): δ 222.28–222.89 (td, 1F, 47, 23 Hz); ^{13}C NMR: δ 205.57, 86.10–84.41 (d, 1C, J = 169.9 Hz), 49.16, 24.07–23.87 (d, 1C, J = 20.7 Hz); FT-IR (neat): 1787.98, 1385.39 cm^{-1}; MS (EI) *m/e* 102 (M^+). Anal. Calcd for C_5H_7FO: C, 58.8; H, 6.9; F, 18.6; Found: C, 58.5; H, 6.8; F, 18.7.

3.1.2. (2S,3R)-(+)-Bis[acetoxymethyl]-1,1-dimethoxycyclobutane (**6**)

To a solution of (2*S*,3*R*)-(+)-bis[hydroxymethyl]-1,1-dimethoxycyclobutane [28] (1 g, 5.67 mmol) in 56.7 mL of pyridine at 5 °C under argon was added acetyl chloride (0.97 mL, 13.6 mmol) over a period of 30 min. The mixture was allowed to warm to room temperature and stirred for 3 h. After this time, the reaction was quenched with 10 mL water and stirred for 30 min. The resulting solution was diluted with 100 mL EtOAc and then treated sequentially with: 100 mL H_2O, 3× 100 mL 3% HCl, 3× 100 mL saturated $NaHCO_3$ solution, 100 mL H_2O and 100 mL brine solution. The organic layer was dried over $MgSO_4$ and evaporated to give the crude diester (+)-6. The residue was chromatographed on a column (hexane:ethyl acetate 4:1) to give (+)-6 (1.28 g, 87%) as a pale yellow oil. ^{1}H NMR: δ 4.28–4.11 (m, 4H), 3.19 (s, 6H), 2.48–2.40 (m, 1H), 2.38–2.35 (m, 1H), 2.11–2.09 (m, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 1.79–1.76 (m, 1H); ^{13}C NMR: δ 170.9, 170.7, 100.1, 66.9, 62.6, 48.8, 48.4, 46.5, 32.0, 28.5, 25.2, 20.8; MS *m/z* 229 (M^+–OCH_3); $[\alpha]_D$ = +22.0° ($CHCl_3$, c 0.06). Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74; Found: C, 55.88; H, 7.71.

3.1.3. (+)-2(S)-Acetoxymethyl-3(R)-hydroxymethyl-1,1-dimethoxycyclobutane (**7**)

A mixture of diacetate **6** (117 mg, 0.45 mmol), PPL (170 mg) in toluene/phosphate buffer solution (pH 7.0) (20 mL, 1/1, v/v) was vigorously stirred for 12 h at room temperature. The solution was then treated with 3× 20 mL CH_2Cl_2 and the combined organic layers dried over $MgSO_4$. The solution was evaporated to dryness under reduced pressure and the residue chromatographed by preparative TLC (ethyl acetate:hexane, 1:1) to give a colorless oil (96 mg, 97%). ^{1}H NMR: δ 4.30–4.15 (m, 2H), 3.64–3.59 (m, 2H), 3.19 (s, 6H), 2.44–2.40 (m, 1H), 2.34–2.29 (m, 1H), 2.07 (s, 3H), 1.96–1.91 (m, 1H), 1.72–1.67 (m, 1H), 1.58 (s, 1H); ^{13}C NMR: δ 171.0, 100.3, 66.0, 63.2, 48.8, 48.4, 46.8, 32.0, 31.5, 28.5, 21.0; MS *m/z* 187 (M^+–OCH_3); $[\alpha]_D$ = +15.7° ($CHCl_3$, c 0.08). Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31; Found: C, 55.10; H, 8.02.

3.1.4. 1(S)-Acetoxymethyl-2(R)-fluoromethylcyclobutanonedimethylacetal (**8**)

A two neck round bottom flask equipped with a condenser, magnetic stirrer and argon inlet was charged with a solution of hydroxy ketal **7** [19] (0.2 g, 0.92 mmol) in anhydrous methylene chloride (50 mL). To the refluxing solution was added dropwise a solution of DAST (1.1 eq) in methylene chloride (5 mL). The resulting mixture was allowed to stir under reflux for 4 h. After this time, the mixture was washed three times with saturated $NaHCO_3$ and the organic layer was extracted and dried over $MgSO_4$. The residue was subjected to preparative TLC (silica gel, hexane:ethyl acetate, 2:1) to yield compound **8** as an oil in 82% yield. ^{1}H NMR: δ 4.48–4.35 (ddd, 2H, J = 47, 4.2, 0.005 Hz), 4.26–4.23 (m, 1H), 4.15–4.10 (m, 1H), 3.26–3.21 (m, 1H), 3.17 (s, 6H), 2.56–2.50 (m, 1H), 2.37–2.32 (m, 1H), 2.04 (s, 3H), 1.84–1.79 (m, 1H); ^{19}F NMR ($CFCl_3$): δ 221.8–222.5 (td, 1F, J = 47, 18.8 Hz).

3.1.5. 1(S)-Acetoxymethyl-2(R)-fluoromethylcyclobutanone (**5**)

In a round bottom flask equipped with magnetic stirrer was added a solution of compound **8** (60 mg, 0.27 mmol) in acetonitrile (CH_3CN) (20 mL). To this solution was added H_2SO_4 (0.257 M, 1 mL) and the mixture was allowed to stir at room temperature for 72 h. After this time, the mixture was diluted with ethyl acetate (50 mL) and washed with 2× 25 mL H_2O. The organic layer was dried over $MgSO_4$. The title compound was isolated as a yellow oil in 10% yield by preparative TLC (silica gel, hexane:ethyl acetate, 3:1) (rf = 0.75). ^{1}H NMR: δ 4.69–4.66 (dm, 2H, J = 47 Hz), 4.33–4.22 (m, 2H), 3.51–3.42 (m, 1H), 3.07–3.01 (m, 2H), 2.69–2.61 (m, 1 H), 2.06 (s, 3H); ^{19}F NMR ($CFCl_3$): δ 224.39–225.10 (td, 1F, 47, 20.7 Hz); ^{13}C NMR: δ 204.04, 170.73, 85.07–83.39 (d, 1C, J = 169.02 Hz), 60.58, 47.03, 28.95, 28.74, 20.72; FT-IR (neat): 1785.95, 1740.20 cm^{-1}; MS (EI) *m/e* 174 (M^+); $[\alpha]_D$ = +32.3° ($CHCl_3$, c 0.07). Anal. Calcd for $C_8H_{11}FO_3$: C, 55.2; H, 6.3; F, 10.9; Found: C, 55.0.; H, 6.7; F, 10.4.

3.1.6. 7-Fluorobicyclo[3,2,0]hept-2-en-6-one (**9**)

A two neck round bottom flask equipped with magnetic stirrer and argon inlet was charged with anhydrous THF (20 mL). The flask was cooled to −78 °C and fluoroacetyl chloride (1 eq) and 1,3-cyclopentadiene (6.5 g, 98 mmol) were added in sequence. While stirring at this temperature, a solution of triethylamine (1.2 eq) in anhydrous THF (5 mL) was added dropwise over a period of 5 min. A creamy precipitate formed instantly. The mixture was warmed to room temperature and left stirring overnight. After this time, the solvent was evaporated. The residue was purified using florisil

(100–200 mesh) flash chromatography using 5% ether:95% petroleum ether as the eluent. The title compound (*endo* isomer) was obtained as a yellow oil in 30% yield. The physical data of the compound were in agreement with the literature values [21]. ^{1}H NMR: δ 5.97–5.96 (d, 1H, J = 3.7 Hz), 5.75–5.74 (m, 1H), 5.67–5.51 (ddd, 1H, J = 53.4, 8.4, 2.9), 3.92–3.89 (m, 1H), 3.53–3.49 (m, 1H), 2.79–2.75 (d, 1H, J = 14.4 Hz), 2.59–2.53 (m, 1H); ^{19}F NMR ($CFCl_3$): δ 185.41–185.69 (d, 1F, J = 53.4z Hz); FT-IR (neat): 1792, 1359.1 cm^{-1}.

*3.1.7. General photolysis procedure for the irradiation of fluoroketones **4** and **9***

A solution of fluorocyclobutanone (4.0×10^{-3} M) in acetonitrile (70 mL) and 6-chloropurine (2 eq) was irradiated at 0 °C for periods ranging from 4 to 44 h after purging with argon for 30 min. After evaporation of the solvent, the residue was subjected to preparative TLC.

*3.1.8. 1-N-(6-Chloropurine-9-yl)-3-fluoromethyl-2,3-dideoxy-α- and -β-D-erythro-furanoside (**10** and **11**)*

Prepared from cyclobutanone **4** after irradiation for 44 h. The mixture of stereoisomers was isolated in 17% yield from the crude mixture by preparative TLC (hexane:ethyl acetate, 1:1.5) and the α- and β-isomers were further separated using TLC by repetitive elutions (hexane:ethyl acetate, 4:3).

α-Anomer **11** (solid, mp > 300 °C)—^{1}H NMR: δ 8.68 (s, 1H), 8.16 (s, 1H), 6.30–6.28 (q, 1H, J = 2.7 Hz), 4.49–4.39 (dt, 2H, J = 46.9, 5.3 Hz), 4.34–4.31 (t, 1H, J = 8.1 Hz), 3.96–3.94 (q, 1H, 5.8 Hz), 3.03–2.96 (m, 1H), 2.81–2.77 (m, 1H), 2.24–2.37 (q, 1H, J = 7.0 Hz); ^{19}F NMR ($CFCl_3$): δ 222.08–222.70 (td, 1F, J = 46.9, 18.8 Hz); MS (EI) *m/e* 256 (M^+), 258 (M^+ + 2), 103 (M^+–6-chloropurine). HRMS *m/e*: Calcd for $C_{10}H_{10}N_4OFCl$, 256.053 (M^+), Found 256.051.

β-Anomer **10** (solid, mp > 300 °C)—^{1}H NMR: δ 8.75 (s, 1H), 8.30 (s, 1H), 6.36–6.32 (t, 1H, J = 6.3 Hz), 4.63–4.50 (dm, 2H, J = 46.5 Hz), 4.27–4.23 (t, 1H, 8.5 Hz), 4.17–4.13 (t, 1H, J = 8.4 Hz), 3.10–2.90 (m, 1H), 2.85–2.77 (m, 1H), 2.57–2.50 (m, 1H); ^{19}F NMR ($CFCl_3$): δ 221.8–222.4 (td, 1F, J = 46.5, 18.8 Hz); MS (EI) *m/e* 256 (M^+), 258 (M^+ + 2), 103 (M^+–6-chloropurine). HRMS *m/e*: Calcd for $C_{10}H_{10}N_4OFCl$, 256.053 (M^+), Found 256.050.

*3.1.9. 1-N-(6-Chloropurine-9-yl)-2-fluorobicyclo[3,2,0]oct-2-en-2,3-dideoxy-α- and -β-D-erythro-furanoside (**12** and **13**)*

Prepared from fluorocyclobutanone **9** after irradiation for 4 h. The α- and β-isomers were separated and purified by preparative TLC (hexane:ethyl acetate, 1:1) in 15 and 8.7% yields, respectively.

β-Anomer **12** (solid, mp > 300 °C)—^{1}H NMR: δ 8.74 (s, 1H), 8.31 (s, 1H), 6.35–6.30 (dd, 1H, J = 21, 3.8 Hz), 5.97–5.95 (m, 1H), 5.72–5.70 (m, 1H), 5.39–5.23 (dm, 1H, J = 51 Hz), 4.83–4.80 (t, 1H, J = 6.1 Hz), 3.81–3.74 (m, 1H), 2.79–2.75 (m, 2H); ^{19}F NMR ($CFCl_3$): δ 197.19–197.68 (td, 1F, J = 51, 18.8 Hz); MS (EI) *m/e* 280 (M^+), 282 (M^+ + 2), 155 (6-chloropurine + 1). Anal. Calcd for $C_{12}H_{10}N_4OFCl$: C, 51.3; H, 3.6; Found: C, 51.1; H, 3.6.

α-Anomer **13** (solid, mp > 300 °C)—^{1}H NMR: δ 8.76 (s, 1H), 8.21 (s, 1H), 6.16–5.97 (m, 3H), 5.78 (m, 1H), 5.16–5.14 (m, 1H), 3.96–3.94 (m, 1H), 2.72–2.71 (broad s, 2H); ^{19}F NMR ($CFCl_3$): δ 193.4–193.7 (ddd, 1F, J = 52, 5.64); MS (EI) *m/e* 280 (M^+), 282 (M^+ + 2), 155 (6-chloropurine + 1). Anal. Calcd for $C_{12}H_{10}N_4OFCl$: C, 51.3; H, 3.6; Found: C, 50.8; H, 3.4.

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