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Stereoselective Synthesis of 3′-Fluoro- and 3′-Azido-4′-methyl-2′,3′-D-*glycero*-pentofuranoside-5-fluorouracils

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Abstract. Total stereoselective synthesis of 2,3-dideoxy-3-fluoro- and 2,3-dideoxy-3-azido-D-*glycero*-pentose and their condensation with 5-fluorouracil is described. The key step in this synthesis is nucleophilic cleavage of a chiral epoxyalcohol, prepared from commercially available 2-methyl-2-butenal.

The objective of this study was the development of a method for total enantio-and stereoselective synthesis of new glycoside derivatives of 5-fluorouracil. It is well known that 3′-substituted nucleosides exhibit high antitumor and antiviral activity.[1,2] However, these compounds seem the least investigated among nucleoside analogues.

We synthesized 2,3-dideoxy-3-fluoro- and 2,3-dideoxy-3-azido-D-*glycero*-pentose and used them in the synthesis of the 5-fluorouracil nucleoside analogue (see Scheme 1).

The starting compound in this synthesis was commercially available 2-methyl-2-butenal **1**. Silylation of **1** was carried out by reaction with chlorotrimethylsilane and triethylamine in the presence of sodium iodide in the binary system acetonitrile-pentane, according to the method described earlier,[3] which led to 1-trimethylsilyloxy-2-methyl-1,3-butadiene **2** in 72% yield. Condensation of **2** with ethyl orthoformate in the presence of $ZnCl_2$ [4] gave 5,5-diethoxy-2-methyl-2-pentenal **3** with 62% yield. Reduction of **3** by Red-Al® (sodium bis-(2-methoxyethoxy)aluminum hydride) led to 5,5-diethoxy-2-methyl-2-penten-1-ol **4** in 85% yield.

Our intention was to prepare carbohydrates of D-configuration, therefore D-(-)-diisopropyl tartrate was used in the reaction of catalytic asymmetric epoxidation of pentenol **4**[5] to prepare (2*R*,3*R*)-5,5-diethoxy-2-methyl-2,3-epoxypentane-1-ol **5** in 72% yield. The enantiomeric purity of **5**, determined by NMR spectroscopy of the Mosher ester derivative,[6] was 94%.

One of the key steps in our study was the cleavage of the epoxyalcohol **5** oxirane ring by a nucleophile, which led to the formation of acyclic acetals of 2′-deoxysugars with the functional group at C-3. As demonstrated by our previous investigations, use of titanium (IV) *iso*propoxides $Ti(O\text{-}iPr)_3X$ (where X = different nucleophilic groups) as nucleophilic agents provided the regioselective character of the reaction, as well as high yield of the desired product.[7] Cleavage of the oxirane ring of (2*R*,3*R*)-5,5-diethoxy-2-methyl-2,3-epoxypentane-1-ol **5** was achieved by reaction with tri(*iso*propoxy)titanium azide $[Ti(O\text{-}iPr)_3N_3]$ in benzene at 20°C; molar ratio was epoxide : $[Ti(O\text{-}iPr)_3N_3]$ (1:1.5). The epoxide conversion was completed in 6 hours. After separation by column chromatography on silica gel, diethyl acetal of 2,3-dideoxy-3-azido-4-methyl-D-glyceropentose **6** was obtained in 90% yield.

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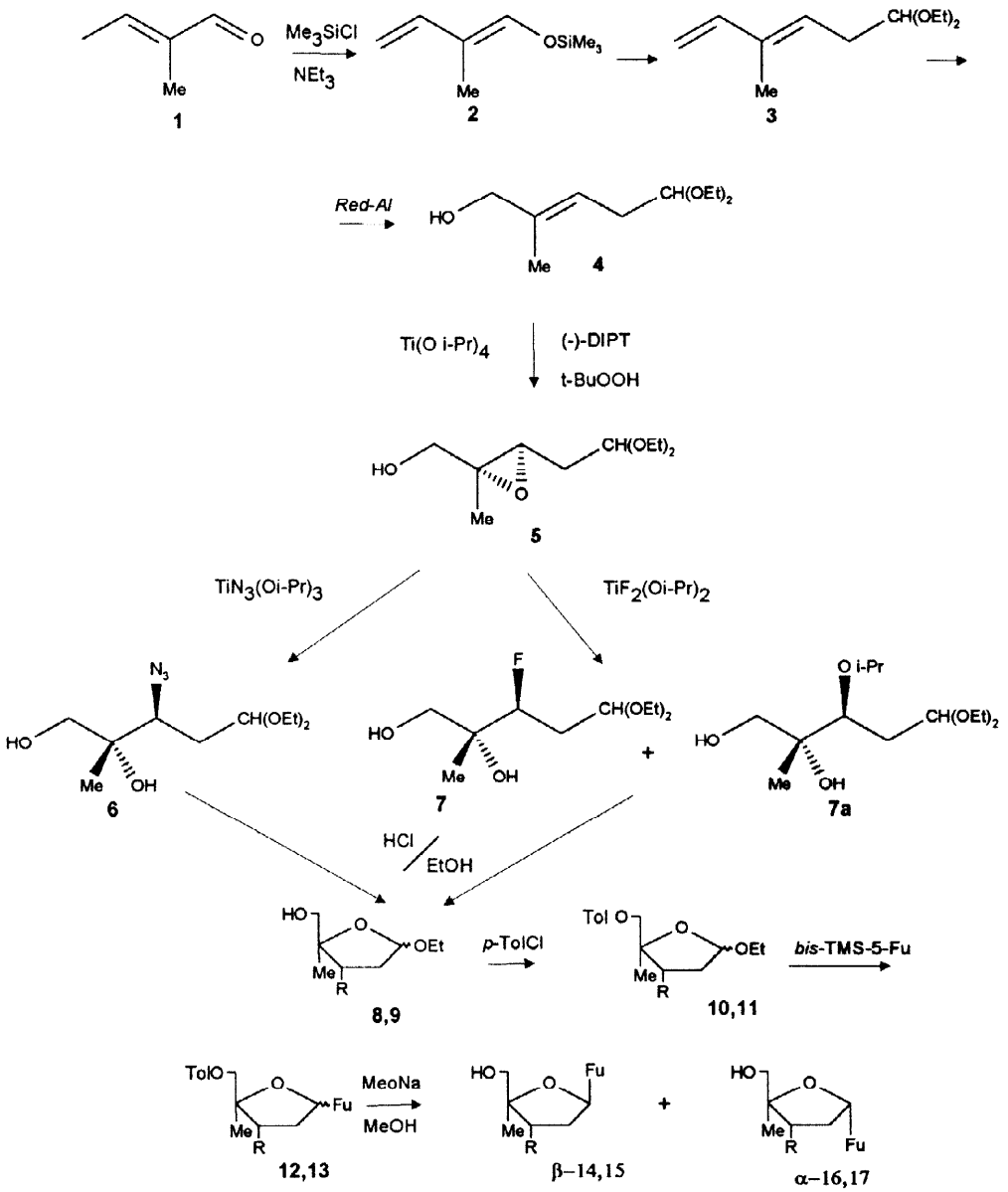
However, the cleavage of the epoxide oxirane ring by nucleophilic agent bis(*iso*propoxy)titanium difluoride $Ti(O\text{-}iPr)_2F_2$ at ambient temperature and at reagent equimolar ratio led to a predominant formation of 2,3-dideoxy-3-*O*-*iso*propylacetal **7a** with 77% yield, but not to 2,3-dideoxy-3-fluoroacetal **7**, which would have been expected. This phenomenon could probably be explained by the higher nucleophilicity of the O-*i*Pr group, as compared to F-substituent. To improve the yield of 3-fluoroacetal **7** we studied the influence of temperature

Scheme 1



8,10,12,14,16: R=N_3
9,11,13,15,17: R=F

Tol = *p*-toluoyl (*p*-$CH_3C_6H_4CO$-)

and reagent molar ratio (epoxide **5**-Ti(O-*i*Pr)$_2$F$_2$) upon the ratio of the products. As follows from the data presented in Table 1 the optimum was achieved at 80°C and molar ratio epoxide **5** : Ti(O-*i*Pr)$_2$F$_2$ (1:2.2), which afforded 45% yield of 3-fluoroacetal **7**.

Regioselective cyclization of the diethyl acetals, 2,3-dideoxy-3-azido-4-methyl-D-glycero-pentose **6** and 2,3-dideoxy-3-fluoro-4-methyl-D-glycero-pentose **7**, was conducted in 1 mM HCl, acyclic acetal concentration was 2-4%. The reaction led to high yields of α,β-anomeric mixtures of ethyl-2,3-dideoxy-3-azido-4-methyl-D-glycero-pentose **8**, or ethyl-2,3-dideoxy-3-fluoro-4-methyl-D-glycero-pentose **9**.

Anomeric mixtures of ethylfuranosides **8,9** were treated with *p*-toluoyl chloride in the presence of pyridine. The resulting 5-*O*-(*p*-toluoyl)-protected ethylfuranosides **10** and **11** were isolated by column chromatography with 70% yield and 73% yield, respectively.

Table 1. Cleavage of the oxirane ring of epoxide **5** by Ti(Oi-Pr)$_2$F$_2$ in benzene

Reaction conditions			Conversion of **5**, %	Composition of mixture, %	
Reagent ratio Acetal **5** : Ti(Oi-Pr)$_2$F$_2$	t°C	Time, h		**7**	**7a**
1	10	1.5	94	12	88
1.5	20	1.0	98	23	77
2	20	1.0	>98	25	75
2	50	0.5	>98	37	63
2	80	0.5	>98	45	55

Table 2. ^{13}C-NMR Data (δ. p.p.m.) for compounds **3-11** in (CD$_3$)$_2$CO

Compound	C_1	C_2	C_3	C_4	C_5	C_4 Me
3*	102.4	45.1	156.7	130.5	190.3	12.2
4*	103.2	103.3	132.7	128.2	65.2	15.4
5*	101.1	40.8	67.9	65.5	61.5	17.0
6	101.7	40.3	65.0	76.9	63.3	19.3
7	100.0	41.5	97.1	76.6	62.7	20.8
8α	102.7	46.7	67.4	84.1	61.4	25.0
8β	104.1	45.9	70.2	87.0	62.9	19.8
9α	103.6	46.6	101.5	86.5	61.9	23.0
9β	104.5	46.3	103.4	87.8	62.8	21.0
10α	102.5	46.4	67.5	85.0	61.7	21.0
10β	103.9	45.8	70.5	86.8	62.5	19.7
11α	103.8	46.4	101.7	86.2	61.4	20.0
11β	104.7	45.9	103.0	87.4	62.9	19.8

*Atom numbering corresponds to numbering of the sugar atoms in compounds **6-11**.

^{13}C-NMR spectra of compounds **3-11** are presented in Table 2.

Condensation of 5-*O*-(*p*-toluoyl)ethylfuranosides **10,11** with *bis*(trimethylsilyl)-5-fluorouracil was conducted in acetonitrile at 20°C in the presence of trimethylsilyl triflate as catalyst. 5′-*O*-Protected nucleosides **12** and **13** were obtained as a mixture of α- and β-anomers.

The mixtures **12** and **13** were deprotected with methanolic sodium methoxide, which led to separable corresponding anomers, by column chromatography on silica gel, which afforded the targeted β-nucleosides **14, 15** and α-nucleosides **16, 17**.

^{13}C-NMR spectra of compounds **12-17** are presented in Table 3.

EXPERIMENTAL

General. – NMR-spectra were recorded on either Bruker AM-360 (90.56 MHz,) or Varian Gemini-300 (75 MHz) spectrometers. Optical rotations were determined with a Jasko polarimeter in methanol. The progress of the reactions was monitored by TLC on Silufol$_{254}$ (Cavalier, Czechoslovakia) silica gel plates in $CHCl_3/CH_3OH$

Table 3. ^{13}C-NMR (δ, p.p.m.) for compounds **12-17** in $(CD_3)_2CO$

Compound	C′1	C′2	C′3	C′4	C′5	C′CH_3	C2	C4	C5	C6
12α	102.3	45.2	68.1	85.4	61.5	20.0	150.2	157.1	141.0	122.9
12β	103.2	45.8	69.5	86.2	61.9	23.0	150.3	156.9	140.7	123.2
13α	103.0	44.8	102.0	86.5	62.2	19.4	150.8	157.0	141.2	123.2
13β	103.4	45.0	102.7	86.8	62.5	19.2	149.7	157.2	141.1	123.0
14α	103.1	44.9	70.1	86.4	62.0	19.8	150.1	157.3	140.4	122.8
15α	103.4	43.9	103.4	87.7	61.5	19.7	150.2	157.6	140.3	122.7
16β	103.5	45.1	71.3	86.9	62.4	20.1	149.9	157.3	141.2	122.9
17β	104.0	44.7	103.9	88.1	61.9	19.9	150.4	157.2	140.9	123.4

(10:1, v/v) with spot detection by UV or by heating. Column chromatography was carried out on silica gel (60 (63-100 μ) Merck), systems are indicated in the text. Melting points were determined in open capillary tubes and are uncorrected. For NMR data see tables 2 and 3.

2-Methyl-1-trimethylsilyloxy-1,3-butadiene (**2**). – To a suspension of anhydrous sodium iodide (90.0 g, 0.5 mol) in dry acetonitrile (150 mL) were added triethylamine (50.5 g, 0.5 mol), 2-methyl-2-butenal (**1**) (42.0 g, 0.5 mol) and pentane (200 mL) at room temperature, followed by the dropwise addition of chlorotrimethylsilane (54.5 g, 0.5 mol) at 35-38°C. The mixture was stirred for 4h at 40-45°C, the resulting solid was filtered and washed with pentane (200 mL), and the solvent was evaporated at room temperature. Distillation of the residue gave **2** (56.0 g, 72%): bp 58-60°C/20 mm Hg; n_D^{20} 1.4485. Anal. Calcd. for $C_8H_{16}OSi$: C, 61.48; H, 10.32; Si, 17.97. Found: C, 61.59; H, 10.24; Si, 17.68.

5,5-Diethoxy-2-methyl-2-pentenal (**3**). – To a mixture of triethyl orthoformate (52.0, 0.7 mol) and 15% solution of $ZnCl_2$ in ethyl acetate (600 mL) was added **2** (52.0 g, 0.7 mol) dropwise with stirring at room temperature. After 1 h at room temperature, saturated aq. $NaHCO_3$ (300 mL) was added. The resulting precipitate was filtered and washed with ether (300 mL). The aqueous phase was separated, the organic layer was washed with saturated aq. $NaHCO_3$ (100 mL), dried (K_2CO_3), and concentrated *in vacuo*. Distillation of the residue gave **3** (41.0 g, 62%): bp 95-97°C/0.1 mm Hg; n_D^{20} 1.4610. Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C,64.72; H, 9.89.

5,5-Diethoxy-2-methyl-2-penten-1-ol (**4**). – Red-Al® (180 mL of a 30% solution in toluene, Aldrich) was added dropwise with stirring at 0°C to a solution of **3** (18.6 g, 0.1 mol) in ether (50 mL), and the mixture was stirred for 1 h at 0-5°C. Saturated aq. NH_4Cl (100 ml) was then added dropwise at 0-5°C, and the mixture was stirred for 30 min at 10-15°C. The precipitated solid was filtered and washed with ether (150 mL). The organic phase

was separated, dried (K_2CO_3), and concentrated *in vacuo*. Distillation of the residue gave **4** (16.0 g, 85%); bp 100-102°C/0.1 mm Hg; n_D^{20} 1.4544. Anal. Calcd. for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 63.71; H, 10.75.

(2R,3R)-5,5-Diethoxy-2,3-epoxy-2-methylpentanol (**5**). – A mixture of powdered activated 4 Å molecular sieve (5 g) and CH_2Cl_2 (300 mL) was cooled to -20°C. D-(-)-Diisopropyl tartrate (3.51 g, 10.0 mmol), titanium (IV) *iso*propoxide (2.84 g, 10.0 mmol), and *tert*-butyl hydroperoxide (45.5 mL, 4.4M in CH_2Cl_2) were added sequentially at -20°C, and the resulting mixture was stirred for 30 min. Solution of **4** (18.8 g, 100 mmol) in CH_2Cl_2 (20 mL) was then added dropwise, and stirring was maintained for 8 h at -20°C. At the end of this time, a 10% aq. A solution of NaOH saturated with sodium chloride (8 mL) was added at -20°C, and anhydrous $MgSO_4$ (8 g) with Celite (1 g) were added at +10°C. The mixture was stirred for 15 min and the mixture was then allowed to stand for an additional 1 h. The resulting suspension was filtered through a Celite pad, and the solid was washed with ether (3 x 50 mL) and filtered, and the washings were combined, dried ($MgSO_4$), and evaporated. Column chromatography (hexane-ether, gradient elution) of the residue on silica gel gave **5** (14.7 g, 72%): R_f 0.35; n_D^{20} 1.4448; $[\alpha]_D$ +15.4° (c 2.8, CH_3OH). Anal. Calcd. for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.76; H, 9.88.

3-Azido-4-methyl-2,3-dideoxy-D-glycero-pentose diethyl acetal (**6**). - To a solution of **5** (2.04 g, 10 mmol) in dry benzene (100 mL) tri(*iso*propoxy)titanium azide (4.0 g) was added. The mixture was stirred at 20°C for 6 h, then saturated aq. $NaHCO_3$ (30 mL) was added, and stirring was continued for 1 h. A precipitate was separated and washed with $CHCl_3$ (50 mL). The organic layer was dried (K_2CO_3) and the solvent was evaporated. The residue was subjected to column chromatography with $CHCl_3/CH_3OH$ (20:1, v/v), to give **6** (2.2 g, 90%): Rf 0.35; $[\alpha]_D$ +10.0° (c 3.5, CH_3OH). Anal. Calcd. for $C_{10}H_{21}N_3O_4$: C, 48.56; H, 8.56, N 16.99. Found: C, 48.61; H, 8.52, N 17.03.

3-Fluoro-4-methyl-2,3-dideoxy-D-glycero-pentose diethyl acetal (**7**). – A suspension of titanium (IV) fluoride (7.44 g, 60 mmol) and powdered potassium carbonate (24 g) in dry benzene (200 mL) was treated with titanium (IV) *iso*propoxide (17.04 g, 60 mmol) and stirred at ambient temperature for 0.5 h. The resultant mixture was heated to reflux and a solution of **5** (6.12 g, 30 mmol) in dry benzene (20 mL) was added dropwise to the reaction mixture. After stirring for 0.5 h, the reaction mixture was cooled to 5-10°C and quenched with saturated aq. $NaHCO_3$ (100 mL). The precipitate was filtered and the precipitate washed thoroughly with ether (5 x 100 mL). The organic phase was dried (K_2CO_3) and concentrated *in vacuo*. The column chromatography of the residue with $CHCl_3/CH_3OH$ (30:1, v/v), gave **7** (2.3 g, 35%): R_f 0.18; $[\alpha]_D$ +14.8° (c 1.3, CH_3OH). Anal. Calcd. for $C_{10}H_{21}FO_4$: C, 53.56; H, 9.44, F 8.47. Found: C, 53.38; H, 9.40, F 8.55.

Ethyl 3-fluoro-4-methyl-2,3-dideoxy-α,β-D-glycero-pentofuranosides (**9**). – To a solution of **7** (2.24 g, 10 mmol) in dry ethanol (180 mL) was added a 10% solution of HCl in ethanol (0.22 mL) at room temperature. The mixture was stirred for 30 min, then K_2CO_3 (0.1 g) was added, and the mixture was stirred for an additional 1 h. The precipitate was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography with $CHCl_3$, which afforded **9** (1.46 g, 90%) as an anomeric mixture. R_f 0.62 (β-anomer) and 0.71 (α-anomer). Anal. Calcd. for $C_8H_{15}FO_3$: C, 53.92; H, 8.49, F 10.66. Found: C, 54.03; H, 8.44, F 10.58.

Ethyl 3-azido-4-methyl-2,3-dideoxy-α,β-D-glycero-pentofuranosides (**8**). - Prepared as **9**, but starting from **7**. R_f 0.68 (β-anomer) and 0.76 (α-anomer). Yield 85%. Anal. Calcd. for $C_8H_{15}N_3O_3$: C, 47.75; H, 7.51, N 20.88. Found: C, 47.80; H, 7.46, N 20.80.

Ethyl 3-fluoro-4-methyl-5-O-toluoyl-2,3-dideoxy-α,β-D-glycero-pentofuranosides (**11**). –A cold -15°C solution of **9** (1.23 g, 6.9 mmol) in dry pyridine (10 mL) was treated with *p*-toluoyl chloride (1.17 g, 7.6 mmol). A mixture was stirred at constant temperature for 16 h, then it was concentrated *in vacuo*. The solution of the residue in $CHCl_3$ (60 mL) was washed in succession by water (5 x 25 mL), saturated aq. $NaHCO_3$ (25 mL) and water (25 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography with $CHCl_3$, which afforded **11** (1.43 g, 70%) as an anomeric mixture. Anal. Calcd. for $C_{16}H_{21}FO_4$: C, 64.85; H, 7.14, F 6.41. Found: C, 64.92; H, 7.11, F 6.45.

Ethyl 3-azido-4-methyl-5-O-toluoyl-2,3-dideoxy-α,β-D-glycero-pentofuranosides (**10**). – Prepared as **9**, but starting from **8.** Yield 73%. Anal. Calcd. for $C_{16}H_{21}N_3O_4$: C, 60.17; H, 6.63, N 13.16. Found: C, 60.22; H, 6.60, N 13.20.

1-[3′-Fluoro-4′-methyl-5′-O-toluoyl-2′,3′-dideoxy-α,β-D-glycero-pentofuranosyl]-5-fluorouracil (**13**). – A solution of **11** (1.56 g, 5.25 mmol) and bis(trimethylsilyloxy)-5-fluorouracil (2.81 g, 10.6 mmol) in dry acetonitrile (30 mL) was treated with trimethylsilyl triflate (2.0 mL, 10.4 mmol). The mixture was stirred at ambient temperature 2.5 h, then cooled to 0°C; reaction was quenched with saturated aq. $NaHCO_3$ (20 mL). The reaction mixture was extracted with $CHCl_3$ (3 x 30 mL), and washed with water (2 x 10 mL), then dried (Na_2SO_4). The organic phase was concentrated *in vacuo.* The residue was purified by column chromatography with $CHCl_3/CH_3OH$ (100:1, v/v), which afforded oily **13** (1.27 g, 63%) as an anomeric mixture. Anal. Calcd. for $C_{18}H_{18}F_2N_2O_5$: C, 56.84; H, 4.77, N 7.37, F 9.99. Found: C, 56.89; H, 4.72, N 7.39, F 10.03.

1-[3-Azido-4′-methyl-5′-O-toluoyl-2′,3′-dideoxy-α,β-D-glycero-pentofuranosyl]-5-fluorouracil (**12**). – Prepared as **13**, but starting from **11.** Yield 69% (oil). Anal. Calcd. for $C_{18}H_{18}FN_5O_5$: C, 53.59; H, 4.50, N 17.36, F 4.71. Found: C, 53.51; H, 4.52, N 17.30, F 4.77.

1-[3′-Fluoro-4′-methyl-2′,3′-dideoxy-α-D-glycero-pentofuranosyl]-5-fluorouracil (**15**) and *1-[3′-fluoro-4′-methyl-2′,3′-dideoxy-β-D-glycero-pentofuranosyl]-5-fluorouracil* (**17**). – A solution of 13 (1.90 g, 5.0 mmol) in dry CH_3OH (50 mL) was treated with 0.2 M methanolic sodium methoxide (20 mL). The mixture was maintained at ambient temperature for 4 h and neutralized with DOWEX® 50W x 1 (H^+-form, 10 mL). The mixture was filtered, the filtrate was concentrated *in vacuo.* The residue was purified by column chromatography with $CHCl_3/CH_3OH$ (50:1, v/v), which afforded oily **15** (0.39 g, 30%): R_f 0.31 and **17** (0,71 g, 54%): mp 196-197°C; R_f 0.38. $[\alpha]_D$ +8.82° (c 0.83, CH_3OH). Anal. Calcd. for $C_{10}H_{12}F_2N_2O_4$: C, 45.81; H, 4.61, N 10.69, F 14.49. Found: C, 45.73; H, 4.66, N 10.71, F 14.42.

1-[3′-Azido-4′-methyl-2′,3′-dideoxy-α-D-glycero-pentofuranosyl]-5-fluorouracil (**14**) and *1-[3′-azido-4′-methyl-2′,3′-dideoxy-β-D-glycero-pentofuranosyl]-5-fluorouracil* (**16**). – Prepared as **15** and **17**, but starting from **12.** α-Anomer **14**: yield 28%, oil; R_f 0.36. β-Anomer **16**: yield 53%; mp 139-140°C; R_f 0.41; $[\alpha]_D$ +6.54° (c 0.52, CH_3OH). Anal. Calcd. for $C_{10}H_{12}FN_5O_4$: C, 42.11; H, 4.24, N 24.56, F 6.66. Found: C, 42.18; H, 4.26, N 24.61, F 6.62.

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