Synthesis of 4-*O*-Methyl-Protected 5-(2-Hydroxyethyl)-2´-deoxyuridine Derivatives and their Nucleophilic Fluorination to 5-(2-Fluoroethyl)-2´-deoxyuridine

Chung-Shan Yu,[1] Franz Oberdorfer*

EUROPET GmbH, PET-Zentrum im Klinikum der Albert-Ludwigs-Universität, Hugstetter Strasse 55, D-79106 Freiburg, Germany
Fax +49(761)2709200, E-mail: Franz.Oberdorfer@t-online.de

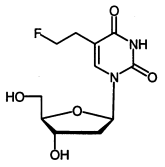
Received 18 January 1999; revised 7 July 1999

Abstract: The novel pyrimidine base, 5-(2-hydroxyethyl)-4-methoxypyrimidin-2(1*H*)-one (**7**) was prepared from the pyrimidine derivative **2** via a three step synthesis in 72% yield. Glycosylation of **7** with an α-chlorosugar provided the 4-*O*-methyl-protected pyrimidine nucleoside **8** in 78% yield with a β:α ratio ranging from 1.5:1 to 2:1. A complete cleavage of the 4-methoxy group of alcohol **8** was achieved using NaI and trimethylsilyl chloride. The synthesis of **14**, an analog of **8**, was also possible by using *N,O*-bis(trimethylsilyl)trifluoroacetimide as silylating reagent and 3,5-di-*O*-*p*-chlorobenzoyl-2-deoxy-α-D-*erythro*-pentofuranosyl chloride as the sugar moiety. A slightly improved ratio of β/α (>2:1) and a yield of 54% of **14** was obtained. The two key precursors for nucleophilic fluorination, the tosylate **9** and triflate **10**, were obtained in 87 and 17% yield, respectively. NOE results of **10**β and **10**α indicated that H-1' of the deoxyribosyl residue interacted strongly with one of the two protons on C-8 of the 5-ethyl side chain. This interaction was even stronger than that between H-1' and H-2'. The unusual downfield chemical shift of C-1' in ^{13}C NMR can not be explained by the structure shown in Scheme 3. Nucleophilic fluorination of the tosylate **9**α under phase transfer catalyzed conditions provided the fluorinated product **11**α (5%), the base-induced elimination product **12**α (24%), and unexpectedly the chloro-substituted product **13**α (26%).

Key words: 5-(2-hydroxyethyl) pyrimidine nucleosides, tosylates, triflates, NOE, phase transfer catalyzed nucleophilic fluorination

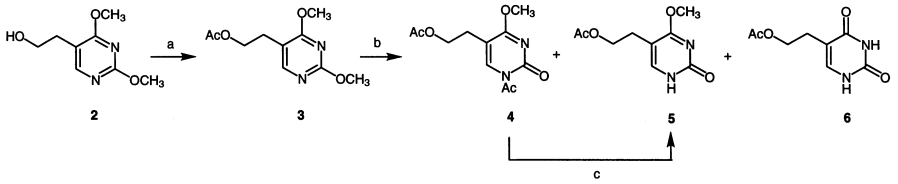
The "suicide" gene therapy is one of the most promising approaches in cancer therapy.[2] The suicide gene is inserted into tumor cells in situ, followed by initiation of the suicide mechanism.[3] Herpes simplex virus type 1 thymidine kinase (HSV-1 TK) is the most intensively studied suicide gene.[4] HSV-1 TK can activate prodrugs[5] such as a nucleoside analog, which we report in this work, to form toxic drugs that may kill the cell.

5-(2-Fluoroethyl)-2'-deoxyuridine (**1**, FEDU) was first reported by Griengl et al.[6] The synthesis of **1** starting from γ-butyrolactone consisted of a ten-step procedure. First 5-(2-fluoroethyl)uracil was prepared[7,6] and then converted into **1** via glycosylation with the α-chlorosugar, 3,5-di-*O*-*p*-toluoyl-2-deoxy-α-D-*erythro*-pentofuranosyl chloride.[8] FEDU (**1**) was obtained in an overall yield of 5% based on the γ-butyrolactone.



1

We did not follow this synthetic route since the 4-oxo group competitively attacks the C-8 position during the nucleophilic fluorination. Wong et al.[9] and Prystaš[10] reported a selective dealkylation of the 2-methoxy group of 2,4-dimethoxypyrimidine in non-aqueous acid. We used this procedure after protecting the 5-(2-hydroxyethyl) group of **2** using acetic anhydride in pyridine (Scheme 1). The acetyl-protected 2,4-dimethoxypyrimidine **3** was then reacted with acetyl chloride for 20 hours in order to obtain **4**. After column chromatography on silica gel, two fractions were identified. First fraction was 5-(2-acetoxyethyl)-4-methoxypyrimidin-2(1*H*)-one (**5**), the second one being 5-(2-acetoxyethyl)uracil (**6**). The chemical shift of C-4 and C-2 of **5** in ^{13}C NMR spectrum was 170.73



Reagents and conditions: (a) Ac_2O/pyridine, r.t., 1 h, 90% (b) acetyl chloride, r.t., 20 h (c) chromatography on silica gel, **5**: 80%, **6**: ~5%

Scheme 1

Table 1 ^{13}C NMR Data (62.90 MHz, $CDCl_3$/TMS, δ) of the Carbon Atoms in Pyrimidine Bases and Nucleosides[a]

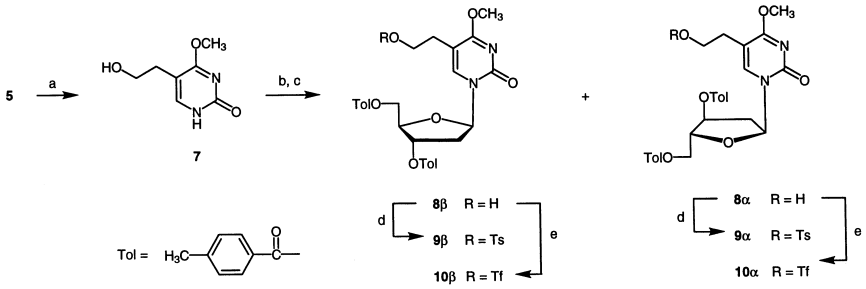
Product	C-2	C-4	C-5	C-6	C-7	C-8	C-1′	C-2′	C-3′	C-4′	C-5′
3	164.41	169.29	110.93	157.67	26.06	62.53	-	-	-	-	-
5	159.62	170.73	104.88	142.77	26.07	62.33	-	-	-	-	-
7[b]	156.63	170.37	103.25	143.87	29.24	59.46	-	-	-	-	-
8β[c]	155.57	170.52	105.72	139.90	29.81	60.96	83.50	39.15	75.16	87.07	64.31
8α[c]	155.64	170.68	104.60	140.74	29.97	61.14	85.83	38.86	75.03	89.19	64.10
14β	155.50	170.54	105.86	139.84	29.75	60.76	83.12	38.88	75.38	87.10	64.52
9β	155.26	169.78	103.23	140.76	26.82	67.70	83.46	39.04	75.09	86.88	64.08
9α	155.36	170.00	102.31	141.24	26.97	67.81	85.62	38.87	74.87	88.94	64.07
10β	156.31	170.16	119.03	158.46	26.91	65.41	104.63	39.23	75.31	82.24	64.98
10α	156.22	170.13	119.38	158.50	27.07	65.01	104.14	39.27	74.54	81.40	64.18
11β[d]	155.49	170.26	104.06	140.33	27.92	81.40	83.48	39.22	75.17	87.00	64.19
11α[c,e]	155.55	170.38	103.15	140.89	28.01	81.59	85.76	38.91	74.94	89.15	64.07
12α	154.94	169.43	106.91	138.94	127.11	114.66	85.76	39.06	74.74	89.24	64.03
13α	155.50	170.31	103.94	140.96	30.44	42.64	85.70	38.84	75.00	89.06	64.03

[a] Protecting groups are exempted.
[b] Recorded in DMSO-d_6.
[c] Recorded at 125.76 MHz.
[d] ^{13}C-^{19}F coupling constants: $^3J_{5,F}$ = 6.1 Hz (d), $^2J_{7,F}$ = 21.6 Hz (d), $^1J_{8,F}$ = 168.7 Hz (d).
[e] ^{13}C-^{19}F coupling constants: $^3J_{5,F}$ = 5.5 Hz (d), $^2J_{7,F}$ = 21.3 Hz (d), $^1J_{8,F}$ = 168.4 Hz (d).

ppm and 159.62 ppm, respectively (Tables 1 and 2). This corresponded to reported data[11] (169.35 ppm for C-4 of 4-methoxypyrimidine; 159.25 ppm for C-2 of 2-hydroxypyrimidine) . We did not isolate the other product, 5-(2-acetoxyethyl)-1-acetyl-4-methoxypyrimidin-2-one (**4**), which was not stable during column chromatography. The enhanced basicity of **4** allowed a proton-mediated deacetylation of N-1. Compound **5** was obtained in 80% yield.

Finally deprotection of the 5-(2-acetoxyethyl) group in **5** delivered 5-(2-hydroxyethyl)-4-methoxypyrimidin-2(1*H*)-one (**7**) in quantitative yield (Scheme 2) which was the expected 4-*O*-protected pyrimidine base meeting the requirements for condensation with an α-chlorosugar to yield the β,α-nucleoside **8**. From elemental analysis, we found the presence of chlorine in **7**. It is assumed that **7** formed an adduct with HCl.

The silylation of compound **7** was tried under the usual conditions, i.e. hexamethyldisilazane (HMDS), and a trace amount of trimethylsilyl chloride (TMSCl) under reflux. Such a relatively harsh condition probably would cleave the 4-methoxy group of the pyrimidine base **7**. We indeed observed a white precipitate [supposed to be 5-(2-hydroxyethyl)uracil] during heating, instead of the expected homogeneous solution. Therefore, a milder silylation method with *N,O*-bis-trimethylsilylacetimid (BSA) was applied and silylation was complete within 10 minutes. The α-chlorosugar was then added. Again, in the elemental analyses we found the presence of chlorine in both the β- and α-anomer of **8**. This contamination was as-



Reagents and conditions: (a) NaOMe/MeOH, r.t., 1 h, HCl/Et_2O, quantitative, (b) BSA/$CHCl_3$, r.t., 10 min; (c) 3,5-di-*O*-*p*-toluoyl-2-deoxy-α-D-*erythro*-pentofuranosyl chloride, 1 h, 78%, β/α = 1.5:1~2:1; (d) *p*-toluenesulfonyl chloride/pyridine, 4°C, 20 h, 87%; (e) $(CF_3SO_2)_2O$/pyridine/CH_2Cl_2, 0°C, 1 h, 17%

Scheme 2

sumed to arise from not identified chlorosilyl compounds formed by the reaction of the silylating reagent (BSA) with the chloride ion. The impurity could not be removed completely by column chromatography. The 4-*O*-methyl-protected nucleoside **8** finally was transformed into tosylate **9** and triflate **10** in 87 and 17% yields, respectively.

For the β-anomeric and α-anomeric triflates **10β**, **10α**, inspection of ^1H and ^{13}C NMR spectra led to some interesting observations. The H-1' exhibited an unusual upfield chemical shift at 5.30 ppm as compared to 6.0–6.5 ppm for "normal" nucleosides. On the other hand, the C-1'carbon resonance was shifted downfield from the normal value of 84 to 104 ppm. The triflates were further analysed with steady-state ^1H-NOE difference experiments (Table 3). The H-1' proton was found to have an unexpected interaction with one of the methylene protons at C-8 (Figure). The NOE values are 6.6 and 4.3% for **10β** and **10α**,

Table 2 ^{13}C NMR Data of the Carbon Atoms in Protecting Groups Present in Pyrimidine Bases and Nucleosides

Product	^{13}C NMR (62.90 MHz, $CDCl_3$/TMS) δ
3	20.67 ($CO\mathit{C}H_3$), 53.76 (2-OCH_3), 54.49 (4-OCH_3), 170.70 ($\mathit{C}OCH_3$)
5	20.76 ($CO\mathit{C}H_3$), 54.49 (4-OCH_3), 171.47 ($\mathit{C}OCH_3$)
7[a]	53.43 (4-OCH_3)
8β[b]	21.69 (arom-CH_3), 21.72 (arom-CH_3), 53.69 (4-OCH_3), 126.37 (C-CH_3, arom), 126.62 (C-CH_3, arom), 129.28 (CH, arom), 129.41(CH, arom), 129.60 (CH, arom), 129.88 (CH, arom), 144.51 (C-CO, arom), 166.20 (arom-CO), 166.23 (arom-CO)
8α[b]	21.62 (arom-CH_3), 21.72 (arom-CH_3), 54.72 (4-OCH_3), 126.30 (C-CH_3, arom), 126.61 (C-CH_3, arom), 129.17 (CH, arom), 129.35 (CH, arom), 129.57 (CH, arom), 129.72 (CH, arom), 144.27 (C-CO, arom), 144.55 (C-CO, arom), 165.58 (arom-CO), 166.17 (arom-CO)
14β	54.73 (4-OCH_3), 127.43 (C-Cl, arom), 127.70 (C-Cl, arom), 128.94 (CH, arom), 129.02 (CH, arom), 130.92 (CH, arom), 131.18 (CH, arom), 140.27 (C-CO, arom), 165.21 (arom-CO), 165.34 (arom-CO)
9β	21.60 (arom-CH_3), 21.68 (arom-CH_3), 54.58 (4-OCH_3), 126.33 (C-CH_3, arom), 126.54 (C-CH_3, arom), 127.68 (CH, arom), 129.23 (CH, arom), 129.42 (CH, arom), 129.48 (CH, arom), 129.72 (CH, arom), 129.83 (CH, arom), 132.82 (C-CH_3, arom), 144.43 (C-CO, arom), 144.46 (C-CO, arom), 144.99 (C-SO, arom), 165.95 (arom-CO), 166.07 (arom-CO)
9α	21.62 (arom-CH_3), 21.69 (arom-CH_3), 54.69 (4-OCH_3), 126.22 (C-CH_3, arom), 126.60 (C-CH_3, arom), 127.69 (CH, arom), 129.16 (CH, arom), 129.36 (CH, arom), 129.51 (CH, arom), 129.73 (CH, arom), 129.77 (CH, arom), 132.80 (C-CH_3, arom), 144.26 (C-CO, arom), 144.58 (C-CO, arom), 145.11 (C-SO, arom), 165.45 (arom-CO), 166.16 (arom-CO)
10β[c]	21.63 (arom-CH_3), 21.67 (arom-CH_3), 55.15 (4-OCH_3), 118 (CF_3), 126.81 (C-CH_3, arom), 127.11 (C-CH_3, arom), 129.10 (CH, arom), 129.14 (CH, arom), 129.70 (CH, arom), 129.76 (CH, arom), 143.86 (C-CO, arom), 144.10 (C-CO, arom), 166.11 (arom-CO), 166.20 (arom-CO)
10α[d]	21.63 (arom-CH_3), 55.17 (4-OCH_3), 118 (CF_3), 126.86 (C-CH_3, arom), 127.02 (C-CH_3, arom), 129.11 (CH, arom), 129.15 (CH, arom), 129.65 (CH, arom), 129.69 (CH, arom), 143.84 (C-CO, arom), 144.09 (C-CO, arom), 166.21 (arom-CO), 166.39 (arom-CO)
11β	21.66 (arom-CH_3), 21.71 (arom-CH_3), 54.75 (4-O-CH_3), 126.36 (C-CH_3, arom), 126.59 (C-CH_3, arom), 129.26 (CH, arom), 129.36 (CH, arom), 129.38 (CH, arom), 129.46 (CH, arom), 129.52 (CH, arom), 144.40 (C-CO, arom), 144.49 (C-CO, arom), 165.06 (arom-CO), 166.16 (arom-CO)
11α[b]	21.67 (arom-CH_3), 54.75 (4-OCH_3), 126.24 (C-CH_3, arom), 126.57 (C-CH_3, arom), 129.10 (CH, arom), 129.33 (CH, arom), 129.55 (CH, arom), 129.69 (CH, arom), 144.24 (C-CO, arom), 144.44 (C-CO, arom), 165.60 (arom-CO), 166.13 (arom-CO)
12α	21.68 (arom-CH_3), 54.77 (4-OCH_3), 126.06 (C-CH_3, arom), 126.52 (C-CH_3, arom), 129.23 (CH, arom), 129.34 (CH, arom), 129.54 (CH, arom), 129.70 (CH, arom), 144.28 (C-CO, arom), 144.43 (C-CO, arom), 165.50 (arom-CO), 166.12 (arom-CO)
13α	21.66 (arom-CH_3), 54.75 (4-OCH_3), 126.23 (C-CH_3, arom), 126.55 ($\mathit{C}CH_3$, arom), 129.12 (CH, arom), 129.32 (CH, arom), 129.51 (CH, arom), 129.67 (CH, arom), 144.23 (C-CO, arom), 144.52 (C-CO, arom), 165.60 (arom-CO), 166.10 (arom-CO)

[a] Recorded in DMSO-d_6.
[b] Recorded at 125.76 MHz.
[c] ^{13}C-^{19}F coupling constant: $^1J_{C,F}$ = 320.8 Hz (q).
[d] ^{13}C-^{19}F coupling constant: $^1J_{C,F}$ = 320.2 Hz (q).

respectively. The unusual downfield chemical shift of C-1' in ^{13}C NMR can not be explained by the structure shown in the Figure.

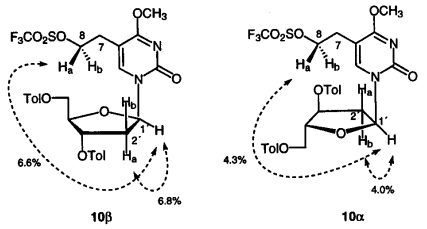
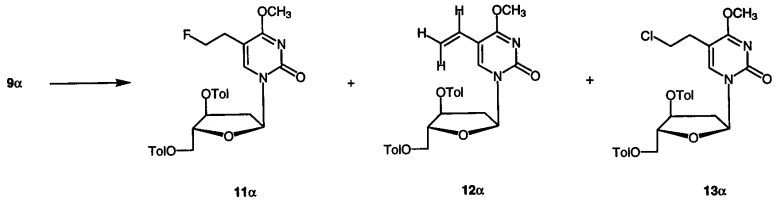


Figure ^{1}H-NOE results between H-1' and H-8a

The contamination with chlorosilyl compounds in **8**β,α did not seriously interfere with the next reaction step but we still found some unexpected results when treating the tosylate **9**α with KF/Kryptofix[2.2.2] as shown in Scheme 3. In addition to the fluorinated product **11**α and the base-induced elimination product **12**α, the chloro-substituted nucleoside **13**α was also formed. We reexamined the procedure for the preparation of the precursor tosylate **9**α. Apparently the contaminating chlorosilyl compounds in our starting material **8**α are the source of chloride for this side-reaction. Compounds **11**α and **13**α were not resolved by column chromatography. The approximate yields of compounds **11**α and **13**α were therefore estimated by TLC.

Relatively few references were available concerning the cleavage of the *O*-alkyl group from a pyrimidine, e.g. 2,4-dibenzyloxypyrimidine.[12] Neither acids such as HCl and CF_3CO_2H[13], nor cationic exchange resins (H^+)[14] were practical in our case to hydrolyse the 4-methoxy group of pyrimidine nucleosides. Hydrolysis proceeded either incompletely or glycosidic bonds were also cleaved. Trimethylsilyl iodide (TMSI) was demonstrated as a mild and



Reagents and conditions: KF/Kryptofix[2.2.2]/MeCN, 85°C, 72 h, 11α: 5% (approximate yield), 12α: 24%, 13α: 26% (approximate yield)

Scheme 3

Table 3 NOE Results (%)[a]

Effected Protons	Irradiated Protons						
	10β				**10**α		
	H-1'	H-8a	H-8b	H-7a,b	H-1'	H-8a	H-7a,b
H-6	0.6[b]	1.5	1.4	9.9[c]	0.3[b]	0.5	8.5[c]
H-4'	0.8	-	-	0.7	-	-	-
H-8b	0.5	24.3	-	8.5	1.6	25.5	9.1
H-8a	6.6[b]	-	25.0	5.4	4.3[b]	-	8.3
H-7a,b		2.4 (2H)	5.0 (2H)	-	-	3.9 (2H)	-
H-2'b	0.6	-	-	-	4.0	-	-
H-2'a	6.8	-	-	-	0.4	-	-
H-1'	-	10.4	1.4	0.8	-	8.1	1.5
OCH_3	-	1.4	-	1.8	-	-	1.8

[a] Protons H-1', H-8a, H-8b (**10**β) and H-7a,b were irradiated individually. The irradiated protons induce a Nuclear Overhauser Effect (NOE) on nearby protons (distance < 5 Å). The NOE is expressed as the % change in the observed proton integral and is approximately proportional to r^{-6}. For example, in the case of **10**β, the geminal protons H-8a,b gave the largest observed NOE (ca. 25%), and H-1'gave an NOE of 6.8% with H-2'a (*cis* relationship) but only 0.6% with H-2'b (*trans* relationship).

[b] The very small NOE between H-1' and H-6 is consistent with an *anti* conformation of the pyrimidine ring. The suprisingly large NOE between H-1' and H-8a can not be explained by the structure shown in the Figure.

[c] The significant NOE between H-7a,b and H-6 is consistent with their proximity.

efficient cleaving reagent.[12,15] NaI and TMSCl in acetonitrile has been used as alternative to TMSI as the sole agent and we observed a complete cleavage of the 4-methoxy group of **8**β,α within 1 minute (yield: 90%).

Optimization of the synthesis of **8** was achieved when the more volatile silylating reagent *N,O*-bistrimethylsilyltrifluoroacetimide (BSTFA)[16] and crystallized 3,5-di-*O*-*p*-chlorobenzoyl-2-deoxy-α-D-*erythro*-pentofuranosyl chloride[17] were used. Compound **14**β was obtained pure as colourless needles with satisfactory elemental analyses and ^{1}H and ^{13}C NMR spectra free from signals of contaminating products.

TLC was carried out with Polygram Sil G/UV 254 plates of Machery and Nagel, Düren. Spots were developed by applying molybdatophosphoric acid (5% in EtOH). Column chromatography was performed on silica gel 60 (40–63 μm), Merck, Darmstadt, with a flow rate ranging from 2–4 mL/min under atmospheric pressure. Chemicals were purchased from Aldrich. $CHCl_3$ and CH_2Cl_2 were dried by passing down a column filled with Al_2O_3 (neutral). MeCN was of DNA-synthesis grade from Merck-Schuchardt. Melting points were determined with a Büchi 535 apparatus and are not corrected. Elemental analysis was performed at the Max Planck Institut für Medizinische Forschung in Heidelberg. Electron ionizaion mass spectra (EI-MS) and high resolution mass spectra (HRMS) were recorded on a Varian MAT 711 device. Electrospray ionization mass spectra (ESI-MS) were carried out with a Finnigan TSQ 7000 triple-quadrupole system. HRMS (FAB) were carried out at Institute of Organic Chemistry, University of Heidelberg. ^{1}H NMR, ^{13}C NMR (DEPT-135), and ^{19}F NMR were recorded on a Bruker AC-250 or AM-500 spectrometer in the Central Department of Spectroscopy of the German Cancer Research Center (DKFZ). ^{13}C NMR data of pyrimidine bases and nucleosides are presented in Table 1, data of protecting groups and functional groups in Table 2. ^{1}H and ^{19}F NMR data and physical data of the compounds prepared are given in Tables 4–6.

5-(2-Acetoxyethyl)-2,4-dimethoxypyrimidine (3)

To a stirred solution of **2** (4.9 g, 26.6 mmol)[6] in pyridine (25 mL) was added Ac_2O (15 mL) at r.t. and the stirring was continued for 1 h. After completion of the reaction (TLC monitoring: product **3**, R_f 0.68; starting material **2**, R_f 0.32; solvent: acetone/toluene, 1:1), $CHCl_3$ (3 mL) was added. The solvent was evaporated at 40°C under vacuum, and the evaporation was continued overnight until no odour of AcOH was detectable (4 mbar); yield: 5.36 g (90%).

5-(2-Acetoxyethyl)-4-methoxypyrimidin-2(1*H*)-one (5)

A 100 mL round-bottomed two-necked flask, dried at 110°C in an oven for 24 h, was flushed with dry N_2 at r.t. To this flask was added compound **3** (5.36 g, 23.69 mmol) and commercial fresh AcCl (50 g, 637 mmol) with stirring. The reaction was continued for ~ 20 h. A small amount (about 5 μL) of the aliquot was taken after 10 h and coevaporated with toluene (0.2 mL) at 35°C under reduced presure and used as reference for TLC (MeOH/$CHCl_3$, 1:19). The product **5** (R_f 0.30) was observed but the amount was low, although **3** (R_f 0.79) was almost consumed. The intermediate **4** (R_f 0.58) was assumed to be the major product. The best reaction time was 20 h. A longer reaction time or traces of moisture increased the amount of the hydrolyzed product 5-(2-acetoxyethyl)uracil (**6**) (R_f 0.21).[7a] After the reaction was complete, the solvent was evaporated at 35°C under vacuum (4 mbar) and coevaporated twice by addition of toluene (2 × 4 mL). The residue was chromatographed using MeOH/$CHCl_3$ (1:19) as eluent. During this step, the intermediate **4** was deacetylated to form the polar product **5**. Pure **5** was obtained by using 200 weight equivalents of silica gel to the amount of the crude product; yield: 4.0 g (80%). Byproduct **6** (approximate yield ~5%) was confirmed by comparison of the R_f value (TLC, MeOH/$CHCl_3$ 1:19) with the reference sample.[7a]

5-(2-Hydroxyethyl)-4-methoxypyrimidin-2(1*H*)-one (7):

Compound **5** (1.2 g, 5.65 mmol) was dissolved in methanol (80 ml) with stirring at rt. NaOMe/MeOH (20 ml, 11.4 mmol, 2 eq) was added. The stirring was continued for 1 h. Product **7** (R_f = 0.22) was formed as observed by TLC (MeOH/$CHCl_3$ 1:9). The R_f value of educt **5** was 0.81. After completion of the reaction, the pH of the solution was slowly adjusted to neutral with 1M HCl/ether. The solvent was evaporated under vacuum (4 mbar). The residue was chromatographed with MeOH/$CHCl_3$ 1:9 to give product **7** in quantitative yield (0.960 g, 5.64 mmol).

1-(3,5-Di-*O*-*p*-toluoyl-2-deoxy-β,α-D-*erythro*-pentofuranosyl)-5-(2-hydroxyethyl)-4-methoxypyrimidin-2-ones (8β,α)

To a stirred solution of **7** (250 mg, 1.47 mmol) in anhyd $CHCl_3$ (15 mL) under exclusion of moisture was added BSA (741 mg, 3.64 mmol). The mixture was stirred until a clear solution appeared (about 10 min). 3,5-Di-*O*-*p*-toluoyl-2-deoxy-α-D-*erythro*-pentofuranosyl chloride (890 mg, 2.29 mmol)[8] and TMSOTf (40 μL, 0.2 mmol) were added sequentially. The colourless solution turned to pale yellow. The reaction was complete after 1 h. $CHCl_3$ (40 mL) was added and the mixture was extracted with aq satd $NaHCO_3$ solution (130 mL) and the aqueous layer further extracted with $CHCl_3$ (60 mL). The combined organic extracts were washed with H_2O (20 mL), dried ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure at 40°C. The residue (ca 1.8 g) was chromatographed (acetone/hexane, 1:1, column: 4.5 × 24 cm, silica gel: 190 g) to give **8**β (95 mg, 0.18 mmol) and a mixture of **8**β,α (500 mg, 0.96 mmol). The mixture was rechromatographed under the same conditions (acetone/hexane, 1:1). Total yield of **8**: 78% with a ratio of β/α = 2:1.

1-(3,5-Di-*O*-*p*-chlorobenzoyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-5-(2-hydroxyethyl)-4-methoxypyrimidin-2-one (14β)

To a stirred solution of **7** (10 mg, 0.059 mmol) in anhyd $CHCl_3$ (0.5 mL) was added BSTFA (99 mg, 0.38 mmol) at r.t. under exclusion of mositure and the stirring was continued for 10 min. No clear solution was obtained. 3,5-Di-*O*-*p*-chlorobenzoyl-2-deoxy-α-D-*erythro*-pentofuranosyl chloride[17] (51 mg, 0.118 mmol) and TMSOTf (2 μL, 0.012 mmol) were added sequentially and the stirring was continued for 1 h. The workup and chromatography (acetone/hexane, 1:1) were carried out under the same conditions used for **8**. Products **14**β (10 mg, 0.017 mmol), **14**α (3 mg, 0.005 mmol) and a mixture of **14**β,α (5 mg, 0.009 mmol) were obtained. The proportion of product **14**β,α (> 2:1) could be roughly determined by TLC (acetone/hexane, 1:1). Total yield of **14**: 54%.

1-(3,5-Di-*O*-*p*-toluoyl-2-deoxy-β,α-D-*erythro*-pentofuranosyl)-5-(2-*p*-toluenesulfonyloxyethyl)-4-methoxypyrimidin-2-ones (9β,α)

A stirred solution of a mixture of **8**β,α (553 mg, 1.06 mmol) in pyridine (5 mL) at r.t. was cooled to 0°C in an ice-bath. To this solution was added *p*-toluenesulfonyl chloride (243 mg, 1.27 mmol) and the stirring was continued at 0°C for 10 min. The mixture was then placed in a refrigerator at 4°C for 20 h. The proceeding of the reaction was monitored by TLC (acetone/hexane, 2:3; starting materials **8**β and **8**α, R_f 0.31 and 0.26 and products **9**β and **9**α, 0.48 and 0.42). After completion of the reaction, the mixture was concentrated at 35°C under vacuum (4 mbar). The residue was chromatographed using acetone/hexane (1:1) as eluent to give **9**β (225 mg, 0.33 mmol), **9**α (280 mg, 0.41 mmol) and a mixture of **9**β,α (120 mg, 0.18 mmol) in 87% total yield. The **9**β,α mixture was rechromatographed under the same conditions (acetone/hexane, 1:1).

Table 5 ^{19}F NMR Data of Compounds **10** and **11**

Product	^{19}F NMR (235.4, $CDCl_3/C_2F_2Cl_4$) δ, *J* (Hz)
10β	2.29 (CF_3)
10α	2.22 (CF_3)
11β	−141.77 (tt, $^2J_{F,H-8}$ = 46.8, $^3J_{F,H-7}$ = 23.2, CFH_2)
11α	−141.59 (tt, $^2J_{F,H-8}$ = 47.0, $^3J_{F,H-7}$ = 24.6, CFH_2)

1-(3,5-Di-*O*-*p*-toluoyl-2-deoxy-β,α-D-*erythro*-pentofuranosyl)-5-(2-trifluoromethanesulfonyloxyethyl)-4-methoxypyrimidin-2-ones (10β,α)

Two 10 mL two-necked round-bottomed flasks were cooled to 0°C in an ice bath and flushed with dry N_2. To one of the two flasks was added $(CF_3SO_2)_2O$ (82 mg, 0.29 mmol) and anhyd CH_2Cl_2 (1.7 mL) while stirring and the other was charged with a mixture of **8**β,α (150 mg, 0.29 mmol), pyridine (23 mg, 0.29 mmol) and anhyd CH_2Cl_2 (1.1 mL) while stirring. The solution of **8**β,α was then added slowly to the solution containing $(CF_3SO_2)_2O$ within 3 min via a syringe. Stirring was continued at 0°C under exclusion of moisture for 1 h. The reaction was monitored by TLC (acetone/hexane, 1:1; **8**β and **8**α, R_f 0.32 and 0.27; **10**β,α, R_f 0.73). After completion of the reaction, CH_2Cl_2 (20 mL) was added and the organic layer was washed with H_2O (10 mL), dried ($MgSO_4$) and filtered. The filtrate was concentrated under reduced pressure at 30°C and the residue (ca 190 mg) was chromatographed (silica gel: 29 g; EtOAc/hexane, 1:4) to give **10**β (14 mg, 0.021 mmol) and **10**α (17 mg, 0.026 mmol) in 17% yield.

Table 6 Physical Data of Compounds Pyrimidine Bases and Nucleotides Prepared[a]

Product	Appearance	mp (°C)	ESI + Q1MS *m/z*	ESI − Q1MS *m/z*
3	colourless oil	-	226 $[M]^+$, 227.1 $[M+H]^+$, 249.0 $[M+Na]^+$	-
5	white solid	119–120	212 $[M]^+$, 213.0 $[M+H]^+$, 235.0 $[M+Na]^+$, 425.1 $[2M+H]^+$, 447.1 $[2M+Na]^+$, 463.1 $[2M+K]^+$	212 $[M^-]$, 211.0 $[M-H]^-$, 247.0 $[M+{}^{35}Cl]^-$, 423.1 $[2M-H]^-$, 445.1 $[2M-2H+Na]^-$
7	silver-white fine needles	152.7–153.7	170 $[M]^+$, 171.0 $[M+H]^+$, 192.9 $[M+Na]^+$	170 $[M^-]$, 169.0 $[M-H]^-$, 205.0 $[M+{}^{35}Cl]^-$
8β	white foam	-	522 $[M]^+$, 523.2 $[M+H]^+$, 545.2 $[M+Na]^+$	522 $[M^-]$, 557.2 $[M+{}^{35}Cl]^-$
8α	white solid	187–189	522 $[M]^+$, 523.2 $[M+H]^+$, 545.2 $[M+Na]^+$, 561.2 $[M+K]^+$, 795.8 $[3M+H+Na]^{2+}$, 803.5 $[3M+H+K]^{2+}$, 1045.5 $[2M+H]^+$, 1067.5 $[2M+Na]^+$	522 $[M^-]$, $[M+{}^{35}Cl]^-$
14β[b]	white needles	216–218	562 $[M]^+$, 562.9 $[M+H]^+$, 584.9 $[M+Na]^+$, 1125.1 $[2M+H]^+$, 1148.9 $[2M+Na]^+$	562 $[M^-]$, 596.8 $[M+Cl]^-$
9β	white solid	71–73	676 $[M]^+$, 677.2 $[M+H]^+$, 699.2 $[M+Na]^+$, 1353.6 $[2M+H]^+$, 1376.6 $[2M+Na]^+$	-
9α	colourless fine needles	137.0–137.5	676 $[M]^+$, 677.3 $[M+H]^+$, 699.2 $[M+Na]^+$, 1353.7 $[2M+H]^+$, 1375.7 $[2M+Na]^+$	-
10β	colourless foam	-	654 $[M]^+$, 655.2 $[M+H]^+$, 677.1 $[M+Na]^+$	654 $[M^-]$, 689.1 $[M+{}^{35}Cl]^-$
10α	colourless foam	-	654 $[M]^+$, 655.2 $[M+H]^+$, 677.2 $[M+Na]^+$	654 $[M^-]$, 689.1 $[M+{}^{35}Cl]^-$
11β	pale yellow crystals	157–158	524 $[M]^+$, 525.2 $[M+H]^+$, 547.2 $[M+Na]^+$, 563.2 $[M+K]^+$	524 $[M^-]$, 559.1 $[M+{}^{35}Cl]^-$
11α	colourless crystals	181.0–182.8	524 $[M]^+$, 525.2 $[M+H]^+$, 547.2 $[M+Na]^+$, 1049.4 $[2M+H]^+$, 1071.4 $[2M+Na]^+$	-
12α	white solid	113–115	504 $[M]^+$, 505.1 $[M+H]^+$, 527.1 $[M+Na]^+$, 1009.4 $[2M+H]^+$, 1031.4 $[2M+Na]^+$	-
13α	white solid	189–192	540 $[M]^+$, 541.2 $[M+H]^+$, 563.1 $[M+Na]^+$, 1081.4 $[2M+H]^+$, 1103.4 $[2M+Na]^+$	540 $[M^-]$, 575.1 $[M+{}^{35}Cl]^-$

[a] Satisfactory microanalyses (C ± 0.16; H ± 0.23; N ± 0.12) or HRMS values (± 0.0191 amu) were obtained.
[b] Isotope clusters centered at M = 562 amu were observed in the mass spectra. The isotope clusters are in accordance with the proposed formula.