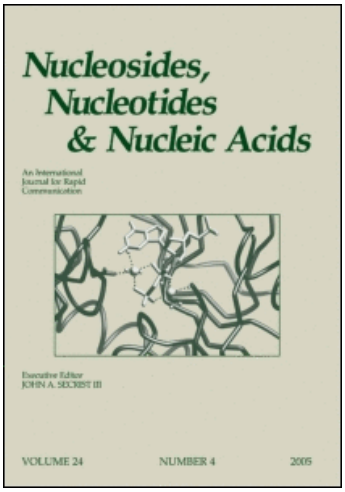


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

The Synthesis of Novel 5-Trifluoroethyl Ethers of Thymidine

P. Kumar[a]; L. I. Wiebe[a]
[a] Faculty of Pharmacy and Pharmaceutical, Sciences University of Alberta, Edmonton, Alberta, Canada

To cite this Article Kumar, P. and Wiebe, L. I.(1990) 'The Synthesis of Novel 5-Trifluoroethyl Ethers of Thymidine', Nucleosides, Nucleotides and Nucleic Acids, 9: 6, 847 — 859
To link to this Article: DOI: 10.1080/15257779008043150
URL: http://dx.doi.org/10.1080/15257779008043150

NUCLEOSIDES & NUCLEOTIDES, 9(6), 847-859 (1990)

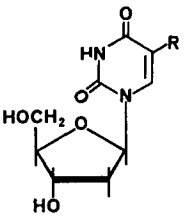
THE SYNTHESIS OF NOVEL 5-TRIFLUOROETHYL ETHERS OF THYMIDINE

P. Kumar and L.I. Wiebe*
Faculty of Pharmacy and Pharmaceutical Sciences
University of Alberta, Edmonton, Alberta, Canada T6G 2N8

ABSTRACT: The syntheses of 5-(2,2,2-trifluoroethoxymethyl)-2'-deoxyuridine 13 and 5-bis(2,2,2-trifluoroethoxy)methyl-2'-deoxyuridine 16 starting from thymidine, are described.

INTRODUCTION

Pyrimidine nucleosides substituted at the C-5 position constitute an important class of xenobiotics which can substitute for physiological nucleosides in transfer RNA[1-4] and DNA.[5-8] Derivatives of 2'-deoxyuridine with C-5 substituents no longer than n-butyl, and with a C atom attached to C-5 are of particular interest as chemotherapeutic agents.[9-12] 5-(2-Bromovinyl)-2'-deoxyuridine (BVDU, 1),[13] 5-(2-chloroethyl)-2'-deoxyuridine (CEDU, 2)[14] and 5-(2-fluoroethyl)-2'-deoxyuridine (FEDU, 3)[15] are among the most potent and selective of this large class of pyrimidine nucleoside analogues.[15,16] BVDU and CEDU effectively inhibit herpes simplex virus type 1 (HSV-1) and varicella zoster virus (VZV) replication, in vitro.[13,14,17-19] Herpes simplex type 2 virus (HSV-2) replication is affected only at considerably higher concentrations of BVDU and CEDU. FEDU inhibits HSV-1 replication at the same or slightly higher concentration than CEDU, and is much less inhibitory to VZV; however it is more active against HSV-2 than is CEDU.[15]



1-8

1. R= (E)CH=CHBr
2. R= CH_2-CH_2Cl
3. R= CH_2-CH_2F
4. R= CF_3
5. R= F
6. R= CH_2OH
7. R= CH_2-CH_2-CF_3
8. R= CH_2OCH_3

5-Trifluoromethyl-2′-deoxyuridine (TFT, 4), a first generation fluoropyrimidine nucleoside synthesized by Heidelberger,[20] shows marked antiviral activity,[21,22] but like most other first generation antiviral nucleosides, TFT is also phosphorylated in uninfected cells, and thereby inhibits DNA synthesis in normal cells.[23] Heidelberger[24] also synthesized 5-fluoro-2′-deoxyuridine (FUdR, 5) and demonstrated its anti-tumor activity. 5-Hydroxymethyl-2′-deoxyuridine (6), when tested against HSV-1 strain V3 (HSV-1-V3) in primary human lung fibroblast cell cultures, showed prominent activity.[25] Recently, Bergstrom *et al*[26] described that 5-(3,3,3-trifluoropropyl)-2′-deoxyuridine (TFPDU, 7) has a potent and unusually selective activity against HSV-1.

5-Methoxymethyl-2′-deoxyuridine (MMdU, 8) has also been reported to exhibit antiviral activity against strains of HSV-1 in primary rabbit kidney cell culture.[27] We now report the synthesis of C-5-trifluoroethoxymethyl pyrimidine nucleosides which were designed to enhance the antiviral potency relative to the corresponding non-fluorinated MMdU.

CHEMISTRY

N-1-substituted uracil bases bearing a halomethyl group at C-5 are very labile in the presence of moisture or protic solvents, since the halogen is easily displaced by nucleophilic solvents (such as water or alcohol) *via* a 1,4-conjugate addition-elimination mechanism.[28,29] Thymidine does not have a dissociable proton at N-1, and therefore, α-bromomethyl and α,α-dibromomethyl thymidine are

expected to be much less susceptible to solvolysis than the corresponding pyrimidine base. Consequently, they can be smoothly converted to their trifluoroethoxide and bistrifluoroethoxide derivatives in an aprotic solvent. In order to effect this reaction, thymidine had to be protected by a group which would be stable during the bromination procedure, and which would be easily removable after the condensation reaction. The *tert*- butyldiphenylsilyl (TBDPS) moiety was chosen for this purpose.[30]

Thymidine 9, on reaction with *tert*-butyldiphenyl chlorosilane in pyridine, gave 3′,5′-bis-O-TBDPS-thymidine, 10, which on bromination yielded 5-α-bromomethyl- 11 or 5-α,α-dibromomethyl-3′,5′-bis-O-TBDPS-thymidine 14, depending on the amounts of bromine used. These bromomethyl nucleosides are not very stable, and therefore, were used as such for further reactions. It was observed that the reaction of these bromonucleosides with the required equivalents of potassium 2,2,2-trifluoroethoxide in presence of an equimolar amount of cuprous iodide gave good yields of 5-(2,2,2-trifluoroethoxymethyl) or 5-bis(2,2,2-trifluoroethoxy)methyl derivatives, whereas in the absence of cuprous iodide, most of the bromomethyl thymidine was hydrolyzed to 5-hydroxymethyl-3′,5′-di-O-TBDPS-thymidine. Thus, 11, on reaction with 2,2,2-trifluoroethoxide-copper complex gave 5-(2,2,2-trifluoroethoxymethyl)-3′,5′-bis-O-TBDPS-deoxyuridine 12, which was easily purified by column chromatography. Similarly, 14 yielded 15. The proton magnetic resonance spectrum of 12 showed a quartet at δ 3.59 ($J_{F,H}$=8.8. Hz) for OCH_2CF_3 protons. The ^{19}F-NMR spectrum of this compound displayed a triplet ($J_{H,F}$=8.8 Hz) at δ 87.65, while a ^{13}C-NMR Jmod spectrum exhibited two quartets. The resonance at δ 124.00 (q, $J_{F,C}$=272 Hz) is due to coupling of fluorine with the tertiary carbon of CF_3 and the other at δ 68.32 (q, $J_{F,C}$=34.9 Hz) arises from fluorine coupling with the methylenic carbon. The ^{1}H-NMR spectrum of 15 displayed a singlet for one 5-CH proton at δ 5.6, and two quartets merged around δ 3.80 ($J_{F,H}$=9.0 Hz) for the four methylenic protons of two OCH_2CF_3 groups. The ^{19}F-NMR spectrum of this compound showed two triplets, one at δ 87.84 ($J_{H,F}$=9.0 Hz) and the other at δ 87.79 ($J_{H,F}$=9.0 Hz). The ^{13}C-NMR Jmod spectrum of the same compound exhibited one quartet at δ 123.44 ($J_{F,C}$=278 Hz) due to the coupling

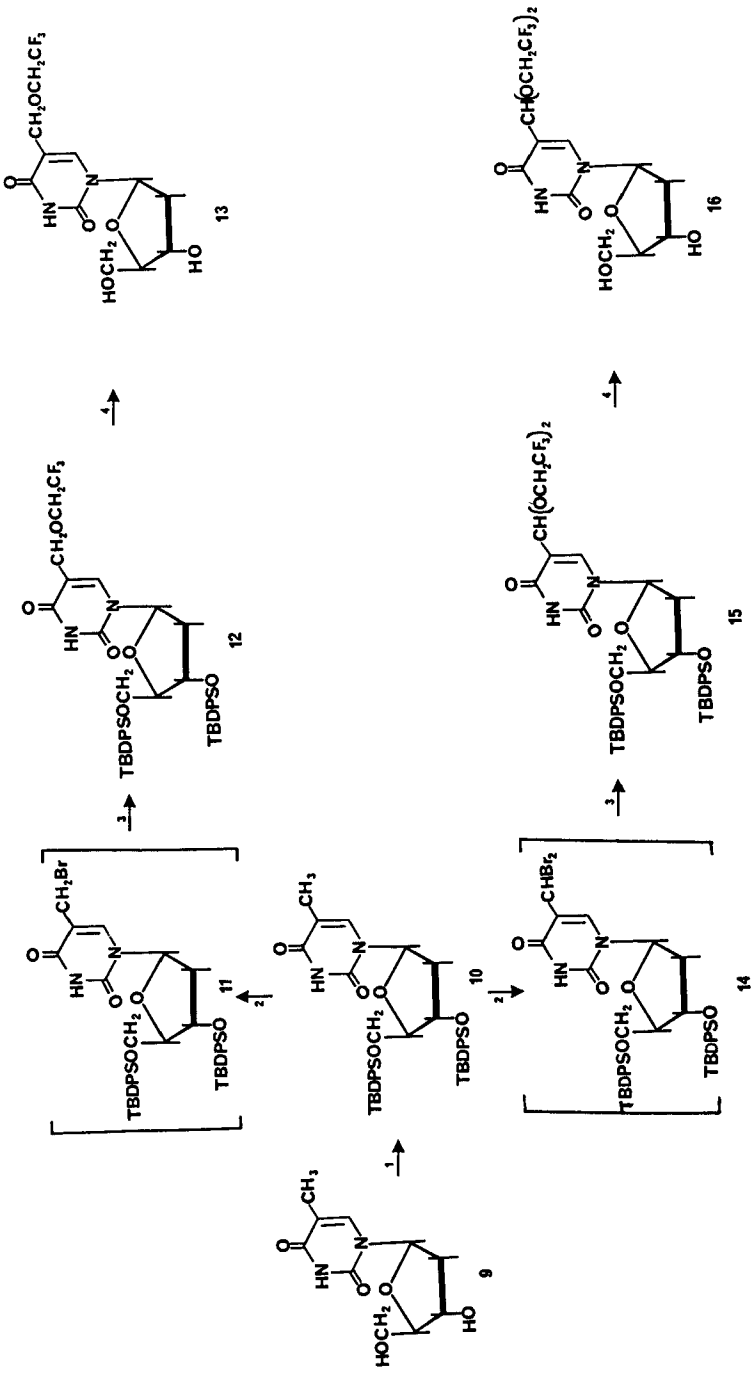
Table 1. ^{1}H, ^{19}F, ^{13}C NMR chemical shifts and coupling constants for the OCH_2CF_3 group as exhibited by compounds 12, 13, 15 and 16.

Compound	^{1}H $OC\underline{H}_2CF_3$ Chemical Shift (δ)	$J_{F,H}$(Hz)	^{19}F $OCH_2C\underline{F}_3$ Chemical Shift (δ)	$J_{H,F}$(Hz)	^{13}C $O\underline{C}H_2CF_3$ Chemical Shift (δ)	$J_{F,C}$(Hz)	^{13}C $OCH_2\underline{C}F_3$ Chemical Shift (δ)	$J_{F,C}$ (Hz)
12	3.59 (q)	8.8	87.65 (t)	8.8	68.32 (q)	34.9	124.00 (q)	272
13	4.00 (q)	8.4	89.44 (t)	8.4	68.63 (q)	34.3	125.75 (q)	272
15	3.80 (q)	9.0	87.84 and 87.79	9.0 (two t)	63.86 (q) (two q merged)	35.7	123.44 (q)	278
16	4.09 (q)	8.8	89.56 (t)	8.8	64.36 (q) (two q merged)	35.0	125.36 (q)	277.3

of fluorine atoms with the carbon of the CF_3 moiety, and two quartets merged in the form of a quintet ($J_{F,C}$=35.7 Hz) at δ 63.86 due to the coupling of fluorine atoms with the methylenic carbon of OCH_2CF_3. A signal for the 5-CH carbon appeared at δ 97.50. Desilylation of 12 and 15, using n-tetrabutylammonium fluoride solution in anhydrous tetrahydrofuran, proceeded very smoothly to yield 5-(2,2,2-trifluoroethoxy)methyl-2′-deoxyuridine 13 and 5-bis(2,2,2-trifluoroethoxymethyl)-2′-deoxyuridine 16, respectively, in crystalline form (Scheme 1). ^{1}H-NMR spectrum of 13 showed a quartet ($J_{F,H}$=8.4 Hz) at δ 4.0 for the methylene protons attached to the CF_3 group. The ^{13}C-NMR spectrum exhibited two quartets, one at δ 125.75 ($J_{F,C}$=272 Hz) for the tertiary carbon of the CF_3 moiety, and the other at δ 68.63 ($J_{F,C}$=34.3 Hz) for the methylenic carbon of OCH_2CF_3. These coupling constants are in accordance with the values reported for fluorine-carbon coupling.[31] The ^{19}F-NMR of this compound showed a triplet ($J_{H,F}$=8.4 Hz) at δ 89.44 (with respect to hexafluorobenzene) because of coupling with neighboring methylenic protons. The ^{1}H-NMR spectrum of 16, which has a bis(trifluoroethoxy)methyl group at C-5 of nucleoside, exhibited two quartets ($J_{F,H}$=8.8 Hz) merged at δ 4.09, for four protons of two methylenic group. The ^{13}C-NMR of 16 also showed two quartets, one at δ 125.36 ($J_{F,C}$=277.3 Hz, for CF_3 group) and the other at δ 64.36 ($J_{F,C}$=35 Hz, CH_2CF_3).

EXPERIMENTAL

Melting points were determined on a Büchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR) were recorded on a Bruker AM 300 spectrometer. Chemical shifts are given in ppm downfield from tetramethylsilane (^{1}H-NMR) and hexafluorobenzene (^{19}F-NMR) as internal standards. ^{1}H-NMR assignments were confirmed by double irradiation experiments. ^{13}C-NMR resonances were assigned by using the J spin echo modulation (Jmod) technique to determine the number of attached hydrogens. Thin layer chromatography was performed on Whatman MK6F silica gel microslides (250 um thickness). The TLC solvent systems employed were A: chloroform/methanol (9.5:0.5 v/v), B:



where 1=tert-Butyldiphenyl chlorosilane/pyridine; 2=$Br_2/h\nu/CCl_4$;3=$CF_3CH_2OK/CuI/DME$;
4=tetrabutyl ammonium fluoride/THf

Scheme 1

chloroform/methanol (8.5:1.5 v/v), C: toluene/ethyl acetate (4:1 v/v). Silica gel column chromatography was carried out using Merck 7734 silica gel (100-200 mesh particle size). Pyridine and carbon tetrachloride were distilled over calcium hydride and used fresh at the time of reaction. Tetrahydrofuran was dried over sodium/benzophenone and distilled fresh at the time of reaction.

3′,5′-Bis-O-tert-butyldiphenylsilyl thymidine (10). Thymidine 9 (5 g, 20.7 mmole) was dissolved in anhydrous pyridine (15 mL) and *tert*-butyldiphenyl chlorosilane (11.8 mL, 45.5 mmole) was added under nitrogen atmosphere. The reaction mixture was stirred at 60°C for 24 h; at this time the TLC showed complete conversion of thymidine to 10. Pyridine was evaporated, *in vacuo*, and the crude reaction mixture was extracted with chloroform/water (3 x 50 mL). The organic phase was collected, dried over anhydrous sodium sulphate, filtered, evaporated and purified on a silica gel column. An elution, starting with toluene and ending with 10% ethyl acetate gave pure 10: yield 12.7 g (85%); mp 88°C; ^{1}H NMR ($CDCl_3$)-δ 8.4 (s, broad, exchanges with D_2O, 1H, NH), 7.70-7.26 (m, 21H, 1H of H-6 and 20H of four phenyls), 6.55 (d, $J_{2",1'}$=9.0 Hz of d, $J_{2',1'}$=4.5 Hz, 1H, H-1′), 4.57 (d, $J_{2',3'}$= $J_{2",3'}$=4.5 Hz, 1H, H-3′), 4.02 (d, $J_{5',4'}$=2.3 Hz, 1H, H-4′), 3.97 (d, $J_{4',5'}$=2.3 Hz of d, J_{gem}=12.0 Hz, 1H, H-5′), 3.34 (d, $J_{4',5"}$=2.3 Hz of d, J_{gem}=12.0 Hz, 1H, H-5"), 2.36 (d, $J_{1',2'}$=$J_{3',2'}$=4.5 Hz of d, $J_{2",2'}$= 13.5 Hz, 1H, H-2′), 2.0 (d, $J_{3',2"}$=4.5 Hz of d, $J_{1',2"}$=9.0 Hz of d, $J_{2',2"}$=13.5 Hz, 1H, H-2"), 1.50 (s, 3H, CH_3), 1.11 and 0.96 (two s, each for 9H of two *t*-butyl); ^{13}C NMR ($CDCl_3$)-δ 163.90 (C-4), 150.44 (C-2), 137.74-125.22 (C-6 and phenyl carbons), 111.02 (C-5), 87.67 (C-4′), 84.70 (C-1′), 73.88 (C-3′), 63.94 (C-5′), 41.25 (C-2′), 26.85 (CH_3's of *t*-butyl group), 19.21 and 18.95 (*tert*.carbon of *t*-butyl) and 11.82 (5-CH_3); anal. calc. for $C_{44}H_{50}N_2Si_2O_5.\frac{1}{4}H_2O$ (719.03); C, 69.71; H, 7.03; N, 3.87; found C, 69.33; H, 6.87; N, 3.90.

5-(2,2,2-Trifluoroethoxymethyl)-3′,5′-bis-O-tert-butyldiphenylsilyl-2′-deoxyuridine (12). Compound 10 (3.23 g, 4.5 mmole) was dissolved in carbon tetrachloride (35 mL) and refluxed under argon on a preheated oil bath. Bromine (0.3 mL, 5.84 mmole) in CCl_4 (10 mL) was added dropwise with stirring, under irradiation by a 75 watt UV lamp.[32]

After the addition was complete, argon was bubbled through the solution to remove the HBr generated in the reaction. The solvent was evaporated under complete exclusion of moisture to give crude 11, which was dissolved in anhydrous dimethoxyethane (20 mL) and added to a solution of trifluoroethoxide-copper complex in DME. This complex was prepared by the reaction of 2,2,2-trifluoroethanol (0.5 mL, 5 mmole) with sodium hydride (0.12 g, 5 mmole) in DME (10 mL), followed by the addition of cuprous iodide (0.95 g, 5 mmole) and stirring this mixture for 1h at 25°C. At this time, the copper complex solution became clear. The mixture of 11 and the copper complex solution was stirred at 25°C for 2 h under argon, and then the contents diluted with diethyl ether (150 mL), extracted with ammonium hydroxide solution (28%, 2x15 mL) and finally with cold water until the pH was neutral. The organic phase was dried over anhydrous magnesium sulphate, filtered and evaporated to give a viscous mass which was purified on a silica gel column using toluene/ethyl acetate (2%, 5%) to give pure 12: yield, 1.28 g (35%); mp 64°C; ^{1}H-NMR ($CDCl_3$) δ 8.75 (s, broad, D_2O exchangeable, 1H, NH), 7.6-7.17 (m, 21H, 20H of four phenyls and 1H of H-6), 6.39 (d, $J_{2',1'}$=4.5 Hz of d, $J_{2'',1'}$=9.0 Hz, 1H, H-1′), 4.93 (d, $J_{2',3'}$=5.3 Hz, 1H, H-3′), 3.94 (m, 1H, H-4′), 3.84 (q, J_{ab}=12.0 Hz, 2H, $C\underline{H}_2OCH_2CF_3$), 3.64 (d, $J_{4',5'}$=3.0 Hz of d, J_{gem}=12.0 Hz, 1H, H-5′), 3.59 (q, $J_{F,H}$=8.8 Hz, 2H, OCH_2CF_3), 3.25 (d, $J_{4',5''}$=3.0 Hz of d, J_{gem}=12.0 Hz, 1H, H-5"), 2.3 (d, $J_{3',2'}$=5.3 Hz of d, J_{gem}=13.5 Hz, 1H, H-2′), 1.86 (septet, $J_{1',2''}$=9.0 Hz, $J_{3',2''}$=4.5 Hz, J_{gem}=13.5 Hz, 1H, H-2"), 1.01 and 0.85 (two s, each for 9H of two *tert*-butyl); ^{19}F NMR ($CDCl_3$ + C_6F_6) δ 87.65 (t, $J_{H,F}$=8.8 Hz); ^{13}C-NMR ($CDCl_3$) δ 162.36 (C-4), 149.86 (C-2), 139.23 (C-6), 135.65-132.25 (phenyl carbons), 124.00 (q, $J_{F,H}$=272 Hz, $\underline{C}F_3$), 110.84 (C-5), 87.97 (C-4′), 85.35 (C-1′), 73.85 (C-3′), 68.32 (q, $J_{F,H}$=34.9 Hz, $O\underline{C}H_2CF_3$), 66.48 ($\underline{C}H_2OCH_2CF_3$), 63.94 (C-5′), 41.47 (C-2′), 26.87 (CH_3 of *tert*-butyl group), 19.22 (*tert*-carbon of *tert*-butyl); anal. calc. for $C_{44}H_{51}F_3N_2O_6Si_2 \cdot \frac{1}{2}H_2O$ (817.06); C, 63.97; H, 6.34; N, 3.39; found; C, 63.60; H, 6.18; N, 3.35.

5-(2,2,2-Trifluoroethoxy)methyl-2′-deoxyuridine (13). Compound 12 (1.28 g, 1.57 mmole) was dissolved in anhydrous tetrahydrofuran (15 ml) and tetrabutylammonium fluoride solution (3.92 mmole, 1M sol. in THF) was added under a nitrogen atmosphere. The reaction mixture was

stirred overnight at 25°C, after which the solvent was evaporated and the crude viscous residue was purified on a silica gel column using 2% methanol in chloroform as eluent, to give 430 mg (81%) of pure 13 which was recrystallized from dichloromethane and few drops of methanol to yield needle shaped crystals: mp 210°C (dec.); ^{1}H NMR (CD_3OD) δ 8.15 (s, 1H, H-6), 6.19 (t, $J_{2',1'}$=6.5 Hz, 1H, H-1'), 4.44-4.34 (m, 3H, 2H of $C\underline{H}_2OCH_2CF_3$ and 1H of H-3'), 4.00 (q, $J_{F,H}$=8.4 Hz, 2H, $OC\underline{H}_2CF_3$), 3.92 (m, 1H, H-4'), 3.80 (d, $J_{4',5'}$=3.8 Hz of d, J_{gem}=12.4 Hz, 1H, H-5'), 3.72 (d, $J_{4',5"}$=3.8 Hz of d, J_{gem}=12.4 Hz, 1H, H-5") and 2.27 (m, 2H, H-2'); ^{19}F NMR ($CD_3OD+C_6F_6$) δ 89.44 (t, $J_{H,F}$=8.4 Hz); ^{13}C NMR (CD_3OD) δ 165.12 (C-4), 152.09 (C-2), 141.83 (C-6), 125.75 (q, $J_{F,C}$=272 Hz, $\underline{C}F_3$), 111.47 (C-5), 89.02 (C-4'), 86.76 (C-1'), 72.09 (C-3'), 68.63 (q, $J_{F,C}$= 34.3 Hz, $O\underline{C}H_2CF_3$), 67.83 ($\underline{C}H_2OCH_2CF_3$), 62.23 (C-5') and 41.48 (C-2'); anal. calc. for $C_{12}H_{15}F_3N_2O_6$ (340.24); C, 42.36; H, 4.44; N, 8.23; found; C, 42.13; H, 4.40; N, 7.99; LRMS; M^+ (1.3%).

5-Bis(2,2,2-trifluoroethoxy)methyl-3',5'-bis-O-tert-butyldiphenylsilyl-2'-deoxyuridine (15). Compound 10 (1.5 g, 2.1 mmole) was taken in anhydrous CCl_4 (30 mL) and refluxed under stirring in argon atmosphere on a preheated oil bath. Bromine (0.27 mL, 5.25 mmole) in anhydrous CCl_4 (10 mL) was added to the refluxing solution of 10 dropwise under irradiation by a 75 watt UV lamp. When the addition was over, argon was bubbled through the reaction mixture to remove HBr formed during the reaction. The solvent was removed under complete exclusion of the moisture to give the crude 14 which was dissolved in anhydrous DME (20 mL) and added to a solution of 2,2,2-trifluoroethoxide-copper complex (5 mmole) in DME (20 mL), already prepared as described in the synthesis of 12. The reaction mixture was stirred overnight at 25°C under argon, diluted with diethyl ether (100 mL) and extracted with ammonium hydroxide solution (28%, 20 mL x 2), and then with cold water until the pH of the solution was neutral. The organic phase was dried over anhydrous magnesium sulphate, filtered and evaporated *in vacuo* to give a viscous mass which, after purification on silica gel column using toluene/ethyl acetate (2%, 5%), yielded 0.35 g (18%) of pure 15: mp 53°C (softened); ^{1}H NMR ($CDCl_3$) δ 8.74 (s, broad, D_2O exchangeable, 1H, NH), 7.78 (s, 1H, H-6), 7.62-7.44 (m, 20H of four phenyl groups), 6.63 (d, $J_{2",1'}$=5.0 Hz of d,

$J_{2',1'}$=8.6 Hz, 1H, H-1'), 5.60 (s, 1H of C<u>H</u>$(OCH_2CF_3)_2$), 4.39 (d, $J_{2',3'}$= 5.0 Hz, 1H, H-3'), 4.08 (m, 1H, H-4'), 3.80 (two q, merged, $J_{F,H}$=9.0 Hz, 4H of two OCH_2CF_3 groups), 3.60 (d, $J_{4',5'}$=4.1 Hz of d, J_{gem}=11.3 Hz, 1H, H-5'), 3.42 (d, $J_{4',5"}$=4.1 Hz of d, J_{gem}=11.3 Hz, 1H, H-5"), 2.38 (d, $J_{3',2"}=J_{1',2"}$=5.0 Hz of d, J_{gem}=13.5 Hz, 1H, H-2"), 1.78 (m, 1H, H-2'), 1.07 and 0.94 (two s, each for 9H of two *tert*-butyl); ^{19}F NMR ($CDCl_3$+C_6F_6) δ 87.84, 87.79 (two t, $J_{H,F}$=9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 161.07 (C-4), 149.27 (C-2), 139.15 (C-6), 135.65-129.85 (phenyl carbons), 123.44 (q, $J_{F,C}$=278 Hz, <u>C</u>F_3), 109.77 (C-5), 97.50 (<u>C</u>H$(OCH_2CF_3)_2$), 88.05 (C-4'), 86.10 (C-1'), 73.70 (C-3'), 63.86 (two q, merged in the form of a quintet, $J_{F,C}$=35.7 Hz, (O<u>C</u>$H_2CF_3)_2$), 63.86 (C-5'), 41.05 (C-2'), 26.87 and 26.80 (CH_3's of two *tert*-butyl), 19.09 and 18.98 (*tert*-carbons of two *tert*-butyl groups); anal. calc. for $C_{46}H_{52}F_6N_2O_7Si_2$ (915.06); C, 60.37; H, 5.73; N, 3.06; found; C, 60.24; H, 6.00; N, 3.01.

5-Bis(2,2,2-trifluoroethoxy)methyl-2'-deoxyuridine (<u>16</u>). Compound <u>15</u> (0.35 g, 0.38 mmole) was dissolved in anhydrous tetrahydrofuran (10 mL), and a 1M solution of tetrabutylammonium fluoride in THF (0.95 ml, 0.95 mmole) was added to it under an inert atmosphere. After stirring the reaction mixture overnight at 25°C, excess of the solvent was evaporated *in vacuo*, and the residue purified on a silica gel column using chloroform/methanol (2%) as eluent to give 0.11 g of <u>16</u> (66%): mp 202°C (dec.); ^1H NMR (CD_3OD) δ 8.24 (s, 1H, H-6), 6.27 (t, $J_{2',1'}$=6.8 Hz, 1H, H-1'), 5.74 (s, 1H, C<u>H</u>$(OCH_2CF_3)_2$), 4.39 (d, $J_{2",3'}$=3.4 Hz of t, $J_{2',3'}=J_{4',3'}$=6.8 Hz, 1H, H-3'), 4.09 (two q, merged, $J_{F,H}$=8.8 Hz, 4H of (O<u>C</u>$H_2CF_3)_2$), 3.98 (d, $J_{5',4'}$=3.4 Hz of d, $J_{3',4'}$=6.8 Hz, 1H, H-4'), 3.78 (d, $J_{4',5'}$=3.4 Hz of d, J_{gem}=13.5 Hz, 1H, H-5'), 3.68 (d, $J_{4',5"}$=3.4 Hz of d, J_{gem}=13.5 Hz, 1H, H-5"), 2.35 (d, $J_{3',2"}=J_{1',2"}$=6.8 Hz of d, J_{gem}=13.5 Hz, 1H, H-2") and 2.24 (quintet, $J_{1',2'}=J_{3',2'}$=6.8 Hz of d, J_{gem}=13.5 Hz, 1H, H-2'); ^{19}F NMR (CD_3OD+C_6F_6) δ 89.56 (t, $J_{H,F}$=8.8 Hz); ^{13}C NMR (CD_3OD) δ 163.86 (C-4), 151.83 (C-2), 125.36 (q, $J_{F,C}$=277.3 Hz, <u>C</u>F_3), 110.36 (C-5), 98.60 (<u>C</u>H$(OCH_2CF_3)_2$), 89.28 (C-4'), 87.30 (C-1'), 72.39 (C-3'), 64.36 (two q, merged, $J_{F,C}$=35 Hz, (O<u>C</u>$H_2CF_3)_2$), 62.85 (C-5') and 41.66 (C-2'); anal. calc. for $C_{14}H_{16}F_6N_2O_7$ (438.29); C, 38.36; H, 3.68; N, 6.39; found; C, 38.43; H, 3.71; N, 6.35; LRMS; M^+ (0.4%).

ACKNOWLEDGEMENTS

The authors wish to thank Mrs. Carolyn Hartwig for typing the manuscript. This work was done with the support of the Medical Research Council of Canada, grant no. MA9684.

REFERENCES

1. Hall, R.H.; in "The Modified Nucleosides in Nucleic Acids", Columbia University Press, New York, N.Y., 1971, *23*, 181 and 286.

2. Dunn, D.B.; Trigg, M.D.M.; *Biochem. Soc. Trans.*, 1975, *3*, 656.

3. Baczynskyj, L.; Biemann, K.; Hall, R.H.; *Science.*, 1968, *159*, 1481.

4. Carbon, J.A.; David, H.; Studier, M.H.; *Science.*, 1968, *161*, 1146.

5. (a) Marmur, J.; Brandon, C.; Neubort, S.; Ehrlich, M.; Mandel, M.; Konvicka, J.; *Nature* (London), New Biol., 1972, *239*, 68; (b) Brandon, C.; Gallop, P.M.; Marmur, J.; Hayashi, H.; Nakanishi, K.; *ibid.*, 1972, *239*, 70.

6. Leob, M.R.; Cohen, S.S.; *J. Biol. Chem.*, 1959, *234*, 364.

7. (a) Callen, R.G., Simon, M.; Marmur, J.; *J. Mol. Biol.*, 1962, *5*, 248; (b) Roscoe, D.H.; Tucker, R.G.; *Biochem. Biophys. Res. Commun.*, 1964, *16*, 106.

8. Kropinski, A.M.B.; Bose, R.J.; Warren, R.A.J.; *Biochemistry.*, 1973, *12*, 151.

9. (a) Shugar, D.; in "Virus-cell interactions and viral antimetabolites", D. Shugar, ed., Academic Press, New York, N.Y., 1972, 193; (b) Shugar, D.; *FEBS Lett.*, 1974, *40*, S48.

10. Swierkowski, M.; Shugar, D.; *J. Med. Chem.*, 1969, *12*, 533.

11. Prusoff, W.H.; Goz, B.; in "Antineoplastic and immunosuppresive Agent", vol 2, Sartorelli, A.C.; Johns, D.G., ed.; Springer-Verlag, West Berlin, 1975, 272; Prusoff, W.H.; Goz, B.; *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, 1973, *32*, 1679.

12. De Clercq, E.; Shugar, D.; *Biochem. Pharmacol.*, 1975, *24*, 1073.

13. De Clercq, E.; Descamps, J.; De Somar, P.; Barr, P.J.; Jones, A.S.; Walker, R.T.; *Proc. Natl. Acad. Sci.*, U.S.A., 1979, *76*, 2947.

14. Griengl, H.; Bodenteich, M.; Hayden, W.; Wanek, E.; Streicher W.; Stutz, P.; Bachmayer, H.; Ghazzouli, I.; Rosenwirth, B.; *J. Med. Chem.*, 1985, *28*, 1679.

15. Griengl, H.; Wanek, E.; Schwarz, W.; Streicher, W.; Rosenwirth, B.; De Clercq, E.; *J. Med. Chem.*, 1987, *30*, 1199.

16. De Clercq, E.; in "Approaches to Antiviral Agents"; Harnden, M.R., eds.; MacMillan, London, 1985, 57.

17. De Clercq, E.; Descamps, J.; Ogata, M.; Shigeta, S.; *Antimicrob. Agents Chemother.*, 1982, *21*, 33.

18. De Clercq, E.; Rosenwirth, B.; *Antimicrob. Agents Chemother.*, 1985, *28*, 246.

19. Rosenwirth, B.; Griengl, H.; Wanek, E.; De Clercq, E.; *Antiviral Res.*, 1985, *suppl. 1*, 21.

20. Heidelberger, C.; Parsons, D.G.; Remy, D.C.; *J. Amer. Chem. Soc.*, 1962, *84*, 3597; *J. Med. Chem.*, 1964, *7*, 1; Ryan, K.J.; Acton, E.M.; Goodmann, L.; *J. Org. Chem.*, 1966, *31*, 1181.

21. Heidelberger, C.; *Cancer Res.*, 1970, *30*, 1549.

22. Carmine, A.A.; Brogden, R.N.; Heel, R.C.; Speight, T.M.; Avery, G.S.; *Drugs*, 1982, *23*, 329.

23. Tone, H.; Heidelberger, C.; *Mol. Pharmacol.*, **1973**, *9*, 783.

24. Heidelberger, C.; in "Antineoplastic and Immunosuppressive Agents", Sartorelli, A.C.; Johns, D.G., eds., **1975**, *2*, 193.

25. Reefschlaeger, J.; Baerwolff, D.; Engelmann, P.; Langeu, P.; Rosenthal, H.A.; *Antiviral Res.*, **1982**, *2(1-2)*, 41.

26. Bergstrom, D.E.; Ruth, J.L.; Reddy, P.A.; De Clercq, E.; *J. Med. Chem.*, **1984**, *27(3)*, 274.

27. Gupta, S.V.; Tourigny, G.; Stuart, A.L.; De Clercq, E.; Quail, J.W.; Ekiel, I.; El-Kabbani, O.A.L.; Delbaere, L.T.J.; *Antiviral Res.*, **1987**, *7*, 69-77.

28. For reviews, see Heidelberg, C.; King, D.H.; *Pharmacol. Ther.*, **1979**, *6*, 427; Carmine, A.A.; Brogden, R.N.; Heel, R.C.; Speight, T.M.; Avery, G.S.; *Drugs*, **1982**, *23*, 329.

29. Cristol, S.J.; *Acc. Chem. Res.*, **1971**, *4*, 393.

30. Hanessian, S.; Lavalee, P.; *Can. J. Chem.*, **1975**, *53*, 2975.

31. Vander Kelen, G.P.; Eeckhaut, Z.; *J. Mol. Spectrosc.*, **1963**, *10*, 141.

32. Barewolff, D.; Langen, P.; in "Nucleic Acid Chemistry" Townsend, L.B.; Tipson, R.S., eds., **1978**, *1*, 359; Wiley Interscience Publisher, New York.

Received February 24, 1990.