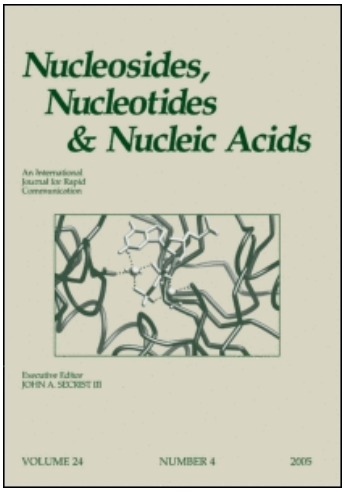

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SYNTHESIS OF A FLUORINATED GANCICLOVIR ANALOG

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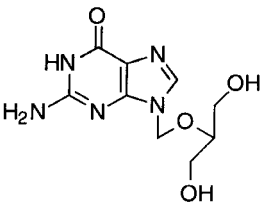
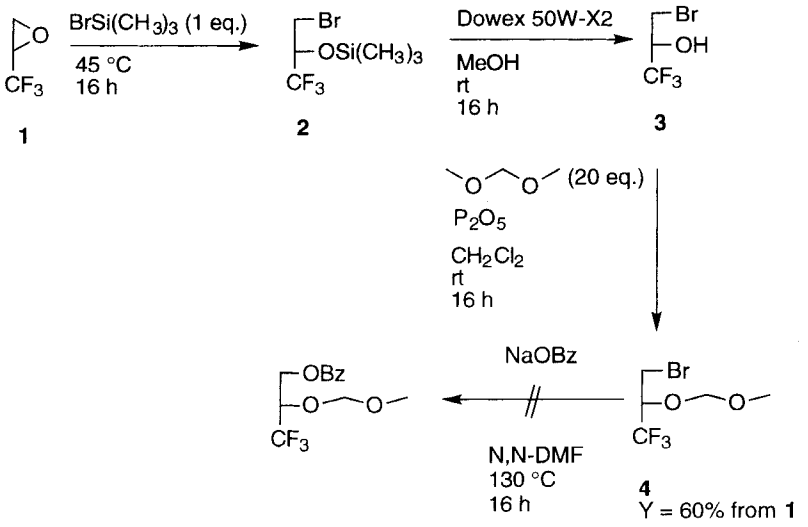
Abstract The synthesis of a new ganciclovir analog with a trifluoromethyl group in the acyclic chain is described.

Introduction Cytomegalovirus (CMV), infects some 50% of adults in developed countries.[1] However, it poses little threat in patients with normal immunity. In immunocompromised patients, when activated, CMV causes pneumonitis, retinitis (which rapidly leads to blindness), and severe colitis. One of the most effective agents against CMV is ganciclovir,[2,3] however it is also quite toxic. As part of an ongoing program dedicated to the development of new and less toxic analogs of ganciclovir we have explored the possibility of replacing one of the hydroxymethylene groups of the side chain with a trifluoromethyl group.



ganciclovir

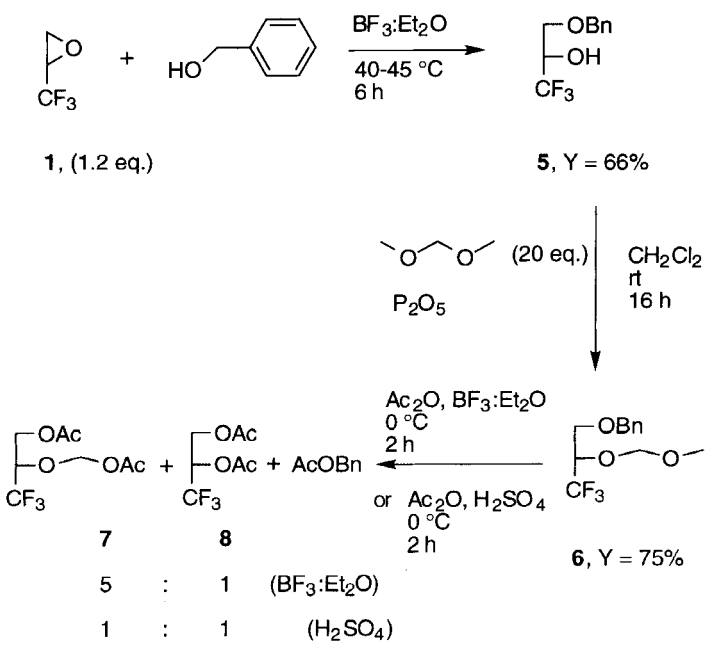
Results and Discussion Ganciclovir derivatives are usually prepared by coupling diacetylguanine and the corresponding acetoxymethoxy side chain.[2] Our first synthetic attempts to prepare the trifluoromethyl side chain are depicted in Scheme 1. The epoxide of the trifluoro derivative **1** was regioselectively opened with TMSBr[4] to afford the 2-*O*-silyl derivative. Removal of the silyl group was achieved with acidic resin[5] to give alcohol **3**. This material was then treated with dimethoxymethane[6] in the presence of P_2O_5 to afford the methoxymethyleneoxy (MOM ether) derivative **4** in 60 % yield from



Scheme 1

the epoxide **1**. Unfortunately all the attempts to displace the bromine with a benzoate group failed: reaction of **4** with sodium benzoate in DMF at high temperatures[7] gave complete decomposition of the starting material, similar results were observed when **4** was treated with DBU and benzoic acid,[8,9] and no reaction was observed using Bu_4NBr and potassium benzoate under phase transfer conditions.[10] Attempts to displace the bromine with strong or mild nitrogen nucleophiles (which could be subsequently converted to an alcoholic group) also gave negative results. These failures may be attributable to the increased acidity of the methine H-2 in the presence of the vicinal trifluoromethyl group. Under the strong basic conditions and high temperatures used in these reactions the hydrogen may be abstracted followed by elimination or other side reactions.

In view of these results we decided on a different approach shown in Scheme 2. Opening of the epoxide ring of **1** with benzyl alcohol[11] in the presence of a Lewis acid gave regioselectively the primary *O*-benzyl derivative **5** in 66 % yield. Treatment of this material with dimethoxymethane as previously described afforded compound **6** in 75 % yield. When this material was treated with Ac_2O in the presence of either a Lewis acid or a strong protic acid, a mixture of three compounds was observed by ^1H-NMR: the acetoxymethoxy derivative **7** in which the primary *O*-benzyl group was replaced by an acetate, the di-*O*-acetyl derivative **8** and benzyl acetate. When the reaction was catalyzed



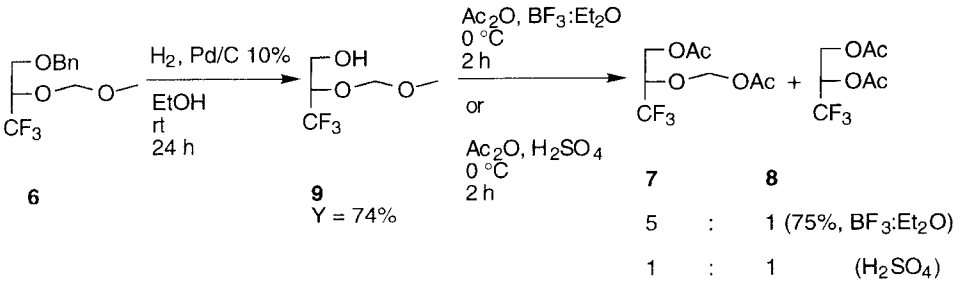
Scheme 2

by BF_3:Et_2O the ratio of **7** to **8** was five to one. Unfortunately, because of their closely similar physical properties, removal of benzyl acetate was extremely difficult.

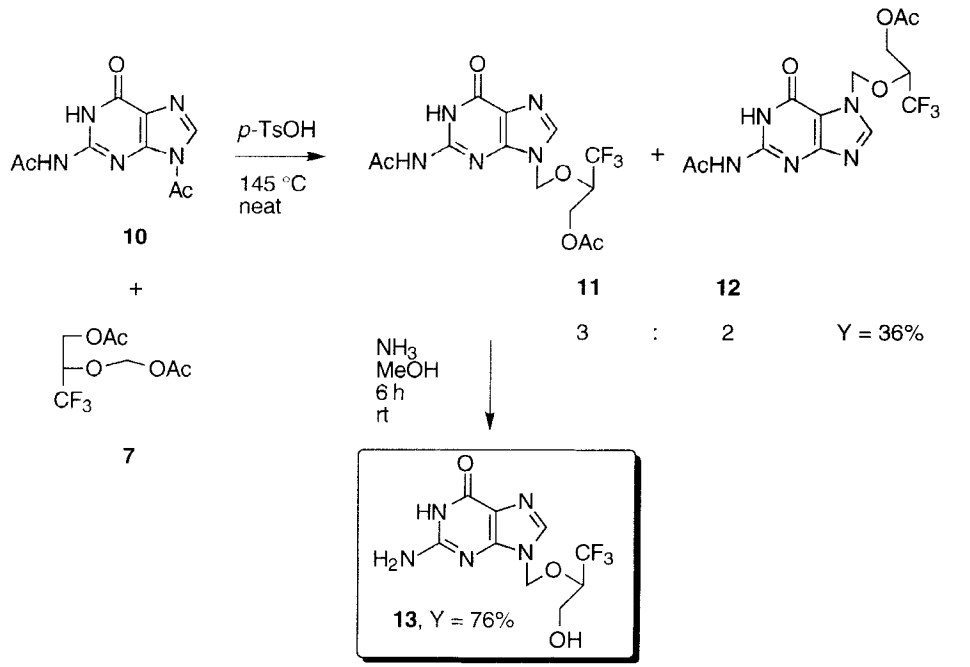
To eliminate its formation, we first removed the benzyl group of **6** by hydrogenation to give **9** in 74 % yield (Scheme 3), then treated this material with Ac_2O as described above. In the presence of BF_3:Et_2O we obtained a 75% yield of a five to one mixture of the desired material (**7**) and **8**. This crude mixture was coupled with diacetylguanine (**10**, Scheme 4) under standard conditions[2,12] to afford a three to two mixture of the N-9 (**11**) and N-7 (**12**) substituted isomers in a combined 36 % yield. After chromatographic separation, the desired nine isomer (**11**) was deacetylated in methanolic ammonia to afford the final compound 9-((2-hydroxy-1-(trifluoromethyl)ethoxy)methyl)guanine (**13**) in 76 % yield.

Compound **13** was inactive in CPE (Cytopathic effect) assay against human cytomegalovirus.

Conclusions In summary, a practical synthesis of the trifluoroside chain **7** has been achieved and succesfully coupled to a guanine base. Coupling of this side chain with different bases could afford nucleoside analogs of biological interest.



Scheme 3



Scheme 4

EXPERIMENTAL SECTION

General methods. Melting points were determined in open glass capillaries by use of a Thomas-Hoover apparatus, and are uncorrected. ^{1}H-NMR spectra were recorded at 300 MHz with a Varian XL-300 spectrometer. CIMS were recorded with a platform mass spectrometer (Fisons Instrument) operated in a APcI (Atmospheric pressure chemical ionization) mode. Evaporations were performed under diminished pressure in a Buchi rotatory evaporator at 40 °C unless otherwise indicated. Solutions were dried over anhydrous Na_2SO_4. TLC was performed on precoated glass plates (0.25 mm) with Silica Gel $60F_{254}$ (E. Merck, Darmstad). Flash column chromatography was performed with Silica Gel 60 (230-400 mesh, E. Merck, Darmstad). Elemental analyses were performed by Atlantic Microlab (Atlanta, GA).

1-Acetoxy-2-(acetoxymethoxy)-3,3,3-trifluoro-propane (7). To a well stirred solution of benzyl alcohol (3.24 g, 30 mmol) and BF_3:Et_2O (62.5 mg, 0.44 mmol) was slowly added **1** (4.0 g, 35.7 mmol). The reaction mixture was stirred at 40-45 °C and followed by GLC until total dissapearance of benzyl alcohol (6 h). The reaction mixture was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL). The organic soluiton was washed with H_2O (2 x 50 mL), dried, filtered and evaporated to afford a syrup that was purified by flash column chromatography (4:1 hexane-AcOEt). Compound **5** (4.2 g, 20 mmol, Y = 66%) was obtained as a yellow syrup. Analytical data for **5**: ^{1}H-NMR δ ($CDCl_3$) 3.60-3.80 (m, 2H, BnOC*H*$_2$CH(CF_3)OH), 4.05-4.25 (m, 1H, BnOCH$_2$C*H*(CF_3)OH), 4.61 (s, 1H, PhC*H*$_2$O-), 7.30-7.45 (m, 5H, Ar-H).

To a well mechanically stirred solution of **5** (4.2 g, 20 mmol) in dry CH_2Cl_2 (90 mL) was first added P_2O_5 (17.0 g, 120 mmol) followed by slow addition of dimethoxymethane (31.95 g, 420 mmol). After stirring at rt for 16 h, the solution was decanted and the solids further washed with CH_2Cl_2. The organic solutions were combined and poured into a cold (0-5 °C) stirred solution of concentrated $NaHCO_3$ (300 mL). After stirring at rt for several minutes, the organic phase was separated and washed with brine (2 x 150 mL), dried, filtered and evaporated to afford **6** (4.0 g, 15 mmol, Y = 75%) as a syrup. Analytical data for **6**: ^{1}H-NMR δ($CDCl_3$) 3.42 (s, 3H, -OCH$_2$OC*H*$_3$), 3.60-3.80 (m, 2H, BnOC*H*$_2$CH(CF_3)O-), 4.20-4.30 (m, 1H, BnOCH$_2$C*H*(CF_3)O-), 4.58 (s, 1H, PhC*H*$_2$O-), 4.75-4.85 (dd, 2H, -OC*H*$_2$OCH$_3$), 7.30-7.40 (m, 5H, Ar-H).

Compound **6** (3.5 g, 13.2 mmol) was hydrogenated in the presence of 10% Pd/C (700 mg) in EtOH (70 mL) at rt for 16 h. After filtration and evaporation, compound **9** (1.7 g, 9.7 mmol, Y = 74%) was obtained as a liquid. Analytical data for **9**: ^{1}H-NMR δ ($CDCl_3$)

3.46 (s, 3H, -OCH_2OCH_3), 3.70-3.90 (m, 2H, $HOCH_2CH(CF_3)O$-), 3.90-4.10 (m, 1H, $HOCH_2CH(CF_3)O$-), 4.79 (bs, 2H, -OCH_2OCH_3).

To a cold (0-5 °C) stirred solution of **9** (1.5 g, 8.6 mmoL) in Ac_2O (6 mL, 63.5 mmol) was slowly added BF_3:Et_2O (383 mg, 2.7mmol). After stirring for 2 h at 0 °C, the reaction mixture was poured into a cold (0-5 °C) stirred solution of concentrated $NaHCO_3$ (200 mL). After stirring for several minutes at rt, the organic phase was separated and washed with $NaHCO_3$ (c) (100 mL) and H_2O (2 x 100 mL), dried, filtered and evaporated to afford a liquid that showed by ^{1}H-NMR a 5:1 mixture of **7** (1.6 g, 6.5 mmol, Y = 75%) and **8** that was used in the next step without any further purification. Analytical data for **7**: ^{1}H-NMR δ ($CDCl_3$) 2.10 (s, 3H, CH_3COO-), 2.13 (s, 3H, CH_3COO-), 4.10-4.30 (m, 3H, $CH_3COOCH_2CH(CF_3)O$- and $CH_3COOCH_2CH(CF_3)O$-), 5.18 (bs, 2H, -OCH_2OOCCH_3).

9-((2-Hydroxy-1-(trifluoromethyl)ethoxy)methyl)guanine (13) A solution of *p*-TsOH•H_2O (230 mg, 1.2 mmol) in dry toluene (30 mL) was refluxed using an oil bath, and 15 mL of toluene were removed by distillation. After cooling to rt, diacetylguanine (**10**, 353 mg, 1.5 mmol) and a solution of **7** (400 mg, 1.64 mmol) in dry toluene (15 mL) were added. The suspension was refluxed and toluene was distilled until dryness. The temperature of the oil bath was rised to 145 °C. After 16 h it was cooled down to rt and the dark solid mixture purified by flash column chromatography (9:1 $CHCl_3$-MeOH). First fraction afforded the 7-substituted isomer (**12**, 80 mg, 0.21 mmol, Y = 14 %) and the second fraction afforded the 9-substituted isomer (**11**, 120 mg, 0.32 mmol, Y = 22%). Total combined yield was 36 %. Analytical data for **11**: ^{1}H-NMR δ(DMSO-d_6) 1.82 and 2.21 (s, 3H each, CH_3COO- and CH_3CON-), 4.04 (dd, J = 6.9 and 12.3, 1H, $AcOCH_2CH(CF_3)O$-), 4.27 (dd, J = 3.2 and 12.3, 1H, $AcOCH_2CH(CF_3)O$-), 4.73 (m, 1H, $AcOCH_2CH(CF_3)O$-), 5.61 (d, 1H, J = 12.3, -NCH_2O-), 5.73 (d, 1H, J = 12.3, -NCH_2O-), 8.22 (s, 1H, H-8), 11.79 and 12.12 (br s, 1H each, AcNH and H-1); ^{19}F-NMR δ (DMSO-d_6) 118.40 (d, J = 6.0); CIMS *m/z* 378 $(M + 1)^+$. Analytical data for **12**: ^{1}H-NMR δ(DMSO-d_6) 1.82 and 2.20 (s, 3H each, CH_3COO- and CH_3CON-), 4.05 (dd, J = 7.1 and 12.2, 1H, $AcOCH_2CH(CF_3)O$-), 4.28 (dd, J = 3.3 and 12.2, 1H, $AcOCH_2CH(CF_3)O$-), 4.85 (m, 1H, $AcOCH_2CH(CF_3)O$-), 5.82 (d, 1H, J = 11.3, -NCH_2O-), 5.93 (d, 1H, J = 11.3, -NCH_2O-), 8.47 (s, 1H, H-8), 11.68 and 12.23 (br s, 1H each, AcNH and H-1); ^{19}F-NMR δ (DMSO-d_6) 118.29 (d, J = 5.9); CIMS *m/z* 378 $(M + 1)^+$.

A solution of **11** (100 mg, 0.27 mmol) in MeOH saturated with NH_3 (10 mL) was stirred at rt for 6 h. A white precipitate appeared. Et_2O was added and after filtration, compound **13** (60 mg, 20 mmol, Y = 76%) was obtained as a white solid. An analytical

sample was prepared by crystallization from MeOH-Et_2O to afford pure **13** as a white solid: mp 275-280 °C; ^{1}H-NMR δ (DMSO-d_6) 3.44 (m, 1H, HOCH_2CH(CF_3)O-), 3.61 (m, 1H, HOCH_2CH(CF_3)O-), 4.40 (m, 1H, HOCH_2CH(CF_3)O-), 5.20 (t, J = 5.7, 1H, OH), 5.55 (br s, 2H, NH_2), 7.88 (s, 1H, H-8), 10.69 (br s, 1H, H-1); ^{19}F-NMR δ (DMSO-d_6) 118.93 (d, J = 9.9); CIMS m/z 294 (M + 1)$^+$.

Anal. Calcd. for $C_9H_{10}F_3N_5O_3$•0.5H_2O: C, 35.77; H, 3.67; N, 23.17. Found: C, 35.80; H, 3.88; N, 23.28.

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