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ASYMMETRIC SYNTHESIS OF ENANTIOMERICALLY PURE 4'-FLUOROALKYL-2',3'-DIDEOXY NUCLEOSIDES

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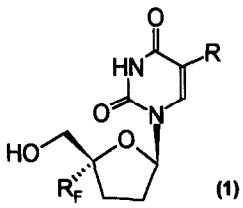
Abstract: Elaboration of 2-(fluoromethyl)-2-[(4-methylphenylsulphinyl)methyl] oxirane (**5**), deriving from p-tolylmethyl sulphoxide (**2**), ethyl fluoroacetate (**3**) and diazomethane, to 4'-fluoromethyl lactol (**10**) followed by condensation with the activated thymine and reductive debenzylation allowed the obtainment of 4'-fluoromethyl-2',3'-dideoxythymidine (**1**).

Nucleoside analogs are one class of potentially useful molecules used against HIV[1] and, although progress had been made in the search for chemoterapeutic agents against AIDS, the efforts are being continued and intensified. Since the discovery of AZT as an effective agent against the virus, mainly 2',3'-dideoxynucleoside analogs, which were assumed to be targeted at the reverse transcriptase step of HIV replication, were synthesized and tested[2]. More recently also several unusual types of nucleosides were synthesized and some of them have shown a potent activity as HIV-inhibitors, although through different mechanisms of action[3].

As a part of a program of developing an asymmetric approach to complex fluorosubstituted molecules[4] such as fluorosubstituted sugars, nucleoside analogs and alcaloids, we envisaged a unified synthetic strategy based upon the stereocontrolled assembly of small fluorinated molecules with chiral sulphoxides, followed by appropriate elaboration of the sulphinyl bearing carbon.

Herein we present a strategy aimed to the asymmetric synthesis of title compounds by means of this "fluorinated sulphoxide chiron" route.



(1)

In this contest a particularly attractive strategy for the asymmetric synthesis of 4'-fluoroalkyl substituted 2',3'-dideoxynucleosides of general formula (**1**) involves: a) the stereocontrolled building up of the C3 synthon (**5**) containing C-3', C-4' and C-5' carbon atoms and the fluoroalkyl group linked to C-4', described on Scheme1,

b) the construction of the glycosyl portion of target molecules by adding C-2' and C-1' atoms and c) the condensation of base portion as shown on Scheme 2.

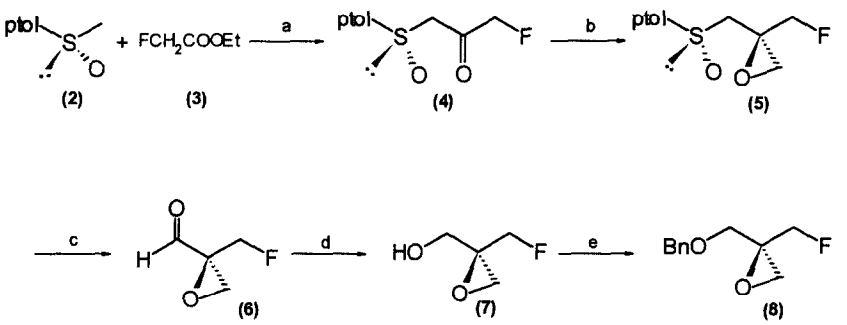
The key intermediate for the preparation of the 4'-monofluoromethyl-2',3'-dideoxythymidine **(1a)** was (−)-2-benzyloxymethyl-2-fluoromethyloxirane **(8)** conveniently prepared in optically pure form in five steps from p-tolylmethyl sulphoxide **(2)**, ethyl fluoroacetate **(3)** and diazomethane by a procedure already described for the enantiomer[5].

Acylation of commercially available (−)-(S)-p-tolylmethyl sulphoxide with ethyl fluroacetate gave (−)-(S)-1-fluoro-3-p-tolylsulphinyl-2-propanone **(4)** in 90% yield which, upon reaction with ethereal diazomethane, afforded the corresponding oxiranes **(5)** in 80% yield and in 7:3 (2R:2S) diastereoisomeric ratio The desired isomer (2R)-5 was isolated in optically pure form after several crystallizations from isopropylether.

A Pummerer rearrangement, performed under strictly controlled conditions with trifluoroacetic anhydride in acetonitrile in the presence of *sym*-collidine afforded, after hydrolysis of the p-tolylthiotrifluoroacetoxy intermediate by mercuric salts, the epoxy aldehyde **(6)** which was reduced with sodium borohydride to give the corresponding primary alcohol **(7)** in 50% overall yield from **(5)**.

The corresponding benzyl protected derivative **(8)**[6] was obtained in 85% yield by the action of benzyl bromide in THF in the presence of sodium hydride.

SCHEME 1



a) LDA, THF, -78°C; b) i, CH_2N_2, MeOH, 0°C; ii, fractional crystallization; c) i, $(CF_3CO)_2O$, s-collidine, CH_3CN, -10°C; ii, $HgCl_2$, -10°C; d) $NaBH_4$, CH_3CN, 0°C; e) NaH, BnBr, THF, 0°C

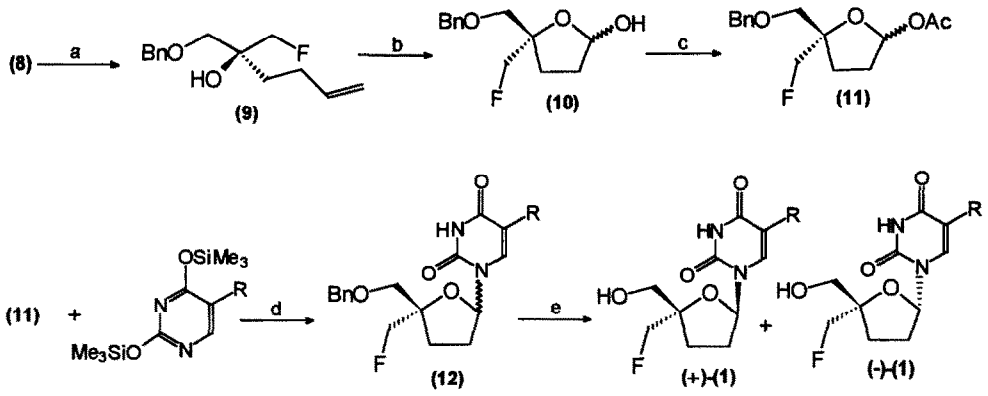
Addition of allylmagnesium chloride to the oxirane **(8)** proceeded with good yield and very high regioselectivity to give 1-O-benzyl-2-fluoromethyl-5-hexen-1,2-diol **(9)** in 88% yield. Such olefin was oxidized to the corresponding 1-pentanal, which was isolated in 75% yield as lactolic form **(10)** by using an excess of $NaIO_4$ in the presence of catalytic amounts of $RuCl_3.nH_2O$. Minor quantities (15%) of the corresponding lactone were separated by flash chromatography and reduced back to the lactol by DIBAL-H .

On the other hand, submission of **(9)** to osmilation conditions ($NaIO_4$, 10% OsO_4) resulted in the formation of mixtures reacher in the lactone .

Acetylation of **(10)** with acetic anhydride in pyridine gave the intermediate **(11)** suitably functionalized and sufficiently reactive for condensation with silylated thymine.

The coupling was performed in the presence of trimethylsilyl triflate as catalyst in methylene chloride and the 5'-O-benzyl protected nucleosides **(12)** were obtained in 95% yield as a nearly 1 to 1 mixture of anomers which were deprotected by hydrogen in ethanol in the presence of palladium on charcoal (10% Pd). Flash chromatographic separation of the free alcohols allowed to obtain the α and β-anomers 4'-fluoromethyl-2',3'-dideoxythymidine [**(1)**; R_F=CH_2F][7] in optically pure form.

SCHEME 2



a) MgCl , THF, 0°C; b) $NaIO_4$, $RuCl_3.nH_2O$ (cat.), CH_3CN, CCl_4, H_2O, rt; c) Ac_2O, Py, rt; d) Me_3SiOTf, CH_2Cl_2, rt; e) H_2, 10% Pd/C, 95% EtOH

The syntheses of some other 4'-fluoroalkyl derivatives [**(1)**; R_F=CHF_2, CF_3, CF_2CF_3; R=Me, F] were accomplished or are underway following the same synthetic scheme. By using, instead of fluorinated esters, the corresponding alkoxy, chloro and bromo derivatives[8], the present methodology should provide a convenient access to many other nucleoside analogs with a great deal of structural diversity at C-4' position.

The stereochemistry of C1' was determined by 2D NOESY experiments on both (+) and (-) 4'-fluoromethyl-2',3'-dideoxythymidine [**(1)**; R_F = CH_2F, R = CH_3]. In one case a diagnostic cross peak due to dipolar coupling was found between the protons of the CH_2OH moiety and the anomeric proton H1', consistent with a *syn* relationship between them as in the α anomer. In the other compound the anomeric proton showed dipolar coupling with protons of the CH_2F group but not with those of CH_2OH, assessing an *anti* relationship between the fluoromethyl group and the anomeric proton, as in the β anomer.

The cytotoxicity of the α and β anomers of **1** was determined by the MTT assay (x) in MT-4 cells together with their ability to prevent the HIV-1-induced cytopathic effect. At 100 μg/ml, neither compound showed significant cytotoxicity or antiviral activity.

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6. $[\alpha]^{20}_D$ - 8.8 (c 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, reference internal TMS) δ: 2.84 (m, 2H, CH_2O), 3.66 (dd, 1H, CH_aOAr), 3,70 (dd, 1H, CH_bOAr), 4.53 (dd, 1H, CH_aF, $^2J_{H\text{-}F}$ = 47.5), 4.60 (dd, 1H, CH_bF), 4.56 (d, 1H, CH_aAr), 4.60 (d, 1H, CH_bAr), 7.25-7.40 (m, 5H, ArH); F: -232.0 ppm.
7. β anomer: T.L.C. R_f 0.35 (6:4 Chloroform/Acetone); $[\alpha]^{20}_D$ + 16.9, $[\alpha]^{20}_{365}$ + 80.6 (c 1.19 $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, reference internal TMS) δ: 8.57 (br. s, 1, NH), 7.35 (q, 1, J=1.3 Hz, H6), 6.07 (dd, 1, J_1=5.9 Hz, J_2=6.8 Hz, H1'), 4.41 (A part of an ABX system, 1, $J_{H\text{-}H}$=9.6 Hz, $J_{H\text{-}F}$=47.4 Hz, C*H*H'F), 4.38 (B part of an ABX system, 1, $J_{H\text{-}H}$=9.6 Hz, $J_{H\text{-}F}$=47.1 Hz, CH*H*'F), 3.80 (A part of an AB system, 1, J=11.2 Hz, C*H*H'OH), 3.69 (B part of an AB system, 1, J=11.2 Hz, CH*H*'OH), 2.52-2.42 (m, 1, H2'α or β), 2.28-2.14 (m, 2, H2'β or α and H3'α or β), 2.06-1.98 (m, 1, H3'β or α), 1.90 (d, 1, J=1.3 Hz, Me5). ^{19}F NMR (235 MHz, $CDCl_3$, reference internal C_6F_6 at δ -162.90 ppm) δ:-230.55 (t, 1, J=47 Hz).
α anomer: T.L.C. R_f 0.30 (6:4 Chloroform/Acetone); $[\alpha]^{20}_D$ -0.7, $[\alpha]^{20}_{365}$ - 43.0 (c 0.913 $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, reference internal TMS) δ: 8.47 (br. s, 1, NH), 7.35 (q, 1, J=1.5 Hz, H6), 6.24 (dd, 1, J_1=6.4 Hz, J_2=6 7 Hz, H1'), 4.64 (dd, 1, $J_{H\text{-}H}$=10.1Hz, $J_{H\text{-}F}$=48.1 Hz, C*H*H'F), 4.47 (dd, 1, $J_{H\text{-}H}$=10.1Hz, $J_{H\text{-}F}$=47.1 Hz, CH*H*'F), 3.56 (s, 2, CH_2OH), 2.46-2.36 (m, 1, H2'α or β), 2.25-2.15 (m, 1, H3'α or β), 2.08-1.95 (m, 2, H3'β or α and H2'β or α) 1.92 (d, 1, J=1.5 Hz, Me5). ^{19}F NMR (235 MHz, $CDCl_3$, reference internal C_6F_6 at δ:-162.90 ppm) δ: -234.55 (t, 1, J=47 Hz).
8. For the synthesis of α-bromo and chloro, α'-sulphinyl ketones: Bravo, P., Resnati, G. *Tetrahedron Lett* 1985, *26*, 5601; for the alkoxy ones: Arnone, A., Bravo, P.; Frigerio, M.; Viani, F. results to be published.

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