Tetrahedron Letters, Vol. 34, No. 48, pp. 7771-7772, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

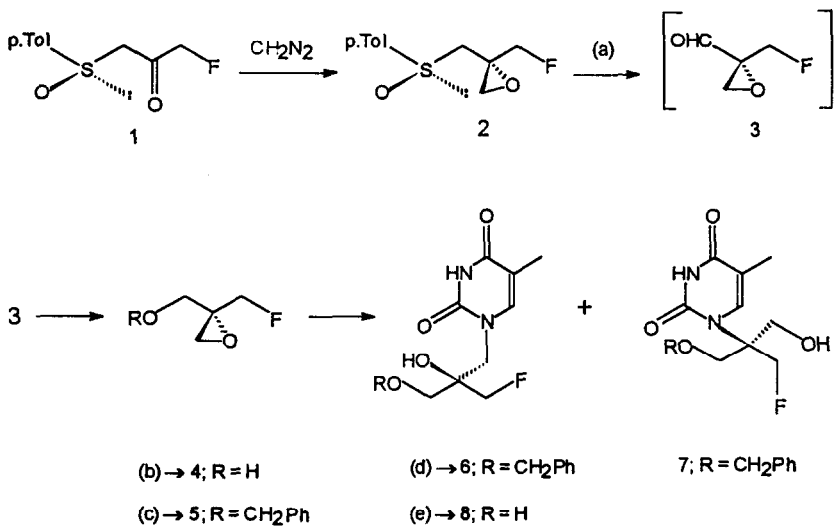
OPTICALLY PURE AND FLUORO SUBSTITUTED CARBOACYCLIC NUCLEOSIDE ANALOGUES

Pierfrancesco Bravo*, Massimo Frigerio, Vadim Soloshonok and FiorenzaViani

CNR - Centro di Studio per le Sostanze Organiche Naturali - Dipartimento di Chimica del Politecnico di Milano, via Mancinelli 7, I-20131 Milano, Italy.

Abstract: Fluorinated analogues of carboacyclic nucleosides are obtained in optically pure form starting from homochiral epoxides through nitrogen nucleophilic opening of the oxirane ring.

Our recent observation[1] of transfer of methylene from diazomethane to the carbonyl of 1-fluoro-3-p-tolylsulphinyl-acetone **1**, occurring with high chemo- and enantio-selectivity, furnished a new versatile fluorinated chiron **2**. We are now developing from chiron **2** a synthetic approach to new nucleoside analogs based on elaboration of sulphinyl to hydroxyl group and on nucleophylic attack of activated purinic and pyrimidinic bases on the epoxide ring[2]. Here are described our preliminary results as shown in the scheme.



(b) → **4**; R = H
(c) → **5**; R = CH_2Ph
(d) → **6**; R = CH_2Ph
(e) → **8**; R = H
7; R = CH_2Ph

a) $(CF_3CO)_2O$, 2,4,6-trimethyl pyridine, CH_3CN, -20°C, $HgCl_2$, K_2CO_3, room temperature; b) $NaBH_4$, 0°C; c) NaH, BnBr, 0°C; d) thymine, HMDS, $(NH_4)_2SO_4$, reflux, $Hg(CN)_2$, C_6H_6, reflux; e) H_2, Pd/C (10%), ethanol, 3 atm, room temperature.

The arylsulphinyl group was substituted by an hydroxyl group through a Pummerer rearrangement promoted by trifluoroacetic anhydride and 2,4,6-trimethylpyridine in acetonitrile, hydrolysis of the labile arylthio-trifluoroacethoxy intermediate to the correspondig aldehyde **3** with mercury chloride, and reduction of the formyl group with sodium boro hydride. The primary alcohol **4** was reacted in situ with benzyl bromide in dimethylformamide at 0°C in the presence of sodium hydride and optically pure 2-benzyloxymethyl-2-fluoromethyl oxirane **5**[3] was obtained in 60% overall yield from **2**. A one pot epoxide-base condensation of **5** with thymine was accomplished[4] and carboacyclic benzyl protected fluorinated nucleosides **6** and **7** were isolated in 70% yield and in a 5 to 1 relative ratio. The removal of the protecting group was performed in a Parr apparatus under hydrogen pressure, in absolute ethanol as solvent and palladium/charcoal activited (10%) as catalyst and final product **8**[5] was isolated in 95% yield from **6**. The compounds structure was confirmed using ^{1}H and ^{19}F NMR spectra.

This synthetic strategy is appealing since it enables us to make use of C-4 synthons similar to **5** for the construction of different members of fluorinated carboacyclic nucleoside analogues. In fact, difluoro-, difluorochloro-, and trifluoromethyl, along with pentafluoromethyl carboacyclic derivatives, analogues to monofluoromethyl **6** were obtained in fair yields[6].

Detailed analytical data and antiviral activity results will be given, for all compounds, in a future paper.

Acknowledgment - National Research Council (CNR) - Targeted Project "Prevention and Control Disease Factors" (104299/41/4303100/01); Subproject "9" is gratefully acknowledged for financial support and CNR - Comitato per le Ricerche Tecnologiche is gratefully acknowledged for a Visiting Fellowship to dr. Vadim Soloshonok on leave from Ukrainian Academy of Sciences, Kiev.

References and Notes

1. Arnone A., Bravo P., Cavicchio G., Frigerio M., Marchetti V., Viani F., Zappalà C., *Tetrahedron Lett.*, **1992**, *33*, 5609-5612.
2. a) Baumgartner H., Marshner C., Pucher R., and Griengl M., *Tetrahedron Lett*, **1991**, 32, 611-614. b) Ramesh K., Wolfe M.S., Lee Y.,Velde D.V., and Borchardt R.T., *J.Org.Chem*, **1992**, 57, 5861-5868. c) Aguilar J.G., Gelpi M.E. , Cadenas R.A., *J. Heterocyclic Chem.*, **1992**, *29*, 401-405.
3. Yellowish oil; $[\alpha]^{20}_{D}$ + 8.8° (c 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 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, $^{2}J_{H-F}$ = 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); ^{19}F : - 232.0 ppm.
4. Bravo P., Resnati G., Viani F., *Tetrahedron*, **1993**, *49*, 713-720.
5. R_F 0.35 (ethyl acetate/methanol 98:2), m.p. 172-174°C (from diisopropylether), $[\alpha]_D^{20}$ - 21.0° (c 0.5, acetone); ^{1}H NMR (CH_3OH) δ: 1.87 (d, 3H, CH_3), 3.44 (dd, 1H, CH_aOH), 3.49 (dd, 1H, CH_bOH), 3.90 (brs, 2H, CH_2N), 4.36 (dd, 1H, CH_aF, $^{2}J_{H-F}$ =47.5 Hz), 4.42 (dd, 1H, CH_bF), 7.44 (d, 1H, CH=C); ^{19}F : - 233.9 ppm.
6. ^{19}F NMR ($CDCl_3$) signals (ppm) of benzyl protected products are given: CHF_2 / -133.5 (dd, $^{2}J_{H-F}$ = 54, $^{2}J_{F-F}$ = 285 Hz), -137.0 (dd, $^{2}J_{H-F}$ = 54, $^{2}J_{F-F}$ = 285 Hz); CF_3 / -81.9 (s); CF_2CF_3 / -80.7 (s), -124.2 (s); CF_2Cl/ -61.0. (s).

(Received in UK 28 July 1993; accepted 24 September 1993)