Synthesis of 2′-Deoxy-5-monofluoromethyluridine (FTDR) and 2′-Deoxy-5-difluoromethyluridine (F_2TDR)

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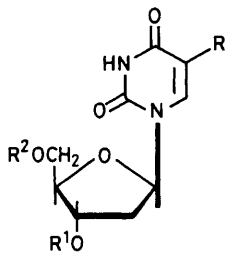
The synthesis of potential anticancer and antitumour nucleosides, 2′-deoxy-5-monofluoromethyluridine (FTDR) and 2′-deoxy-5-difluoromethyluridine (F_2TDR) was achieved in four steps from thymidine including monosilylation with t-butyldiphenylsilyl chloride, photochemical bromination, followed by AgF treatment and subsequent desilylation.

The synthesis of 2′-deoxyuridine derivatives containing a partially fluorinated methyl group at C-5 has been the subject of extensive studies[1] since the discovery of the antitumour and antiviral activities of 2′-deoxy-5-trifluoromethyluridine or F_3TDR (**1**; $R^1 = R^2 = H$).[2] 5-Difluoromethyluracil has been prepared and reported to be extremely labile in aqueous media.[1] All attempts to synthesize 5-monofluoromethyluracil have failed due to instability of the product.[1] It is quite conceivable that the dissociation of H-1 would assist release of fluoride ion from a 5-fluoromethyluracil base. Nucleosides of 5-monofluoromethyluracil or 5-difluoromethyluracil, which do not bear a dissociable proton at N-1, may be reasonably



(1) R = CF_3 (F_3TDR; $R^1 = R^2 = H$)
(2) R = CH_2F (FTDR; $R^1 = R^2 = H$)
(3) R = CHF_2 (F_2TDR; $R^1 = R^2 = H$)
(4) R = Me
(5) R = CH_2Br
(6) R = $CHBr_2$
a; R^1 = R^2 = Acetyl
b; R^1 = H, R^2 = $SiPh_2Bu^t$

stable although the aglycons themselves are quite susceptible to hydrolysis. We therefore undertook synthesis of 2′-deoxy-5-monofluoromethyluridine (**2**, $R^1 = R^2 = H$) (FTDR) and 2′-deoxy-5-difluoromethyluridine (**3**, $R^1 = R^2 = H$) (F_2TDR) from a preformed nucleoside.

Di-*O*-acetylthymidine (**4a**) was converted into the bromomethyl derivative (**5a**) or (**6a**) by photochemical bromination according to the Baerwolff–Langen procedure.[3] Treatment of crude (**5a**) with excess of AgF in MeCN for 15 minutes at room temperature afforded di-*O*-acetyl-2′-deoxy-5-monofluoromethyluridine (**2a**) which was purified on a silica gel column (n-hexane–EtOAc 1:1 to 1:2) and crystallized from CH_2Cl_2–Et_2O–petroleum ether, m.p. 24—27 °C (32% yield). The product was analysed correctly for $C_{14}H_{17}FN_2O_7$, and showed a double doublet for CH_2F at δ 5.19 ($J_{H,F}$ = 47.48, $J_{H,H}$ = 3.29 Hz). In a similar manner, (**3a**) was obtained as a colourless foam from (**6a**); the CHF_2 signal appeared as a triple doublet at δ 6.69 ($J_{H,F}$ = 54.96, $J_{H,6}$ = 2.56 Hz). Attempts at de-*O*-acetylation of (**2a**) in base resulted in complete conversion into 2′-deoxy-5-hydroxymethyluridine. Deacetylation in acid was always accompanied by partial solvolysis of the 5-fluoromethyl group, and isolation of FTDR in a pure state was very difficult. FTDR, m.p. 140 °C (decomp.), was prepared from (**2b**) by desilylation with Bu^n_4NF in tetrahydrofuran (THF).

The t-butyldiphenylsilyl protecting group, however, was found to be suitable for preparation of the unprotected 5-fluoromethyluracil nucleosides, FTDR and F_2TDR, since it is resistant to HBr during the bromination step and is readily removable with Bu^n_4NF in THF. Selective silylation[4] of thymidine with t-butyldiphenylsilyl chloride in pyridine afforded 5′-*O*-t-butyldiphenylsilylthymidine (**4b**), m.p. 170—171 °C, which was brominated under the Baerwolff–Langen conditions. The crude monobromide (**5b**) was directly treated with AgF in MeCN, and the monofluoromethyl product (**2b**) was isolated in 38% yield after preparative t.l.c. purification (n-hexane–EtOAc 1:3) followed by crystallization from CH_2Cl_2–n-hexane; m.p. 129—131 °C, a doublet for CH_2F appeared at δ 4.80 ($J_{H,F}$ = 47.92 Hz).

In a similar manner, the protected difluoromethyluracil nucleoside (**3b**), m.p. 156—158 °C, and F_2TDR, m.p. 159—160 °C, were also prepared. Thus, for the first time the synthesis of thymidine analogues containing a partially fluorinated methyl group has been achieved.

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