Synthesis of acyclic 2-*O*-alkyl analogues of 3-dideoxythymidine

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Nucleoside coupling of **2** with sodium salt of **1a–f** gave **3a–f** which were oxidised and hydrolysed to afford **4a–f**.

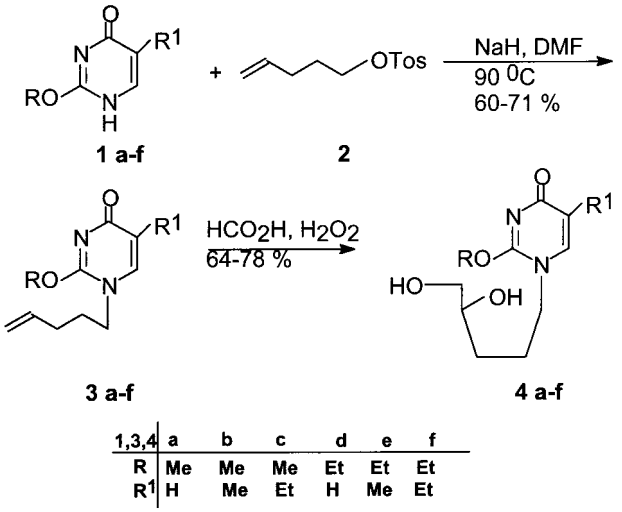
Keywords: acyclic 2-*O*-alkyl analogues, 3-dideoxythymidine

The advent of acquired immunodeficiency syndrome (AIDS) followed by the identification of the retrovirus human immunodeficiency virus (HIV), as the causative agent of AIDS,[1] has increased the interest in compounds that can block the replication of retroviruses. In order to obtain an improved selectivity, many nucleoside analogues have been designed and synthesised by modifying of the carbohydrate moiety[2] and/or the base unit.[3]

In this context, we were successful in synthesising a series of *O*[2]-alkylated 2-uracil nucleoside derivatives[4] in order to find new active compounds with less prominent side effects than those observed for AZT, FLT and ddC.[5] The present paper deals with the synthesis of 4,5-dihydroxypentyl derivatives of 2-*O*-alkyluracils[6] which are new acyclic analogues of 2′,3′-dideoxycytidine (ddC)[7] and 3′-dideoxythymidine (ddThd)[8], known to be active against HIV.

4-Pentenyl *p*-toluenesulfonate (**2**),[9,10] was reacted with the sodium salts of 2-*O*-alkyluracils (**1a–f**) in DMF to give 1-(4-pentenyl)-2-*O*-alkyluracils (**3a–f**) according to the protocol described by Sasaki *et al*.[11] Compounds **3a–f** were then oxidised with peroxyformic acid, which was prepared *in situ* from formic acid and hydrogen peroxide.[12] The resulting formyloxy hydroxy compounds were hydrolysed in basic medium to give **4a–f** in 64–78% yield.

The acyclic 2-*O*-alkyl analogues of ddThd **4a–f** are currently undergoing biological evaluation.



1,3,4	a	b	c	d	e	f
R	Me	Me	Me	Et	Et	Et
R1	H	Me	Et	H	Me	Et

Scheme 2

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Techniques used ^{1}H and ^{13}C NMR including 2D NMR (^{1}H-^{1}H, ^{1}H-^{13}C COSY) and EIMS.

Schemes: 2

References: 12

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References

1 R.C. Gallo, S.Z. Salahuddin, M. Popovic, G.M. Shearer, M. Kaplan, B.F. Haynes, T.J. Palker, R. Redfield, J. Olesky, B. Safari, G. White, P. Foster and P. D Markham. *Science* 1984, **224**, 500.
2 P. Herdewijin and E. DeClercq, *Design of Anti-AIDS Drugs; DeClercq, E., Editor; Pharmacochemistry Library* 1990, Vol. 14, pp 141–174.
3 M. Nasr, C. Litterst and McGowan *Antiviral Res*. 1990, **14**, 125.
4 H.M. Abdel-Bary,; A.A.-H. Abdel-Rahman, E.B. Pedersen and C. Nielsen, *Monatsh. Chem.* 1995, **126**, 811; I.F. Zeid, A.A.-H. Abdel-Rahman, *J. Chem. Res.*, 1999, *(S)*, 192 ; *(M)*, 977.
5 S. Border, *Pharm. Technol.* 1988, **12**, 24.
6 G.E. Hilbert and E.F. Jansen, *J. Am. Chem. Soc.*, 1935, **57**, 552.
7 E. DeClercq, *Adv. Drug Res.* 1988, **17**, 1.
8 C. Schou, E.B. Pedersen and C. Nielsen, *Acta Chem. Scand.* 1993, **47**, 889.
9 L.A. Brooks and H.R. Synder, *Org. Synth. Coll.* **3**, 698.
10 M. Cerny, *Collect. Czech. Chem. Commun.* 1977, **42**, 3069.
11 T. Sasaki, K. Minamoto, T. Suzuki and S. Yamashita, *Tetrahedron* 1980, **36**, 865.
12 P. Roveri, V. Caurini and R. Gatti, *Il Farmaco-Ed. Sci.* 1984, **39**, 346.

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