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A NEW SYNTHESIS OF (±)-CARBOCYCLIC 2'-DEOXYURIDINES

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ABSTRACT: (±)-Carbocyclic 2'-deoxyuridine (1a) and its (E)-5-(2-bromovinyl) derivative (1b) have been synthesized in 8 steps from (1α,3α,5α)-6-oxabicyclo[3.1.0]hexan-3-ol (2).

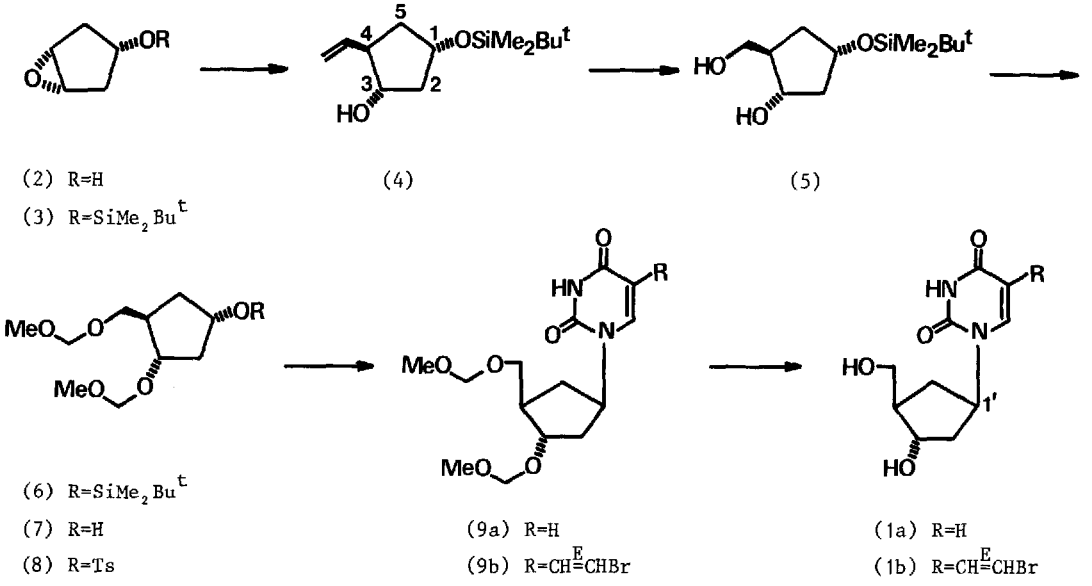
Carbocyclic analogues of nucleosides are attracting increasing attention as potential antiviral agents. For example, cyclaradine (carbocyclic arabinofuranosyladenine) inhibits the replication of herpes simplex virus (HSV) types 1 and 2, and its 5'-methoxyacetate prodrug exhibits significant efficacy in the treatment of genital herpes in guinea pigs[1]. Carbocyclic 5-halo[2]- and (E)-5-(2-bromovinyl)[3,4]-2'-deoxyuridines also possess good activity in vitro against HSV-1. The latter class of compounds are prepared from (±)-carbocyclic 2'-deoxyuridine (1a) or its 3',5'-diacetate derivative. However, the existing synthesis of (1a) is non-regiospecific and requires separation of positional isomers at an early stage of the synthetic sequence[5,6]. Furthermore, the uracil ring is constructed stepwise onto (±)-cis-4-amino-trans-2-hydroxycyclopentanemethanol[6]. An alternative approach has involved a multistep deoxygenation sequence starting from (±)-carbocyclic uridine[4].

We now describe a new synthesis of (1a) and its (E)-5-(2-bromovinyl) derivative (1b) (C-BVDU) which circumvents the above shortcomings. The key feature of this route is the direct introduction of the 2,4(1H,3H)-pyrimidinedione moiety via nucleophilic displacement at an appropriately functionalized cyclopentyl tosylate (8).

The easily synthesized epoxyalcohol (2)[7] was converted to the t-butyldimethylsilyl ether (3) (95% yield) using t-butyldimethylsilyl chloride and imidazole in DMF. Cuprous iodide catalysed ring-opening of (3) with vinylmagnesium bromide in THF (-30°,15min then 0°,2h) afforded the alcohol (4) [79% yield, ^{1}H NMR($CDCl_3$) δ2.80(m,4-H), 3.88(m,3-H), 4.36(m,1-H), 5.00(m,CH_2=CH), 5.72 (ddd,J=18,10,7Hz;CH_2=CH)], thereby introducing the 3- and 4-substituents with the correct relative stereochemistry. Ozonolysis of (4) in dichloromethane-methanol (-70°), followed by sodium borohydride work-up, generated the diol (5) [78% yield, ^{1}H NMR($CDCl_3$) δ4.37(m,1-H), 4.04(m,3-H), 3.46, 3.64(ABX,CH_2OH)]. Subsequent protection of the two hydroxyl groups was accomplished with methoxymethyl chloride and diisopropylethylamine in dichloromethane to give compound (6) in 88% yield. Removal of the t-butyldimethylsilyl group of (6) using tetra-n-butylammonium fluoride in THF (RT,4h)[8] gave the secondary alcohol (7) (97% yield). Treatment of (7) with p-toluenesulphonyl chloride and pyridine gave the key intermediate tosylate (8) [(70% yield), 35% overall yield from (2)] which contains the requisite functionality in the

correct stereochemical configuration to allow completion of the synthesis. Nucleophilic displacement of the tosylate group with uracil (K_2CO_3,DMSO,90°,15h) gave the protected β-configuration carbocyclic nucleoside (9a) (44-48% yield), which was subjected to acid catalysed de-etherification (p-TsOH, MeOH, reflux, 1h) to provide (±)-carbocyclic 2'-deoxyuridine (1a) [90% yield, m.p. 159-162° (lit.[6] m.p. 160-163°); UV: λmax 269nm (H_2O), 269(0.1N HCl), 266(0.1N NaOH) confirms N-1 alkylation]. Similarly, reaction of (8) with (E)-5-(2-bromovinyl)uracil (K_2CO_3,DMSO,room temp.,48h) gave (9b) (43% yield), de-blocking of which (p-TsOH,MeOH,reflux,2h) afforded C-BVDU (1b), identical to the material prepared previously[3,9].

The tosylate (8) is a potentially versatile intermediate which should allow the direct introduction of other heterocyclic bases, thereby providing access to a range of carbocyclic 2'-deoxyribonucleosides[10].



(2) R=H
(3) R=$SiMe_2Bu^t$
(4)
(5)
(6) R=$SiMe_2Bu^t$
(7) R=H
(8) R=Ts
(9a) R=H
(9b) R=$CH\overset{E}{=}CHBr$
(1a) R=H
(1b) R=$CH\overset{E}{=}CHBr$

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9. All new compounds have analytical and n.m.r. spectral data consistent with the assigned structures. C-1'configuration of (1a) and (1b) was confirmed by ^1H n.m.r. spectroscopy. For a full discussion see R. C. Cookson, P. J. Dudfield and G. Klinkert, J. Chem. Soc., Perkin Trans. 1, in press.
10. Since the completion of our work C. K. H. Tseng and V. E. Marquez, [Tetrahedron Letters, 26, 3669, (1985)] have described an analogous approach to Neplanocins.

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