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A NOVEL APPROACH TO CARBOCYCLIC ANALOGUES OF NUCLEOSIDES

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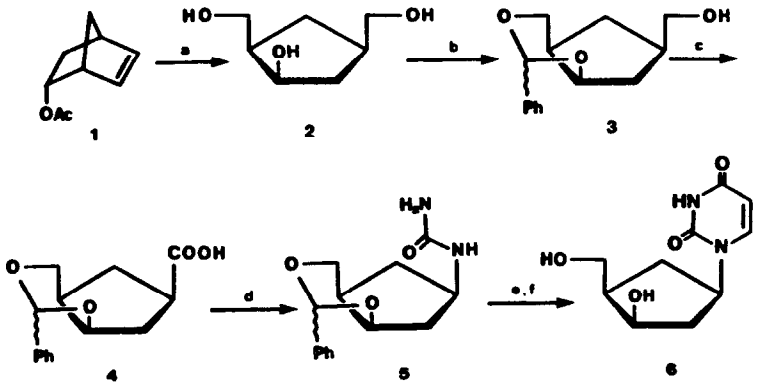
Abstract: (±)-1-[(1α,3α,4α)-3-Hydroxy-4-hydroxymethylcyclopentyl]-(1*H*,3*H*)-pyrimidin-2,4-dione (**6**) was synthesized starting from *endo*-5-norbornen-2-yl acetate via the urea derivative **5** in 32% overall yield.

Carbocyclic analogues of nucleosides, the sugar moiety of which is replaced by a cyclopentane ring, have been the object of a number of synthetic efforts[1-3] and their interesting biological properties[4] such as antiviral, antitumor and antimicrobial [5] activity have generated considerable interest in this field. Yet, only a few synthetic carbocyclic pyrimidine and purine nucleoside analogues have been obtained enantiomerically pure by a chemoenzymatic approach[3], by multistep synthesis[3,5] or by enzymatic resolution in case of the monophosphate of racemic aristeromycin[7]. Therefore, we developed a general synthetic strategy which should open an easy access to large quantities of enantiomerically pure carbocyclic nucleoside analogues.

Starting from *endo*-norbornenyl acetate **1**, which can be obtained in high enantiomeric purity by enzymatic resolution of the racemate using lipase from *Candida cylindracea*[8], a straightforward synthesis can be performed.



a, i: O_3/MeOH/-70°; ii: $LiAlH_4$; iii: aqueous $MgSO_4$ solution. b, Benzaldehyde dimethylacetal/HBF_4/rt. c, PDC/DMF/rt/6 h. d, i: Ethyl chloroformate/-40°C/30 min; ii: NaN_3/-10°C/30 min; iii: Curtius rearrangement in benzene/ 80°C/30 min; iv: NH_3(g). e, Ethoxyacryloyl chloride/pyridine/rt/24 h. f, 2 *N* H_2SO_4/95°C/2 h

(±)-(1α,3α,4α)-4-Hydroxycyclopentan-1,3-dimethanol **2**[10] (for all compounds only one enantiomer is given in the scheme) was obtained by ozonolysis of norbornenyl acetate **1** in methanol with subsequent reductive workup ($LiAlH_4$) of the crude methyl hydroperoxide in THF[11] at -30 °C in 93% yield. Acetalisation of **2** using benzaldehyde dimethylacetal/HBF_4[12] gave the protected compound **3** as an oil (80% yield)[13], which was converted into the carboxylic acid **4** by oxidation with pyridinium dichromate in dimethylformamide[14] (quant. yield). This acid was used in the following steps without purification.

Treatment of **4** with ethyl chloroformate and sodium azide followed by Curtius rearrangement in benzene and addition of gaseous ammonia to the intermediate isocyanate in a one pot procedure[8b] furnished the crystalline urea derivative **5** (58%, mp 165-166°C, 2-propanol)[15]. Conversion of **5** into the carbocyclic uridine analogue **6** was achieved by reaction with 2-ethoxyacryloyl chloride [16]. A subsequent deprotection and cyclisation step by heating with 2 *N* H_2SO_4 gave (±)-1-[(1α,3α,4α)-3-hydroxy-4-hydroxymethylcyclopentyl]-(1*H*,3*H*)-pyrimidin-2,4-dione (**6**)[17] (74% yield).

In summary, this synthesis has proved to be an efficient approach to carbocyclic nucleoside analogues and further investigations especially on enantiomerical pure compounds are currently being undertaken in our laboratory.

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