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SYNTHESIS OF NOVEL CYCLOPROPANE NUCLEOSIDE ANALOGUES

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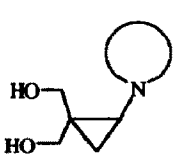
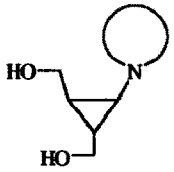
Abstract: The short syntheses of the (±)-1-cyano-2-(hydroxymethyl)cyclopropyl derivatives and the related (±)-2,3-methanobutyrolactone-2-yl derivatives of uracil, thymine and cytosine are described. The key step is the condensation of an N-cyanomethyl-pyrimidinedione base with epibromohydrin.

Carbocyclic nucleosides are an important source of new antiviral and anticancer agents. A variety of cyclopentane and cyclobutane analogues have been studied, some of which have potent antiviral activities.[1] Cyclopropane analogues present a particular interest: not only should they be resistant to hydrolases, like other carbocyclic nucleosides, but the reactivity of the strained three-membered ring presents the additional opportunity for enzyme inhibition through irreversible ring opening processes.[2] Very few cyclopropane nucleoside analogues have been reported so far, however: 2,2-bis(hydroxymethyl)cyclopropyl derivatives **A** have been reported for uracil,[3] adenine[3] and guanine,[4] while *cis* and *trans* 2,3-bis(hydroxymethyl)-cyclopropyl derivatives **B** of adenine, thymine and 5-fluorouracil have been prepared.[5]

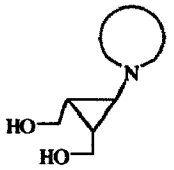
Previous work in this laboratory[6] has shown that simple aminoacetonitriles react with epibromohydrin in the presence of strong base to give 2-(hydroxymethyl)cyclopropyl derivatives. As an extension of this methodology, we envisaged a rapid access to cyclopropane nucleoside analogues of type **C**, starting from acetonitrile derivatives of nucleic bases. In this communication we disclose our initial findings for the pyrimidine base series.



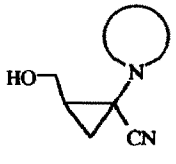
A



trans- **B**

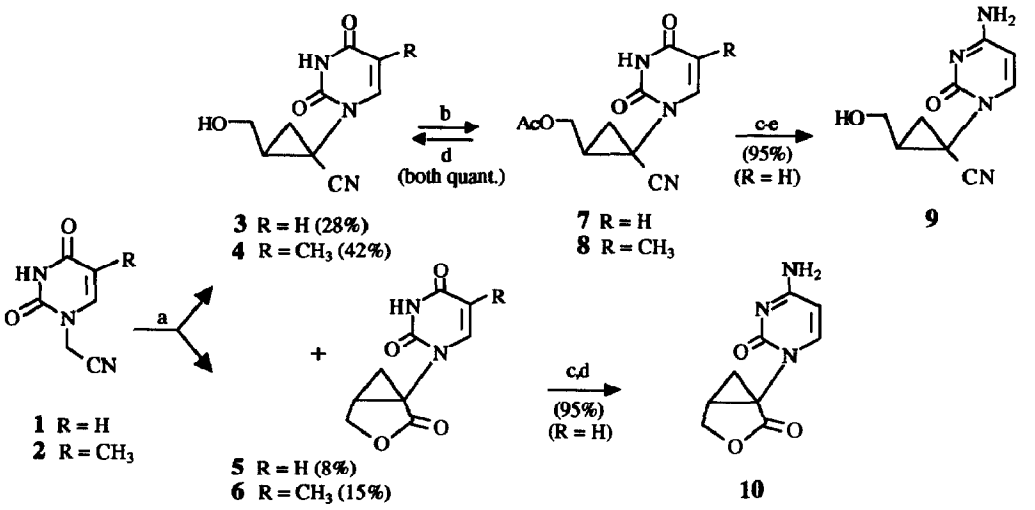


cis- **B**



C

1-(Cyanomethyl)uracil **1**[7] reacted with (±)-epibromohydrin in the presence of an excess of LDA-HMPA to give a mixture of *cis* and *trans* cyclopropanes **3** and **5** (Scheme).[8] Alkylation of the uracil N-3 was not observed. Separation of the two components was best achieved by first treating the mixture with acetyl chloride to esterify the primary alcohol selectively, followed by conventional chromatography (silica; EtOAc), which allowed isolation of **7** and **5** (28% and 8% of transformed **1**, respectively). The former was treated with ammonia to liberate alcohol **3**, and also served as an intermediate in the preparation of the cytosine analogue **9** in high yield using conventional procedures.[9] Likewise, the lactone **5** was transformed into cytosine derivative **10**. Analogous reactions starting from 1-(cyanomethyl)thymine **2** (prepared as for **1**) furnished alcohol **4** (42%) and lactone **6** (15%), separated after transformation of the former to ester **8**.



a: i) 5 equiv. LDA-HMPA, THF, -70°C; ii) (±)-epibromohydrin, -70°C; iii) H_3O^+
b: AcCl, pyridine; c: triazole, $POCl_3$, Et_3N, MeCN; d: NH_4OH; e: NH_3, MeOH

SCHEME

This short synthetic scheme provides a convenient access to novel cyclopropane nitrile and fused lactone nucleoside analogues. The consequences of the extra substituent at the C-1' centre lie in relatively unexplored territory, but interesting biological activities have been discovered for the few reported examples of quaternary C-1' furanose nucleosides.[10] The scope for development of other C-1' substituents through chemical transformation of the nitrile of **3**, **4** and **9** is under investigation. The biological activities of all new compounds will be reported in due course.

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