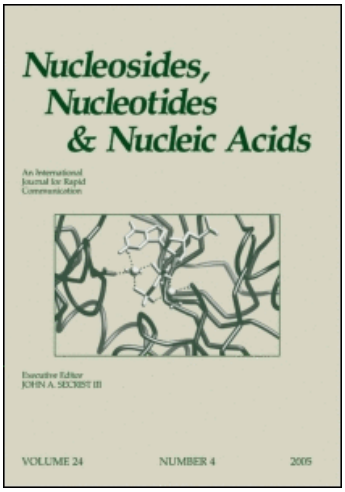

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

1,2-DISUBSTITUTED CYCLOHEXANE CARBOCYCLIC ANALOGUES OF NUCLEOSIDES

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Online publication date: 31 March 2001

To cite this Article Viña, D. , Santana, L. and Uriarte, E.(2001) '1,2-DISUBSTITUTED CYCLOHEXANE CARBOCYCLIC ANALOGUES OF NUCLEOSIDES', Nucleosides, Nucleotides and Nucleic Acids, 20: 4, 1363 — 1365
To link to this Article: DOI: 10.1081/NCN-100002556
URL: http://dx.doi.org/10.1081/NCN-100002556

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 20(4–7), 1363–1365 (2001)

1,2-DISUBSTITUTED CYCLOHEXANE CARBOCYCLIC ANALOGUES OF NUCLEOSIDES

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ABSTRACT

Several compounds of a new series of cyclohexane-based 1,2-disubstituted carbonucleoside analogues, were synthesized. The adenine and uridine derivatives, were prepared by construction of the heterocyclic base on the primary amino group of 2-aminocyclohexylmethanol, and the thymine derivative by condensation of 2-hydroxycyclohexylmethanol with thymine using the Mitsunobu reaction.

We previously reported on the synthesis of a series of 1,2-disubstituted cyclopentane-based carbocyclic nucleosides (OTCs). For further evaluation of the pharmacological effects of 1,2-disubstitution in nucleoside analogues, we have now obtained the adenine (**1**), uracil (**2**), and thymine (**3**) members of the homologous cyclohexane series. These compounds were synthesized using the two most useful methods for preparing nucleoside analogues: either by constructing the heterocyclic base on the appropriate substrate, or by condensation of the heterocyclic base with the sugar or the ring taking its place.

The adenine and uracil derivatives (**1** and **2**) were prepared in racemic *cis* form in 42% and 25% overall yields respectively starting from (±)-*cis*-2-aminocyclohexylmethanol and constructing the purine (1) or pyrimidine (2) base on the primary amino group as shown in Scheme 1. The starting aminoalcohol was prepared in three steps from cyclohexene by treatment with chlorosulfonylisocyanate, hydrolysis of the resulting lactam, and final reduction (3) (overall yield 25%).

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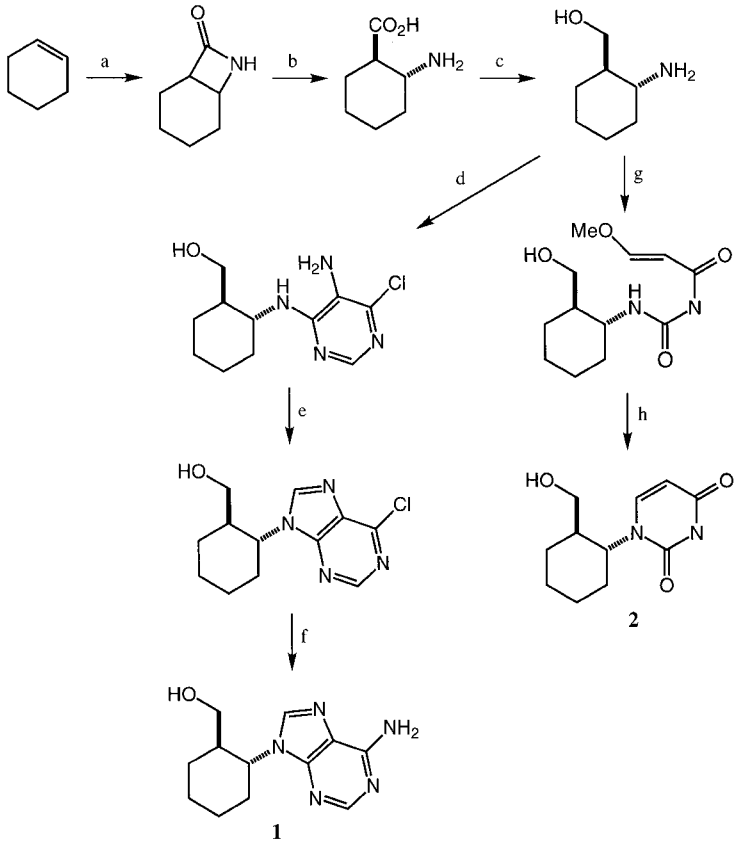
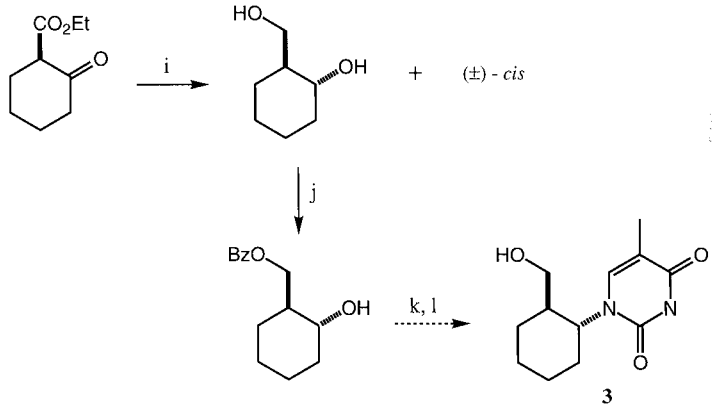


a) Chlorosulfonylisocyanate; b) HCl; c) $LiAlH_4$; d) 5-amino-4,6-dichloropyrimidine; e) ethylorthoformiate; f) NH_4OH; g) 3-methoxymethacryloylisocyanate; h) H_2SO_4

Scheme 1.



i) $NaBH_4$; j) BzCl; k) thymine, Ph_3P, diethylazodicarboxylate; l) MeONa/methanol

Scheme 2.

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The thymine derivative (**3**) was synthesized in a moderate 20% unoptimized yield by direct Mitsunobu condensation (4) of thymine and (±)-*cis*-2-hydroxycyclohexylmethanol following benzoylation of the primary hydroxyl group using benzoyl chloride, as shown in Scheme 2. The diol was prepared by $NaBH_4$ reduction of ethyl 2-oxocyclohexanecarboxylate (5).

An extensive series of cyclohexane-based OTCs is currently being synthesized for pharmacological evaluation.

ACKNOWLEDGMENT

We thank the Spanish Ministry of Science and Tecnology (PM990125) and the Xunta de Galicia (PGIDT00PX120317PR) for financial support.

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