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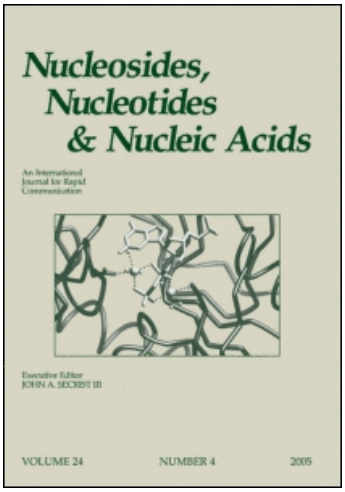

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Simple and Stereoselective Syntheses of Nucleoside Analogues with a Benzo[c]furan Glycone Moiety

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NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 559–563 (1999)

SIMPLE AND STEREOSELECTIVE SYNTHESES OF NUCLEOSIDE ANALOGUES WITH A BENZO[c]FURAN GLYCONE MOIETY

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ABSTRACT: A series of d4T analogues have been synthesised in which the 2',3'-didehydro-2',3'-dideoxyribose moiety is replaced by a benzo[*c*]furan core. A simple strategy has been developed to access a range of compounds for biological screening. In addition, a stereoselective approach has been achieved with view to permit more detailed studies.

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INTRODUCTION

2',3'-Dideoxynucleosides such as AZT and ddI have been identified as potent and selective inhibitors of the human immunodeficiency virus (HIV). Also the analogous 2',3'-didehydro-2',3'-dideoxynucleosides such as d4T and carbovir (Scheme 1) are known to be effective anti-HIV agents. The more radical modification of completely removing the C-2', C-3' fragment produces an acyclic glycone, and nucleoside analogues such as acyclovir also show potent antiviral (herpes) activity[1].

The present study is centred on an hitherto unknown modification to the classical glycone, which is the annulation of a benzene ring across the 2',3' bond to produce a novel type of bicyclic nucleoside with a benzo[*c*]furan core in the glycone (Scheme 1). Compounds of this family have the potential to exert their biological activity in a similar manner to dideoxynucleosides through chain termination and reverse transcriptase inhibition. Furthermore, the increased lipophilicity of this type of compound may increase transmembrane transport. Thus migration to and binding with intracellular receptor sites may be enhanced relative to that observed in conventional nucleosides. It was also reported that d4C was readily hydrolyzed following the mechanism[2] in Scheme 2. It is likely that a 2',3' aromatic bond would inhibit this mode of hydrolysis.

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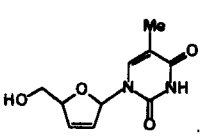
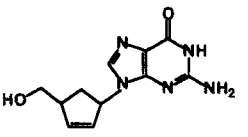
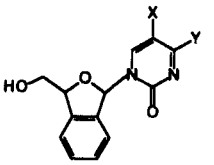


d4T

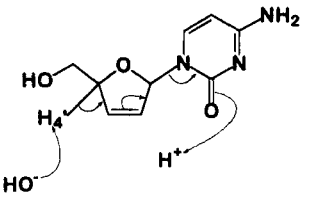


Carbovir



Benzo[*c*]furan nucleoside analogues

Scheme 1



Scheme 2

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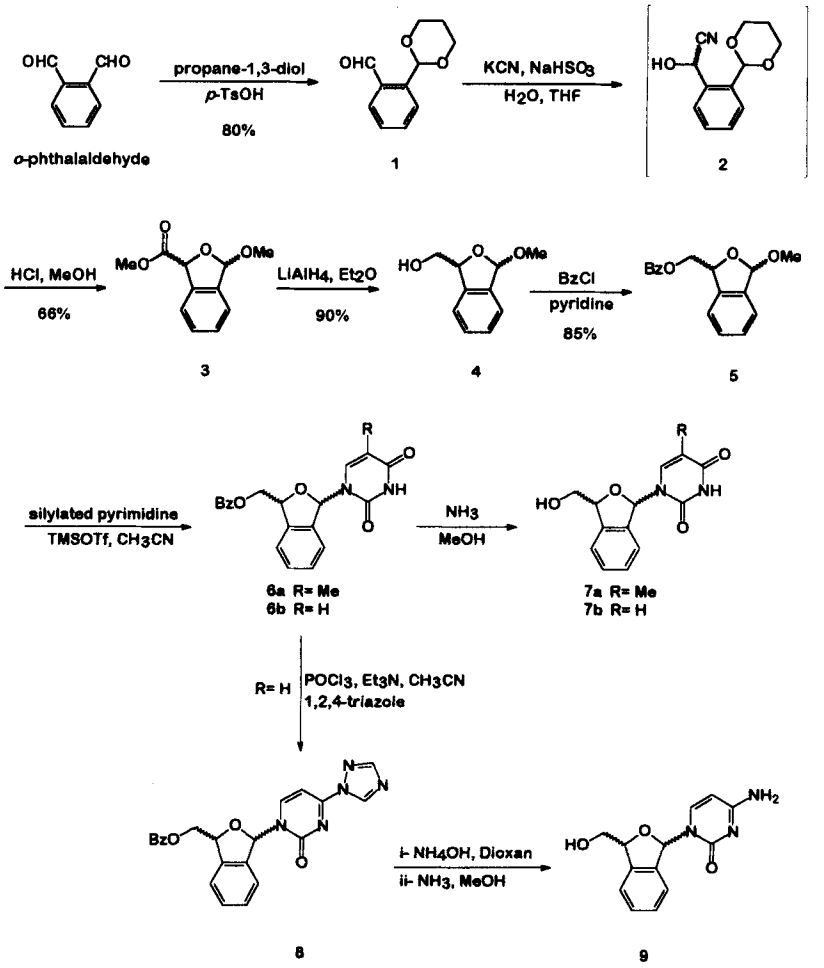
As an extension of our work on sugar-modified nucleosides, we report the synthesis of d4T analogues in which the carbon atoms C-2' and C-3' are part of an aromatic ring.

CHEMISTRY

Two synthetic strategies were explored as routes to benzo[*c*]furan nucleoside analogues. The first strategy was designed to provide convenient access to four stereoisomers for each chosen base attachment for initial biological evaluation. This initial study was directed towards pyrimidine nucleosides analogous to d4T and d4C. The second strategy was undertaken to illustrate the feasibility of obtaining such types of compounds stereoselectively.

In the first strategy *o*-phthalaldehyde (**1**) was converted to 3-hydroxymethyl-1,3-dihydro-1-methoxybenzo[*c*]furan (**5**) in three steps (Scheme 3). Treatment of **1** with potassium cyanide in the presence of sodium bisulfite in THF-water at 5°C afforded the cyanohydrin intermediate **2** which was reacted, without isolation, with dry gaseous hydrogen chloride



Scheme 3

in methanol to give 3-methyl-1,3-dihydro-1-methoxybenzo[*c*]furan carboxylate **3** (66%) and the corresponding 1-hydroxy derivative (6%). Reduction of the ester group in **3** with $LiAlH_4$ gave the desired 1,3-dihydro-3-hydroxymethyl-1-methoxybenzo[*c*]furan (**4**) (90%). Protection of the hydroxymethyl group of **4** gave **5**· was obtained as a pair of diastereoisomers in a ratio of 1.25: 1 (85%). The minor isomer (*cis*) was obtained in a pure form by crystallisation. Compound **5** was coupled with silylated uracil in the presence of trimethylsilyl triflate in acetonitrile to give the **6b***trans* and **6b***cis* diasteroisomers in a ratio 1.25:1 (70%) which were separated by chromatography. Removal of the protecting group afforded the desired nucleosides **7b***trans* and **7b***cis* (Scheme 3). Similar condensation of **5** with silylated thymine gave *cis/ trans* isomers in the ration 1:1.8. The

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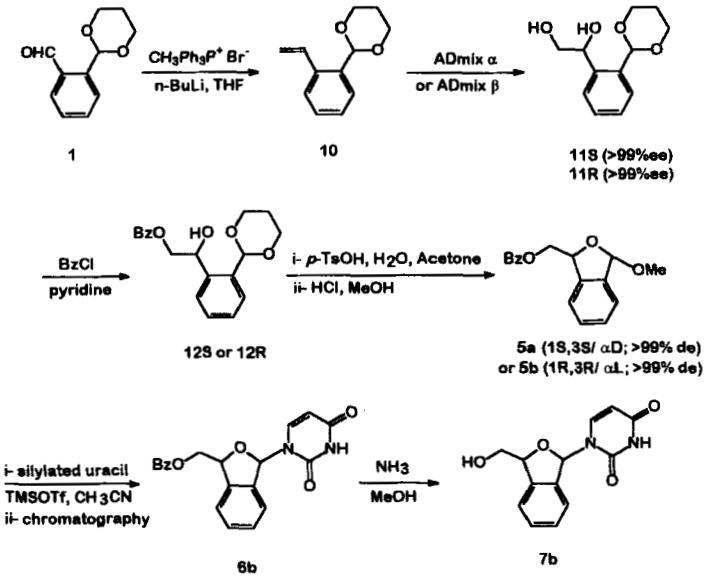

Scheme 4

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minor isomer has the *cis* configuration and crystallised preferentially from ethanol. It was finally obtained stereochemically pure, whereas the *trans* isomer was 70% pure.

Treatment of **6b***cis* with phosphoryl chloride/1,2,4-triazole/triethylamine in acetonitrile[3] at room temperature gave, quantitatively, the 4-(1,2,4-triazol-1-yl) derivative **8**. This was treated sequentially at ambient temperature with aqueous ammonia in 1,4-dioxane followed by ammonia in methanol and gave after chromatography the d4C analogue **9***cis* (80%). Analogous treatment of **6b***trans* gave the corresponding cytidine nucleoside **9***trans* (88%).

The diasteroisomeric assignment of these nucleosides was established by ^{1}H NMR, principally on the basis of the value of *J*(H-1,H-3) which is *ca* 2Hz in the *trans* isomers and <0.5Hz in the *cis* isomers[4].

The sequence described constitutes an efficient synthesis of the racemic benzo[*c*]furan glycone **5** in four steps without any purification and with an overall yield of 38%

The second strategy also made use of the monoprotected *o*-phthalaldehyde intermediate **1** which with methyl triphenylphosphonium bromide in the presence of n-BuLi in THF gave the olefin **10** in 90% yield. The asymmetric dihydroxylation of the double bond using Admixα or Admixβ[5] afforded quantitatively the diols **11S** (>99% ee, $[\alpha]_D$= +32.8°) and

11R (>99% ee, $[\alpha]_D$= −33.5°) respectively. (The configurations were assigned using the "asymmetric dihydroxylation mnemonic rules[6]") Selective benzoylation of the primary hydroxyl group of **11S** and **11R** followed by cyclisation and methylation of the anomeric hydroxyl group gave, in each case, one stereoisomer; respectively **5(1S, 3S *or* αD)** (>99% de, $[\alpha]_D$= +53.4°) and **5(1R, 3R *or* αL)** (>99% de, $[\alpha]_D$= −54.2°); it is curious to note that these compounds have an enantiomeric relationship. The structures of **5** were assigned on the basis of NMR and optical rotations. Coupling of **5** with silylated uracil in the presence of TMSOTf in CH_3CN provided the nucleoside **6b** as a pair of anomers which were separated by chromatography and deprotected separately to give the desired nucleosides **7b**. Thus the four stereoisomers of the uracil nucleoside **7b** were each obtained in an optically pure form.

Antiviral studies of these nucleoside analogues are in progress and will be reported elsewhere.

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