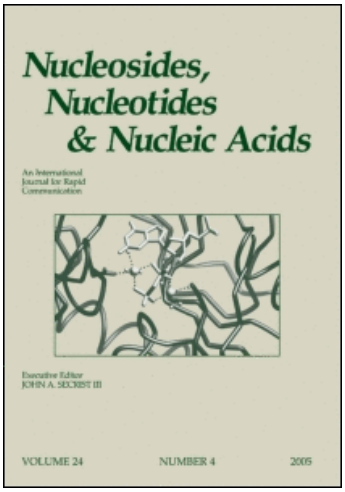

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Carbocyclic Nucleoside Analogues. Synthesis and Properties of 1-(4-Hydroxymethyl-2-cyclopenten-1-YL)-Thymine

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CARBOCYCLIC NUCLEOSIDE ANALOGUES. SYNTHESIS AND PROPERTIES OF 1-(4-HYDROXYMETHYL-2-CYCLOPENTEN-1-YL)-THYMINE.

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Abstract:

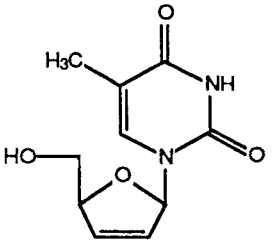
The title compound, a potential anti-Aids drug, was prepared via construction of the thymine ring on a suitably substituted aminocyclopentene. NOE difference spectroscopy was used for establishing the stereochemistry of the products.

The recent application of some nucleoside analogues as drugs for the treatment of AIDS has strongly stimulated synthetic activity in this field of organic chemistry[1]. A variety of compounds have been prepared, which, like Azidothymidine (AZT) can in principle act as inhibitors of reverse transcriptase and/or as chain terminators in the DNA biosynthesis[2].

During the last couple of years, we have been engaged in the synthesis of nucleoside analogues in which the anomeric bond between base and (deoxy)ribose is stabilized towards both chemical and enzymatic hydrolysis by removing either the nitrogen atom from the nucleobase[3], or the oxygen atom from the (deoxy)ribose moiety[4]. Except for the improved stabilization, the aim of these structural variations is to prepare a nucleoside analogue, which might still exhibit antiviral properties, while mammalian cells are not effected by these compounds, since their enzymes are usually more selective and may not be inhibited or do not accept these derivatives as substrates. In this way a higher therapeutic index may be obtained. Since the anti-HIV activity of 2',3'-dideoxy-2',3'-didehydro-thymidine (**1**) is well documented[5], we prepared the corresponding carbocyclic analogue **2a**.

A recent preliminary communication by Vince et al.[6] in which the properties of compound **2a** are described, prompts us to report on this part of our work on carbocyclic nucleosides.

Amino alcohol **4** was prepared via Diels-Alder addition of tosylcyanide to cyclopentadiene, according to literature procedures[7] with minor modifications. Hydrolysis without isolation afforded the bicyclic lactam **3** (m.p. 56-58 °C), which was



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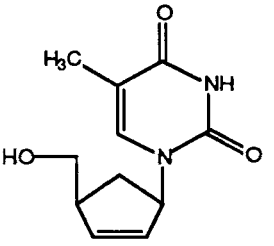
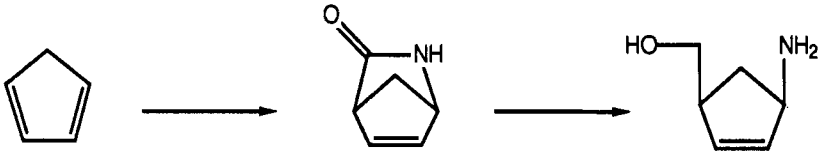


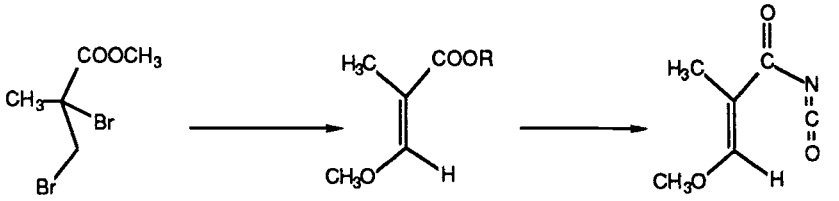
2a

hydrolyzed with HCl and esterified with methanol[8]. Reduction with Lithium triethyl borohydride afforded **4** as a racemate of cis isomers. In this reaction both reduction of the double bond and epimerization of the ester function, due to the basic conditions, have been observed[9]. Reaction with three equ. of the borohydride under carefully controlled conditions produced **4**, isolated as its hydrochloride without epimerization, according to NMR analysis[10].



3 **4**

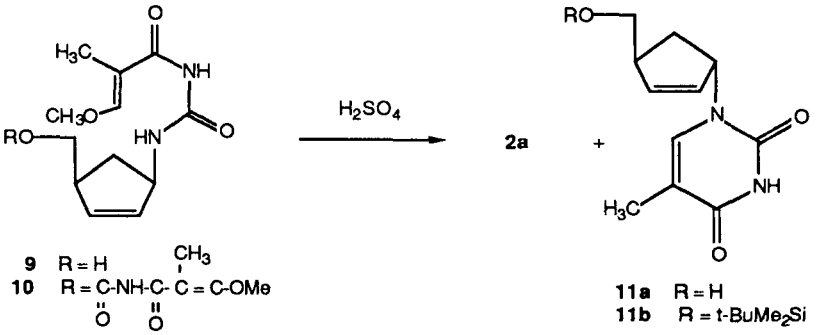
Thymine synthon **8** was prepared via literature procedures[11]. Due to its reactivity compound **8** has to be used immediately in the reaction with primairy amines.



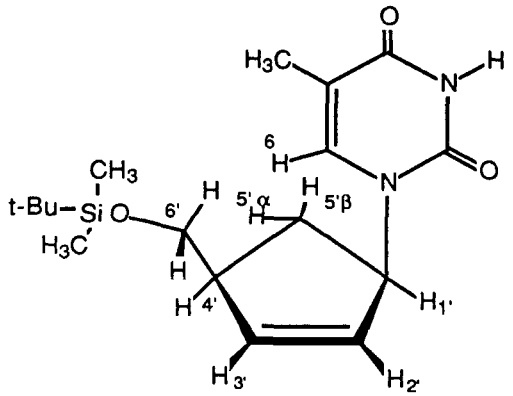
5 **6** R=CH_3 , E:Z = 4:1 **8**
7 R=H , E

Addition of amino alcohol **4** to the isocyanate **8** produced a mixture of compounds in which one product **10** dominates, formed by reaction of both the amino function

and the hydroxyl group with **8**. The mixture of **9**, **10** and other products could be used in the cyclization to **2a**, since under the reaction conditions



(refluxing 1 M sulfuric acid. 3.5 h) the carbamate is hydrolyzed, giving rise to a unexpected mixture of **2a** and a second product **11a** in almost equal amounts. Since according to TLC and NMR, **4** was used as the pure cis isomer, we have to assume, that epimerization to **11a** has occurred during the acid treatment. Chromatographic separation was rather difficult in this stage, so the mixture was converted into the corresponding t-butyl dimethyl silyl ethers, which could be partly separated over a silica column, resulting in pure **2b**[12] and fractions containing a mixture of **2b** and **11b**. Deprotection to give pure **2a**[13] could be realized by treatment with acetic acid (80%).Because of its solubility in deuterated chloroform, the silyl ether **2b** was extremely suitable for NOE difference spectroscopy. In natural nucleosides, assignment of anomeric configuration can be deduced from the coupling pattern of the anomeric proton[14]. In C-ribonucleosides and in carbocyclic nucleosides, this procedure is less straightforward[15,16] In previous work, we applied successfully NOE difference spectroscopy to establish the β configuration of glutarimide C-nucleosides, in which we could detect the interaction of C-1' with C-4' [16]. In carbocyclic nucleosides like **2a,b**, the extra methylene group makes the assignment even simpler, since the chemical shift of the two protons H-5' is rather different.Irradiating H-6 (7.07 ppm) gives an enhancement of the signal of H-2' (5.60 ppm) and H-5'β (1.43 ppm). Irradiating both H-4' (2.88 ppm) and H-1' (5.70 ppm) gives an effect on H-5'α (2.57 ppm). In this way the cis orientation of the substituents at the cyclopentene ring was unequivocally established.



2 b

Compounds **2a**, **2b** and **11a** were tested against H9 / HLTV III b , incubated in human T 4 lymphocytes (C8166). **2a** and **11a** did not inhibit syncytia formation, but **2b** showed strong cytotoxicity(ID_{50} = 10 μM). This unexpected activity of a silyl ether is currently under investigation.

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8. Methyl (cis) 4-aminocyclopent-2-enecarboxylate HCl. m.p: 91-94 °C. ^{1}H NMF (250 MHz, $CDCl_3$) δ: 8.3 (NH_3^+), 6.1, 6.2 (H-2, H-3), 4.48 (m, H-4), 3.71 (s, CH_3O), 3.60 (m, H-1), 2.54 (m, H-5), 2.36 (ddd, H-5). In D_2O, the chemical shift of the two protons at C-5 is considerably different,i.e. δ = 2.72 and 2.10.
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10. **4**: viscous oil, the cis orientation is established both from the difference in chemical shift of the protons at C-5 (δ = 2.49 and 1.29 in D_2O) and the fact, that couplings with H-1 and H-4 are equal (8.2 and 5.8 resp. for both protons C-5). A trans orientation corresponds with a chemical shift of the protons at C-5 of 2.13 and 2.03 ppm (which is clearly a smaller difference) and with different couplings of each proton at C-5 with H-1 and H-4 (5.2 + 8.1 Hz and 8.2 + 3.9 Hz resp.). See also reference 9.

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12. **2b**: m.p. 148-151 °C.. UV (EtOH): 212, 272 nm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.70 (bs, 1H, NH), 7.07 (q, 1H, J= 1.0, H-6), 6.06 (ddd, 1H, J= 5.6, 2.1, 2.2, H-3'),5.70 (m, 1H, H-1'), 5.60 (ddd, 1H, J= 5.6, 2.1, 2.2, H-2'), 3.72 (dd, 1H, J= 10.1, 4.5, H-6'), 3.55 (dd, 1H, J= 10.1, 4.9, H-6'), 2.88 (m, 1H, H-4'), 2.57 (ddd, 1H, J= 13.6, 8.5, 8.5, H-5'α), 1.88 (d, 3H, J= 1.0, methyl), 1.43 (ddd, 1H J= 13.6,7.2, 6.8, H-5'β), 0.88 (s, 9H, t-butyl), 0.04 (s, 6H, methyl -Si). NOE-difference: see text. MS: (FI: 337, M+H, EI: 279, M minus t-Butyl).
13. **2a**: m.p. 203-205 °C. ^{1}H NMR (250 MHz, D_2O) δ: 7.45 (q,J=1.2, H-6), 6.15 (ddd,J=5.7, 2.1, 2.1, H-3'), 5.73 (ddd,J=5.7, 2.2, 2.2, H-2'), 5.25 (dddd,J=8.7, 6.3, 2.2, 2.1, H-1'),3.65 (dd,J=11.2, 5.4, H-6'), 3.58 (dd,J=11.2, 5.2, H-6'), 2.95 (m, H-4'), 2.66 (ddd,J=13.8, 8.7, 8.7, H-5'α), 1.83,(d,J=1.2, methyl),1.39 (ddd,J =13.9, 6.3, 6.3, H-5'β). Mass: 222.1002778, calculated for $C_{11}H_{14}N_2O_3$: 222.10042.
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