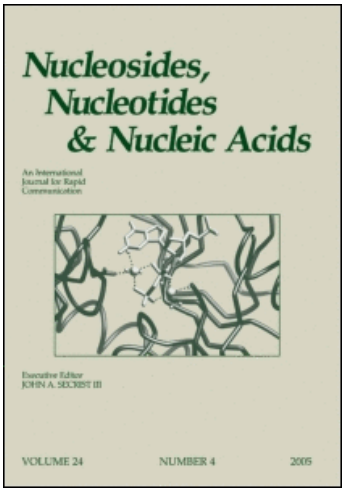

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SYNTHESIS OF 2',3'-DIDEOXYCYCLOPENTENYL CARBOCYCLIC NUCLEOSIDES AS POTENTIAL DRUGS FOR THE TREATMENT OF AIDS

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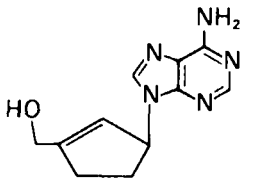
ABSTRACT: The recently discovered antiviral activity of 2',3'-dideoxynucleosides against the AIDS virus in vitro prompted the synthesis of 2',3'-dideoxycyclopentenyl adenine and cytosine. A sequence of two consecutive reductive deoxygenations using 1,1'-thiocarbonyldiimidazole followed by reduction with tributyltin hydride afforded the desired target compounds. Neither compound showed activity in the in vitro assay against the HTLV-III/LAV virus.

The 2',3'-dideoxy (dd) nucleosides of the naturally occurring bases cytosine (C), thymine (T), adenine (A), hypoxanthine (Hx), and guanine (G) have been recently reported to be effective agents in protecting cells against the cytopathic effects of the human T-lymphotropic virus type III (HTLV-III)/ lymphadenopathy-associated virus (LAV) in vitro.[1] The 5'-triphosphates of these compounds function as DNA chain terminators after being incorporated into DNA by the retroviral DNA polymerase (reverse transcriptase), while the DNA polymerase alpha which is required for DNA replication during normal cell growth does not recognize them as good substrates.[1,2] The order of potency for these dd nucleosides against HTLV-III/LAV in vitro is ddC > ddA ~ ddI ~ ddG >> ddT. Specifically, ddC at the non-cytotoxic concentrations of 0.5 and 5.0 μM, provided essentially 100% protection of ATH8 cells infected with HTLV-III/LAV, while ddA concentrations ranging from 5 to 20 μM afforded the same level of protection.[1]

We and others have reported on the significant changes in biological activity that the incorporation of the cyclopentene moiety imparts to the resulting carbocyclic nucleoside relative to conventional nucleosides .[3-7] Neplanocin A and cyclopentenyl cytosine (CPE-C) are representative examples of this carbocyclic series that possess potent antitumor and antiviral properties.[5,7]

Based on these two independent findings (dideoxy; cyclopentenyl) we decided to combine both types of structural modifications in one molecule. For this purpose, the first selected target compounds were dideoxycyclopentenyl adenine (ddCPE-A, 1) and dideoxycyclopentenyl cytosine (ddCPE-C, 2). Additionally, since conventional dd nucleosides are inherently unstable under acidic conditions undergoing cleavage of the glycosidic bond,[8] it was felt that ddCPE nucleosides offered the possibility of improved hydrolytic stability.



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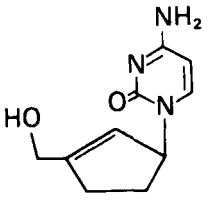
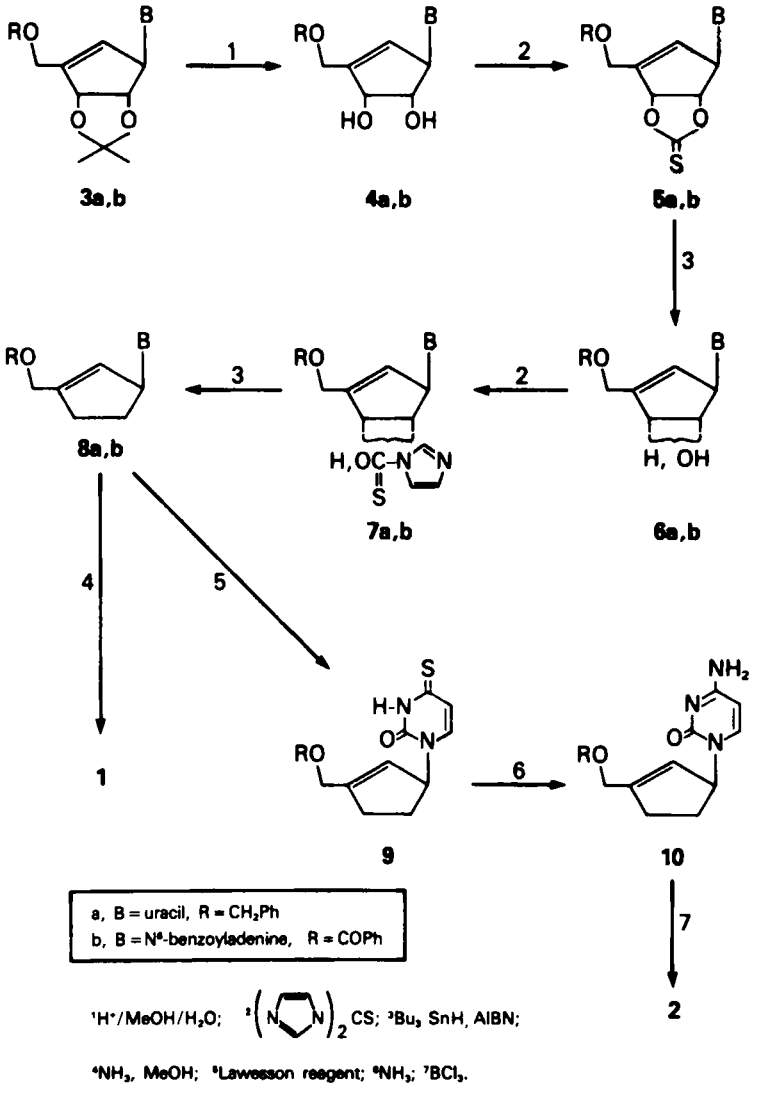


2

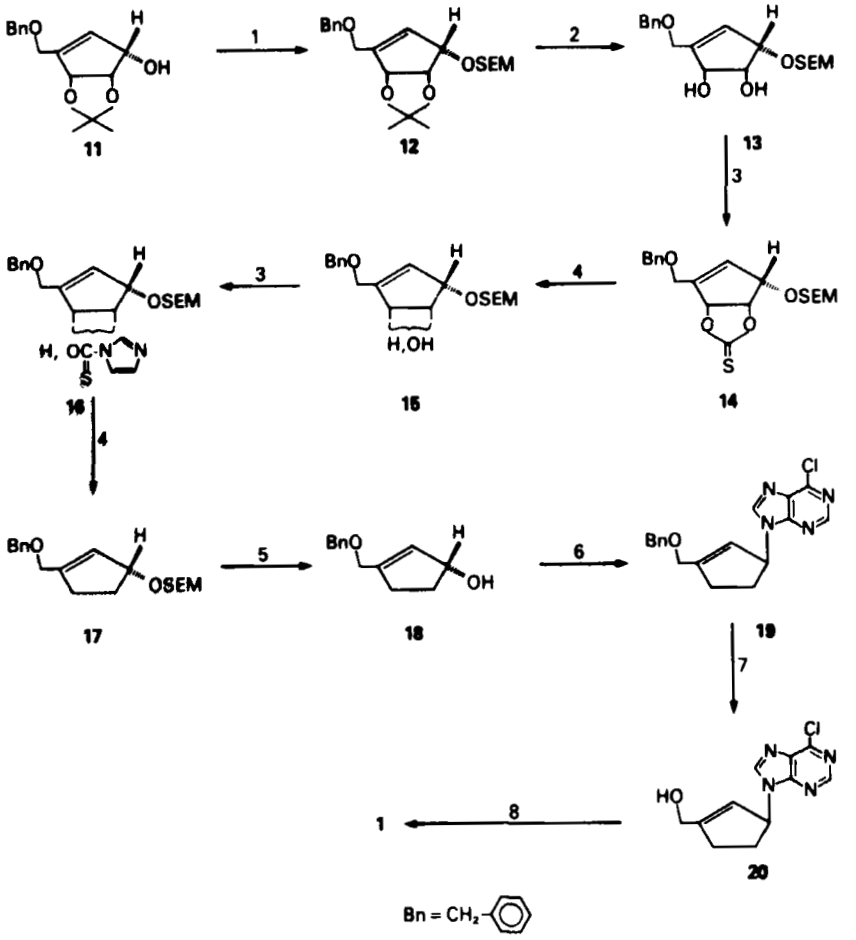
Our approach to both 1 and 2 consisted of performing two consecutive reductive deoxygenations[9] starting with the corresponding cyclopentene nucleoside isostere, or a suitable precursor, with the ribose configuration.

As shown in Scheme 1, the uridine precursor 3a was deblocked to 4a in 95% yield after treatment with 30 equiv of AG50W-X8 (H^+) resin in methanol (50°C, 16 h). Reaction of 4a with 1,1'-thiocarbonyldiimidazole (Im_2CS, 1.5 equiv in DMF, 25°C, 40 h) afforded the cyclic thiocarbonate 5a (87% yield) which was then treated with tributyltin hydride (n-Bu_3SnH, 3.0 equiv) in the presence of α,α'-azaisobutyronitrile (AIBN, 1.75 equiv) in refluxing toluene for 1 hr to give a mixture hydroxy compounds 6a (95% yield). The separated mixture was treated in the same fashion as before with Im_2CS in DMF to give a mixture of monothiourethanes (7a). Even under these rather mild reaction conditions the 2'-O(1-imidazolyl)-thiocarbonyl isomer underwent an intramolecular reaction to form the



SCHEME 1

corresponding anhydride (40% yield) which was isolated by column chromatography. The remaining 3'-O-(1-imidazolyl)thiocarbonyl isomer (60%) was reduced with n-Bu_3SnH to the corresponding dideoxy analogue 8a (67% yield). Conversion of 8a to the thio analogue 9 was accomplished in 58% yield after reacting with 1.3 equiv of 2,4-bis-(4-methoxyphenyl)1,3,2,4-dithiaphosphetane-2,4-disulfide (Lawesson reagent)[10] in benzene (reflux,



[1]$Me_3SiCH_2CH_2OCH_2Cl$(SEM-Cl); [2]80% HOAc; [3]$(N_2C)_2CS$; [4]nBu_3SnH; [5](n-$Bu)_4NF$; [6]Ph_3P, DEAD, 6-chloropurine; [7]BCl_3; [8]NH_3

SCHEME 2

45 min). Ammonolysis of 9 with saturated methanolic ammonia in a pressure bottle (80°C, 20 h) gave 63% of the benzyl protected ddCPE-C analogue 10 which was deblocked to 2 with BCl_3 in CH_2Cl_2 (5 equiv, -78°C → 24°C, 2 h, 80%); ^1H NMR (D_2O) δ 1.73 (m, 1H), 2.46 (m, 3H), 4.26 (s, 2H, H-6'$_{a,b}$), 5.58 (br s, 2H, H-1' and H-5'), 5.95 (d, J = 7 Hz, 1H, H-5), 7.50 (d, J = 7 Hz, 1H, H-6); FABMS m/z (rel intensity) 208 (MH^+, 71), 112 (b + 2H, 100).

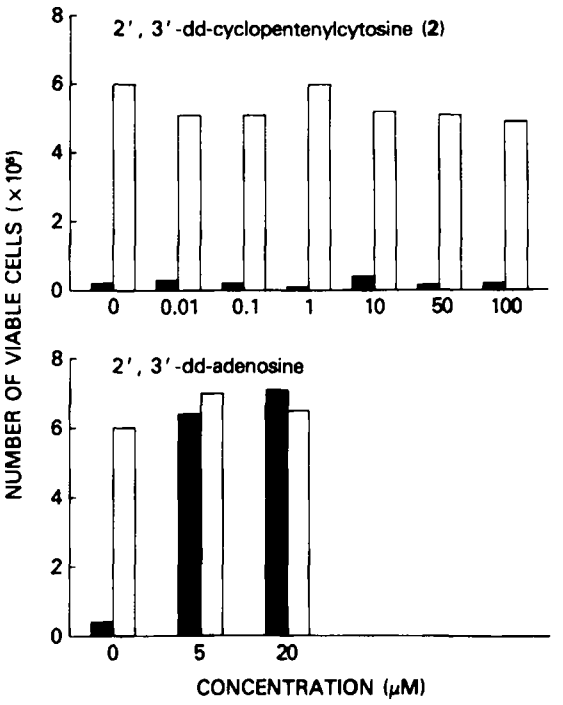


Figure 1: Inhibition of cytopathic effect of HTLV-III/LAV by ddCPE-C (2) and ddA in ATH8 cells. Control cells (open columns) were similarly treated, but were not exposed to the virus.

A similar set of reactions performed on $O^{6'}$,N^{6}-dibenzoyl-(2',3'-O-isopropylidene)neplanocin A (3b) afforded the purine target ddCPE-A (1). This compound was also approached via the Mitsunobu reaction[11] between dd-cyclopentene-1'-ol 18 and 6-chloropurine (Scheme 2). Conversion of the resulting condensation product 19 to ddCPE-A (2) was accomplished in two steps after ammonolysis and debenzylation. The synthesis of intermediate 18 started with the already known cyclopentene precursor 11[12] which was subjected to a similar sequence of two reductive deoxygenations. The 1'-hydroxy group was initially protected with the 2-(trimethylsilyl)ethoxy-methyl (SEM) group (Scheme 2).

The biological experiments were disappointing since the compounds showed no protection of ATH8 cells infected with HTLV-III/LAV. The results for ddCPE-C (2) are shown in Figure 1 together with the results of an active standard ddA.

The inactivity of these compounds could be due to their poor anabolism to the mono, di, or triphosphate levels, or to the poor substrate properties of the 5'-triphosphates towards the viral encoded reverse transcriptase. Experiments aimed at resolving this issue are being conducted in our laboratories.

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