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Design and Synthesis of 2'-Hydroxyethylcyclopropyl Carbocyclic Nucleosides

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Abstract. The enantiomeric synthesis of β-D-cyclopropyl carbocyclic nucleosides was achieved *via* the key intermediate **5**. Thymine and uracil derivatives **7** and **9** were obtained by oxidation, Curtius rearrangement and the standard construction method of pyrimidines. The cytosine derivative **10** was prepared from **9** *via* the 4-triazole intermediate.

In search for novel nucleosides as potential antiviral agents, various classes of nucleosides have been extensively investigated.[1-3] Among these compounds, carbocyclic nucleosides have shown interesting antiviral activities against herpes simplex virus (HSV),[4] human cytomegalovirus (HCMV),[5] hepatitis B virus (HBV)[6] and human immunodeficiency virus (HIV).[7,8] They possess the metabolic stability to glycosidic bond cleavage against nucleoside phosphorylases due to their structural characteristics.[9] Among these nucleosides, carbovir[7] and its 6-cyclopropylamino analog (1592U89)[10] are particularly interesting since they both exhibited potent anti-HIV activities.

As part of our drug discovery program, recently we have reported the synthesis of enantiomerically pure cyclopropyl D- and L-nucleosides as potential antiviral agents, in which the ribofuranose moiety of the natural nucleoside was substituted with a hydroxymethyl cyclopropyl moiety.[11,12] In order to be biologically active, nucleosides have to be phosphorylated by the endogenous nucleoside kinases in the host cells. This requires an optimal geometry between the kinase and the nucleoside, particularly the 5'-OH moiety of nucleosides. Keeping this in mind, in an attempt to design new lead structures with improved biological activities, we reexamined a number of cyclopropyl nucleosides by molecular modeling due to the inactivity of the previously synthesized cyclopropyl nucleosides.[11,12] The distances between N1 and O5' in a dideoxy nucleoside and various hydroxyalkyl cyclopropyl nucleosides were compared to those of biologically active dideoxy nucleosides. Among these structures, the hydroxyethyl cyclopropyl nucleosides best fit their requirements when compared to that of ddC (Figure 1).[13,14]

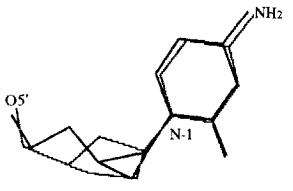
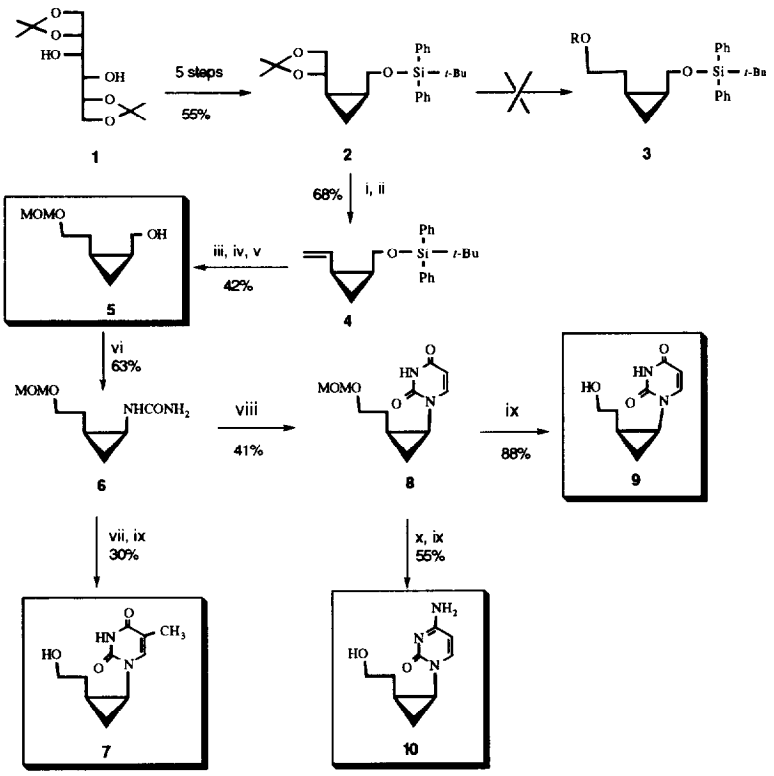


Figure 1. Multifit of ddC and compound **10**.

Based on these molecular modeling studies, we wish to report the synthesis of pyrimidine derivatives of the 2'-hydroxyethylcyclopropyl nucleosides, **7**, **9** and **10**. The cyclopropyl derivative **2** was obtained as described previously in 5 steps from protected D-mannitol in 55% yield (scheme 1).[12,15] The initial approach to prepare the hydroxyethyl derivative **3** was to utilize the cyclopropyl derivative **2** by successive deblocking of the isopropylidene group, protection of the primary hydroxyl group, preparation of xanthate derivative of the secondary hydroxyl group followed by a reduction with tributyltin hydride. However, it was found that the reduction with tributyltin hydride was detrimental to the cyclopropyl ring, resulting in the opening of the cyclopropyl ring. As an alternate approach, the

isopropylidene group of compound **2** was deprotected with 80% acetic acid in water at 50 °C for 1 h to give the diol in 90% yield followed by the oxidative cleavage of the diol by either sodium periodate or lead tetraacetate.

Scheme 1



i. (a) 80% AcOH; (b) $NaIO_4$, MeOH or $Pb(OAc)_4$, EtOAc; ii. $Ph_3P{=}CH_2$, THF; iii. (a) BH_3,THF; (b) 30%H_2O_2, 1 N NaOH; iv. MOMCl, $(isopropyl)_2NEt$; v. n-Bu_4NF, THF; vi. (a) $NaIO_4$, RuO_2, K_2CO_3, $CHCl_3$:CH_3CN:H_2O (2:2:3); (b) $ClCO_2Et$, Et_3N, NaN_3, acetone; (c) toluene, Δ; (d) NH_3, MeOH; vii. (a) β-methoxy-α–methylacryloyl chloride, CH_2Cl_2, pyridine; (b) 30% NH_4OH, EtOH in sealed bomb; viii. (a) β-methoxyacryloyl chloride, CH_2Cl_2, pyridine; (b) 30% NH_4OH, EtOH in sealed bomb; ix. conc. HCl, EtOH, THF, x. (a) 4-Chlorophenyldichloro phosphate, 3-Nitro-1,2,4-triazole, pyridine; (b) 30% NH_4OH.

The resulting aldehyde was treated with methyltriphenylphosphonium bromide to obtain the olefin **4** in 75% overall yield from compound **2**. Olefin **4** was readily converted to the hydroxyethyl group by hydroboration and the resulting primary hydroxy group was protected with the methoxymethyl (MOM) ether group. Deprotection of the silyl group provided the key intermediate **5** in an overall yield of 42% from **4**. The oxidation of alcohol **5** by $NaIO_4$ utilizing RuO_2 as a catalyst gave an acid which was readily converted to intermediate **6** by Curtius rearrangement.[16] The pyrimidine nucleosides were synthesized by utilizing the synthetic methodology developed by Shaw and Warrener.[17] Thus, thymine derivative **7** was obtained by reacting the urea derivative **6** with β-methoxy-α-methylacryloyl chloride followed by deprotection of the MOM group with

conc HCl in methanol.[18] Treatment of the urea **6** with β-methoxyacryloyl chloride gave compound **8**. Deprotection of the MOM group afforded the desired uridine derivative **9**.[19] Compound **8** was treated with chlorophenyl phosphorodichloridate and 3-nitro-1,2,4-triazole[20] to obtain the 4-(3-nitro)triazolide of the uracil derivative. The triazolide was treated with ammonium hydroxide followed by the deprotection of the MOM group, which afforded the cytosine derivative **10**.[21]

Compounds **7**, **9** and **10** were evaluated for their anti-HIV and anti-HBV activities in PBM and 2.2.15 cells, respectively. However, none of the compounds showed any significant antiviral activity. The lack of activity may be due to several reasons, among which the low efficiency of phosphorylation by the nucleoside kinase might be the major factor. Although molecular modeling studies suggested an optimal distance between N1 and 5'-OH, other factors may have also played a role.

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13. Molecular modeling studies were performed on a Silicon Graphics Indy workstation using SYBYL v. 6.1 molecular modeling software (Tripos Associates, St. Louis, MO).
14. The optimized geometry and the point charges on the molecules were calculated by the PM3 method

through MOPAC interface available in SYBYL. The molecules were then subjected to conformational search and the lowest energy conformers were used for fitting.

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18. Compound **7**: UV (H_2O) λ_{max} 272.5 nm (pH 2.0, ε 16,693 $M^{-1}cm^{-1}$), 272.0 nm (pH 7.0, ε 17,396 $M^{-1}cm^{-1}$), 270.5 nm (pH 11.0, ε 19,896 $M^{-1}cm^{-1}$); $[\alpha]_D^{24}$ -93.1° (c 0.4, MeOH); ^1H NMR (DMSO-d_6) δ 0.76 (m, 1H), 0.88 (m, 1H), 1.00 (m, 1H), 1.17 (m, 1H), 1.53 (m, 1H), 1.73 (s, 3H), 3.04 (ddd, 1H, J = 11.9, 7.5, 4.5 Hz), 3.39 (m, 2H), 4.45 (t, 1H, OH, J = 5.3 Hz), 7.41 (s, 1H), 11.21 (s, 1H, NH); Anal. Calcd for $C_{10}H_{14}O_3N_2 \cdot 0.75\ H_2O$: C, 53.68; H, 6.98; N, 12.52. Found: C, 53.89; H, 6.96; N, 12.55.
19. Compound **9**: UV (EtOH) λ_{max} 263.0 nm; $[\alpha]_D^{24}$ -180.7° (c 0.2, MeOH); ^1H NMR (DMSO-d_6) δ 0.51 (m, 1H), 1.08 (m, 1H), 1.21 (m, 1H), 1.36 (m, 1H), 1.98 (m, 1H), 3.22 (m, 1H), 3.40 (m, 2H), 5.33 (d, J=8.0 Hz, 1H), 7.20 (d, J=8.0 Hz, 1H); High res mass (FAB): 197.0928 (calcd. 197.0926, MH^+).
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21. Compound **10**: mp 210.0 °C (dec.); UV (H_2O)λ_{max} 283.0 nm (pH 2.0, ε 9,583 $M^{-1}cm^{-1}$), 274.5 nm (pH 7.0, ε 6,342 $M^{-1}cm^{-1}$), 278.5 nm (pH 11.0, ε 6,688 $M^{-1}cm^{-1}$); $[\alpha]_D^{22}$ -258.2° (c 0.1, MeOH); ^1H NMR (DMSO-d_6) δ 0.73 (m, 1H), 0.87 (m, 1H), 1.01 (m, 1H), 1.16 (m, 1H), 1.52 (m, 1H), 3.12 (m, 2H), 3.23 (m, 1H), 4.48 (brs, 1H, D_2O exch), 5.69 (d, J=8.0 Hz, 1H), 7.05 (brs, 1H, D_2O exch), 7.21 (brs, 1H, D_2O exch), 7.56 (d, J=8.0 Hz, 1H); Mass (ESI): 195.1 (MH^+); Anal. Calcd for $C_9H_{13}N_3O_2 \cdot HCl$: C, 46.66; H, 6.09; N 18.14. Found: C, 46.37; H, 6.06; N, 17.70.

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