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# Synthesis of Enantiomerically Pure Cyclopropyl Carbocyclic Nucleosides

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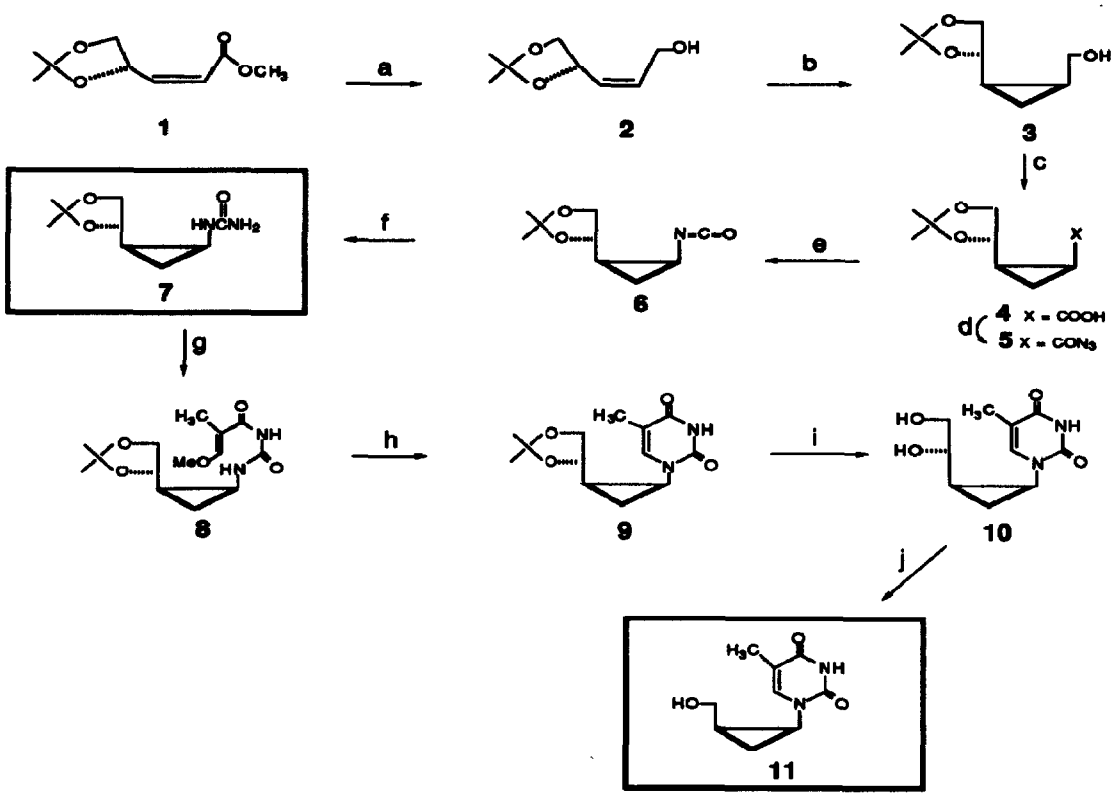
**Abstract:** The enantiomeric synthesis of cyclopropyl carbocyclic nucleosides has been achieved and the key intermediate was characterized by X-ray crystallography.

A number of carbocyclic nucleosides have been synthesized as potential chemotherapeutic agents.[1,2] Among these, carbovir[3] and cyclobut-G[4] are particularly interesting since they exhibit potent anti-HIV activities and carbovir is currently undergoing preclinical studies. Although AZT, ddC and ddI are currently available for the treatment of AIDS and HIV infection, their toxicities and side effects, as well as the emergence of the drug resistant viral strains, limit their usefulness as antiretroviral agents.[5-7] Therefore, it is critical to search for new and less toxic anti-HIV agents which are not cross-resistant with the existing drugs.

As part of our drug discovery program for AIDS and hepatitis, we have been interested in the synthesis and biological evaluation of cyclopropyl carbocyclic nucleosides. Recently, several laboratories have reported the synthesis of cyclopropyl nucleosides. For example, Katagiri *et al*.[8] synthesized the cyclopropyl analogs of oxetanocin and its derivatives. They also reported the cyclopropyl homo-nucleosides.[9] In an attempt to improve the initial phosphorylation step by nucleoside kinases, Kato *et al*.[10] synthesized 2,2-bis-hydroxymethyl-cyclopropyl adenine and uracil carbocyclic nucleosides. The initial phosphorylation of nucleosides is considered to be the critical step for biological activity. The above reported synthesis of the cyclopropyl nucleosides, however, did not involve any asymmetric steps. As a consequence, the nucleosides were prepared as racemic mixtures.[8-11] Thus, herein we wish to report the synthesis of enantiomerically pure novel carbocyclic cyclopropyl nucleosides from chiral intermediates. Our synthetic strategy (Scheme 1) utilized the known intermediate **1**, which could be readily prepared in two steps from 1,2:5,6-di-O-isopropylidene-D-mannitol. Although the α, ß-unsaturated ester **1** was attempted to directly convert to a cyclopropyl derivative, a low yield (ca. 10%) of the cyclopropyl product was obtained. Thus, the ester **1** was reduced to the alcohol **2** (84% yield), which was treated with $Zn(Et)_2/ICH_2Cl$ at 0 °C to give the desired cyclopropyl derivative **3** in 54% yield.

SCHEME 1




a) DIBAL-H, $CH_2Cl_2$, -78 °C; b) $Zn(Et)_2$, $ICH_2Cl$, DCE, 0 °C; c) $RuO_2$/ $NaIO_4$;
d) 1. $ClCO_2Et$, $Et_3N$, 2. $NaN_3$; e) toluene, 90–100 °C; f) $NH_3$;
g) β-methoxyacryloyl chloride, Pyridine; h) $NH_4OH$, EtOH, 85 °C;
i) HCl, MeOH; j) 1. $NaIO_4$, 2. $NaBH_4$.

After the synthesis of 3 had been completed as an intermediate for the preparation of cyclopropyl nucleosides in our laboratory, compound 3 was recently reported by Morikawa et. al.[12] However, our synthetic procedure was somewhat different from the reported (we used $ICH_2Cl$ instead of $CH_2I_2$), from which a higher yield (54%) of 3 (reported[12]: 36%) was obtained with a ~55% diastereomeric excess, in contrast to the reported 17%.[12] It should be noted that the allyl alcohol obtained from L-glyceraldehyde was subjected to the same cyclopropanation conditions for 2 to give the enantiomer of 3 as the major product. Additionally, the E-isomer of 2

was also subjected to the cyclization conditions, from which a mixture of two diastereomers was obtained in a ratio of 3:2. The stereochemistry of these two diastereomers has not been established yet. The alcohol **3** was treated with $RuO_2/NaIO_4$ to give the acid **4**, which was converted to the azide **5** by the treatment of chloroethylformate followed by $NaN_3$. The azide **5** was subjected to the Curtius rearrangement conditions (toluene/90-100 °C) to give the isocyanate **6** as an intermediate, which was treated with ammonia to afford the urea derivative **7** in 38% yield from **3**. The structural confirmation of **7** was made based on the single crystal X-ray crystallographic data (Figure 1) along with $^1$H-NMR spectoscopy.[13] The urea derivative was then reacted with ß-methoxyacryloyl chloride in pyridine to provide the intermediate **8**, which, without isolation, was cyclized to the thymine derivative **9**[14] by treatment with ammonium hydroxide at 85 °C in ethanol. The isopropylidene group of **9** was removed by HCl/MeOH at room temperature to give the diol derivative **10**[15] in 72% yield from **7**. The diol nucleoside **10** was treated with $NaIO_4$ to give an aldehyde which was directly reduced to the desired nucleoside **11**.[15] Compounds **10** and **11** were evaluated against HIV-1 in human peripheral blood mononuclear cells. However, both compounds did not exhibit any significant anti-HIV activity up to 100 µM.

In summary, we have developed a synthetic method for the key intermediate **7** from the readily available α,ß-unsaturated ester **1**, from which the synthesis of a new optically active cyclopropyl thymidine derivative **11** was accomplished. Further utilization of the key intermediates **6** and **7** for the synthesis of enantiomerically pure cyclopropyl carbocyclic pyrimidine and purine nucleosides are in progress.

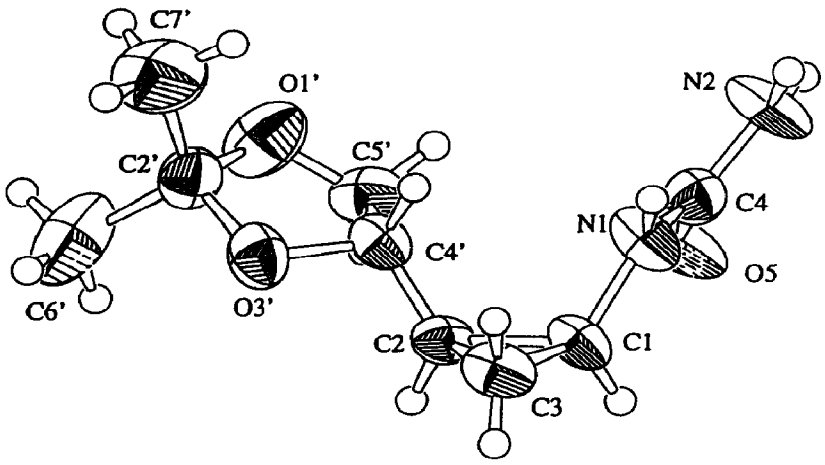



Fig. 1. ORTEP Drawing of Compound **7**.

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13. **Compound 7**: white crystals; $[\alpha]\ ^{24}_{D}$ -117.1° (c 0.52, MeOH); mp 189-190 °C, $^1$H-NMR ($CDCl_3$) δ 0.75 (1H, m), 1.13 (2H, m), 1.35 (3H, s), 1.45 (3H, s), 2.73 (1H, m), 3.77 (1H, dd, J = 8.1, 7.3 Hz), 3.88 (1H, m), 4.15 (1H, dd, J = 8.1, 5.9 Hz), 4.66 (2H, br s, $NH_2$), 4.86 (1H, br s, NH); Anal. Calcd for $C_9H_{16}O_3N_2$: C, 53.98; H, 8.05; N, 13.99. Found: C, 53.94; H, 8.08; N, 13.94.
14. All key intermediates and final compounds in Scheme 1 gave the correct elemental analysis (±0.4%).
15. **Compound 10**: white crystals; $[\alpha]^{24}_{D}$ -222.2° (c 0.50, MeOH); mp 161-162.5 °C; $^1$H-NMR (DMSO-$d_6$) δ 0.95 (1H, ddd, J = 8.4, 8.4, 5.4Hz), 1.19 (2H, m), 1.73 (3H, s), 3.08 (2H, m), 3.27 (1H, ddd, J = 11.4, 6.4, 5.7 Hz), 3.36 (1H, ddd, J = 11.4, 5.7, 4.8 Hz), 4.43 (1H, d, J = 5.2 Hz, OH), 4.48 (1H, t, J = 5.7 Hz, OH), 7.43 (1H, s), 11.18 (1H, s, NH); UV ($H_2O$) $\lambda_{max}$ (pH7) 272.0 (ε 8261), (pH2) 272.0 (ε 10607), (pH11) 270.5 (ε 11426); Anal. Calcd for $C_{10}H_{14}O_4N_2$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.10; H, 6.23; N, 12.37. **Compound 11**: white crystals; $[\alpha]\ ^{24}_{D}$ -100.9° (c 0.50, MeOH); mp 181-182 °C, $^1$H-NMR (DMSO-$d_6$) δ 0.83 (1H, ddd, J = 6.4, 6.4, 4.6 Hz), 1.05 (1H, ddd, J = 9.0, 7.5, 6.4 Hz), 1.35 (1H, m), 1.73 (3H, s), 3.04 (1H, ddd, J = 7.5, 7.5, 4.5 Hz), 3.25 (2H, m), 4.34 (1H, t, J = 5.4 Hz, OH), 7.46 (1H, s), 11.24 (1H, s, NH); UV ($H_2O$) $\lambda_{max}$ (pH7) 270.5 (ε 6485), (pH2) 270.5 (ε 9314), (pH11) 268.5 (ε 6456); Anal. Calcd for $C_9H_{12}O_3N_2$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.19; H, 6.15; N, 14.22.


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