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ASYMMETRIC SYNTHESIS AND ANTI-HIV ACTIVITY OF L-CARBOCYCLIC 2′,3′-DIDEHYDRO-2′,3′-DIDEOXYADENOSINE

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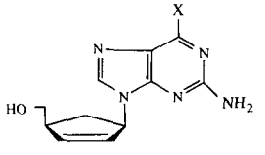
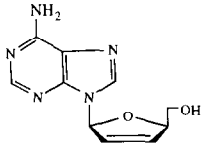
Abstract: Asymmetric synthesis of L-carbocyclic 2′,3′-didehydro-2′,3′-dideoxyadenosine and its analogs were accomplished and their anti-HIV activities were evaluated. It was found that L-carbocyclic 2′,3′-didehydro-2′,3′-dideoxyadenosine exhibited moderately potent anti-HIV (EC_{50} = 2.4 μM) activity in human PBM cells without cytotoxicity up to 100 μM.

A number of carbocyclic nucleosides have shown interesting antiviral and antitumor activities.[1,2] Among them, carbovir[3] **1** and its 6-cyclopropylaminopurine analog 1592U89[4] **2** (abacavir) are of particular interest since they both exhibit potent anti-HIV activity and 1592U89 is currently undergoing phase III clinical trials. Furthermore, a novel carbocyclic nucleoside, BMS-200475[5] has shown potent anti-hepatitis B virus activity, which is currently undergoing phase II clinical trials.

Recently, a number of L-nucleosides have proven to be of great importance as antiviral and antitumor agents, among which 3TC,[6] L-FTC,[7] L-OddC,[8] and L-FMAU,[9] have shown to be the most promising L-nucleosides. Some of these L-nucleosides are more potent and less toxic than that of their L-counterparts.[10,11] The racemic carbocyclic 2′, 3′-didehydro-2′, 3′-dideoxyadenosine also showed anti-HIV activity.[12] Therefore, it was of interest to synthesize the corresponding L-enantiomers in the search for novel antiviral agents. Previously, we have reported that β-L-2′, 3′-didehydro-2′,3′-dideoxyadenosine (β-L-d4A) (**3**) exibited significant anti-HIV and anti-HBV activities.[13] Herein, we wish to report preliminary results of synthesis of carbocyclic β-L-2′, 3′-didehydro-2′, 3′-dideoxyadenosine (**4**) and its analogs as well as results of in vitro biological evaluation.



1 X = O
2 X = NH



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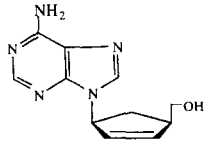

4

Our synthetic strategy for **4** utilized the known (+)-cyclopentenone **5** as a chiral starting material, which was prepared in 3 steps from D-ribose.[14] The alcohol **6** was synthesized by regioselective addition to the enone **5** followed by DIBAL-H reduction.[15] The hydroxyl group of compound **6** was benzoylated to give benzoate **7** in

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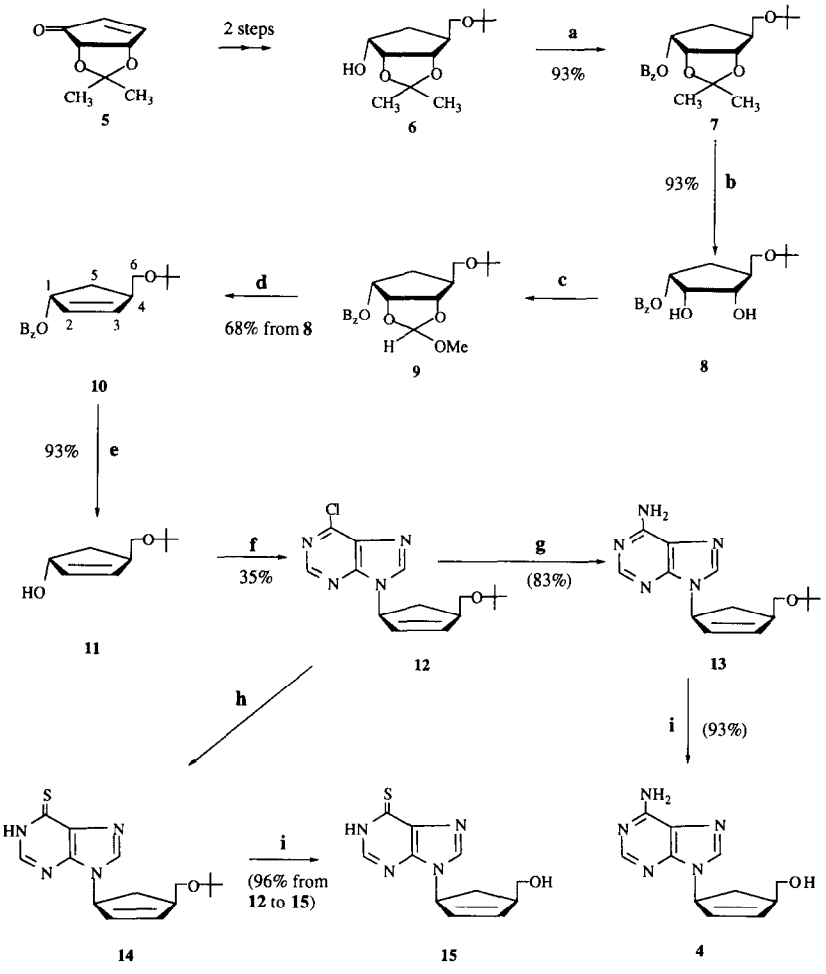
Scheme 1



a: BzCl, Pyr, rt, 12 h. **b**: concd HCl: MeOH (1:70, v/v), rt, 2.5 h. **c**: $CH(OMe)_3$, pyridinium toluene-*p*-sulphonate, rt, 2 h. **d**: Ac_2O, 120-130°C, 3 h. **e**: 2 N NaOH/MeOH, rt, 1.5 h. **f**: 6-chloropurine, Ph_3P, diethyl azodicarboxylate, dioxane, rt, 10 h . **g**: NH_3/MeOH, 80-90 °C, 20 h. **h**: thiourea, EtOH, reflux, 1 h. **i**: CF_3CO_2H/ H_2O (2:1), 50 °C, 3 h.

93% yield. The isopropylidene protection group of compound 7 was removed using a mixture of HCl and methanol (1:70, v/v) at room temperature for 2.5 h to give the diol **8** in 93% yield. Treatment of compound **8** with trimethyl orthoformate in the presence of catalytic pyridinium toluene-*p*-sulphonate at room temperature for 2 h gave the cyclic orthoester **9**, which was subjected to a thermal elimination reaction[16] with acetic anhydride at 120–130 °C for 6 h to give the required cyclopentene **10**.[17] Stereochemical assignments was determined based on NOESY experiments, in which a correlation between H-1 and H-6 of compound **10** was observed, indicating that

they are on the same side. Deblocking of compound **10** with 2 N NaOH in methanol gave alcohol **11**, which was then reacted without isolation with nucleobase by Mitsunobu-type condensation.[18] Reaction of the alcohol **11** with 6-chloropurine in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) at room temperature gave **12** in 35% yield. The compound **12** was then treated with saturated ammonia in methanol in a steel bomb at 80 to 90 °C to provide the adenine derivative **13** in 83%. Deprotection of **13** with CF_3CO_2H/H_2O (2:1, v/v) at 50 °C afforded **4**[19] in 86% yield. The 6-mercaptopurine analog **15**[20] was obtained by the treatment of **12** with thiourea in refluxing ethanol followed by deprotection. (Scheme 1).

The anti-HIV activity of the synthesized nucleosides were evaluated in vitro in peripheral blood mononuclear (PBM) cells. The adenine analog **4** exhibited moderately potent anti-HIV activity (EC_{50} = 2.4 μM) without cytotoxicity up to 100 μM in PBM, CEM, and Vero cells. (Table 1)

Table 1. Anti-HIV-1 activity and cytotoxicity of compound **4** and **15** in vitro

Compound	Anti-HIV Activity in PBM Cells		Toxicity (IC_{50} μM)		
	(EC_{50} μM)	(EC_{90} μM)	PBM	CEM	Vero
4	2.4	11.7	>100	>100	>100
15	>100	ND	>100	>100	>100
AZT	0.004	ND	>100	14.0	27.7

ND: not determined

In summary, the asymmetric synthesis of several carbocyclic β-L-2′, 3′-didehydro-2′, 3′-dideoxy-nucleosides has been accomplished. Among the nucleosides synthesized the adenosine analog **4** exhibited moderately potent anti-HIV activity. Synthesis of other enantiomerically pure carbocyclic L-2′, 3′-didehydro-2′, 3′-dideoxy-pyrimidine and purine nucleosides are in progress.

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17. Compound **10**: $[\alpha]^{27}_{D}$ 259.89° (*c* 1.45, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.40–8.03 (m, 5H, Ar-H), 6.15 (m, 1H, 2 H), 5.98 (m, 1H, 3-H), 5.95 (m, 1H, 1-H), 3.28 (d, *J* = 6.9 Hz, 1H, 6-H), 3.13 (m, 1H, 4-H), 2.10 (m, 1H, 5-Hab), 1.19 (s, 9H, *tert*-Butyl). Anal. calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.53; H, 8.21. HR-FABMS: Obsd; *m/z* 275.1645. Calcd for $C_{17}H_{23}O_3$; *m/z* 275.1647 $(M + H)^+$.

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19. Compound **4**: mp 189–192 °C. $[\alpha]^{24}_{D}$ 4.81° (*c* 0.52, MeOH). UV (H_2O) λ_{max} 260.5 (ε 14944) (pH 2), 261.5 (ε 16043) (pH 7), 261.5 nm (ε 15151) (pH 11); ^1H NMR (DMSO-d_6) δ 8.13 (s, 1H, 2-H), 8.04 (s, 1H, 8-H), 7.21(br s, 2H, NH_2, D_2O exchangeable), 6.14 (m, 1H, 2′-H), 5.92 (m, 1H, 3′-H), 5.58 (m, 1H, 1′-H), 4.75 (t, *J* = 5.4 Hz, 1H, OH, D_2O exchangeable), 3.46 (m, 2H, 6′-Ha,b), 2.90 (m, 1H, 4′-H), 2.67 (dt, *J* = 13.7, 8.8, 8.6 Hz, 1H, 5′-Ha), 1.63 (m, 1H, 5′-Hb). Anal. calcd for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.28. Found: C, 57.19; H, 5.69; N, 30.21. HR-FABMS: Obsd; *m/z* 232.1181. Calcd for $C_{11}H_{14}N_5O$; *m/z* 232.1198 $(M + H)^+$.

20. Compound **15**: mp 235–237 °C. $[\alpha]^{24}_{D}$ –41.61° (*c* 0.22, Pyr). UV (H_2O) λ_{max} 322.5 (ε 12953) (pH 2), 320.0 (ε 19421) (pH 7), 310.5 nm (ε 20659) (pH 11); ^1H NMR (DMSO-d_6) δ 13.72 (br s, 1H, NH, D_2O exchangeable), 8.20 (s, 1H, 2-H), 8.19 (s, 1H, 8-H), 6.17 (m, 1H, 2′-H), 5.92 (m, 1H, 3′-H), 5.58 (m, 1H, 1′-H), 4.74 (t, *J* = 5.3 Hz, 1H, OH, D_2O exchangeable), 3.45 (t, *J* = 5.6 Hz, 2H, 6′-Ha,b), 2.90 (m, 1H, 4′H), 2.67 (dt, *J* = 13.8, 8.8, 8.7 Hz, 1H, 5′-Ha), 1.63 (dt, *J* = 13.8, 5.6, 5.6 Hz, 1H, 5′-Hb). Anal. calcd for $C_{11}H_{12}N_4OS$: C, 53.21; H, 4.87; N, 22.56. Found: C, 53.12; H, 4.90; N, 22.53. HR-FABMS: Obsd; *m/z* 249.0821. Calcd for $C_{11}H_{13}N_4OS$; *m/z* 249.0810 $(M + H)^+$.