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ASYMMETRIC SYNTHESIS OF L-CYCLOPENTYL CARBOCYCLIC NUCLEOSIDES

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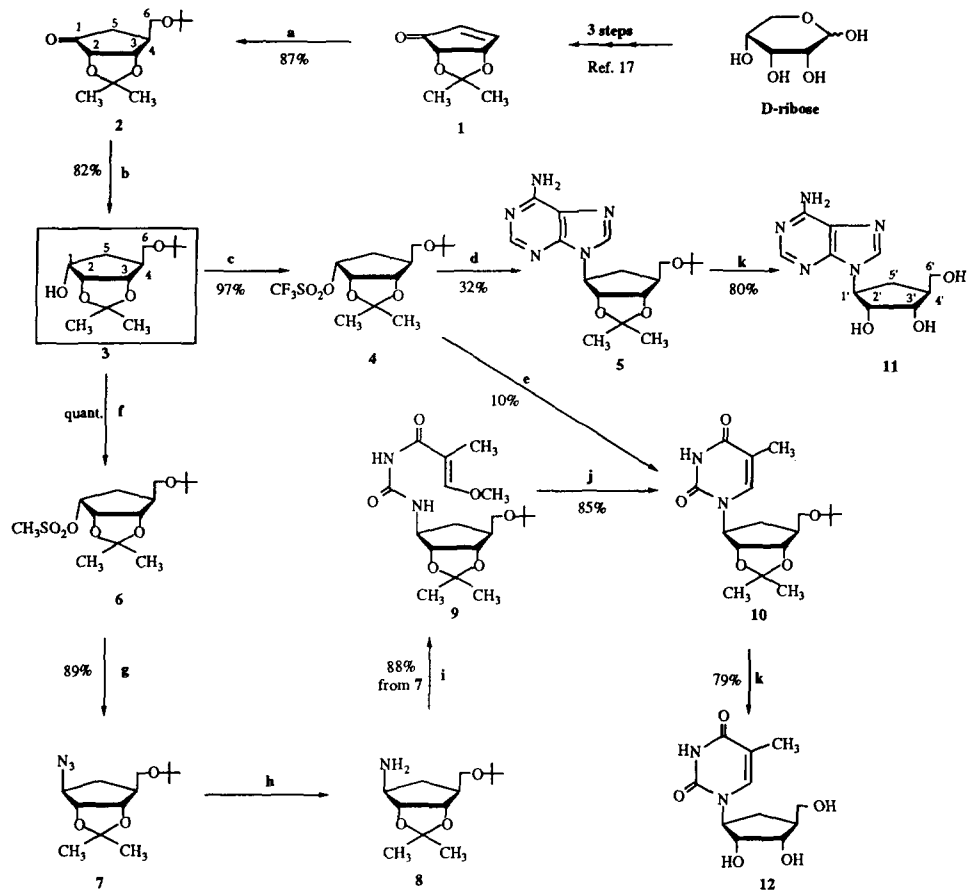
Abstract: Asymmetric synthesis of L-carbocyclic nucleosides, (+)-β-L-aristeromycin (**11**) and its thymine analog (**12**) was accomplished. The key intermediate **3** was synthesized by a regioselective conjugate addition to the enone **1** followed by DIBAL-H reduction. Coupling of **4** with heterocycle or construction of heterocyle by a linear approach gave **11** and **12**. This is the first asymmetric synthesis of L-cyclopentyl carbocyclic nucleosides.

A number of carbocyclic nucleosides have shown interesting antiviral and antitumor activities.[1,2] Among them, carbovir[3] and its 6-cyclopropyl analog 1592U89[4] are of particular interest since they both exhibit potent anti-HIV activity and 1592U89 is currently undergoing clinical studies. Recently, a number of L-nucleosides have been synthesized as antiviral agents, among which 3TC,[5] FTC,[6] L-FddC[7] and L-FMAU,[8] have shown to be the most promising L-nucleosides. Some of these nucleosides are more potent and less toxic than their D-counterparts.[9,10] Therefore, it is of interest to synthesize the corresponding L-enantiomers of biologically interesting D-nucleosides in the search for more potent and less toxic antiviral agents.

Carbocyclic adenosine, (–)-β-D-aristeromycin and its related compounds are believed to exhibit their antiviral activity by inhibiting *S*-adenosyl-L-homocysteine hydrolase, an important enzyme in RNA methylation[11]. Racemic (±)-aristeromycin and racemic thymine cyclopentyl carbocyclic nucleosides were first prepared by Shealy et al.[12,13] The first optically pure synthesis of natural (–)-β-D-aristeromycin was reported by Ohno and co-workers[14] by a chemoenzymatic method. Until now, several L-carbocyclic nucleosides have been separated from racemic mixtures by enzymatic resolutions.[15,16] As part of our drug discovery program, we initiated the asymmetric synthesis of L-cyclopentyl carbocyclic nucleosides as potential antiviral and anticancer agents. Herein, we wish to report the syntheses of L-aristeromycin and its thymine analog.

Our synthetic strategy utilized the known compound, (+)-cyclopentenone **1** as a chiral starting material, which was prepared in 3 steps from D-ribose[17] (Scheme 1). We synthesized the key intermediate cyclopentanone **2** by the modified procedure of Wolfe[18] et al. The conjugate addition of the *tert*-butoxymethyl cuprate-lithium complex to **1** yielded cyclopentanone **2** as a single isomer in 87% yield. The structure of **2**[19] was determined by ^{1}H-NMR spectroscopy along with single crystal X-ray crystallography (Figure 1). Stereoselective reduction of the carbonyl group of **2** with diisobutylaluminum hydride afforded α-alcohol **3**[20] in 82% yield. NOESY experiments showed that H-1 correlated with H-2 and H-3, indicating that the OH group of C-1 is *cis* to the isopropylidene group. The stereoselectivities of reactions from **1** to **2** and **2** to **3** are probably due to the electronic effect as well as steric hindrance of the oxygen of the isopropylidene group which prevents the nucleophiles attacking from the same side of the isopropylidene group. The alcohol **3** was then converted

Scheme 1



a: (t-BuOCH$_2$)$_2$CuLi, t-BuOMe/THF, -30° C, 30 min. b: DIBAL-H, CH_2Cl_2, -78° C, 2 h. c: $(CF_3SO_2)_2O$, py, 0° C, 30 min. d: adenine/NaH, 18-crown-6, DMF, 0-20° C , 30 h. e: thymine, K_2CO_3, 18-crown-6, DMF, 0-20° C, 18 h. f: CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0° C, 30 min. g: LiN_3, DMF, 140° C, 4 h. h: 5%Pd/C, EtOH, rt, 20 psi, 1.5 h. i: β-methoxy-α-methacryloyl isocyanate, DMF, -20 to 20° C, 10 h. j: 30% NH_4OH, EtOH, 80-100° C, 10 h. k: CF_3CO_2H/H_2O (2:1), 50° C, 3 h.

to triflate **4** with trifluoromethanesulfonic anhydride. The condensation reaction of the triflate **4** with the sodium salt of adenine in the presence of 18-crown-6 in DMF led to the product **5** in 32% yield. A similar reaction was carried out by the treatment of the triflate **4** with thymine, K_2CO_3 and 18-crown-6 in DMF, however, it gave a low yield of **10** (10%).

In order to improve the yield of the thymine analogue, a linear approach was initiated as described below: Treatment of alcohol **3** with methanesulfonyl chloride gave the mesyl derivative **6** in quantitative yield,[21] which was treated with lithium azide in DMF at 140°C to give cyclopentyl azide **7** in 89% yield. Reductive hydrogenation of **7** in the presence of 5% Pd/C followed by the treatment with β-methoxy-α-methacryloyl isocyanate[13] provided acrylurea **9** in 88% yield. The compound **9** was then cyclized to the thymine derivative **10** in 85% yield by the treatment with ammonium hydroxide in ethanol in a steel bomb at 80 to 100 °C. Deprotection of **5** with CF_3CO_2H/H_2O at 50°C resulted in (+)-β-L-aristeromycin **11**[22] in 80% yield. Similarly, the protecting group of **10** was removed to give the desired (+)-β-L-thymine nucleoside **12**[23] in 79% Yield. The anti-HIV activity for the compounds **11** and **12** was evaluated. However, both compounds did not show any significant antiviral activity (EC_{50} > 100μM). Other biological evaluations are in progress.

In summary, the first asymmetric synthesis of β-L-cyclopentyl carbocyclic nucleoside, (+)-aristeromycin and the thymine analog has been accomplished. Synthesis of other optically pure L-cyclopentyl carbocyclic pyrimidine and purine nucleosides are in progress in our laboratory.

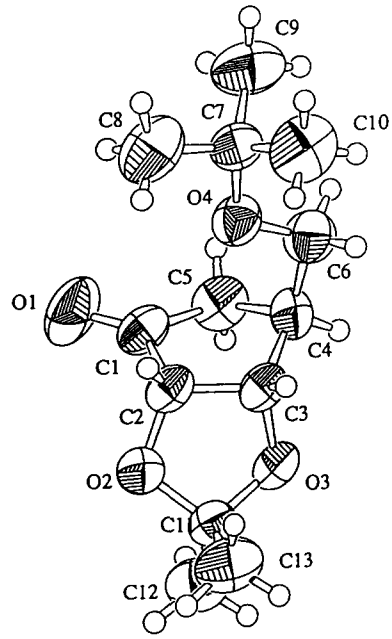


Fig. 1. ORTEP Drawing of Compound 2

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19. Compound **2**: mp. 63-65 °C; $[\alpha]^{26}_D$ +183.36 ° (c 1.15, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.62 (d, *J*=5.3 Hz, 1H, 2-H), 4.23 (d, *J*=5.3 Hz, 1H, 3-H), 3.54 (dd, *J*=2.3,8.5 Hz, 1H, 6-H), 3.35 (dd, *J*=2.6, 8.5 Hz, 1H, 6-H), 2.71 (dd, *J*=8.9,17.9 Hz, 1H, 5-H), 2.54 (d, *J*=8.9 Hz, 1H, 4-H), 2.05 (d,*J*=17.9 Hz, 1H, 5-H), 1.43 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.11 (s, 9H, *tert*-Butyl); Anal.Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.18; H, 9.13. HRMS(FAB) calcd for $C_{13}H_{23}O_4[(M+H)^+]$ 243.1596, found 243.1596.
20. Compound **3**: $[\alpha]^{25}_D$ +11.81 ° (c 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.45 (m, 2H, 2-H and 3-H), 4.24 (m, 1H, 1-H), 3.32(dd, *J*=4.4, 8.8 Hz, 1H, 6-H), 3.21 (dd, *J*=4.6, 8.8 Hz, 1H, 6-H), 2.45 (d, *J*=8.9 Hz, 1H, OH, D_2O exchangeable), 2.22 (m, 1H, 4-H), 1.84-1.88 (m, 2H, H-5), 1.36 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.14 (s, 9H, *tert*-butyl); Anal. Calcd for $C_{13}H_{24}O_4 \cdot 0.25H_2O$: C, 62.74; H, 9.92. Found: C, 62.73; H, 9.80. HRMS(FAB) calcd for $C_{13}H_{25}O_4[(M+H)^+]$ 245.1753, found 245.1728.
21. All other key intermediates and final products in Scheme 1 have been fully characterized.
22. Compound **11**: mp. 215-217 °C (dec); $[\alpha]^{25}_D$ +55.45 ° (c 0.38, DMF) [lit[16] $[\alpha]^{23}$ + 51.1 ° (c 0.3, DMF), mp 208-120 °C; lit.[18] for the (–)- enantiomer: mp 211-213 °C (dec.); $[\alpha]^{25}_D$ –56 ° (c 0.366, DMF)]; UV(H_2O) λ_{max} 259.5 nm (ε 17169)(pH 2), 261.0 nm (ε 17639)(pH 7), 261.5 nm (ε 17120)(pH 11); ^1H NMR (DMSO-d_6) δ 8.20 and 8.12 (two s, 1H, 2-H and 8-H), 7.19 (br s, 2H, NH_2, D_2O exchangeable), 4.94 (d, *J*=6.6 Hz, 1H, 6'-OH D_2O exchangeable), 4.73 (t, *J*=5.3 Hz, 1H, 1'-H), 4. 66-4.71 (m, 2H, 2'-OH and 3'-OH, D_2O exchangeable), 4.34 (dt, *J*=6.2, 9.1 Hz, 1H, 2'-H), 3.84 (m, 1H, 3'-H), 3.48-3.54 (m, 2H, 6'-H), 2.23 (dt, *J*=8.1, 8.8 Hz, 1H, 5'-H), 2.02-2.06 (m, 1H, 4'-H), 1.68-1.76 (m, 1H, 5'-H); Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 49.84; H, 5.67; N, 26.26. MS(FAB) m/z 266 $(M+H)^+$
23. Compound **12**: mp. 122-124 °C (hygroscopic); $[\alpha]^{24}_D$ +42.49 ° (c 0.41, MeOH); UV(H_2O) λ_{max} 273 nm (ε 9236)(pH 2), 273 nm (ε 8686)(pH 7), 272 nm (ε 7032)(pH 11); ^1H NMR (DMSO-d_6) δ 11.19 (s, 1H, NH, D_2O exchangeable),7.54 (s,1H, 6-H), 4.81 (d, *J*=6.5 Hz, 1H, OH, D_2O exchangeable), 4.66 (t, *J*=5.2 Hz, 1H, OH, D_2O exchangeable), 4.60 (m, 1H, 1'-H), 4.54 (d, *J*=4.1 Hz, 1H, OH, D_2O exchangeable), 3.96 (m, 1H, 2'-H), 3.69 (m, 1H, 3'-H), 3.39 (m, 2H, 6'-H), 1.88-1.96 (m, 2H, 4'-H and 5'-H), 1.76 (s, 3H, CH_3), 1.23 (m, 1H, 5'-H); Anal .Calcd for $C_{11}H_{16}N_2O_5 \cdot 0.75H_2O$: C, 48.96; H, 6.54; N, 10.38. Found: C, 48.87; H, 6.51; N, 10.20. MS(FAB) m/z 257 $(M+H)^+$

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