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Facile synthesis of 9-[(1′*R*,2′*S*)-2′-hydroxy-3′-oxocyclopentan-1′-yl]-9-*H*-adenine possessing inhibitory activity against human recombinant *S*-adenosyl-L-homocysteine hydrolase

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Abstract—Treatment of 4′-*O*-methanesulfonyl-2′,3′-*O*-isopropylidenenoraristeromycin with KOBu^t gave the corresponding 3′,4′-dehydro derivative, and subsequent deprotection resulted in the formation of 9-[(1′*R*,2′*S*)-2′-hydroxy-3′-oxocyclopentan-1′-yl]-9-*H*-adenine possessing inhibitory activity against human recombinant *S*-adenosyl-L-homocysteine hydrolase (EC 3.3.1.1). In sharp contrast to KOBu^t, when lithium azide was adopted as a base, 9-[(1′*R*,2′*S*,3′*R*)-2′,3′-*O*-isopropylidenedioxy-4′-cyclopenten-1′-yl]-9-*H*-adenine was selectively obtained, and subsequent deprotection afforded DHCeA, which is a well-known potential antiviral agent.

The cellular enzyme *S*-adenosyl-L-homocysteine (SAH) hydrolase (EC 3.3.1.1) has emerged as a target enzyme for the molecular design of antiviral agents.[1] SAH is formed after the donation of the methyl group of *S*-adenosyl-L-methionine (SAM) to a methyl acceptor and is hydrolyzed to adenosine and homocysteine by SAH hydrolase physiologically. Therefore, inhibition of SAH hydrolase results in cellular accumulation of SAH, which is a potent feedback inhibitor of SAM-dependent biological methylation such as the cap-structure at the 5′-end of eukaryotic mRNA.[1,2] The eukaryotic mRNA must possess a methylated 5′-cap structure for stability against phosphatases and ribonucleases, for proper binding to ribosomes, and for the promotion of splicing. An uncapped mRNA, therefore, is much less likely to be translated into its respective protein. In addition to the antiviral effects of SAH hydrolase inhibitors, several SAH hydrolase inhibitors have shown other pharmaceutical effects of clinical importance including antiparasitic,[3] antiarthritic[4] and immunosuppressive[5] effects.

In this paper, we describe a method for the preparation of a new SAH hydrolase inhibitor derived from noraristeromycin possessing SAH hydrolase inhibitory activity and its inhibitory effect against human recombinant SAH hydrolase.

Compound **2** was prepared by palladium-coupling reaction of (1*S*,4*R*)-*cis*-4-acetoxy-2-cyclopenten-1-ol (**1**) with N^6-benzoyladenine.[6] Osmium oxidation of **2** gave N^6-benzoylnoraristeromycin (**3**). Subsequent two-step reaction from **3** afforded 2′,3′-*O*-isopropylidenenoraristeromycin (**4**). Reaction of **4** with methanesulfonyl chloride in the presence of triethylamine and 4-*N*,*N*-dimethylaminopyridine in dichloromethane gave the corresponding 4′-*O*-methanelsulfonyl derivative (**5**) in 80% yield (Scheme 1). Treatment of **5** with potassium *tert*-butoxide (KOBu^t) in DMF at room temperature gave [(1′*R*,2′*S*)-2′,3′-*O*-isopropylidenedioxy-3′-cyclopenten-1′-yl]-9-*H*-adenine (**10**) in 34% yield in Scheme 2. Deprotection of **10** with aqueous trifluoroacetic acid gave 9-[(1′*R*,2′*S*)-2′-hydroxy-3′-oxocyclopentan-1′-yl]-9-*H*-adenine (**11**), quantitatively. In sharp contrast to KOBu^t, when lithium azide was adopted as a base, 9-[(1′*R*,2′*S*,3′*R*)-2′,3′-*O*-isopropylidenedioxy-4′-cyclopenten-1′-yl]-9-*H*-adenine (**12**) was predominantly obtained in 86% yield by the reaction of **5** with 2 equiv. of LiN_3 at 130°C. Deprotection of **12** with aqueous trifluoroacetic acid afforded 9-[(1′*R*,2′*S*,3′*R*)-2′,3′-dihydroxy-4′-cyclopenten-1′-yl]-9-*H*-adenine (DHCeA, **13**), which is a well-known potential antiviral agent.[7] This

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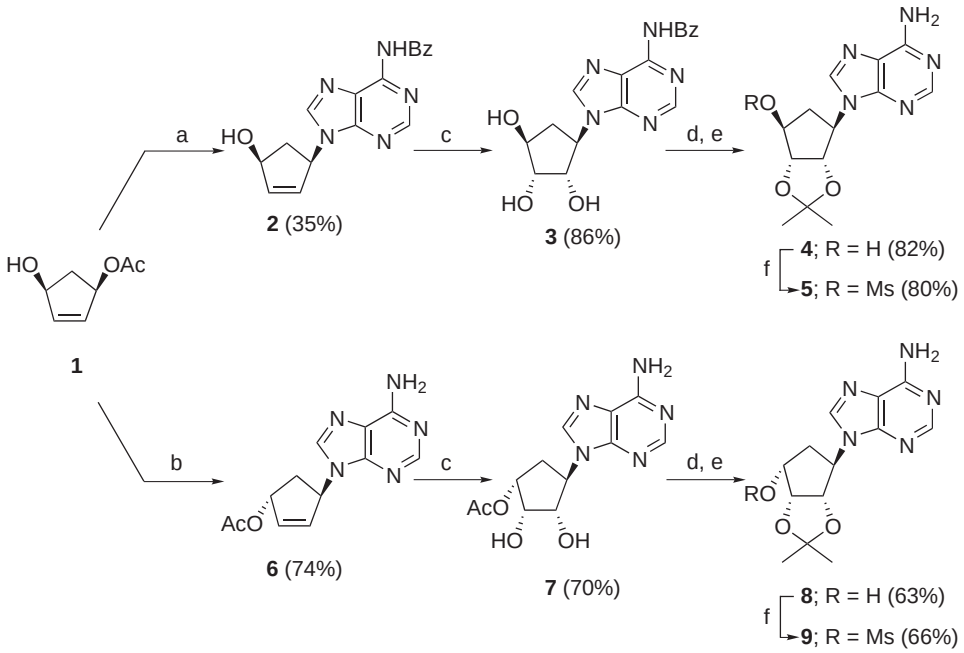
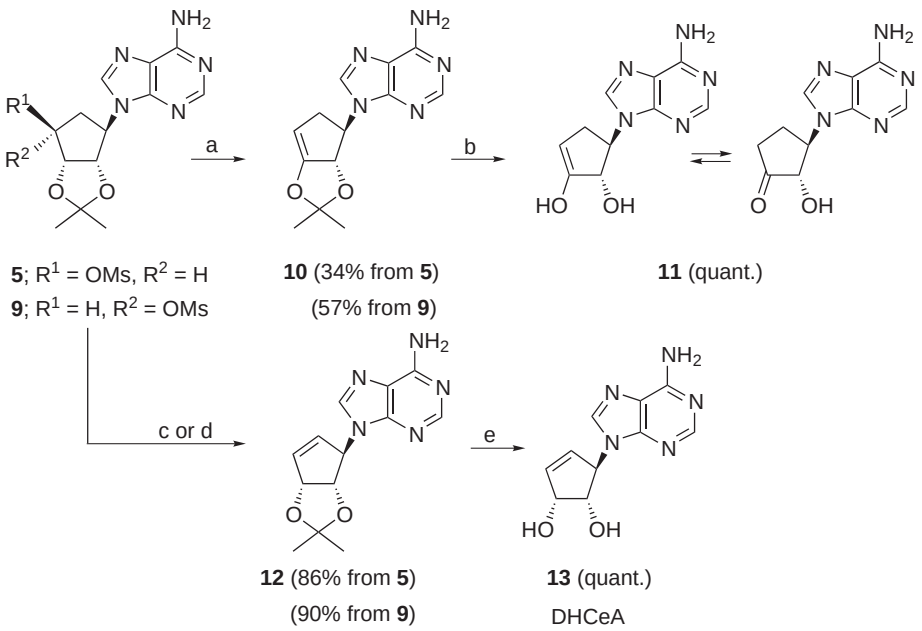
methodology is very convenient for the preparation of antiviral DHCeA (**13**). The 4′-methanesulfonyl compound **5** is a versatile precursor for the preparation of modified carbocyclic nucleosides. On the other hand, reaction of the 4′-enantimer (**9**) of **5** was prepared via the Mitsunobu reaction of **1** with adenine as shown in Scheme 1. Treatment of **9** with LiN_3 in DMF for 7 h at 130°C gave **12** in 90% yield. Treatment of **9** with KOBu^t resulted in the formation of **10** in 57% yield.

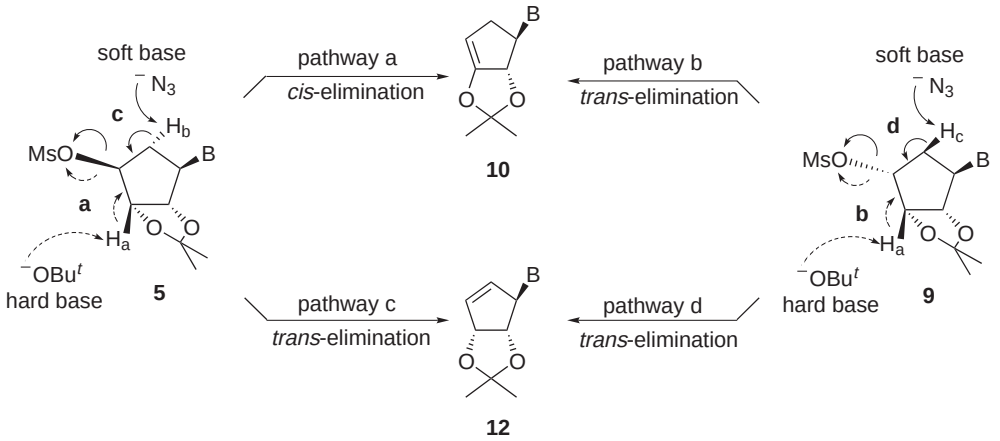
Taking into consideration the above results, the mechanism for the formation of **10** and **12** was explained in terms of the HSAB principle (see Scheme 3). Thus, a hard base ($^-$OBu^t) attacked the hard acid Ha of the 3′-position of **5** to give **10** according to *cis*-elimination (pathway a). When the 4′-anomer **9** was adopted as the starting material, $^-$OBu^t also attacked the same hard acid Ha to give **10** via *trans*-elimination (pathway b). The *trans*-elimination of the 4′-anomer **9** would smoothly proceed rather than the *cis*-elimination of **5**. In the case of NaN_3, a soft base ($^-N_3$) attacked the hydrogen (Hb) of **5** or the hydrogen (Hc) of **9** to afford **12** via the corresponding *trans*-elimination (shown in pathways c and d).



Scheme 1. (a) N^6-benzoyladenine, NaH, $(Ph_3P)_4Pd$, Ph_3P, DMSO, THF; (b) adenine, DEAD, Ph_3P, THF; (c) OsO_4, NMO, THF, H_2O; (d) acetone, PTSAM, $CH(OEt)_3$; (e) NH_3-MeOH; (f) MsCl, DMAP, Et_3N, CH_2Cl_2.



Scheme 2. (a) KOBu^t (5 equiv.), DMF, rt, 15 min; (b) TFA 67%, rt, 15 min; (c) for 5, LiN_3 (2 equiv.), DMF, 130°C, 3 h; (d) for 9, LiN_3 (3.5 equiv.), DMF, 130°C, 7 h; (e) TFA, rt, 15 min.



Scheme 3.

The structure of these compounds (**2–13**) was fully supported by spectral data (^{1}H NMR, ^{13}C NMR, MS, and HRMS).[8] Compound **11** showed inhibitory effect against human recombinant SAH hydrolase[9] with IC_{50} value of 15 μM.[10]

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8. Selected data for **10**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.41 (6H, s, isopropylidene), 2.79–2.93 (2H, m, H-5′), 4.90 (1H, t, $J=5.6$ Hz, H-1′), 5.47 (1H, d, $J=6.0$ Hz, H-2′), 6.33 (2H, brs, NH_2), 6.68 (1H, m, H-4′), 8.28 and 8.39 (each 1H, each s, H-2 and H-8). MS m/z (%): 273 (M^+, 28), 215 (100), 186 (63). HRMS m/z: 273.1219 ($C_{13}H_{15}N_5O_2$, requires 273.1226). Selected data for **11**: ^{1}H NMR (D_2O, 400 MHz): δ 2.73 (1H, d, $J=16.8$ Hz, H-5′), 2.73 (1H, d, $J=16.8$ Hz, H-5′), 4.37 (1H, m, H-1′), 4.94 (1H, d, $J=5.2$ Hz, H-2′), 6.37 (1H, s, H-4′), 8.27 and 8.32 (each 1H, each s, H-2 and H-8). MS m/z (%): 233 (M^+, 36), 204 (100), 186 (21). HRMS m/z: 233.0919 ($C_{10}H_{11}N_5O_2$, requires 233.0913). Selected data for **12**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H, s, isop), 1.48 (3H, s, isop), 4.68 (1H, d, $J=5.2$ Hz, H-2′), 5.47 (1H, d, $J=5.2$ Hz, H-1′), 5.62 (1H, s, H-3′), 5.94 (1H, dd, $J=6.0$, 1.0 Hz, H-5′), 6.05 (2H, brs, NH_2), 6.31 (1H, dd, $J=6.0$, 1.0 Hz, H-4′), 7.66 and 8.36 (each 1H, each s, H-2 and H-8). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.73, 27.33, 65.65, 83.93, 84.67, 112.42, 119.89, 129.32, 138.41, 138.70, 149.96, 152.49, 155.10. MS m/z (%): 273 (M^+, 12), 215 (100), 186 (86). HRMS m/z: 273.1220 ($C_{13}H_{15}N_5O_2$, requires 273.1226). Selected data for **13** (DHCeA): ^{1}H NMR ($(CD_3)_2SO$, 400 MHz): δ 4.30 (1H, m, H-2′), 4.54 (1H, d, $J=3.2$ Hz, H-3′), 5.38 (1H, d, $J=5.8$ Hz, H-1′), 5.98 (1H, m, H-5′), 6.13 (1H, m, H-4′), 7.42 (2H, brs, NH_2), 8.12 and 8.15 (each 1H, each s, H-2 and H-8). ^{13}C NMR ($(CD_3)_2SO$, 100 MHz): δ 64.76, 72.49, 76.16, 119.75, 132.30, 136.02, 140.02, 151.36, 155.27. MS m/z (%): 233 (M^+, 8), 136 (100), 108 (13). HRMS m/z: 233.0913 ($C_{10}H_{11}N_5O_2$, requires 233.0913)
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10. Compounds **3** and **13** showed moderate inhibitory activity, giving IC_{50} values of 281 and 562 μM, respectively. Compound **7** had no inhibitory activity against human recombinant SAH hydrolase.