Enantiospecific Synthesis of the Fluoro and Epimeric Derivatives of 5′-Noraristeromycin

Suhaib M. Siddiqi, Frank P. Oertel, Xing Chen and Stewart W. Schneller*

Department of Chemistry, University of South Florida, Tampa, Florida, USA 33620-5250

The synthesis of derivatives of 5′-noraristeromycin **1** in which its C-4′ hydroxy group has been (*i*) replaced by a fluorine atom (**5**) and (*ii*) inverted (**6**) is described starting from the diacetate of (*Z*)-cyclopentene-3,5-diol.

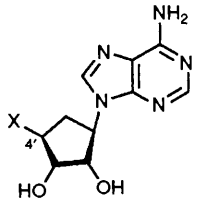
Inhibition of (*S*)-adenosyl-L-homocysteine (AdoHcy) hydrolase by derivatives of adenosine (*e.g.* carbocyclic adenosine or aristeromycin, **1**) has been a productive area in the pursuit of antiviral agents.[1] A common problem with these compounds that limits their potential usefulness, however, is the associated toxicity arising from conversion to the 5′-phosphates.[2,3] To circumvent this undesirable consequence recent efforts have focused on derivatives of **1** either less likely to undergo phosphorylation (*e.g.* **2**)[4] or incapable of doing so (*e.g.* **3**[5] and **4**[6]). Both **2** and **3** are promising antiviral candidates that inhibit AdoHcy hydrolase while showing little or no toxicity.

In exploring the lead provided by **2** and **3**, the fluoro derivative **5** arose as a meaningful target compound. Compound **5** is related (*i*) to **2** owing to the similarity of the fluorine atom to the hydroxy group in size, electronegativity and ability to participate in hydrogen bonding,[7] and (*ii*) to **3** because structural modifications in which a hydrogen is replaced by a fluorine atom have found relevance in the production of biologically useful compounds[8] owing to similarities in the van der Waals radii of hydrogen and fluorine but dramatic differences in their electronegativities.[9] The synthetic approach to **5** was designed also to avail a means to the epimer of **2** (that is, **6**) to provide a molecule that could be used to ascertain the biological consequences of C-4′ hydroxy inversion There is little literature precedence[6a,10] to predict how significant the configuration at the C-4′ centre of carbocyclic adenosines (*e.g.* **1**) is to the inhibition of AdoHcy hydrolase.

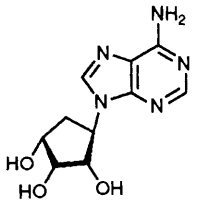
The synthesis of both **5** and **6** (Scheme 1) began with subjecting the diacetate of (*Z*)-cyclopentene-3,5-diol **7**[11] to hydrolysis with *Pseudomonas cepacia* lipase (PCL)[12] under carefully monitored conditions (pH) to assure monohydrolysis.[6b,13] The resultant monoacetate (+)-**8**† underwent the Mitsunobu reaction[15] with 6-chloropurine to yield **9**. Standard glycolization conditions on **9** led to a mixture of the desired **10**‡§ and **11**‡§ in approximately a 2:1 ratio. Following separation of this mixture using flash column chromatography, **10** and **11** were distinguished by a 1D nuclear Overhauser enhancement determination. In this regard, pre-irradiation of H-2′ in **10** resulted in enhancement of the H-3′, H-4′ and H-5′$_a$ protons; no enhancement was observed for H-1′ and H-5′$_b$. This confirmed the *cis*-relationship between the hydroxy groups and the acetate.

Ammonolysis of **10** provided **6**‡¶ whereas isopropylidenation (to **12**) followed by hydrolysis resulted in **13**.§ Using diethylaminosulfur trifluoride (DAST),[16] **13** was converted into **14**. Ammonolysis of **14** with subsequent deprotection yielded the target compound **5**.‡‖

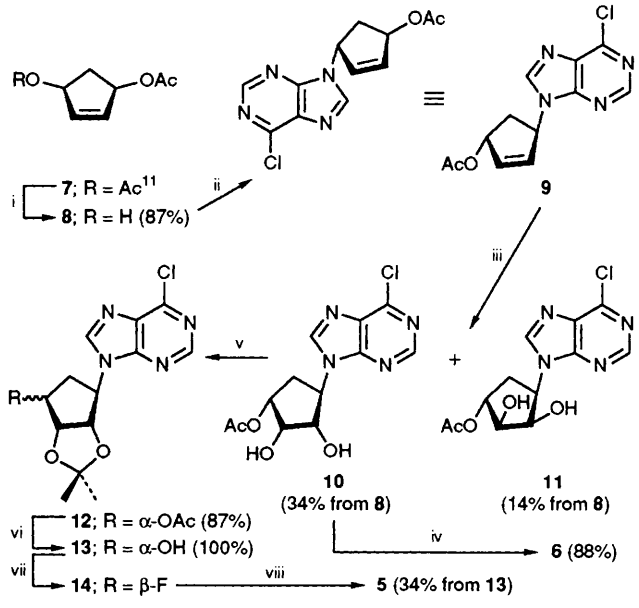
The biological properties of **5** and **6** will be reported as they become available.



1; X = CH_2OH
2; X = OH
3; X = H
4; X = Me
5; X = F



6



Scheme 1 *Reagents and conditions*: i, *Pseudomonas cepacia* lipase, 0.1 mol dm^{-3} phosphate buffer, pH 7, 25 °C; ii, 6-chloropurine–PPh_3–diethyl azodicarboxylate in tetrahydrofuran (THF), room temp.; iii, OsO_4–*N*-methylmorpholine *N*-oxide in THF–H_2O, room temp.; iv, NH_3 in MeOH, 100 °C; v, 2,2-dimethoxypropane–catalytic *p*-Me-$C_6H_4SO_3H$ in acetone, room temp.; vi, K_2CO_3 in aq. MeOH, room temp.; vii, DAST in CH_2Cl_2, −78 °C to room temp.; viii, (*a*) NH_3 in MeOH, 100 °C; (*b*) dil. HCl.

† $[\alpha]_D^{25}$ + 67.30 (*c* 0.27, $CHCl_3$) {lit.[14a] $[\alpha]_D^{23}$ +66.30 (*c* 1.53, $CHCl_3$), enantiomeric excess 99%; lit.[14b] $[\alpha]_D^{20}$ +65.60 (*c* 2.3, $CHCl_3$ + 1% EtOH)}].

‡ Satisfactory microanalytical data was obtained for this compound.

§ Satisfactory ^1H and ^{13}C NMR spectral data were recorded for this compound.

¶ *Data* for **6**: pale-yellow solid; m.p. 220 °C (decomp.); $[\alpha]_D^{25}$ −43.7 (*c* 1.0, dimethylformamide); ^1H NMR [$(CD_3)_2SO$] δ 1.90–1.94 (m, 1 H, H-5′), 2.50–2.75 (m, 1 H, H-5′), 3.20 (br, 1 H, OH), 3.45 (m, 1 H, H-1′), 3.86 (m, 1 H, H-4′), 4.15 (m, 2 H, H-2′ and H-3′), 5.09 (m, 2 H, OH), 7.19 (s, 2 H, NH_2), 8.13 (s, 1 H, H-2), 8.18 (s, 1 H, H-8); ^{13}C NMR [$(CD_3)_2SO$] δ 39.50, 52.77, 71.62, 73.52, 78.72, 140.59, 141.02, 151.37, 151.86, 155.70. The spectral data for this compound is different from **2**[4] assuring that no inversion of configuration had occurred in the conversion of **10** into **6**.

‖ *Data* for **5**: white solid; m.p. 128–130 °C; $[\alpha]_D^{25}$ −40.38 (*c* 1.0, MeOH); ^1H NMR [$(CD_3)_2SO$] δ 2.10–2.86 (m, 2 H, H-5′), 3.40 (br, 2 H, OH), 4.11 (m, 1 H, H-1′), 4.60 (m, 1 H, H-4′), 5.03–5.62 (m, 2 H, H-2′ and H-3′), 7.22 (s, 2 H, NH_2), 8.16 (s, 1 H, H-2), 8.18 (s, 1 H, H-8); ^{13}C NMR [$(CD_3)_2SO$] δ 33.56 (d, J_{CCF} 21.97 Hz), 52.66, 74.01, 74.49 (d, J_{CCF} 24.41 Hz), 95.40 (d, J_{CF} 178.23 Hz), 140.48, 140.69, 150.08, 152.45, 156.41.

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