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

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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.* 3⁵ and 4⁶). 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 compounds8 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 reaction¹⁵ 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



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

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 $6\ddagger$ 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 $5.\ddagger$

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



Scheme 1 Reagents and conditions: i, Pseudomonas cepacia lipase, 0.1 mol dm⁻³ phosphate buffer, pH 7, 25 °C; ii, 6-chloropurine–PPh₃-diethyl azodicarboxylate in tetrahydrofuran (THF), room temp.; iii, OSO_4 -N-methylmorpholine N-oxide in THF-H₂O, room temp.; iv, NH₃ in MeOH, 100 °C; v, 2,2-dimethoxypropane–catalytic *p*-Me-C₆H₄SO₃H in acetone, room temp.; vi, K₂CO₃ in aq. MeOH, room temp.; vii, DAST in CH₂Cl₂, -78 °C to room temp.; viii, (*a*) NH₃ in MeOH, 100 °C; (*b*) dil. HCl.

[‡] 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 [(CD₃)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, NH₂), 8.13 (s, 1 H, H-2), 8.18 (s, 1 H, H-8); ¹³C NMR [(CD₃)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 2⁴ 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 [(CD₃)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, NH₂), 8.16 (s, 1 H, H-2), 8.18 (s, 1 H, H-8); ¹³C NMR [(CD₃)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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