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(±)-3'-DEOXYARAARISTEROMYCIN VIA A SURPRISING REARRANGEMENT

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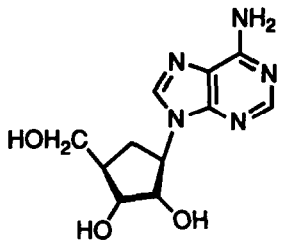
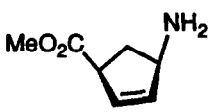
Summary: Hydrolysis of (±)-3β-acetoxy-4α-benzamido-1α-cyclopentanemethyl acetate (**5**) with 6 N hydrochloric acid has been found to give an amine in which the configuration at C-3 has been inverted. This conclusion was reached following conversion of the amine into (±)-3'-deoxyaraaristeromycin (**8**) by following a standard adenine formation process of (i) reaction with 5-amino-4,6-dichloropyrimidine, (ii) ring closure with diethoxymethyl acetate, and (iii) ammonolysis. Use of basic hydrolysis conditions with **5** led to the expected (±)-3'-deoxyaristeromycin (**7**).

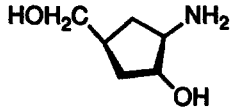
Carbocyclic nucleosides are becoming increasingly important as a source of antiviral agents.[1] An important group among this class of nucleosides is compounds derived from, and including, carbocyclic adenosine (aristeromycin, **1**), many of which express their activity as inhibitors of *S*-adenosyl-L-homocysteine hydrolase.[1c,2,3] To develop a synthetic means to new carbocyclic adenosines, we considered the use of (±)-**2**[4] as a functionally rich molecule that could be converted[1a] into (±)-2'- and (±)-3'-substituted carbocyclic adenosines. Following exploratory work with (±)-**2**, enantiomerically pure products[5] could then be prepared in a similar fashion.



(-)-**1**



(±)-**2**

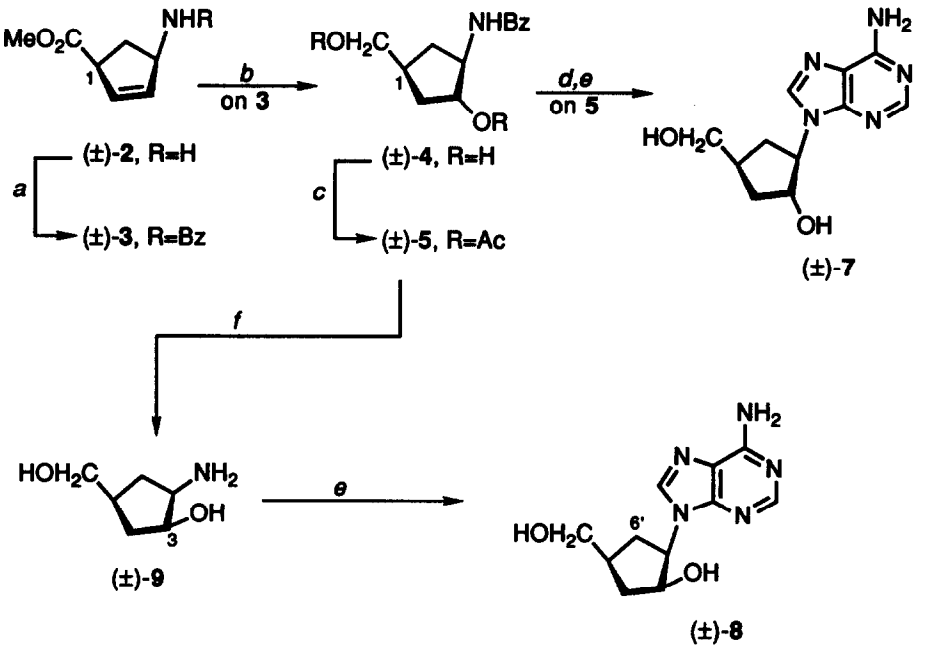


(±)-**6**

This plan began with the hydroboration of (±)-**3**[6-8] (Scheme 1) to give a 78% yield of a product (**4**) that was purified and characterized (including X-ray analysis) as its diacetate derivative **5**.[7,9] Hydrolysis of **5** using barium hydroxide[10] provided (±)-**6** whose structure was assigned by its conversion into the known[11] (±)-3'-deoxyaristeromycin (**7**) following a standard preparative sequence: (i) reaction with 5-amino-4,6-dichloropyrimidine, (ii) ring closure with diethoxymethyl acetate, and (iii) ammonolysis.[3]

Interestingly, when **5** was treated with 6 N hydrochloric acid, which are stronger conditions[12] than has customarily been used for hydrolysis of similar cyclopentyl amide-acetates,[4,13] a product resulted (originally assumed to be **6**) that, when carried through the same sequence of reactions that gave **7**, yielded a carbocyclic adenosine different than **7**. Using 2-D nmr techniques, the new material was identified as 3'-deoxyaraaristeromycin (**8**).[7,14] In this regard, a DEPT 135 experiment showed there to be three methylene

Scheme 1

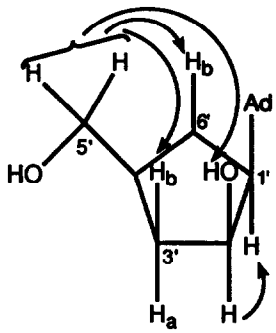


Reaction conditions: *a*, BzCl/pyridine/Et_3N in CH_2Cl_2; *b*, (i) BH_3•THF; (ii)3 M NaOH then 30% H_2O_2; *c*, Ac_2O/pyridine; *d*, $Ba(OH)_2/H_2O$/heat; *e*, (i) 5-amino-4,6-dichloropyrimidine/Et_3N in 2-methoxyethanol; (ii) $AcOCH(OEt)_2$ then conc. HCl; (iii) NH_3/MeOH, 100 °C; *f*, 6 N HCl, reflux

carbons and five methine carbons. Following this, a standard COSY 90 experiment allowed assignment of the protons,[14,15] and, together with a subsequent HMQC[16] experiment, permitted assignment of the protonated carbons.[14,15] With this information available, a nuclear Overhauser enhancement-difference (nOe-difference) experiment was carried out to determine the stereochemical relationships of the cyclopentyl substituents. The Figure (next page) shows the relevant nOe responses that were observed after irradiation of the H-5' and the H-2' hydrogens. In the former regard, irradiation of H-5' demonstrated that nOe was transferred to the H_b-6', H_b-3', and the 2'-OH whereas no nOe was transferred to H-2'. Furthermore, irradiation of H-2' caused nOe to be transferred to H-1' with no nOe transfer to the H-5' hydrogens. This data proves conclusively that the H-5' and 2'-OH substituents are located on the same face of the cyclopentyl and that the H-2' and the H-1' are similarly related to one another on the other face. This structural analysis of **8** points to (±)-**9** as the product arising from acidic hydrolysis of (±)-**5**.

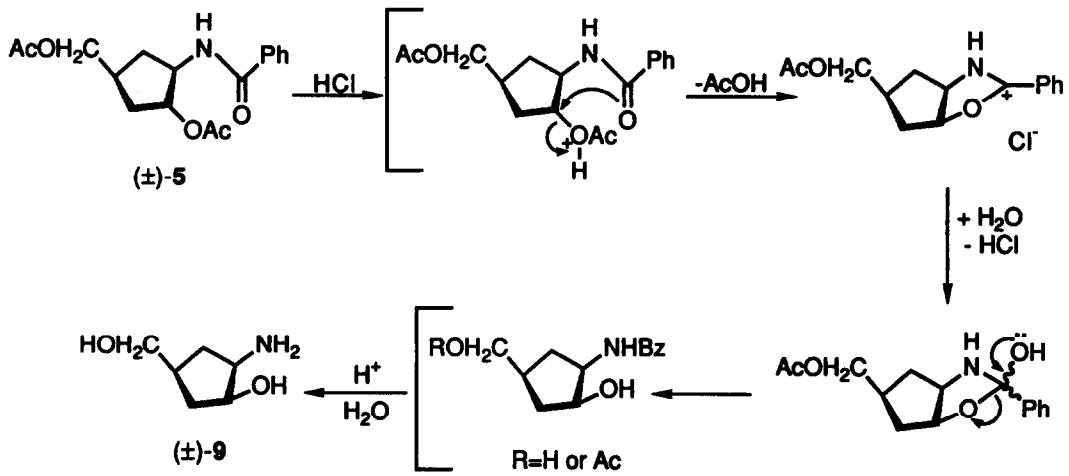
In analyzing the formation of **9**, we assumed that the conditions used for building the purine ring from a cyclopentylamine were not likely to cause the observed C-2' epimerization. As a consequence, the inversion of the hydroxyl substituent at the C-2 center of (±)-**5** is proposed to occur via the pathway shown in Scheme 2.

Acknowledgments. This research was supported by funds from the Department of Health and Human Services (NO1-AI-72645) and this is appreciated. We are also grateful to Dr. Lyle Castle for his assistance in the nmr spectral analysis of **8**.



Figure

Scheme 2[17]



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6. The benzoyl derivative of (±)-2 (that is, 3)[8] was chosen in preference to the acetyl derivative[4] due to a concern that hydroboration of the latter material could have caused reduction of the N-acetyl group to an ethyl substituent that could have been recalcitrant to eventual removal. On the other hand, if a similar reduction occurred with (±)-3, an N-benzyl group would result, which could be hydrogenolytically removed to give the desired primary amine for subsequent transformation into a carbocyclic nucleoside.
7. Satisfactory microanalytical data was obtained for this compound.
8. Compound (±)-3: white crystals; mp 72-73 °C; R_f = 0.23 (hexane-AcOEt, 2:1); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.85-2.70 (2 m, 2 H, H-5), 3.60-3.75 (m, 1 H, H-1), 3.74 (s, 3 H, OMe), 5.10-5.30 (m, 1 H, H-4), 5.90-6.10 (m, 2 H, H-2 and H-3), 6.95 (brd, 1 H, NH), 7.40-7.50 (m, 3 H, 3 Ar-H), 7.80-7.90 (m, 2 H, 2 Ar-H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 34.58, 49.35, 52.39, 54.52, 126.99, 128.52, 131.37, 131.80, 134.45, 134.86, 166.20, 177.52.
9. Compound (±)-5: white crystals; mp 76-77 °C; R_f = 0.35 (hexane-AcOEt, 1:1); R_f for an unknown by-product = 0.50 (hexane-AcOEt, 1:1); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.31-1.38 (m, 1 H, H-1), 1.87-1.91 (m, 2 H, H-2), 2.03 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 2.50-2.55 (m, 2 H, H-5), 3.96-4.03 (m, 2 H, CH_2-OAc), 4.33-4.37 (m, 1 H, H-4), 5.16-5.29 (m, 1 H, H-3), 7.12 (d, 1 H, NH), 7.37-7.49 (m, 3 H, 3 Ar-H), 7.77 (d, 2 H, 2 Ar-H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 20.89, 21.13, 32.56, 33.82, 34.00, 56.72, 67.43, 77.93, 127.01, 128.50, 131.50, 134.21, 167.49, 171.10, 171.66.
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12. Efforts to use less concentrated hydrochloric acid failed to cause hydrolysis of the benzamide group.
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14. Compound (±)-8: white crystals; mp 208-209 °C; R_f = 0.30 (CH_2Cl_2-MeOH, 5:1); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.53 (m,1 H, H_b-3'), 2.01-2.52 (m, 4 H, H_a-3', H-4', and H-6'), 3.49 (d, 2 H, H-5'), 4.15 (m, 1 H, H-2'), 4.71-4.74 (m, 2 H, H-1' and 5'-OH), 4.95 (brs, 1 H, 2'-OH), 7.09 (brs, 2 H, NH_2), 8.12 (s, 1 H, H-2), 8.13 (s, 1 H, H-8); ^{13}C NMR (360 MHz, DMSO-d_6) δ 31.3 (C-6'), 35.9 (C-3'), 36.7 (C-4'), 57.6 (C-1'), 65.5 (C-5'), 70.1 (C-2'), 118.51 (C-5), 140.21 (C-8), 149.71 (C-4), 151.88 (C-2), 155.73 (C-6).
15. The exocyclic methylene is designated as H-5'; the endocyclic methylenes are represented as H-3' and H-6'.
16. The HMQC spectrum was acquired using the standard Bruker pulse program invbdgtp using the BIRD sequence optimized $^1J_{CH}$ = 165 Hz.
17. The point at which the C-5' acetate hydrolysis occurs is not explicitly depicted in this Scheme.

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