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5′-Homoaristeromycin. Synthesis and antiviral activity against orthopox viruses

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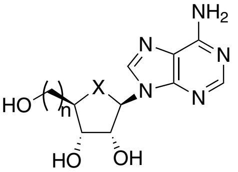
Abstract—An efficient synthesis of 5′-homoaristeromycin has been developed. This permitted an extensive antiviral analysis, which found potent activity toward vaccinia, cowpox, and monkeypox viruses. For comparative purposes, 5′-homoadenosine was made available by a newly designed route and found to be inactive.

Inhibitors of *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase have shown promise as antiviral agents[1,2] by disrupting essential viral macromolecular methylation processes.[2] Carbocyclic nucleosides [3] represent a prominent class of compounds whose antiviral potential has been traced to such an effect.[1] Within that group, carbocyclic adenosine (aristeromycin, **1**) is at the center of these investigations[4] but its promise is limited by a toxicity arising from 5′-phosphate formation.[5]

Structural modifications of **1** with the aim of reducing phosphate-based toxicity have yielded meaningful drug candidates.[6] An approach not explored, however, is extension of the C-5′ hydroxymethyl side chain by a methylene group to provide the C-5′ homolog of aristeromycin (**2**). This analog can be expected[7] to have displaced the phosphate-susceptible hydroxyl from the phosphate-transfer zone in the kinases responsible for metabolism to **1** to its nucleotides. In support of this, **2** has been reported[8] to be inactive against HSV-1 and HSV-2, possibly, due to its failure to be phosphorylated (Fig. 1).



1, X = CH_2, n = 1
2, X = CH_2, n = 2
3, X=O, n=2

Figure 1.

To investigate **2** more thoroughly as a possible antiviral agent a more practical synthesis of it was necessary. For comparative antiviral purposes, 5′-homoadenosine (**3**) was also sought by a much more efficient way than exists in the literature.[9] The results of this effort are communicated here.

Existing methods[8,10,11] for preparing 5′-homoaristeromycin (**2**) suffer from too many steps, limited scale-up, low yields and, in one case, resulting in a racemic product. Therefore, an efficient and stereoselective synthesis of **2** was needed. Starting from enone **4**[12] (Scheme 1), 1,4-addition of ethyl trimethylsilylacetate followed by in situ cleavage of the trimethylsilyl group furnished, stereoselectively, the ketone ester **5** as the only product. The stereochemistry at C-4 of **5** was derived from the fact (i) that a 1,4-addition to the concave structure of **5** can be expected[13] to give a β (up) product and (ii) that **5** was converted into the known **2**. Reduction of **5** with sodium borohydride provided the coupling precursor **6**, which has been reported via a more tedious way.[14] Mitsunubo coupling reaction of **6** with 6-chloropurine furnished **7**. Selective reduction of **7** with diisobutylaluminum hydride (DIBAL) yielded the desired alcohol **8**.

Keywords: Carbocyclic nucleosides; Nucleoside homologation; Monkeypox.

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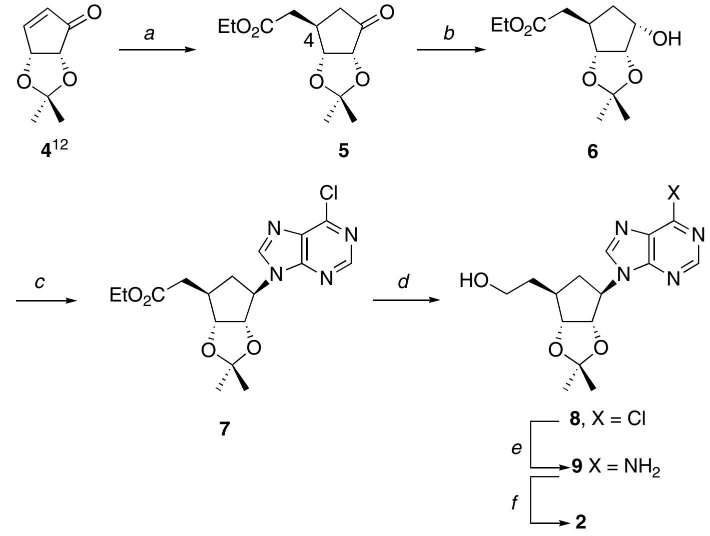
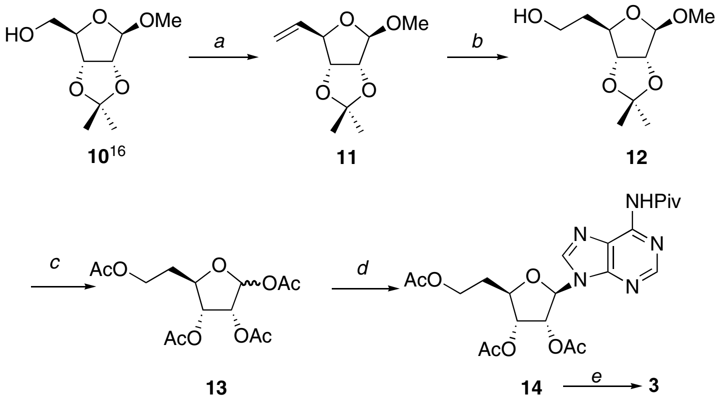


Scheme 1. Reagents and conditions: (a) (i) ethyl (trimethylsilyl)acetate, *n*-BuLi, DIPA, HMPA/THF, −78 °C, (ii) KF, EtOH/H_2O, rt, 84% for two steps from **4**; (b) $NaBH_4$, MeOH, ice temp, 100%; (c) 6-chloropurine, Ph_3P, DIAD, THF, 0–50 °C, 52%; (d) DIBAL, CH_2Cl_2, −50 °C, 80%; (e) NH_3/MeOH, 94%; (f) HCl/MeOH, 95%.



Scheme 2. Reagents and conditions: (a) (i) DMSO, DIPEA, SO_3-Py, CH_2Cl_2, 90%, (ii) Ph_3PCH_3Br, *t*-BuOK, Et_2O, 75%; (b) 9-BBN, THF, then NaOH, H_2O_2, 97%; (c) (i) 70% AcOH, 85 °C; (ii) Ac_2O, DMAP, pyridine, 85% for two steps from **12**; (d) Adpiv, HMDS, TMSCl, TMSOTf, 60%; (e) NH_3/MeOH, 91%.

Ammonolysis of **8** (to **9**) followed by hydrolytic deprotection smoothly afforded **2** in good overall yield.[15]

The known syntheses of 6′-homoadenosine[9] (**3**) either involved many steps[9a] or suffer a low yield of the final product.[9b,c] Our plan (Scheme 2) envisioned beginning with homologation of **10**.[16] Side chain oxidation of **10** followed by Wittig olefination afforded **11**. Submitting **11** to regioselective hydroboration with 9-BBN followed by oxidative hydrolysis, smoothly provided **12** in high yield. Hydrolysis of **12** with acetic acid produced a tetrol, which was fully protected with acetic anhydride to provide the anomeric acetate **13**. The coupling reaction of **13** with *N*-pivaloyl protected adenine under Vorbrüggen glycosylation conditions yielded the desired N-9 product **14** as the only isolated product. Deprotection of **14** with ammonia furnished **3** in good overall yield[17] from D-ribose.

Compounds **2** and **3** were evaluated against a wide variety of both DNA viruses and RNA viruses.[18] From this, very significant effects were seen for **2** toward vaccinia (IC_{50} 1.2 μg/mL), cowpox (IC_{50} 0.12 μg/mL), and monkeypox (IC_{50} 0.12 μg/mL) viruses, all in Vero 76 cells with $CC_{50} > 100$ μg/mL. This observation is particularly noteworthy since it is well known that vaccinia is susceptible to AdoHcy hydrolase inhibitors but cowpox was thought not to be.[18e] In any case, details of this investigation and the, possibly, less notable activity of **2** toward other viruses[18] will be forthcoming, including its potency toward variola.[19] Analog **3** was inactive in all of the assays employed.[18]

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15. Selected data for **2**: mp 178–179 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 8.11 (s, 1H), 7.17 (s, 2H), 4.90 (d, $J = 6.27$ Hz, 1H), 4.68 (d, $J = 4.63$ Hz, 1H), 4.57 (m, 1H), 4.43 (t, $J = 5.12$ Hz, 1H), 4.35 (m, 1H), 3.71 (m, 1H), 3.46 (m, 2H), 2.24 (m, 1H), 1.97 (m, 1H), 1.74 (m, 2H), 1.58 (m, 1H);[8] ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 152.1, 149.6, 140.2, 119.3, 74.9, 74.3, 59.9, 59.4, 40.0, 37.4, 32.5. Anal. Calcd for $C_{12}H_{17}N_5O_3$: C, 51.60; H, 6.14; N, 25.08. Found: C, 51.39; H, 6.18; N, 24.81.
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17. Selected data for **3**: mp 223–224 °C (lit.[9c] 231.5–232.5 °C); ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.27 (s, 1H), 8.10 (s, 1H), 7.24 (s, 2H), 5.79 (d, $J = 5.3$ Hz, 1H), 5.36 (d, $J = 5.7$ Hz, 1H), 5.11 (d, $J = 5.1$ Hz, 1H), 4.61 (m, 1H), 4.44 (t, $J = 5.1$ Hz, 1H), 4.03 (m, 1H), 3.93 (m, 1H), 3.42 (m, 2H), 1.76 (m, 2H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 156.1, 152.6, 149.4, 139.9, 119.2, 87.4, 81.0, 73.4, 72.9, 57.5, 36.6. Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.85; H, 5.48; N, 24.63.
18. For leading references on the procedures used for the assays see (a) Ref. 5; (b) Siddiqi, S. M.; Chen, X.; Schneller, S. W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1994**, *37*, 551; (c) Seley, K. L.; Schneller, S. W.; Korba, B. *Nucleosides Nucleotides* **1997**, *16*, 2095; (d) http://www.usu.edu/iar/Brochure/brochure.html (September 6, 2004); and; (e) Baker, R. O.; Bray, M.; Huggins, J. W. *Antiviral Res.* **2003**, *57*, 13.
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