

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.

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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 nucleosides³ 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 investigations⁴ 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 expected⁷ 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 reported⁸ to be inactive against HSV-1 and HSV-2, possibly, due to its failure to be phosphorylated (Fig. 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

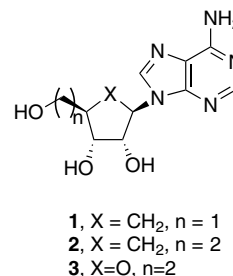


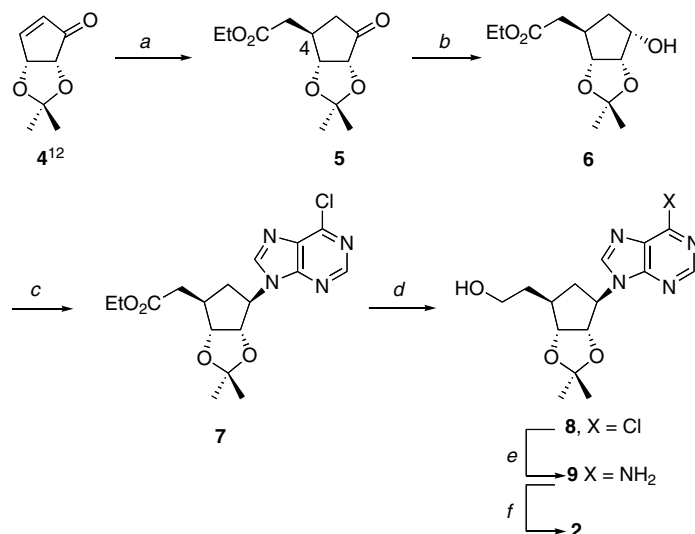
Figure 1.

in the literature.⁹ The results of this effort are communicated here.

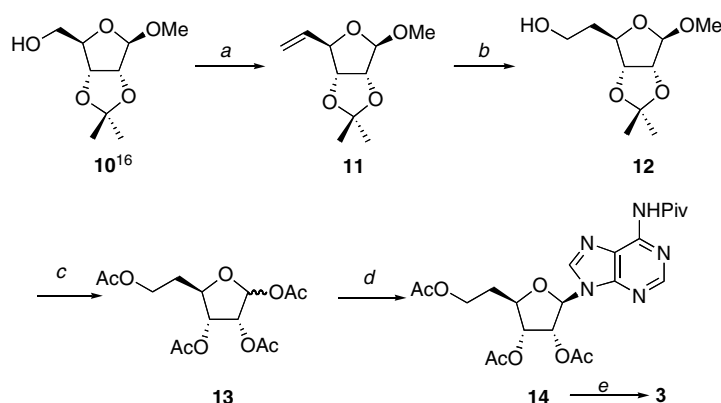
Existing methods^{8,10,11} for preparing 5'-homoaristeromycin (**2**) suffer from too many steps, limited scale-up, low yields and, in one case, resulting in a racemic product. Therefore, an efficient and stereoselective synthesis of **2** was needed. Starting from enone **4**¹² (Scheme 1), 1,4-addition 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 expected¹³ 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 Mitsunobu 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/H₂O, rt, 84% for two steps from **4**; (b) NaBH₄, MeOH, ice temp, 100%; (c) 6-chloropurine, Ph₃P, DIAD, THF, 0 – 50°C , 52%; (d) DIBAL, CH₂Cl₂, -50°C , 80%; (e) NH₃/MeOH, 94%; (f) HCl/MeOH, 95%.



Scheme 2. Reagents and conditions: (a) (i) DMSO, DIPEA, SO₃-Py, CH₂Cl₂, 90%, (ii) Ph₃PCH₃Br, *t*-BuOK, Et₂O, 75%; (b) 9-BBN, THF, then NaOH, H₂O₂, 97%; (c) (i) 70% AcOH, 85°C ; (ii) Ac₂O, DMAP, pyridine, 85% for two steps from **12**; (d) Adpiv, HMDS, TMSCl, TMSOTf, 60%; (e) NH₃/MeOH, 91%.

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

The known syntheses of 6'-homoadenosine⁹ (**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 yield¹⁷ 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 (IC₅₀ 1.2 μg/mL), cowpox (IC₅₀ 0.12 μg/mL), and monkeypox (IC₅₀ 0.12 μg/mL) viruses, all in Vero 76 cells with CC₅₀ > 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 viruses¹⁸ will be forthcoming, including its potency toward variola.¹⁹ Analog **3** was inactive in all of the assays employed.¹⁸

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