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5′-Hydroxy-5′-homoaristeromycin: Synthesis and antiviral properties

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ABSTRACT

Synthetically combining the C-4′ side-chain structural features of the antiviral candidates 5′-methylaristeromycin and 5′-homoaristeromycin into a diastereomeric pair of C-4′ side-chain dihydroxylated aristeromycins (**6** and **7**) is reported. Broad antiviral analyses of the both targets found promising effects towards HBV (**6**, 6.7 μM and **7**, 7.74 μM) and HCMV (only **7**, 0.72 μM). No other activity was found. Neither of the diastereomers was cytotoxic in the assays performed.

While the report of biologically inactive carbocyclic thymidine (**1**) in 1962[1] introduced a new class of nucleosides, it was the synthesis of racemic carbocyclic adenosine (aristeromycin, **2**)[2] and subsequent isolation of the (−)-enantiomer from *Streptomyces citricolor*[3] that the era of carbocyclic nucleosides began and became a focal point for the pursuit of carbocyclic nucleosides as therapeutic candidates and as probes for biological processes.[4] Our interest in aristeromycin and analogs therefrom began with the report of 5′-noraristeromycin (**3**) with activity towards human cytomegalovirus.[5] Over the years[6] since 1992 we have looked back to see what analogs lie in the wake of our work that suggested a further look into structural possibilities. Recently, in that regard, we were drawn to our reports that 5′-methylaristeromycin (**4**)[7] and 5′-homoaristeromycin (**5**)[8] have meaningful antiviral properties that had not been developed through analog design. This stimulated us to consider combining the two side chain features of **4** and **5** into diastereomers **6** and **7** (whose designation is derived from 5′-homoaristeromycin in blue possessing a 5′-hydroxyl). The outcome of that pursuit is presented here (see Fig. 1).

Oxidation of alkenes to glycols is well established in the synthetic organic toolbox. Thus, for this investigation, the known N-6 protected carbocyclic adenine nucleoside with the unsaturated C-4′ side chain **8** (available from D-ribose)[9] served as the starting point. To achieve the requisite diastereomers **9a** and **9b** ADmix-α (for **9a**) and ADmix-β (for **9b**) were employed, respectively. Deprotection of **9a** and **9b** with 2 N hydrochloric acid produced **6** and **7**. The stereochemistry of **6** and **7** was determined by mesylation of **9a**/**9b** to **10a**/**10b** that were deprotected to **11a**/**11b**. Reductive removal of the 6′-mesylate with lithium aluminum hydride yielded **12a**/**12b** (a convenient, alternative synthesis of those diastereomers). The spectroscopic properties of **12a** were identical to that previously reported for **4** (same as **12a**).[7] To address any possible structural ambiguity in this study, confirmation of **6** was achieved by an X-ray structural analysis.[10]

In an antiviral analysis,[11] both **6** and **7** showed moderate activity towards hepatitis B (EC_{50} 7.1 μM and 7.4 μM, respectively; CC_{50} >100 μM)) while only **7** was potent against human cytomegalovirus (EC_{50} 0.72 μM; CC_{50} >300 μM). Compound **6** was found to lack the significant yellow fever properties reported for **4** indicating addition of a hydroxyl to the methyl carbon of **4** (**12a**), resulted in an undesirable outcome for future development of **4** as a yellow fever antiviral candidate. A similar conclusion can be reached for the loss of the orthopox activity of **5** due to the presence of the extra hydroxyl group on the C-5′ position of both diastereomers **6** and **7** (see Scheme 1.).

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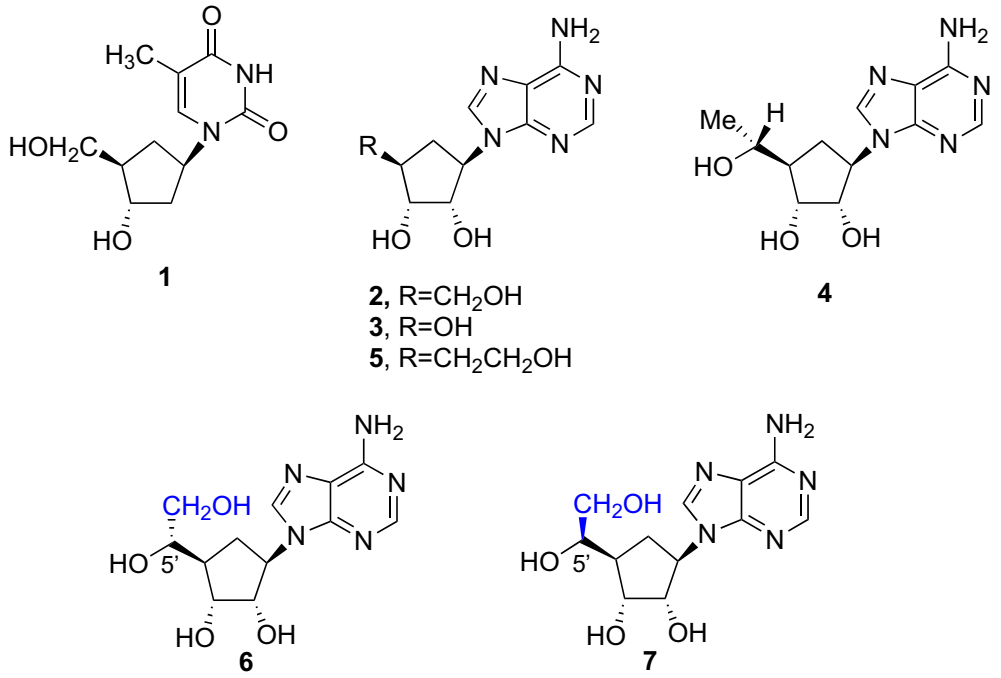
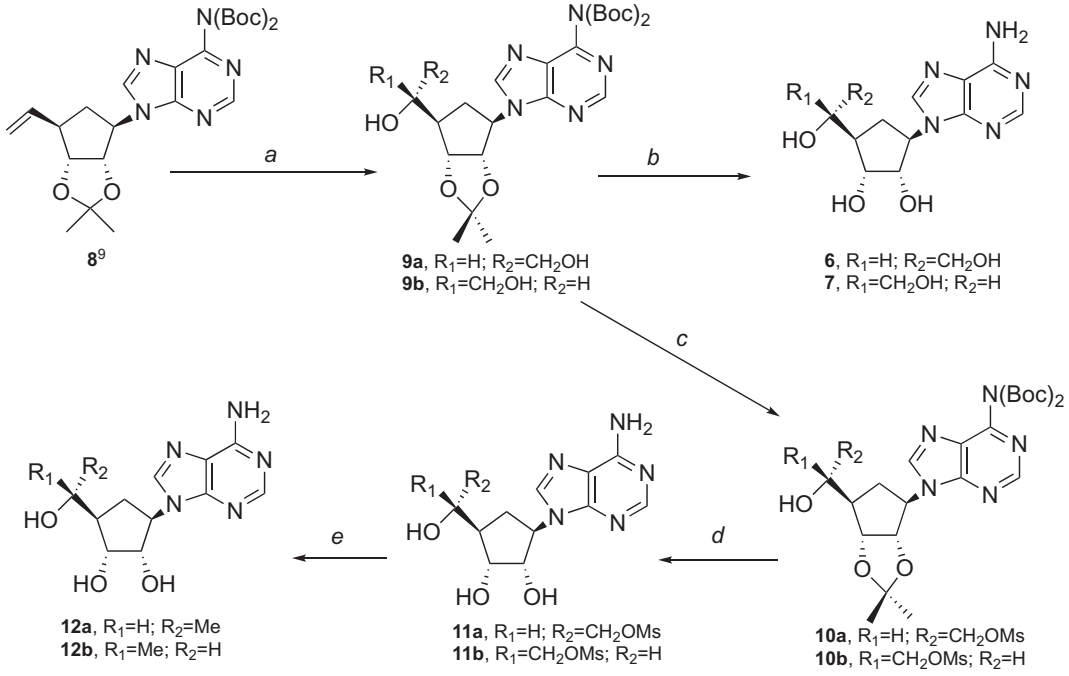


Fig. 1. Relevant carbocyclic nucleosides.



Scheme 1. Synthetic steps to targets **6** and **7**. Reagents and conditions: *(a)* ADmix-α for **9a**; ADmix-β for **9b**, *t*-butyl alcohol, H_2O, 67% for **9a**; 79% for **9b**; *(b)* 2 N HCl, MeOH, 93% for **6**, 86% for **7**; *(c)* MsCl, Et_3N, CH_2Cl_2, 80% for **10a**, 78% for **10b**; *(d)* 2 N HCl, MeOH, 79% for **11a**, 78% for **11b**; *(e)* $LiAlH_4$, THF, 89% for **12a**, 90% for **12b**.

Compounds **6** and **7** were inactive towards polio virus, SARS coronavirus, respiratory syncytial virus, hepatitis C virus, herpes simplex 1 and 2 viruses, vaccinia virus, dengue, Rift Valley fever, Venezuelan equine encephalitis, H1N1 influenza A virus, and West Nile virus. No cytotoxicity was found for either **6** or **7** in the assays conducted.

In conclusion, a convenient synthesis of the diastereomeric hybridization of 5′-methylaristeromycin (**4**) and 5′-homoaristeromycin (**5**) to 5′-hydroxy-5′-homoaristeromycin (**6** and **7**) has provided a new C-4′ structural entity for the aristeromycin family of analogs that showed potent HBV (**6** and **7**) and moderate HCMV activities (**7**). It should be noted that the hydroxyl substituents offer the opportunity of making substituent changes at those centers for possible new aristeromycin structural variations.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bmcl.2018.03.088.

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10. Crystallographic data (excluding structure factors) for **6** has been deposited with the Cambridge Crystallographic Data Centre with deposition number CCDC 1578521. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
11. These assays are presented in reference 12 (strain, host cell): yellow fever (17D, Vero), human cytomegalovirus (AD169, HFF), hepatitis B (ayw, 2.2.15), polio virus (type 1, LLC-MK2 clone 7.1), SARS coronavirus (Toronto-2, Vero 6), respiratory syncytial virus (A, Hep 2), hepatitis C virus (CON-1, Huh-Luc/Neo), herpes simplex 1 (E-377, HFF) and 2 (G, HFF), vaccinia virus (Copenhagen, HFF), dengue (Type 2/New guinea, Vero76), Rift Valley fever (MP-12, Vero 76), Venezuelan equine encephalitis (TC-83, Vero), H1N1 influenza A virus (Influenza A/California/7/2009, MDCK), and West Nile virus (KERN 515/WN02, Vero 76).
12. For the assay methods see reference 12 in Chen Q, Liu C, Komazin G, Bowlin T, Schneller SW. *Bioorg Med Chem*. 2014;22:6961–6964.