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5'-Fluoro-5'-deoxyaristeromycin

Weikuan Li, Xueqiang Yin, and Stewart W. Schneller*

Department of Chemistry and Biochemistry, Auburn University, Auburn, Alabama 36849-5312

Abstract

5'-Fluoro-5'-deoxyaristeromycin (**2**) has been prepared via a Mitsunobu coupling of (1*S*,2*S*,3*R*,4*S*)-2,3-(cyclopentylidenedioxy)-4-fluoromethylcyclopentan-1-ol with *N*⁶-*bis*-*boc* protected adenine. This procedure is adaptable to preparing a number of 5'-fluoro-5'-deoxycarbocyclic nucleoside analogs with diversity in the heterocyclic base. Antiviral analysis found promising activity for **2** towards measles but no other viruses. No cytotoxicity was observed for **2**.

Keywords

carbocyclic nucleoside; Grubbs reaction; fluorinated cyclopentyl derivative; Mitsunobu coupling

Aristeromycin (**1**) owes its diverse biological properties to (1) formation of its 5'-mono-, di-, and triphosphate nucleotides and (2) inhibition of biomethylations that occur with *S*-adenosylmethionine (AdoMet) as cofactor and *S*-adenosylhomocysteine as a product biofeedback methylation control element.¹ In an effort to investigate aristeromycin derivatives that are participants in only one of those pathways we, for some time, have sought aristeromycin analogs where C-5' phosphorylation is not likely^{2–4} or not possible.⁵ For this collection, 5'-fluoro-5'-deoxyaristeromycin (**2**) presents a relevant target owing to the well documented beneficial biological consequences of a fluoro-for-hydroxyl exchange, which, for the purposes here, also precludes the traditional hydroxyl reactions (such as, phosphate esterification).⁶ Additionally, **2** represents the carbocyclic analog of 5'-fluoro-5'-deoxyadenosine, which has demonstrated a broad range of biological properties.⁷ Our preliminary results in this regard is reported.

Our original plan to **2** was to carry out a direct fluorination at the C-5' center of the known aristeromycin precursors **3** or **4**.⁸ In that direction we found it synthetically more practical to prepare the unknown cyclopentyl protected derivative **5** employing a series of new cyclopentyl derivatives (via Scheme 1). However, various attempts at converting **5** to **6** (for example, using DAST shown as example in Scheme 1) were unsuccessful.

Attention then turned to creating a fluoro-bearing cyclopentyl unit for coupling with an appropriately functionalized purine base. Scheme 2 presents the steps employed to the requisite precursor **15**. To circumvent the interference by the C-6 amino substituent of adenine under the Mitsunobu coupling conditions,⁹ *N*⁶-*bis*-*boc* protected adenine was employed with **15** in the presence of diisopropyl azodicarboxylate to yield **19**. Acidic deprotection of **19** led to the desired **2**.¹⁰

*Corresponding author. Tel.: 334-844-5737; fax: 334-844-5748; e-mail: E-mail: schnest@auburn.edu.

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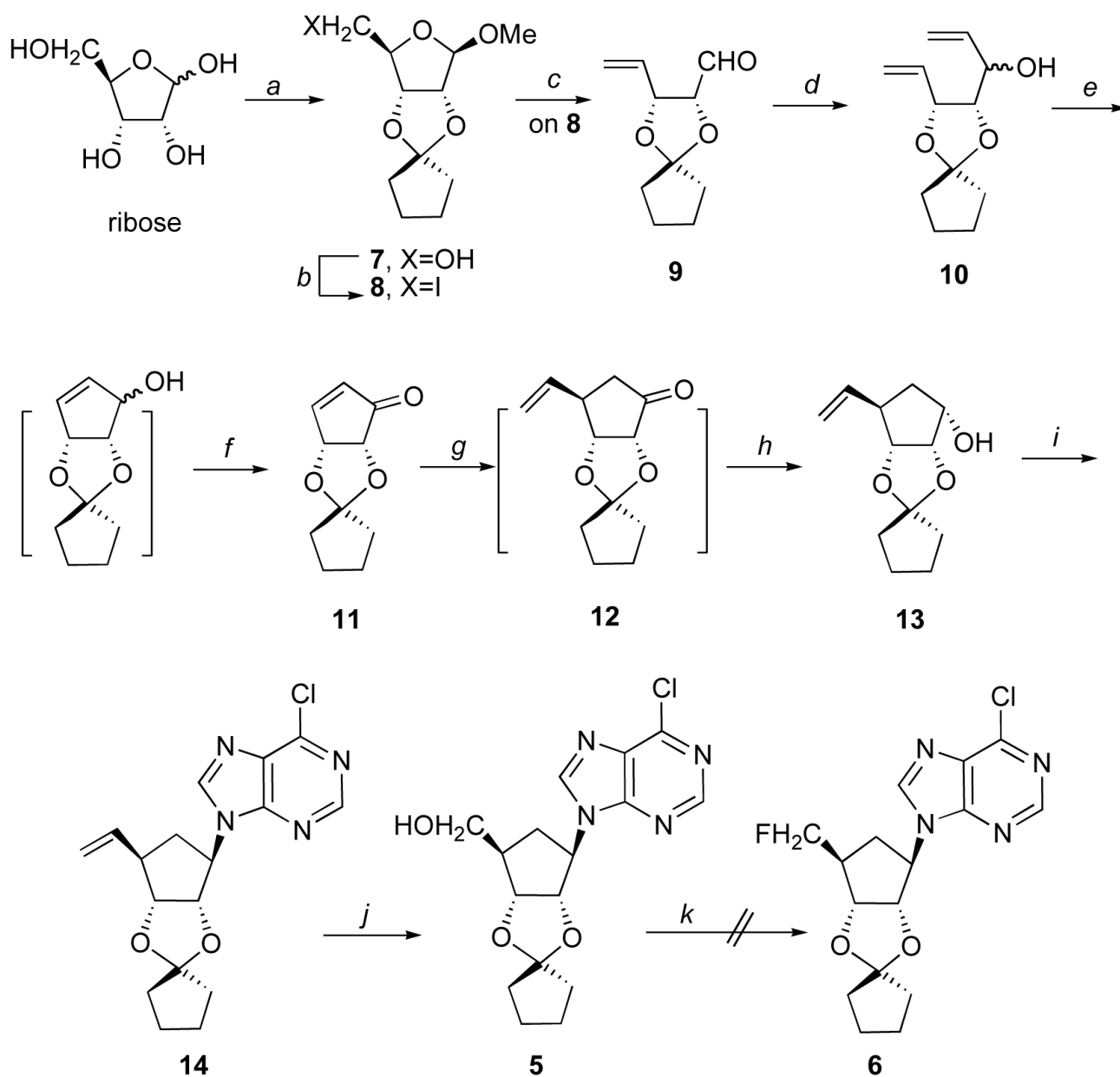
To gain a glimpse into the biological potential of **2**, it was subjected to antiviral analysis versus herpes simplex-1, herpes simplex-2, herpes simplex-1 (TK⁻), vaccinia, cowpox, vesicular stomatitis, coxsackie B4, respiratory syncytial, parainfluenza 3, reovirus-1, Sinbis, Punta Toro, rhinovirus, adenovirus, hepatitis C, and West Nile, and feline coronavirus.¹¹ No activity was found for these viruses. However, effects towards measles (MO6) were observed (EC₅₀ 2.8 μM, neutral red assay; EC₅₀ 13 μM, visual assay). As a member of the paramyxoviridae family of viruses it might be expected that some activity would be seen with an aristeromycin analog since this viral family is susceptible to inhibition of S-adenosylhomocysteine metabolism.¹² It is surprising, however, that the other paramyxo representatives (respiratory syncytial and parainfluenza) and none of the other viruses (for example, vaccinia, cowpox, vesicular stomatitis, and reo) that are vulnerable to such interference were not effected by **2**.¹² Perhaps, another mechanism is selectively operative for **2** towards measles.¹³ No cytotoxicity arose in the cell lines used for the antiviral assays.¹⁴

Acknowledgments

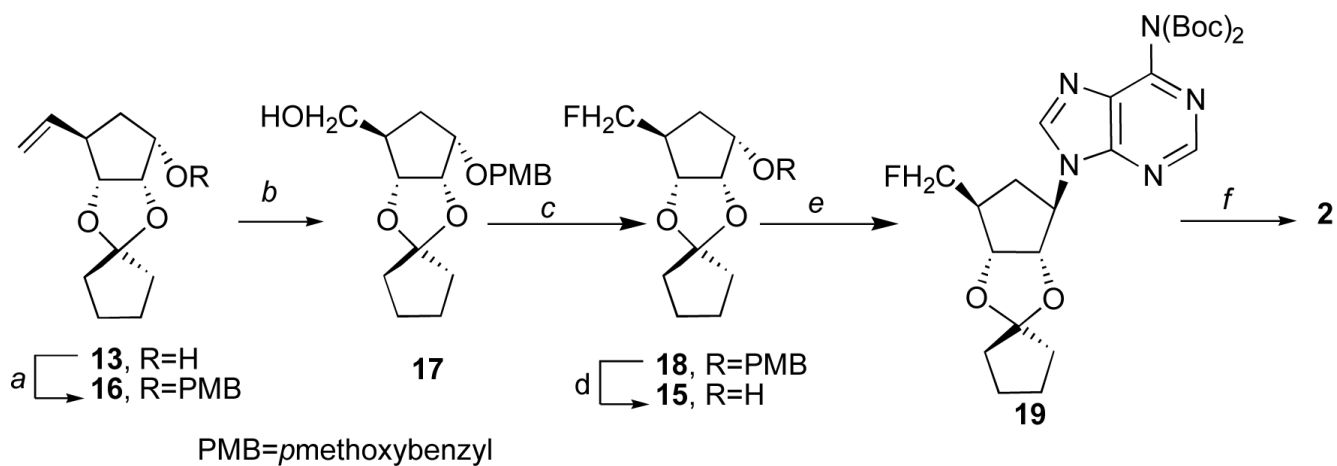
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References and Notes

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10. Selected data for **2**: white solid; mp 168–169 °C. ¹H NMR (400 MHz, DMSO), δ 8.19 (s, 1H), 8.12 (s, 1H), 7.20 (s, 2H), 5.06 (d, *J*=6.0 Hz, 1H), 4.91 (d, *J*=4.0 Hz, 1H), 4.70 (m, 1H), 4.58 (m, 1H), 4.45 (m, 1H), 4.35 (m, 1H), 3.89 (m, 1H), 2.27 (m, 2H), 1.80 (m, 1H). ¹³C NMR (100 MHz, DMSO) δ 156.01, 152.11, 149.68, 140.17, 119.35, 84.55 (d, *J*=165 Hz), 74.26, 70.76 (d, *J*=5Hz), 59.13, 43.40 (d, *J*=18 Hz), 27.86 (d, *J*=6 Hz). Calcd mass for C₁₁H₁₄FN₅O₂: 267.1132, found: 267.1131.
11. For leading references for the antiviral and cytotoxicity procedures used see (a) Rajappan VP, Schneller SW, Williams SL, Kern ER. *Bioorg Med Chem* 2002;10:883. [PubMed: 11836094](b) Siddiqi SM, Chen X, Schneller SW, Ikeda S, Snoeck R, Andrei G, Balzarini J, De Clercq E. *J Med Chem* 1994;37:551. [PubMed: 8120872](c) <http://www.usu.edu/iar/Brochure/brochure.html>. [(October 1, 2007)];
12. De Clercq E. *Nucleosides Nucleotides* 1998;17:625. [PubMed: 9708366]
13. The 5'-fluoro-5'-deoxyneplanocin A analog of **2** also shows activity towards measles but it also had an effect on other viruses susceptible to inhibition of S-adenosylhomocysteine metabolism (Shuto S, Obara T, Toriya M, Hosoya M, Snoeck R, Andrei G, Balzarini J, De Clercq E. *J Med Chem* 1992;35:324. [PubMed: 1732550])
14. Cell lines used for the antiviral assays: HEL, HeLa, Vero, CV-1, MA-104, A-549, MDCK, CRFK, HFF, Huh7ET.

**Scheme 1.**

Reactions and conditions: *a*, cyclopentanone, MeOH, (MeO)₃CH, 5% *p*TSA, reflux, 85%; *b*, I₂, imidazole, TPP, toluene/MeCN, reflux, 80%; *c*, *n*BuLi, -78 °C, ether, 80%; *d*, CH₂CHMgBr, dry Et₂O, -78 °C~rt, 80%; *e*, 1st gen. Grubbs cat. 1% mol, reflux, CH₂Cl₂; *f*, SO₃-pyridine, DIPEA, DMSO, CH₂Cl₂, 0 °C, 70% two steps; *g*, CH₂CHMgBr, CuBr-Me₂S, TMSCl, THF, -78 °C~rt; *h*, LiAlH₄, THF, 62% two steps; *i*, 6-Cl-purine, DIAD, THF, 60 °C, 2 days, 60%; *j*, NaIO₄, OsO₄, MeOH/H₂O, then NaBH₄, MeOH, 68%; *k*, one example, DAST, CH₂Cl₂, reflux.

**Scheme 2.**

Reactions and conditions. *a*, NaH, PMBCl, DMF, 0 °C, 81%; *b*, NaIO₄, OsO₄, MeOH/H₂O, then NaBH₄, MeOH, 53%; *c*, DAST, pyridine, CH₂Cl₂, 76%; *d*, DDQ, CH₂Cl₂/H₂O, 60%; *e*, DIAD, TPP, Ad(Boc)₂; *f*, 3N HCl/MeOH, 58% for two steps.

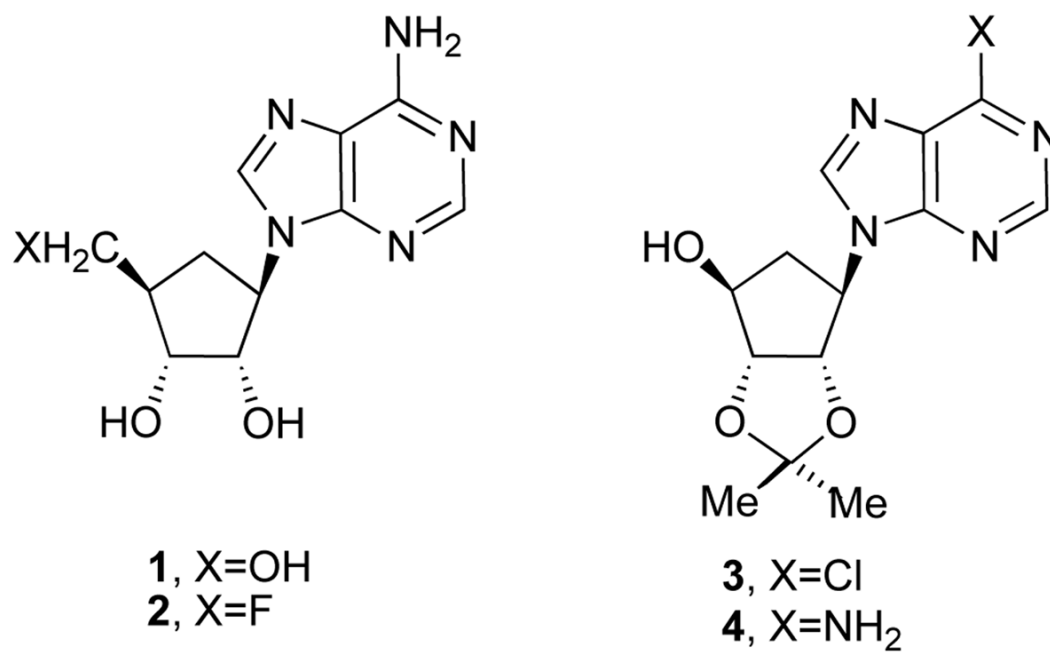


Figure.