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5'-Fluoro-5'-deoxyaristeromycin

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Abstract—5'-Fluoro-5'-deoxyaristeromycin (2) has been prepared via a Mitsunobu coupling of (1S,2S,3R,4S)-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 toward measles but no other viruses. No cytotoxicity was observed for 2.

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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 are reported (Fig. 1).

Our original plan to 2 was to carry out a direct fluorination at the C-5' center of the known aristeromycin precursor 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 5–6 (e.g., 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 di*iso*'propyl azodicarboxylate to yield **19**. Acidic deprotection of **19** led to the desired **2**.¹⁰

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, Sindbis, Punta Toro, rhinovirus, adenovirus, hepatitis C, and West Nile, and feline coronavirus.¹¹ No activity was found for these viruses. However, effects toward measles (MO6) were observed (EC₅₀ 2.8 μ M, neutral red assay; EC₅₀ 13 μ M, visual assay). As a member of the paramyxoviridae



Figure 1.

Keywords: Carbocyclic nucleoside; Grubbs reaction; Fluorinated cyclopentyl derivative; Mitsunobu coupling.

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Scheme 1. Reagents and conditions: (a) cyclopentanone, MeOH, $(MeO)_3CH$, 5% *p*-TSA, reflux, 85%; (b) I₂, imidazole, TPP, tolune/MeCN, reflux, 80%; (c) *n*-BuLi, -78 °C, ether, 80%; (d) CH₂CHMgBr, dry Et₂O, -78 °C to rt, 80%; (e) 1st gen. Grubbs cat. 1% mol, reflux, CH₂Cl₂; (f) SO₃-pyrridine, DIPEA, DMSO, CH₂Cl₂, 0 °C, 70% two steps; (g) CH₂CHMgBr, CuBr–Me₂S, TMSCl, THF, -78 °C to 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. Reagents 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) 3 N HCl/MeOH, 58% for two steps.

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 (e.g., vaccinia, cowpox, vesicular stomatitis, and reo) that are vulnerable to such interference were not affected by **2**.¹² Perhaps, another mechanism is selectively operative for **2** toward measles.¹³ No cytotoxicity arose in the cell lines used for the antiviral assays.¹⁴

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References and notes

- 1. Wolfe, M. S.; Borchardt, R. T. J. Med. Chem. 1991, 34, 1521.
- For a recent 5'-noraristeromycin leading reference, see Roy, A.; Serbessa, T.; Schneller, S. W. *Bioorg. Med. Chem.* 2006, 14, 4980.
- 3. Ye, W.; Schneller, S. W. J. Org. Chem. 2006, 71, 8641.
- 4. Yang, M.; Schneller, S. W. Bioorg. Med. Chem. Lett. 2005, 15, 149.
- Siddiqi, S. M.; Schneller, S. W. Nucleosides Nucleotides 1993, 12, 185.
- 6. For a leading reference, see Kirk, K. L. J. Fluorine Chem 2006, 127, 1013.
- 7. Ashton, T. D.; Scammells, P. J. Bioorg. Med. Chem. Lett. 2005, 15, 3361.
- Yang, M.; Ye, W.; Schneller, S. W. J. Org. Chem. 2004, 69, 3993.
- (a) Mitsunobu, O. Synthesis 1981, 1; (b) Hughes, D. L. Org. Prep. Proced. Int. 1996, 28, 127.

- 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 = 5 Hz), 59.13, 43.40 (d, J = 18 Hz), 27.86 (d, J = 6 Hz). Calcd mass for C₁₁H₁₄FN₅O₂: 267.1132. Found: 267.1131.
- For leading references for the antiviral and cytotoxicity procedures used, see (a) Rajappan, V. P.; Schneller, S. W.; Williams, S. L.; Kern, E. R. *Bioorg. Med. Chem.* 2002, 10, 883;; (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) http://www.usu.edu/iar/ Brochure/brochure.html (October 1, 2007).
- 12. De Clercq, E. Nucleosides Nucleotides 1998, 17, 625.
- The 5'-fluoro-5'-deoxyneplanocin A analog of 2 also shows activity toward 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.
- Cell lines used for the antiviral assays: HEL, HeLa, Vero, CV-1, MA-104, A-549, MDCK, CRFK, HFF, Huh7ET.