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Tetrahedron Letters 46 (2005) 7535–7538
Tetrahedron Letters

Chiral syntheses of 6′-β-fluoroaristeromycin, 6′-β-fluoro-5′-noraristeromycin and aristeromycin

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Received 25 June 2005; revised 26 August 2005; accepted 31 August 2005
Available online 19 September 2005

Abstract—Carbocyclic nucleosides substituted at the C-6′ position are receiving increasing attention. Chiral synthetic accessibility to the biologically promising 6′-β-fluoroaristeromycin is lacking. Its preparation and that of the 5′-nor analogue are described. Along the way, a new method to aristeromycin arose as an outgrowth of a requisite structure proof.

In using the nucleoside scaffold for medicinal agent and biochemical mechanistic investigations, the C-6′ site of the carbocyclic nucleoside framework[1] (see aristeromycin, **1**, Fig. 1) offers a center for modification[2] not available in the more common ribofuranosyl based nucleosides. Because of the promising properties synthetically derived fluorinated carbocyclic nucleosides have displayed,[3] we were attracted to (±)-6′-β-fluoroaristeromycin (**2**) as a representative of the C-6′ substituted carbocyclic series that has shown promising potential as an antiviral (orthopox) agent.[2b] This latter property, however, has not been fully developed. In that direction, a chiral synthesis of the enantiomer of **2** (i.e., **3**) resembling the parent aristeromycin (**1**) has been completed in our laboratory. This undertaking concurrently prompted an interest in seeking access to the 5′-noraristeromycin fluoro analogue **4** (and its enantiomer, **5**) as an extension of our work with 5′-noraristeromycin (**6**)[4] as a source of new antiviral candidates. Accompanying these investigations was a convenient preparation of aristeromycin (**1**). The results of these efforts are communicated here.

In designing synthetic procedures to carbocyclic nucleosides, our laboratory has always sought a common starting point. In that regard, the approach to **3**–**5** (that also opened a means to **1**) was built upon (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (**7**),[5] which has served us well in our studies.[6] From this, two guiding features followed in the plan to **3**: (i) an enantiospecific synthesis of **8** (Scheme 1) for conversion into **3** following the literature precedence[2b] and (ii) application of our recent report employing a stereo-controlled epoxide formation with subsequent nucleophilic opening as a means to polyfunctionalized cyclopentanes.[7]

To begin, **10**, obtained from **7**,[8] was subjected to a Tamao oxidation[8] to **11** whose primary alcohol center was protected as its *tert*-butyldiphenylsilyl derivative **12** (Scheme 1). Mitsunobu inversion of the secondary alcohol of **12** followed by glycolization, *iso*propylidene protection and ammonolysis (to remove the acetate from the inverted alcohol) formed **13**. Confirmation of the functional group stereochemistry depicted in **13** was accomplished by transforming it into **1** by, first, pyridinium chlorochromate oxidation followed by Luche reduction to **14**. Mitsunobu coupling of **14** with 6-chloropurine and subsequent desilylation led to **15**. Ammonolysis of **15** and, then, acidic deprotection yielded **1** whose spectral properties were identical to those reported by us[9] and others in the literature.[10]

Confident of the structure of **13**, and after evaluating a number of procedures, a Mitsunobu-type elimination reaction (Scheme 1, step h) resulted in the conversion of **13** into **16**. Drawing upon our previous results,[7] conversion of **16** into **8** required primary alcohol protection with a benzyl group. Thus, desilylation/benzylation led to **9**. Subjecting **9** to the sequence[7] of (i) de*iso*propylidenation, (ii) epoxidation, (iii) sodium azide ring opening,

Keywords: Carbocyclic nucleosides; Epoxide ring opening; Pentasubstituted cyclopentanes.
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doi:10.1016/j.tetlet.2005.08.163

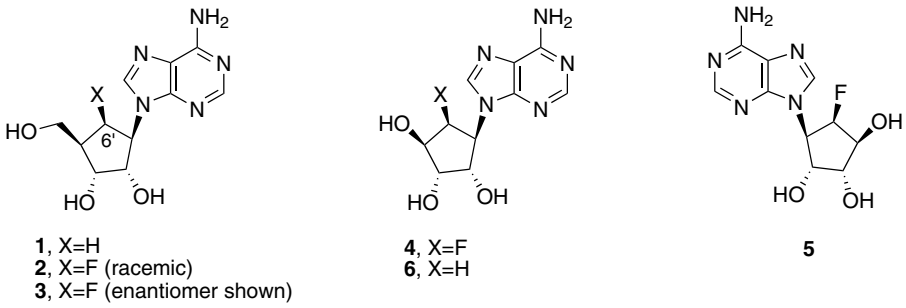
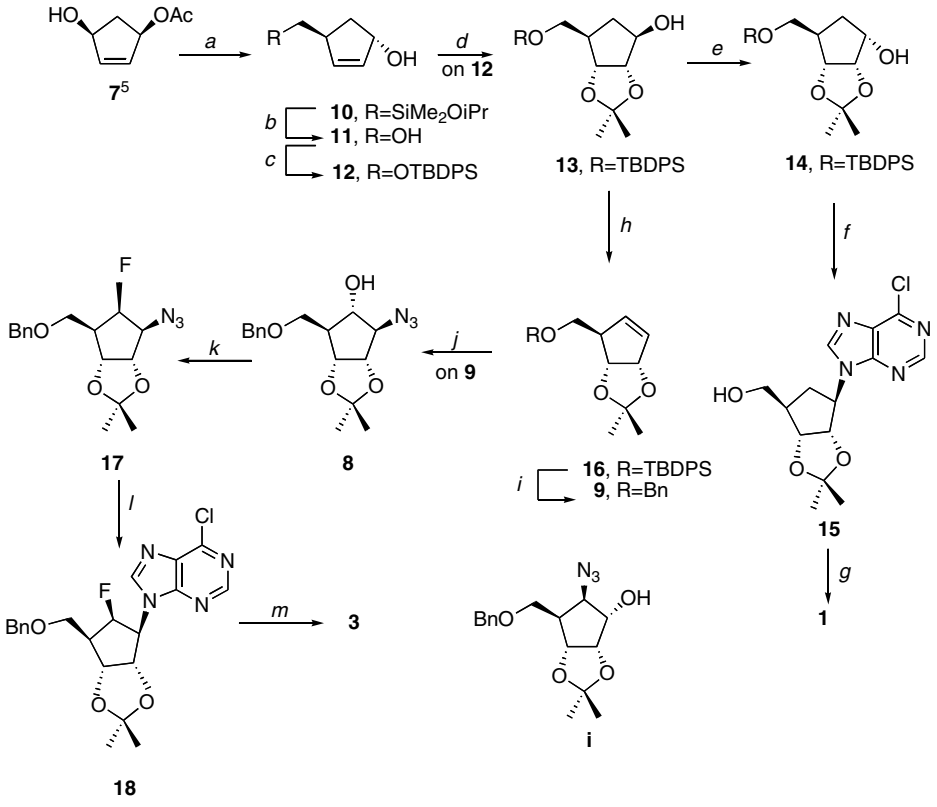


Figure 1.



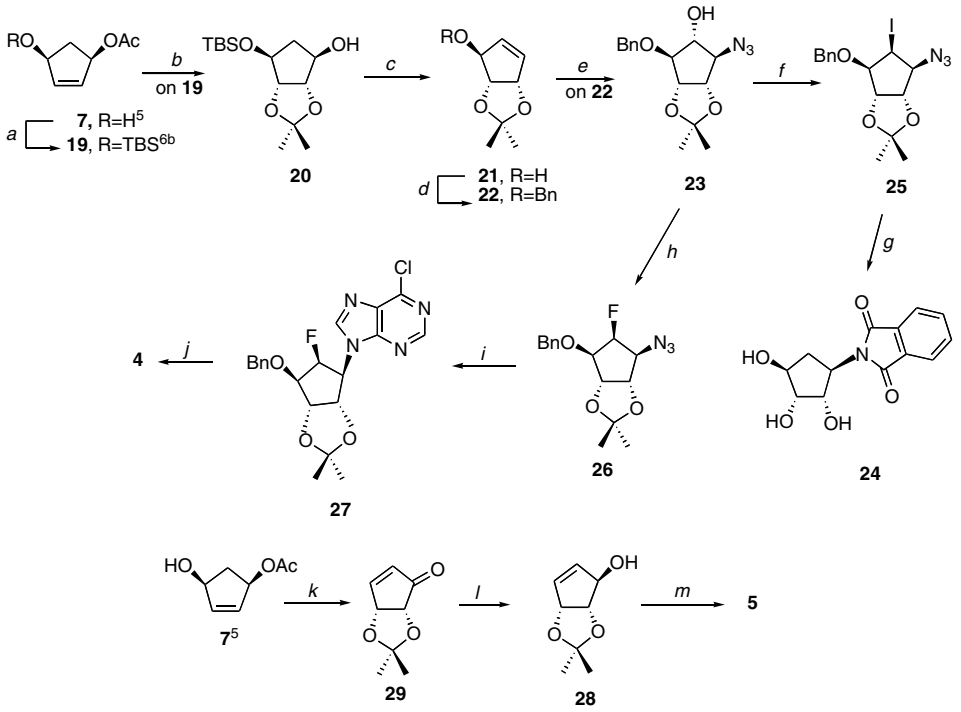
Scheme 1. Reagents and conditions: (a) Ref. 8; (b), KF, H_2O_2, MeOH/THF/H_2O, 87%; (c) TBDPSCl, imidazole, CH_2Cl_2, 70%; (d) (i) TPP, DIAD, AcOH, THF; (ii) NMO, OsO_4, acetone/THF/H_2O; (iii) $Me_2C(OMe)_2$, acetone, *p*TSA, 61% for three steps; (iv) NH_3, MeOH, 86%; (e) (i) PCC, Celite, CH_2Cl_2; (ii) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 90% for two steps; (f) (i) TPP, DIAD, 6-chloropurine, THF; (ii) TBAF, THF, 71% for two steps; (g) Ref. 9b; (h) TPP, DIAD, toluene, 80 °C, 10 h, 82%; (i) (i) TBAF, THF, 95%; (ii) BnBr, NaH, DMF, 91%; (j) (i) HCl, MeOH; (ii) *m*CPBA, CH_2Cl_2; (iii) NaN_3, DMF/H_2O, (iv) $Me_2C(OMe)_2$, acetone, *p*TSA, 63% for 4 steps; *k*, (i) Tf_2O, pyridine, CH_2Cl_2; (ii) TASF, THF, 85% for two steps[2b]; (l) (i) Lindlar catalyst, H_2, MeOH; (ii) 5-amino-4,6-dichloropyrimidine, Et_3N, 1-BuOH, 105 °C; (iii) $(EtO)_2CHOAc$, reflux, 38% for three steps;[2b] (m) (i) NH_3, MeOH, 69%; (ii) $Pd(OH)_2/C$, cyclohexene, EtOH, reflux; (iii) 1 N HCl, MeOH, 70 °C, 86% for two steps.[2b]

and (iv) *iso*propylidenation gave **8**[10] in a 4:1 ratio along with its isomer **i**. The structure of **8** was confirmed by comparing its NMR spectral data with the reported racemic **8** prepared in another way.[10]

Alcohol **8** was then converted into **3**[11] by utilizing a reported procedure[2b] as delineated in Scheme 1.

With the intent of utilizing a similar epoxide-sodium azide ring opening path to **4** and **5**, silyl protection of **7**–**19**[6b] was followed by glycolization and, then, *iso*propylidenation and ammonolysis of the resultant acetate to afford **20**.[12] Subjecting **20** to the Mitsunobu process used with **13** followed by desilylation gave **21**, which was converted into the benzyl derivative **22**. Following the same series of steps used for the **9** to **8** process, **22** yielded **23** (Scheme 2). To confirm the stereochemical orientation of **23**, it was converted into the known **24**[13]: (i) iodination with inversion to **25**, (ii) removal of the iodine concurrently with reduction of the azide, (iii) reaction of the free amino with phthalic anhydride, and (iv) subsequent debenzylation with de*iso*propylidenation.

Returning to the preparation of **4**, fluorinative inversion of **23** to **26** was followed by azide reduction to the primary amine, which lent itself to the standard stepwise



Scheme 2. Reagents and conditions: (a) TBSCl, imidazole, CH_2Cl_2, 91%; (b) (i) OsO_4, NMO, acetone/H_2O; (ii) $Me_2C(OMe)_2$, acetone, *p*TSA, 90% for two steps; (iii) NH_3, MeOH, 85%; (c) (i) TPP, DIAD, toluene, 80 °C, 93%; (ii) TBAF, THF, 95%; (d) BnBr, NaH, DMF, 97%; (e) (i) HCl, MeOH; (ii) *m*CPBA, CH_2Cl_2; (iii) NaN_3, DMF/H_2O; (iv) $Me_2C(OMe)_2$, acetone, *p*TSA, 59% for four steps; (f) (i) Tf_2O, pyridine, CH_2Cl_2; (ii) LiI, THF 92% for two steps; (g) (i) H_2, Pd/C, MeOH, 90%; (ii) phthalic anhydride, Ac_2O, pyridine; (iii) $Pd(OH)_2$/C, cyclohexene, EtOH, 56% for two steps; (h) (i) Tf_2O, pyridine, CH_2Cl_2; (ii) TASF, THF, 77% for two steps; (i) (i) Lindlar catalyst, H_2, MeOH; (ii) 5-amino-4,6-dichloropyrimidine, Et_3N, 1-BuOH; (iii) $(EtO)_2CHOAc$, reflux, 35% for three steps;[2b] (j) (i) NH_3, MeOH, 75%; (ii) $Pd(OH)_2$/C, cyclohexene, EtOH, 100%; (iii) 1 N HCl, MeOH, 96%;[2b] (k) Ref. 17; (l) Refs. 5c and 7; (m) steps (d), (e), (h), (i), and (j).

purine construction process[2b,14] (Scheme 2, step i) to provide **27**. Ammonolysis, debenzylation and then de*iso*propylidenation yielded **4**.[15]

Enantiomer **5**[16] was prepared from **28** using a procedure similar to that for obtaining **4**.

The biological analysis of **3**–**5** is underway and will be presented in the full paper on this class of nucleoside derivatives.

Acknowledgements

This research was supported by funds from the NIH (AI 56540).

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15. Data for **4**: $[\alpha]_D^{23.4}$ +66.3 (*c* 0.135, DMSO); ^{1}H NMR (DMSO, 400 Hz) δ 8.24 (s, 1H), 8.18 (s, 1H), 7.31 (br s, 2H), 5.71 (d, $J = 7.1$ Hz, 1H), 5.42 (d, $J = 8.3$ Hz, 1H), 5.24 (d, $J = 6.2$ Hz, 1H), 4.90 (m, 2H), 4.71 (m, 1H), 4.14 (dd, $J = 12.8$, 4.8 Hz, 1H), 3.99 (s, 1H); ^{13}C NMR (DMSO, 62.5 Hz) δ 155.9, 152.4, 149.9, 140.1, 118.4, 92.1 (d, $J = 187.0$ Hz, 1C), 75.8 (d, $J = 17.0$ Hz, 1C), 73.7, 72.4, 57.6 (d, $J = 15.4$ Hz, 1C); ^{19}F (DMSO, 250 Hz) −211.4 (m, 1F). Anal. Calcd for $C_{10}H_{12}FN_5O_3$: C, 44.61; H, 4.49; N, 26.01. Found: C, 44.49; H, 4.58; N, 25.72.
16. For **5**: $[\alpha]_D^{23.2}$ −16.5 (*c* 0.025, DMSO).
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