# 2′-Deoxy-2′-fluoro-*ara*-Aristeromycin, a New Anti-herpes Agent: the First Direct Introduction of a 2′-Fluoro Substituent into a Carbocyclic Nucleoside

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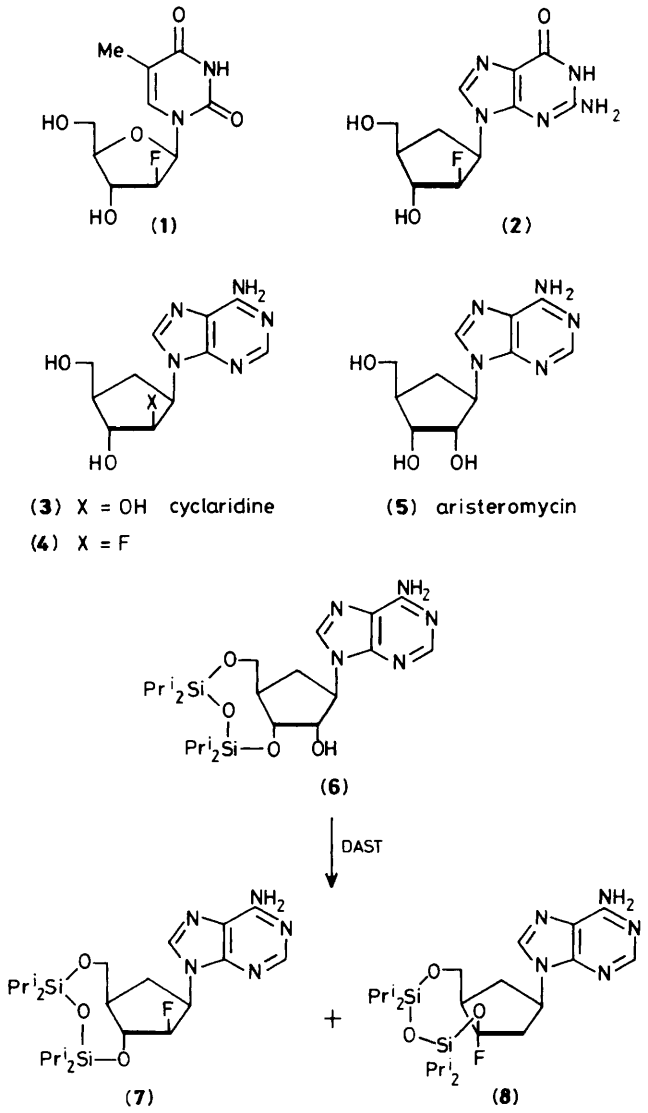
Aristeromycin has been converted in four stages into its 2′-deoxy-2′-fluoro-*ara*-analogue (**4**); compound (**4**) displayed potent anti-herpes activity both *in vitro* and *in vivo*.

The presence of a 2′-*ara*-fluoro substituent has been found to confer potent anti-herpes activity to certain pyrimidine nucleoside analogues[1] [*e.g.*, 1-(2-deoxy-2-fluoro-β-arabinofuranosyl)-5-methyluracil (FMAU) (**1**)] and more recently, in the carbocyclic series, to the guanosine analogue 9-(2-deoxy-2-fluoroarabinocyclopentanosyl)guanine (**2**).[2] The carbocyclic analogue of *ara*-adenosine (cyclaridine)[3] (**3**) has also been extensively studied as a potential anti-herpetic but its 2′-*ara*-fluoro analogue (**4**) has not been described. Carbocyclic nucleosides are commonly prepared in racemic form but recent studies have established that their anti-viral activity resides largely, if not entirely, in the 'natural' enantiomer.[2,4] An attractive starting material for the synthesis of optically pure carbocyclic adenosine analogues is aristeromycin (**5**),

which is readily available from fermentation of *Streptomyces citricolor*.[5] However, although a variety of 2'-*ara*-substituents have been introduced into intact purine nucleosides,[6] the direct introduction of a 2'-*ara*-fluoro substituent has met with very limited success[7] and has not been previously reported in the carbocyclic series. In this communication we report an efficient conversion of aristeromycin into its 2'-fluoro-*arabino*-analogue (**4**), by use of diethylaminosulphur trifluoride (DAST).

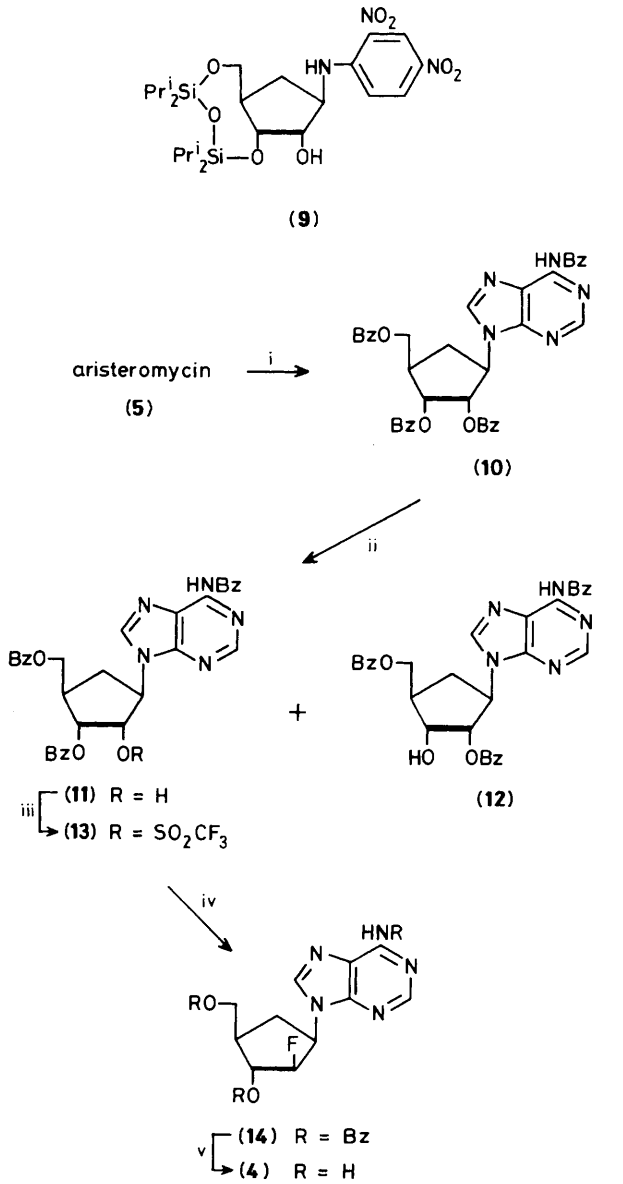
Aristeromycin (**5**) was first protected by formation of its 3',5'-*O*-disiloxanediyl derivative (**6**); the compatibility of this protecting group and DAST has recently been exploited to introduce fluorine into the 2'-position of some carbocyclic nucleoside precursors.[8] However, reaction of compound (**6**) with DAST provided only a very low yield (*ca.* 5%) of the required 2'-*ara*-fluoro derivative (**7**) (Scheme 1). The major product was the 3'-fluoro derivative (**8**) (*ca.* 50%). A similar rearrangement has been observed previously[8] in the reaction of the closely related dinitrophenylamino derivative (**9**) with DAST, but in that case the required 2'-*ara*-fluoro derivative was the major product (*ca.* 70%).

The hydride shift responsible for the formation of the unwanted 3'-fluoro product was expected to be less favourable

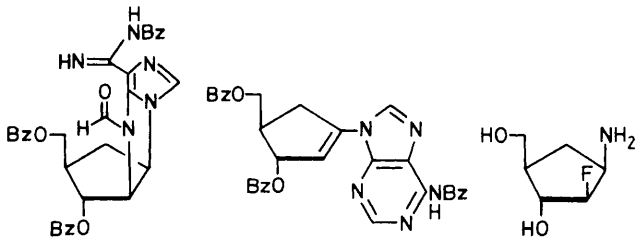



**Scheme 1**

if the 3'-hydroxy group was instead protected as an ester. To explore this possibility the selective 2'-debenzoylation recently reported for natural nucleosides[9] was applied to aristeromycin tetrabenzoate (**10**) (Scheme 2). Perbenzoylation of aristeromycin (**5**) followed by *in situ* treatment of the resulting pentabenzoate with methanolic ammonia provided the crystalline tetrabenzoate (**10**) in 75% yield. Reaction of compound (**10**) with potassium t-butoxide (3.5 equiv.) in tetrahydrofuran (THF) at −35 °C afforded a *ca.* 6 : 1 mixture of the *N*,3',5'- (**11**) and *N*,2',5'- (**12**) tribenzoyl derivatives, from which the crystalline isomer (**11**) was readily isolated in 72% yield; m.p. 232—234 °C, $[\alpha]_D^{22}$ −112° ($Me_2SO$). Reaction of compound (**11**) with DAST (2 equiv.) in dichloromethane at room temperature then provided the required 2'-*ara*-fluoro derivative (**14**) in 55% yield. The major by-product in this reaction was the cyclonucleoside (**15**) (*ca.* 10%), arising *via* internal displacement of the leaving group generated at C-2' by the purine N-3, followed by hydrolysis




**Scheme 2.** *Reagents and conditions*: i, BzCl, pyridine then $NH_3$, MeOH; ii, KOBu$^t$, THF, −35 °C; iii, $CF_3SO_2Cl$, $NEt_3$, 4-dimethylaminopyridine, $CH_2Cl_2$, 0 °C; iv, DAST, $CH_2Cl_2$ on (**11**) or Bu$^n_4$NF, THF on (**13**); v, $NH_3$, MeOH.



(15) (16) (17)

during work-up. Similar participation has been observed in natural nucleosides at C-3'[10] and C-5'.[11]

The 2'-*ara*-fluoro substituent could also be introduced in a two-step sequence involving activation of the alcohol (**11**) as its trifluoromethanesulphonate (**13**) followed by reaction with tetra-n-butylammonium fluoride in THF. However, this approach provided compound (**14**) in much lower yield (*ca.* 25%) than with DAST; the major by-product in this case was the 1',2'-olefin (**16**) (*ca.* 25%).

Deprotection of compound (**14**) with sodium methoxide in methanol completed a four-stage synthesis of 2'-deoxy-2'-fluoro-*ara*-aristeromycin (**4**), m.p. 109—113 °C, $[\alpha]_D^{22}$ +81° ($H_2O$). By contrast, synthesis of compound (**4**) from cyclopentadiene *via* standard elaboration[12] of the amino fluoro diol (**17**)[13] involved 15 stages and afforded the product as a racemic mixture.

Compound (**4**) was shown to be at least 10 times more active than cyclaridine (**3**) against HSV1 and HSV2 in the plaque reduction assay and more active than acyclovir against HSV2 in the mouse systemic test.

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## References

1 T.-L. Su, K. A. Watanabe, R. F. Shinazi, and J. J. Fox, *J. Med. Chem.*, 1986, **29**, 151; anon, *Drugs of the Future*, 1986, **11**, 332, 618.
2 A. D. Borthwick, S. Butt, K. Biggadike, A. M. Exall, S. M. Roberts, P. M. Youds, B. E. Kirk, B. R. Booth, J. M. Cameron, S. W. Cox, C. L. P. Marr, and M. D. Shill, *J. Chem. Soc., Chem. Commun.*, 1988, 656; A. D. Borthwick, D. N. Evans, B. E. Kirk, K. Biggadike, and L. Stephenson, Eur. Pat. Appl. 0212 956/1987.
3 W. M. Shannon, L. Westbrook, G. Arnett, S. Daluge, H. Lee, and R. Vince, *Antimicrob. Agents and Chemother.* 1983, **24**, 538.
4 K. Biggadike, A. D. Borthwick, A. M. Exall, B. E. Kirk, S. M. Roberts, and P. Youds, *J. Chem. Soc., Chem. Commun.*, 1987, 1083; P. Herdewijn, J. Balzarini, E. De Clercq, and H. Vanderhaeghe, *J. Med. Chem.*, 1985, **28**, 1385; J. A. Secist, III, J. A. Montgomery, Y. F. Shealy, C. A. O'Dell, and S. J. Clayton, *ibid.*, 1987, **30**, 746.
5 T. Kusaka, H. Yamamoto, M. Muroi, T. Kishi, and K. Mizuno, *J. Antibiot.*, 1968, **21**, 255.
6 R. Ranganathan and D. Larwood, *Tetrahedron Lett.*, 1978, **45**, 4341: K. Fukukawra, T. Meda, and T. Hirano, *Chem. Pharm. Bull.*, 1983, **31**, 1582.
7 P. Herdewijn, R. Pauwels, M. Baba, J. Balzarini, and E. De Clercq; *J. Med. Chem.*, 1987, **30**, 2131; K. W. Pankiewicz, B. Nawrot, and K. A. Watanabe, 193rd ACS National Meeting, Denver, 1987.
8 K. Biggadike, A. D. Borthwick, D. N. Evans, A. M. Exall, B. E. Kirk, S. M. Roberts, L. Stephenson, and P. Youds, *J. Chem. Soc., Perkin Trans. 1*, 1988, 549.
9 S. Nishino, H. Takamura, and Y. Ishido, *Tetrahedron*, 1986, **42**, 1995.
10 M. J. Robins, Y. Fouron, and R. Mengel, *J. Org. Chem.*, 1974, **39**, 1564.
11 G. W. Craig and J. G. Moffatt, *Nucleosides Nucleotides,* 1986, **5**, 399.
12 R. Vince, J. Brownell, and S. Daluge, *J. Med. Chem.*, 1984, **97**, 1358.
13 K. Biggadike, A. D. Borthwick, D. Evans, A. M. Exall, B. E. Kirk, S. M. Roberts, L. Stephenson, P. Youds, A. M. Z. Slawin, and D. J. Williams, *J. Chem. Soc. Chem. Commun.*, 1987, 251.