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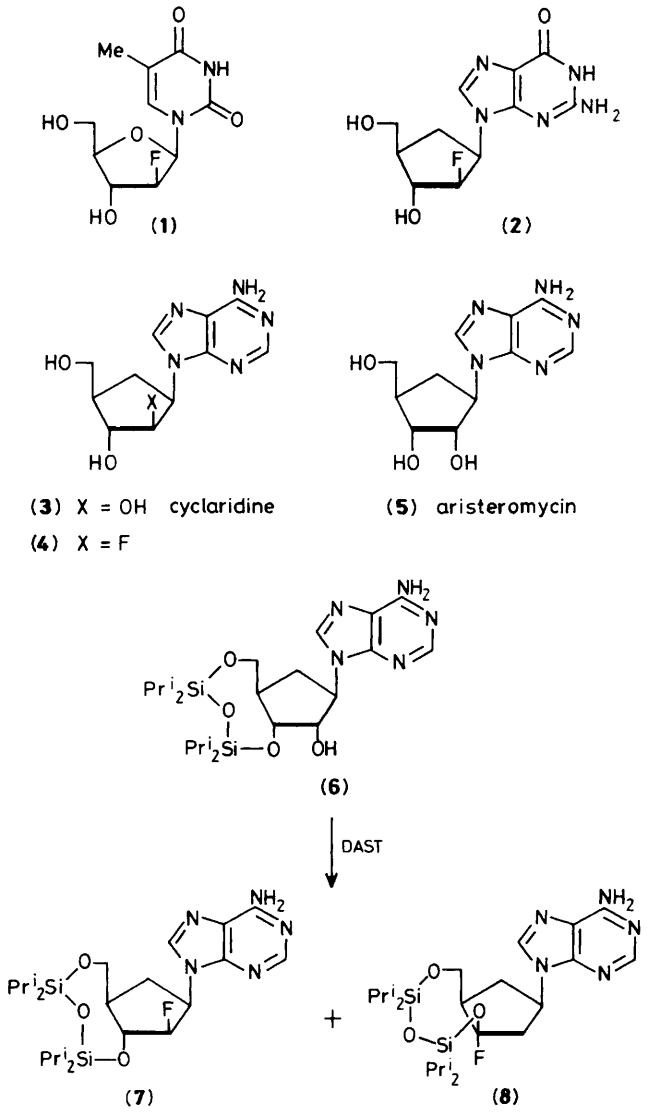
Aristeromycin has been converted in four stages into its 2′-deoxy-2′-fluoro-*ara*-analogue (**4**); compound (**4**) displayed potent anti-herpes activity both *in vitro* and *in vivo*.

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-arabino-furanosyl)-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).

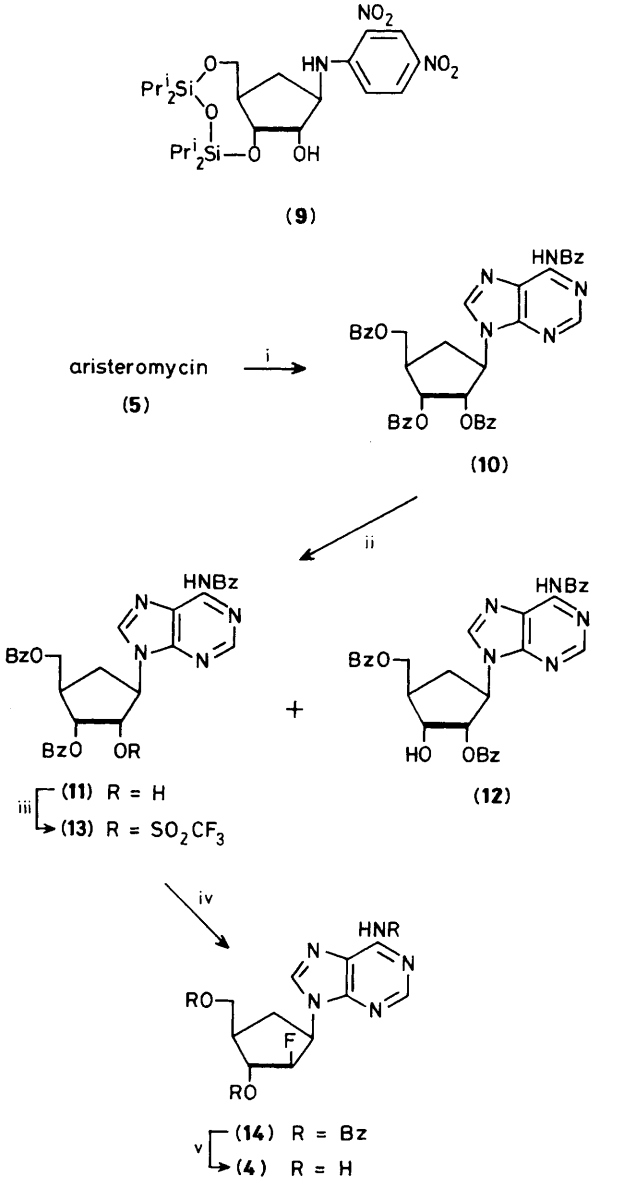
Aristeromycin (**5**) was first protected by formation of its 3′,5′-*O*-disiloxanediyl derivative (**6**); the compatibility of this protecting group and DAST has recently been exploited to introduce fluorine into the 2′-position of some carbocyclic nucleoside precursors.[8] However, reaction of compound (**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

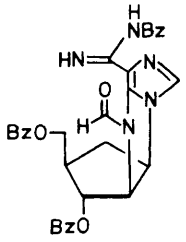


Scheme 1

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.



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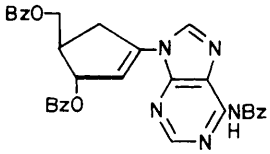

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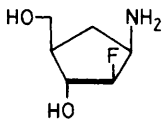

(17)

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.

We thank Mr. D. J. Knight, Dr. J. A. V. Coates, and Dr. D. M. Ryan for the biological results; further data will be reported elsewhere.

Received, 10th March 1988; Com. 8/00980E

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