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3'- Deoxy-3'-fluoro-xylo-Neplanocin A

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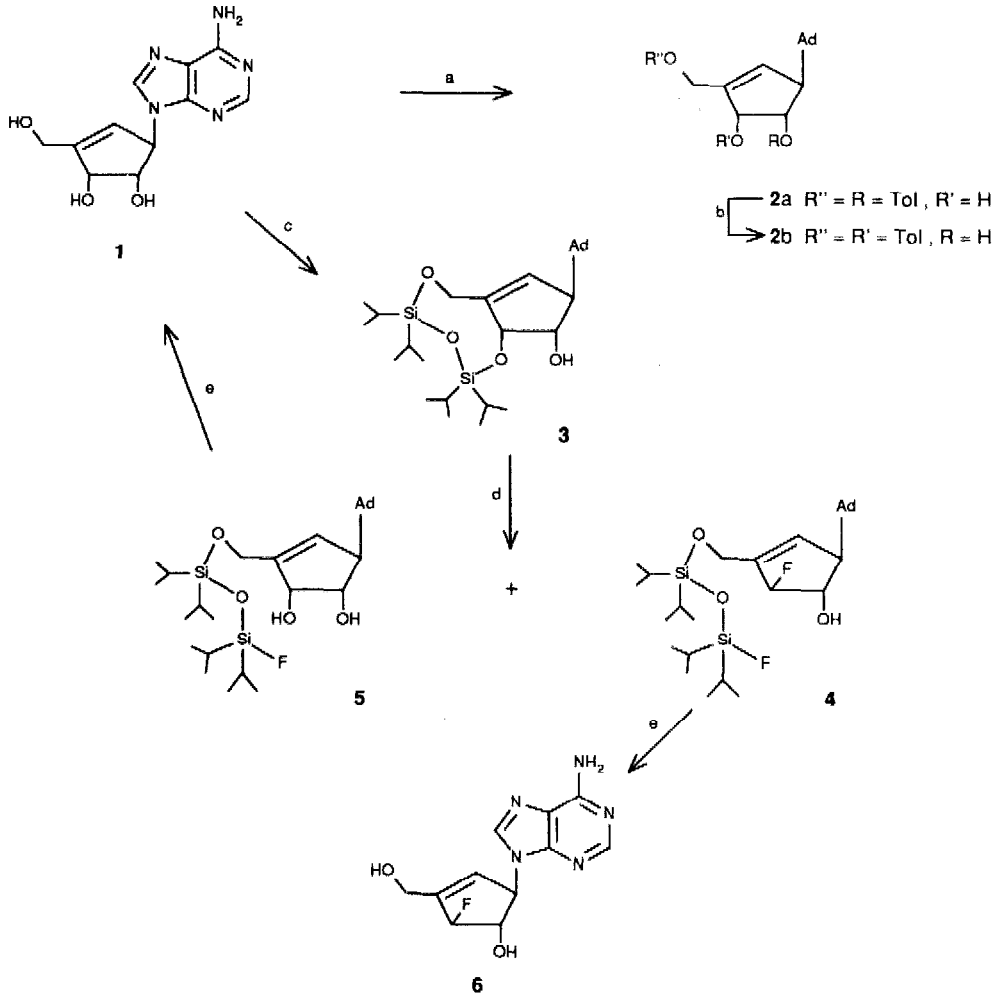
Abstract: Neplanocin A has been efficiently converted in three steps into its 3'-deoxy-3'-fluoro-*xylo*-analogue.

Fluorine substitution in nucleosides has a pronounced effect on their biological activity. The position and configuration of the fluorine substitution is crucial for the enhancement of their activity against Herpes and Retroviruses[1]. In the carbocyclic series[2], we have shown recently that 2'$\beta^{3,4}$, 4'α^{5} and 6'α^{3} fluoro substitution of purine derivatives has a marked effect on increasing their antiviral activity. The unsaturated carbocyclic nucleoside neplanocin A **1** and its analogues[6] display antiviral and antitumour activity but, surprisingly, fluoro substition in the cyclopentene ring has not been described. Having successfully[4] introduced a 2'-*ara*-fluoro substituent into aristeromycin we turned our attention to fluorination of neplanocin A.

Treatment of neplanocin A **1** with toluyl chloride (2 equiv.) in pyridine gave a quantitative yield of the 2',5'-ditoluate **2a**. In the presence of SiO_2 this gave a mixture of the 2',5'-ditoluate **2a** and 3',5'-ditoluate **2b**, from which **2b** crystallised in 23% yield (m.p.118°C)(Scheme 1). However, treatment of the 3',5'-ditoluate **2b** with diethylaminosulphur trifluoride (DAST) (2 equiv., R.T., 1.5h) failed to give the required fluoro substitution and gave instead an equilibrium mixture of **2a** and **2b**. Because of the lability of the ester protecting groups in **2b**, we turned our attention to the TIPS protecting group which we had previously shown[4,7] was compatible with DAST.

Reaction of the 3',5'-*O*-TIPS derivative **3** of neplanocin A with DAST (2.4 equiv., 5°C, 1.5h) in methylene chloride gave a 1:1 mixture of the 3'-fluoro derivative **4**[8] and the diol **5**[9] in 38% yield. However, slow addition of **3** to a stirred solution of 3 equiv. of DAST/pyridine (1:1) in methylene chloride at 0°C during 45 mins followed by a further 15 mins at this temperature gave **4** in 65% yield together with a only a small quantity (5%) of the diol **5**. Deprotection of **4** with TBAF (R.T. 15min) gave in a quantative yield 3'-deoxy-3'-fluoro-*xylo*-neplanocin A **6** $[\alpha]_D^{22}$ -62° (c 0.5, MeOH), m.p. 225-227°C. The position and configuration of the fluorine atom in **6** was indicated by NMR[10] and was confirmed by X-Ray crystallography[11]. A similar deprotection of the diol **5** regenerated neplanocin A **1** in quantitative yield.

Scheme 1

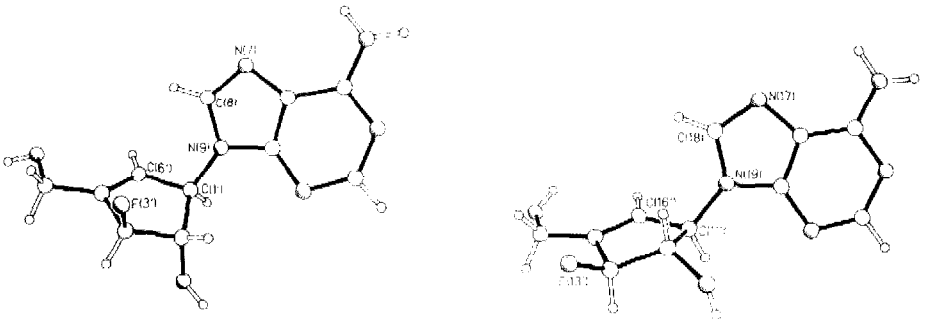


Reagents: (a) pMePhCOCl, py ,RT, 1h 20min (b) SiO_2 (c) TIPS Cl, imidazole, DMF, RT, 1h (d) DAST/py, 0°C (e) TBAF

Interestingly, a single crystal X-Ray analysis of **6** reveals 2 crystallographically independant molecules A and B (Figure 1). Both have the adenine base in the usual anti-conformation. For molecule A the torsion angle about the N(9)-C(1') bond ϕ[C(8)-N(9)-C(1')-C(6')] is +36.8° while the corresponding torsion angle for B is -12.5°. However, the pucker of the cyclopentene ring is quite different; while A has a C-2'exo,C-3'endo conformation as seen in neplanocin A **1**[12] and 2'-*ara*-mercapto-2'-deoxyneplanocin A[13], the conformation of the cyclopentene ring in B is C-2'-endo,C-3'-exo.

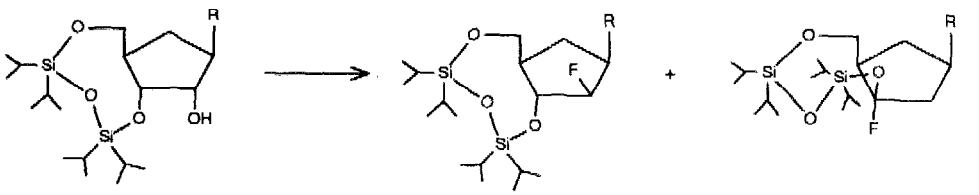
We have previously shown [4,7] that the DAST reaction of a 2'-secondary hydroxyl adjacent to the TIPS

Figure 1



A B

protecting group in a cyclopentane ring **7** gives a mixture of two products, the 2'-fluoride **8** with inversion and the 3'-fluoride **9** with retention *via* hydride transfer. The ratio of **8** to **9** depends on the substituent at the 1'-position.



7 **8** **9**

However in the cyclopentene ring **3** (Scheme 1), the fluoride ion attacks the allylic 3'-position with inversion. A similar substution in the DAST reaction on a 3'-*O*-t-butyldimethylsilyl derivative of adenosine has been reported by Herdewijin et al.[14]. Further studies are under way aimed at elucidating the mechanism of this reaction.

The recent interest in 3'-fluoro carbocyclic nucleosides as antiviral[15] and antitumour agents[16] together with the recent synthetic transformations[2] of carbocyclic adenine nucleosides into their imidazole, 8-*aza*-guanine, guanine and inosine analogues makes this efficient introduction of fluorine into the carbocyclic ring of neplanocin A a potentially useful transformation.

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8. **4**: mp 104-105°C (MeOH); ^{1}H NMR($CDCl_3$) δ 0.96-1.14 (28H, bs, 4 $CHMe_3$), 4.44-4.66 (3H, m, 2H-5', H-2'), 5.20 (1H, bs, H-1'), 5.51 (1H, dd, J_{HF}=56 Hz, H-3'), 5.70 (2H, s, NH_2,exchange D_2O), 5.82 (1H, s, OH, exchange D_2O), 6.23 (1H, s, H-6'), 7.82 (1H, s, H-2), 8.34 (1H, s, H-8); MS(CI) (isobutane) m/z: 528 (MH^+), 508 (MH^+-HF), 136 ($C_5H_5H_4$); Anal.calcd.for $C_{23}H_{39}F_2N_5O_3Si_2$: C, 52.34; H, 7.45; N, 13.27; F, 7.20. Found: C, 52.25; H, 7.52; N, 13.02; F, 6.90.
9. **5**: mp 179-181°C (MeOH); ^{1}H NMR(Me_2SO-d_6) δ 0.94-1.04 (28H, bs, 4 $CHMe_3$), 4.36 (1H, dd, *J*=5, 6.25 Hz, H-2'), 4.42-4.50 (3H, bs, H-3', 2H-5'), 5.02 (1H, d, *J*=6.25 Hz, OH exchange D_2O), 5.22 (1H, d, *J*=7.25 Hz, OH exchange D_2O), 5.37(1H, bs, H-1'), 5.73 (1H, d, *J*=2.5 Hz H-6'), 7.22 (2H, bs, NH_2 exchange D_2O), 8.04 (1H, s, H-2), 8.12 (1H, s, H-8); MS(CI) (isobutane) m/z: 526(MH^+), 506 (MH^+-HF), 136 ($C_5H_5H_4$); HRMS(-FAB) calcd. for $C_{23}H_{39}N_5O_4Si_2F$ $[M-H]^-$ 524.2524, found 524.2506
10. **6**: ^{1}H NMR (Me_2SO-d_6) δ 4.14 (2H, bs, 2H-5'), 4.69 (1H, dm, J_{HF}= 24 Hz, H-2'), 5.11 (1H, t, *J*=5.6 Hz, 5'OH exchange D_2O), 5.19 (1H, bs, H-1'), 5.38 (1H, dd, *J*=3.75 Hz, J_{HF}=56 Hz, H-3'), 5.85 (1H, bs, H-6'), 6.05 (1H, d, *J*=6.25 Hz, 2'OH exchange D_2O), 7.26 (2H, s NH_2), 8.12,8.14 (2H, 2s, H-8,H-2). ^{13}C NMR (Me_2SO-d_6) 157.4 (C-6), 153.8 (C-2), 150.9 (C-4), 146.4 (J_{CF}=20 Hz, C-4'), 140.9 (C-8), 127.3 (J_{CF}=7 Hz, C-6'), 120.5 (C-5), 100.9 (J_{CF}=172 Hz, C-3'), 84.0 (J_{CF}=20 Hz, C-2'), 63.8 (J_{CF}=6 Hz, C-1'), 58.5 (C-5'); Anal.calcd.for $C_{11}H_{12}FN_5O_2$: C, 49.81; H, 4.56; N, 26.41; F, 7.12. Found: C, 49.66; H, 4.70; N, 26.54; F, 6.90.
11. *Crystal data:* **6**, $C_{11}H_{12}FN_5O_2$, *M* = 265.25, monoclinic, a = 7.060(1), b = 12.955(3), c = 13.250(5)Å, β = 103.85(2)°, V = 1177(1)Å^3, λ = 1.54184Å, space-group $P2_1$ (No. 4), Z = 4, D_C = 1.50g cm^{-3}, F(000) = 552, μ(Cu-Kα) = 9.7cm^{-1}; crystal size: 0.44× 0.32× 0.14 mm. Nicolet R3m/V diffractometer, 1614 reflections measured ($0 < 2\theta < 115°$) of which, 1505 reflections had $I > 3.0\ \sigma(I)$. Full matrix least-squares refinement with anisotropic thermal parameters was used for all non-hydrogen atoms. Hydrogen atoms were refined in riding mode. Individual weights were applied according to the scheme $w = [\ \sigma^2(F_O) + 0.0038\ |F_O|^2]^{-1}$ refinement converged at R 0.039, R_W 0.043, goodness-of-fit = 1.01. All computations were carried out using the SHELXTL PLUS (μ-VAX II) system of programs (G.M.Sheldrick, SHELXTL release 3.4. Copyright 1988 Nicolet Instrument Corporation). Atomic parameters, bond lengths, and angels have been deposited at the Cambridge Data Centre.
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