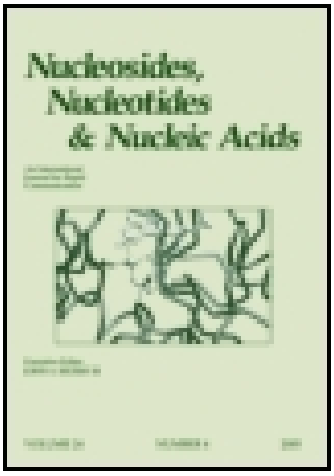

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Synthesis of Some Pyrrolo[2,3-d]Pyrimidine Isodideoxynucleosides of (S,S)-Stereochemistry

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SYNTHESIS OF SOME PYRROLO[2,3-*d*]PYRIMIDINE ISO-DIDEOXYNUCLEOSIDES OF (*S,S*)-STEREOCHEMISTRY

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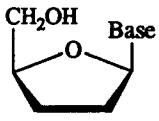
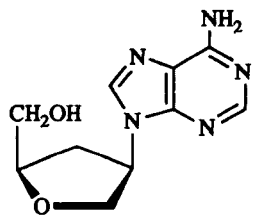
ABSTRACT: The pyrrolo[2,3-*d*]pyrimidine isodideoxynucleosides **7**, **8**, and **9**, related to the (*S,S*)-enantiomers of iso-2',3'-dideoxy-adenosine, -inosine and -guanosine respectively, have been prepared from D-xylose.

Introduction

2',3'-Dideoxynucleosides are well established as inhibitors of the reverse transcriptase (RT) of HIV-1, and indeed dideoxyinosine (ddI, **1a**)[1] and dideoxycytidine (ddC, **1b**)[2] are in clinical use for patients with HIV infections. However, dideoxynucleosides of type **1** undergo rapid degradation through hydrolysis of the glycosidic link under acidic conditions similar to those in the gastric environment.[3] There has thus been an incentive to develop other nucleoside analogues with significantly greater stability to acid, and this led to the reports of 'iso-dideoxynucleosides' such as iso-dideoxyadenosine (iso-ddA, **2**) and iso-dideoxyguanosine (iso-ddG, **3**), from both Hoffmann La Roche[4] and Glaxo[5] laboratories. Since they lack an acid-labile glycosidic bond, these compounds proved, as would be expected, to have high stability towards acids, and they were also shown to have strong and selective anti-HIV activity.[4]



1a, Base = hypoxanthin-9-yl
1b, Base = cytosin-1-yl



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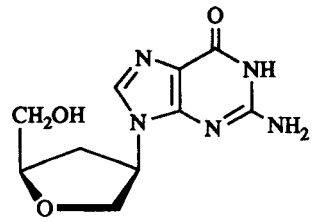

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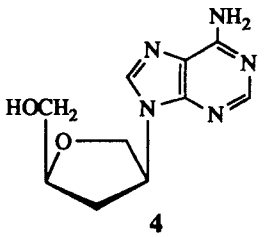
Isonucleosides **2** and **3** have the (*R*,*R*)-stereochemistry which gives them close structural similarity to the 2',3'-dideoxynucleosides **1**. However, it has become apparent in recent years that nucleoside analogues of the enantiomeric ('L-') series can also demonstrate marked antiviral activity, as for example in the cases where the deoxyribose unit is replaced by a 1,3-dioxolane[6] or 1,3-oxathiolane[7] ring. Recently, Nair and colleagues have prepared iso-dideoxynucleosides in the enantiomeric series, and (*S*,*S*)-iso-ddA (**4**), enantiomeric with **2**, proved the most interesting compound of those reported with regard to anti-HIV activity.[8] Compounds such as **4** can also be regarded as analogues of the normal ('D-') nucleosides in which the base has been transposed from C-1' to C-2'. Other workers have also reported similar structures with an additional substituent on the isosugar ring, such as **5**, with anti-HIV activity being found in some cases,[9] and the AZT analogue **6** and related compounds have also been described.[10]



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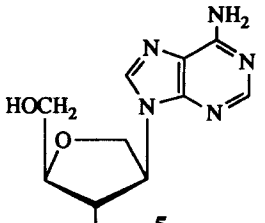

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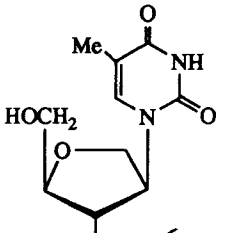

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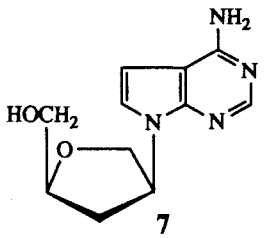
The antiviral activities found encouraged us to prepare structures related to iso-dideoxynucleosides containing other biologically-significant bases. Here we report the synthesis of the pyrrolo[2,3-*d*]pyrimidine analogues **7**, **8** and **9**, related to the (*S*,*S*)-enantiomers of iso-ddA (**4**), iso-ddI and iso-ddG respectively. Incorporation of the pyrrolo[2,3-*d*]pyrimidine (7-deazapurine) system into bioactive nucleoside analogues is well documented;[11] it is perhaps particularly noteworthy that the 7-deaza-analogues of ddA, of ddG, and of their 2',3'-didehydroderivatives, are all, as their 5'-triphosphates, powerful inhibitors of HIV reverse transcriptase.[11e]



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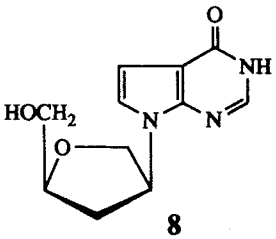

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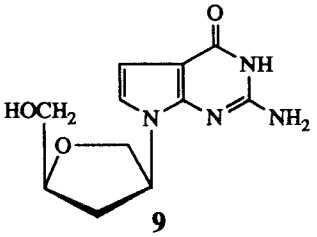

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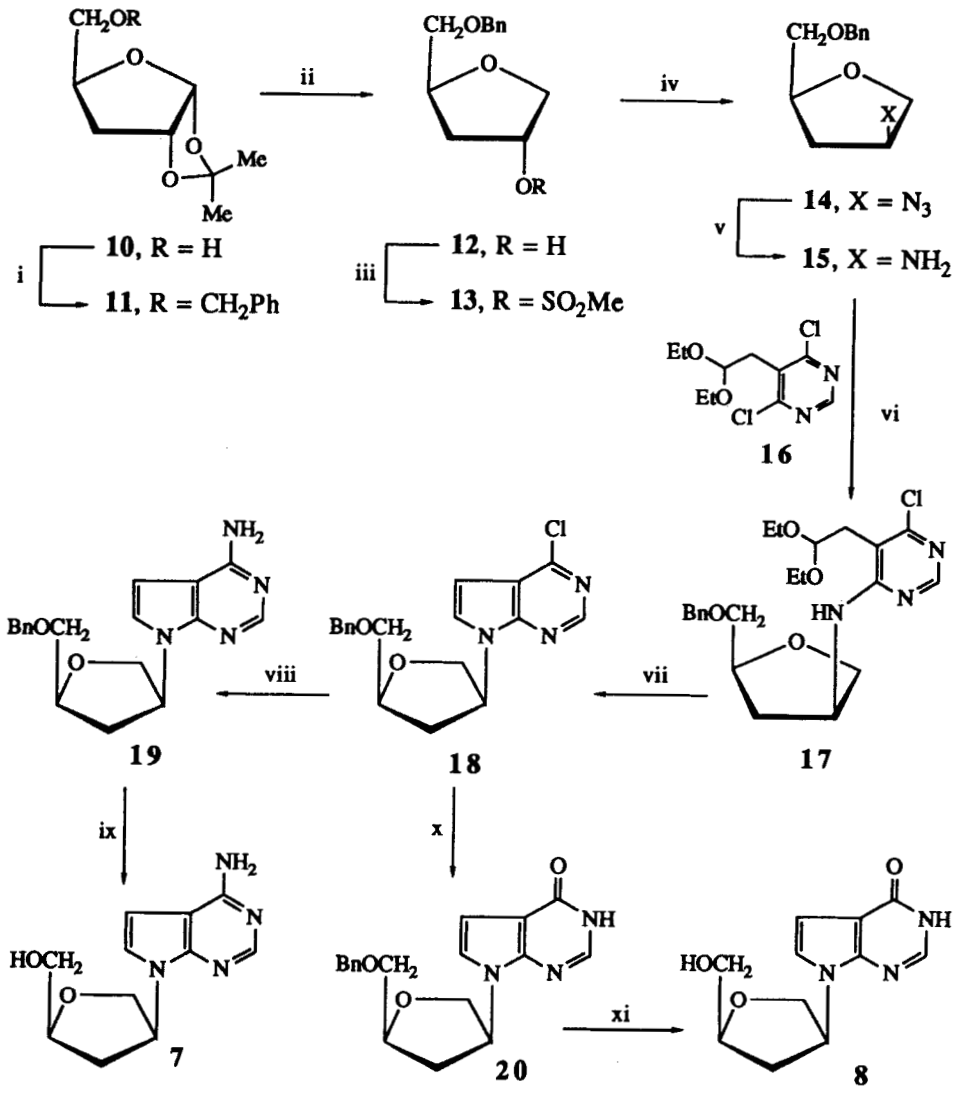
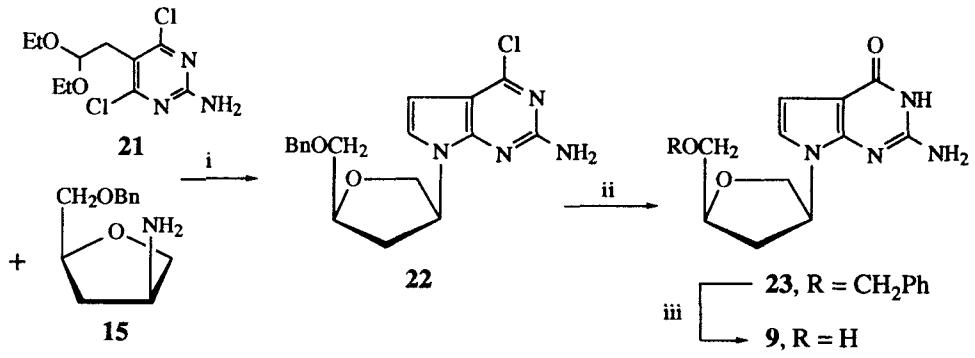
Results and Discussion

Our route to the adenosine and inosine analogues **7** and **8** is indicated in Scheme 1.



Scheme 1. i, NaH, BnBr, DMF (95%); ii, MeOH, IR-120(H^+), then Et_3SiH, $BF_3.Et_2O$, CH_2Cl_2 (48%); iii, MsCl, Et_3N (98%); iv, NaN_3, DMSO, 100 °C (93%); v, H_2, PtO_2, EtOH (88%); vi, Et_3N, $EtOCH_2CH_2OH$, reflux; vii, dioxan-HCl aq., r.t. (48% from **15**); viii, MeOH, NH_3, 100 °C (60%); ix, $Pd(OH)_2/C$, cyclohexene, EtOH, reflux (55%); x, dioxan-NaOH aq., reflux (76%); xi, as ix (70%).



Scheme 2. i, Et_3N, $EtOCH_2CH_2OH$, reflux, then dioxan-HCl aq., r.t. (34%); ii, dioxan-NaOH aq., reflux (80%); iii, $Pd(OH)_2/C$, cyclohexene, EtOH, reflux (93%).

The alcohol **10**[12] was prepared from D-xylose using known procedures,[13] and was converted into its benzyl ether **11** in high yield. Methanolysis of this, followed by reduction of the intermediate methyl glycoside with triethylsilane and boron trifluoride etherate[8a] gave the tetrahydrofuran **12** in moderate yield, and this was converted via the mesylate **13** and the azide **14** into the amine **15** in 80% overall yield. The pyrrolopyrimidine ring could then be constructed by reaction of **15** with the dichloropyrimidine **16**[14] in the presence of triethylamine to give the pyrimidinylamine **17**, which, on acid treatment gave the pyrrolopyrimidine **18**. The chlorocompound **18** gave the amine **19** by reaction with methanolic ammonia at 100 °C, and this could be converted into the adenosine analogue **7**, obtained as a crystalline solid, by debenzylation using transfer hydrogenation. The synthesis of the enantiomer of **7** has recently been described.[15]

The chlorocompound **18** also gave rise to **20** by alkaline hydrolysis, and deprotection of this by transfer hydrogenolysis produced the inosine-type analogue **8**.

A similar approach was used to prepare the analogue **9** related to dideoxyguanosine (Scheme 2). Thus interaction of amine **15** with the dichloropyrimidine **21**,[11c] followed directly by acid treatment of the intermediate pyrimidinylamine, gave the pyrrolopyrimidine **22** in moderate yield, which on alkaline hydrolysis gave the pyrrolopyrimidinone **23**. This, on debenzylation using $Pd(OH)_2$-on-charcoal in the presence of cyclohexene gave the target **9** in high yield; other workers have reported the synthesis of the enantiomer of **9**.[11b]

Antiviral Testing - Compounds **7**, **8** and **9**, and the benzyl ethers **19**, **20** and **23** were tested against HIV-1_{IIIB} in C8166 cells, and the results are given below. Thus none of

these compounds possess significant anti-HIV activity associated with low toxicity. However in the light of previous findings,[11e,16] it remains of interest to evaluate **7**, **8** and **9** as their triphosphates against HIV-1 reverse transcriptase.

Compound	$EC_{50}(\mu M)^a$	$TC_{50}(\mu M)^b$
7	10	>1000
8	>1000	>1000
9	200	>1000
19	16	50
20	8	400
23	4	20
AZT	0.016	>1000

[a] Concentration which reduces Ag gp120 by 50% in infected cell cultures
[b] Concentration which reduces uninfected cell growth by 50%

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker WP 200 SY instrument operating at 200.13 and 50.32 MHz, respectively, with $CDCl_3$ as solvent unless otherwise stated. Coupling constants (*J*) are quoted in Hz, and primed locants refer to positions on the tetrahydrofuran ring. Specific rotations were measured on a Bendix-NPL 143D automatic polarimeter; units for $[\alpha]_D$ values are 10^{-1} deg cm^2 g^{-1}. Organic extracts were dried over anhydrous magnesium sulfate, and light petroleum refers to material of boiling range 40-60 °C. Column chromatography was carried out using Kieselgel H type 60 (Merck), an external pressure being applied to the top of columns.

5-O-Benzyl-3-deoxy-1,2-O-isopropylidene-α-D-erythro-*pentofuranose* (**11**)- To a slurry of sodium hydride (0.929 g, 38.7 mmol) in dry DMF (50 ml) at 0 °C was added with stirring a solution of alcohol **10**[12,13] (6.13 g, 35.2 mmol) in DMF (20 ml). After 1h, benzyl bromide (6.62 g, 38.7 mmol) was added dropwise and the mixture was stirred at room temperature overnight. The residue after evaporation was dissolved in dichloromethane (100 ml) and washed with water (2 x 50 ml) and brine (100 ml). The dried organic layer was evaporated and the residue was chromatographed on silica gel with ethyl acetate-light petroleum (1:1) as eluant to give the benzyl ether **11** (8.78 g, 95%) as an oil, $[\alpha]_D$ -15.1 (*c* 1.7, $CHCl_3$); δ_H 1.31 and 1.50 (each 3H, s, CMe_2), 1.77 (1H, ddd, J_{gem} 13.4, $J_{3\beta,4}$ 10.8, $J_{3\beta,2}$ 4.8, 3β-H), 2.04 (1H, dd, $J_{3\alpha,4}$ 4.5, 3_α-H), 3.55 (1H, dd, *J* 10.6, 4.9, 5_a-H), 3.64(1H, dd, *J* 10.6, 3.6, 5_b-H), 4.39 [1H, dq, *J* 10.8 and ~4 (x3)], 4.58 (2H, s, OCH_2Ph), 4.72 (1H, t, *J* 4.2, 2-H), 5.83 (1H, d, *J* 3.7, 1-H), 7.3-7.4 (5H, m, Ph) [Found: M^+ (EI) 264.13621. Calc. for $C_{15}H_{20}O_4$, 264.13604].

(2S, 4R)-2-*Benzyloxymethyl*-4-*hydroxytetrahydrofuran* (**12**). - A solution of **11** (8.59 g, 32.5 mmol) in dry methanol (250 ml) was heated under reflux with IR-120 (H^+) resin for

16 h. The residue after filtration and evaporation was evaporated with toluene (2 x 50 ml), dissolved in dichloromethane (250 ml) at 0 °C and treated with triethylsilane (11.16 g, 96 mmol) and boron trifluoride etherate (9.7 ml, 80 mmol). After 16 h at room temperature, a further portion of $BF_3.Et_2O$ (2.4 ml) was added. After a further 24 h, the mixture was quenched into saturated aqueous $NaHCO_3$ (200 ml). The organic phase was washed with water (100 ml) and brine (100 ml), dried and evaporated. The residue was chromatographed on silica gel, with dichloromethane-methanol (99:1) as eluant, to give the alcohol **12** (3.2 g, 48%) as an oil, $[\alpha]_D$ +2.4 (*c* 2.5, $CHCl_3$); δ_H 1.7-2.0 (2H, m, 3-H_2), 2.9 (1H, br. s, OH), 3.4-3.6 (2H, AB of ABX, *J* 13, 6, 3, CH_2 OBn), 3.75 (1H, d, *J* 9, 5$_\alpha$-H), 3.94 (1H, dd, *J* 9, 4, 5$_\beta$-H), 4.3-4.5 (2H, m, 2-H and 4-H), 4.56 (2H, s, OCH_2Ph), 7.2-7.3 (5H, m, Ph) (Found: M^+, 208.10821. Calc. for $C_{12}H_{16}O_3$, 208.10994).

(2S, 4R)-2-*Benzyloxymethyl*-4-*(methylsulfonyloxy)tetrahydrofuran* (**13**)- To a solution of alcohol **12** (3.04 g, 14.7 mmol) and triethylamine (1.48 g, 17.7 mmol) in dichloromethane (30 ml) was added at 0 °C with stirring methylsulfonyl chloride (2.02 g, 17.7 mmol). The mixture was allowed to warm to room temperature and after 1 h was washed with $NaHCO_3$ solution (saturated, 2 x 25 ml), water (50 ml) and brine (50 ml). The organic phase was dried and evaporated, and the residue was chromatographed on silica gel with ethyl aceate-light petroleum (1:1) as eluant to give the sulfonate **13** (4.12 g, 98%) as an oil, $[\alpha]_D$ +6.4 (*c* 1.27, $CHCl_3$); δ_H 2.12 (1H, ddd, *J* 15.0, 9.2, 5.5, 3$_\beta$-H), 2.28 (1H, dd, *J*, 15.0, 6.2, 3$_\alpha$-H), 3.03 (3H, s, $MeSO_2$), 3.45-3.65 (2H, AB of ABX, *J* 11, 5, 3, CH_2 OBn), 4.02 (1H, br. d, *J* 10.8, 5$_\alpha$-H), 4.14 (1H, dd, *J* 10.8, 4.1, 5$_\beta$-H), 4.35 (1H, m, 2-H), 4.56 (2H, s, OCH_2Ph), 5.32 (1H, m, 4-H), 7.3 (5H, br. s, Ph) (Found: C, 55.0; H, 6.0; H, 6.0; S, 11.6. $C_{13}H_{18}O_5S$ requires C, 54.73; H, 6.31; S, 11.22%. Found: M^+ 286.0859. Calc. for $C_{13}H_{18}O_5S$, 286.0814).

(2S, 4S)-4-*Azido*-2-*(benzyloxymethyl)tetrahydrofuran* (**14**) - A solution of mesylate **13** (3.58 g, 12.6 mmol) and sodium azide (2.45 g, 37.7 mmol) in dry DMSO was maintained at 100 °C for 5h. The residue after evaporation was dissolved in ethyl acetate (50 ml) and the solution was washed with water (2 x 25 ml) and brine (25 ml), dried and evaporated. Chromatography of the residue on silica gel, with dichloromethane-methanol (99:1) as eluant gave the azide **14** (2.73g, 93%) as an oil, $[\alpha]_D$ -4.8 (*c* 1.62, $CHCl_3$); δ_H 1.81 (1H, dddd, *J* 13.6, 6.6, 3.8 and 1.0, 3$_a$-H), 2.31 (1H, dt, *J* 13.6, 7.7, 7.7, 3$_b$-H), 3.47-3.64, (2H, AB of ABX, *J* 10.0, 3.9, 6.0, CH_2 OBn), 3.82 (1H, dd, *J* 9.8, 5.2, 5$_a$-H), 3.92 (1H, ddd, *J* 9.8, 2.9, 0.9, 5$_b$-H), 4.05-4.20 (2H, m, 2-H, 4-H), 4.59 (2H, AB dd, *J* 12.1, OCH_2Ph), 7.25-7.35 (5H, m, Ph); δ_c 34.4 (C-3), 60.8, 72.1, 72.6, 73.5, 77.9, 127.7, 127.8, 128.4 and 138.1 [Found: MH^+ (FAB) 234.1259. Calc. for $C_{15}H_{16}N_3O_2$, 234.1243].

(2S, 4S)-4-*Amino*-2-(*benzyloxymethyl)tetrahydrofuran* (**15**). - The azide **14** (2.61 g, 11.3 mmol) was hydrogenated in ethanol (50 ml) at 1 atm at room temperature over PtO_2 (30 mg) for 24 h. The residue after filtration and evaporation was chromatographed on silica gel, with dichloromethane-methanol (95:5) as eluant, to give the amine **15** (2.03 g, 88%) as an oil, $[\alpha]_D$ -14.8 (*c* 1.42, $CHCl_3$); δ_H 1.50 (1H, ddd, *J* 12, 7, 5, 3_a-H), 2.25 (1H, dt, 12, 7.5, 7.5, 3_b-H), 3.45-3.65 (4H, m, CH_2OBn, 5-H_2), 3.80 (1H, m, 4-H), 4.10 (1H, m, 2-H), 4.58 (2H, s, OCH_2Ph), 7.3 (5H, br.s, Ph); δ_C 38.0 (C-3), 52.4 (C-2), 72.6, 73.4, 76.4, 78.0, 127.6, 127.7, 128.3 and 138.2 (Found: MH^+ 208.13375. Calc. for $C_{12}H_{18}NO_2$, 208.13206).

7-[(2S,4S)-(2-*Benzyloxymethyl)-tetrahydrofuran*-4-*yl*]-4-*chloropyrrolo*[2,3-d]*pyrimidine* (**18**). - A solution of amine **15** (1.10 g, 5.32 mmol), dichloropyrimidine **16** (1.69 g, 6.38 mmol) and triethylamine (10 ml) in 2-ethoxyethanol (20 ml) was heated under reflux for 5 h. The residue after evaporation was partitioned between ethyl acetate (50 ml) and water (2 x 50 ml). The dried organic layer was evaporated and the residue was chromatographed on silica, with dichloromethane-methanol (98:2) as eluant, to give the pyrimidinylamine **17** [δ_H 1.15 (6H, dt), 1.7 (1H, ddd), 2.43 (1H, dt), 2.85 (2H, d), 3.4-3.8 (8H, m), 3.94 (1H, dd), 4.15 (1H, m), 4.5-4.7 (3H, m), 6.55 (1H, br. d), 7.3 (5H, br.s), 8.30 (1H, s); Found: MH^+ 435.19252; Calc. for $C_{22}H_{30}{}^{35}ClN_3O_4$, 435.19248].

This material was treated with HCl aq. (0.3M, 15 ml) and dioxan (24 ml) for 3 days at r.t. The solution was neutralized with aqueous ammonia and lyophilized. The residue was chromatographed on silica, with dichloromethane-methanol (98:2), as eluant, to give the pyrrolopyrimidine **18** (0.874 g, 48%) as an oil, $[\alpha]_D$ -4.1 (*c* 1.22, $CHCl_3$); δ_H 2.05 (1H, ddd, *J* 13, 8, 4, $3'_a$-H), 2.66 (1H, dt, *J* 13, 7.5, 7.5, $3'_b$-H), 3.55-3.80 (2H, AB of ABX, *J* 10, 5, 3, CH_2OBn), 4.0-4.1 (2H, m, 5'-H_2), 4.12-4.28 (1H, m, 2'-H), 4.62 (2H, s, OCH_2Ph), 5.58 (1H, m, 4'-H), 6.50 (1H, d, *J* 3.7, 5-H), 7.32 (5H, br.s, Ph), 7.61 (1H, d, *J* 3.7, 6-H), 8.59 (1H, s, 2-H).

4-*Amino*-7-[(2S, 4S)-2-(*benzyloxymethyl)-tetrahydrofuran*-4-*yl*]*pyrrolo*[2,3-d]*pyrimidine* (**19**). - A solution of chlorocompound **18** (515 mg, 1.5 mmol) in saturated methanolic ammonia (40 ml) was heated at 100 °C in a pressure vessel for 3 days. The residue after evaporation was chromatographed on silica, with dichloromethane-methanol (95:5) as eluant, to give the amine **19** (289 mg, 60%), m.p. 138-140 °C (from ethyl acetate), $[\alpha]_D$ -9.5 (*c* 1.05, MeOH); δ_H (DMSO-d_6) 1.91 (1H, ddd, *J* 13.0, 8.0, 5.5, $3'_a$-H), 2.53 (1H, dt, *J* 13.0, 7.7, 7.7, $3'_b$-H), 3.61 (2H, d, *J* ~4, CH_2OBn), 3.8-4.0 (2H, AB of ABX, *J* 9.0, 7.5, 4.5, 5'-H_2), 4.10 (1H, m, 2'-H), 4.53 (2H, s, PhCH_2O), 5.33 (1H, m, 4'-H), 6.51 (1H, d, *J* 3.5, 5-H), 6.97 (2H, br.s, NH_2), 7.22 (1H, d, *J* 3.5, 6-H), 7.25-7.35 (5H, m, Ph), 8.04 (1H, s, 2-H), δ_C (DMSO-d_6) 35.2 (C-3'), 53.5 (C-2'), 72.0, 72.6 and 72.8 (all CH_2), 78.1 (C-4'), 99.6 (C-5), 102.7 (C-4a), 121.5 (C-6), 127.9 and 128.9 (CH, Ph), 138.8 (q, Ph),

150.0 (C-7a), 151.9 (C-2), 157.9 (C-4); *m/z* 324 (M^+), 233 $(M\text{-}PhCH_2)^+$, 134 (Base $^+$), 91 ($PhCH_2^+$) (Found: M^+, 324.1586. Calc. for $C_{18}H_{20}N_4O_2$ 324.1586).

4-*Amino*-7-[(2S,4S)-2-(*hydroxymethyl*)-*tetrahydrofuran*-4-*yl*]*pyrrolo*[2,3-d]*pyrimidine* (**7**). - The benzyl ether **19** (0.133 g, 0.41 mmol) was heated under reflux with $Pd(OH)_2/C$ (20%, 100 mg) in cyclohexene (10 ml) and ethanol (10 ml) for 24 h. After filtration through celite and evaporation, the residue was chromatographed on silica, with dichloromethane-methanol (95:5) as eluant, to give the alcohol **7** (53 mg, 55%), m.p. 148-150 °C (from ethyl acetate), $[\alpha]_D$ -17.5 (*c* 0.52, MeOH); δ_H (DMSO-d_6) 1.92 (1H, ddd, *J* 13.5, 8.4, 6.0, 3'$_a$-H), 2.50 (1H, m, partially obscured by solvent, 3'$_b$-H), 3.55 (2H, m, C*H*$_2$OH), 3.80-4.05 (3H, m, 2'-H, 5'-H_2), 4.88 (1H, t, *J* 6.0, OH), 5.32 (1H, m, 4'-H), 6.53 (1H, d, *J* 3.5, 5-H), 7.0 (2H, br.s, NH_2), 7.28 (1H, d, *J* 3.5, 6-H), 8.03 (1H, s, 2-H); δ_C (DMSO-d_6) 34.9 (C-3'), 53.7 (C-2'), 63.2 (CH_2OH), 72.6 (C-5'), 80.1 (C-4'), 99.6 (C-5), 102.7 (C-4a), 121.5 (C-6), 150.0 (C-7a), 152.0 (C-2), 157.9 (C-4); λ_{max} (H_2O, pH 7) 272 nm (ε 8600) [Found: MH^+ (NH_3 CI) 235.1195. Calc. for $C_{11}H_{15}N_4O_2$, 235.1195].

7-[(2S,4S)-2-(*Benzyloxymethyl*)-*tetrahydrofuran*-4-*yl*]-*pyrrolo*[2,3-d]*pyrimidin*-4(3H)-*one* (**20**). - Chlorocompound **18** (0.25 g, 0.72 mmol) was heated under reflux in dioxan (15 ml) and NaOH aq. (1M, 5 ml) for 48 h. After neutralization to pH7 with aqueous HCl, the mixture was lyophilized and the residue was chromatographed on silica, with dichloromethane-methanol (20:1) as eluant, to give the pyrrolopyrimidinone **20** (0.18 g, 76%), m.p. 114-116 °C (from ethyl acetate); δ_H (DMSO-d_6) 1.90 (1H, ddd, *J* 13.7, 8.2, 5.5, 3'$_a$-H), 2.58 (1H, dt, *J* 13.7, 8.8, 8.8, 3'$_b$-H), 3.60 (2H, m), 4.30-4.50 (2H, m), 4.13 (1H, m, 2'-H), 4.53 (2H, s, PhC*H*$_2$O), 5.30 (1H, m, 4'-H), 6.42 (1H, d, *J* 3.5, 5-H), 7.20 (1H, d, *J* 3.5, 6-H), 7.25-7.35 (5H, m, Ph), 7.87 (1H, s, 2-H), 11.9 (1H, br. s, NH) [Found: MH^+ (NH_3 CI) 326.1505. Calc. for $C_{18}H_{20}N_3O_3$, 326.1505].

7-[(2S,4S)-2-(*Hydroxymethyl*)-*tetrahydrofuran*-4-*yl*]-*pyrrolo*[2,3-d]*pyrimidin*-4(3H)-*one* (**8**). - The benzyl ether **20** (150 mg, 0.46 mmol) and Pd $(OH)_2/C$ (20%, 50 mg) were heated under reflux in cyclohexene (10 ml) and ethanol (15 ml) for 5 h. The mixture was filtered through celite and evaporated. The residue was chromatographed on silica, with dichloromethane-methanol (20:1) as eluant, to give the alcohol **8** (76 mg, 70%), m.p. 146-148 °C (from ethyl acetate), $[\alpha]_D$ -16.6 (*c* 0.78, MeOH); δ_H (DMSO-d_6) 1.90 (1H, ddd, *J* 13.6, 8.5, 5.6, 3'$_a$-H), 2.50 (1H, obscured by solvent, 3'$_b$-H), 3.45-3.65 (2H, m, C*H*$_2$OH), 3.80-4.05 (3H, m, 2'-H, 5'-H_2), 4.88 (1H, t, OH), 5.31 (1H, m, 4'-H), 6.49 (1H, d, *J* 3.5, 5-H), 7.27 (1H, d, *J* 3.5, 6-H), 7.87 (1H, s, 2-H), 11.85 (1H, br.s, NH); δ_C (DMSO-d_6) 35.0 (C-3'), 54.3 (C-2'), 63.0 (CH_2OH), 72.8 (C-5'), 80.1 (C-4'), 102.5 (C-5), 108.1 (C-4$_a$), 121.1 (C-6), 143.8 (C-2), 147.4 (C-7a), 158.7 (C-4) λ_{max} (H_2O, pH 7) 265 nm (ε 11200) [Found: MH^+ (FAB) 236.1026. Calc. for $C_{11}H_{14}N_3O_3$ 236.1035].

2-*Amino*-7-[(2S,4S)-2-(*benzyloxymethyl*)-*tetrahydrofuran*-4-*yl*]-4-*chloropyrrolo*[2,3-d] *pyrimidine* (**22**). - A solution of amine **15** (0.82 g, 4.0 mmol), dichloropyrimidine **21**[11c] (1.40 g, 5.0 mmol) and triethylamine (10 ml) in 2-ethoxyethane (20 ml) was heated under reflux for 7 h. The residue after evaporation was partitioned between ethyl acetate (50 ml) and water (2 x 25 ml). The organic layer was evaporated and the residue was treated with dil. HCl (0.3M, 15 ml) and dioxan (24 ml) for 3 days at r.t. The mixture was neutralized with aqueous ammonia and evaporated. Chromatography of the residue on silica, with dichloromethane-methanol (97:3) as eluant, gave the pyrrolopyrimidine **22** (0.484 g, 34%) as an oil, $[\alpha]_D$ +22.6 (*c* 4.2, $CHCl_3$); δ_H 1.98 (1H, ddd, *J* 13.2, 8.4, 4.2, 3'$_a$-H), 2.61 (1H, dt, *J* 13.2, 8.3, 8.3, 3'$_b$-H), 3.6-3.8 (2H, AB of ABX, *J* 10.2, 4.8, 6.6, CH_2OBn), 3.9-4.2 (3H, m, 2'-H, 5'-H_2), 4.60 (1H, s, OCH_2 Ph), 5.2 (2H, br. s, NH_2), 5.37 (1H, m, 4'-H), 6.32 (1H, d, *J* 3.7, 5-H), 7.20 (1H, d, *J* 3.7, 6-H), 7.3-7.4 (5H, m, Ph); *m/z* (EI) 358 (M^+), 267 ($M-PhCH_2O)^+$, 168 (base)$^+$ (Found: M^+ 358.11970. Calc. for $C_{18}H_{19}{}^{35}ClN_4O_2$ 358.11965).

2-*Amino*-7-[(2S,4S)-2-(*benzyloxymethyl*)-*tetrahydrofuran*-4-*yl*]-*pyrrolo*[2,3-d]*pyrimidin*-4(3H)-*one* (**23**). - A solution of chlorocompound **22** (0.454 g, 1.26 mmol) in dioxan (20 ml) and aqueous NaOH (1M, 20 ml) was heated under reflux for 24h. After neutralization with acetic acid to pH7 and evaporation, the residue was chromatographed on silica, with dichloromethane-methanol (95:5) as eluant to give the pyrrolopyrimidinone **23** (0.343 g, 80%), m.p. 208-210 °C; δ_H (DMSO-d_6) 1.83 (1H, ddd, *J* 14.0, 9.0, 6.4, 3'$_a$-H), 2.48 (1H, m, 3'$_b$-H), 3.60 (2H, d, *J* 5.0, CH_2 OBn), 3.75-3.95 (2H, AB of ABX, *J* 9.2, 4.5, 7.0, 5'-H_2), 4.1 (1H, m, 2'-H), 4.52 (2H, s, OCH_2 Ph), 5.05 (1H, m, 4'-H), 6.18 (1H, d, *J* 3.5, 5-H), 6.21 (2H, br. s, NH_2), 6.79 (1H, d, *J* 3.5, 6-H), 7.25-7.35 (5H, m, Ph), 10.25 (1H, brs, NH) [Found: MH^+ (FAB) 341.1599. Calc. for $C_{18}H_{21}N_4O_3$ 341.1614].

2-*Amino*-7-[(2S,4S)-2-*(hydroxymethyl)-tetrahydrofuran*-4-*yl*]*pyrrolo*[2,3-d]*pyrimidin*-4(3H)-*one* (**9**). - The benzyl ether **23** (0.22 g, 0.64 mmol) and $Pd(OH)_2$/C (20%, 0.135 g) were heated under reflux in cyclohexene (10 ml) and ethanol (15 ml) for 24 h. The mixture was filtered through celite, which was washed well with methanol. The combined filtrates were evaporated and the residue was chromatographed on silica gel, with dichloromethane-methanol (95:5) as eluant, to give the alcohol **9** (0.15 g, 93%), m.p. 224-226 °C, $[\alpha]_D$ +5.8 (*c* 1.04, MeOH); δ_H (DMSO-d_6) 1.85 (1H, ddd, *J* 13.5, 8.0, 6.5, 3'$_a$-H), 2.41 (1H, dt, *J* 13.5, 8.0, 8.0, 3'$_b$-H), 3.50-3.60 (2H, m, CH_2OH), 3.73 - 3.96 (3H, m, 2'-H, 5'-H_2), 4.88 (1H, t, *J* 5.6, OH), 5.10 (1H, m, 4'-H), 6.20 (2H, br.s, NH_2), 6.24 (1H, d, *J* 3.6, 5-H), 6.85 (1H, d, *J* 3.6, 6-H), 10.30 (1H, br. s, NH); δ_C (DMSO-d_6) 34.9 (C-3'), 53.5 (C-2'), 63.2 (CH_2OH), 72.6 (C-5'), 80.0 (C-4'), 100.1 (C-4a), 102.3 (C-5), 117.3 (C-6), 150.6 (C-7a), 152.7 (C-2) and 159.2 (C-4); λ_{max} (H_2O, pH 7) 262 nm (ε 11400), 283 (sh) [Found: MH^+ (FAB) 251.1145. Calc. for $C_{11}H_{15}N_2O_5$ 251.1144].

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