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Synthesis of some Pyrrolo[2,3-*d*]pyrimidine and 1,2,3-Triazole Isonucleosides

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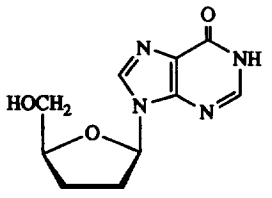
Abstract: Nucleoside analogues **8**, **9**, **10** and **11**, in which a pyrrolo[2,3-*d*]pyrimidine ring is linked to a 2-hydroxymethyl-3-hydroxytetrahydrofuran, have been prepared. The azide **16** used as an intermediate in the routes to these compounds also gave access to the 1,2,3-triazole isonucleosides **12** and **13**.

INTRODUCTION

It has been recognised for some time that 2',3'-dideoxynucleosides can be effective inhibitors of the reverse transcriptase of HIV-1, and indeed dideoxyinosine (ddI, didanosine, **1**)[1] and dideoxycytosine (ddC, zalcitabine, **2**)[2] are in clinical use against HIV infections. It has also become apparent in recent years that, in addition to the deletion of the 3'-hydroxy function of deoxynucleosides, as in the 2', 3'-dideoxynucleosides, or its replacement by another functional group, as in AZT,[3] good antiviral activity can be shown by compounds with a more extensive modification of the deoxyribose unit. Notable compounds of this type with potent anti-HIV activity include those in which the tetrahydrofuran ring is replaced by a 1,3-dioxolane[4] or a 1,3-oxathiolane ring, as in the very promising 3-thiacytidine (lamivudine, **3**), where the stereoisomer shown displayed the best anti-viral activity.[5]



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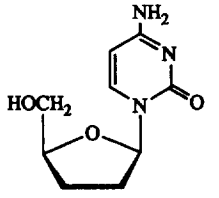

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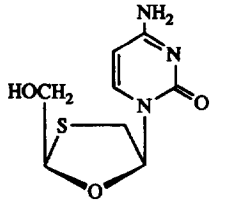
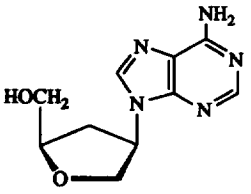


3

Also of interest in this area, showing significant and selective anti-HIV activity, are the 'iso-dideoxy-nucleosides' such as iso-dideoxyadenosine (iso-ddA, **4**) and iso-ddG (**5**), investigated by workers in both Hoffman-La Roche[6] and Glaxo laboratories.[7] Recently, Nair and colleagues have prepared iso-dideoxynucleosides in the enantiomeric series, and *S*,*S*-iso-ddA (**6**), enantiomeric with **4**, proved the most interesting compound of those reported with regard to anti-HIV activity.[8] Other workers have also reported similar compounds with an additional substituent on the isosugar ring, such as **7**, and again anti-HIV activity was found in some cases.[9]



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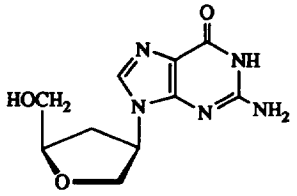

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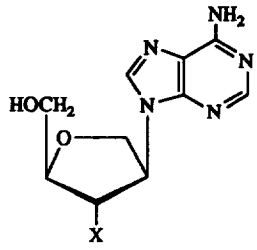
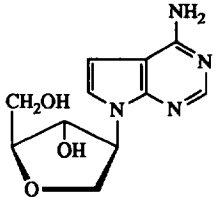


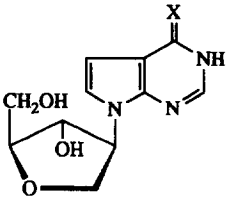
6, X = H
7, X = OH

2',3'-Dideoxynucleosides such as **1** and **2** have the disadvantage as medicinal agents of undergoing rapid hydrolysis of the glycosidic bond under acidic conditions similar to those in the gastric environment.[10] Iso-dideoxynucleosides such as **4** and **5** are, as would be expected, of much greater stability towards acids, with neither of these compounds undergoing detectable decomposition over 24 hours at pH 3 and 37 °C, whereas 2',3'-dideoxyadenosine (ddA) and 2',3'-dideoxyguanosine (ddG) had half-lives of <1 h and ~2 h respectively under these conditions.[6] There is, therefore, encouragement to synthesise a range of compounds related to iso-ddA (**4**) including examples with other biologically-significant bases.

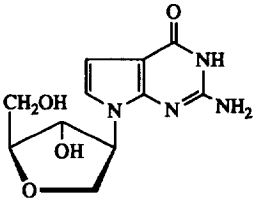
In this work we describe the synthesis of compounds **8** - **11** related to iso-ddA but in which the adenine moiety is replaced by a pyrrolo[2,3-*d*]pyrimidine ring. Incorporation of the pyrrolo[2,3-*d*]pyrimidine (7-deazapurine) system into bioactive nucleoside analogues is well documented;[11] it is 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.[11c] The 8-aza-analogue of iso-ddA is also, as its 5'-triphosphate, an active inhibitor of HIV-1 recombinant reverse transcriptase.[12]



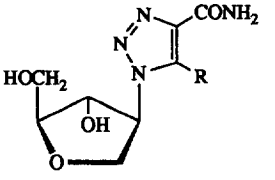
8



9, X = O
10, X = S



11



12, R = $CONH_2$
13, R = H

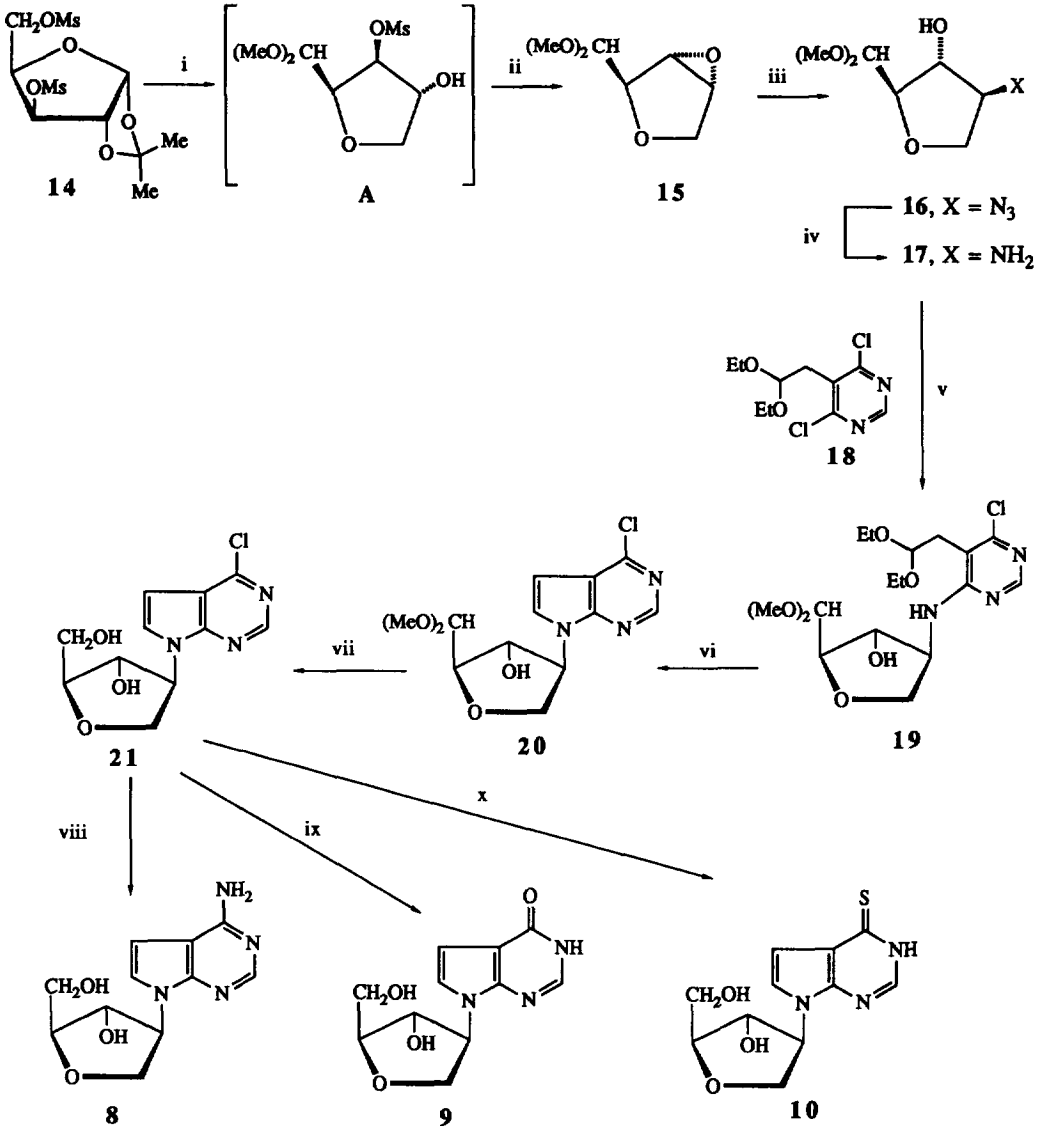
The presence of an extra hydroxy function in the isosugar ring of these compounds gives scope for the synthesis of other analogues with various other functionalities, as well as the iso-dideoxynucleosides themselves by removal of the hydroxy group. Its presence also gives the opportunity for incorporation of iso-nucleosides (with either the normal nucleobases or modified ones) into oligonucleotide analogues, in which the iso-nucleosides could be linked either by phosphodiester links, or by one of the many phosphorus-free linkages that have been investigated in recent years in connection with antisense research.[13]

The use of azido-intermediates in the routes to **8** - **11** also permitted the synthesis of the 1,2,3-triazole isonucleosides **12** and **13**.

RESULTS AND DISCUSSION

The route used for synthesis of the pyrrolopyrimidine isonucleosides **8**, **9** and **10** is indicated in Scheme 1, and is similar to an approach previously reported very briefly for gaining access to such analogues.[14] 1,2-*O*-isopropylidene-α-D-xylofuranose[15] was converted conventionally into its dimesylate **14**, and this, on heating

under reflux in methanol containing 1% (v/v) of trifluoroacetic acid, followed by treatment with anhydrous K_2CO_3, gave the acetal-epoxide **15** in high yield. The tetrahydrofuran **A** is assumed to be formed as an intermediate after the acid treatment, by analogy with other similar cyclizations.[16] The epoxide **15** could be converted cleanly into one regioisomeric azidoalcohol **16** on treatment with NaN_3 and NH_4Cl in aqueous ethanol as reflux,[14] and catalytic hydrogenation then gave the aminoalcohol **17**.

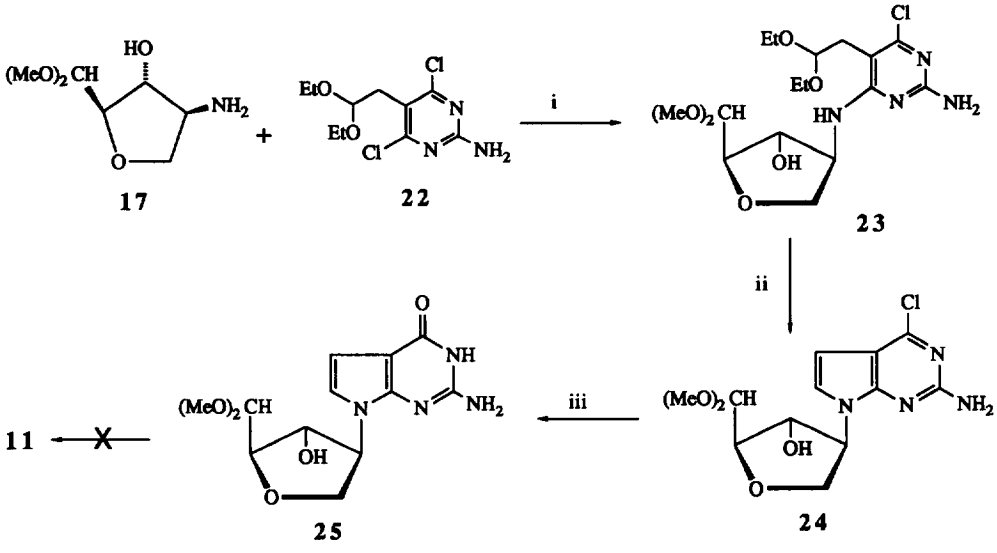


Scheme 1. i, MeOH, TFA, reflux; ii, K_2CO_3, r.t. (86% overall); iii, NaN_3, NH_4Cl, H_2O/EtOH (94%); iv, H_2, PtO_2, EtOH (90%); v, Et_3N, $EtOCH_2CH_2OH$, reflux (72%); vi, THF, HCl aq., r.t. (81%); vii, TFA, THF/H_2O, 80 °C, then $NaBH_4$ (70%); viii, NH_3, MeOH, 100 °C (68%); ix, NaOH, dioxan/H_2O, reflux (63%); x, thiourea, *n*-propanol, reflux (67%).

The pyrrolopyrimidine ring could then be constructed by reaction of amine **17** with the dichloropyrimidine **18** (prepared from the known aldehyde[17] by treatment with NH_4Cl in ethanol at reflux) in the presence of Et_3N to give the substitution product **19**, which, on stirring in THF and aqueous HCl at room temperature underwent smooth cyclization to the pyrrolopyrimidine **20**. The second acetal grouping in **19** was stable to these mild acidic conditions, presumably due to the electron-withdrawing effect of the oxygen of the tetrahydrofuran ring. The structure of **20** was assured by NMR studies, including COSY experiments to define the connectivities, and these experiments served to confirm the regiochemistry in the nucleophilic opening of the epoxide **15**.

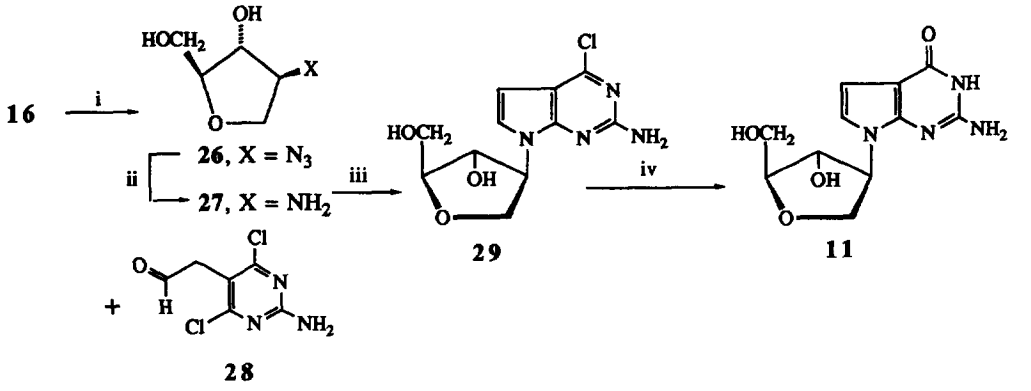
Hydrolysis of **20** under more vigorous acidic conditions, followed by treatment with $NaBH_4$, gave the diol **21** as a crystalline solid, which could be converted into the adenosine analogue **8** by treatment with methanolic ammonia at 100 °C. The chlorocompound **21** could also act as a precursor for the inosine analogue **9**, into which it was converted by alkaline hydrolysis, and for the thione **10**, which was obtained (67%) when **21** was heated under reflux with thiourea in *n*-propanol.

Our initial approach to the guanosine analogue **11** proceeded along similar lines (Scheme 2). Thus the amine **17**, on reaction with the dichloropyrimidine **22**[11c] gave the bis-acetal **23** which again underwent clean cyclization to the pyrrolopyrimidine **24** (76%) on treatment with THF and dilute aqueous HCl at room temperature. Substitution of the chloro-function to give **25** proceeded smoothly, but attempts at hydrolysis of **25** under various acidic conditions, and subsequent reduction, either using borohydride or by catalytic hydrogenation,[18] proved unrewarding. Similarly, attempts at the selective hydrolysis of the acetal of **24** and subsequent reduction did not prove successful.



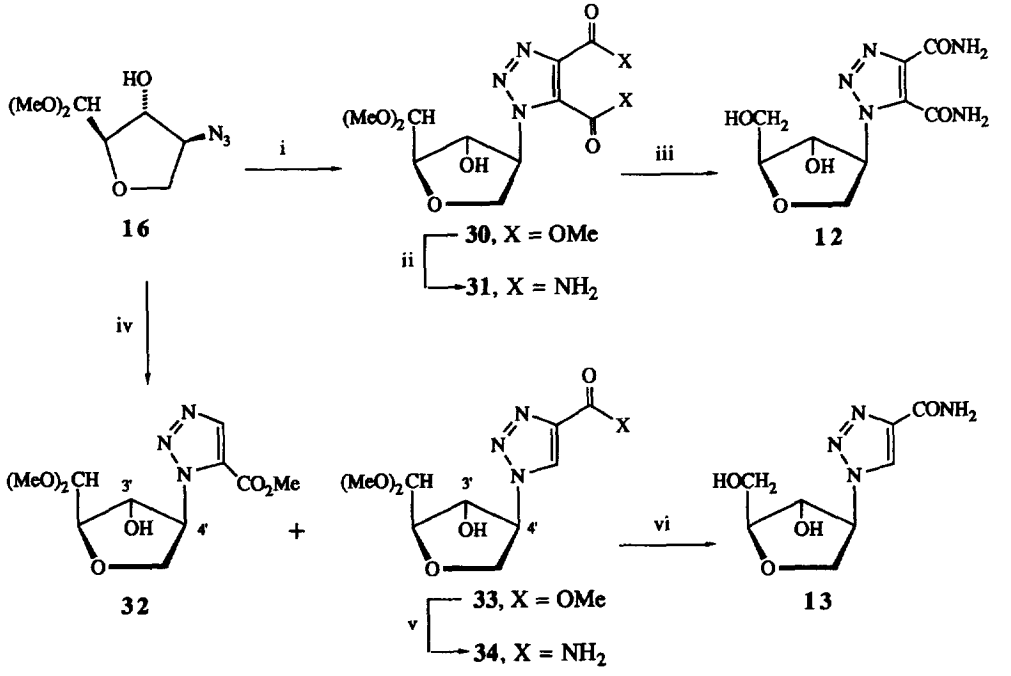
Scheme 2. i, Et_3N, $EtOCH_2CH_2OH$, reflux (62%); ii, THF, HCl aq., r.t. (76%); iii, NaOH, dioxan/H_2O, reflux (72%).

Thus we chose to introduce the primary alcohol at an earlier stage (Scheme 3). Acidic hydrolysis of **16**, followed by treatment with controlled amounts of $NaBH_4$ gave the azidodiol **26** in moderate yield, and this was reduced catalytically to aminodiol **27** in high yield. Condensation of **27** with dichloropyrimidine aldehyde **28**[11c] (Et_3N, ethoxyethanol, reflux) gave the pyrrolopyrimidine **29**, and this on acidic hydrolysis gave the desired guanosine analogue **11**.



Scheme 3. i, dioxan, HCl aq., reflux, then $NaBH_4$ (46%); ii, H_2, PtO_2, EtOH (90%); iii, Et_3N, $EtOCH_2CH_2OH$, reflux (38.5%); iv, HCl aq (1M), reflux (58%).

The use of azide intermediates in the routes to the pyrrolopyrimidines suggested that they could also provide access to 1,2,3-triazole nucleoside analogues. Cyclization of **16** with DMAD gave (Scheme 4) the adduct **30** in high yield, and this could be cleanly converted to the diamide **31** with methanolic ammonia. Acidic hydrolysis, followed by treatment with $NaBH_4$ then gave the triazole isonucleoside **12**.



Scheme 4. i, DMAD, DME, reflux (96%); ii, NH_3, MeOH, r.t. (92%); iii, dioxan/TFA/H_2O, r.t., then $NaBH_4$, MeOH (45%); iv, methyl propiolate, DME, reflux (96%); v, NH_3, MeOH, r.t. (90%); vi, as iii (61%).

When **16** was heated under reflux in DME with methyl propiolate, two cycloadducts **32** (14%) and **33** (79%) were obtained. The regiochemical assignments were supported by the observation that, in the ^{1}H-NMR

spectrum of the minor isomer **32**, the signals for both 3'-H and 4'-H appeared at lower field (δ 4.87 and 5.59 respectively) than did the equivalent signals for the major product **33** (δ 4.58 and 5.15), as would be expected from the deshielding effect of the carbonyl group. Ammonolysis of **33** gave the crystalline amide **34**, convertible in the usual manner into the isonucleoside **13**, which can be regarded as an analogue of the well-established antiviral nucleoside ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, virazole).[19]

Antiviral Testing - Compounds **8** - **13**, **21**, **24**, **31** and **34** weretested against HIV-1_{MN} in C8166 cells, but in all cases concentrations >200 μM were necessary to reduce Ag gp120 by 50% in infected cells. However in the light of previous findings,[11e,12] it remains of interest to evaluate these compounds as their triphosphates at the primary alcohol group against HIV-1 reverse transcriptase.

EXPERIMENTAL

NMR spectra were recorded on a Bruker WP 200 SY spectrometer. ^{1}H-Spectra were obtained at 200 MHz, and ^{13}C-spectra at 50 MHz, in $CDCl_3$ as solvent unless otherwise stated. Coupling constants are measured in Hz. Mass spectrometry was performed using V.G. updated MS 9 and V.G. ZABE high resolution EI/FAB instruments. Specific rotations were measured at room temperature using a Bendix-NPL 143D automatic polarimeter (path length 1 cm); units for $[\alpha]_D$ values are 10^{-1} deg cm^2 g^{-1}. Melting points were determined using an Electrothermal MK II melting point apparatus and are uncorrected.
Column chromatography was carried out using Kieselgel H type 60 (Merck), an external pressure being applied to the top of columns. Organic extracts were dried over anhydrous sodium sulphate. Light petroleum refers to material of boiling range 40-60 °C.

1,2-O-*Isopropylidene*-3,5-*di*-O-*methanesulfonyl*-α-D-*xylofuranose* (**14**).- To a solution of 1,2-*O*-isopropylidene-α-D-xylofuranose[15] (15.8 g, 83 mmol) and triethylamine (18.5 g, 183 mmol) in dry dichloromethane (200 ml) at 0°C was added dropwise with stirring methanesulfonyl chloride (21.0 g, 183 mmol). The mixture was allowed to warm to r.t., stirred for 1 hour, washed with saturated $NaHCO_3$ aq. (2 x 100ml) and brine (100 ml), dried and evaporated. The residue was chromatographed on silica gel, with dichloromethane-methanol (98:2) as eluant to give the dimesylate **14** (21.8 g, 76%) as an oil; δ_H 1.31 and 1.50 (each 3H, s, CMe_2), 3.08 and 3.12 (each 3H, s, SO_2Me), 4.40 (2H, d, *J* 6.6, 5-H_2), 4.56 (1H, dt, *J* 6.6, 6.6 and 3.2, 4-H), 4.82 (1H, d, *J* 3.7, 2-H), 5.07 (1H, d, *J* 3.2, 3-H), 5.97 (1H, d, *J* 3.7, 1-H) (Found: C, 35.0; H, 5.5; S, 18.1. $C_{20}H_{18}O_9S_2$ requires C, 34.68; H, 5.20, S, 18.49%).

(2R, 3R, 4R)-2-(*Dimethoxymethyl*)-3,4-*epoxytetrahydrofuran* (**15**) - A solution of the dimesylate **14** (21.3 g, 61.5 mmol) in dry methanol (400 ml) containing TFA (4 ml) was heated under reflux for 40 h. The mixture was cooled to r.t. and stirred with anhydrous K_2CO_3 (24.2 g, 0.175 mol) overnight. The mixture was filtered and the solids washed with dichloromethane (2 x 50 ml). The combined filtrates were evaporated and the residue was chromatographed on silica gel, with ethyl acetate - light petroleum (1:1) as eluent to give the epoxide **15** (8.46 g, 86%) as an oil, $[\alpha]_D$ +19.5 (*c* 1.02, $CHCl_3$); δ_H 3.43 and 3.45 (each 3H, s, O Me), 3.75-3.85 (3H, m, 3-H, 4-H, 5β-H), 3.96 (1H, br d, *J* 10.1, 5α -H), 4.07 (1H, br.d, *J* 4.6, 2-H), 4.27 [1H, d, *J* 4.4, *CH*(O Me)$_2$]; *m/z* (FAB) 161 (MH^+), 129 $(M\text{-}OMe)^+$ (Found: C, 52.2; H, 7.8. $C_7H_{12}O_4$ requires C, 52.50; H, 7.50%).

(2R, 3R, 4S)-4-*Azido*-2-*dimethoxymethyl*-3-*hydroxytetrahydrofuran* (**16**) - A solution of epoxide **15** (6.0 g, 37.5 mmol), sodium azide (4.88 g, 75 mmol) and ammonium chloride (4.97 g, 94 mmol) in water (40 ml) and ethanol (140 ml) was heated under reflux for 24 h. The residue after evaporation was extracted with dichloromethane (2 x 100 ml). After evaporation, the residue was chromatographed on silica, with ethyl acetate-light petroleum (2:3) as eluent to give the azidoalcohol **16** (7.13 g, 94%) as an oil, $[\alpha]_D$ +38.7 (*c* 3.15, $CHCl_3$); ν_{max} (film) 3425 (br) and 2104 cm^{-1}; δ_H 2.3 (1H, br.s, OH), 3.43 and 3.47 (each 3H, s, OMe), 3.76

(1H, dd, *J* 6.3 and 5.4, 2-H), 3.85 (1H, dd, *J* 8.9 and 3.6, 5_a-H), 4.0 (1H, m, 4-H), 4.05 (1H, dd, *J* 8.8 and 5.8, 5_b-H), 4.20 (1H, dd, *J* 5.2 and 3.5, 3-H), 4.38 [(1H, d, *J* 6.3, C*H* $(OMe)_2$]; δ_C 54.2, 55.9, 66.8 and 70.4 (OMe), 77.6, 84.2 and 104.7 [*C*H$(OMe)_2$] (Found: C, 41.4; H, 6.6. $C_7H_{13}N_3O_4$ requires C,41.37; H, 6.40%).

(2R, 3R, 4S)-4-*Amino*-2-*dimethoxymethyl*-3-*hydroxytetrahydrofuran* (**17**) - A solution of azide **16** (7.0 g, 34.5 mmol) in ethanol (100 ml) was stirred with PtO_2 (100 mg) under hydrogen overnight. After filtration through celite and evaporation, the residue was chromatographed on silica gel, with dichloromethane-methanol (20:1) as eluent, to give the amine **17** (5.48 g, 90%) as an oil, $[\alpha]_D$ +24.3 (*c* 1.28, $CHCl_3$); δ_H 3.40-3.45 (1H, m, 4-H), 3.45 and 3.50 (each 3H, s, OMe), 3.6-3.8 (2H, m), 3.95 - 4.1 (2H, m), 4.42 [1H, d, *J* 6.0, C*H* $(OMe)_2$]; *m/z* 177 (M^+), 146 $(M\text{-}OMe)^+$, 102 $[M\text{-}CH(OMe)_2]^+$ (Found: C, 45.7; H, 9.0; N, 7.5. $C_7H_{15}NO_4$ requires C, 45.40; H, 8.64; N, 7.56%).

4,6-*Dichloro*-5-(2,2-*diethoxyethyl*)*pyrimidine* (**18**). - To a solution of sodium periodate (25.9 g, 121 mmol) and osmium tetroxide (75 mg) in water (130 ml) was added 5-allyl-4,6-dichloropyrimidine[17] (9.18 g, 48.5 mmol) in methanol (130 ml). The mixture was stirred at 0 °C for 5 h and then overnight at r.t. Aqueous sodium sulfite (5%, 100 ml) was added, the solids were filtered, and the solution was lyophilised. The residue was partitioned between dichloromethane (200 ml) and water (2 x 50 ml). Evaporation of the dried organic phase gave the crude aldehyde (8.1 g) as an oil. This material and ammonium chloride (0.224 g, 4.2 mmol) were heated under reflux in dry ethanol for 3 h. The residue after evaporation was chromatographed on silica, with ethyl acetate-petrol (5:95) as eluent, to give the acetal **18** (9.8 g, 88%) as an oil; δ_H 1.11 (6H, t, *J* 7.5, OCH_2CH_3), 3.25 (2H, d, *J* 6.0, $ArCH_2$), 3.35-3.5 and 3.6-3.8 (each 2H, m, OCH_2CH_3), 4.78 [1H, t, *J* 6.0, C*H*$(OEt)_2$], 8.61 (1H, s, Ar-H).

(2'R, 3'R, 4'S)-4-*Chloro*-5-(2,2-*diethoxyethyl*)-6-(2'-*dimethoxymethyl*-3'-*hydroxytetrahydrofuran*-4'-*yl*)-*amino-pyrimidine* (**19**). - A solution of amine **17** (1.77 g, 10 mmol), dichloropyrimidine **18** (2.65 g, 10 mmol) and triethylamine (20 ml) in 2-ethoxyethanol (40 ml) was heated under reflux for 7 h. The residue after evaporation was partitioned between dichloromethane (100 ml) and water (2 x 20 ml). The organic layer was dried and evaporated, and the residue was chromatographed on silica, with dichloromethane-methanol (20:1) as eluent, to give the aminopyrimidine **19** (2.91 g, 72%) as an oil; δ_H 1.25 (6H, q, *J* 7, OCH_2Me), 2.92 (2H, d, *J* 5.5, CH_2 benzylic), 3.44 and 3.46 (each 3H, s, OMe), 3.40 - 3.65 (2H, m), 3.7 - 3.8 (3H, m), 3.95 (1H, t, *J* 5.5), 4.12 (1H, dd, *J* 5.5 and 4.5), 4.2 - 4.4 (2H, m), 4.41 [1H, d, *J* 4.9, C*H*$(OMe)_2$], 4.60 [1H, t, *J* 5.5, C*H*$(OEt)_2$], 6.65 (1H, br d, NH), 8.30 (1H, s, 2-H) (Found: C, 50.4; H, 7.1; N, 10.3. $C_{17}H_{28}ClN_3O_6$ requires C, 50.37; H, 6.91; N, 10.37%).

(2'R,3'R,4'S)-4-*Chloro*-7-(2'-*dimethoxymethyl*-3'-*hydroxy-tetrahydrofuran*-4'-*yl*)*pyrrolo*[2,3-d]*pyrimidine* (**20**) - A solution of the bis-acetal **19** (0.542 g, 1.33 mmol) in THF (10 ml) and aqueous HCl (1.5M, 2.5 ml) was stirred at r.t. for 72 h. The mixture was neutralised with NaOH aq. and lyophilized. The residue was chromatographed on silica gel, with dichloromethane-methanol (99:1) as eluent, to give the pyrrolopyrimidine **20** (0.34 g, 81%) as an amorphous solid, $[\alpha]_D$ -25.3 (*c* 1.18, $CHCl_3$); δ_H 2.6 (1H, br s, OH), 3.45 (6H, s, OMe), 4.01 (1H, t, *J*~6, 2'-H), 4.27 (1H, dd, *J* 9.9 and 5.2, $5'_a$-H), 4.45 (1H, dd, *J* 9.8, 6.7, $5'_b$-H), 4.46 [1H, d, *J* 5.0, C*H* $(OMe)_2$], 4.55 (1H, dd, *J* 5.5 and 4.5, 3'-H), 5.17 (1H, ddd, *J* 6.6, 5.0, 4.5, 4'-H) 6.63 (1H, d, *J* 3.5, 5-H), 7.37 (1H, d, *J* 3.5, 6-H), 8.63 (1H, s, 2-H) (Found: C, 49.5; H, 5.0; N, 13.1. $C_{13}H_{16}ClN_3O_4$ requires C, 49.68; H, 5.09; N, 13.37%).

(2'S, 3'R, 4'S)-4-*Chloro*-7-(3'-*hydroxy*-2'-*hydroxymethyl-tetrahydrofuran*-4'-*yl*)*pyrrolo*[2,3-d]*pyrimidine* (**21**). - A solution of the dimethyl acetal **20** (208 mg, 0.66 mmol) in THF (1.6 ml) and aqueous TFA (1%, 1 ml) was stirred at 80°C for 5 h. After cooling, the solution was neutralized with NaOH aq. (1M) to pH7, sodium borohydride (25 mg, 0.66 mmol) was added, and the mixture stirred for 1 h. After quenching with acetic acid, evaporation gave a residue that was chromatographed on silica gel, with dichloromethane-methanol (95:5) as eluent, to give the diol **21** (124 mg, 70%), m.p. 178-180 °C (from methanol), $[\alpha]_D$ +21.1 (*c* 0.9, DMSO); δ_H

(DMSO-d_6) 3.5 - 3.7 (3H, m, 2'-H, CH_2OH), 4.02 (1H, dd, *J* 9.6 and 5.0, 5'$_a$-H), 4.18 (1H, dd, *J* 9.6 and 6.4, 5'$_b$-H), 4.30 (1H, q, *J* ~5, 3'-H), 4.95 (1H, t, *J* 5, CH$_2$O*H*), 5.18 (1H, dt, *J* 6.4, 5.0, 5.0, 4'-H), 5.75 (1H, d, *J* 6, OH), 6.70 (1H, d, *J* 4.0, 5-H), 7.85 (1H, d, *J* 4.0, 6-H), 8.68 (1H, s, 2-H); *m/z* 269/271 (M^+) (Found: M^+ 271.0512; calc for $C_{11}H_{12}{}^{37}ClN_3O_3$, 271.0512. Found: C, 48.9; H, 4.7; N, 15.7. $C_{11}H_{12}ClN_3O_3$ requires C, 49.09; H, 4.46; N, 15.61%).

(2'S, 3'R, 4'S)-4-*Amino*-7-(3'-*hydroxy*-2'-*hydroxymethyl*-*tetrahydrofuran*-4'-*yl*) *pyrrolo* [2,3-d]*pyrimidine* (**8**) - A solution of the chlorocompound **21** (135 mg, 0.5 mmol) in saturated methanolic ammonia (25 ml) was heated in a pressure reactor at 100 °C for 24 h. The residue after evaporation was chromatographed on silica gel, with dichloromethane-methanol (9:1) as eluent, to give the aminocompound **8** (85 mg, 68%), m.p. 190-192 °C (from methanol), $[\alpha]_D$ +13.9 (*c* 1.01, MeOH); δ_H (DMSO-d_6) 3.45-3.70 (3H, m, 2'-H, CH_2OH), 3.89 (1H, dd, *J* 9.5 and 5.0, 5^1_a-H), 4.12 (1H, dd, *J* 9.4 and 6.9, 5'$_b$-H), 4.24 (1H, q, *J*~5.5, 3'-H), 4.88 (1H, t, CH$_2$O*H*), 5.02 (1H, dt, *J* 6.7, 5.0, 5.0; 4'-H), 5.65 (1H, d, *J* 5.5, OH), 6.55 (1H, d, *J* 3.6, 5-H), 7.0 (2H, br.s, NH_2), 7.22 (1H, d, *J* 3.6, 6-H), 8.04 (1H, s, 2-H); δ_C (DMSO-d_6) 61.0 (*C*H$_2$OH), 61.5 (C-2'), 70.1 (C-3'), 76.2 (C-5'), 85.7 (C-4'), 99.0 (C-5), 102.3 (C-4a), 121.4 (C-6), 151.4 (C-2), 149.6 and 157.4 (C-4 and C-7a); *m/z* (EI) 250 (M^+), 134 (Base$^+$) [Found: MH^+ (FAB) 251.1144 Calc. for $C_{11}H_{15}N_4O_3$ 251.1144].

(2'S, 3'R, 4'S)-7-(3'-*Hydroxy*-2'-*hydroxymethyl*-*tetrahydrofuran*-4'-*yl*)*pyrrolo*[2,3-d]*pyrimidine*-4(3H)-*one* (**9**). - A solution of chlorocompound **21** (94 mg, 0.35 mmol) in dioxan (15 ml) and NaOH aq (1M, 5 ml) was heated under reflux for 42 h. After neutralization with HCl aq (1M) and lyophilization, the residue was chromatographed on silica gel, with dichloromethane-methanol (9:1) as eluent, to give the pyrrolopyrimidinone **9** (56 mg, 63%), m.p. 202-204 °C (from methanol); δ_H (DMSO-d_6) 3.5 - 3.7 (3H, m, 2'-H, CH_2OH), 3.86 (1H, dd, *J* 9.3 and 5.3, 5'$_a$-H), 4.12 (1H, dd, *J* 9.3 and 6.6, 5'$_b$-H), 4.23 (1H, q, *J* ~6, 3'-H), 4.80 (1H, t, *J* ~7, OH), 5.02 (1H, q, *J* ~6, 4'-H), 5.65 (1H, d, *J* 6, OH), 6.50 (1H, d, *J* 4.0, 5-H), 7.23 (1H, d, *J* 4.0, 6-H), 7.90 (1H, s, 2-H), 11.9 (1H, br s, NH); *m/z* (EI) 251 (M^+), 135 (Base$^+$) [Found: MH^+ (NH_3 CI) 252.0984. Calc. for $C_{11}H_{14}N_3O_4$, 252.0984]

(2'S, 3'R, 4'S)-7-(3'-*Hydroxy*-2'-*hydroxymethyl*-*tetrahydrofuran*-4'-*yl*)*pyrrolo*[2,3-d]*pyrimidin*-4(3H)-*thione* (**10**). - A solution of chlorocompound **21** (96 mg, 0.36 mmol) and thiourea (28 mg, 0.36 mmol) in *n*-propanol was heated under reflux for 4h. The residue on evaporation was chromatographed on silica gel, with dichloromethane-methanol (20:1) as eluent, to give the thione **10** (64 mg, 67%), m.p. 198-200 °C (from methanol), $[\alpha]_D$ +65.4 (*c* 1.03, MeOH); δ_H (DMSO-d_6 + D_2O) 3.4-3.7 (3H, m, 2'-H, CH_2OH), 3.96 (1H, dd, *J* 9.0 and 4.7, 5'$_a$-H), 4.1-4.3 (2H, m, 3'-H, 5'$_b$-H), 5.02 (1H, m, 4'-H), 6.69 (1H, d, *J* 3.5, 5-H), 7.39 (1H, d, *J* 3.5, 6-H), 8.07 (1H, s, 2-H); a spectrum recorded in DMSO-d_6 also showed signals at δ 4.9 (1H, br.s, OH), 5.70 (1H, d, OH) and 13.50 (1H, br.s, NH); δ_c (DMSO-d_6) 60.8 and 62.2 (CH), 70.2 (C-5'), 76.8 (CH), 85.4 (CH), 105.0 (C-5), 120.4 (q), 125.2 (C-6), 143.1 (C-2), 143.4 (q), 175.8 (C=S) [Found: MH^+ (FAB) 268.0768. Calc. for $C_{11}H_{14}N_3O_3S$, 268.0756].

(2'R, 3'R, 4'S)-2-*Amino*-4-*chloro*-5-(2,2-*diethoxyethyl*)-6-(2'-*dimethoxymethyl*-3'-*hydroxy*-*tetrahydrofuran*-4'-*yl*)-*aminopyrimidine* (**23**). - Amine **17** (1.77 g, 10 mmol) and dichloropyrimidine **22** (2.8 g, 10 mmol) were treated and processed as in the preparation of **19** to give the diaminopyrimidine **23** (2.61 g, 62%) as an oil; δ_H 1.20 (6H, q, *J* 7, OCH$_2$*Me*), 3.30 (2H, d, *J* 5.0, benzylic), 3.44 and 3.46 (each 3H, s, OMe), 3.45 - 3.6 (2H, m) 3.60 - 3.85 (3H, m), 3.93 (1H, t, *J* 6.0, 2'-H), 4.1 - 4.4 (3H, m), 4.40 [1H, d, *J* 5, C*H* (O Me)$_2$], 4.48 [1H, t, *J* 5.0, C*H* (OEt)$_2$], 5.20 (2H, br.s, NH_2), 6.55 (1H, br.d, NH) (Found: C, 48.3; H, 6.6, N, 13.4. $C_{17}H_{29}ClN_4O_6$ requires C, 48.57; H, 6.9; N, 13.33%).

(2'R, 3'R, 4'S)-2-*Amino*-4-*chloro*-7-(2'-*dimethoxymethyl*-3'-*hydroxytetrahydrofuran*-4'-*yl*)-*pyrrolo*[2,3-d] *pyrimidine* (**24**). - A solution of the bisacetal **23** (1.51 g, 3.59 mmol) in THF (40 ml) and HCl aq. (1.5M, 10 ml) was stirred at r.t. for 3 days. The mixture was neutralized with IR-45 resin (OH^- form), filtered and evaporated. Chromatography of the residue on silica gel, with dichloromethane-methanol (98:2) as eluent,

gave the pyrrolopyrimidine **24** (0.90 g, 76%) as a syrup, $[\alpha]_D$ -73.8 (*c* 0.975, $CHCl_3$); δ_H 3.42 and 3.45 (each 3H, s, OMe), 4.01 (1H, t, *J* 5.5, 2'-H), 4.24 (1H, dd, *J* 10.0 and 5.0, 5'$_a$-H), 4.3-4.4 [2H, m, 5'-H$_b$, C*H* (OMe)$_2$], 4.47 (1H, dd, *J* 5.5 and 4.7, 3'-H), 4.93 (1H, m, 4'-H), 5.5 (1H, br.s, OH), 6.43 (1H, d, *J* 3.7, 5-H), 6.98 (1H, d, *J* 3.7, 6-H); *m/z* (FAB) 329 (MH^+), 297 $(M\text{-}MeO)^+$ (Found: C, 47.3; H, 5.0; N, 16.8. $C_{13}H_{17}ClN_4O_4$ requires C, 47.56; H, 5.18; N, 17.07%).

(2'R, 3'R, 4'S)-2-*Amino*-7-(2'-*dimethoxymethyl*-3'-*hydroxytetrahydrofuran*-4'-*yl*)*pyrrolo*[2,3-d]*pyrimidine*-4(3H)-*one* (**25**). - A solution of chlorocompound **24** (463 mg, 1.41 mmol) in dioxan (10 ml) and NaOH aq. (1M, 10 ml) was heated under reflux for 24 h. The mixture was cooled, neutralized to pH 7 with HCl aq (1M) and evaporated. Chromatography on silica gel, with dichloromethane-methanol (20:1) as eluent, gave the pyrrolopyrimidinone **25** (320 mg, 73%) as an amorphous solid; δ_H (DMSO-d_6) 3.35 (6H, s, OMe), 3.70 (1H, t, *J* 5.0, 2'-H), 3.86 (1H, dd, *J* 9.8, 6.0, 5'$_a$-H), 4.05 (1H, dd, *J* 9.8, 7.0, 5'$_b$-H), 4.28 (1H, q, *J* ~ 6, 3'-H), 4.80 (1H, m, 4'-H), 5.15 (1H, d, *J* 6, OH), 6.2 (2H, br.s, NH_2), 6.26 (1H, d, *J* 3.5, 5-H), 6.86 (1H, d, *J* 3.5, 6-H), 10.3 (1H, br.s, NH) [Found: MH^+ (FAB) 311.1362. Calc for $C_{13}H_{19}N_4O_5$ 311.1355].

(2S, 3R, 4S)-4-*Azido*-3-*hydroxy*-2-(*hydroxymethyl*)*tetrahydrofuran* (**26**) - A solution of acetal **16** (2.39 g, 11.8 mmol) in dioxan (24 ml) and HCl aq. (0.3 M, 15 ml) was heated under reflux for 3 h. After cooling, the mixture was adjusted to pH 7 with NaOH aq. (1 M) and treated with sodium borohydride (446 mg, 11.8 mmol) for 1h. Acetic acid was added to destroy excess borohydride and the mixture was lyophilized. Chromatography on silica, with dichloromethane-methanol (9:1) as eluent gave the azidodiol **26** (0.855 g, 46%) as an oil, $[\alpha]_D$ +2.2 (*c* 1.8, MeOH); δ_H (DMSO-d_6) 3.35-3.60 (3H, m), 3.69 (1H, dd, *J* 9.6 and 3.0, 5$_a$-H), 3.80-4.0 (3H, m), 4.80 (1H, t, *J* 5.5, CH_2OH), 5.60 (1H, d, *J* 4.6, OH); δ_C (DMSO-d_6) 61.3, 67.3, 69.4, 76.1 and 86.0 [Found: MH^+ (NH_3 CI) 160.0722. Calc for $C_5H_{10}N_3O_3$, 160.0722].

(2S, 3R, 4S)-4-*Amino*-3-*hydroxy*-2-(*hydroxymethyl*)*tetrahydrofuran* (**27**) - Azide **26** (0.80 g, 5.0 mmol) in ethanol (50 ml) was hydrogenated at 1 atm. over PtO_2 (30 mg) for 24h. The mixture was filtered through celite which was washed well with methanol. Evaporation and chromatography of the residue over silica gel, with dichloromethane-methanol (9:1) as eluent, gave the aminodiol **27** (0.605 g, 90%) as an oil; δ_H (DMSO-d_6) 3.10 (1H, m, 4-H), 3.2 (4H, br. s) 3.35-3.55 (3H, m), 3.6-3.7 (2H, m), 3.76 (1H, dd, *J* 10, 6, 5'-H); δ_C (DMSO-d_6) 61.5 (CH_2), 67.2 (CH), 69.4 (CH_2), 76.5 (CH), 86.4 (CH). [Found: MH^+ (NH_3 CI) 134.0810. Calc for $C_5H_{12}NO_3$ 134.0816].

(2'S, 3'R, 4'S)-2-*Amino*-4-*chloro*-7-[(3'-*hydroxy*-2'-*hydroxymethyl*)-*tetrahydrofuran*-4'-*yl*]-*pyrrolo*[2,3-d] *pyrimidine* (**29**) - A solution of amine **27** (0.543 g, 4.08 mmol), dichloropyrimidine **28** (0.925 g, 4.5 mmol) and triethylamine (10 ml) in 2-ethoxyethanol (20 ml) was heated under reflux for 5h. The residue after evaporation was chromatographed on silica gel, with dichloromethane-methanol (9:1) as eluent, to give the pyrrolopyrimidine **29** (0.445 g, 38.5%), m.p. 146-148 °C (from methanol-ethyl acetate), $[\alpha]_D$ -47.8 (*c* 1.01, MeOH); δ_H 3.4-3.7 (3H, m, 2'-H, C*H*$_2$ OH), 3.84 (1H, dd, *J* 9.6 and 4.9, 5'$_a$-H), 4.10 (1H, dd, *J* 9.6 and 6.8, 5'$_b$-H), 4.23 (1H, q, *J* ~5, 3'-H), 4.85-4.95 (2H, m, 4'-H, CH_2OH), 5.55 (1H, d, *J* 5.6, OH), 6.34 (1H, d, *J* 3.7, 5-H), 6.70 (2H, br. s, NH_2), 7.27 (1H, d, *J* 3.7, 6-H); δ_C (DMSO-d_6) 61.2 (CH_2OH), 61.9 (CH), 70.6 (C-5), 76.5 (CH), 86.2 (CH), 99.7 (C-5), 108.9 (q), 124.0 (C-6), 151.6, 154.0 and 159.6 [Found: MH^+ (FAB) 285.0758. Calc for $C_{11}H_{14}{}^{35}ClN_4O_3$, 285.0754].

(2'S,3'R,4'S)-2-*Amino*-7-[(3'-*hydroxy*-2'-*hydroxymethyl*)-*tetrahydrofuran*-4'-*yl*]*pyrrolo*[2,3-d]*pyrimidin*-4(3H)-*one* (**11**). - A solution of chlorocompound **29** (0.284 g, 1 mmol) in HCl aq. (1M, 20 ml) was heated under reflux for 16 h and then lyophilized. The residue was evaporated with ethanol (2 x 25ml), dissolved in methanol, and adjusted to pH 7 with NaOH aq. (1M). The residue after evaporation was chromatographed on silica gel, with dichloromethane-methanol (9:1) as eluent to give the pyrrolopyrimidinone **11** (153 mg, 58%), m.p. 196-200 °C (dec.) (from methanol), $[\alpha]_D$ +3.3 (*c* 0.92, MeOH); δ_H (DMSO-d_6) 3.45 - 3.65 (3H, m, 2'-H, C*H*$_2$OH), 3.81 (1H, dd, *J* 9.5 and 4.9, 5'$_a$-H), 4.05 (1H, dd, *J* 9.5 and 6.9, 5'$_b$-H), 4.19 (1H, dd, $J_{2',3'}$ 5.5, $J_{3',4'}$

4.5, 3'-H), 4.83 (1H, dt, *J* 6.6, ~ 4.7, ~ 4.7, 4'-H), ~6.0 (4H, br.s, NH_2, OH), 6.30 (1H, d, *J* 3.5, 5-H), 6.85 (1H, d, *J* 3.5, 6-H), 10.7 (1H, br.s, NH) [Found: MH^+ (FAB) 267.1095. Calc for $C_{11}H_{15}N_4O_4$, 267.1093].

(2'R, 3'R, 4'S)-4,5-*Bis(methoxycarbonyl)*-1-(2'-*dimethoxymethyl*-3'-*hydroxytetrahydrofuran*-4'-*yl*)-1,2,3-*triazole* (**30**). - A solution of azide **16** (2.03 g, 10 mmol) and DMAD (1.85 g, 13 mmol) in 1, 2-dimethoxyethane (20 ml) was heated under reflux for 3 h. The residue after evaporation was chromatographed on silica gel, with dichloromethane-methanol (50:1) as eluent, to give the triazole **30** (3.31 g, 96%) as an oil, $[\alpha]_D$ +7.9 (*c* 3.02, $CHCl_3$); δ_H 3.45 [6H, s, $CH(OMe)_2$], 3.90 (1H, t, *J* 5.5, 2'-H), 3.96 and 3.99 (each 3H, s, CO_2Me), 4.37 (1H, dd, *J* 10.0 and 7.0, $5'_a$-H), 4.41 (1H, dd, *J* 10.0 and 4.5, $5'_b$-H), 4.53 [1H, d, *J* 5.5, *CH*$(OMe)_2$], 4.82 (1H, dd, *J* 7.0, 5.5, 3'-H), 5.28 (1H, dt, *J* 7.0, 7.0, 4.5, 4'-H) (Found: C, 45.5; H, 5.4; N, 11.9. $C_{13}H_{19}N_3O_8$ requires C, 45.21; H, 5.50; N, 12.17%).

(2'R, 3'R, 4'S)-4,5-*Bis (carboxamido)*-1-(2'-*dimethoxymethyl*-3'-*hydroxytetrahydrofuran*-4'-*yl*)-1,2,3-*triazole* (**31**). A solution of diester **30** (1.67 g, 4.83 mmol) in saturated methanolic ammonia was left to stand at r.t. overnight. The residue after evaporation was crystallized from ethyl acetate to give the diamide **31** (1.42 g, 92%), m.p. 114-116°C, $[\alpha]_D$ +66.3 (*c* 2.0, MeOH); δ_H (DMSO-d_6) 3.32 and 3.35 (each 3H, s, OMe), 3.78 (1H, dd, *J* 7.0 and 5.0, 2'-H), 3.92 (1H, dd, *J* 10.0 and 3.5, $5'_a$-H), 4.17 (1H, dd, *J* 10.0 and 6.0, $5'_b$-H), 4.54 (1H, d, *J* 7.0, *CH*$(OMe)_2$], 4.85 (1H, m, 3'-H), 5.75 (2H, m, 4'-H, OH), 8.15, 8.20, 8.50 and 10.30 (each 1H, NH); δ_C (DMSO-d_6) 53.4 and 54.2 (OMe), 68.6, 71.2, 76.1, 85.1, 103.2 [*CH*$(OMe)_2$], 131.4 and 139.1 (C-4, C-5), 158.3 and 163.0 (amide); *m/z* (FAB) 338 $(MNa)^+$, 316 $(MH)^+$, 284 $(M\text{-}MeO)^+$ [Found: $(M\text{-}MeO)^+$ (EI) 284.09914. Calc for $C_{10}H_{14}N_5O_5$ 284.09949].

(2'S, 3'R, 4'S)-4,5-*Bis(carboxamido)*-1-(3'-*hydroxy*-3'-*hydroxymethyltetrahydrofuran*-4'-*yl*)-1,2,3-*triazole* (**12**). - A solution of acetal **31** (0.654 g, 2.07 mmole) in dioxan (8 ml) and aqueous TFA (25%, 10 ml) was stirred at r.t. for 48 h. The residue after evaporation, dissolved in methanol (20 ml) and dioxan (20 ml), was treated with sodium borohydride (98 mg, 2.6 mmol) for 1 h. The mixture was quenched with acetic acid and lyophilized. Chromatography on silica gel with dichloromethane-methanol (95:5) as eluant gave the diol **12** (254 mg, 45%) m.p. 210-212°C (from ethyl acetate), $[\alpha]_D$ +52.7 (*c* 1.02, H_2O); δ_H (DMSO-d_6) 3.5-3.8 (3H, m, 2'-H, *CH*$_2$OH), 3.92 (1H, dd, *J* 9.6 and 4.8, $5'_a$-H), 4.22 (1H, dd, *J* 9.6 and 7.2, $5'_b$-H), 4.73 (1H, q, *J* ~4, 3'-H), 4.85 (1H, t, *J* 6, CH_2O*H*), 5.66 (1H, d, *J* 6, OH), 5.85 (1H, m, 4'-H), 8.12, 8.20, 8.50 and 10.2 (each 1H, br.s, NH_2) [Found: MH^+ (NH_3 CI) 272.0995. Calc for $C_9H_{14}N_5O_5$ 272.0995].

(2'R, 3'R, 4'S)-1-(2'-*Dimethoxymethyl*-3'-*hydroxytetrafuran*-4'-*yl*)-5-*methoxycarbonyl*-1,2,3-*triazole* (**32**) and (2'R, 3'R, 4'S)-1-(2'-*Dimethoxymethyl*-3'-*hydroxytetrafuran*-4'-*yl*)-4-*methoxycarbonyl*-1,2,3-*triazole* (**33**). - A solution of azide **16** (1.015 g, 5.0 mmol) and methyl propiolate (0.546 g, 6.5 mmol) in dimethoxyethane (10 ml) was heated under reflux for 5 h. The residue after evaporation was chromatographed on silica, with dichloromethane-methanol (99:1) as eluent to give firstly the 5-methoxycarbonyl isomer **32** (0.200 g, 14%), as an oil; δ_H 2.1 (1H, br. s, OH), 3.45 and 3.47 [each 3H, s, $CH(OMe)_2$], 3.94 (3H, s, CO_2Me), 3.95 (1H, t, *J*~6, 2'-H), 4.37 (1H, dd, *J* 10.0, 7.5, $5'_a$-H), 4.48 (1H, dd, *J* 10.0, 4.0, $5'_b$-H), 4.53 [1H, d, *J* 6.5, *CH*$(OMe)_2$], 4.87 (1H, dd, *J* 6.0, 4.5, 3'-H), 5.59 (1H, m, 4'-H), 8.18 (1H, s, 5-H) [Found: $(M\text{-}MeO)^+$ (EI) 256.09258. Calc. for $C_{10}H_{14}N_3O_5$ 256.09335].

Further elution of the column gave the the 4-methoxycarbonyltriazole **33** (1.128 g, 79%) as an oil, $[\alpha]_D$ +76.6 (*c* 1.4, MeOH); δ_H 3.48 and 3.50 [each 3H, s, $CH(OMe)_2$], 3.92 (1H, t, *J* 5.0, 2'-H), 3.94 (3H, s, CO_2Me), 4.27 (1H, dd, *J* 10.0, 4.0, $5'_a$-H), 4.37 (1H, dd, *J* 10.0, 5.5, $5'_b$-H), 4.50 [1H, d, *J* 5.0, *CH*$(OMe)_2$], 4.58 (1H, dd, *J* 5.0, 3.0, 3'-H), 5.15 (1H, m, 4'-H), 8.36 (1H, s, 5-H) (Found: C, 45.8; H, 6.1; N, 14.5. $C_{11}H_{17}N_3O_6$ requires C, 45.99; H, 5.92; N, 14.63%).

(2'R, 3'R, 4'S)-4-*Carboxamido*-1-(2'-*dimethoxymethyl*-3'-*hydroxytetrahydrofuran*-4'-*yl*)-1,2,3-*triazole* (**34**). - A solution of ester **33** (0.948 g, 3.3 mmol) in saturated methanolic ammonia was maintained at r.t. overnight then lyophilized. The residue was crystallized from ethyl acetate to give amide **34** (0.852 g, 90%) m.p. 152-

154 °C, $[\alpha]_D$ +70.9 (*c* 1.72, MeOH); δ_H (DMSO-d_6) 3.30 (6H, s, OMe), 3.75 (1H, t, *J* 5.0, 2'-H), 4.18 (2H, d, *J* 6.0, 5'-H_2), 4.33 [1H, d, *J* 5.5, C*H* (OMe)$_2$], 4.45 (1H, m, 3'-H), 5.00 (1H, q, *J* ~5, 4'-H), 5.95 (1H, br.s, OH), 7.50 and 7.90 (each 1H, br.s, NH_2), 8.52 (1H, s, 5-H); δ_C (DMSO-d_6) 53.6 and 54.9 (OMe), 68.0 and 69.7 (CH), 77.0 (C-5'), 84.9 (CH), 103.5 [*C*H (OMe)$_2$], 125.5 (C-5), 142.8 (C-4) 161.3 (amide); *m/z* (FAB) 273 (MH^+), 241 $(M\text{-}MeO)^+$ [Found: C, 44.4; H, 6.1; N, 20.8. $C_{10}H_{16}N_4O_5$ requires C, 44.11; H, 5.88; N, 20.58%. Found: $(M\text{-}OMe)^+$ (EI) 241.08707. Calc. for $C_9H_{13}N_4O_4$, 241.09368].

(2'S, 3'R, 4'S)-4-*Carboxamido*-1-(3'-*hydroxy*-2'-*hydroxymethyltetrahydrofuran*-4'-*yl*)-1,2,3-*triazole* (**13**). - The amide **34** (0.41 g, 1.5 mmol) was treated and processed as in the preparation of **12** above to give the diol **13** (0.21g, 61%), m.p. 182-184 °C (from ethyl acetate), $[\alpha]_D$ + 73.9 (*c* 1.1, MeOH); δ_H (DMSO-d_6) 3.4-3.7 (3H, m, 2'-H, CH_2OH), 4.09 (1H, dd, *J* 9.9 and 4.4, 5'$_a$-H), 4.17 (1H, dd, *J* 10.0 and 5.5, 5'$_b$-H), 4.32 (1H, dd, *J* 5.7 and 4.2, 3'-H), 4.92 (1H, br.s, OH), 5.05 (1H, dt, *J* 6.2, 4.2 and 4.2, 4'-H), 5.90 (1H, br.s, OH), 7.48 and 7.89 (each 1H, br.s, NH_2), 8.54 (1H, s, 5-H); δ_C (DMSO-d_6) 61.0 (CH_2OH), 68.4 (CH), 70.4 (C-5'), 77.1 (CH), 86.3 (CH), 125.9 (C-5), 143.5 (C-4), 161.9 (amide) [Found: MH^+ (FAB) 229.0958. Calc. for $C_8H_{13}N_4O_4$, 229.0937].

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