C-Nucleoside Studies. Part 18.[1] The Synthesis of *C*-Nucleoside Analogues of the Antiviral Agent (*S*)-9-(2,3-Dihydroxypropyl)adenine

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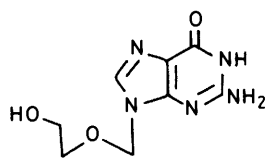
1-Methylsulphonyl-3-(1-*O*-methylsulphonyl-2,3-*O*-isopropylidene-D-*erythro*-trihydroxypropyl)-pyrazole (**22**), available in 56% overall yield from 1,2:5,6-di-*O*-isopropylidene-3-*O*-*p*-tolylsulphonyl-α-D-allofuranose (**15**), was treated with sodium borohydride to give 3(5)-[(*S*)-2,3-*O*-isopropylidene-dihydroxypropyl]pyrazole (**23**) in 90% yield. This was elaborated into 4-amino-3(5)-cyano-5(3)-[(*S*)-2,3-di-*O*-acetyldihydroxypropyl]pyrazole (**30**), which on treatment with formamidine acetate in refluxing ethanol, followed by sodium methoxide in methanol, gave 7-amino-3-[(*S*)-2,3-dihydroxypropyl]pyrazolo[4,3-*d*]pyrimidine (**6**), a *C*-nucleoside analogue of the potent antiviral agent (*S*)-9-(2,3-dihydroxypropyl)adenine (**3**). Treatment of (**6**) with nitrous acid formed 3-[(*S*)-2,3-dihydroxypropyl]pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one (**7**), an analogue of (**3**) containing the chromophore of formycin B.

Treatment of (**30**) with nitrous acid, basification, and photolysis of the resultant diazopyrazole in aqueous acetone yielded 3(5)-cyano-5(3)-[(*S*)-2,3-di-*O*-acetyldihydroxypropyl]-4-hydroxypyrazole (**33**) in 67% yield. Two further steps gave the pyrazofurin analogue 5(3)-carbamoyl-3(5)-[(*S*)-2,3-dihydroxypropyl]-4-hydroxypyrazole (**8**).

A major development in antiviral chemotherapy over recent years has been the recognition that potent antiviral activity is displayed by certain analogues of the normal nucleosides[2] in which the ribose unit is replaced by a truncated acyclic residue. Important compounds of this type include the guanosine analogues 9-(2-hydroxyethoxymethyl)guanine [acycloguanosine, acyclovir, (**1**)],[3] which is in clinical use against herpes infections, and 9-{[2-hydroxy-1-(hydroxymethyl)-ethoxy]methyl}guanine [BIOLF-62, 2′-NDG, DHPG, (**2**)],[4] together with the adenosine analogue (*S*)-9-(2,3-dihydroxypropyl)adenine [(*S*)-DHPA, (**3**)].[5] The mode of action of acycloguanosine (**1**) is well established[2] as involving its phosphorylation by virus-encoded deoxythymidine kinase, and subsequent inhibition of DNA polymerase by competition with dGTP; virally-coded deoxythymidine kinases have much less stringent requirements than the normal mammalian cell enzymes, and a number of important antiviral agents are activated in this way.[2] It seems very likely[4b] that guanosine analogue (**2**) also acts in the same manner. The mode of action of (*S*)-DHPA (**3**) is less well established, but there is evidence[6] that it acts as an inhibitor of *S*-adenosyl-L-homocysteine hydrolase; the resultant build up of *S*-adenosylhomocysteine could then inhibit methylation reactions, including the methylation of viral mRNA.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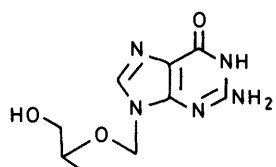
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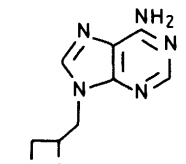
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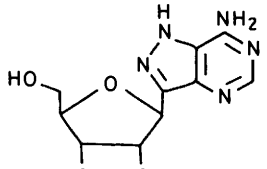
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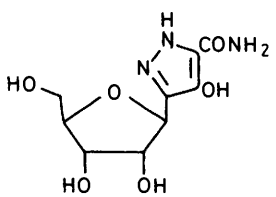
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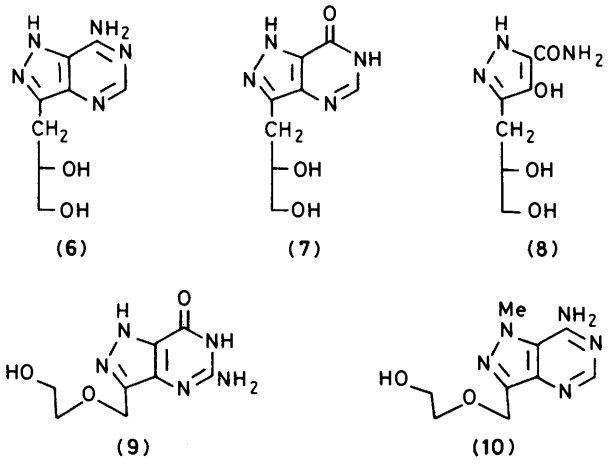
Previous papers in this series have reported new syntheses of the *C*-nucleoside antibiotics formycin (**4**)[7] and pyrazofurin (**5**)[8], and we have also reported on the synthesis of the D-arabinofuranosyl analogue of formycin.[9] Formycin (**4**) has activity against influenza and vaccinia virus,[10] and has anti-tumour properties.[11] Pyrazofurin (**5**) is active against a range of viruses,[12] and also displays anti-tumour activity. Unfortunately both formycin and pyrazofurin[12] have proved to be too toxic for development as antivirals, although pyrazofurin has undergone evaluation as an anti-tumour agent.[13]

The above considerations suggested that it could be of interest to prepare analogues of formycin (**4**) and pyrazofurin (**5**) containing the acyclic chains of active antivirals such as (**1**)—(**3**). Such analogues might interfere with nucleic acid biosynthesis only in virus-infected cells. In this paper we describe the synthesis of compounds (**6**), (**7**) and (**8**), *C*-nucleoside analogues of (*S*)-DHPA (**3**) containing the chromophores of formycin, formycin B, and pyrazofurin respectively. During the course of our work preliminary reports have appeared[14] concerning the synthesis of the pyrazolopyrimidine (**9**) related to acycloguanosine (**1**), and the *N*-methylformycin analogue (**10**) has also been reported.[15]

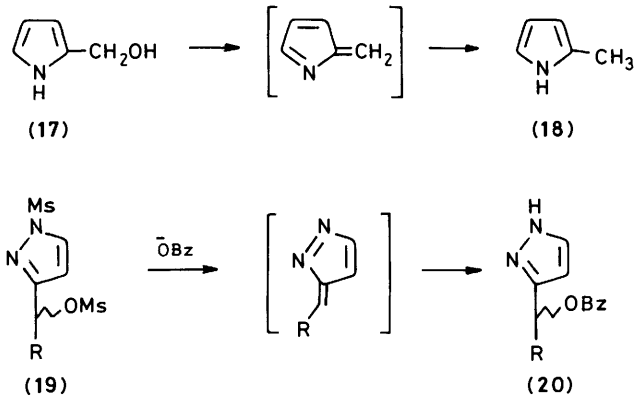
Our previous work on the synthesis of the pyrazole-con-



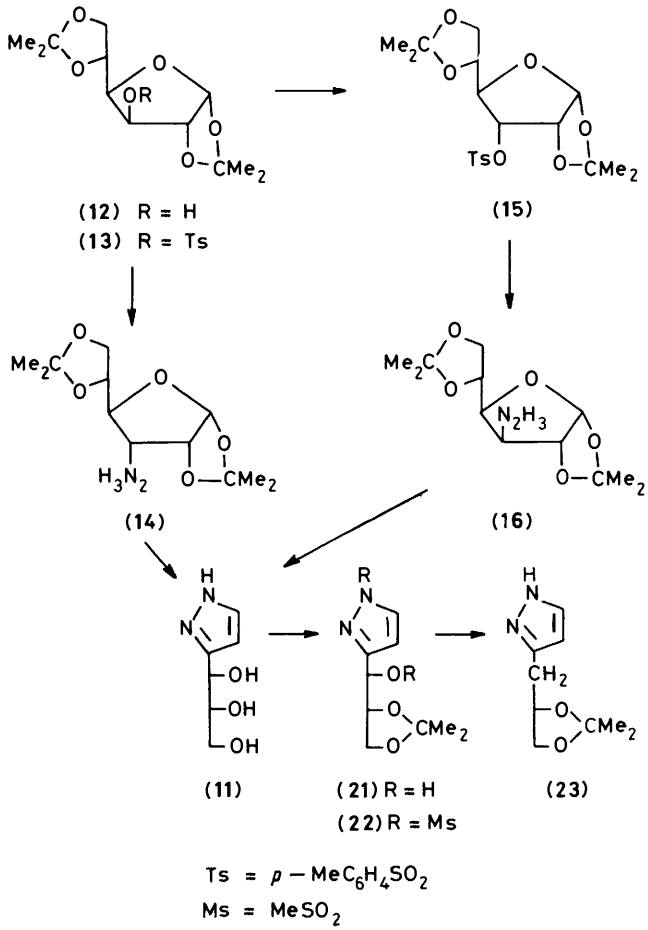
(6) (7) (8) (9) (10)

taining *C*-nucleosides[7,8] and their analogues[9] had involved the initial formation of a pyrazole ring substituted at the 3(5)-position by a protected carbohydrate unit of appropriate configuration, followed by further functionalisation of the pyrazole ring in the later stages of the synthesis. We were therefore attracted by literature reports[16,17] describing the ready availability of the substituted pyrazole (**11**) (see Scheme 1). 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**12**) was converted into its 3-toluene-*p*-sulphonate (**13**),[18] but in our hands the reported hydrazinolysis[19] proceeded sluggishly, and acid-catalysed hydrolysis and cyclisation[16] of the hydrazino derivative (**14**) gave (**11**) only after a difficult purification sequence. Much better overall yields were achieved by converting (**12**) into the epimeric *allo*-tosylate (**15**) by standard methods.[20] Hydrazinolysis by a modification of the method of Smit and co-workers[17] proceeded cleanly, and the product (**16**), without rigorous purification, was treated with dilute hydrochloric acid to give, after neutralisation, the triol (**11**) in 68% yield from (**15**).

Clearly the preparation of analogues (**6**)—(**8**) requires the removal of the 1′-hydroxy function of (**11**). We felt that this could be done by hydride reduction. Lithium aluminium hydride reduction of hydroxymethyl-pyrroles and -indoles is known to give the methyl derivatives as, for example, in the conversion of (**17**) into (**18**).[21] The involvement of the intermediate shown is supported by the fact that the *N*-methyl derivative of (**17**) is inert to reduction under these conditions.[21] Similarly, we have observed in earlier work[22] that pyrazoles of type (**19**) can give substitution products of type (**20**), with *retention* of configuration in some cases; again an azafulvene intermediate seems implicated.



(17) (18) (19) (20)



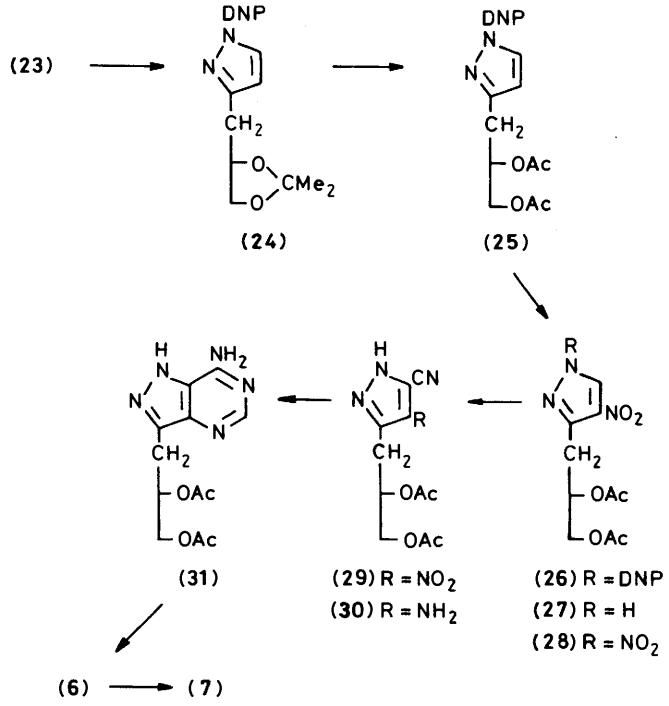
(12) R = H
(13) R = Ts
(14) (15) (16)
(11) (21) R = H (22) R = Ms (23)

Ts = *p*-$MeC_6H_4SO_2$
Ms = $MeSO_2$

Scheme 1.

The triol (**11**) was converted into its 2′,3′-*O*-isopropylidene derivative (**21**) in 87% yield (Scheme 1), on treatment with 2,2-dimethoxypropane and concentrated sulphuric acid in tetrahydrofuran (THF). The conditions for this isopropylidenation were somewhat critical to ensure a good yield; use of alternative conditions produced a range of other products. Treatment of (**21**) with methanesulphonyl chloride in pyridine gave the crystalline dimesylate (**22**). The ^{13}C n.m.r. spectra of (**21**) and (**22**) clearly indicated that they each possessed a five-membered dioxolane ring, and not a six-membered dioxane system.[23] The ^1H n.m.r. spectrum of (**21**) showed 1′-H as a doublet at δ 4.67, whilst (**22**) shows a one-proton doublet at δ 5.72, clearly indicating that the dioxolane ring spans the 2′- and 3′-oxygens. We were pleased to find that (**22**) underwent hydride reduction readily; treatment with lithium aluminium hydride in THF, or, preferably, with sodium borohydride in ethanol gave the 1′-deoxy compound (**23**) in 90% yield.

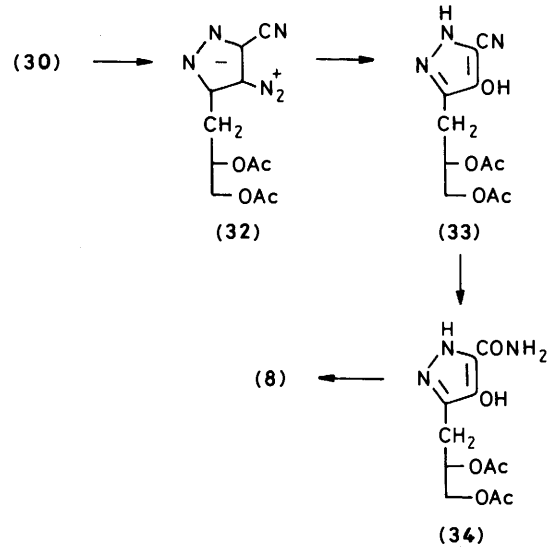
The subsequent transformation of (**23**) into the targets (**6**)—(**8**) was closely based on our previous work,[7–9] with functionalisation at C-4 being effected by nitration of an *N*-substituted pyrazole, and the carbon substituent at C-5 being introduced by means of a *cine*-substitution reaction on a 1,4-dinitro pyrazole.[7,24] Thus, (**23**) was treated with 2,4-dinitrofluorobenzene and triethylamine to give the *N*-dinitrophenyl (DNP) pyrazole (**24**) in 82% yield (see Scheme 2). The isopropylidene protecting group was unsuitable for later acidic reaction conditions, so (**24**) was hydrolysed (methanol–THF, H^+ ion exchange resin) and acetylated to give the diacetyl derivative (**25**) (92%). Nitration of (**25**) proceeded smoothly, the best



Scheme 2.

conditions involving the use of ammonium nitrate in trifluoroacetic anhydride and trifluoroacetic acid,[9,25] which produced (**26**) in 82% yield. The dinitrophenyl group had now to be removed, and this could be achieved cleanly and selectively by the use of piperidine in THF, giving (**27**) in 92% yield. This material could be converted into the 1,4-dinitropyrazole (**28**) (83%) by treatment with cupric nitrate in acetic anhydride,[7] and when (**28**) was treated briefly with potassium cyanide in aqueous ethanol,[7] a smooth *cine*-substitution[24] occurred to produce the nitro nitrile (**29**) in 95% yield. The nitro group could be reduced catalytically to give the amino nitrile (**30**), and cyclisation to the pyrazolopyrimidine (**31**) was achieved in 65% yield using formamidine acetate in refluxing ethanol;[26] use of the more conventional higher-boiling solvent ethoxyethanol gave a complex product, possibly arising through *O*→*N* acetyl migration. Finally, deacetylation with sodium methoxide in methanol gave the formycin analogue (**6**) in 89% yield; this compound displayed an electronic spectrum virtually identical with those of other 7-aminopyrazolo[4,3-*d*]pyrimidines, including formycin.[27] The conversion of (**6**) into the formycin B analogue (**7**) could be achieved using nitrous acid; we found, however, that in contrast to the reported conversion of formycin into formycin B,[28] long reaction times and a large excess of sodium nitrite were necessary for complete reaction, as monitored by t.l.c. After ion-exchange chromatography and crystallisation, (**7**) was isolated in 50% yield; it displayed the typical chromophore of the pyrazolo[4,3-*d*]pyrimidin-7-one system.[27]

The intermediate aminonitrile (**30**) could be used to prepare the pyrazofurin analogue (**8**). Treatment of (**30**) with sodium nitrite in aqueous acetic acid, followed by basification,[8] gave the diazopyrazole (**32**) (Scheme 3), which without rigorous purification was photolysed in aqueous acetone using a medium-pressure mercury lamp and Pyrex filter[8] to yield the 4-hydroxypyrazole (**33**) in 67% overall yield as a colourless syrup. When nitrile (**33**) was treated with nickel acetate tetrahydrate in refluxing acetic acid,[8] the corresponding amide (**34**) was obtained in 69% yield. Both (**33**) and (**34**) gave positive tests



Scheme 3.

with ferric chloride. Deacetylation of (**34**) with ammonia in aqueous ethanol then produced the pyrazofurin analogue (**8**) of (*S*)-DHPA as a syrup, in 65% yield.

Biological Data.—The three novel acyclic *C*-nucleoside analogues prepared in this study (**6**), (**7**), and (**8**) were tested for activity against representative RNA and DNA viruses in cell cultures. At concentrations up to 100 μg/ml, none of them inhibited the replication of influenza A (HK/1/68) virus or parainfluenza type 1 (Sendai) virus in Madin-Darby canine kidney cells nor of herpes simplex type 1 (HFEM) virus or herpes simplex type 2 (MS) virus in Vero (African green monkey kidney) cells. At the concentrations examined, none of the compounds was toxic for the cell monolayer.

Experimental

For general directions, see part 15.[9] Organic solvents were dried with anhydrous magnesium sulphate.

3(5)-(D-erythro-*Trihydroxypropyl*)*pyrazole* (**11**).—A solution of the tosylate (**15**) (50 g) in anhydrous hydrazine (250 ml) was heated under reflux for 48 h. The hydrazine solution was extracted with ether; the ether extracts were washed with 50% (w/v) potassium hydroxide, dried ($MgSO_4$), and evaporated to yield a colourless syrup. To the syrup was added 2M-hydrochloric acid and the mixture was stirred for 20 h. The reaction mixture was concentrated to 50 ml and applied to a column of Dowex 50 W (H^+) ion exchange resin. Elution with 1M-hydrochloric acid provided after evaporation the crude hydrochloride salt of (**11**). The salt was dissolved in water (20 ml) and applied to a column of Dowex 1 (OH) ion exchange resin. Elution with water and evaporation provided the pyrazole (**11**) (13 g, 68%) as a colourless solid. Recrystallisation from ethanol provided an analytically pure sample, m.p. 135—137 °C; $[\alpha]_D$ +21.0° (*c* 2.07 in H_2O); $\nu_{max.}$(KBr) 3 300br cm^{-1} (OH); δ_H (100 MHz, D_2O) 3.48—4.12 (3 H, m, 2′-, 3′-H), 6.20 (1 H, d, *J* 2 Hz, 4-H), 7.66 (1 H, d, *J* 2 Hz, 5-H), 1′-H obscured by HOD signal at δ 4.70; δ_C (50.32 MHz, D_2O) 65.30, 70.79, 76.88, (C-1′ -3′), 106.14 (C-4), 135.68 (C-5), and 152.62 (C-3) (Found: C, 45.8; H, 6.4; N, 17.75. $C_6H_{10}N_2O_3$ requires C, 45.57; H, 6.33; N, 17.72%).

3(5)-2,3-O-*Isopropylidene*-(D-erythro-*trihydroxypropyl*)-*pyrazole* (**21**).—The triol (**11**) (1 g) was stirred in THF (100 ml)

containing 2,2-dimethoxypropane (5 ml) and concentrated sulphuric acid (0.5 ml) until the mixture was homogenous. The reaction mixture was cooled to *ca.* 5 °C and neutralised with gaseous ammonia; the precipitated salt was filtered off and the filtrate evaporated. Chromatography on silica of the resultant syrup with ether–hexane (4:1) and then ether as eluants gave the *isopropylidenepyrazole* (**21**) (1.1 g, 87%) as a colourless syrup, $[\alpha]_D$ +31.5° (*c* 0.3 in $CHCl_3$); $\nu_{max.}$(film) 3 280br (NH, OH), 1 384 and 1 373 cm^{-1} (CMe_2); δ_H (200 MHz, $CDCl_3$) 1.34, 1.39 (each 3 H, s, CMe_2), 3.96 (1 H, dd, *J* 11.0, 5.8 Hz, 3′$_a$-H), 3.99 (1 H, dd, *J* 11.0, 6.7 Hz, 3′$_b$-H), 4.35 (1 H, q, *J* 6.0 Hz, 2′-H), 4.89 (1 H, d, *J* 4.8 Hz, 1′-H), 6.24 (1 H, s, 4-H), and 7.46 (1 H, s, 5-H); δ_C (20.15 MHz, $CDCl_3$) 25.24, 26.49 (*CMe*$_2$), 65.66 (C-3′), 68.01 (C-2′), 78.4 (C-1′), 103.17 (C-4), 109.75 (*C*Me$_2$), 133.03 (C-5), and 148.88 (C-3) (Found: M^+, 198.1002. $C_9H_{14}N_2O_3$ requires *M*, 198.1004).

1-*Methylsulphonyl*-3-(1-O-*methylsulphonyl*-2,3-O-*isopropylidene*-D-erythro-*trihydroxypropyl*)*pyrazole* (**22**).—Methanesulphonyl chloride (2.2 g) was added dropwise to a solution of the isopropylidenepyrazole (**21**) (1.5 g) in dry pyridine (15 ml). The mixture was left at room temperature for 6 h, and then partitioned between dichloromethane and water. The aqueous layer was extracted with dichloromethane; the dried organic extracts were evaporated to yield a solid which on recrystallisation from benzene gave the *dimesylate* (**22**) (2.4 g, 95%) as colourless plates, m.p. 88—89 °C, $[\alpha]_D$ +43.3° (*c* 1 in $CHCl_3$); $\nu_{max.}$(KBr) 1 385, 1 375 (CMe_2), and 1 180 cm^{-1} (SO_2); δ_H (100 MHz, $CDCl_3$) 1.33, 1.38 (each 3 H, s, CMe_2), 3.00 (3 H, s, OMs), 3.30 (3 H, s, NMs), 4.08 (2 H, m, 3′-H), 4.60 (1 H, m, 2′-H), 5.72 (1 H, d, *J* 4 Hz, 1′-H), 6.61 (1 H, d, *J* 2 Hz, 4-H), and 8.04 (1 H, s, *J* 2 Hz 5-H); δ_C (50.32 MHz, $CDCl_3$) 25.12, 26.39 (*CMe*$_2$), 39.02 (OMs), 41.42 (NMs), 65.39, 75.85, 75.99 (C-1′ -3′), 108.33 (C-4), 110.38 (*C*Me$_2$), 132.28 (C-5), and 153.42 (C-3) (Found: C, 37.3; H, 5.3; N, 8.0. $C_{11}H_{18}N_2O_7S_2$ requires C, 37.29; H, 5.08; N, 7.91%).

3(5)-[(S)-2,3-O-*Isopropylidenedihydroxypropyl*]*pyrazole* (**23**).—Sodium borohydride (1.3 g) was added in portions to a stirred solution of the dimesylate (**22**) (4 g) in ethanol (100 ml) and THF (25 ml). After the mixture had been stirred overnight, it was concentrated and the residue partitioned between dichloromethane and water; evaporation of the dried organic layer gave a residue which was chromatographed on silica with ether–hexane (1:1) as eluant to give the *deoxypyrazole* (**23**) (1.85 g, 90%) as a colourless syrup, $[\alpha]_D$ −13.8° (*c* 1.09 in $CHCl_3$); $\nu_{max.}$(film) 3 190br (NH), 1 381, and 1 374 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 1.36, 1.42 (each 3 H, s, CMe_2), 2.93 (1 H, dd, *J* 14.9, 5.6 Hz, 1′$_a$-H), 2.96 (1 H, dd, *J* 14.9, 6.6 Hz, 1′$_b$-H), 3.63 (1 H, dd, *J* 8.2, 7 Hz, 3′$_a$-H), 4.06 (1 H, dd, *J* 8.2, 6 Hz, 3′$_b$-H), 4.37 (1 H, m, 2′-H), 6.13 (1 H, d, *J* 1.9 Hz, 4-H), and 7.49 (1 H, d, *J* 2 Hz, 5-H); δ_C (50.32 MHz, $CDCl_3$) 25.60, 26.88 (*CMe*$_2$), 31.17 (t, C-1′), 68.87 (t, C-3′), 75.07 (d, C-2′), 104.55 (d, C-4), 109.32 (s, *C*Me$_2$), 134.16 (d, C-5), and 144.01 (s, C-3) (Found: C, 59.4; H, 7.8; N, 15.2. $C_9H_{14}N_2O_2$ requires C, 59.34; H, 7.69; N, 15.38%).

1-(2,4-*Dinitrophenyl*)-3-[(S)-2,3-O-*isopropylidenedihydroxypropyl*]*pyrazole* (**24**).—A solution of the deoxypyrazole (**23**) (3 g) in benzene (60 ml) containing 2,4-dinitro-1-fluorobenzene (5.2 g) and triethylamine (4 ml) was heated under reflux for 24 h. Concentration of the reaction mixture and chromatography on silica with ether–hexane (1:20) followed by ether–hexane (1:1) as eluants gave the *pyrazole* (**24**) (4.7 g, 82%). Recrystallisation from ether–hexane provided an analytically pure sample, m.p. 134—136 °C, $[\alpha]_D$ −3.6° (*c* 0.55 in $CHCl_3$); $\nu_{max.}$(KBr) 1 609, 1 550, 1 539, and 1 512 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.36, 1.42 (each 3 H, s, CMe_2), 2.88 (1 H, dd, *J* 14.8, 7.1 Hz, 1′$_a$-H), 3.01 (1 H, dd, *J* 14.8, 5.8 Hz, 1′$_b$-H), 3.67 (1 H, dd, *J* 8.33, 6.6 Hz, 3′$_a$-H), 4.08 (1 H, dd, *J* 8.33, 6 Hz, 3′$_b$-H), 4.40 (1 H, quin, *J ca.* 6.3 Hz, 2′-H), 6.46 (1 H, d, *J* 2.6 Hz, 4-H), 7.74 (1 H, d, *J* 2.6 Hz, 5-H), 7.77 (1 H, d, *J* 8.8 Hz, 6″-H),* 8.48 (1 H, dd, *J* 8.86, 2.5 Hz, 5″-H), and 8.63 (1 H, d, *J* 2.5 Hz, 3″-H); δ_C (50.32 MHz, $CDCl_3$) 25.72, 27.06 (CMe_2), 32.86 (C-1′), 69.24 (C-3′), 74.82 (C-2′), 109.32 (CMe_2), 110.51 (C-4), 121.18, 125.15, 127.30, 130.14 (C-5, 3″, 5″, 6″), 137.31, 143.17, 145.46, and 154.14 (quaternary aromatics) (Found: C, 51.7; H, 4.75; N, 16.6. $C_{15}H_{16}N_4O_6$ requires C, 51.72; H, 4.59; N, 16.09%).

1-(2,4-*Dinitrophenyl*)-3-[(S)-2,3-*di*-O-*acetyldihydroxypropyl*]*pyrazole* (**25**).—To the isopropylidenepyrazole (**24**) (3.85 g) in THF (50 ml) and methanol (100 ml) was added Dowex 50 W resin (H^+ form, 10 g dry weight) and the mixture was stirred for 48 h. Filtration of the resin followed by evaporation of the solvent gave the crude diol. Pyridine (60 ml) and acetic anhydride (30 ml) were added and the mixture left overnight. The reaction mixture was poured onto water and the aqueous solution extracted with dichloromethane. The dichloromethane extracts were washed with 0.5M-hydrochloric acid, dried, and evaporated. Chromatography of the residue on silica with hexane–ether (2:3) as eluant gave the *diacetate* (**25**) (4 g, 92%) as an oil, $[\alpha]_D$ +5.9° (*c* 4.91 in $CHCl_3$); $\nu_{max.}$(film) 3 120, 3 085, 2 950, and 1 740 cm^{-1} (CO); δ_H (200 MHz, $CDCl_3$) 2.05, 2.07 (each 3 H, s, OAc) 2.99 (2 H, d, *J* 6.6 Hz, 1′-H), 4.07 (1 H, dd, *J* 12, 5.95 Hz, 3′$_a$-H), 4.28 (1 H, dd, *J* 12, 3.5 Hz, 3′$_b$-H), 5.33 (1 H, m, 2′-H), 6.42 (1 H, d, *J* 2.5 Hz, 4-H), 7.73 (1 H, d, *J* 2.5 Hz, 5-H), 7.78 (1 H, d, *J* 8.8 Hz, 6″-H), 8.48 (1 H, dd, *J* 2.5, 8.9 Hz, 5″-H), and 8.63 (1 H, d, *J* 2.5 Hz, 3″-H); δ_C (20.15 MHz, $CDCl_3$) 20.71, 20.96 (each OAc), 29.71 (t, C-1′), 64.25 (t, C-3′), 70.31 (d, C-2′), 109.99, 121.07, 125.35, 127.46, 130.49 (each d, C-4, 5, 3″, 5″, 6″), 137.10, 142.97, 145.36, 152.74 (each s, quaternary aromatics), 170.27, and 170.60 (CO) (Found: C, 49.0; H, 4.2; N, 14.3. $C_{16}H_{16}N_4O_8$ requires C, 48.98; H, 4.08; N, 14.28%).

1-(2,4-*Dinitrophenyl*)-3-[(S)-2,3-*di*-O-*acetylidihydroxypropyl*]-4-*nitropyrazole* (**26**).—A solution of compound (**25**) (5.8 g) and ammonium nitrate (1.42 g) in trifluoroacetic acid (50 ml) was cooled in an ice-bath, and trifluoroacetic anhydride (7.6 ml) was added dropwise. The solution was allowed to warm to room temperature and after 6 h the mixture was poured into water (100 ml) and dichloromethane (100 ml). The aqueous phase was extracted with dichloromethane and the organic extracts were washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated. Chromatography on silica of the resultant syrup with ether–hexane (1:1) as eluant gave *nitropyrazole* (**26**) (5.3 g, 82%) as a syrup, $[\alpha]_D$ −12.6° (*c* 1.0 in $CHCl_3$); $\nu_{max.}$(film) 1 749 (CO), 1 550, and 1 350 cm^{-1} (C-NO_2); δ_H (200 MHz, $CDCl_3$) 1.99, 2.05 (each 3 H, s, OAc) 3.23 (1 H, dd, *J* 15.3, 7.7 Hz, 1′$_a$-H), 3.33 (1 H, dd, *J* 15.3, 5.3 Hz, 1′$_b$-H), 4.11 (1 H, dd, *J* 11.97, 5.5 Hz, 3′$_a$-H), 4.27 (1 H, dd, *J* 11.98, 3.75 Hz, 3′$_b$-H), 5.44 (1 H, sept, *J* 5.3, 7.4 Hz, 2′-H), 7.90 (1 H, d, *J* 8.8 Hz, 6″-H), 8.60 (1 H, dd, *J* 2.46, 8.8 Hz, 5″-H), 8.70 (1 H, s, 5-H), and 8.75 (1 H, d, *J* 2.4 Hz, 3″-H); δ_C (20.15 MHz, $CDCl_3$) 20.68, 20.87 (each OAc), 28.79 (C-1′), 64.31 (C-3′), 68.96 (C-2′), 121.50, 127.31, 128.20, 131.20 (C-5, 3″, 5″, 6″), 135.90, 136.40, 144.08, 147.44, 147.59 (quaternary aromatics), 170.36, and 170.67 (CO) (Found: C, 44.15; H, 3.4; N, 15.8. $C_{16}H_{15}N_5O_{10}$ requires C, 43.93; H, 3.43; N, 16.02%).

3(5)-[(S)-2,3-*Di*-O-*acetyldihydroxypropyl*]-4-*nitropyrazole* (**27**).—Piperidine (1.2 ml) was added dropwise to the pyrazole (**26**) (4.15 g) in THF (175 ml). After 24 h a further portion of piperidine (0.3 ml) was added. After a further 5 h the reaction mixture was neutralised with 2M-acetic acid, evaporated, and

* Double primed numbers refer to the dinitrophenyl group.

the residue chromatographed on silica with hexane–ether (1:10) as eluant to give (**27**) (2.37 g, 92%) as a colourless syrup, $[\alpha]_D$ −18.2° (*c* 0.1 in $CHCl_3$); $\nu_{max.}$(film) 3 280 (NH), 1 740 (CO), 1 555, and 1 375 cm^{-1} (C-NO_2); δ_H (200 MHz, $CDCl_3$) 2.07, 2.10 (each 3 H, s, OAc), 3.37 (1 H, dd, *J* 15, 7.5 Hz, 1′$_a$-H), 3.46 (1 H, dd, *J* 15, 5 Hz, 1′$_b$-H), 4.19 (1 H, dd, *J* 12.5, 6 Hz, 3′$_a$-H), 4.37 (1 H, dd, *J* 12.5, 4 Hz, 3′$_b$-H), 5.55 (1 H, m, 2′-H), and 8.30 (1 H, s, 5-H); δ_C (50.32 MHz, $CDCl_3$) 20.57, 20.76 (each OAc), 27.80 (C-1′), 64.38 (C-3′), 69.33 (C-2′), 132.58, 133.59, 142.22 (C-3, 4, 5), 170.69, and 171.12 (CO) [Found: C, 44.6; H, 5.0; N, 15.4. $C_{10}H_{13}N_3O_6$ requires C, 44.28; H, 4.80; N, 15.50%. Found: $(MH)^+$, 272.0887. $C_{10}H_{14}N_3O_6$ requires 272.0883].

3-[(S)-2,3-*Di*-O-*acetyldihydroxypropyl*]-1,4-*dinitropyrazole* (**28**).—Cupric nitrate trihydrate (6.0 g) and acetic anhydride (40 ml) were stirred for 1.5 h and nitropyrazole (**27**) (1.95 g) was then added. The mixture was stirred for 20 h, poured into water, and extracted with ethyl acetate. The ethyl acetate extracts were dried and evaporated to give a syrup. Chromatography on silica with ether–hexane (2:3) as eluant gave the *dinitropyrazole* (**28**) (1.28 g, 83%) as a colourless syrup, $[\alpha]_D$ +3.3° (*c* 2.12 in $CHCl_3$); $\nu_{max.}$(film) 1 740 (CO), 1 645 and 1 280 (N-NO_2), and 1 560 and 1 370 cm^{-1} (C-NO_2); δ_H (200 MHz, $CDCl_3$) 2.01, 2.11 (each 3 H, s, OAc), 3.28 (1 H, dd, *J* 15, 8.3 Hz, 1′$_a$-H) 3.46 (1 H, dd, *J* 15, 4.5 Hz, 1′$_b$-H), 4.23 (1 H, dd, *J* 12, 5.3 Hz, 3′$_a$-H), 4.34 (1 H, dd, *J* 12, 3.86 Hz, 3′$_b$-H), 5.50 (1 H, sext. *J* 4, 4 Hz, 2′-H), and 9.01 (1 H, s, 5-H); δ_C (50.32 MHz, $CDCl_3$) 20.63, 20.77 (each OAc), 29.04 (C-1′), 64.24 (C-3′), 68.93 (C-2′), 124.38 (C-4, 5), 144.3 (C-3), 170.15, and 170.44 (CO) [Found: C, 38.3; H, 3.9; N, 17.4. $C_{10}H_{12}N_4O_8$ requires C, 37.97; H, 3.80; N, 17.72%. Found: $(MH)^+$ 317.0726. $C_{10}H_{13}N_4O_8$ requires 317.0733].

3(5)-*Cyano*-5(3)-[(S)-2,3-*di*-O-*acetyldihydroxypropyl*]-4-*nitropyrazole* (**29**).—The dinitropyrazole (**28**) (1.8 g) in ethyl acetate (15 ml) and ethanol (15 ml) added dropwise to a stirred solution of potassium cyanide (3 g) in water (25 ml) and ethanol (75 ml). The reaction mixture was stirred for a further 5 min, neutralised with acetic acid, and diluted with ethyl acetate (300 ml) and water (150 ml). The aqueous layer was extracted with ethyl acetate. The dried organic extracts were evaporated to give a syrup which on chromatography on silica with hexane–ether (1:9) as eluant gave *nitrile* (**29**) (1.67 g, 99%) as a colourless syrup, $[\alpha]_D$ −34.5° (*c* 0.9 in $CHCl_3$); $\nu_{max.}$(film) 3 240 (NH), 2 260 (CN), 1 750 (CO), and 1 525 and 1 370 cm^{-1} (C-NO_2); δ_H (360 MHz, $CDCl_3$) 2.09, 2.13 (each 3 H, s, OAc), 3.36 (1 H, dd, *J* 15.8, 6.2 Hz, 1′$_a$-H), 3.57 (1 H, dd, *J* 15.8, 5.7 Hz, 1′$_b$-H), 4.15 (1 H, dd, *J* 12.15, 5.3 Hz, 3′$_a$-H), 4.34 (1 H, dd, *J* 12.15, 4.7 Hz, 3′$_b$-H), and 5.36 (1 H, quin, *J* 5.4 Hz, 2′-H); δ_C (50.32 MHz, $CDCl_3$) 20.72, 20.82 (each OAc), 26.99 (C-1′), 63.97 (C-3′), 68.90 (C-2′), 110.50 (C-5), 122.97 (C≡N), 134.33, 139.92 (C-3, 4), 170.77, and 171.69 (CO); [Found: $(M - 18)^+$, 278.063. $C_{11}H_{10}N_4O_5$ requires 278.065. Found: $(M - HOAc)^+$ 236.058, $C_9H_8N_4O_4$ requires 236.054].

4-*Amino*-3(5)-*cyano*-5(3)-[(S)-2,3-*di*-O-*acetyldihydroxypropyl*]*pyrazole* (**30**).—A solution of the nitro compound (**29**) (0.7 g) in ethanol (10 ml) was hydrogenated overnight using a 5% platinum on charcoal catalyst. The reaction mixture was filtered through Celite, which was then washed well with ethyl acetate. The residue after evaporation was chromatographed on silica with hexane–ether (1:9) as eluant to give the *amino nitrile* (**30**) (0.44 g, 70%) as a colourless syrup, $[\alpha]_D$ −6.1° (*c* 1.3 in $CHCl_3$); $\nu_{max.}$(film) 3 400—3 130br (NH), 2 218 (CN), and 1 740 cm^{-1} (CO); δ_H (360 MHz, $CDCl_3$) 2.068, 2.072 (each 3 H, s, OAc), 2.90 (1 H, dd, *J* 14.13, 3.8 Hz, 1′$_a$-H), 2.93 (1 H, dd, *J* 14.13, 4.3 Hz, 1′$_b$-H), 3.59 (2H, br, NH_2), 4.10 (1H, dd, *J* 12, 5.7 Hz, 3′$_a$-H), 4.24 (1 H, dd, *J* 12, 3.7 Hz, 3′$_b$-H), 5.14 (1 H, m, 2′-H); δ_C (50.32 MHz, $CDCl_3$) 20.62, 20.89 (each OAc), 25.60 (C-1′), 63.87 (C-3′), 70.23 (C-2′), 112.25, 113.07, 128.08, 133.66 (quaternary carbons), 170.65, and 171.00 (CO) (Found: M^+, 266.101. $C_{11}H_{14}N_4O_4$ requires 266.101).

7-*Amino*-3-[(S)-2,3-*di*-O-*acetyldihydroxypropyl*]*pyrazolo*-[4,3-d]*pyrimidine* (**31**).—The aminonitrile (**30**) (0.18 g) and formamidine acetate (0.75 g) were heated under reflux in ethanol (10 ml) for 1.5 h. The reaction mixture was concentrated and the residue chromatographed on silica gel with ethyl acetate–ethanol (97:3) as eluant to give *pyrazolopyrimidine* (**31**) (0.13 g, 65%) as a crystalline solid. Recrystallisation from ethanol–ether–hexane provided an analytical sample as colourless crystals, m.p. 155—156 °C, $[\alpha]_D$ +15.1° (*c* 0.53 in $CHCl_3$); $\nu_{max.}$(film) 3 340 (NH) and 1 745 cm^{-1} (CO); δ_H (200 MHz, $CDCl_3$) 1.93, 1.98 (each 3 H, s, OAc), 3.25 (1 H, dd, *J* 15.0, 6.6 Hz, 1′$_a$-H), 3.35 (1 H, dd, *J* 15.0, 6.4 Hz, 1′$_b$-H), 4.11 (1 H, dd, *J* 11.96, 6.4 Hz, 3′$_a$-H), 4.32 (1 H, dd, *J* 11.96, 3.4 Hz, 3′$_b$-H), 5.52 (1 H, octet, *J* 6.4, 3.4 Hz, 2′-H), and 8.27 (1 H, s, 5-H); δ_C (50.32 MHz, $CDCl_3$) 20.79, 21.24 (each OAc), 27.17 (C-1′), 64.88 (C-3′), 70.79 (C-2′), 123.12 (C-8), 140.45 (C-9), 140.82 (C-3), 151.09 (C-5), 151.96 (C-7), 171.28, and 171.90 (CO) (Found: C, 48.6; H, 5.1; N, 23.6. $C_{12}H_{15}N_5O_4$ requires C, 49.14; H, 5.12; N, 23.89%. Found: M^+, 293.1114. $C_{12}H_{15}N_5O_4$ requires 293.1124).

7-*Amino*-3-[(S)-2,3-*dihydroxypropyl*]*pyrazolo*[4,3-d]-*pyrimidine* (**6**).—A solution of sodium methoxide in methanol (1M; 3 ml) was added to the diacetate (**31**) (0.4 g) in methanol (50 ml). After 4 h the mixture was neutralised with acetic acid and evaporated. The residue was dissolved in water and applied to a Dowex 50 W (H^+) column. Elution with dilute ammonia, evaporation of the extract, and recrystallisation of the residue from ethanol provided the *diol* (**26**) (0.25 g, 89%), m.p. 232—235 °C (decomp.), $[\alpha]_D$ −21.7° (*c* 0.88 in H_2O); $\nu_{max.}$(KBr) 3 500—3 000br (NH, OH), 1 676, and 1 562 cm^{-1}; δ_H (200 MHz, D_2O) 3.23 (1 H, dd, *J* 15.0, 7.7 Hz, 1′$_a$-H), 3.30 (1 H, dd, *J* 15.0, 5.6 Hz, 1′$_b$-H), 3.69 (1 H, dd, *J* 11.7, 6.5 Hz, 3′$_a$-H), 3.81 (1 H, dd, *J* 11.7, 4.0 Hz, 3′$_b$-H), 4.31 (1 H, m, 2′-H), and 8.18 (1 H, s, 5-H); δ_C (50.32 MHz, D_2O) 31.58 (C-1′), 67.77 (C-3′), 73.43 (C-2′), 140.44, 142.05, 142.20 (C-3, 8, 9), and 153.85 (C-5, 7 coincident); $\lambda_{max.}$(H_2O) 295 nm (ε 12 096); $\lambda_{max.}$ (in alkali), 236 nm (19 855) and 306 nm (7 472); $\lambda_{max.}$ (in acid), 233 nm (11 652) and 297 nm (10 711) (Found: M^+, 209.0919. $C_8H_{11}N_5O_2$ requires 209.0913).

3-[(S)-2,3-*Dihydroxypropyl*]*pyrazolo*[4,3-d]*pyrimidin*-7-*one* (**7**).—Sodium nitrite was added to a solution of the amino compound (**6**) (60 mg) in water (2 ml) and glacial acetic acid (1 ml). The flask was stoppered tightly and left at room temperature for 5 days, after which t.l.c. indicated that there was no starting material present. The mixture was concentrated and the residue was dissolved in water and applied to a Dowex 50 W (NH_4^+) column. Elution with water, evaporation, and recrystallisation of the colourless solid from water–ethanol gave (**7**) (31 mg, 50%), m.p. 242—244 °C, $[\alpha]_D$ −26.3° (*c* 0.95 in H_2O); $\nu_{max.}$(KBr) 1 684 and 1 595 cm^{-1}; δ_H (200 MHz, D_2O) 2.90 (1 H, dd, *J* 14.95, 7.9 Hz, 1′$_a$-H), 3.00 (1 H, dd, *J* 14.95, 5.3 Hz, 1′$_b$-H), 3.38 (1 H, dd, *J* 11.77, 6.65 Hz, 3′$_a$-H), 3.51 (1 H, dd, *J* 11.77, 4.0 Hz, 3′$_b$-H), 3.97 (1 H, m, 2′-H), and 7.81 (1 H, s, 5-H); $\lambda_{max.}$(H_2O) 219 (ε 8 155) and 282nm (4 123); $\lambda_{max.}$ (in alkali) 224 (5 166) and 289 nm (4 396); $\lambda_{max.}$ (in acid) 219 (7 938) and 282 nm (3 794) (Found: C, 44.2; H, 4.7; N, 25.15. $C_8H_{10}N_4O_3 \cdot 0.5H_2O$ requires C, 43.83; H, 5.02, N, 25.57%).

3(5)-*Cyano*-5(3)-[(S)-2,3-*Di*-O-*acetyldihydroxypropyl*]-4-*hydroxypyrazole* (**33**).—To a stirred solution of the amino-pyrazole (**30**) (0.53 g) in glacial acetic acid (12 ml) at 5—10 °C was added sodium nitrite (0.3 g) in water (3 ml). The solution was stirred, at 5—10 °C, for 10 min, then at room temperature for 0.25 h. The solvents were evaporated below 30 °C, water (10

ml) was added, and the solution made basic by the addition of aqueous sodium hydrogen carbonate. The aqueous mixture was extracted with ethyl acetate; evaporation of the organic layer provided the crude diazopyrazole (**32**) (0.55 g) [$\nu_{max.}$(film) 2 242 (CN) and 2 190 cm^{-1} (N_2)]. This was dissolved in acetone–water (2:1 v/v; 120 ml). The solution was deoxygenated by bubbling nitrogen through it for 0.5 h after which it was irradiated using a medium-pressure mercury lamp with Pyrex filters. The volatile solvents were evaporated, dichloromethane and water were added, and the aqueous layer was extracted with dichloromethane. The dried organic extracts were evaporated and the residue chromatographed on silica, with ether–chloroform (1:10) as eluant to give *hydroxy nitrile* (**33**) (0.35 g, 67%) as a colourless syrup, $[\alpha]_D$ +13.6° (*c* 0.3 in $CHCl_3$); $\nu_{max.}$(film) 3 280br (OH, NH), 2 240 (CN), 1 745, and 1 720 cm^{-1} (CO); δ_H (200 MHz, $CDCl_3$) 2.08 (6 H, s, 2 OAc), 3.00 (2 H, m, 1′-H), 4.09 (1 H, dd, *J* 12.1, 6.1 Hz, 3′$_a$-H), 4.26 (1 H, dd, *J* 12.1, 3.6 Hz, 3′$_b$-H), 5.26 (1 H, m, 2′-H) (Found: C, 49.4; H, 5.44. $C_{11}H_{13}N_3O_5$ requires C, 49.44; H, 4.87%. Found: M^+, 267.086. $C_{11}H_{13}N_3O_5$ requires 267.086).

3(5)-*Carbamoyl*-5(3)-[(S)-2,3-*Di*-O-*acetyldihydroxypropyl*]-4-*hydroxypyrazole* (**34**).—Nickel acetate tetrahydrate (1.1 g) was added to a solution of the cyanopyrazole (**33**) (0.19 g) in glacial acetic acid (45 ml). The mixture was refluxed for 1 h, cooled, and added to water (75 ml) containing disodium ethylenediaminetetra-acetate (2.25 g). The product was isolated using dichloromethane. The residue after removal of solvents was chromatographed on silica gel with hexane–ether (1:20) as eluant to give *amide* (**34**) (0.14 g, 69%) as a colourless syrup, $[\alpha]_D$ 10.0° (*c* 0.5 in $CHCl_3$); $\nu_{max.}$(film) 3 310br (NH, OH), and 1 740 and 1 660 cm^{-1} (CO); δ_H (200 MHz, $CDCl_3$) 2.08, 2.09 (each 3 H, s, OAc), 2.93 (1 H, dd, *J* 15.2, 5.6 Hz, 1′$_a$-H), 3.03 (1 H, dd, *J* 15.2, 6.6 Hz, 1′$_b$-H), 4.12 (1 H, dd, *J* 12.08, 6.08 Hz, 3′$_a$-H), 4.28 (1 H, dd, *J* 12.08, 3.77 Hz, 3′$_b$-H), and 5.21 (1 H, m, 2′-H) (Found: M^+, 285.099. $C_{11}H_{15}N_3O_6$ requires 285.096).

3(5)-*Carbamoyl*-5(3)-[(S)-2,3-*Dihydroxypropyl*]-4-*hydroxypyrazole* (**8**).—A solution of the diacetate (**34**) (10.2 g) in ethanol (10 ml) and concentrated ammonia (7.5 ml) was stirred at room temperature for 24 h. The mixture was concentrated and the residue was chromatographed on silica. Elution with ethyl acetate removed the acetamide and elution with ethanol–ethyl acetate (1:20) gave *diol* (**8**) (0.095 g, 65%) as a syrup, $[\alpha]_D$ −11.3° (*c* 0.96 in EtOH); $\nu_{max.}$(film) 3 500—3 000br (OH, NH), 1 660, and 1 610 cm^{-1} (amide); δ_H (200 MHz, D_2O) 2.66 (1 H, dd, *J* 15.6, 8.0 Hz, 1′$_a$-H), 2.77 (1 H, dd, *J* 15.6, 5.15 Hz, 1′$_b$-H) 3.39 (1 H, dd, *J* 11.7, 6.5 Hz, 3′$_a$-H), 3.51 (1 H, dd, *J* 11.7, 4.1 Hz, 3′$_b$-H), 3.90 (1 H, m, 2′-H); $\nu_{max.}$(EtOH) 203 (ε 12 683) and 265 nm (4 999); $\nu_{max.}$(basic) 212 (ε 10 602) and 308 nm (6 331) (Found: M^+, 201.075. $C_7H_{11}N_3O_4$ requires 201.075).

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