C-Nucleoside Studies. Part 21.[1] Synthesis of Some Hydroxyalkylated Pyrrolo- and Thieno-[3,2-*d*]pyrimidines Related to Known Antiviral Acyclonucleosides

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Treatment of (*S*)-4,5-isopropylidenedioxypentanonitrile **17** with ethyl formate and sodium hydride gave a hydroxymethylene derivative which interacted with aminoacetonitrile to give 3-cyanomethyleneamino-2-[(*S*)-isopropylidenedioxypropyl]acrylonitrile **19**; this was elaborated *via* 3-amino-2-cyano-4-[(*S*)-2,3-isopropylidenedioxypropyl]pyrrole **22** into 4-amino-7-[(*S*)-2,3-dihydroxypropyl]pyrrolo[3,2-*d*]pyrimidine **9**. Treatment of the hydroxymethylene derivative of **17** with methanesulphonyl chloride, followed by acetylthioacetonitrile and sodium carbonate in ethanol gave 3-amino-2-cyano-4-[(*S*)-2,3-isopropylidenedioxypropyl]thiophene **25**, convertible in two steps into 4-amino-7-[(*S*)-2,3-dihydroxypropyl]thieno[3,2-*d*]pyrimidine **10**.

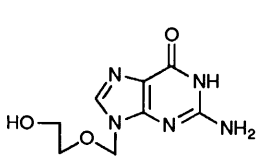
Similar chemistry was employed for the conversion of 5,6-isopropylidenedioxyhexanonitrile **30** into the higher homologues 4-amino-7-(3,4-dihydroxybutyl)pyrrolo- and thieno-[3,2-*d*]pyrimidine **11** and **12**, and for the preparation of 4-amino-7-(4-hydroxy-3-hydroxymethylbutyl)pyrrolo[3,2-*d*]pyrimidine **13** from 6-benzyloxy-5-benzyloxymethylhexanonitrile **41**. The hydroxyalkylated products **9**–**13** are *C*-nucleoside analogues of known antiviral agents, but did not display antiviral activity.

Since the discovery of the potent and selective antiherpes activity of acyclovir **1**, considerable effort has been expended on the synthesis of related acyclonucleosides.[2] Compounds which have emerged from this work and which display strong antiviral activity include ganciclovir **2**,[3] penciclovir (BRL 39123), **3**,[4] (*S*)-DHPA **4**[5] and (*R*)-9-(3,4-dihydroxybutyl)guanine **5**.[6] There has recently been renewed interest in (*S*)-DHPA **4** with the recognition that its phosphonomethyl analogue **6** displays very useful broad-spectrum antiviral activity.[7]

We,[1,8] and others[2,9,10] have been interested in the synthesis of *C*-nucleoside analogues of effective antiviral acyclonucleosides. We have previously reported the synthesis of the pyrazolo[4,3-*d*]pyrimidine analogue **7** of (*S*)-DHPA,[8] but this, and similar compounds,[1] did not display antiviral activity. However, the 8-aza-analogue **8** of acyclovir **1** is much less active as an antiherpes agent than is acyclovir iself.[11] Thus we were prompted to investigate whether replacement of the corresponding nitrogen atom in acyclic *C*-nucleosides such as **7** would lead to increased antiviral activity. In this paper, we report the synthesis of the pyrrolo[3,2-*d*]pyrimidine **9** and thieno[3,2-*d*]pyrimidine **10**, related to **7** and to (*S*)-DHPA **4**, the racemic higher homologues **11** and **12**, structurally similar to **5**, and the branched-chain pyrrolo[3,2-*d*]pyrimidine **13** with the side-chain of penciclovir **3**. Other workers have reported syntheses of some related pyrrolo[2,3-*d*]pyrimidine (7-deazapurine) acyclonucleosides.[11,12]

Our synthetic methods were based upon those developed for pyrrolo[3,2-*d*]pyrimidines by the Sloan–Kettering group,[13] applied by them to the synthesis of pyrrolo[2,3-*d*]pyrimidine *C*-nucleosides[14–16] and extended to thieno[3,2-*d*]pyrimidine systems.[15,17] The principle of this method, as applied to an adenosine analogue, is outlined retrosynthetically in Scheme 1; an appropriately functionalized acetonitrile derivative is seen to act as the precursor of the heterocyclic system.

Thus, for the synthesis of **9** and **10**, 1,2:5,6-di-*O*-isopropylidene-D-mannitol **14**[18] was treated with aqueous sodium periodate to give a solution of 2,3-*O*-isopropylidene-D-glyceraldehyde **15** (Scheme 2); this solution was treated directly with diethyl cyanomethylphosphonate and potassium carbonate to give the alkene **16**, shown by ^{1}H NMR spectroscopy to be predominantly the *E*-isomer[19] (*E*:*Z* *ca.* 3:1), in 89% overall yield. The alkene **16** could also be obtained, but with the *Z*-isomer predominating, by a Wittig reaction between **15** and cyanomethylenetriphenylphosphorane,[10] but the yield was somewhat inferior to that from the direct Wadsworth–Emmons method. We were also concerned that the need for isolation of **15** might lead to some racemization. Indeed, although the alkene **16** from either route could be reduced catalytically to the alkane **17**,[10] material from the Wittig approach displayed a



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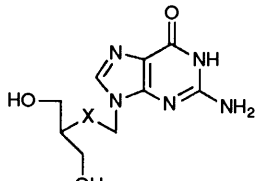
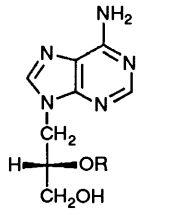
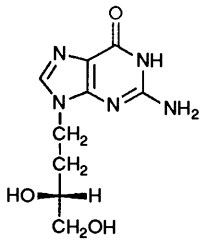


2; X = O
3; X = CH_2



4; R = H
6; R = $CH_2PO_3H_2$



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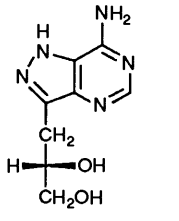

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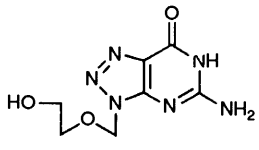

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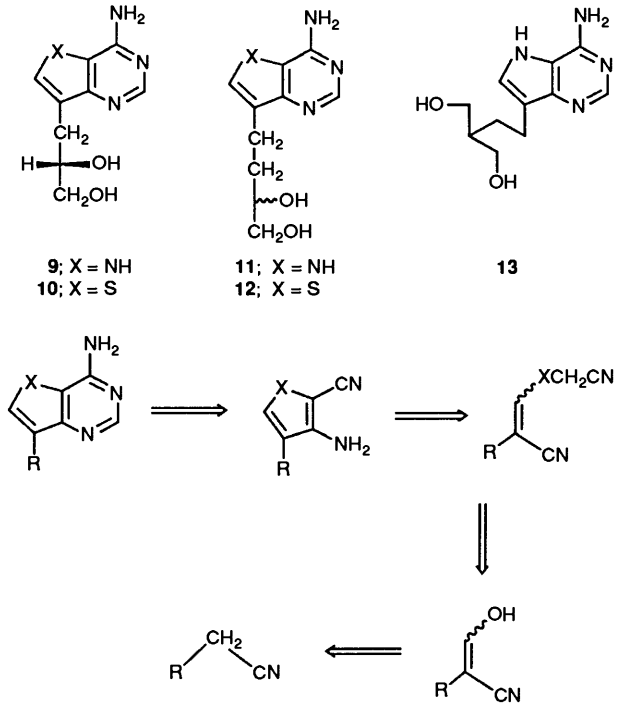


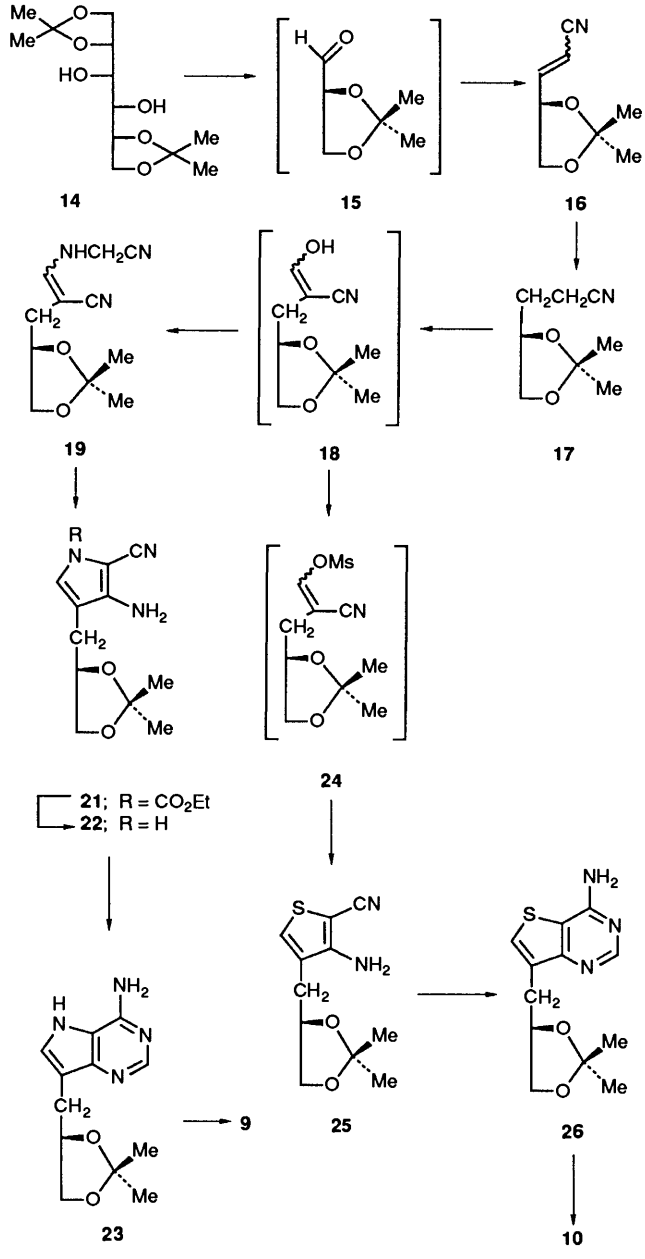
Scheme 1

considerably reduced optical rotation value as compared with that from the Wadsworth–Emmons synthesis.

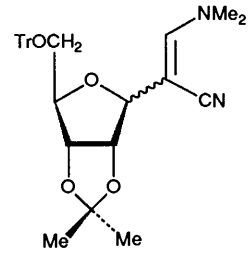
The introduction of an α-formyl (hydroxymethylene) group into **17** could, after some experimentation, be accomplished using ethyl formate and sodium hydride in ether plus a little ethanol; the presumed intermediate **18** was not isolated, but could be trapped by reaction with aminoacetonitrile to give the aminomethylene compound **19** in 45% overall yield. Although obtained as a crystalline solid, **19** was seen by ^{1}H NMR to be a mixture (3:1) of two isomers about the double bond. Attempts to carry out the formylation of **17** using formamide acetals[20] were unsuccessful, as were similar reactions with other nitriles (see below) and with simple model aliphatic nitriles; this contrasts with the successful formation of **20** from interaction of the corresponding acetonitrile derivative and bis(dimethylamino)-t-butoxymethane,[21] and may reflect the slightly lesser acidity of the α-methylene positions in our nitriles as opposed to the equivalent position in the precursor of **20**.

It had previously been demonstrated that cyclization of compounds such as **19** into pyrroles required protection of the amino function.[13,14] Accordingly, **19** was treated with ethyl chloroformate and diazabicyclononane (DBN); when the *N*-ethoxy-carbonyl derivative had formed (TLC), an additional equivalent of DBN was added to effect formation of the *N*-ethoxycarbonylpyrrole **21** (71%). This could be deprotected on nitrogen using sodium carbonate in methanol to give **22**, which on treatment with formamidine acetate in ethanol gave the pyrrolopyrimidine **23**. Hydrolysis of the isopropylidene group with aqueous acetic acid then gave dihydroxypropylpyrrolo-pyrimidine **9**.

To prepare the thienopyrimidine system, intermediate **18** was prepared as described above, and, again without purification, was treated with methanesulphonyl chloride and triethylamine in chloroform to product the *O*-mesyl derivative **24**. The formation of **24**, as a mixture of *E* and *Z*-isomers, could be seen by ^{1}H NMR, but this product proved somewhat unstable and so was directly treated with acetylthioacetonitrile and sodium carbonate in ethanol[15] to give the thiophene **25** as a crystalline solid after chromatography. This thiophene could then be converted through reaction with formamidine acetate into the

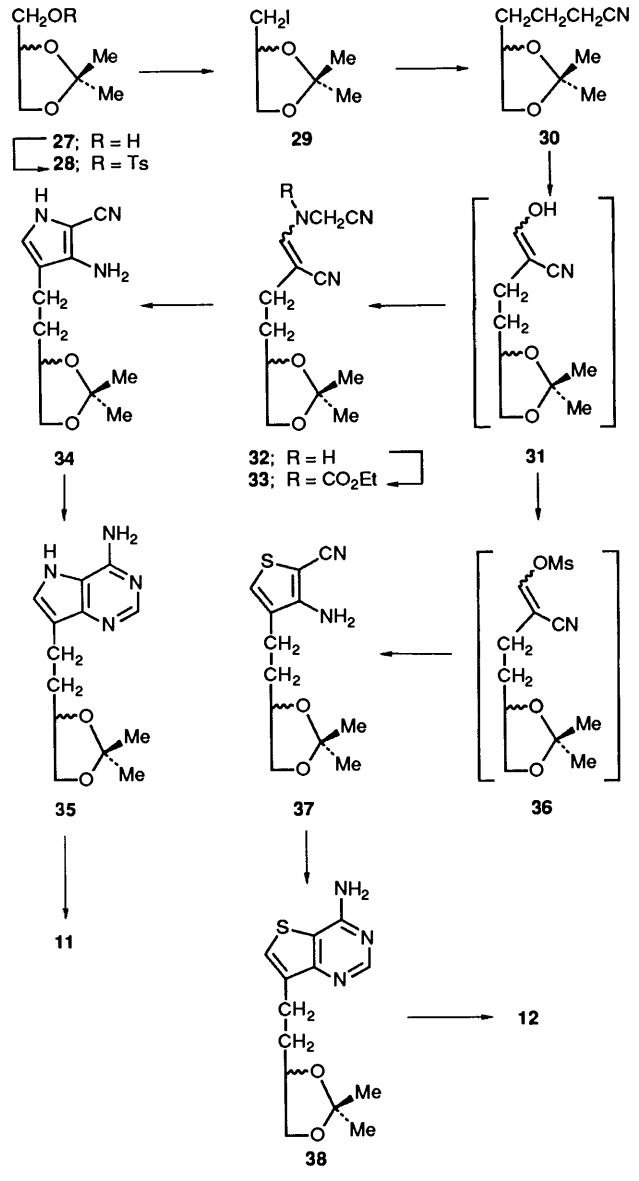


Scheme 2



protected thienopyrimidine **26**, and thence by acid hydrolysis into **10**, in good yield.

For the synthesis of the higher homologues **11** and **12**, 1,2-*O*-isopropylidene-glycerol (solketal, **27**), was converted (Scheme 3) *via* the tosylate **28** into the iodide **29**.[22] Treatment of this iodide with acrylonitrile and sodium borohydride in the presence of tributylstannyl chloride and with irradiation from a medium-pressure mercury lamp[23] gave the nitrile **30** in 66%



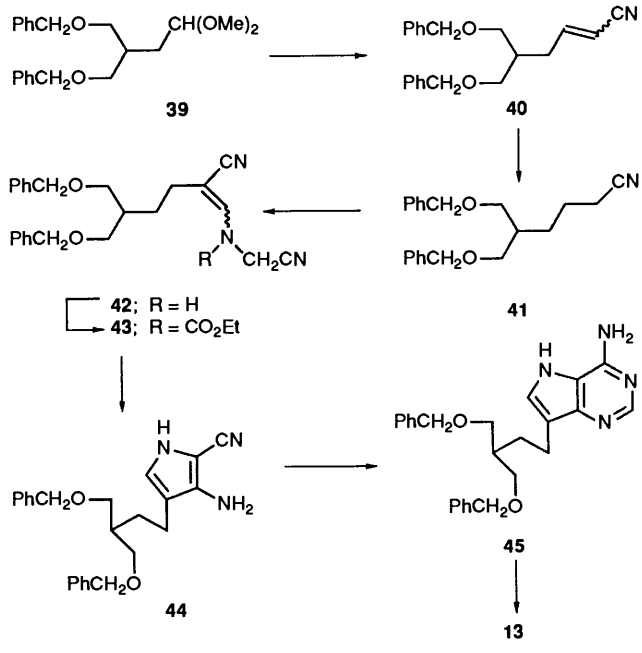
Scheme 3

yield. Formylation of **30** proceeded poorly even under the best conditions found (see above); when the hydroxymethylene derivative **31** was allowed to react with aminoacetonitrile, the enaminonitrile **32** was formed in only 9% overall yield, although a 66% recovery of unchanged nitrile **30** could be obtained. As in the case of the lower homologue, **32** was found to be a 3:1 mixture of geometrical isomers; since in the ^{1}H NMR spectrum the major isomer showed the alkene proton at lower field (δ 6.67) than did the minor isomer (δ 6.47), the major isomer is tentatively assigned the *E*-stereochemistry.

When **32** was treated with ethyl chloroformate and DBN, the *N*-ethoxycarbonyl derivative **33** was formed, but, in contrast to the case of the lower homologue, this material did not cyclize on further treatment with DBN, and the derivative **33** could be isolated in moderate yield after chromatography; it is noteworthy that this material appeared by NMR to be a single geometrical isomer, but it was not possible to assign the stereochemistry. Cyclization of **33** did occur however on treatment of the latter with the stronger base, sodium ethoxide in ether, when the resultant reaction mixture was added to water, and stirred for 1 h, hydrolysis of the *N*-ethoxycarbonyl group occurred and the pyrrole **34** could be isolated in 73% yield after chromatography as a crystalline solid. The bicyclic heterocycle could then be formed as previously by reaction with formamidine acetate, and the resultant pyrrolopyrimidine **35** could be deprotected in the sidechain to give 4-amino-7-(3,4-dihydroxybutyl)pyrimidine **11**.

Synthesis of the thienopyrimidine **12** followed the same procedure as used for the lower homologue **10**. Thus, the hydroxymethylene derivative **31** was treated with methanesulphonyl chloride and triethylamine to give the methanesulphonate **36** as evidenced by spectroscopic data; two isomers were apparent from the ^{1}H NMR spectrum. The instability of **36** precluded its full characterization, and it was converted directly into the thiophene **37** by the action of acetylthioacetonitrile and sodium carbonate in ethanol. The overall yield of the crystalline thiophene **37** was only *ca.* 5% based on the nitrile **30**, but again the bulk of the nitrile could be recovered unchanged after the formylation step. Condensation of **37** with formamidine acetate then gave the thienopyrimidine **38** which was deprotected with aqueous acetic acid to provide the target compound **12**.

For the synthesis of the analogue **13**, we commenced from the known intermediate **39**,[24] accessible in three steps from diethyl malonate and bromoacetaldehyde dimethyl acetal. The acetal function of **39** was hydrolysed with aqueous trifluoroacetic acid (Scheme 4) and the aldehyde was directly treated with cyano-



Scheme 4

methylenetriphenylphosphorane to give the alkene **40** (91%) as a 3:2 mixture of *E*- and *Z*-isomers. Hydrogenation of this material proceeded smoothly to give the saturated nitrile **41**. Formylation of nitrile **41** again proceeded in low yield to give, after reaction with aminoacetonitrile, the enaminonitrile **42** in 13% yield, but as in the previous cases a good recovery of unchanged nitrile **41** was possible. Treatment of **42** with ethyl chloroformate and DBN gave the *N*-ethoxycarbonyl derivative **43**. Once again, this did not cyclize directly to the pyrrole with an excess of DBN, but on treatment of crude **43**, identifiable by ^{1}H NMR, with sodium hydride and ethanol in ether followed by aqueous work-up, the pyrrole **44** was obtained as a white crystalline solid. The pyrrolopyrimidine **45** could be obtained from **44** by reaction with formamidine acetate, and side-chain deprotection by transfer hydrogenation gave the acyclonucleoside analogue **13**. Satisfactory analytical data could not be obtained for **13**, the figures obtained being consistently low for nitrogen (see Experimental below). The compound did, however, give a satisfactory high-resolution mass measurement

for the molecular ion (FAB mode), and the material was of high purity by HPLC.

Biological Data.—The acyclonucleoside analogues **9–13** were evaluated for activity against representative RNA and DNA viruses in cell cultures. At concentrations up to 100 μg ml^{-1}, no inhibition of replication was observed against influenza A(HK/1/68) virus or parainfluenza type 1 (Sendai) in Madin-Darby canine kidney cells, against HSV-1(HFEM) in Vero (African green monkey kidney) cells, or against HSV-1(SC 16), HSV-2(MS), Varicella zoster virus (Ellen) and cytomegalovirus (AD 169) in MRC-5 (human fibroblast) cells. At the concentrations examined, none of the compounds was toxic to the cell monolayer.

Experimental

IR spectra were recorded on Perkin-Elmer 157G or 580 instruments; UV spectra were obtained on a Shimadzu UV-240 spectrophotometer. Mass spectrometry was performed using an updated M.S.9, or VG 70-70 and ZAB instruments. NMR spectra were recorded on Perkin-Elmer R12B, JEOL PMX60, Bruker WP 200SY and JEOL 270 MHz spectrometers with deuteriochloroform as solvent unless otherwise stated; *J* values are in Hz: primed locants refer to the sidechain atoms. Specific rotations were measured at room temperature on a Bendix-NPL 143D automatic polarimeter (path length 1 cm). M.p.s were determined in capillaries and are uncorrected. Adsorption chromatography was carried out on Kieselgel H type 60 (Merck 7734); an external pressure was applied to the top of columns. For TLC, pre-coated aluminium-backed plates [Kieselgel HF_{254} type 60 (Merck)] were used. Light petroleum refers to material of b.p. 40–60 °C. Organic extracts were dried with anhydrous magnesium sulphate.

(S)-4,5-*Isopropylidenedioxypent-2-enonitrile* **16**.—A solution of sodium periodate (4.9 g) in water (15 ml) was added dropwise to a stirred suspension of 1,2:5,6-di-*O*-isopropylidene-D-mannitol **14**[18] (5 g) and aqueous sodium hydrogen carbonate (5% w/v; 50 ml) at 0 °C. The mixture was stirred for 1 h at room temperature and then cooled to 0 °C, when diethyl cyanomethylphosphonate (7.5 g) was added, followed by aqueous potassium carbonate (6 mol dm^{-3}; 65 ml). After 20 h at room temperature, the stirred mixture was extracted with dichloromethane (3 × 100 ml). The washed, dried extracts were evaporated to dryness and the resultant syrup was chromatographed on silica, with toluene–ether (5:1) as eluent to give the unsaturated nitrile **16** (5.2 g, 89%) as an oil; ν_{max}(film)/cm^{-1} 2220 (C≡N) and 1630 (C=C); δ_H(200 MHz) 1.32, 1.40 (each 3 H, s, CMe_2), 3.61 (0.75 H, dd, *J* 8.5, 6.5, 5-H_a *trans*), 3.63 (0.25 H, dd, *J* 8.5, 6.6, 5-H_a *cis*), 4.14 (0.75 H, dd, *J* 8.5, 6.8, 5-H_b *trans*), 4.20 (0.25 H, dd, *J* 8.5, 6.5, 5-H_b *cis*), 4.59 (0.75 H, m, 4-H *trans*), 4.92 (0.25 H, m, 4-H *cis*), 5.43 (0.25 H, dd, *J* 11.1, 1.2, 2-H *cis*), 5.66 (0.75 H, dd, *J* 16.1, 1.75, 2-H *trans*), 6.43 (0.25 H, dd, *J* 11.1, 8.2, 3-H *cis*) and 6.64 (0.75 H, dd, *J* 16.1, 4.6, 3-H *trans*).

(S)-4,5-*Isopropylidenedioxypentanonitrile* **17**.—The alkene **16** (2.0 g) in methanol (50 ml) was hydrogenated over palladium–charcoal (5%). The reaction mixture was filtered and evaporated, and the residue was chromatographed on silica, with toluene–ether (3:1) as eluent, to give the saturated nitrile **17**[10] (1.6 g, 79%) as a colourless oil, $[\alpha]_D$ −27.3° (*c* 1.1 in $CHCl_3$); ν_{max}/cm^{-1} 2240 (C≡N); δ_H(200 MHz) 1.19, 1.28 (each 3 H, s, CMe_2), 1.71 (2 H, m, 3-H_2), 2.35 (2 H, m, 2-H_2), 3.45 (1 H, dd, *J* 8.0, 5.5, 5-H_a), 3.93 (1 H, dd, *J* 8.0, 6.2, 5-H_b) and 4.03 (1 H, m, 4-H).

3-*Cyanomethyleneamino*-2-[(S)-2,3-*isopropylidenedioxypropyl*]*acrylonitrile* **19**.—A mixture of ethyl formate (12 ml), ethanol (0.3 ml) and ether (25 ml) was added dropwise over 8 h to a suspension of sodium hydride (2.88 g of 50%) and the nitrile **17**. After the mixture had been stirred for a further 15 h at room temperature it was diluted with water (50 ml) and the layers were separated. The aqueous phase, containing the sodium salt of **18**, was neutralized with dilute hydrochloric acid and extracted with chloroform (3 × 75 ml). The dried extracts were evaporated to give crude **18**, which was dissolved in methanol (100 ml), to which was added anhydrous sodium acetate (2.6 g), aminoacetonitrile hydrochloride (2.6 g) and water (4.4 ml). The mixture was stirred for 20 h, diluted with chloroform (300 ml) and poured onto ice. The washed, dried organic layer was evaporated to give a yellow solid which was purified by chromatography on silica, with toluene–ether (1:1) as eluent. Recrystallization from methanol–toluene gave *enaminonitrile* **19** (2.0 g, 45%), m.p. 120 °C, $[\alpha]_D$ −13.9° (*c* 0.72 in MeOH); ν_{max}(KBr)/cm^{-1} 3280 (NH), 2205 (C≡N) and 1640 (C=C); δ_H(200 MHz) 1.33, 1.34, 1.39, 1.42 (total 6 H, 4 s, CMe_2), 2.31 (2 H, m, 1′-H), 3.59 (0.25 H, dd, *J* 8.1, 7.3, 3′-H_a), 3.61 (0.75 H, dd, *J* 8.0, 6.2, 3′-H_a), 3.98, 4.00 (2 H, 2 s, CH_2CN), 4.03 (0.25 H, dd, *J* 8.0, 6.5, 3′-H_b), 4.05 (0.75 H, dd, *J* 8.0, 6.1, 3′-H_b), 4.2 (1 H, m, 2′-H), 5.77 (0.25 H, br, NH), 6.22 (0.75 H, br, NH), 6.54 (0.25 H, d, *J* 12, C*H*NH) and 6.76 (0.75 H, d, *J* 12, C*H*NH); δ_C(50 MHz) 25.3 and 26.6 (CMe_2), 30.9 and 34.4 (C-1′), 34.9 and 35.4 (C-4), 68.1 and 68.2 (C-3′), 74.7 and 75.6 (C-2′), 77.5 and 79.4 (C-2), 109.3 and 109.5 (CMe_2), 115.9, 116.0, 118.7 and 122.1 (CN) and 148.7 (C-3) (Found: C, 59.3; H, 6.7; N, 18.8%; M^+, 221.1164. $C_{11}H_{15}N_3O_2$ requires C, 59.7; H, 6.8; N, 19.0%; M, 221.1163).

Ethyl 3-*Amino*-2-*cyano*-4-[(S)-2,3-*isopropylidenedioxypropyl*]*pyrrole*-1-*carboxylate* **21**.—The nitrile **19** (5 g) in dichloromethane (115 ml) was treated at 0 °C with DBN (5.7 g) and a solution of ethyl chloroformate (3.94 g) in dichloromethane (23 ml). When formation of the *N*-ethoxycarbonyl derivative was complete (by TLC; *ca.* 1 h), further DBN (2.85 g) was added and the mixture was stirred at room temperature for 20 h. After evaporation to dryness the residue was chromatographed on silica, with toluene–ether (2:1) as eluent. Recrystallization from ether–light petroleum gave the *ester* **21** (4.7 g, 71%) as white crystals, m.p. 61 °C, $[\alpha]_D$ −11.6° (*c* 0.9 in MeOH); ν_{max}(KBr)/cm^{-1} 3370 (NH), 2190 (C≡N) and 1720 (C=O); δ_H(200 MHz) 1.33, 1.40 (each 3 H, s, CMe_2), 1.40 (3 H, t, *J* 7.1, OCH_2CH_3), 2.49 (1 H, dd, *J* 15.2, 6.5, 1′-H_a), 2.68 (1 H, dd, *J* 15.1, 3.5, 1′-H_b), 3.55 (1 H, dd, *J* 8.1, 7.5, 3′-H_a), 4.03 (1 H, dd, *J* 8.1, 6.2, 3′-H_b), 4.22 (1 H, m, 2′-H), 4.42 (2 H, q, OCH_2CH_3), 4.45 (2 H, br s, NH_2) and 7.10 (1 H, s, 5-H); δ_C(50 MHz) 13.9 (OCH_2CH_3), 25.3 and 26.4 (CMe_2), 28.0 (C-1′), 63.9 (OCH_2CH_3), 68.2 (C-3′); 75.6 (C-2′), 86.3, 109.4 (CMe_2), 113.4, 114.5 (CN), 123.9 (C-5), 148.4 and 148.7; *m/z* 293 (M^+) and 278 $(M-CH_3)^+$ (Found: C, 57.3; H, 6.5; N, 14.3. $C_{14}H_{19}N_3O_4$ requires C, 57.3; H, 6.5; N, 14.3%).

3-*Amino*-2-*cyano*-4-[(S)-2,3-*isopropylidenedioxypropyl*]*pyrrole* **22**.—A solution of **21** (10 g) in methanol (120 ml) was stirred with anhydrous sodium carbonate (0.36 g) for 1 h. Filtration, evaporation and chromatography of the residue on silica, eluting with toluene–ether (1:1) gave a solid which on recrystallization from ether–light petroleum gave the *pyrrole* **22** (6.3 g, 84%), as white crystals, m.p. 85 °C, $[\alpha]_D$ −3.3° (*c* 0.9 in MeOH); ν_{max}/cm^{-1} 3430 (NH), 2205 (C≡N) and 1630; δ_H(200 MHz) 1.33 and 1.39 (each 3 H, s, CMe_2), 2.53 (1 H, dd, *J* 15.0, 6.8, 1′-H_a), 2.68 (1 H, dd, *J* 15.0, 4.3, 1′-H_b), 3.58 (1 H, t, *J* 7.9, 3′-H_a), 3.98 (2 H, br s, NH_2), 4.03 (1 H, dd, *J* 8.0, 6.1, 3′-H_b), 4.25 (1 H, m, 2′-H), 6.51 (1 H, s, 5-H) and 8.32 (1 H, br s, NH); δ_C(50 MHz) 25.5 and 26.7 (CMe_2), 28.2 (C-1′), 68.5 (C-3′), 76.5 (C-2′), 87.0, 109.4, 109.6, 115.1 (CN), 122.6 (C-5) and 143.2 (Found: C,

59.7; H, 6.6; N, 18.9. $C_{11}H_{15}N_3O_2$ requires C, 59.7; H, 6.8; N, 19.0%).

4-*Amino*-7-[(S)-2,3-*isopropylidenedioxypropyl*]*pyrrolo*[3,2-d]*pyrimidine* **23**.—A solution of **22** (0.75 g) and formamidine acetate (1.06 g) in ethanol (15 ml) was heated under reflux for 5 h, and evaporated to dryness. The residue was triturated with water, filtered and recrystallized from methanol–ether to give the *pyrrolopyrimidine* **23** (0.45 g, 54%) as a white solid, m.p. 305–308 °C (decomp.), $[\alpha]_D$ −12.1° (*c* 0.4 in MeOH); ν_{max}(KBr)/cm^{-1} 3400 and 3320 (NH) and 1650; δ_H(270 MHz, CD_3OD) 1.32 and 1.37 (each 3 H, s, CMe_2), 2.95 (1 H, dd, *J* 14.6, 6.5, 1′-H_a), 3.04 (1 H, dd, *J* 14.6, 6.8, 1′-H_b), 3.65 (1 H, dd, *J* 8.1, 7.1, 3′-H_a), 3.97 (1 H, dd, *J* 8.2, 6.0, 3′-H_b), 4.44 (1 H, m, 2′-H), 6.70 (2 H, br s, NH_2), 7.39 (1 H, s, 6-H), 8.13 (1 H, s, 2-H) and 10.70 (1 H, br s, NH); δ_C(50 MHz, CD_3OD) 25.7 and 26.9 (CMe_2), 28.2 (C-1′), 69.3 (C-3′), 76.6 (C-2′), 109.2 (*C*Me_2), 110.5, 114.1, 132.5 (C-6), 136.2, 145.7 (C-2) and 154.0; λ_{max}(MeOH)/nm 249 (ε 10 540) and 288 (10 710) (Found: C, 57.8; H, 6.5; N, 22.4%; M^+, 248.1272. $C_{12}H_{16}N_4O_2$ requires C, 58.1; H, 6.5; N, 22.6%; M, 248.1274).

4-*Amino*-7-[(S)-2,3-*dihydroxypropyl*]*pyrrolo*[3,2-d]*pyrimidine* **9**.—A solution of the protected compound **23** (0.2 g) in aqueous acetic acid (80%; 15 ml) was heated under reflux for 0.5 h. Evaporation gave a white solid which was crystallized from methanol to give the *diol* **9** (145 mg, 86%), m.p. 245 °C (decomp.), $[\alpha]_D$ −35.4° (*c* 0.5 in MeOH); ν_{max}/cm^{-1} 3400 and 3320 (OH, NH) and 1650; δ_H(270 MHz, [$^2H_6$]-DMSO) 2.65 (1 H, dd, *J* 14.5, 6.8, 1′-H_a), 2.86 (1 H, dd, *J* 14.6, 5.0, 1′-H_b) 3.22 (1 H, dd, *J* 11.0, 5.8, 3′-H_b), 3.30 (1 H, dd, *J* 11.0, 5.5, 3′-H_b), 3.5 (1 H, br s, OH), 3.69 (1 H, m, 2′-H), 3.69 (1 H, m, 2′-H), *ca.* 5.3 (1 H, br, OH), 6.7 (2 H, br s, NH_2), 7.33 (1 H, d, *J* 2.5, 6-H), 8.08 (1 H, s, 2-H) and 10.7 (1 H, br, NH); δ_C(50 MHz, D_2O) 26.7 (C-1′), 64.5 (C-3′), 71.1 (C-2′), 108.0, 112.0, 131.7 (C-6), 134.1, 143.8 (C-2) and 150.8; λ_{max}(EtOH)/nm 256 (ε 10 600) and 286 (12 820) (Found: MH^+, 209.1021. $C_9H_{12}N_4O_2$ requires 209.1038).

3-*Amino*-2-*cyano*-4-[(S)-2,3-*isopropylidenedioxypropyl*]-*thiophene* **25**.—The nitrile **17** (5.0 g) was converted into the crude α-formyl derivative **18** (3.0 g) as described above for the preparation of **19**. This material in chloroform (100 ml) was treated with triethylamine (2.75 ml), followed by dropwise addition at 0 °C of methanesulphonyl chloride (2.06 g) in chloroform (40 ml). After 1 h at 0 °C, the organic layer was washed well with brine, dried and evaporated to give crude mesylate **24** (3.4 g) as a yellow oil; δ_H(60 MHz) 1.24 and 1.32 (each 3 H, s, CMe_2), 2.36 (2 H, m, 1′-H_2) 3.08 and 3.13 (3 H, 2 s, $MeSO_2$). 3.50 (1 H, m), 3.8–4.3 (2 H, m) and 7.06 and 7.28 (1 H, 2 s, 3-H).

This material, acetylthioacetonitrile (3.0 g), and anhydrous sodium carbonate (2.8 g) were heated under reflux in ethanol (150 ml) under nitrogen for 3 h. The residue after evaporation was partitioned between chloroform (100 ml) and water (100 ml). The organic phase was washed, dried and evaporated and the residue chromatographed on silica, with hexane–ether (1:1) as eluent to give *thiophene* **25** (1.1 g, 14.3% from **17**) as white crystals, m.p. 61–62 °C, $[\alpha]_D$ −25.3° (*c* 0.4 in MeOH); ν_{max}/cm^{-1} 3400 (NH_2), 2180 (C≡N) and 1650; δ_H(270 MHz) 1.36 and 1.40 (each 3 H, s, CMe_2), 2.65 (1 H, dd, *J* 15.1, 7.1, 1-H_a), 2.83 (1 H, dd, *J* 15.1, 3.4, 1′-H_b), 3.61 (1 H, t, *J* 7.9, 3′-H_a), 4.10 (1 H, dd, *J* 8.1, 6.2, 3′-H_b), 4.28 (1 H, m, 2′-H), 4.91 (2 H, br s, NH_2) and 7.04 (1 H, s, 5-H); δ_C(70 MHz) 25.5 and 26.6 (CMe_2), 32.0 (C-1′), 68.4 (C-3′), 75.9 (C-2′), 109.8 (*C*Me_2), 115.3 (CN), 128.7, 129.3 (C-5) and 155.4 (Found: C, 55.3; H, 5.9; N, 11.7%; M^+, 238.0769. $C_{11}H_{14}N_2O_2S$ requires C, 55.5; H, 5.9; N, 11.8%; M, 238.0776).

4-*Amino*-7-[(S)-2,3-*isopropylidenedioxypropyl*]*thieno*[3,2-d]*pyrimidine* **26**.—Formamidine acetate (4.0 g) was added in several portions over a 4-day period to a refluxing solution of the thiophene **25** (1.0 g) in ethanol (60 ml). After evaporation, the residue was extracted with chloroform. The extracts were washed, dried and evaporated. Chromatography of the resultant material on silica, with hexane–ether (1:2) as eluent, followed by crystallization from chloroform–hexane gave the *thienopyrimidine* **26** (0.75 g, 67%) as white crystals, m.p. 143–145 °C, $[\alpha]_D$ −20.6° (*c* 0.6 in MeOH); ν_{max}(KBr)/cm^{-1} 3300 (NH_2) and 1560; δ_H(270 MHz) 1.36 and 1.44 (each 3 H, s, CMe_2), 3.14 (1 H, dd, *J* 14.6, 6.9, 1′-H_a), 3.22 (1 H, dd, *J* 14.7, 5.4, 1′-H_b), 3.70 (1 H, dd, *J* 8.2, 6.9, 3′-H_a), 4.06 (1 H, dd, *J* 8.1, 6.2, 3′-H_b), 4.55 (1 H, m, 2′-H), 5.33 (2 H, br s, NH_2), 7.63 (1 H, s, 6-H) and 8.64 (1 H, s, 2-H); δ_C(70 MHz) 25.6 and 27.0 (CMe_2), 31.6 (C-1′), 68.9 (C-3′), 74.8 (C-2′), 109.2 (*C*Me_2), 115.0, 128.9 (C-6), 133.9, 154.6 (C-2), 158.0 and 159.2; λ_{max}(MeOH)/nm 250 (ε 8600) and 293 (9970) (Found: C, 54.2; H, 5.7; N, 15.8%; M^+, 265.0869. $C_{12}H_{15}N_3O_2S$ requires C, 54.3; H, 5.7; N, 15.8%; M, 265.0885).

4-*Amino*-7-[(S)-2,3-*dihydroxypropyl*]*thieno*[3,2-d]*pyrimidine* **10**.—The derivative **26** (400 mg) was treated with acetic acid–water (1:1; 150 ml) at 70 °C for 1 h. Evaporation of the mixture and recrystallization of the residue from methanol–ether gave the *diol* **10** as white crystals, m.p. 160–161 °C, $[\alpha]_D$ −34.0° (*c* 1.4 in MeOH); ν_{max}(KBr)/cm^{-1} 3300 and 1560; δ_H(270 MHz, [$^2H_6$]-DMSO) 2.75 (1 H, dd, *J* 14.3, 7.7, 1′-H_a), 3.00 (1 H, dd, *J* 14.3, 4.7, 1′-H_b), 3.30 (2 H, m, 3′-H_2), 3.80 (1 H, m, 2′-H), 4.67 (1 H, t, *J* 6, OH), 4.87 (1 H, d, *J* 5, OH), 7.39 (2 H, br s, NH_2), 7.77 (1 H, s, 6-H) and 8.38 (1 H, s, 2-H); δ_C(70 MHz, [$^2H_6$]-DMSO) 31.9 (C-1′), 65.4 (C-3′), 70.7 (C-2′), 114.0, 129.2 (C-6), 134.5, 154.3 (C-2), 158.50 and 158.54; λ_{max}(EtOH)/nm 262 (ε 13 030) and 315 (11 260); *m*/*z* (FAB) 226 (MH^+) (Found: C, 47.7; H, 5.0; N, 18.5. $C_9H_{11}N_3O_2S$ requires C, 48.0; H, 4.9; N, 18.7%).

5,6-*Isopropylidenedioxyhexanonitrile* **30**.—A solution of the iodide **29**[22] (20 g), acrylonitrile (56 ml) and sodium borohydride (4.8 g) in ethanol (500 ml) was irradiated with a medium-pressure mercury lamp at room temperature whilst tributylstannyl chloride (5.3 g) in ethanol (40 ml) was added dropwise over 15 min. After being irradiated for a further 1.5 h, the mixture was treated with a solution of potassium fluoride (20 g) in water (16 ml) for 4 h, filtered through $MgSO_4$, dried and evaporated. The residue was chromatographed on silica, with toluene–ether (4:1) as eluent to give the *nitrile* **30** (9.2 g, 66%) as a colourless oil; ν_{max}/cm^{-1} 2240 (CN); δ_H(270 MHz) 1.35, 1.41 (each 3 H, s, CMe_2), 1.65–1.9 (4 H, m, 3-H_2, 4-H_2), 2.43 (2 H, t, *J* 7, 2-H_2), 3.54 (1 H, dd, *J* 7.3, 6.2, 6-H_a) and 4.1 (2 H, m, 5-H, 6-H_b); δ_C(70 MHz) 17.2 (C-3), 22.1 (C-4), 25.6 and 26.9 (CMe_2), 32.4 (C-2), 69.2 (C-6), 75.1 (C-5), 109.2 (*C*Me_2), 119.5 (CN); *m*/*z* 168 $(M - H)^+$ and 154 $(M - Me)^+$ [Found: $(M - H)^+$, 168.1041. $C_9H_{14}NO_2$ requires 168.1024].

3-*Cyanomethyleneamino*-2-(3,4-*isopropylidenedioxybutyl*)-*acrylonitrile* **32**.—To the nitrile **30** (16 g) and sodium hydride (50%; 14.0 g) in ether (125 ml) was added dropwise over 8 h a mixture of ethyl formate (50 ml), ethanol (1 ml) and ether (125 ml). After a further 15 h at room temperature, water (200 ml) was added and the layers were separated. The aqueous phase was neutralized with dilute HCl (2 mol dm^{-3}) and extracted with chloroform (3 × 300 ml). Drying and evaporation of the chloroform extract gave the crude hydroxymethylene derivative **31** (*ca.* 5 g). [Unchanged nitrile **3** (10.5 g) could be recovered from the ether layers.] Crude compound **31** in methanol (100 ml) was treated with anhydrous sodium acetate (3.25 g), aminoacetonitrile hydrochloride (3.25 g) and water (5.5 ml). After being stirred for 20 h, the mixture was partitioned between

chloroform (400 ml) and ice–water (100 ml). The washed, dried organic layer was evaporated and the residue chromatographed on silica, with toluene–ether (1:1) as eluent, to give the *enamino nitrile* **32** (1.9 g, 8.5%) as a pale yellow oil; ν_{max}/cm^{-1} 3350 (NH), 2200 (CN) and 1650 (C=C); δ_H(200 MHz) 1.31, 1.33, 1.38 and 1.40 (total 6 H, 4 s, CMe_2), 1.72 (2 H, m, 2′-H_2), 2.20 (2 H, m, 1′-H_2), 3.56 (1 H, m, 4′-H_a), 3.9–4.2 (4 H, m, 3′-H, 4′-H_b, CH_2CN), 5.01 (0.25 H, m, NH), 5.41 (0.75 H, m, NH), 6.47 (0.25 H, d, *J* 12.5, 3-H) and 6.67 (0.75 H, d, *J* 12.5, 3-H); δ_C(major isomer) 22.6 (C-2′), 25.7 and 26.9 (CMe_2), 31.5 (C-1′), 35.4 (CH_2CN), 69.1 (C-4′), 73.9 (C-3′), 83.1 (C-2), 109.1 (CMe_2), 116.0 (CN), 121.6 (CN) and 146.9 (C-3); *m/z* 235 (M^+), 222 ($M - CH_3$)$^+$ and 134 ($M - C_5H_9O_2$)$^+$ (Found: M^+, 235.1350. $C_{12}H_{17}N_3O_2$ requires 235.1342).

3-(N-*Ethoxycarbonyl*)*cyanomethyleneamino*-2-(3,4-*isopropylidenedioxybutyl*)*acrylonitrile* **33**.—To a solution of the amine **32** (2.5 g) and DBN (2.63 g) in dichloromethane at 0 °C was added dropwise ethyl chloroformate (1.71 g) in dichloromethane (10 ml). After 1 h, evaporation of the mixture and column chromatography of the residue on silica, with toluene-ether (2:1) as eluent, gave the *urethane* **33** (1.52 g, 47%) as a pale yellow oil; ν_{max}/cm^{-1} 2200 (C≡N), 1730 (C=O) and 1650 (C=C); δ_H(200 MHz) 1.31 and 1.40 (each 3 H, s, CMe_2), 1.34 (3 H, t, CH_2CH_3), 1.8 (2 H, m, 2′-H_2), 2.4 (2 H, m, 1′-H_2), 3.55 (1 H, m, 4′-H_a), 4.05 (2 H, m, 4′-H_b, 3′-H), 4.34 (2 H, q, OCH_2CH_3), 4.91 (2 H, s, CH_2CN) and 7.25 (1 H, s, 3-H); δ_C(50 MHz) 14.2 (Me), 25.5 and 26.8 (CMe_2), 30.0 (C-2′), 32.4 (C-1′), 33.6 (CH_2CN), 64.8 (OCH_2CH_3), 69.0 (C-4′), 74.2 (C-3′), 93.7 (C-2), 109.0 (CMe_2), 114.4 and 116.8 (CN), 137.1 (C-3) and 152.2 (CO) (Found; M^+, 307.1560. $C_{15}H_{21}N_3O_2$ requires 307.1531).

3-*Amino*-2-*cyano*-4-(3,4-*isopropylidenedioxybutyl*)*pyrrole* **34**.—To the ethoxycarbonyl compound **33** (1.5 g) in ether (30 ml) were added sodium hydride (50%; 0.48 g) and ethanol (0.1 ml). The mixture was stirred for 3 h and then diluted with water (5 ml); the two-phase mixture was then stirred vigorously for 1 h. The organic layer was separated, washed, dried and evaporated. Chromatography of the residue on silica, with toluene–ether (2:1) as eluent, gave the *pyrrole* **34** (1.1 g, 73%) as a white solid, m.p. 92–93 °C; ν_{max}(KBr)/cm^{-1} 3300 (NH), 2200 (C≡N) and 1630; δ_H(200 MHz) 1.35 and 1.42 (each 3 H, s, CMe_2), 1.74 (2 H, m, 2′-H_2), 2.43 (2 H, m, 1′-H_2), 3.52 (1 H, t, 4′-H_a), 3.76 (2 H, br s, NH_2), 4.1 (2 H, m, 3′-H, 4′-H_b), 6.50 (1 H, s, 5-H) and 8.48 (1 H, s, NH); δ_C 19.8 (C-2′), 25.6 and 26.9 (CMe_2), 33.7 (C-1′), 69.2 (C-4′), 74.9 (C-3′), 86.5, 108.9 (CMe_2), 112.5, 115.3, 121.6 and 142.4 (Found: M^+, 235.1342. $C_{12}H_{17}N_3O_2$ requires 235.1320).

4-*Amino*-7-(3,4-*isopropylidenedioxybutyl*)*pyrrolo*[3,2-d]*pyrimidine* **35**.—Formamidine acetate (0.9 g) and the pyrrole **34** (0.7 g) were heated under reflux in ethanol for 5 h. After evaporation of the mixture the residue was partitioned between ethyl acetate and water. The washed, dried organic extracts were then evaporated to give a solid which on crystallization from ethanol–toluene–light petroleum gave the pyrrolopyrimidine **35** (0.44 g, 57%), m.p. 280–283 °C (decomp.); δ_H(200 MHz, [$^2H_6$]-DMSO) 1.25 and 1.33 (each 3 H, s, CMe_2), 1.87 (2 H, m, 2′-H_2), 2.7 (2 H, m, 1′-H_2), 3.42 (1 H, m, 4′-H_a), 4.0 (2 H, m, 3′-H, 4′-H_b), 6.7 (2 H, br s, NH_2), 7.32 (1 H, s, 6-H), 8.09 (1 H, s, 2-H) and 10.6 (1 H, br s, NH); δ_C(50 MHz) 20.0 (C-2′), 25.6 and 26.8 (CMe_2), 33.7 (C-1′), 68.5 (C-4′), 75.1 (C-3′), 107.7 (CMe_2), 113.9, 114.3, 124.8, 125.0, 145.8, 149.7 and 150.2 (Found: MH^+, 263.1495. $C_{13}H_{19}N_4O_2$ requires 263.1508. Found: C, 59.2; H, 6.9; N, 21.9. $C_{13}H_{18}N_4O_2$ requires C, 59.5; H, 6.9; N, 21.4%).

4-*Amino*-7-(2,3-*dihydroxybutyl*)*pyrrolo*[3,2-d]*pyrimidine* **11**.—The protected compound **35** (0.3 g) in aqueous acetic acid (1:1; 10 ml) was heated at 70 °C for 3 h. Evaporation and recrystallization from water–methanol–ether gave the *diol* **11** (0.186 g, 73%) m.p. 260–262 °C; ν_{max}/cm^{-1} 3200 (NH) and 1660; δ(200 MHz, [$^2H_6$]-DMSO) 1.55 and 1.79 (each 1 H, m, 2′-H), 2.7 (2 H, m, 1′-H_2), 3.3–3.5 (5 H, m, 3′-H, 4′-H_2, 2 × OH), 6.7 (2 H, br s, NH_2), 7.30 (1 H, d, *J* 2.5, 6-H), 8.06 (1 H, s, 2-H) and 10.6 (1 H, br s, NH); δ_C(50 MHz, [$^2H_6$]-DMSO) 19.6 (C-2′), 34.1 (C-1′), 65.9, 70.5, 113.7, 115.0, 125.1, 145.7, 149.5 and 150.2; λ_{max}(EtOH)/nm 252 (ε 10 500) and 252 (7320) (Found: MH^+, 223.1211. $C_{10}H_{15}N_4O_2$ requires 223.1195. Found: C, 50.5; H, 6.7; N, 23.7. $C_{10}H_{14}N_4O_2 \cdot H_2O$ requires C, 50.0; H, 6.7; N, 23.3%).

3-*Amino*-2-*cyano*-4-(3,4-*isopropylidenedioxybutyl*)*thiophene* **37**.—The nitrile **30** (10 g) was α-formylated as described above for the preparation of **32** to give crude compound **31** (2 g) and recovered **30** (7.6 g). Crude compound **31** in chloroform (40 ml) containing triethylamine (2 ml) was treated dropwise at 0 °C with methanesulphonyl chloride (1.0 ml) in chloroform (25 ml). After 1 h, further chloroform (80 ml) was added, and the solution was washed (brine), dried and evaporated. Column chromatography of the residue on silica, with hexane–acetone (1:1) as eluent, gave the mesylate **36** (1.7 g); ν_{max}/cm^{-1} 2220 (CN), 1380 and 1190 (SO_2); δ_H(90 MHz) 1.34 and 1.42 (each 3 H, s, CMe_2), 1.8 (2 H, m, 2′-H), 2.4 (2 H, m, 1′-H), 3.21 and 3.26 (3 H, 2 s, SO_2Me), 3.5 (1 H, m), 4.1 (2 H, m) and 7.33 and 7.57 (1 H, 2 s, 3-H).

This material (1.5 g), acetylthioacetonitrile (1.2 g), and anhydrous sodium carbonate (1.2 g) were heated under reflux in ethanol (70 ml) for 7 h. The residue after evaporation was partitioned between chloroform and water (75 ml of each). The washed, dried organic layer was evaporated, and the residue was chromatographed on silica, with hexane–acetone (2:1) as eluent, to give, after recrystallization from ether–light petroleum, the *thiophene* **37** [0.64 g, 4.7% from **30**] as white crystals, m.p. 79–80 °C; ν_{max}/cm^{-1} 3350 (NH_2) and 2200 (CN); δ_H(270 MHz) 1.37, 1.44 (each 3 H, s, CMe_2), 1.8 (2 H, m, 2′-H_2), 2.6 (2 H, m, 1′-H_2), 3.55 (1 H, m, 4′-H_a), 4.1 (2 H, m, 3′-H, 4′-H_b), 4.7 (2 H, br s, NH_2) and 7.01 (1 H, s, 5-H); δ_C(70 MHz, [$^2H_6$]-DMSO) 23.4 (C-2′), 25.6 and 26.9 (CMe_2), 31.9 (C-1′), 66.4 (C-4′), 74.6 (C-3′), 76.0, 107.9 (CMe_2), 116.1 (CN), 127.6 (C-5), 131.9 and 155.7 (Found: M^+, 252.0937. $C_{12}H_{16}N_2O_2S$ requires 252.0932).

4-*Amino*-7-(3,4-*isopropylidenedioxybutyl*)*thieno*[3,2-d]*pyrimidine* **38**.—Formamidine acetate (4.0 g) was added in several portions over 4 days to a refluxing solution of the pyrrole **37** (1.0 g) in ethanol (50 ml). After evaporation, the product was extracted into chloroform. The washed, dried, chloroform solution was evaporated and the residue chromatographed on silica, with toluene–ether (1:1) as eluent. Recrystallization of the residue from ether–light petroleum gave the *thienopyrimidine* **38** (0.55 g, 50%) as white crystals, m.p. 113–114 °C; ν_{max}(KBr)/cm^{-1} 3350 (NH_2) and 1660; δ_H(200 MHz) 1.35 and 1.42 (each 3 H, s, CMe_2), 2.0 (2 H, m, 2′-H_2), 3.0 (2 H, m, 1′-H_2), 3.57 (1 H, dd, *J* 7.6, 7.2, 4′-H_a), 4.04 (1 H, dd, *J* 7.7, 5.9, 4′-H_b), 4.13 (1 H, m, 3′-H), 5.4 (2 H, br s, NH_2), 7.40 (1 H, s, 6-H) and 8.62 (1 H, s, 2-H); δ_C(50 MHz) 24.1 (C-2′), 25.7 and 27.0 (CMe_2), 32.9 (C-1′), 69.3 (C-4′), 75.4 (C-3′), 108.8 (CMe_2), 115.3, 126.7 (C-6), 137.8, 154.7 (C-2), 158.0 and 159.3 (Found: C, 55.8; H, 6.1; N, 15.4%; M^+, 279.1048. $C_{13}H_{17}N_3O_2S$ requires C, 55.9; H, 6.1; N, 15.1%; M, 279.1041).

4-*Amino*-7-(3,4-*dihydroxybutyl*)*thieno*[3,2-d]*pyrimidine* **12**.—The isopropylidene derivative **38** (0.4 g) was treated with acetic acid–water (1:1; 15 ml) at 70 °C for 0.5 h. Evaporation and recrystallization of the residue from methanol–ether gave the *diol* **12** (0.265 g, 77%), m.p. 173–174 °C; ν_{max}(KBr)/cm^{-1}

3340 (NH), 3150 (OH) and 1660; δ_H(200 MHz, [$^2H_6$]-DMSO) 1.6 (1 H, m, 2′-H_a) 1.85 (1 H, m, 2′-H_b), 2.85 (2 H, m, 1′-H_2), 3.3 (2 H, m), 3.4 (1 H, m), 4.50 (1 H, t, OH), 4.65 (1 H, d, OH), 7.4 (2 H, br s, NH_2), 7.72 (1 H, s, 6-H), 8.37 (1 H, s, 2-H); δ_C(50 MHz, [$^2H_6$]-DMSO) 23.4 (C-2′), 33.0 (C-1′), 65.9 (C-4′), 70.6 (C-3′), 114.2, 127.3 (C-6), 137.6, 154.4 (C-2), 158.4 and 158.5; λ_{max}(EtOH)/nm 250 (ε 11 620) and 293 (13 320); *m/z* 239 (M^+), 238 $(M - H)^+$ and 221 $(M - H_2O)^+$ [Found: $(M - H)^+$ 238.0653. $C_{10}H_{12}N_3O_2S$ requires 238.0650. Found: C, 46.6; H, 5.6; N, 16.3. $C_{10}H_{13}N_3O_2S{\cdot}H_2O$ requires C, 46.7; H, 5.8; N, 16.3%].

6-Benzyloxy-5-benzyloxymethylhex-2-enonitrile **40**.—The acetal **39**[24] (10 g) was stirred for 2 h with trifluoroacetic acid (10 ml) and water (100 ml) at room temperature. The mixture was neutralized with aqueous potassium carbonate (6 mol dm^{-3}) and extracted with dichloromethane (2 × 300 ml). The extract was evaporated to *ca.* 100 ml, and this was then added dropwise to a solution of cyanomethylenetriphenylphosphorane (12 g) in dichloromethane (100 ml). After 0.5 h, the solvent was evaporated and the residue chromatographed on silica, with toluene–ether (2:1) as eluent, to give *unsaturated nitrile* **40** (8.5 g, 91%) as a colourless oily mixture of *E*- and *Z*-isomers; ν_{max}(film)/cm^{-1} 2210 (C≡N) and 1630 (C=C); δ_H(200 MHz) 2.10 (1 H, m, 5-H), 2.35 (1.2 H, dt, *J* 7.3, 1.5, 4-H_2 *trans*), 2.58 (0.8 H, dt, *J* 7.7, 1.4, 4-H_2 *cis*), 3.45 (4 H, m, CH_2OBn), 4.45 (2.4 H, s, CH_2Ph *trans*), 4.47 (1.6 H, s, CH_2Ph *cis*), 5.23 (0.6 H, dt, *J* 16.3, 1.5, 2-H *trans*), 5.30 (0.4 H, dt, *J* 10.9, 1.5, 2-H *cis*), 6.51 (0.4 H, dt, *J* 10.9, 7.7, 3-H *cis*), 6.66 (0.6, dt, *J* 16.3, 7.5, 3 H-*trans*) and 7.32 (10 H, m, Ph) (Found: M^+, 321.1719. $C_{21}H_{23}NO_2$ requires 321.1729).

6-Benzyloxy-5-(benzyloxymethyl)hexanonitrile **41**.—The alkene **40** (8.5 g) was hydrogenated in methanol (100 ml) over 5% Pd-on-C as catalyst. The mixture was filtered and evaporated and the residue chromatographed on silica, with toluene–ether (10:1) as eluent to give the *nitrile* **41** (6.38 g, 75%) as a colourless oil, ν_{max}(film)/cm^{-1} 2240 (C≡N); δ_H(200 MHz) 1.5–1.8 (4 H, m, 3-H_2, 4-H_2), 1.95 (1 H, septet, *J* 5.5, 5-H), 2.31 (2 H, t, *J* 6.9, 2-H_2), 3.48 (2 H, AB of ABX, CH_2OBn), 4.50 (4 H, s, CH_2Ph) and 7.32 (10 H, m, Ph); δ_C(50 MHz) 17.3 (C-3), 23.1 (C-2), 28.2 (C-4), 38.9 (C-5), 70.6 (C-6), 73.1 (CH_2Ph), 119.6 (CN), 127.5, 128.3 and 138.4 (Found: M^+, 323.1883. $C_{21}H_{25}NO_2$ requires 323.1884).

2-[4-Benzyloxy-(3-benzyloxymethyl)butyl]-3-(cyanomethyleneamino)acrylonitrile **42**.—To a stirred mixture of the nitrile **41** (10 g), sodium hydride (60%; 3.8 g) and ether (40 ml) was added dropwise, over 8 h, a mixture of ethyl formate (20 ml), ethanol (1 ml) and ether (40 ml). After a further 15 h, the sodium salt of the formylated nitrile was extracted into water (100 ml) [unchanged nitrile **41** (7 g) could be recovered from the ether layer.] The aqueous layer was neutralized (1M HCl) and extracted with chloroform (3 × 200 ml). The dried extracts were evaporated and the residue (*ca.* 2 g) in methanol (30 ml) was treated with anhydrous sodium acetate (0.92 g), aminoacetonitrile hydrochloride (0.92 g) and water (1 ml). The mixture was stirred for 20 h and then partitioned between chloroform (100 ml) and ice–water (40 ml). The washed, dried, organic layer was evaporated and chromatography of the residue on silica, with toluene–ether (4:1) as eluent, gave the *enaminonitrile* **42** (1.5 g, 13%) as an oily mixture (*ca.* 3:1) of isomers, unstable on storage; ν_{max}(film)/cm^{-1} 3350 (NH), 2200 (CN) and 1650 (C=C); δ_H(200 MHz) 1.6 (2 H, m, 2′-H_2), 1.95 (1 H, m, 3′-H), 2.2 (2 H, t, 1′-H_2), 3.02 (2 H, d, CH_2CN), 3.55 (4 H, m, CH_2OBn), 4.5 (4 H, m, CH_2Ph), 4.95 and 5.50 (1 H, 2 m, NH), 6.30 (0.3 H, d, *J* 12.8, 3-H), 6.43 (0.7 H, d, *J* 12.8, 3-H) and 7.37 (10 H, m, Ph); δ_C(50 MHz, major isomer) 24.4 (C-2′), 29.4 (C-1′), 34.4 (*C*H_2CN), 37.1 (C-3′), 73.1 (C-4′), 73.5 (CH_2Ph), 83.5 (C-2), 116.1 and 122.0 (CN), 128.1, 128.8, 137.8 and 146.4 (C-3) (Found: M^+, 389.2127. $C_{24}H_{27}N_3O_2$ requires 389.2102).

3-Amino-4-[4-benzyloxy-(3-benzyloxymethyl)butyl]-2-cyanopyrrole **44**.—A solution of compound **42** (2.0 g) in dichloromethane (45 ml) at 0 °C was treated with DBN (1.3 ml), followed by ethyl chloroformate (0.82 ml) in dichloromethane (5 ml). After 1 h the mixture was evaporated and the residue chromatographed on silica, with toluene–ether (2:1) as eluent to give the *N*-ethoxycarbonyl derivative **43** (1.1 g); δ_H(60 MHz) 1.3 (3 H, t), 1.4–2.4 (5 H, m), 3.4 (4 H, m), 4.2 (2 H, q), 4.4 (4 H, s), 4.8 (2 H, s) and 7.2 (11 H, m). This material in ether (20 ml) was treated with sodium hydride (60%; 0.3 g) and ethanol (0.1 ml) for 3 h at room temperature. Water was added, and the two-phase mixture was stirred vigorously for 1 h. The organic layer was separated, washed, dried and evaporated. Chromatography of the residue, eluting with toluene–ether (3:1), and recrystallization of the product from ether–light petroleum gave the pyrrole **44** (0.79 g, 40%), m.p. 92–93 °C; ν_{max}(KBr)/cm^{-1} 3340 (NH) and 2200 (C≡N); δ_H(200 MHz) 1.65 (2 H, m, 2′-H_2), 2.0 (1 H, m, 3′-H), 2.35 (2 H, m, 1′-H_2), 3.49 (4 H, AB of ABX, 2 × CH_2OBn), 4.48 (4 H, s, CH_2Ph), 6.39 (1 H, d, *J* 3.1, 5-H) and 7.3 (10 H, m, Ph); δ_C(50 MHz) 21.1 (C-2′), 28.8 (C-1′), 38.7 (C-3′), 71.1 (C-4′), 73.2 (*C*H_2Ph), 86.5, 113.5, 115.2 (CN), 121.4 (C-5), 127.8, 128.4, 138.4 and 142.1 (Found: MH^+ (FAB) 390.2163. $C_{24}H_{28}N_3O_2$ requires 390.2180. Found: C, 74.0; H, 7.0; N, 10.7. $C_{24}H_{27}N_3O_2$ requires C, 74.0; H, 6.9; N, 10.8%).

4-Amino-7-[4-benzyloxy-(3-benzyloxymethyl)butyl]pyrrolo[3,2-d]pyrimidine **45**.—The pyrrole **44** (0.3 g) and formamidine acetate (0.25 g) were heated under reflux in ethanol (10 ml) for 5 h. The residue after evaporation was partitioned between ether and water. The washed, dried ether layers were evaporated to provide a solid which on recrystallization from ether–light petroleum gave the *pyrrolopyrimidine* **45** (226 mg, 70%) as white crystals, m.p. 82–83 °C; ν_{max}(KBr)/cm^{-1} 3420, 3100 (NH) and 1650; δ_H(200 MHz, CD_3OD) 1.75 (2 H, m, 2′-H_2), 1.94 (1 H, m, 3′-H), 2.71 (2 H, m, 1′-H_2), 3.5 (4 H, m, 2 × CH_2OBn), 4.44 (4 H, s, CH_2Ph), 7.10 (1 H, s, 6-H), 7.27 (10 H, m, Ph), 7.8 (1 H, br, NH) and 7.87 (1 H, s, 2-H); λ_{max}(EtOH)/nm 253 (ε 15 150) and 302 (5550) (Found: MH^+, 417.2251. $C_{25}H_{29}N_4O_2$ requires 417.2289. Found: C, 72.5; H, 6.9; N, 13.5. $C_{25}H_{28}N_4O_2$ requires C, 72.1; H, 6.7; N, 13.5%).

4-Amino-7-[4-hydroxy-(3-hydroxymethyl)butyl]pyrrolo[3,2-d]pyrimidine **13**.—The dibenzyl ether **45** (136 mg) and palladium-on-charcoal (5%; 30 mg) were heated under reflux in ethanol (8 ml) and cyclohexene (4 ml) for 12 h. The mixture was filtered, evaporated and recrystallized from ethanol–chloroform to give the *diol* **13** (40 mg, 52%), m.p. 260–262 °C; ν_{max}(KBr)/cm^{-1} 3500–3100 (NH, OH) and 1670; δ_H(270 MHz, [$^2H_6$]-DMSO) 1.6 (3 H, m, 2′-H_2, 3′-H), 2.70 (2 H, m, 1′-H_2), 3.45 (4 H, m, CH_2OH), 6.65 (2 H, br s, NH_2), 7.30 (1 H, s, 6-H), 8.07 (1 H, s, 2-H) and 10.6 (1 H, br s, NH); λ_{max}(EtOH)/nm 253 (ε 13 540) and 302 (6000) [Found: C, 55.5; H, 6.8; N, 20.3. $C_{11}H_{16}N_4O_2$ requires C, 55.9; H, 6.8; N, 23.7%. Found: MH^+ (FAB) 237.1327. $C_{11}H_{17}N_4O_2$ requires 237.1350].

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