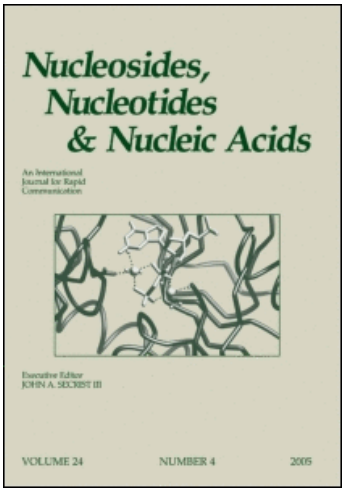

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A Direct Approach to the Synthesis of Famciclovir and Penciclovir

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A DIRECT APPROACH TO THE SYNTHESIS OF FAMCICLOVIR AND PENCICLOVIR

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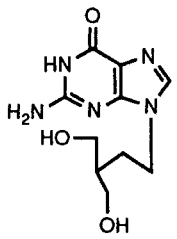
Abstract : Reaction of 2-amino-6-chloropurine with triethyl 3-bromopropane-1,1,1-tricarboxylate followed by decarbethoxylation/transesterification of the unpurified product was the key sequence in synthesising both the anti-herpesvirus agent penciclovir and its oral form famciclovir in three isolated steps.

Penciclovir **1** and its oral form famciclovir **2** are potent and selective anti-herpesvirus agents[1]. Although closely structurally related, penciclovir has a terminally dihydroxylated isoamyl side chain attached to the N-9 of a guanine nucleus, whereas in famciclovir the side chain hydroxyl functions are acetylated, and the guanine nucleus is replaced by a similarly N-9 alkylated 2-aminopurine.



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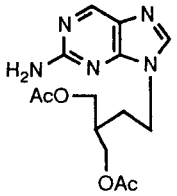
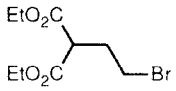


2

We required a concise, efficient synthesis allowing the moderate to large scale preparation of both of these target molecules, achievable in a single step from a common precursor. Most of the published syntheses of penciclovir[2] and famciclovir[3] are designed such that the majority of the chemistry on the side chain is conducted prior to purine alkylation. This strategy allows minimum consumption of formerly scarce purine reagents, and the least likelihood of side chain chemistry conflicting with functionality present on the purine nucleus, but suffers from the need to purify a number of liquid intermediates. We, however, envisaged a purine alkylation at an early stage to allow facile and inexpensive purification by crystallisation of the resulting solids.

The choice for the purine reagent for this synthesis was 2-amino-6-chloropurine **3**[4]. This material is nowadays readily available, and N-alkylated derivatives are easily transformed to the corresponding guanines by acid hydrolysis, or 2-aminopurines by hydrogenation. The desired reagent for introduction of the five carbon side chain was less obvious, but needed to be readily accessible from a commercially available precursor, if not obtainable itself.



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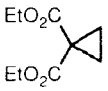
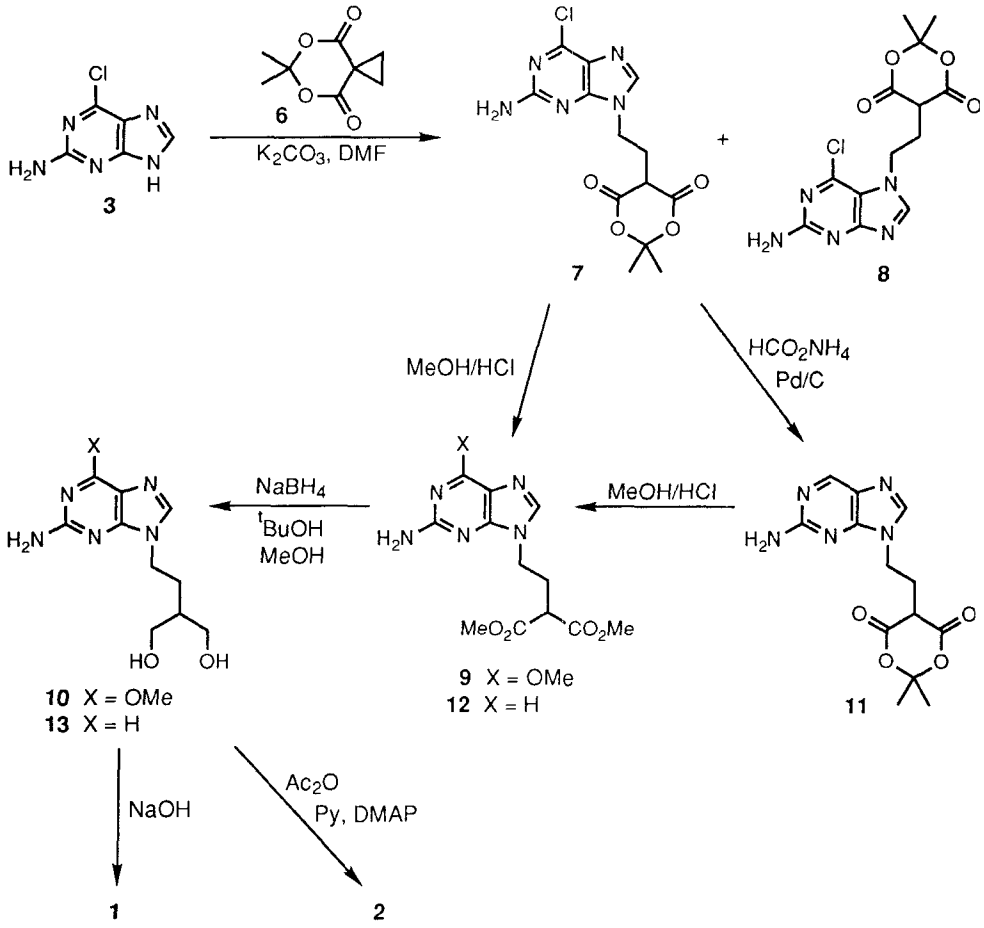


5

Perhaps a first choice would be diethyl-2-(2-bromoethyl)malonate **4**, but this molecule is known to be inaccessible, readily undergoing intramolecular cyclisation to the cyclopropane **5**. The diester cyclopropane **5** undergoes nucleophilic attack with concomitant ring opening, but only under harsh conditions[5]. However, the commercially available cyclic analogue **6** is much more susceptible to this type of reaction, and was therefore the subject of initial studies to find a suitable N-alkylating agent for our purposes[6].

Reaction of 2-amino-6-chloropurine **3** with **6** under basic conditions was straightforward, and as expected afforded a mixture of the N-9 and N-7 alkylated isomers **7** and **8**, (Scheme 1). However, the regioselectivity was poor (less than 2:1 in favour of the desired N-9 isomer **7**), and isolation of the products was complicated by their acidity at C-3'. Chromatographic work-up resulted in **7** and **8** being isolated as their water-soluble potassium salts, the neutral molecules being obtained by acidifying their aqueous solutions.

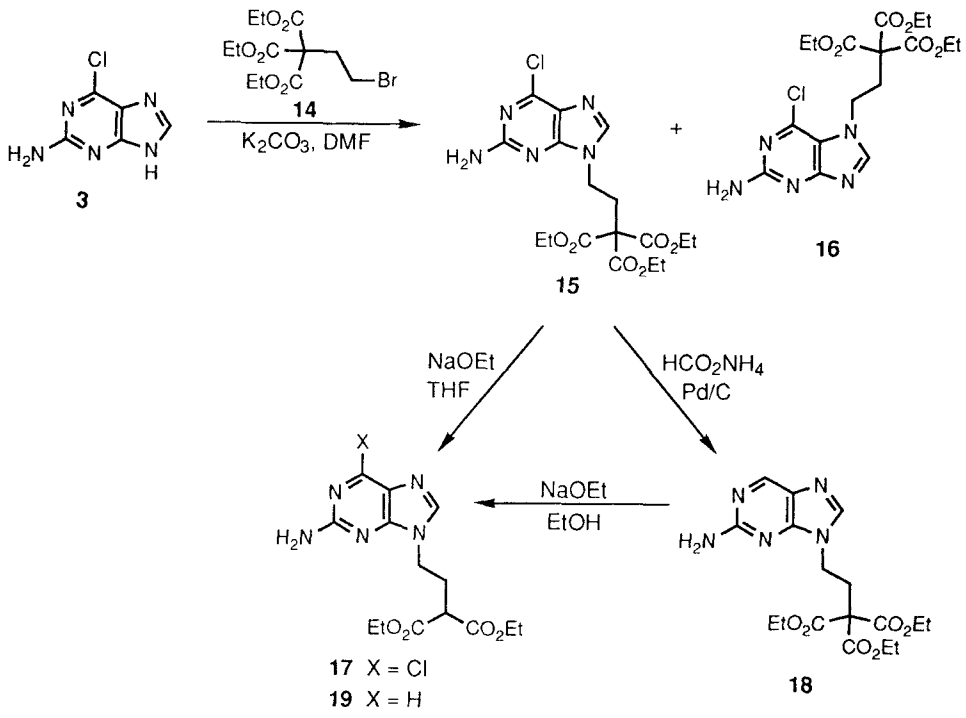
The acidity of the C-3' proton in **7** also compromised the subsequent ester reduction, transesterification being required before clean diol formation was observed.



Scheme 1

The use of methanolic hydrogen chloride for this purpose resulted in the 6-chloro function being transformed to the methyl ether **9**. From **9**, the preparation of penciclovir **1** was uneventful, just requiring reduction to the diol **10** (the sodium borohydride/methanol/*tert*-butanol method worked well[7]), and basic cleavage of the 6-methoxy group.

For famciclovir **2**, the 6-chloro function of **7** was first reduced hydrogenolytically to give the 2-amino purine **11**, followed by transesterification of **11** to the dimethyl ester **12**. Ester reduction to the diol **13** and subsequent O-acetylation afforded **2** in five steps overall.

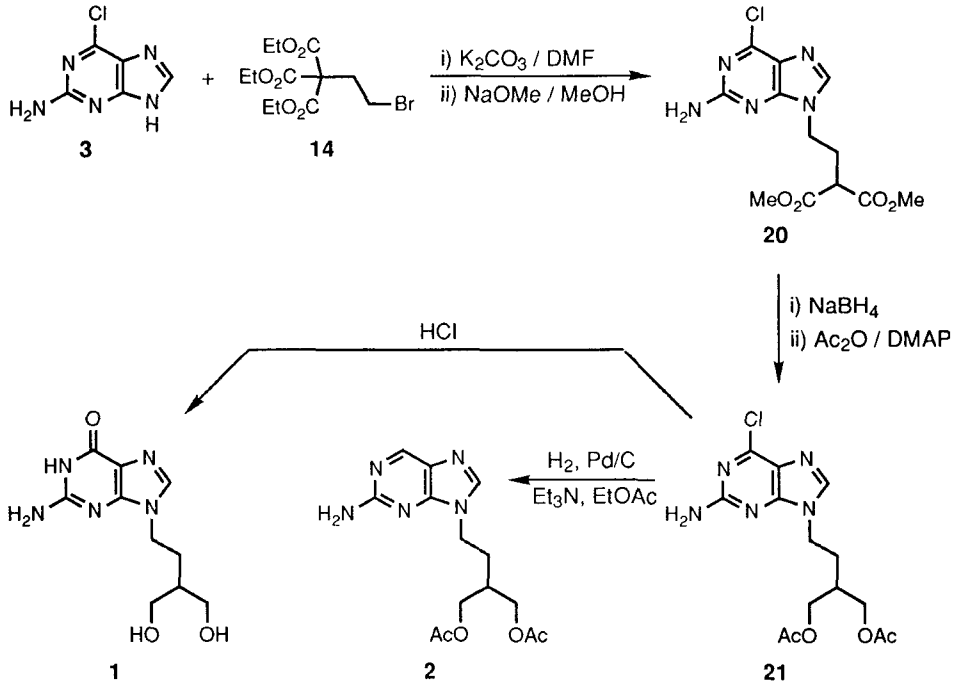


Scheme 2

Although this synthesis offered concise preparations of both penciclovir **1** and famciclovir **2**, the overall yields were poor, and there were other drawbacks, particularly in purifying and conducting chemistry on **7** and similar compounds. The paths to **1** and **2** also diverged at an early stage. We therefore examined the use of an alternative surrogate for **4**, triethyl 3-bromopropane-1,1,1-tricarboxylate **14**[5,8]. Although not itself commercially available, it is easily prepared in quantity by the method of Padgett *et al.*[5] from triethyl methane-1,1,1-tricarboxylate and 1,2-dibromoethane, both readily obtained.

Reaction of **3** with **14** was much slower than with **6**, requiring warming to achieve complete reaction in a reasonable time, but the N-9:N-7 product ratio was favourable (ca. 6.5:1, **15**:**16**), and the alkylated products were easily separated chromatographically, (Scheme 2). Treatment of **15** with sodium ethoxide in tetrahydrofuran effected smooth decarbethoxylation to give **17** (the 6-chloro function remaining intact), and the corresponding 2-aminopurine **19** was readily prepared *via* **18**.

Diester **19** is an obvious precursor to famciclovir **2** (c.f. **12**), whilst **17** is capable of furnishing both **1** and **2** in two or three steps, and is a pointer to the versatility ultimately required.



Scheme 3

Although this approach showed considerable promise, we were hoping to be able to reduce the number of isolated intermediates and avoid chromatography. Direct crystallisation of **15** gave only moderate recoveries, since not only was the N-7 isomer **16** a contaminant, but small amounts of the diethyl ester counterparts of **15** and **16** were usually present in the crude product mixture. However, it was found that purification at this stage was unnecessary. Instead, the crude isolate from the alkylation reaction was evaporated to a gum, which was treated with sodium methoxide in methanol, (Scheme 3). On cooling the resulting solution the dimethyl ester **20** crystallised directly in 68% yield, (the more polar N-7 isomer is much more soluble in this solvent). Sodium borohydride reduction of the methyl esters, and O-acetylation to give **21** was then accomplished, in 65% yield, without purification of the intermediate diol.

Both penciclovir **1** and famciclovir **2** are available in a single step from **21**, which fulfils the role of the desired late stage common intermediate[9]. The chemistry is robust and scales up well, typical overall yields of high quality material being 40-45% for penciclovir and 35-40% for famciclovir, (from **3**)[10]. This sequence therefore constitutes

an efficient synthesis of either target molecule in three isolated steps from available reagents.

EXPERIMENTAL

All ^1H NMR spectra were recorded on a Bruker AMX 400 spectrometer at 400MHz. All ^{13}C NMR spectra were recorded on the same instrument at 100MHz. Signals are quoted as δppm downfield from internal tetramethylsilane. Unless otherwise stated, all NMR spectra were obtained in hexadeuteriodimethyl sulphoxide solution.

All mass spectra were obtained on a Fisons VG Biotic Trio 2 instrument.

5-(2-(2-Amino-6-chloropurin-9-yl)ethyl)-2,2-dimethyl-1,3-dioxacyclohexane-4,6-dione 7, and
5-(2-(2-Amino-6-chloropurin-7-yl)ethyl)-2,2-dimethyl-1,3-dioxacyclohexane-4,6-dione 8.

A mixture of 2-amino-6-chloropurine **3** (10.4g, 61.4mmol), 2,2-dimethyl-1,3-dioxaspiro[5.2]octane-4,6-dione **6** (10.4g, 61.2mmol), and potassium carbonate (12.7g, 92.0mmol) in dry N,N-dimethylformamide was stirred at room temperature under an atmosphere of nitrogen for 16 hours. The reaction mixture was then filtered, and the filter cake washed well with N,N-dimethylformamide. Solvent evaporation afforded a brownish foam, which was purified by column chromatography on silica gel, eluting with 30-50% methanol in dichloromethane. Evaporation of the relevant fractions gave **7** (14.0g, 60%) and **8** (7.8g, 34%) as their potassium salts.

The neutral materials were obtained by dissolving the salts in water, acidifying with 2M HCl until no further precipitation was observed, filtering, washing with water and diethyl ether, and vacuum drying.

7, m.p. >300°C.

^1H NMR : 1.67 (s,3H,CH_3), 1.80 (s,3H,CH_3), 2.41 (m,2H,H-2'), 4.29 (t,2H,H-1'), 4.49 (t,1H,H-3'), 6.84 (brs,2H,NH_2), 8.14 (s,1H,H-8). ^{13}C NMR : 25.7 (CH_3), 26.1 (C-2'), 28.1 (CH_3), 40.9 (C-1'), 43.9 (C-3'), 105.1 (OCO), 123.5 (C-5), 143.2 (C-8), 149.3 (C-6), 154.4 (C-4), 159.7 (C-2), 165.5 (2xCO).

EI-MS 339 M^+, 238 $(MH\text{-}CO_2C(CH_3)_2O)^+$, 209 $(M\text{-}CO_2C(CH_3)_2O, CO)^+$.

Found; C:46.08, H:4.11, N:20.65. $C_{13}H_{14}N_5O_4Cl$ requires; C:45.96, H:4.15, N:20.61%.

8, m.p. >300°C.

^1H NMR : 1.68 (s,3H,CH_3), 1.82 (s,3H,CH_3), 2.45 (m,2H,H-2'), 4.4-4.6 (m,3H,H-1' and H-3'), 6.62 (brs,2H,NH_2), 8.36 (s,1H,H-8). ^{13}C NMR : 25.9 (CH_3), 27.6 (C-2'), 28.0 (CH_3), 44.0 (C-3'), 44.4 (C-1'), 105.1 (OCO), 115.1 (C-5), 142.6 (C-6), 149.2 (C-8),

160.0 (C-2), 163.6 (C-4), 165.6 (2xCO).
FAB-MS 340 MH^+, 238 $(M\text{-}CO_2C(CH_3)_2O)^+$.
Found; C:43.73, H:4.39, N:19.68. $C_{13}H_{14}N_5O_4Cl{\cdot}H_2O$ requires; C:43.65, H:4.51, N:19.58%.

Dimethyl 2-(2-(2-amino-6-methoxypurin-9-yl)ethyl)malonate 9.

The potassium salt of the N-9 alkylated purine **7** (1.70g, 4.5mmol) was suspended in methanol saturated with hydrogen chloride (35ml), the suspension diluted with methanol (35ml), and stirred at room temperature under an atmosphere of nitrogen for 16 hours to give a clear, yellowish solution. The solvent was evaporated, and the residue dissolved in water (70ml), neutralised with saturated sodium bicarbonate solution, and extracted with dichloromethane (5x100ml). The organic phases were combined, dried ($MgSO_4$), filtered and evaporated to give **9** as a pale glass, (1.27g, 87%).

The product was crystallised from n-butanol to give fine crystals, m.p. 136.5-137°C.
^1H NMR : 2.31 (q,2H,H-2'), 3.48 (t,1H,H-3'), 3.62 (s,6H,2xCH_3), 3.96 (s,3H,OCH_3), 4.08 (t,2H,H-1'), 6.39 (brs,2H,NH_2), 7.81 (s,1H,H-8). ^{13}C NMR : 28.2 (C-2'), 40.1 (C-1'), 48.3 (C-3'), 52.4 (2xCH_3), 53.0 (OCH_3), 113.7 (C-5), 139.5 (C-8), 154.1 (C-4), 159.7 (C-2), 160.5 (C-6), 168.7 (2xCO).
EI-MS 323 M^+, 179 $(MH\text{-}CH_2CH(CO_2CH_3)_2)^+$, 178 $(M\text{-}CH_2CH(CO_2CH_3)_2)^+$.
Found; C:48.34, H:5.23, N:21.52. $C_{13}H_{17}N_5O_5$ requires; C:48.30, H:5.30, N:21.66%.

2-Amino-6-methoxy-9-(4-hydroxy-3-hydroxymethylbutyl)purine 10.

The diester **9** (1.81g, 5.60mmol) was dissolved in t-butanol (66ml) at 60°C under an atmosphere of dry nitrogen. Sodium borohydride (1.05g, 27.7mmol) was added and the mixture heated under reflux while methanol (6.4ml) was added dropwise over 1.75 hours. The mixture was then cooled, methanol (50ml) added, and after effervescence had ceased the solvents were evaporated. The residue was dissolved in water (50ml) and the solution neutralised with 2M HCl. Evaporation afforded a colourless solid which was purified by column chromatography on silica gel, eluting with 15% methanol in dichloromethane. Evaporation of the relevant fractions gave the desired product **10** as a colourless gum (0.85g, 57%) which crystallised on trituration with methanol, m.p. 93-95°C.
^1H NMR : 1.45 (m,1H,H-3'), 1.74 (q,2H,H-2'), 3.36 (m,2H,H-4'), 3.41 (m,2H,H-5'), 3.96 (s,3H,OCH_3), 4.07 (t,2H,H-1'), 4.32 (t,2H,2xOH), 6.38 (brs,2H,NH_2), 7.86 (s,1H,H-8).
^{13}C NMR : 28.5 (C-2'), 40.7 (C-3'), 41.0 (C-1'), 53.8 (OCH_3), 61.2 (C-4',5'), 113.7 (C-5), 139.6 (C-8), 154.0 (C-4), 159.6 (C-2), 160.5 (C-6).
EI-MS : 267 M^+, 250 $(M\text{-}OH)^+$, 236 $(M\text{-}CH_2OH)^+$.

Found; C:48.18, H:6.79, N:23.53. $C_{11}H_{17}N_5O_3$·MeOH requires; C:48.15, H:7.07, N:23.40%.

9-(4-Hydroxy-3-hydroxymethylbutyl)guanine 1, from 10.

The diol **10** (2.0g, 7.5mmol) was dissolved in 2M sodium hydroxide solution (20ml), and heated to 90°C for 3 hours. The solution was allowed to cool, neutralised with 2molar HCl, and filtered to give the desired product **1** as a colourless solid, (1.44g, 76%), m.p. 275-277°C.

^{1}H NMR : 1.49 (m,1H,H-3'), 1.75 (q,2H,H-2'), 3.43 (m,4H,H-4',5'), 4.05 (t,2H,H-1'), 4.52 (t,2H,2xOH), 6.54 (brs,2H,NH_2), 7.75 (s,1H,H-8), 10.76 (brs,1H,NH). ^{13}C NMR : 28.9 (C-2'), 40.8 (C-3'), 41.2 (C-1'), 61.4 (C-4',5'), 116.6 (C-5), 137.6 (C-8), 151.3 (C-4), 153.5 (C-2), 157.1 (C-6).

CI-MS : 254 $(MH)^+$.

Found; C:47.44, H:5.95, N:27.64. $C_{10}H_{15}N_5O_3$ requires; C:47.43, H:5.97, N:27.65%.

5-(2-(2-Aminopurin-9-yl)ethyl)-2,2-dimethyl-1,3-dioxacyclohexane-4,6-dione 11.

A mixture of the chloro compound **7** (3.07g, 9.05mmol), ammonium formate (2.3g, 36.2mmol) and 5% palladium on charcoal (0.25g) in methanol (100ml) was heated under reflux for 3 hours. The mixture was cooled, filtered and evaporated to leave an off-white solid, which was recrystallised from methanol to give the ammonium salt of **11** (1.70g, 58%) as colourless crystals, m.p. >300°C.

^{1}H NMR : 1.40 (s,6H,2xCH_3), 2.55 (t,2H,H-2'), 4.04 (t,2H,H-1'), 6.44 (brs,2H,NH_2), 7.20 (brs,4H,NH_4), 7.91 (s,1H,H-8), 8.53 (s,1H,H-6). ^{13}C NMR : 24.8 (C-2'), 25.7 (2xCH_3), 41.9 (C-1'), 68.2 (C-3'), 99.1 (OCO), 126.9 (C-5), 142.6 (C-8), 148.4 (C-6), 153.0 (C-4), 160.2 (C-2), 165.4 (2xCO).

EI-MS 306 MH^+, 221 $(M\text{-}CO_2C(CH_3)_2)^+$.

Found; C:47.08, H:6.01, N:23.99. $C_{13}H_{18}N_6O_4$.MeOH requires; C:47.45, H:6.26, N:23.72%.

Dimethyl 2-(2-(2-aminopurin-9-yl)ethyl)malonate 12.

The dioxan **11** (140mg, 4.6mmol), was suspended in methanol saturated with hydrogen chloride (10ml), diluted with methanol (10ml), and stirred for 16 hours at room temperature. The resulting clear solution was evaporated, the residue dissolved in water (20ml) and neutralised with saturated sodium bicarbonate solution. The mixture was extracted with dichloromethane (6x25ml), the combined extracts dried ($MgSO_4$), filtered and evaporated to leave **12** (110mg, 82%) as an oil, which crystallised from water, m.p. 110-112°C.

^{1}H NMR : 2.32 (q,2H,H-2'), 3.49 (t,1H,H-3'), 3.58 (s,6H,2xCH_3), 4.10 (t,2H,H-1'), 6.45 (brs,2H,NH_2), 7.98 (s,1H,H-8), 8.54 (s,1H,H-6). ^{13}C NMR : 28.0 (C-2'), 39.9 (C-1'), 48.4 (C-3'), 52.4 (2xCH_3), 126.8 (C-5), 142.5 (C-8), 148.9 (C-6), 152.9 (C-4), 160.4 (C-2), 168.7 (2xCO).
EI-MS : 293 M^+, 149 $(MH\text{-}CH_2CH(CO_2CH_3)_2)^+$.
Found; C:49.23, H:4.97, N:23.76. $C_{12}H_{15}N_5O_4$ requires; C:49.14, H:5.16, N:23.88%.

2-Amino-9-(4-hydroxy-3-hydroxymethylbutyl)purine 13.

The dimethyl ester **12** (110mg, 0.38mmol) was dissolved in t-butanol (4.5ml), at 60°C under an atmosphere of dry nitrogen. Sodium borohydride (84mg, 2.22mmol) was added, the mixture heated under reflux, and methanol (0.4ml) added over 2hrs. The mixture was cooled, water (10ml) added, and the solution neutralised with 2M HCl. The solution was evaporated to leave a colourless solid, which was purified by column chromatography on silica gel, eluting with 33% methanol in chloroform to give the diol **13** as colourless crystals (50mg, 55%), m.p. 153-155°C (ethanol).
^{1}H NMR : 1.47 (m,1H,H-3'), 1.78 (q,2H,H-2'), 3.38 (m,2H,H-4'), 3.43 (m,2H,H-5'), 4.12 (t,2H,H-1'), 4.45 (t,2H,2xOH), 6.47 (brs,2H,NH_2), 8.07 (s,1H,H-8), 8.56 (s,1H,H-6). ^{13}C NMR : 28.5 (C-2'), 40.9 (C-1',3'), 61.4 (C-4',5'), 127.0 (C-5), 142.8 (C-8), 149.0 (C-6), 153.1 (C-4), 160.5 (C-2).
EI-MS : 237 M^+, 148 $(M\text{-}CH_2CH(CH_2OH)_2)^+$, 136 $(MH\text{-}CHCH_2CH(CH_2OH)_2)^+$.
Found; C:50.54, H:6.43, N:29.42. $C_{10}H_{15}N_5O_2$ requires; C:50.62, H:6.37, N:29.52%.

9-(4-Acetoxy-3-acetoxymethylbutyl)-2-aminopurine 2, from 13.

A mixture of the diol **13** (5.9g, 25mmol), acetic anhydride (5.7ml, 60mmol), pyridine, (6ml, 75mmol), and 4-dimethylaminopyridine (300mg) in dry tetrahydrofuran (100ml) was stirred at room temperature for 3 hours. The solvents were evaporated, and the residue dissolved in water (100ml) and extracted with dichloromethane (3x100ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to give an oil which was triturated with diethyl ether to give **2** as a pale solid (6.2g, 74%), m.p. 102-103°C (n-butanol).
^{1}H NMR : 1.88 (q,2H,H-2'), 1.93 (m,1H,H-3'), 2.00 (s,6H,2xCH_3), 4.04 (d,4H,H-4',5'), 4.15 (t,2H,H-1'), 6.48 (brs,2H,NH_2), 8.10 (s,1H,H-8), 8.59 (s,1H,H-6). ^{13}C NMR : 20.5 (2xCH_3), 27.8 (C-2'), 34.4 (C-3'), 40.1 (C-1'), 63.4 (C-4',5'), 126.9 (C-5), 142.6 (C-8), 148.9 (C-6), 152.9 (C-4), 160.4 (C-2), 170.3 (2xCO).
EI-MS : 321 M^+, 262 $(M\text{-}OCOCH_3)^+$.
Found; C:52.19, H:6.00, N:21.75. $C_{14}H_{19}N_5O_4$ requires; C:52.33, H:5.96, N:21.79%.

Diethyl 2-[2-(2-amino-6-chloropurin-9-yl)ethyl]-2-carbethoxymalonate 15, and Diethyl 2-[2-(2-amino-6-chloropurin-7-yl)ethyl]-2-carbethoxymalonate 16.

A mixture of 2-amino-6-chloropurine **3** (3.4g, 20mmol), triethyl 3-bromopropane-1,1,1-tricarboxylate **14** (6.8g, 20mmol), and potassium carbonate (4.15g, 30mmol) in dry N,N-dimethylformamide (75ml) was stirred at 40°C for 16 hours. The mixture was filtered, the filter cake washed well with N,N-dimethylformamide and the filtrate evaporated to give a gum. This was purified by column chromatography on silica gel, eluting with 3 to 5% methanol in dichloromethane. Evaporation of the relevant fractions afforded the N-9 and N-7 alkylated products, **15** and **16**.

15, 5.2g, 61%; m.p. 110-111°C (aq. ethanol).
^{1}H NMR : 1.19 (t,9H,3xCH_3), 2.61 (t,2H,H-2'), 4.18 (q,6H,3xOCH_2), 4.30 (t,2H,H-1'), 6.89 (brs,2H,NH_2), 8.05 (s,1H,H-8). ^{13}C NMR : 13.5 (3xCH_3), 31.8 (C-2'), 39.4 (C-1'), 62.2 (3xOCH_2), 63.6 (C-3'), 123.3 (C-5), 143.1 (C-8), 149.3 (C-6), 154.0 (C-4), 159.7 (C-2), 165.8 (3xCO).
EI-MS : 428 $(MH)^+$, 427 M^+, 196 $(M\text{-}C(CO_2Et)_3)^+$.
Found; C:47.92, H:5.15, N:16.47. $C_{17}H_{22}N_5O_6Cl$ requires; C:47.72, H:5.18, N:16.37%.

16, 0.8g, 9%; m.p. 140°C (dec.) (ethyl acetate).
^{1}H NMR : 1.19 (t,9H,3xCH_3), 2.60 (t,2H,H-2'), 4.17 (q,6H,3xOCH_2), 4.54 (t,2H,H-1'), 6.64 (brs,2H,NH_2), 8.25 (s,1H,H-8). ^{13}C NMR : 13.5 (3xCH_3), 33.7 (C-2'), 42.2 (C-1'), 62.3 (3xOCH_2), 63.4 (C-3'), 114.7 (C-5), 141.9 (C-6), 149.6 (C-8), 159.9 (C-2), 164.2 (C-4), 165.7 (3xCO).
EI-MS : 427 M^+, 355 $(MH\text{-}CO_2Et)^+$, 196 $(M\text{-}C(CO_2Et)_3)^+$.
Found; C:47.71, H:5.04, N:16.34. $C_{17}H_{22}N_5O_6Cl$ requires; C:47.72, H:5.18, N:16.37%.

Diethyl 2-[2-(2-amino-6-chloropurin-9-yl)ethyl]malonate 17.

A solution of the triester **15** (1.0g, 2.34mmol) in dry tetrahydrofuran (2.5ml) was added to a suspension of sodium ethoxide (0.48g, 7.0mmol) in dry tetrahydrofuran (7.5ml), and the mixture stirred at room temperature for 8hrs. The reaction was cooled in an ice bath, and acidified to pH2 with 2molar HCl (7ml), extracted with dichloromethane (3x25ml), and the combined organic extracts washed with water and brine, dried ($MgSO_4$), and evaporated to give a solid. This was purified by column chromatography on silica gel, eluting with 10% methanol in dichloromethane. Evaporation of the relevant fractions afforded the diester **17** (0.78g, 94%) as a colourless solid, m.p. 123-124°C.
^{1}H NMR : 1.14 (t,6H,2xCH_3), 2.35 (q,2H,H-2'), 3.49 (t,1H,H-3'), 4.05 (m,4H,2xCH_2O), 4.14 (t,2H,H-1'), 6.89 (brs,2H,NH_2), 8.08 (s,1H,H-8). ^{13}C NMR : 13.7 (2xCH_3), 27.7 (C-2'), 41.0 (C-1'), 48.8 (C-3'), 61.1 (2xCH_2O), 123.3 (C-5), 143.0 (C-8), 149.2 (C-6),

154.1 (C-4), 159.6 (C-2), 168.2 (2xCO).
CI-MS : 355 MH^+, 183 $(M\text{-}CH_2CH(CO_2Et)_2)^+$.
Found; C:47.35, H:4.97, N:19.64. $C_{14}H_{18}N_5O_4Cl$ requires; C:47.26, H:5.10, N:19.68%.

Diethyl 2-[2-(2-amino-purin-9-yl)ethyl]-2-carbethoxymalonate 18.

A mixture of the chloro compound **15** (21.4g, 0.05mol), ammonium formate (20g), and 5% palladium on charcoal (4g) in methanol (200ml) was heated under reflux for 2 hours. After cooling, the reaction mixture was filtered through Celite, and the solvent evaporated. The residue was taken up in water (400ml), and extracted with dichloromethane (3x200ml). The combined organic extracts were dried ($MgSO_4$), and evaporated to give **18** as a pale oil, (19.3g, 98%), which crystallised slowly on standing. An analytical sample was recrystallised from diethyl ether, m.p. 66-68°C.
^1H NMR : 1.21 (t,9H,3xCH_3), 2.62 (t,2H,H-2'), 4.18 (q,6H,3xOCH_2), 4.33 (t,2H,H-1'), 6.50 (brs,2H,NH_2), 7.98 (s,1H,H-8), 8.58 (s,1H,H-6). ^{13}C NMR : 13.6 (3xCH_3), 32.1 (C-2'), 38.9 (C-1'), 62.3 (3xOCH_2), 63.7 (C-3'), 127.1 (C-5), 142.7 (C-8), 149.0 (C-6), 153.1 (C-4), 160.6 (C-2), 166.0 (3xCO).
EI-MS : 393 M^+, 320 $(M\text{-}CO_2Et)^+$, 162 $(M\text{-}C(CO_2Et)_3)^+$.
Found; C:51.80, H:5.82, N:17.65. $C_{17}H_{23}N_5O_6$ requires; C:51.90, H:5.89, N:17.80%.

Diethyl 2-[2-(2-aminopurin-9-yl)ethyl]malonate 19.

To a stirred solution of sodium (6g, 0.26mol) in ethanol (300ml) was added a solution of the triester **18** (34.0g, 86mmol) in ethanol (200ml), resulting in the formation of a colourless precipitate. The mixture was stirred at room temperature for 1hr, then acidified to pH3 with 2M HCl giving a clear solution. The solvent was evaporated and the residue extracted with dichloromethane (2x250ml). The combined organic extracts were dried ($MgSO_4$), and evaporated to give a yellowish solid, which was recrystallised from n-butanol, affording **19** as off-white crystals, (21.5g, 78%), m.p. 94.5-95°C.
^1H NMR : 1.13 (t,6H,2xCH_3), 2.33 (q,2H,H-2'), 3.49 (t,1H,H-3'), 4.04 (m,4H,2xCH_2O), 4.13 (t,2H,H-1'), 6.48 (brs,2H,NH_2), 8.00 (s,1H,H-8), 8.56 (s,1H,H-6). ^{13}C NMR : 13.8 (2xCH_3), 28.0 (C-2'), 40.5 (C-1'), 48.9 (C-3'), 61.2 (2xCH_2O), 126.9 (C-5), 142.7 (C-8), 149.0 (C-6), 153.1 (C-4), 160.5 (C-2), 168.4 (2xCO).
EI-MS : 321 M^+, 149 $(M\text{-}CHCH(CO_2Et)_2)^+$.
Found; C:52.59, H:5.88, N:21.59. $C_{14}H_{19}N_5O_4$ requires; C:52.33, H:5.96, N:21.79%.

Dimethyl 2-[2-(2-amino-6-chloropurin-9-yl)ethyl]malonate 20.

A mixture of 2-amino-6-chloropurine **3** (9.18g, 53.1mmol), triethyl 3-bromopropane-1,1,1-tricarboxylate **14** (20.33g, 57.3mmol), and potassium carbonate

(11.1g, 80.3mmol) in dry N,N-dimethylformamide (190ml) was stirred at 60°C for 22 hours. The mixture was filtered while still warm, the filter cake washed well with N,N-dimethylformamide and the filtrate evaporated to give a gum. This was dissolved in methanol (140ml), cooled to 20°C, and a solution of sodium methoxide (1.2g) in methanol (40ml) added with stirring. Stirring was continued for 1 hour, during which time a precipitate formed. The reaction mixture was then cooled to 15°C and held at this temperature for 30 minutes. The product **20** (12.0g, 68%) was filtered off, washed with methanol (10ml) and dried.

An analytical sample, m.p. 140-141°C, may be obtained by recrystallisation from methanol.

^{1}H NMR : 2.35 (q,2H,H-2'), 3.55 (t,1H,H-3'), 3.62 (s,6H,2xCH_3), 4.14 (t,2H,H-1'), 6.90 (brs,2H,NH_2), 8.09 (s,1H,H-8). ^{13}C NMR : 27.8 (C-2'), 40.9 (C-1'), 48.4 (C-3'), 52.5 (2xCH_3), 123.3 (C-5), 143.0 (C-8), 149.2 (C-6), 154.1 (C-4), 159.7 (C-2), 168.7 (2xCO).

CI-MS : 328 MH^+.

Found; C:44.05, H:4.28, N:21.54. $C_{12}H_{14}N_5O_4Cl$ requires; C:43.96, H:4.27, N:21.37%.

9-(4-Acetoxy-3-acetoxymethylbutyl)-2-amino-6-chloropurine 21.

A mixture of dimethyl 2-[2-(2-amino-6-chloropurin-9-yl)ethyl]malonate **20** (32.7g, 0.1mol), sodium borohydride (11.5g, 0.3mol) and dichloromethane (125ml) was stirred at 20°C. Methanol (75ml) was added dropwise over a 2 hour period while the reaction temperature was maintained in the range 20-22°C with cooling, and the reaction was stirred for a further 1.5 hours. Water (100ml) was added, followed by the dropwise addition of conc. HCl (ca. 20ml) to pH 7.0, again maintaining the reaction temperature in the range 20-22°C with cooling. The organic solvents were removed under vacuum until a reaction volume of 150ml was reached. The reaction mixture was then cooled to 5°C, stirred at this temperature for 30 minutes, and the resulting precipitate filtered off and washed with cold water.

The damp solid was stirred with triethylamine (15ml) and 4-dimethylaminopyridine (1.0g) in dichloromethane (250ml). Acetic anhydride (75ml, 0.79mol) was added dropwise over 25 minutes at such a rate as to control the reflux. After completion of the addition, the reaction mixture was heated under reflux for a further 1.5hrs. The reaction was cooled to 20°C and neutralised with 20% w/w sodium hydroxide solution to pH 6.5. The organic phase was separated, and the aqueous extracted with dichloromethane (100ml). The combined organic phases were evaporated to dryness, and the resulting solid recrystallised from 3:1 methanol:water (75ml), cooling the precipitate to -5°C for 1hr before filtration. The product **21** (23.0g, 65%), m.p. 134-136°C was washed with cold 3:1 methanol:water, and dried.

^{1}H NMR : 1.88 (q,2H,H-2'), 1.94 (m,1H,H-3'), 2.01 (s,6H,2xCH_3), 4.04 (d,4H,H-4',5'), 4.16 (t,2H,H-1'), 6.89 (brs,2H,NH_2), 8.18 (s,1H,H-8). ^{13}C NMR : 20.5 (2xCH_3), 27.7 (C-2'), 34.4 (C-3'), 40.8 (C-1'), 63.4 (C-4',5'), 123.4 (C-5), 143.1 (C-8), 149.3 (C-6), 154.0 (C-4), 159.7 (C-2), 170.3 (2xCO).
EI-MS : 356 MH^+, 296 $(M\text{-}OCOCH_3)^+$.
Found; C:47.14, H:4.97, N:19.69. $C_{14}H_{18}N_5O_4Cl$ requires; C:47.26, H:5.10, N:19.68%.

9-(4-Hydroxy-3-hydroxymethylbutyl)guanine 1, from 21.

9-(4-Acetoxy-3-acetoxymethylbutyl)-2-amino-6-chloropurine **21** (14.8g, 42mmol) was dissolved in 2M HCl (150ml), and stirred under reflux for 3 hours. The solution was then cooled, basified to pH13 with 40% aqueous sodium hydroxide, and stirred for a further 90 minutes at ambient temperature. The solution was neutralised with conc. HCl, the vessel cooled, and the precipitate filtered off. Recrystallisation from water afforded the product **1** (9.9g, 94%) as colourless plates[2a].

9-(4-Acetoxy-3-acetoxymethylbutyl)-2-aminopurine 2, from 21.

A mixture of 9-(4-acetoxy-3-acetoxymethylbutyl)-2-amino-6-chloropurine **21** (15.4g, 43.mmol), 5% palladium on charcoal (6.16g), and triethylamine (6.6ml, 47mmol) was stirred at 50°C in ethyl acetate (77ml) under a hydrogen atmosphere of 1 bar pressure in an autoclave for 4 hours. The warm reaction mixture was then filtered through Celite, and the filter bed washed with warm ethyl acetate (60ml). The combined filtrates were washed with water (46ml), and evaporated to dryness to give a colourless solid. Recrystallisation from n-butanol gave **2** (11.3g, 81%) as colourless crystals[3a].

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REFERENCES AND NOTES

1. Harnden, M.R. *Drugs of the Future*, **1989**, *14*, 347-358; and references cited therein.
2. a) Pandit, U.K.; Grose, W.F.A.; Eggelte, T.A. *Synth. Commun.*, **1972**, *2*, 345-351. b) Tippie, M.A.; Martin, J.C.; Smee, D.F.; Matthews, T.R.; Verheyden, J.P.H. *Nucleosides, Nucleotides*, **1984**, *3*, 525-535. c) Harnden, M.R.; Jarvest, R.L. *Tetrahedron Lett.*, **1985**, *26*, 4265-4268. d) Harnden, M.R.; Jarvest, R.L.; Bacon, T.H.; Boyd, M.R. *J. Med. Chem.*, **1987**, *30*, 1636-1642. e) Hannah, J.; Tolman, R.L.; Karkas, J.D.; Liou, R.; Perry, H.C.; Field, A.K. *J. Het. Chem.*,

1989, *26*, 1261-1271. f) Choudary, B.M.; Geen, G.R.; Grinter, T.J.; MacBeath, F.S.; Parratt, M.J. *Nucleosides, Nucleotides*, **1994**, *13*, 979-996.

3. a) Harnden, M.R.; Jarvest, R.L.; Boyd, M.R.; Sutton, D.; Vere Hodge, R.A. *J. Med. Chem.*, **1989**, *32*, 1738-1743. b) Geen, G.R.; Grinter, T.J.; Kincey, P.M.; Jarvest, R.L. *Tetrahedron*, **1990**, *46*, 6903-6914. c) Geen, G.R.; Kincey, P.M.; Choudary, B.M. *Tetrahedron Lett.*, **1992**, *33*, 4609-4612.
4. a) Beecham Group PLC. *Eur. Pat.*, 203 685 A2, (1986). b) SmithKline Beecham PLC. *Wo. Pat.*, 92 13 859, (1992). c) Sumika Fine Chemicals Co. *Eur. Pat.*, 543 095, (1993).
5. Padgett, H.C.; Csendes, I.G.; Rapoport, H. *J. Org. Chem.*, **1979**, *44*, 3492-3496.
6. Danishefsky, S.; Singh, R.K. *J. Am. Chem. Soc.*, **1975**, *97*, 3239-3241.
7. Soai, K.; Oyamada, H.; Ookawa, A. *Synth. Commun.*, **1982**, *12*, 463-467.
8. Newkome, G.R.; Baker, G.R. *Org. Prep. Proc. Intl.*, **1986**, *18*, 117-144.
9. Harnden, M.R.; Jarvest, R.L.; Slawin, A.M.Z.; Williams, D.J. *Nucleosides, Nucleotides*, **1990**, *9*, 499-513.
10. SmithKline Beecham PLC. *Int. Pat. Appl.*, WO/28402, (1995).

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