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A New Route to Famciclovir via Palladium Catalysed Allylation

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Abstract—An efficient route to the acyclic nucleoside analogue famciclovir has been developed based on a palladium(0) catalysed coupling of 2-amino-6-chloropurine and an allylic carbonate sidechain derived from 2,2-dimethyl-1,3-dioxan-5-one. The reaction proceeds via a highly N-9 regioselective purine allylation step involving a novel palladium mediated N-7 to N-9 rearrangement.

Introduction

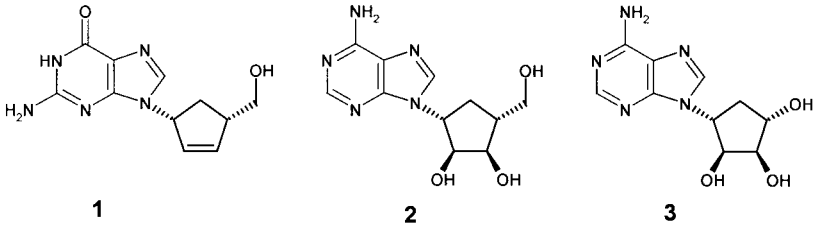
Purine nucleosides form an important class of pharmacologically active compounds demonstrating activity against a wide range of viral infections. The synthesis of these compounds has therefore attracted considerable interest.[1] In particular over recent years there have been numerous reports of the synthesis of carbocyclic analogues of nucleosides via palladium catalysed coupling between a purine base and a π-allyl system typically derived from a cyclopentenyl epoxide, carbonate or acetate. Examples include the syntheses of carbovir **1**,[2] aristeromycin **2**[3] and noraristeromycin **3**[4] (Fig. 1).

However, to date, while carbocyclic systems have attracted considerable attention, there has been no reported synthesis of an acyclic nucleoside analogue by this methodology. We now wish to report a novel concise approach to the pharmaceutically important antiherpetic nucleoside analogue famciclovir **4**[5] proceeding via an efficient regioselective palladium mediated allylation.

Results and Discussion

A number of approaches have been used to synthesise famciclovir.[5,6] Of these, the most frequently employed involves base mediated N-alkylation of a 6-substituted 2-aminopurine with an alkyl halide. A shortcoming of this methodology is the modest regioselectivity seen in the coupling step which leads to a mixture of N-9 and N-7 isomers.[7] Although regioselective alkylations of purines have been achieved by the use of α-halo or α-acetoxy ether alkylating agents[8] and Michael acceptors,[9] neither approach offers a convenient synthesis to famciclovir. The former approach is precluded by the all carbon backbone of the alkylating agent while the latter suffers from a problematic synthesis of the required chloroethylidene malonate sidechain. Therefore in an attempt to develop a more efficient synthesis of **4**, we decided to investigate the possibility of constructing the required molecular framework via a palladium catalysed allylation (Scheme 1).

The key step in this synthetic strategy involves coupling of the purine nucleus (conveniently the commercially



1 2 3

Figure 1.

Keywords: purine; allylation; rearrangement.

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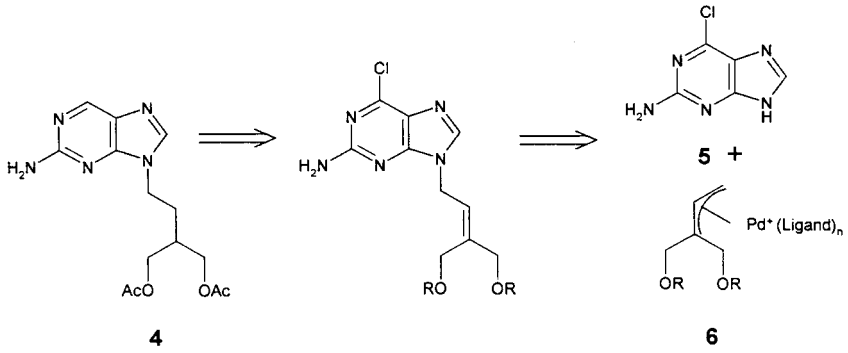
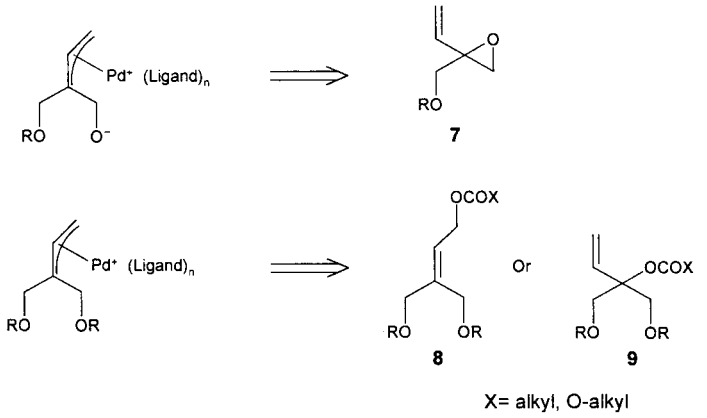


Scheme 1.

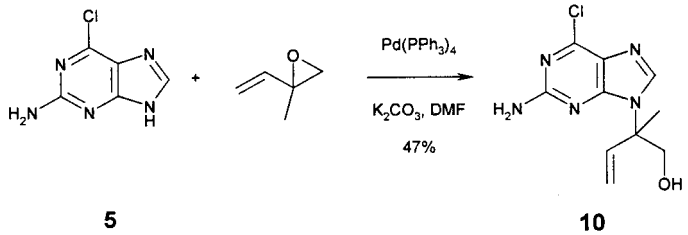
available 2-amino-6-chloropurine **5**) at the least substituted terminus of an acyclic π-allyl system **6**. The required sidechain for our approach, containing the protected 1,3-diol functionality, could conceivably be obtained from either an allylic epoxide **7** or an activated allylic alcohol **8** or **9** as shown below (Scheme 2).

Although there are numerous examples of palladium catalysed allylations of purines with carbocyclic π-allyl systems, there is little precedent in the literature for the corresponding reactions with acyclic sidechains.[10] Of the alternative sidechains, the use of allylic epoxides was considered initially. It has been reported that the palladium mediated reaction of nitrogen heterocycles with allylic epoxides does not give the required reaction at the terminus of the intermediate π-allyl system but instead proceeds via 1,2- or proximal attack.[11] Indeed in our hands, the model reaction involving coupling of **5** with isoprene monoepoxide failed to give the desired 1,4-regioselectivity but instead afforded the N-9 alkylated purine **10** as the major product (Scheme 3).

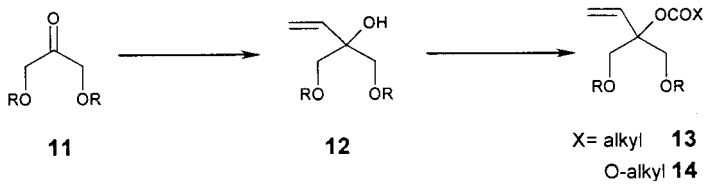
Attention then turned to the generation of the active π-allyl species from an allylic acetate or allylic carbonate sidechain. Either of the isomeric sidechains, **8** or **9** would be expected to lead to the required π-allyl system as the positional identity in the precursor is lost once the leaving group has departed. Although the allylic alcohol required for the preparation of **8** has been described,[12] a more concise approach to the allylic system **9** was conceived in which the required tertiary centre in the sidechain could be generated by addition of a vinyl carbanion to a 1,3-dioxygenated ketone **11**. Conversion of the intermediate alcohol **12** to the acetate **13** or preferably the more reactive alkyl carbonate **14**[13] would then generate the desired sidechain (Scheme 4).



Scheme 2.



Scheme 3.



Scheme 4.

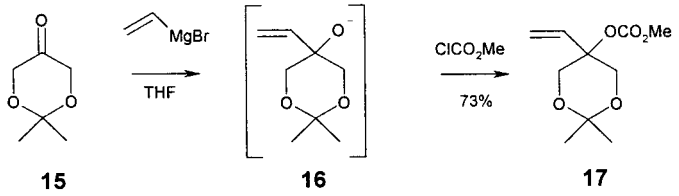
The dihydroxyacetone derivative, 2,2-dimethyl-1,3-dioxan-5-one **15**[14] provided a convenient starting point for the synthesis of the sidechain. Reaction of **15** with 2.4 equiv. of vinylmagnesium bromide and an in situ quench of the resulting alkoxide **16** with methyl chloroformate afforded the allylic carbonate **17** in 73% yield from **15** (Scheme 5).

Focus was then directed towards the coupling of **17** with the nucleoside base. Reaction of **5** and **17** in the presence of 10 mol% $Pd(PPh_3)_4$ at 60°C afforded a 2:1 ratio of **18** and **19** in a combined yield of 63% following column chromatography[15] (Scheme 6).

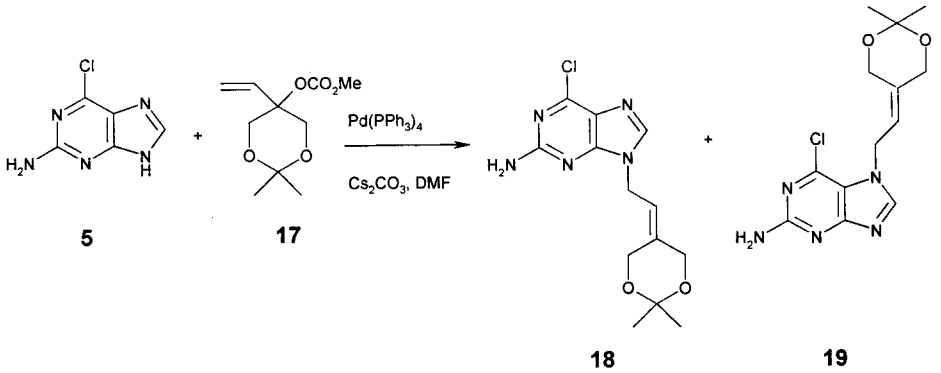
Although **18** was the major product from the above reaction, this result was disappointing as the N-9 selectivity was lower than that obtained from the corresponding coupling of **5** with alkyl halides (typically 5:1), and also the often highly selective couplings reported for carbocyclic π-allyl palladium species. It is known, however, that a number of factors influence the regioselectivity of purine alkylations including the size and nature of the electrophile.[10] Therefore it was decided to investigate whether the different steric and electronic properties offered by the wide range of available phosphine or phosphite ligands could affect the nature of the sidechain and hence influence the N-9 selectivity in the coupling step. A large number of catalyst/ligand combinations was investigated and the dramatic effect on both the efficiency and regioselectivity of the coupling can be seen in the examples shown in Table 1.

The results show a dramatic increase in the N-9:N-7 isomer ratio when the bidentate phosphine ligand, dppe is used in conjunction with Pd_2dba_3. The very high regioselectivity is attributable to the fact that the coupling reaction involves a two stage process. HPLC analysis of the reaction after 1 h found complete consumption of starting materials (**5** and **17**) with the formation of an equal amount of the two purine regioisomers. During the following stir period the ratio of **18** to **19** was then found to increase to >95:5. It would seem that for the combination of Pd_2dba_3 and dppe, the coupling of **5** with the π-allyl species is reversible, i.e. oxidative addition of Pd(0) to **19** regenerates the π-allyl species **20** which is then able to further alkylate the purine nucleus (Scheme 7). This cycle of oxidative addition and reductive elimination ultimately leads to a product mixture containing almost exclusively the thermodynamically preferred N-9 product.[6c] Although N-7 to N-9 alkyl migrations have been previously reported for substituted purines,[8,9] we believe this to be the first example of a such a rearrangement catalysed by palladium(0).

Further evidence to support the above mechanism was obtained when it was demonstrated that isolated **19** can be converted to **18** in the presence of the Pd_2dba_3/dppe catalytic species.[16]



Scheme 5.



Scheme 6.

Table 1. Notes: (a) Reaction conditions: 10 mol% Cs_2CO_3, DMF, 80°C, overnight. For entries 1–4: 5 mol% Pd_2dba_3, 20 mol% ligand. For entries 5–6: 5 mol% Pd_2dba_3, 10 mol% ligand. For entries 7–8: 10 mol% $Pd(OAc)_2$, 20 mol% ligand; (b) Pd_2dba_3—Tris(dibenzylideneacetone)dipalladium (0), TMPP—Trimethylolpropane phosphite, BINAP—(R)-(+)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl, dppe—1,2-Bis(diphenylphosphino)ethane; (c) Yields and isomer ratios were determined by HPLC analysis of reaction mixtures using reference samples of **18** and **19** of known purity and are corrected for peak area response

Entry No.	Pd source	Ligand	Yield **18** (%)	Ratio **18**:**19**
1	Pd_2dba_3	$P(OMe)_3$	60	3:1
2	Pd_2dba_3	$P(O^iPr)_3$	65	3:1
3	Pd_2dba_3	$P(OPh)_3$	0	–
4	Pd_2dba_3	TMPP	80	9:1
5	Pd_2dba_3	BINAP	46	2:1
6	Pd_2dba_3	dppe	85	35:1
7	$Pd(OAc)_2$	PPh_3	0	–
8	$Pd(OAc)_2$	TMPP	55	5:1

The rearrangement was found to be dependent on a precise set of conditions. The N-7 to N-9 migration is not observed with other classes of phosphine or phosphite ligands. Although an improved selectivity was obtained with the bicyclic phosphite ligand TMPP, the observed ratio of the isomeric purine products immediately following consumption of **5** and **17** did not change significantly on extended stirring. The sensitivity of the rearrangement step to the choice of ligand is further emphasised by the fact that even within the series of alkyl bidentate phosphines only dppe and to a lesser extent dppp promote the conversion of **19** to **18** (Table 2).

The efficiency of the rearrangement was shown to be dependent on a number of other factors. The optimum charge of the Pd_2dba_3 catalyst was 2.5 mol%. The stoichiometry of Pd_2dba_3 to donor ligand in the active catalytic species was found to be critical as increasing the ratio of dppe to

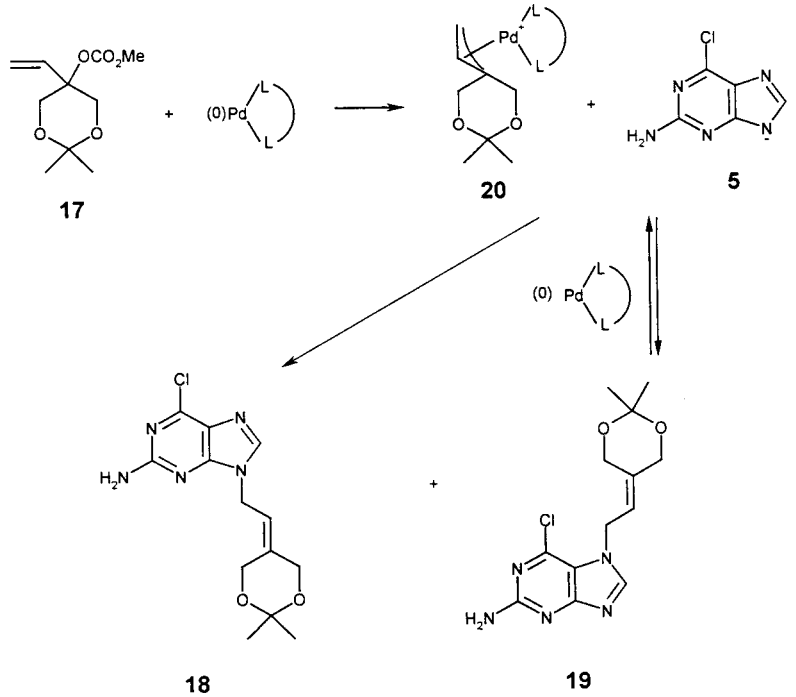
Table 2.

Ligand	N-9 to N-7 ratio
Bis(diphenylphosphino)methane (dppm)	2:1
1,2-Bis(diphenylphosphino)ethane (dppe)	35:1
1,3-Bis(diphenylphosphino)propane (dppp)	11:1
1,4-Bis(diphenylphosphino)butane (dppb)	1:1

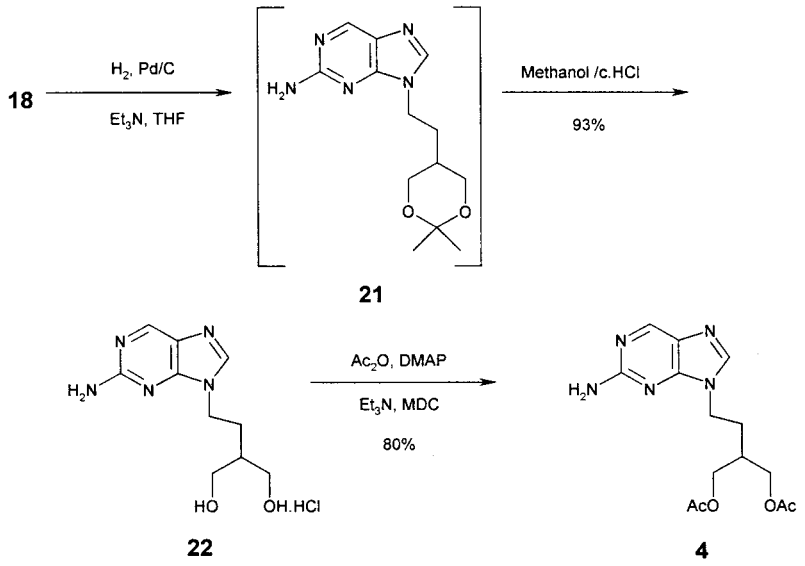
palladium(0) from 1:1 to 2:1 resulted in poor regioselectivity in the coupling reaction suggesting that saturation of the four donor sites in the palladium complex with phosphine donor atoms prevents the oxidative addition step to **19** necessary for the regeneration of the π-allyl system.[17] In addition to the stringent requirements for the palladium and ligand combination, a further requirement was a flow of inert gas either over or preferably bubbled through the reaction mixture. Although the precise reason for this effect has not been established, it is believed that either atmospheric oxygen or possibly carbon monoxide (present from decomposition of DMF at the elevated reaction temperatures) is more efficiently purged. It was shown that the rearrangement step is inhibited when the coupling reaction is carried out under an atmosphere of argon containing low levels of either of the two gases.[18]

Although palladium catalysed displacement of allylic carbonates can be carried out under neutral conditions,[19] the use of catalytic base was found to be essential for efficient reaction. Of the range of inorganic and amine bases investigated, 1 mol% Cs_2CO_3 gave the best results (i.e. 94% in situ yield of **18**). Increasing the charge of Cs_2CO_3 resulted in a lower yield due to product degradation.

The synthesis of famciclovir **4** was completed as shown below (Scheme 8). Hydrogenation of **18** over palladium



Scheme 7.



Scheme 8.

on carbon reduced both the double bond and the 6-chloro group. The facile reduction of the alkene moiety was carried out at 12–15°C to minimise a side reaction involving migration of the double bond into the dioxane ring.[20] The subsequent hydrogenolysis of the 6-chloro group to give **21** was then completed by heating the reaction mixture to 50°C.[21]

In situ hydrolysis of the acetonide protecting group in **21** by addition of concentrated hydrochloric acid resulted in the precipitation of the hydrochloride salt of the diol **22** which, following isolation, was acetylated to afford famciclovir **4** in an overall yield of 53% from **5**.

Conclusion

In conclusion we have developed a novel efficient route to famciclovir based on a palladium(0) catalysed allylation of 2-amino-6-chloropurine. This chemistry has now been run on a large laboratory scale to give pharmaceutical grade material.

Experimental

General

Melting points are uncorrected and were determined using either an Electrothermal IA9000 or Mettler FP90/FP81HT melting point apparatus. ^{1}H NMR spectra of isolated compounds were recorded on Bruker AMX400 spectrometers or on a Bruker AR400 NMR spectrometer tuned to 400 MHz. Samples were dissolved in deuterochloroform or d_6-dimethylsulphoxide. Signals are quoted as δppm downfield of trimethylsilane (TMS) by referencing internally to TMS or to residual protons of the NMR solvent. The values for coupling constants (J) are given in Hz. ^{13}C NMR spectra were recorded on the same instruments at 100 MHz and the chemical shifts reported in parts per million (ppm) down field of tetramethylsilane (TMS) by referencing to the ^{13}C signal of the NMR solvent. ^{1}H NMR analysis of reaction mixtures was carried out using a Bruker AC250 spectrometer tuned to 250 MHz (samples were concentrated prior to analysis and then dissolved in d_6-dimethylsulphoxide to obtain spectra). Mass spectra were obtained using a (Micromass) Trio-2 single quadrupole mass spectrometer. Elemental analyses were carried out at Surrey and Warwick Universities. Infrared spectra were recorded on a Perkin–Elmer 2000 or Perkin–Elmer Spectrum One FT-IR spectrometer. HPLC chromatograms were run on a Merck-Hitachi L400UV/L6200A system (eluent 80% 0.01 M ammonium acetate: 20% THF, Waters Symmetry C8 3.5 μm column 75×4.6 mm i.d., 1.0 mL/min flow, peak detection at 260 nm).

Preparation of 2-amino-6-chloro-9-(1-hydroxy-2-methylbut-3-en-2-yl)purine (10)

2-Amino-6-chloropurine **5** (4.25 g, 25 mmol), isoprene monoepoxide (2.3 g, 27.4 mmol), potassium carbonate (6.9 g, 50.0 mmol) and tetrakistriphenylphosphine palladium(0) (0.725 g, 0.63 mmol) were stirred in DMF (50 mL) under argon at room temperature overnight. The inorganics were removed by filtration and the filtrate concentrated to give an oil which was purified by silica gel chromatography (eluent dichloromethane/methanol 95:5) to give the title compound **10** as a white solid (2.95 g; 47%). mp 166–168°C (decomp.). (Found: C, 47.2; H, 4.8; N, 27.7; $C_{10}H_{12}ClN_5O$ requires C, 47.3; H, 4.8; N, 27.6%); ν_{max}cm^{-1} (Nujol mull) 3397, 3310, 1636, 1616, 1550, 913; δ_H (DMSO-d_6): 8.05 (1H, s, CH), 6.80 (2H, s, NH_2), 6.30 (1H, dd, J=17.5 and 10.8 Hz, C=CH), 5.25 (1H, dd, J=10.8 and 0.7 Hz, *cis* C=CH_2), 5.18 (1H, t, J=6 Hz, OH), 5.04 (1H, dd, J=17.5 and 0.7 Hz, *trans* C=CH_2), 4.13 (1H, dd, J=11.4 and 6 Hz, CH_2), 3.80 (1H, dd, J=11.4 and 6 Hz, CH_2), 1.75 (3H, s, CH_3); δ_C (DMSO-d_6): 158.98 (q), 154.20 (q), 149.59 (q), 142.35(CH), 138.79 (CH), 124.38 (q), 115.88 (CH_2), 65.07 (CH_2), 64.39 (q), 21.10 (CH_3); *m/z* 253 (M+).

Preparation of methyl 2,2-dimethyl-5-ethenyl-1,3-dioxane-5-carbonate (17)

2,2-Dimethyl-1,3-dioxan-5-one **15** (38.0 g, 0.29 mol) in THF (250 mL) was added dropwise to a 1 M solution of vinylmagnesium bromide in THF (700 mL, 0.7 mol) under argon, maintaining a temperature of less than −60°C. The reaction mixture was then cooled to −78°C and stirred at this temperature for 0.5 h. Methyl chloroformate (75 mL, 0.97 mol) was added dropwise and the resulting mixture was then stirred at −78°C for 15 min before being allowed to warm to room temperature. The solvent was then removed by evaporation under reduced pressure. Ethyl acetate (2×500 mL) was added and the solvent was removed by distillation after each addition. The residue was dissolved in ethyl acetate/hexane 40:60 and the resulting solution passed through a short silica column. The column was eluted with further ethyl acetate/hexane 40:60 (2×1 L) and the combined fractions concentrated to give an oil. The crude product was purified by silica column chromatography (eluent hexane/ ethyl acetate 90:10, then 85:15) to afford methyl 2,2-dimethyl-5-ethenyl-1,3-dioxane-5-carbonate **17** as a pale yellow oil (46.0 g, 73%). (Found: C, 55.4; H, 7.8; $C_{10}H_{16}O_5$ requires C, 55.5; H, 7.5%); $\nu_{max}cm^{-1}$ (Neat) 2993, 1750 and 1442; δ_H ($CDCl_3$): 6.01 (1H, dd, J=11.3 and 17.8 Hz, =CH), 5.35 (1H, d, J=17.8 Hz, *trans*=CH_2), 5.33 (1H, d, J=11.3 Hz *cis* =CH_2), 4.10 and 3.96 (4H, abq, J=12.6 Hz, 2×CH_2), 3.75 (3H, s, OCH_3), 1.44 (3H, s, CH_3), 1.42 (3H, s, CH_3); δ_C ($CDCl_3$): 154.01 (q), 135.18 (CH), 117.05 (CH_2), 98.76 (q), 78.30 (q), 65.44 (CH_2), 54.54 (CH_3), 25.26 (CH_3), 21.45 (CH_3); *m/z* 217 (M+1).

2,2-Dimethyl-5-[2-(2-amino-6-chloropurin-9-yl)]-ethylidene-1,3-dioxane (18)

1,2-Bis(diphenylphosphino)ethane (0.378 g, 0.95 mmol) was dissolved in DMF (22 mL) under argon. Tris(dibenzylideneacetone)dipalladium(0) (0.435 g, 0.475 mmol) was added and the resulting solution was degassed under vacuum and then stirred under argon for 10 min. The pre-formed catalytic species was then added to a stirred suspension of methyl 2,2-dimethyl-5-ethenyl-1,3-dioxane-5-carbonate **17** (4.32 g, 20 mmol), 2-amino-6-chloropurine **5** (3.21 g, 18.9 mmol) and cesium carbonate (0.063 g, 0.19 mmol) in degassed dimethylformamide (45 mL) maintained under argon at room temperature. The mixture was heated to 80°C and stirred at this temperature for 7.5 h. After standing overnight at room temperature the reaction mixture was filtered and concentrated to give a gummy solid which was slurried in methanol, filtered and then recrystallised from methanol to give the title compound **18** (4.2 g, 72% yield). mp 158–159°C. (Found: C, 50.1; H, 5.1; N, 22.4; $C_{13}H_{16}ClN_5O_2$ requires C, 50.4; H, 5.2; N, 22.6%); $\nu_{max}cm^{-1}$ (Neat) 3466, 3291, 3182, 1615, 1558, 1466; δ_H (DMSO-d_6): 8.12 (1H, s, CH), 6.91 (2H, s, NH_2), 5.45 (1H, t, J=7.0 Hz, CH), 4.65 (2H, d, J=7.0 Hz, CH_2), 4.55 (2H, s, CH_2), 4.18 (2H, s, CH_2), 1.34 (6H, s, CH_3); δ_C (DMSO-d_6): 159.86 (q),153.87 (q),149.43 (q),142.84 (CH), 137.57 (q), 123.36 (q), 116.45 (CH), 98.64 (q), 62.85 (CH_2), 58.8 (CH_2), 39.34 (CH_2), 23.90 (CH_3); *m/z* 310 (M+1).

2,2-Dimethyl-5-[2-(2-amino-6-chloropurin-7-yl)]-ethylidene-1,3-dioxane (19)

This compound was isolated from the reaction mixture as a minor product by chromatography (dichloromethane/ methanol 95:5). mp 162–164°C (decomp.). (Found C, 50.2; H, 5.1; N, 22.4; $C_{13}H_{16}ClN_5O_2$ requires C, 50.4; H, 5.2; N, 22.6%); $\nu_{max}cm^{-1}$ (Neat) 3400, 3304, 3194, 2986, 1628, 1541, 1504; δ_H (DMSO-d_6): δ 8.39 (1H, s, CH), 6.65 (2H, s, NH_2), 5.45 (1H, t, J=6.6 Hz, CH), 4.92 (2H, d, J=6.6 Hz, CH_2), 4.51 (2H, s, CH_2), 4.19 (2H, s, CH_2), 1.34 (6H, s, CH_3); δ_C (DMSO-d_6): 164.21 (q), 159.92 (q), 149.06 (CH), 142.24 (q), 136.94 (q), 117.47 (CH), 114.83 (q), 98.49 (q), 62.77 (CH_2), 58.67 (CH_2), 42.74 (CH_2), 23.80 (CH_3); *m/z* 310 (M+1).

Rearrangement of 2,2-dimethyl-5-[2-(2-amino-6-chloropurin-7-yl)]ethylidene-1,3-dioxane (19)

Tris(dibenzylideneacetone)dipalladium(0) (17 mg, 0.018 mmol) and 1,2-bis(diphenylphosphino)ethane (13 mg, 0.033 mmol) were added to a solution of 2,2-dimethyl-5-[2-(2-amino-6-chloropurin-7-yl)]ethylidene-1,3-dioxane **19** (0.1 g, 0.32 mmol) in degassed DMF (20 mL). The resulting solution was stirred under a flow of argon at 80°C overnight. ^1H NMR showed the complete consumption of starting material and the formation of 2,2-dimethyl-5-[2-(2-amino-6-chloropurin-9-yl)]ethylidene-1,3-dioxane **18** (60% solution yield determined by HPLC analysis of the reaction mixture).

Preparation of 2-amino-9-(4-hydroxy-3-hydroxymethylbut-1-yl)purine hydrochloride (22)

Palladium (5%) on carbon (100 g, 50% water paste) was stirred in THF (1400 mL) and triethylamine (100 mL, 0.72 mol). The vessel was purged with nitrogen and the catalyst slurry hydrogenated at 11°C and 50 psi for 1 h. A solution of 2,2-dimethyl-5-[2-(2-amino-6-chloropurin-9-yl)]ethylidene-1,3-dioxane **18** (200 g, 0.65 mol) in THF (4190 mL) was then added and the whole hydrogenated at 12–15°C for 2.5 h at 50 psi. The temperature was then increased to 50°C and hydrogenation continued overnight. The catalyst was removed by filtration and the filter washed with THF (750 mL). Methanol (1450 mL) was added to the combined filtrate and wash and concentrated hydrochloric acid (118 mL) added to the vigorously stirred solution. The resulting suspension was stirred at room temperature for 2.5 h. Filtration afforded 2-amino-9-(4-hydroxy-3-hydroxymethylbut-1-yl)purine hydrochloride **22** (164.4 g, 93%) as a white solid. mp 174–175°C. (Found C, 43.7; H, 6.1; N, 25.4; Cl, 13.1; $C_{10}H_{16}N_5ClO_2$ requires C, 43.8; H, 5.9; N, 25.6; Cl, 13.0%); $\nu_{max}cm^{-1}$ (Neat) 3328, 3078, 1666, 1431; δ_H (DMSO-d_6): 8.98 (1H, s, CH), 8.64 (1H, s, CH), 8.10 (2H, brs, NH_2), 4.19 (2H, t, J=7.4 Hz, CH_2), 3.45 (2H, dd, J=10.7 and 5.7 Hz, CH_2), 3.36 (2H, dd J=10.7 and 5.7 Hz, CH_2), 1.81 (2H, m, CH_2), 1.55–1.45 (1H, m, CH); δ_C (DMSO-d_6): 157.55 (q), 155.32 (q), 150.30 (CH), 139.62 (CH), 126.80 (q), 62.13 (CH_2), 42.8 (CH_2), 41.73 (CH), 28.99 (CH_2).

Preparation of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-aminopurine (4)

Acetic anhydride (109 mL, 1.15 mol) was added to a stirred suspension of 2-amino-9-(4-hydroxy-3-hydroxymethylbut-1-yl)purine hydrochloride **22** (150 g, 0.55 mol), triethylamine (266 mL, 1.9 mol) and 4-dimethylaminopyridine (3.03 g, 24.8 mmol) in dichloromethane (3 L) over 15 min at 28–32°C. The resulting mixture was then stirred at ambient temperature for 2 h. Methanol (750 mL) was added and the solution stirred for 1 h before being evaporated to dryness. The crude solid was dissolved in water (1650 mL) and the aqueous solution extracted with dichloromethane (1900 and 950 mL). The combined organic extracts were washed with water (700 mL), dried over anhydrous sodium sulphate and concentrated to give an off white solid. The crude solid was recrystallised from hot propan-2-ol (930 mL) and the product collected by filtration, washed with cold propan-2-ol (125 mL) and then dried under vacuum to give the title compound **4** as a white solid (140.8 g, 80%). mp 102–103°C (Lit[5] mp 102–104°C). (Found C, 52.3; H, 6.0; N, 22.2; $C_{14}H_{19}N_5O_4$ requires C, 52.3; H, 6.0; N, 21.8%); δ_H (DMSO-d_6): 8.57 (1H, s, CH), 8.09 (1H, s, CH), 6.47 (2H, s, NH_2), 4.14 (2H, t, J=7.2 Hz, CH_2), 4.03 (4H, d, J=5.6 Hz, CH_2), 1.99 (6H, s, CH_3), 1.99–1.95 (3H, m, CH and CH_2); δ_C (DMSO-d_6): 170.30 (q), 160.42 (q), 152.92 (q), 148.94 (CH), 142.60 (CH), 126.88 (q), 63.43 (CH_2), 40.16 (CH_2), 34.46 (CH), 27.81 (CH_2), 20.54 (CH_3).

All of the above analytical data are consistent with those obtained from an authentic sample of **4**.

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