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Synthesis and full characterisation of 6-chloro-2-iodopurine, a template for the functionalisation of purines

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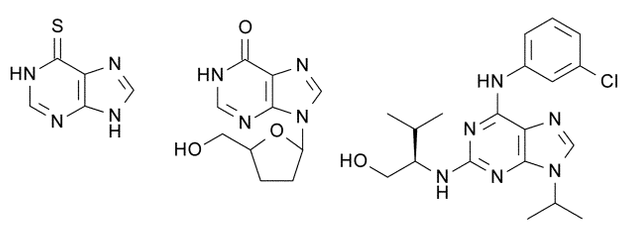
A simple and efficient synthesis of 6-chloro-2-iodopurine from hypoxanthine has been achieved. This strategy relied on a regiospecific lithiation/quenching sequence of 6-chloro-9-(tetrahydropyran-2-yl)purine using Harpoon's base and tributyltin chloride. HMBC NMR studies on the product and intermediates confirmed the regioselectivity of this methodology. The molecular structures of the final dihalogenopurine and its 9-protected precursor were determined by single crystal X-ray diffraction.

Introduction

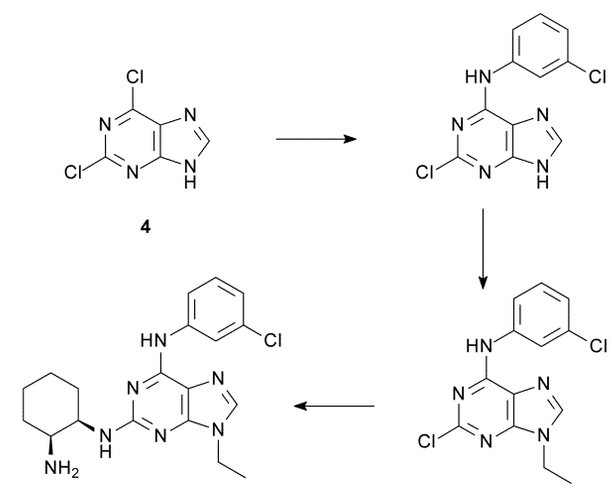
The biological importance of purine bases has long been recognised. Furthermore, some purine nucleosides and nucleotides have been found to act as crucial hormones, neurotransmitters or coenzymes. Isosteres of purines have been isolated from natural sources and have displayed significant anti-microbial and anti-cancer activity, leading to important new medicines.[1–3] Finally, the accelerated search for improved anti-tumour, anti-viral and anti-AIDS agents including a purine scaffold prompted a renewed interest in purine chemistry, resulting in numerous synthetic methodologies. Amongst the known synthetic purine analogues are 6-mercaptopurine **1**, used for treating leukaemia,[4] and dideoxyinosine (DDI) **2**, an anti-AIDS agent.[5] The more recent identification of 2,6,9-trisubstituted purines such as purvalanol A **3**,[6] as potent cyclin dependent kinase (CDK) inhibitors led to the preparation of chemical libraries of 2,6-diaminopurine analogues.[6,7] These ubiquitous enzymes are key players in the control and timing of cellular proliferation and various families of CDK inhibitors have shown important therapeutic potential as antineoplastic agents.[8]



1 **2** **3**

The available synthetic methodologies for the preparation of 2,6-diaminopurine analogues of **3** are all based on the nucleophilic displacement of 2,6-dihalogenopurines with primary amines. 2,6-Dichloropurine **4** is a commercially available, albeit expensive, starting material that can afford analogues of purine **3** as shown on Scheme 1.[9] Following displacement of the 6-chloro substituent with various anilines, selective N-(9)-alkylation with an alkyl iodide is possible. Finally, nucleophilic displacement at C-(2) is achievable at higher temperature (150 °C) with *cis*-2-aminocyclohexylamine. Alternatively, a total synthesis of 6-chloro-2-iodo-9-isopropylpurine **5** has been reported from 2,5-diamino-4,6-dihydroxypyrimidine (see below, Scheme 2).[10]

Due to the higher reactivity of the 2-iodide,[11] milder conditions for the nucleophilic displacement with amines with respect to the 2-chloride of purine **4** are possible. However, despite the practical advantages over 2,6-dichloropurine, we found the chlorinating step difficult to implement and low yielding.



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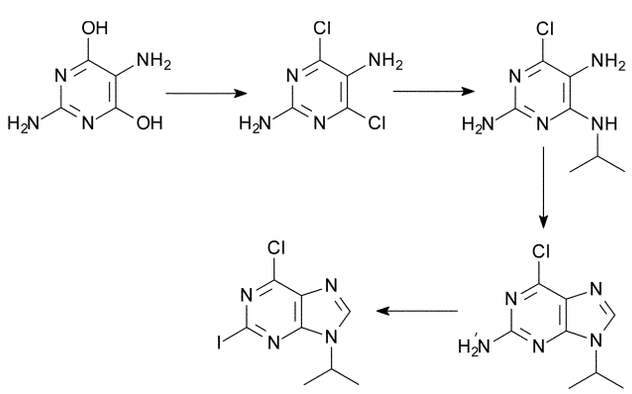
Scheme 1



5

Scheme 2

In our efforts to prepare 6-chloro-2-iodopurine as a template for the preparation of purine CDK inhibitors, we have developed a total synthesis of this novel heterocyclic compound using a regiospecific lithiation–quenching sequence with Harpoon's base (lithium 2,2,6,6-tetramethylpiperidide) and tributyltin chloride. The 2-stannylated purine was subsequently reacted with iodine to afford the 2-iodo derivative in high yield. The present paper describes a new synthetic route for 6-chloro-

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2-iodopurine, including full NMR and crystallographic characterisation of the product and intermediates.

Results and discussion

Preparation of 6-chloro-2-iodopurine

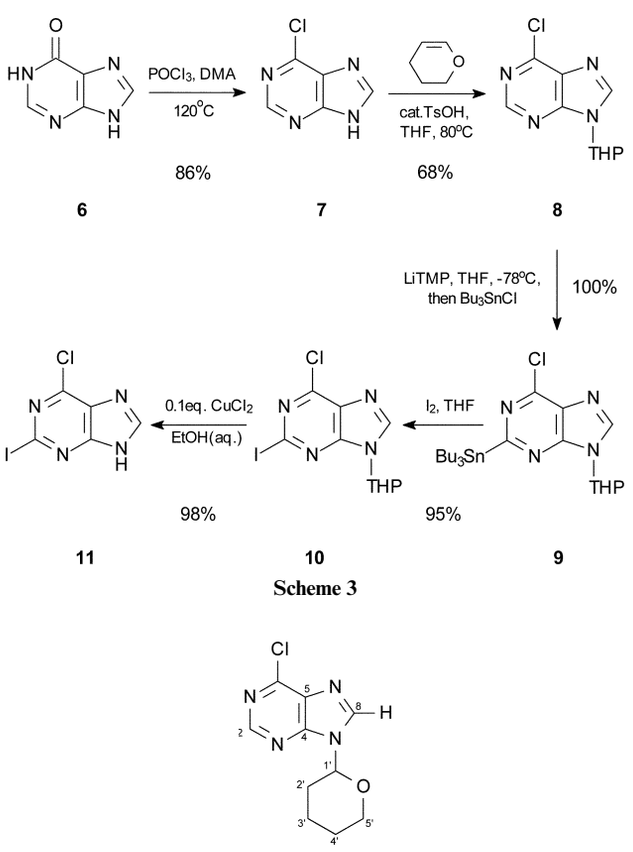
When hypoxanthine **6** was treated with excess phosphorus oxychloride in the presence of *N*,*N*-dimethylaniline at 120 °C for 2 hours under a nitrogen atmosphere,[12] 6-chloropurine **7** was isolated as monohydrated crystals in 86% yield, after two recrystallisations of the crude solid from boiling water (see Scheme 3). The purine N-9 was protected as the tetrahydropyran-2-yl (THP) derivative **8** by reacting **7** with the carbocation formed *in situ* from 2,3-dihydropyran and catalytic amounts of *p*-toluenesulfonic acid in refluxing THF. The regioselectivity of this reaction had been extensively investigated in previous reported work by UV-VIS spectroscopy[13] and similar studies have also shown that reactions of 6-chloropurine with carbocations are selective for N-9.[14] We found from NMR and X-ray diffraction studies of crystals of **8** that the N-7 isomer was not present in the recrystallised product. It must be noticed that the THP carbon C1′ is stereogenic thus purine **8** was obtained as a mixture of enantiomers. Further PENDANT and ^{1}H–^{13}C HMBC (Heteronuclear Multiple Bond Connectivity) experiments enabled the complete regiochemical assignment of the 9-THP product **8**. According to the structure of **8** shown below, the purine carbon atoms are all bound to two electronegative atoms, apart from C-5, thus the highest field ^{13}C resonance in the aromatic region (δ 131.3) was assigned to C-5. In theory, $^{3}J(^{1}H–^{13}C)$ long-range couplings would be observed between H-8 and the purine carbons C-5 and C-4, even possibly with the THP carbon C-1′. Indeed, such couplings were seen by HMBC NMR between a purine proton (δ 8.79), C-5 (δ 131.3) and another aromatic carbon, which is assignable to the purine C-4 (δ 151.6). Furthermore, the regiospecificity of the N-9 protection was confirmed since $^{3}J(^{1}H–^{13}C)$ couplings were observed between the lowest field aliphatic THP proton H-1′ (δ 5.76) and the purine carbons C-8 (δ 145.1) and C-4 (δ 151.6).

Due to the presence of two acidic protons, H-2 and H-8, treating the 9-THP purine **8** with a strong deprotonating base could produce complex mixtures of mono and dilithiated species. However, according to the work of Tanaka *et al.*,[15] then of the Legraverend group,[16] a regioselective 2-lithiation of 6-chloropurine derivatives is achievable at low temperature in THF with 5 equivalents of Harpoon's base (lithium 2,2,6,6-tetramethylpiperidide). Quenching the lithiated species with 5 equivalents of tributyltin chloride affords, after chromatography on silica gel, the 2-stannylated product exclusively in very high yields.

Using these conditions, we managed to prepare quantitatively the 2-stannylated purine **9**. Full characterisation by NMR, IR, low and high resolution MS and elemental analysis was obtained after purification of the crude oil by flash chromatography on silica gel with hexane/ethyl acetate (4 : 1). ^{1}H NMR showed only one purine proton (δ 8.15), assignable to either H-8 or H-2, as a result of a 2- or 8-substitution respectively. The ^{1}J, ^{2}J, and $^{3}J(^{13}C–^{119}Sn)$ couplings between the tin atom and the corresponding *n*-butyl aliphatic carbons were observed in ^{13}C NMR. As for its precursor **8**, $^{1}H–^{13}C$ correlation by long-range coupling enabled the verification of the regioselectivity of this lithiation-quenching strategy and full assignment of the 2-tributylstannylated purine **9** was thus possible. As previously, $^{3}J(^{1}H–^{13}C)$ correlations were detected between H-8 (δ 8.15) and the purine carbons C-5 (δ 129.2) and C-4 (δ 149.1). Besides, another couple of $^{1}H–^{13}C$ correlations of the THP proton H-1′ (δ 5.71), the lowest field aliphatic proton resonance due to the electronegative atoms N-9 and the THP oxygen, were seen with C-8 (δ 140.6) and C-4 (δ 149.1).

While often highly toxic, organotin compounds such as the purine derivative **9** undergo a range of useful substitution reactions with various electrophiles under mild conditions. Access to 2-halogenopurines (iodo, bromo, chloro[15] and even fluoro[17]) is possible. The Stille reaction enables C–C bond formation to synthesise the 2-benzyl, -phenyl, -alkenyl, and -alkynyl analogues of **9**.[15,18] Reacting **9** with excess iodine at room temperature in THF afforded the 2-iodopurine **10** in 95% yield, after trituration in *n*-hexane to separate the product from the very soluble purine **9** and the tributyltin iodide by-product. Flash chromatography on silica gel with ethyl acetate/*n*-hexane (1 : 1) was used when the product required further purification. The HMBC studies showed the same $^{3}J(^{1}H–^{13}C)$ correlations that were observed for the precursors **8** and **9** and are not reported here. Crystallographic studies by X-Ray Diffraction (XRD) of a single crystal of the 2-iodopurine **10** revealed the structure in Fig. 1.

Hydrolysis in acidic conditions has been used predominantly to cleave a tetrahydropyran-2-yl group from a protected amine,



Scheme 3

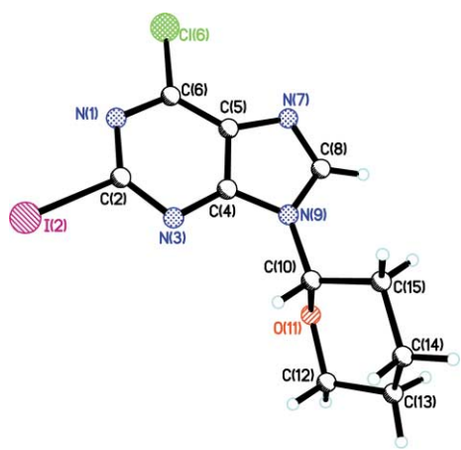


Fig. 1 Crystal structure of purine **10**.

Table 1 Selected bond lengths [Å] and angles [°] for purine **10** and **11**

Purine	**10**	**11**
Bond length		
Cl(6)–C(6)	1.730(4)	1.718(5)
I(2)–C(2)	2.108(4)	2.100(5)
C(2)–N(3)	1.325(5)	1.336(6)
N(1)–C(2)	1.335(6)	1.348(6)
N(1)–C(6)	1.321(6)	1.344(6)
C(4)–N(9)	1.370(6)	1.359(6)
C(4)–C(5)	1.403(6)	1.396(7)
C(5)–C(6)	1.378(6)	1.377(6)
C(5)–N(7)	1.385(5)	1.394(6)
N(7)–C(8)	1.299(6)	1.308(7)
C(8)–N(9)	1.375(5)	1.370(7)
N(9)–C(10)	1.454(6)	
C(10)–O(11)	1.432(5)	
C(10)–C(15)	1.507(6)	
C(12)–C(13)	1.496(7)	
Bond angle		
C(6)–N(1)–C(2)	116.2(4)	117.3(4)
N(3)–C(2)–N(1)	130.0(4)	128.2(4)
N(3)–C(4)–N(9)	127.7(4)	127.6(4)
C(2)–N(3)–C(4)	110.7(4)	111.7(4)
N(1)–C(6)–C(5)	122.3(4)	120.6(4)
N(1)–C(6)–Cl(6)	117.7(3)	117.9(3)
C(5)–C(6)–Cl(6)	119.9(3)	121.5(4)
C(8)–N(7)–C(5)	104.1(3)	103.4(4)
N(7)–C(8)–N(9)	114.7(4)	114.6(4)

while neutralisation of the aqueous solution with ammonia or sodium hydroxide afforded the free base.[19] Preliminary attempts with 2.5 M aqueous hydrochloric acid then water/trifluoroacetic acid (1 : 1), followed by neutralisation by dropwise addition of concentrated ammonia to precipitate the free base of purine **11** proved to be unsatisfactory. Refluxing the 9-THP purine **10** with 10 mol% of copper(II) dichloride in ethanol/water (95 : 5)[20] was however a highly efficient deprotection (98% yield). The isolation of analytically pure 6-chloro-2-iodopurine **11** product was achieved by flash column chromatography on silica gel using ethyl acetate/*n*-hexane (1 : 1). Single crystal structure determination confirmed the identity of **11** (Fig. 2). It appears that the recrystallisation solvent favoured the π-stacking of the heterocyclic rings as several hydrogen-bonds are found between the I(2), Cl(6) and N(7) atoms of the purine and the hydrogen atoms of water. Finally, a fourth type of hydrogen-bond within the structure was observed between the N(9)-hydrogen of the purine and the oxygen atom of water. Selected bond lengths and angles for purines **10** and **11** are given in Table 1.

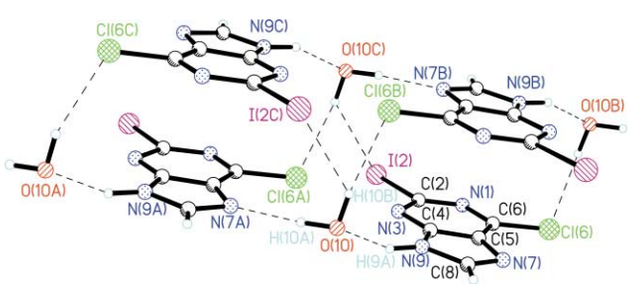
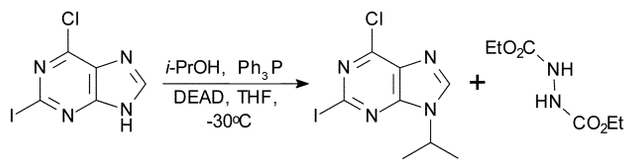


Fig. 2 Crystal structure of purine **11** (dotted lines represent H-bond interactions).

Synthetic applications of 6-chloro-2-iodopurine 11

Using Mitsunobu chemistry developed for selective N-9 alkylation of 6-chloro-2-aminopurine,[6] we reacted our 2-iodopurine **11** with isopropanol at −30 °C in THF in the presence of triphenylphosphine and diethyl azodicarboxylate. Following flash column chromatography of the residue after evaporation to dryness, the expected N-9 isopropyl analogue of **11** was isolated as an equimolar mixture with the diethyl hydrazine dicarboxylate side-product (Scheme 4 below). The original paper did mention that their N-alkylated purine was contaminated with both triphenylphosphine oxide and hydrazine side-products. However, the reaction was indeed found regiospecific for N-9 at this low temperature as no N-7 isomer was detected on ^{1}H NMR and the reaction yield was estimated to be 75%. Optimising the work-up and isolation procedures would lead to a six-step synthesis of 6-chloro-2-iodo-9-isopropylpurine **5**, a valuable intermediate in the synthesis of 2,6-diaminopurine CDK inhibitors.[10]



11 **5**

Scheme 4

Furthermore, the dihalogeno-purine **11** could be used for the synthesis of a large variety of compounds. Various 6-chloropurine derivatives have been reacted successfully not only with amines, but also with other nucleophilic species like alcohols,[21] thiols[22] or cyanide.[23] Palladium catalysed cross-couplings with the 2-iodide could give entry to a range of 2-phenyl, 2-alkynyl, or 2-alkenyl analogues of **11**.[15,24] N-7 and N-9 alkylations have been reported for a long time under Mitsunobu conditions[25] or nucleophilic reactions with alkyl halides[9] but the regioselectivity has often been an issue. Finally, coupling with a suitably protected sugar would enable the preparation of purine nucleoside mimics with potential medicinal applications.[25–27]

Conclusion

6-Chloro-2-iodopurine **11** can be prepared in five steps and at an overall yield of 54% from hypoxanthine. A high yielding lithiation/quenching sequence on the 2-position of 6-chloro-9-THP-purine **8** was achieved with lithium 2,2,6,6-tetramethylpiperidide and tributyltin chloride. Treating the 2-stannylated purine with iodine readily afforded the 2-iodo analogue and the regioselectivity of this strategy was confirmed with HMBC NMR and crystallographic studies. A total and mild deprotection with 0.1 equivalent of copper dichloride in refluxing aqueous ethanol gave the final dihalogenopurine **11**. An attempt to prepare the 9-isopropyl analogue of **11** by reaction with isopropanol under Mitsunobu conditions resulted in a mixture of the alkylated purine and the hydrazine side-product. Further synthetic potential has not been fully tested yet. Finally, scaling-up the experimental procedures has been achieved up to 25 grams of starting hypoxanthine for most steps, apart from the lithiation which required hazardous amounts of *n*-butyllithium and tributyltin chloride.

Experimental

Unless otherwise stated, experiments were performed under a nitrogen atmosphere using standard Schlenk techniques. *N*,*N*-Dimethylaniline (DMA) was freshly distilled from calcium hydride, tetrahydrofuran (THF) from sodium–benzophenone and hexane from sodium. Other solvents and reagents were used as received from BDH, Acros, Aldrich or Lancaster. Flash column chromatography was performed on silica gel 60 Å (35–70 μm) (Fluorochem). Thin layer chromatography was performed on Kieselgel UV_{254} 0.20 mm plates (Macherey-Nagel), and visualised under UV light at 254 nm or after exposure to

aqueous potassium permanganate. ^{1}H NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer using the residual solvent peak as an internal reference. Chemical shifts δ are given in parts per million (ppm). Coupling constants, J, are given in Hz. ^{13}C NMR spectra were recorded on the above spectrometer or on a Bruker Aspect 3000, both operating at 75.4 MHz. Additional PENDANT, HMBC and HMQC experiments were performed for full assignment where necessary. IR spectra were run on an FTIR Perkin-Elmer 2000 spectrophotometer as KBr pellets or as liquid films on KBr plates. Mass spectra were either performed by the St Andrews Analytical Services or by the EPSRC Mass Spectrometry Service at Swansea, using electron impact (EI), chemical ionisation (CI) or electrospray (ESI) techniques. Elemental analyses were performed by the St Andrews Analytical Service within the School of Chemistry Service.

6-Chloro-9*H*-purine monohydrate 7

To a stirred mixture of hypoxanthine **6** (7.00 g, 11.2 mmol) in dry DMA (18 mL, 140 mmol) was added dropwise at 0 °C phosphoryl oxychloride (175 mL, 1.9 mol) over a 30 minute period. The pale green mixture was heated at reflux for 2 hours to give a red solution. Following evaporation to dryness into a reddish oil, icy water (200 mL) was slowly added and the green solution was carefully neutralised to pH 9 with concentrated ammonia. The solution was evaporated to dryness into a yellow solid which was recrystallised twice from water to afford 6-chloropurine **7** (8.26 g, 86%) as a pale yellow crystalline solid, decomposition at 280 °C (lit., mp 250 °C); δ_H (300 MHz, d_6-dmso) 3.49 (s, 2H, H_2O), 8.67 (s, 1H, H8), 8.71 (s, 1H, H2); δ_C (75.4 MHz, d_6-dmso) 129.4 (C5), 146.1 (C8), 147.7 (C6), 151.4 (C2) 154.2 (C4); MS (CI): *m*/*z* 155 $[M + H]^+$; IR (KBr): 3478s, 3428s, 3121m, 3059m, 2974m, 2808m, 2710m, 2544m, 1655w, 1607s, 1574s, 1478w, 1449m, 1427w, 1397s, 1332s, 1285w, 1239s, 1157w, 1114w, 1002w, 940m, 922w, 861s, 730m, 678w, 639s, 603m, 556m, 508m cm^{-1}. Anal. Found: C, 34.80; H, 2.92; N, 32.47. Calc. for $C_5H_3ClN_4$: C, 35.02; H, 2.62; N, 32.39%.

6-Chloro-9-(tetrahydro-pyran-2-yl)-9*H*-purine 8

To a stirred mixture of 6-chloropurine **7** (4.35 g, 28.2 mmol) and *p*-toluenesulfonic acid (72 mg, 0.4 mmol) in dry THF (40 mL) was added at 80 °C 2,3-dihydropyran (3 mL, 32.9 mmol). Reflux under a nitrogen atmosphere was continued overnight, concentrated ammonia (2.5 mL) was added dropwise following cooling to room temperature. After evaporation to dryness, the yellowish oil was dissolved in ethyl acetate (100 mL) and extracted with brine (50 mL), water (2 × 50 mL) then dried over anhydrous sodium sulfate. The organic extracts were concentrated *in vacuo* into a yellow oil that was extracted with boiling petroleum ether 60–80 °C. The ether extracts were cooled in a fridge overnight to precipitate a colourless powder that was recrystallised from petroleum ether 60–80 °C to afford 6-chloro-9-THP-purine **8** (3.38 g, 68%) as colourless crystals (needles), mp 70 °C (lit., 69–71 °C); δ_H (300 MHz, d_6-dmso) 1.58 (m, 3H, THP), 1.74 (m, 2H, THP), 2.00 (m, 2H, THP), 2.30 (m, 1H, THP), 3.70 (m, 1H, THP H3′), 4.00 (dm, $^3J(^1H–^1H)$ 10.8 Hz, 1H, THP H2′), 5.76 (dd, $^3J(^1H–^1H)$ 2.3 & 11 Hz, 1H, THP H1′), 8.79 (s, 1H, purine H8), 8.90 (s, 1H, purine H2); δ_C (75.4 MHz, d_6-dmso) 22.5 (THP C3′), 24.8 (THP C4′), 30.0 (THP C2′), 68.1 (THP C6′), 82.0 (THP C1′), 131.3 (purine C5), 145.9 (purine C8), 149.6 (purine C6), 151.6 (purine C4), 152.1 (purine C2); MS (EI): *m*/*z* 238 $[M]^+$, 210 $[M - (CH_2)_2]^+$, 155 $[M - THP]^+$; IR (KBr): 3107m, 2959m, 2938m, 2873m, 1595s, 1568s, 1491m, 1467w, 1450m, 1396m, 1337s, 1300w, 1268w, 1218s, 1180m, 1145m, 1086s, 1045s, 951s, 907m, 878w, 856m, 822w, 794w, 783w, 648m, 636m, 596m cm^{-1}. Anal. Found: C, 50.32; H, 4.65; N, 23.47. Calc. for $C_{10}H_{11}ClN_4O$: C, 50.63; H, 4.51; N, 23.48%.

6-Chloro-9-(tetrahydro-pyran-2-yl)-2-(tributylstannyl)-9*H*-purine 9

To a stirred solution of 2,2,6,6-tetramethylpiperidine (19.5 mL, 115.5 mmol) in dry hexane (15 mL) and dry THF (30 mL) was added dropwise at −78 °C *n*-butyllithium (48.5 mL, 2.6 M solution in hexanes, 121.3 mmol) over 30 minutes. Following stirring at the same temperature for 1 hour, was added dropwise a solution of 9-protected purine **8** (5.5 g, 23.1 mmol) in dry THF (30 mL). After 30 minutes of stirring at −78 °C was added dropwise to the dark mixture tributyltin chloride (31.3 mL, 115.5 mmol) and stirring at the same temperature was continued for 1 hour. The resulting dark solution was quenched by dropwise addition of a saturated aqueous ammonium chloride solution (50 mL). Following overnight warming to room temperature with stirring, saturated aqueous sodium carbonate (50 mL) was added. Extraction with ethyl acetate (2 × 50 mL) and drying of the combined organics over magnesium sulfate afforded after evaporation to full dryness a yellowish oil. Purification by flash column chromatography using hexane/ethyl acetate (4 : 1) afforded the 2-stannylated purine **9** (12.20 g, 100%) as a colourless oil; R_f 0.11 [hexane/ethyl acetate 4 : 1]; δ_H (300 MHz, $CDCl_3$) 0.81 (t, $^3J(^1H–^1H)$, 7.4 Hz, 9H, $[CH_3(CH_2)_3]_3Sn$), 1.13 (t, $^3J(^1H–^1H)$ 7.9 Hz, 6H, $[CH_3(CH_2)_2CH_2]_3Sn$), 1.27 (m, $^3J(^1H–^1H)$ 7.7 Hz, 6H, $[CH_3CH_2(CH_2)_2]_3Sn$), 1.55 (m, $^3J(^1H–^1H)$ 7.7 Hz, 9H $[CH_3\ CH_2CH_2CH_2]_3Sn$ and THP), 1.75 (m, 2H, THP) 2.10 (m, 2H, THP), 3.72 (td, $^3J(^1H–^1H)$ 3.3 & 11.8 Hz, 1H, THP H3′), 4.13 (dm, $^3J(^1H–^1H)$, 11.5 Hz, 1H, THP H3′), 5.71 (dd, $^3J(^1H–^1H)$ 2.8 & 7.2 Hz, 1H, THP H1′), 8.15 (s, 1H, purine H8); δ_C (75.4 MHz, $CDCl_3$) 9.7 (t, $^1J(^{13}C–^{119}Sn)$ 165.3 Hz, $[CH_3(CH_2)_2CH_2]_3Sn$), 12.7 ($[CH_3(CH_2)_3]_3Sn$), 21.7 (THP C4′), 23.9 (THP C3′), 26.2 (t, $^2J(^{13}C–^{119}Sn)$ 27.1 Hz, $[CH_3CH_2CH_2CH_2]_3Sn$), 27.9 (t, $^3J(^{13}C–^{119}Sn)$ 10.5 Hz, $[CH_3CH_2CH_2CH_2]_3Sn$), 30.8 (THP C2′), 67.7 (THP C5′), 81.5 (THP C1′), 129.2 (purine C5), 140.6 (purine C8), 148.2 (purine C6), 149.1 (purine C4), 180.8 (purine C2); MS (ESI): *m*/*z* 529 $[M + H]^+$, 155 $[M - THP - Sn(Bu)_3]^+$; Found (ESI): *m*/*z* 529.1746 $[M + H]^+$; $C_{22}H_{37}ClN_4OSn$ requires 529.1751; IR (KBr): 3110m, 2955s, 2873s, 2731m, 2669m, 2637w, 2585w, 2419w, 2217w, 2050w, 1929w, 1743w, 1651m, 1582s, 1538s, 1486s, 1464s, 1414s, 1394s, 1377s, 1342s, 1309s, 1279s, 1225s, 1210s, 1180s, 1155s, 1138s, 1087s, 1059s, 1046s, 1023s, 1005s, 945s, 935m, 911s, 877s, 857s, 844m, 823m, 788s, 769w, 747w, 694s, 650s, 590m, 545w, 509m cm^{-1}. Anal. Found: C, 50.04; H, 7.07; N, 10.62. Calc. for $C_{22}H_{37}ClN_4OSn$: C, 50.04; H, 7.34; N, 10.82%.

6-Chloro-2-iodo-9-(tetrahydro-pyran-2-yl)-9*H*-purine 10

To a stirred solution of 2-stannylated purine **9** (12.20 g, 23.1 mmol) in dry THF (200 mL) was added iodine (9 g, 35.3 mmol) portionwise. Stirring was continued for 24 hours under a nitrogen atmosphere. Following treatment with excess iodine with saturated sodium metabisulfite, and subsequent stirring for one hour, the solution was extracted with dichloromethane (3 × 100 mL). The combined organics were washed with brine (100 mL), water (100 mL), dried over magnesium sulfate, then evaporated to full dryness into a yellowish oil. Trituration with *n*-hexane (75 mL) precipitated the 2-iodopurine **10** (8.0 g, 95%) as a pale yellow solid, mp 114 °C (lit., 112–113 °C); R_f 0.28 [hexane/ethyl acetate 1 : 1]; δ_H (300 MHz, $CDCl_3$) 1.46 (m, 3H, THP), 1.78 (m, 2H, THP), 2.01 (m, 1H, THP), 3.72 (td, $^3J(^1H–^1H)$ 3.6 & 11.5 Hz, 1H, THP H3′), 4.10 (dm, $^3J(^1H–^1H)$ 1.8 & 11.8 Hz, 1H, THP H2′), 5.70 (dd, $^3J(^1H–^1H)$ 2.3 & 10.5 Hz, 1H, THP H1′), 8.22 (s, 1H, purine H8); δ_C (75.4 MHz, $CDCl_3$) 22.4 (THP C4′), 24.6 (THP C3′), 32.0 (THP C2′), 68.9 (THP C5′), 82.3 (THP C1′), 116.5 (purine C5), 131.5 (purine C2), 143.0 (purine C8), 150.3 (purine C6), 151.6 (purine C4); MS (ESI): *m*/*z* 365 $[M + H]^+$, 239 $[M - I]^+$; Found (ESI): *m*/*z* 364.9665 $[M + H]^+$; $C_{10}H_{22}ClIN_4O$ requires 364.9661; IR (KBr): 3111m, 2957m, 2684m, 1795w, 1589s, 1546s, 1485m, 1471m, 1454w,

Table 2 Crystallographic data for purines **7**, **8**, **10** and **11**

	7	**8**	**10**	**11**·H_2O
Empirical formula	$C_5H_5ClN_4O$	$C_{10}H_{11}ClN_4O$	$C_{10}H_{10}ClIN_4O$	$C_5H_4ClIN_4O$
M	172.58	238.68	364.57	298.47
Crystal system	triclinic	monoclinic	monoclinic	monoclinic
Space group	$P\bar{1}$	*P*2(1)/n	*P*2(1)/c	*P*2(1)/c
a (Å)	7.8757(18)	11.478(5)	4.8021(10)	7.172(2)
b (Å)	8.4609(19)	4.5766(16)	11.860(2)	16.732(5)
c (Å)	10.502(2)	21.703(10)	21.790(4)	7.577(2)
α (°)	83.428(4)			
β (°)	82.374(4)	97.701(18)	95.098(4)	115.863(4)
γ (°)	76.546(4)			
U (Å^3)	672.0(3)	1129.8(8)	1236.1(4)	818.2(4)
Z	4	4	4	4
μ (mm^{-1})	0.506	0.322	2.796	4.194
Temperature (K)	125	293	293	125
Reflections measured	3354	4027	5159	4704
Independent reflections	1875	1737	1726	1448
Final R_1, wR_2 [$I > 2\sigma(I)$]	0.0343, 0.0726	0.0524, 0.0928	0.0279, 0.0625	0.0302, 0.0727

1443m, 1418m, 1400w, 1371m, 1342s, 1309m, 1280w, 1260w, 1227s, 1205s, 1180s, 1148s, 1135s, 1105m, 1082s, 1057m, 1042s, 955s, 936m, 909s, 901m, 879m, 861s, 822m, 789m, 714w, 658w, 634w, 601s, 546w cm^{-1}. Anal. Found: C, 32.75; H, 2.62; N, 15.74. Calc. for $C_{10}H_{10}ClIN_4O$: C, 32.95; H, 2.76; N, 15.37%.

6-Chloro-2-iodo-9*H*-purine 11

To a stirred solution of 9-protected purine **10** (34.58 g, 95 mmol) in 95 : 5 ethanol/water (250 mL) was added at room temperature copper(II) dichloride (1.345 g, 10 mmol). The resulting mixture was refluxed at 85 °C for 5 hours with vigorous stirring. Following evaporation to dryness into a tan residue, purification by flash column chromatography using hexane/ethyl acetate (1 : 1) afforded 6-chloro-2-iodo-purine **11** (26 g, 98%) as a colourless solid, decomposition at 200 °C; R_f 0.12 [hexane/ethyl acetate 1 : 1]; δ_H (300 MHz, d_6-dmso) 8.68 (s, 1H, H8); δ_C (75.4 MHz, d_6-dmso) 117.1 (C5), 129.3 (C2), 146.8 (C8), 147.1 (C6), 155.9 (C4); MS (EI): *m*/*z* 280 $[M]^+$, 153 $[M - I]^+$; Found (EI): *m*/*z* 280.9019 $[M]^+$; $C_5H_2ClIN_4O$ requires 280.9013; IR (KBr): 3423m, 3098w, 3064w, 2922w, 2542w, 2347w, 1803w, 1686m, 1649w, 1604m, 1559s, 1492w, 1475w, 1400w, 1373w, 1344s, 1292m, 1239m, 1216s, 1149s, 1004w, 952m, 899w, 855s, 788w, 731m, 659w, 642m, 609m, 542m, 525w cm^{-1}. Anal. Found: C, 21.59; H, 0.93; N, 19.53. Calc. for $C_5H_2ClIN_4O$: C, 21.41; H, 0.72; N, 19.98%.

X-Ray crystallography

Details of the structure determination are given in Table 2.† X-Ray diffraction measurements were made with graphite-monochromated Mo Kα X-radiation ($\lambda = 0.71073$ Å) at 125 K using a Siemens SMART diffractometer. Intensity data were collected using 0.3° width ω steps accumulating area detector frames spanning a hemisphere of reciprocal space for all structures (data were integrated using the SAINT program). All data were corrected on the basis of multiple equivalent reflections. Structures were solved by direct methods and refined by full-matrix least-squares against F^2 (SHELXTL). C–H hydrogen atoms were assigned isotropic displacement parameters and were constrained to idealised geometries. All calculations were made with SHELXTL.[28]

† CCDC reference numbers 221982 (**10**) and 221983 (**11**). See http://www.rsc.org/suppdata/ob/b3/b312629c/ for crystallographic data in.cif or other electronic format.

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