Synthesis of 2-substituted 2′-deoxyguanosines and 6-*O*-allylguanines *via* the activation of C-2 by a trifluoromethanesulfonate group

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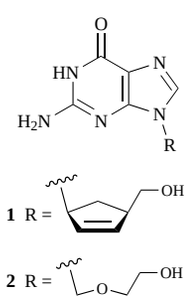
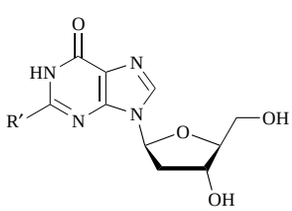
A new general synthesis of 2-substituted 2′-deoxyguanosine and 6-*O*-allylguanine analogues is reported. 2-*O*-Trifluoromethylsulfonyl-6-*O*-allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyxanthosine 8 can be converted into a 2-substituted 2′-deoxyguanosine analogue by substitution of the triflate (trifluoromethanesulfonate) moiety using a selected nucleophile, followed by deprotection. Therefore, a 2′-deoxyguanosine may overall be converted into a 2-substituted 2′-hypoxanthosine analogue in seven steps. Similar methodology has been used to synthesize 2-substituted 6-*O*-allylguanines which are of particular interest as potential resistance-modifying agents in cancer chemotherapy.

Introduction

The biological properties of nucleotide analogues have been of great interest over the last 20 years, especially in the fields of antiviral and anticancer chemotherapy. A great deal of attention has been devoted to devise general synthetic methods for the preparation of both purine- and pyrimidine-base analogues and their corresponding nucleosides. Several potent antiviral agents, based on guanosine, have been developed including the anti-HIV drug carbovir **1**[1] and the highly selective anti-HSV drug acyclovir **2**.[2] Both of these compounds include a variation in the sugar moiety.





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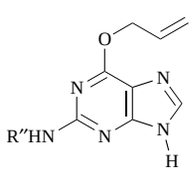

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Little attention has so far been given to the effect of substitution at C-2 of 2′-deoxyguanosine, however, N^2-phenyl-2′-deoxyguanosine has been found to be a selective inhibitor of herpes simplex virus (HSV) thymidine kinase.[3,4] It is usual to prepare such derivatives from 2-bromohypoxanthine,[5,6] but as a result of our interest in the mechanism of carcinogenesis by the metabolites of aromatic amines, we have developed an efficient protocol by which 2-substituted 2′-deoxyguanosines **3** can be synthesized *via* the corresponding 2-trifluoromethanesulfonate.[7,8] A modification of this methodology, by which 2-*N*-substituted 6-*O*-allylguanines **4** can be efficiently prepared, is also described. These compounds are of particular interest as potential inhibitors of the DNA repair protein 6-*O*-methylguanine-DNA methyltransferase (MGMT), and hence may be useful as resistance modifying agents in cancer chemotherapy.

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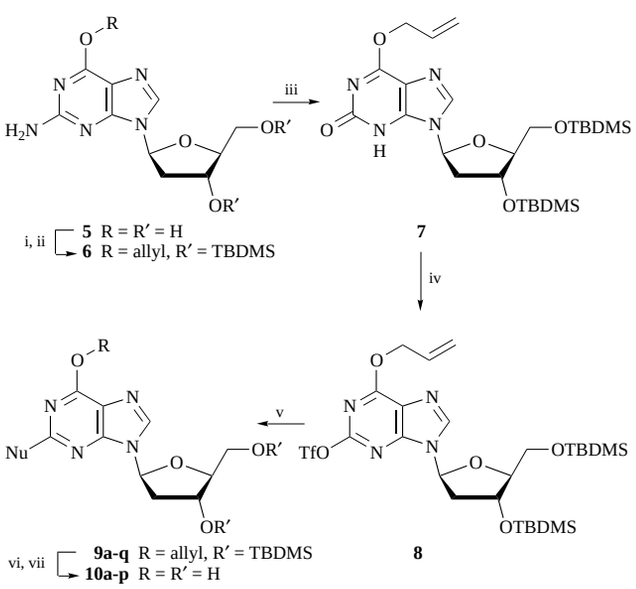
Results and discussion

2-Substituted 2′-deoxyguanosines

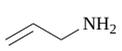
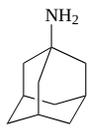
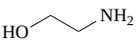
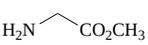
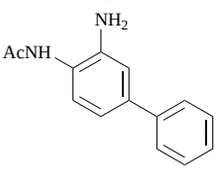
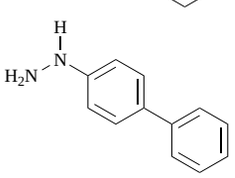
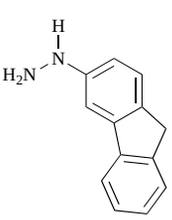
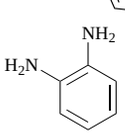
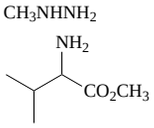
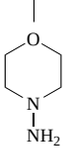
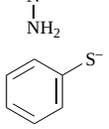
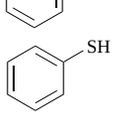
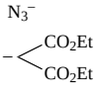
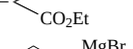
We have found that 6-*O*-allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-*O*-trifluoromethylsulfonylxanthosine **8** can be converted into a 2-substituted 2′-deoxyguanosine analogue by substitution of the triflate moiety using a selected nucleophile, followed by deprotection (Scheme 1). Therefore,



Scheme 1 *Reagents and conditions*: i, TBDMSCl, imidazole, DMF, room temp.; ii, allyl alcohol, Ph_3P, DEAD, THF, room temp.; iii, *tert*-BuONO, 0 °C to room temp.; iv, CF_3SO_2Cl, Et_3N, DMAP, CH_2Cl_2, 0 °C; v, Nu, DMF, room temp.; vi, TBAF (1.1 M), THF, room temp.; vii, $(Ph_3P)_3RhCl$, EtOH, H_2O, reflux

2′-deoxyguanosine may overall be converted into a 2-substituted 2′-hypoxanthosine analogue in seven steps. First, protection of the 3′- and 5′-hydroxy groups of 2′-deoxyguanosine **5**,[9] followed by allylation of O-6 using Mitsunobu methodology,[10,11] gave the fully protected compound **6**. Deamination of compound **6** using *tert*-butyl nitrite gave compound **7**. Formation of the triflate **8** was achieved with trifluoromethanesulfonyl chloride and triethylamine in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP),[9] and substitution of the triflate proceeded smoothly at room temperature in dimethylformamide (DMF) with a range of nucleophiles.

Table 1 Reaction conditions and products when compound **8** was treated with a variety of nucleophiles at room temperature; typically 0.06 M solution of **8** in DMF; 4-fold excess of nucleophile

Nucleophile	Product	Reaction time	Yield (%)
	**9a**	4 days	87
	**9b**	20 days	79
	**9c**	3 days	85
	**9d**	5 days	86
	**9e**	3 days [a,b]	30
	**9f**	14 days [a]	77
	**9g**	14 h [a]	69
	**9h**	3 days [a]	70
	**9i**	<2 min	94
	**9j**	28 days	67
	**9k**	2 days	14 [c]
	**9l**	45 min	61
	**9l**	7 days	0
	9m	2 h	39
N_3^-	**9n**	<1 h	26 [d]
	**9o**	3 days [e]	26
	**9p**	*e*	0

[a] 0.03 M Solution of **8**; 10-fold excess of nucleophile. [b] 80 °C. [c] 37% Isolated as its triflate salt. [d] Substantial amount of compound **7** isolated. [e] Reaction carried out in THF.

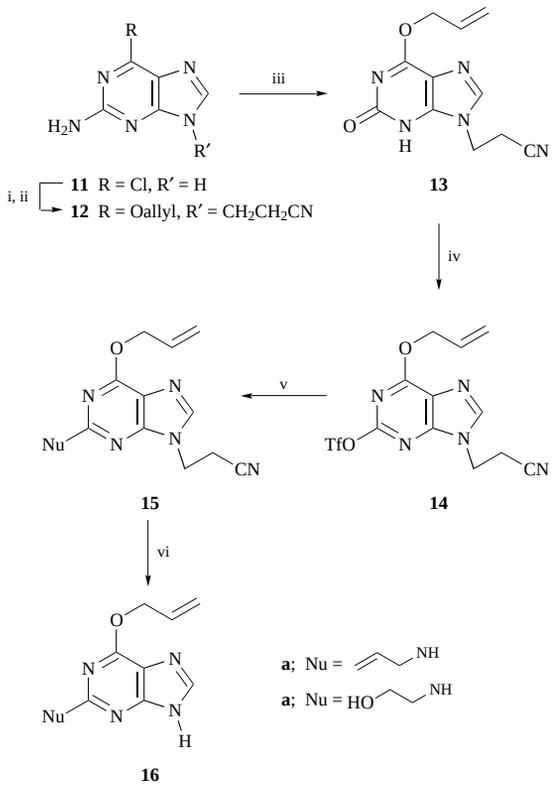
Compound **8** was successfully treated with small and bulky amines, amino acids (protected as their methyl ester), hydrazines, diethyl malonate (sodium salt), azide ion, an amino alcohol, and both an aromatic and aliphatic thiolate; however, no reaction occurred with benzenethiol (Table 1). It is interesting to note that compound **9n** appears to exist entirely in the azide form {IR [liquid film, KBr disc] $\nu_{max} = 2140$ cm^{-1}; $\delta_H(CDCl_3)$ shows one isomer only} and does not cyclise through N-1 or N-3 to give one of two possible tetrazoles.[12,13] The reaction of compound **8** with a Grignard reagent (allylmagnesium bromide) did not proceed smoothly, but produced a mixture of products. Deprotection of **9a–g** using, first, tetrabutylammonium fluoride (TBAF) and, secondly, removal of the allyl group from 6-O using Wilkinson's catalyst in aq. ethanol[14] gave 2-substituted 2′-deoxyinosines **10a–g** (**10l** was isolated only in very small amounts as the deallylation step was quite unreproducible).

2-Substituted-6-*O*-allylguanines

Alkylating agents are an important class of anticancer drugs, *e.g.* the chloroethylnitrosoureas (CNUs) which act by cross-linking DNA.[15] Unfortunately, tumour cells which have previously been responsive to alkylating drugs such as CNUs may develop resistance due to an increased production of the DNA repair protein 6-*O*-methylguanine-DNA methyltransferase (MGMT).[16,17] Cells which are known to lack the MGMT protein have also been shown to be more susceptible to alkylating agents.[17] Inactivation of MGMT has demonstrated a significant enhancement in the cytotoxic response of human tumour cells and tumour xenografts to chemotherapeutic drugs, such as CNUs, whose mechanism of action involves the formation of a 6-*O*-alkylguanine adduct.[16] MGMT is known to repair 6-*O*-alkylguanine residues in double-stranded DNA by the stoichiometric transfer of an alkyl group from the 6-*O*-position of guanine to an internal cysteine residue at the protein active site. The protein is thereby irreversibly inactivated. 6-*O*-Methylguanine itself has been found to inhibit MGMT, although it is 10^7–10^8-times less potent as a substrate for the protein than 6-*O*-methylguanine in double-stranded DNA.[18] 6-*O*-Benzylguanine, 6-*O*-allylguanine, and analogues thereof, have been found to inhibit MGMT more effectively than 6-*O*-methylguanine.[19–21]

Several analogues, in which the effect of different groups at the 6-O, N^7 and N^9 positions has been investigated, have been synthesized.[19–21] Compounds which possess a group other than amino at C-2 are relatively inaccessible; however, it is known that replacement of the amino group by hydrogen significantly reduces the activity of a given compound.[19,20] 2,6-Dichloropurine is commercially available, and preferential displacement of chloride at the 6-position is usually quite simple, but subsequent replacement of the C-2 chloro group by nucleophiles *e.g.* amines, requires high temperature and/or pressure, under which conditions a group such as allyloxy will not be stable. The introduction of a triflate moiety at C-2 of 6-*O*-allylguanine, suitably protected at N-9, would enable substitution at this centre under mild conditions.

6-*O*-Allylguanine has been synthesized from 2-amino-6-chloropurine **11** (Scheme 2) using the sodium salt of allyl alcohol.[22] Protection of N-9 by a 2-cyanoethyl group has been achieved by using acrylonitrile in DMF in the presence of a catalytic amount of potassium carbonate to give compound **12**.[23] When the protecting group was introduced before displacement of the 6-chloro group by allyloxy, the 2-cyanoethyl moiety was found to be unstable under the reaction conditions, suggesting that, *e.g.* sodium ethoxide may be the reagent of choice for the ultimate deprotection. Deamination of compound **12** in *tert*-butyl nitrite did not proceed due to its insolubility, but if the amino compound was dissolved in a suitable solvent prior to the addition of *tert*-butyl nitrite, it was possible to isolate the required compound **13**. Dichloromethane appears to be appropriate here, although it is possible to introduce an alkoxy group at the 2-position if the reaction is carried out in the corresponding alcohol. When the deamination was carried out in acetonitrile, the corresponding 2-acetamido compound was isolated (comparison with an authentic sample prepared from compound **12** and acetyl chloride in pyridine in the pres-



Scheme 2 *Reagents and conditions*: i, sodium allyloxide, reflux; ii, acrylonitrile, cat, K_2CO_3, DMF, room temp.; iii, *tert*-BuONO, CH_2Cl_2, room temp.; iv, CF_3SO_2Cl, Et_3N, DMAP, CH_2Cl_2, 0 °C; v, Nu, DMF, room temp.; vi, EtO^-, EtOH, reflux

ence of DMAP catalyst), and in aqueous solution both deamination and deallylation were found to occur. A substitution reaction involving the triflate **14** has been successful with both allylamine and 2-ethanolamine. Final deprotection was effected in high yield by refluxing with sodium ethoxide in ethanol for *ca*. 10 min to give the desired 2-substituted-6-*O*-allylguanine **16**.

Experimental

^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC 300 and *J*-values are given in Hz. Mass spectra (electron impact and field desorption) were measured on a Varian MAT CH 7a (EI) or a Varian MAT 711 (FD). Ethyl acetate, light petroleum (40–60 °C), diethyl ether and ethanol were distilled before general use. Dichloromethane was freshly distilled as required from CaH_2. Tetrahydrofuran (THF) was distilled as required from sodium/benzophenone. Triethylamine was distilled from CaH_2 and stored over NaOH pellets. Acrylonitrile and acetyl chloride were purified by simple distillation. Sodium was washed twice in light petroleum and once in methanol immediately prior to use. 'Dry' ethanol was obtained by distillation from Mg/I_2. All other reagents were used as received. For aqueous solutions 'house-distilled' water was used.

2-Substituted 2′-deoxyguanosines

Compounds **6–8**[7] and **9e–h**[8] were synthesized as previously reported.

Substitution reactions involving the triflate 8 (9a,b,j and k). 6-*O*-Allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-*O*-trifluoromethylsulfonylxanthosine **8** (200 mg, 0.3 mmol) was dissolved in DMF (5 cm^3), the selected nucleophile (1.2 mmol) was added, and the reaction mixture was left (with stirring for heterogeneous mixtures) at room temperature until no starting material was observed by TLC. The solvent was removed *in vacuo* and the desired product was isolated by column chromatography using 20% ethyl acetate in light petroleum as the eluting solvent.

After 4 days, 2-*N*,6-*O*-diallyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine **9a** was isolated as an oil (150 mg, 87%); δ_H(300 MHz; $CDCl_3$) 0.00 (6 H, s, SiMe), 0.03 (6 H, s, SiMe), 0.83 (9 H, s, ^{t}Bu), 0.84 (9 H, s, ^{t}Bu), 2.21–2.29 (1 H, m, 2′-H), 2.51–2.57 (1 H, m, 2′-H), 3.67–3.77 (2 H, m, 5′-H_2), 3.89 (1 H, m, 4′-H), 3.99 (2 H, pseudo-t, *J* 5.7, NHCH_2), 4.51 (1 H, m, 3′-H), 4.92 (2 H, d, *J* 5.7, OCH_2), 5.05 (1 H, dd, *J* 1.4 and 10.3, NCH_2CH=C*H*H), 5.06 (1 H, br t, NH), 5.12–5.21 (2 H, m, OCH_2CH=C*H*H and NCH_2CH=CH*H*), 5.34 (1 H, dd, *J* 1.4 and 17.3, OCH_2CH=CH*H*), 5.84–5.94 (1 H, m, $NHCH_2CH$=), 6.00–6.06 (1 H, m, OCH_2CH=), 6.23 (1 H, pseudo-t, *J* 6.6, 1′-H) and 7.78 (1 H, s, 8-H); δ_C(75 MHz; $CDCl_3$) −5.4, −5.3, −4.7, −4.6, 18.1, 18.5, 25.8, 26.1, 40.8, 44.6, 63.1, 67.1, 72.2, 83.9, 87.7, 115.5, 115.8, 118.2, 133.0, 135.5, 137.5, 153.7, 158.9 and 160.6; *m/z* (EI) 575 (M^+, 12%), 258 (20), 231 ([M − riboseSi$_2$]$^+$, 73), 190 (20), 89 (46) and 73 (100).

After 20 days, 2-*N*-(1-adamantyl)-6-*O*-allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine **9b** was isolated as an oil (158 mg, 79%); δ_H(300 MHz; $CDCl_3$) 0.00 (6 H, s, $SiMe_2$), 0.01 (6 H, s, $SiMe_2$), 0.83 (18 H, s, ^{t}Bu), 1.62 (6 H, m, adamantyl), 2.05 (9 H, m, adamantyl), 2.25–2.31 (1 H, m, 2′-H), 2.41–2.47 (1 H, m, 2′-H), 3.69 (2 H, m, 5′-H_2), 3.91 (1 H, m, 4′-H), 4.47 (1 H, m, 3′-H), 4.90 (2 H, m, OCH_2), 4.96 (1 H, br t, NH), 5.17 (1 H, dd, *J* 1.5 and 10.3, CH=C*H*H), 5.33 (1 H, dd, *J* 1.5 and 17.3, CH=CH*H*), 6.00–6.09 (1 H, m, C*H*=CH_2), 6.22 (1 H, pseudo-t, *J* 6.2, 1′-H) and 7.78 (1 H, s, 8-H); δ_C(75 MHz; $CDCl_3$) −5.5, −5.4, −4.8, −4.7, 17.9, 18.4, 25.7, 26.0, 29.6, 36.7, 37.4, 41.2, 42.0, 51.4, 67.0, 72.2, 83.8, 87.6, 114.8, 117.7, 133.0, 136.9, 153.4, 158.2 and 160.0; *m/z* (EI) 669 (M^+, 18%), 325 ([M − riboseSi$_2$]$^+$, 48), 261 (27) and 73 (100).

After 28 days, 6-*O*-allyl-3′,5′-bis-*O*-(*tert*-butyl-dimethylsilyl)-2′-deoxy-2-*N*-(1-methoxycarbonyl-2-methylpropyl)guanosine **9j** was isolated as an oil (130 mg, 67%); δ_H(300 MHz; $CDCl_3$) 0.00 (6 H, s, SiMe), 0.03 (6 H, s, SiMe), 0.82 (9 H, s, ^{t}Bu), 0.84 (9 H, s, ^{t}Bu), 0.96 (6 H, d, *J* 6.8, CH*Me*$_2$), 2.08–2.20 (1 H, m, C*H*Me$_2$), 2.21–2.30 (1 H, m, 2′-H), 2.48 (1 H, m, 2′-H), 3.61 (3 H, s, OMe) 3.71 (2 H, m, 5′-H_2), 3.89 (1 H, m, 4′-H), 4.48 (2 H, m, 3′-H and NHC*H*), 4.90 (2 H, m, OCH_2), 5.18 (1 H, dd, *J* 1.4 and 10.5, CH=C*H*H), 5.34 (1 H, dd, *J* 1.4 and 17.2, CH=CH_2), 5.35 (1 H, br s, NH), 6.00–6.08 (1 H, m, C*H*=CH_2), 6.23 (1 H, pseudo-t, *J* 6.5, 1′-H) and 7.82 (1 H, s, 8-H); δ_C(75 MHz; $CDCl_3$) −5.6, −5.5, −4.9, −4.8, 17.9, 18.3, 19.1, 25.7, 25.9, 31.1, 40.9, 51.7, 60.2, 62.8, 67.0, 71.9, 83.7, 87.6, 115.6, 117.9, 132.8, 137.5, 153.4, 158.4, 160.4 and 173.5; *m/z* (EI) 649 (M^+, 11%), 592 ([M − Oallyl]$^+$, 16), 305 ([M − riboseSi$_2$]$^+$, 26), 246 (70), 191 (30), 89 (41) and 73 (100).

After 2 days, 6-*O*-allyl-3′,5′-*O*-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-*N*-morpholinoguanosine **9k** was obtained as an oil which crystallised on storage at −10 °C (26 mg, 14%). An appreciable amount of compound **9k** was isolated as its triflate salt by removal of the top layer of silica from the column, extraction with ethanol, followed by removal of the solvent and recrystallisation from ethyl acetate (65 mg, 37%), mp 184–186 °C; Free base: δ_H(300 MHz; $CDCl_3$) 0.01 (6 H, s, SiMe), 0.04 (6 H, s, SiMe), 0.85 (9 H, s, ^{t}Bu), 0.85 (9 H, s, ^{t}Bu), 2.22–2.30 (1 H, m, 2′-H), 2.54–2.62 (1 H, m, 2′-H), 3.70 (10 H, m, 5′-H_2 and morpholine), 3.90 (1 H, m, 4′-H), 4.52 (1 H, m, 3′-H), 4.94 (2 H, d, *J* 5.8, OCH_2), 5.19 (1 H, dd, *J* 1.4 and 10.5, CH=C*H*H), 5.35 (1 H, dd, *J* 1.4 and 17.3, CH=CH*H*), 6.00–6.11 (1 H, m, C*H*=CH_2), 6.26 (1 H, pseudo-t, *J* 6.6, 1′-H) and 7.81 (1 H, s, 8-H); *m/z* (EI) 605 ([M − 15]$^+$, 18%), 261 ([M − 15 − riboseSi$_2$]$^+$, 82), 220 (21), 89 (40), 73 (100) and 43 (36).

Triflate salt: (Found: C, 46.53; H, 6.93; N, 10.83. $C_{30}H_{53}F_3N_6O_8SSi_2$ requires C, 46.73; H, 6.93; N, 10.90%); δ_H(300 MHz; [$^2H_6$]DMSO) 0.00 (6 H, s, SiMe), 0.07 (6 H, s, SiMe), 0.81 (9 H, s, ^{t}Bu), 0.85 (9 H, s, ^{t}Bu), 2.30–2.39 (1 H, m, 2′-H), 2.82–2.92 (1 H, m, 2′-H), 3.64–3.71 (2 H, m, 5′-H_2), 3.84–3.97 (5 H, m, 4′-H and morpholine), 4.10–4.21 (2 H, m, morpholine), 4.22–4.35 (2 H, m, morpholine), 4.53 (1 H, m, 3′-H), 5.20 (2 H, d, *J* 5.8, OCH_2), 5.33 (1 H, dd, *J* 1.4 and 10.3, CH=C*H*H), 5.47

(1 H, dd, *J* 1.4 and 17.2, CH=C*H*H), 6.09–6.15 (1 H, m, C*H*=CH_2), 6.40 (1 H, pseudo-t, *J* 6.6, 1′-H), 6.53 (2 H, br s, NH_2) and 8.78 (1 H, s, 8-H); *m/z* (EI) 261 ([M − 15 − riboseSi$_2$]$^+$, 9%), 155 (60) and 75 (100).

6-*O*-Allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-*N*-(2-hydroxyethyl)guanosine 9c. 6-*O*-Allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-*O*-trifluoromethanesulfonylxanthosine **8** (900 mg, 1.35 mmol) was dissolved in DMF (20 cm^3), ethanolamine (329 mg, 5.39 mmol) was added, and the reaction mixture was left at room temperature for 3 days. The solvent was removed *in vacuo* and the desired product was isolated by column chromatography using 1:1 ethyl acetate–light petroleum as eluent. The title compound was isolated as an oil (665 mg, 85%); δ_H(300 MHz; $CDCl_3$) 0.01 (6 H, s, SiMe), 0.04 (6 H, s, SiMe), 0.84 (18 H, s, ^{t}Bu), 2.24–2.34 (1 H, m, 2′-H), 2.39–2.49 (1 H, m, 2′-H), 3.50–3.58 (2 H, m, CH_2), 3.64–3.80 (4 H, m, CH_2 and 5′-H_2), 3.90 (1 H, m, 4′-H), 4.50 (1 H, m, 3′-H), 4.92 (2 H, m, OCH_2), 5.19 (1 H, dd, *J* 1.5 and 10.4, CH=C*H*H), 5.35 (1 H, dd, *J* 1.5 and 17.2, CH=CH*H*), 5.56 (1 H, br t, NH), 5.99–6.08 (1 H, m, C*H*=CH_2), 6.22 (1 H, pseudo-t, *J* 6.4, 1′-H) and 7.85 (1 H, s, 8-H); δ_C(75 MHz; $CDCl_3$) −5.5, −5.4, −4.8, −4.7, 17.9, 18.4, 25.7, 25.9, 41.1, 44.7, 62.7, 63.0, 67.2, 71.7, 83.7, 87.6, 115.3, 118.1, 132.6, 137.3, 153.2, 159.4 and 160.6; *m/z* (EI) 579 (M$^+$, 10%), 262 (19), 235 ([M − riboseSi$_2$]$^+$, 52), 204 (46), 73 (100) and 43 (25).

6-*O*-Allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-phenylthioinosine 9l. 6-*O*-Allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-*O*-trifluoromethylsulfonylxanthosine **8** (618 mg, 0.9 mmol) was dissolved in DMF (15 cm^3) and triethylamine (0.5 cm^3) was added. The solution was cooled in an ice–bath and thiophenol (395 mg, 3.59 mmol) was added dropwise over a period of 5 min. After 45 min, the solvent was removed *in vacuo* and the desired product was isolated by column chromatography using 20% ethyl acetate in light petroleum as the eluting solvent. The title compound was isolated as an oil which crystallised at −10 °C (344 mg, 61%); δ_H(300 MHz; $CDCl_3$) 0.03 (6 H, s, SiMe), 0.04 (6 H, s, SiMe), 0.85 (9 H, s, ^{t}Bu), 0.86 (9 H, s, ^{t}Bu), 2.22–2.28 (1 H, m, 2′-H), 2.48–2.56 (1 H, m, 2′-H), 3.63–3.75 (2 H, m, 5′-H_2), 3.90 (1 H, m, 4′-H), 4.46 (1 H, m, 3′-H), 4.73 (2 H, d, *J* 5.9, OCH_2), 5.12 (1 H, dd, *J* 1.3 and 10.4, CH=C*H*H), 5.19 (1 H, dd, *J* 1.3 and 17.2, CH=CH*H*), 5.83–5.92 (1 H, m, C*H*=CH_2), 6.24 (1 H, pseudo-t, *J* 6.5, 1′-H), 7.33–7.36 (3 H, m, Ph), 7.58–7.61 (2 H, m, Ph) and 8.03 (1 H, s, 8-H); δ_C(75 MHz; $CDCl_3$) −5.4, −5.3, −4.7, −4.6, 18.1, 18.5, 25.8, 26.0, 41.1, 62.9, 67.6, 72.1, 84.7, 88.0, 118.8, 119.5, 128.8, 129.0, 130.6, 132.4, 135.7, 140.1, 152.6, 159.6 and 164.6.

6-*O*-Allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-(methoxycarbonylmethyl)guanosine 9d. Glycine methyl ester hydrochloride (573 mg, 4.56 mmol) was suspended in DMF (5 cm^3) and triethylamine (0.5 cm^3) was added to the stirred mixture. After 5 min, the resulting solution was filtered and added to a solution of 6-*O*-allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-*O*-trifluoromethylsulfonylxanthosine **8** (762 mg, 1.14 mmol) in DMF (5 cm^3). The reaction mixture was left at room temperature for 5 days. After this time, the solvent was removed *in vacuo* and the desired product was isolated by column chromatography using 25% ethyl acetate in light petroleum as the eluting solvent (597 mg, 86%); δ_H(300 MHz; $CDCl_3$) 0.04 (6 H, s, SiMe), 0.06 (6 H, s, SiMe), 0.87 (18 H, s, 2 × ^{t}Bu), 2.25–2.34 (1 H, m, 2′-H), 2.46–2.56 (1 H, m, 2′-H), 3.73 (3 H, s, OMe), 3.69–3.80 (2 H, m, 5′-H_2), 3.93 (1 H, m, 4′-H), 4.15 (2 H, d, *J* 5.7, NHCH_2), 4.52 (1 H, m, 3′-H), 4.95 (2 H, d, *J* 5.7, OCH_2), 5.21 (1 H, dd, *J* 1.4 and 10.4, CH=CH*H*), 5.37 (1 H, dd, *J* 1.4 and 17.2, CH=CH*H*), 5.58 (1 H, br t, NH), 6.00–6.14 (1 H, m, C*H*=CH_2), 6.27 (1 H, pseudo-t, *J* 6.5, 1′-H) and 7.89 (1 H, s, 8-H); δ_C(75 MHz; $CDCl_3$) −5.5, −5.4, −4.7, −4.6, 18.0, 18.4, 25.8, 26.0, 41.0, 44.0, 52.1, 62.9, 67.2, 72.0, 83.9, 87.7, 115.8, 128.2, 132.8, 137.7, 153.5, 158.2, 160.7 and 171.5; *m/z* (EI) 607 (M$^+$, 5%), 550 (13), 290 (27), 263 ([M − riboseSi$_2$]$^+$, 43), 231 (17), 204 (30) and 73 (100).

6-*O*-Allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-*N*-(methylamino)guanosine 9i. 6-*O*-allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-*O*-(trifluoromethylsulfonyl)xanthosine **8** (1.13 g, 1.7 mmol) was dissolved in DMF (12 cm^3) and methylhydrazine (312 mg, 6.8 mmol) was added. After storage at room temperature for 5 min, the solvent was removed *in vacuo* and the desired product was isolated by column chromatography using 1:1 ethyl acetate–light petroleum as the eluting solvent. The title compound was isolated as an oil (907 mg, 94%); δ_H(300 MHz; $CDCl_3$) 0.00 (6 H, s, SiMe), 0.03 (6 H, s, SiMe), 0.83 (9 H, s, ^{t}Bu), 0.84 (9 H, s, ^{t}Bu), 2.22–2.31 (1 H, m, 2′-H), 2.38–2.48 (1 H, m, 2′-H), 3.30 (3 H, s, NH*Me*), 3.70 (2 H, m, 5′-H), 3.89 (1 H, m, 4′-H), 4.50 (1 H, m, 3′-H), 4.95 (2 H, d, *J* 5.7, OCH_2), 5.18 (1 H, dd, *J* 1.2 and 10.5, CH=C*H*H), 5.35 (1 H, dd, *J* 1.2 and 16.8, CH=CH*H*), 5.38 (2 H, br m, NHNH), 5.97–6.13 (1 H, m, C*H*=CH_2), 6.28 (1 H, pseudo-t, *J* 6.6, 1′-H) and 7.83 (1 H, s, 8-H); δ_C(75 MHz; $CDCl_3$) −5.5, −5.4, −4.8, −4.7, 18.0, 18.4, 25.7, 25.9, 39.2, 40.8, 63.0, 67.1, 72.1, 83.7, 87.6, 114.5, 118.1, 132.8, 137.6, 153.7, 160.1 and 160.4; *m/z* (EI) 564 (M$^+$, 9%), 220 ([M − riboseSi$_2$]$^+$, 72) and 73 (100).

6-*O*-Allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-(propylthio)inosine 9m. 6-*O*-Allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-*O*-(trifluoromethylsulfonyl)xanthosine **8** (100 mg, 0.15 mmol) was dissolved in DMF (2.5 cm^3) and sodium hydride (60%; 24 mg, 0.6 mmol) was added. The solution was cooled in an ice-bath and propane-1-thiol (46 mg, 0.6 mmol) was added dropwise. After 2 h, the solvent was removed *in vacuo* and the desired product was isolated by column chromatography using 20% ethyl acetate in light petroleum as eluent. The title compound was isolated as an oil (35 mg, 39%); δ_H(300 MHz; $CDCl_3$) 0.04 (6 H, s, SiMe), 0.05 (6 H, s, SiMe), 0.86 (18 H, s, ^{t}Bu), 1.01 (3 H, t, *J* 7.3, CH_3CH$_2$), 1.67–1.81 (2 H, m, CH_3CH_2), 2.30–2.41 (1 H, m, 2′-H), 2.47–2.58 (1 H, m, 2′-H), 3.10 (2 H, t, *J* 7.3, SCH_2), 3.78–3.84 (2 H, m, 5′-H_2), 3.94 (1 H, m, 4′-H), 4.53 (1 H, m, 3′-H), 5.02 (2 H, d, *J* 5.8, OCH_2), 5.23 (1 H, dd, *J* 1.4 and 10.5, CH=C*H*H), 5.39 (1 H, dd, *J* 1.4 and 17.2, CH=CH*H*), 6.04–6.10 (1 H, m, C*H*=CH_2), 6.37 (1 H, pseudo-t, *J* 6.4, 1′-H) and 8.05 (1 H, s, 8-H); δ_C(75 MHz; $CDCl_3$); −5.6, −5.5, −4.9, −4.8, 13.4, 17.8, 18.3, 22.8, 25.6, 25.8, 29.6, 31.8, 41.3, 62.8, 67.4, 71.9, 84.2, 87.8, 118.4, 132.4, 139.4, 152.5, 159.4 and 164.8; *m/z* (EI) 594 (M$^+$, 1%), 537 ([M − Oallyl]$^+$, 15), 277 (33), 207 (19), 89 (56), 73 (100) and 41 (23).

6-*O*-Allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-[bis(ethoxycarbonyl)methyl]inosine 9o. Diethyl malonate (96 mg, 0.6 mmol) was added to a suspension of sodium hydride (60%; 24 mg, 0.6 mmol) in THF (2.5 cm^3). After 10 min, 6-*O*-allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-*O*-trifluoromethylsulfonylxanthosine **8** (100 mg, 0.15 mmol) was added. After a further 3 days, the solvent was removed and the desired product was isolated by column chromatography using 20% ethyl acetate in light petroleum as eluent. The title compound was isolated as an oil (26 mg, 26%); δ_H(300 MHz; $CDCl_3$) 0.04 (6 H, s, SiMe), 0.05 (6 H, s, SiMe), 0.85 (9 H, s, ^{t}Bu), 0.86 (9 H, s, ^{t}Bu), 1.25 (6 H, t, *J* 7.1, 2 × CH_2CH_3), 2.39 (2 H, m, 2′-H_2), 3.78–3.84 (2 H, m, 5′-H_2), 3.95 (1 H, m, 4′-H), 4.28 (4 H, q, *J* 7.1, 2 × CH_2CH$_3$), 4.50 (1 H, m, 3′-H), 4.95 [1 H, s, C*H*(CO_2Et)$_2$], 5.01 (2 H, d, *J* 5.9, OCH_2), 5.23 (1 H, dd, *J* 1.2 and 10.4, CH=C*H*H), 5.37 (1 H, dd, *J* 1.2 and 17.2, CH=CH*H*), 6.13–6.01 (1 H, m, C*H*=CH_2), 6.41 (1 H, pseudo-t, *J* 6.3, 1′-H) and 8.28 (1 H, s, 8-H).

6-*O*-Allyl-2-azido-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine 9n. 6-*O*-Allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-*O*-trifluoromethylsulfonylxanthosine **8** (100 mg, 0.15 mmol) was dissolved in DMF (2.5 cm^3) and sodium azide (39 mg, 0.6 mmol) was added. After stirring of the mixture for a further 1 h, the solvent was removed *in vacuo* and the desired product was isolated by column chromatography using 20% ethyl acetate in light petroleum as the eluting solvent. The title compound was isolated as an oil (22 mg, 26%). An amount of compound **7** was also obtained from the column after elution

of the required azide; $\nu_{max}(CHCl_3)/cm^{-1}$ 2140 (N_3); δ_H(300 MHz; $CDCl_3$) 0.06 (12 H, s, SiMe), 0.87 (9 H, s, ^{t}Bu), 0.87 (9 H, s, ^{t}Bu), 2.42–2.32 (1 H, m, 2′-H), 2.36–2.45 (1 H, m, 2′-H), 3.86–3.79 (2 H, m, 5′-H), 3.95 (1 H, m, 4′-H), 4.54 (1 H, m, 3′-H), 5.05 (2 H, d, *J* 5.9, OCH_2), 5.27 (1 H, dd, *J* 1.3 and 10.4, CH=C*H*H), 5.43 (1 H, dd, *J* 1.3 and 17.2, CH=CH*H*), 6.02–6.17 (1 H, m, C*H*=CH_2), 6.37 (1 H, pseudo-t, *J* 6.4, 1′-H) and 8.15 (1 H, s, 8-H); δ_C(75 MHz; $CDCl_3$) −5.5, −5.4, −4.8, −4.7, 18.0, 18.4, 25.7, 25.9, 41.5, 62.8, 68.0, 71.8, 84.4, 87.9, 119.2, 119.5, 132.0, 140.5, 152.9, 155.7 and 160.9; *m/z* (EI) 504 ([M − Oallyl]$^+$, 7%), 261 (29), 89 (61) and 73 (100).

Alcohol deprotection of compounds 9a,b,c,d,l

2-*N*,6-*O*-Diallyl-2′-deoxyguanosine. 2-*N*,6-*O*-Diallyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)–2′-deoxyguanosine **9a** (879 mg, 1.53 mmol) was dissolved in THF (15 cm^3) and the solution was cooled in an ice-bath. TBAF (1.1 M in THF; 6.6 cm^3) was added and the reaction mixture was allowed to reach room temperature. After 90 min, the solvent was removed and the product was isolated by flash column chromatography on silica gel, using 20% ethanol in ethyl acetate as the eluent. The title compound was isolated as an oil (794 mg).This compound was not fully characterised, but was used directly in the next step. ^{1}H NMR analysis showed the required product, together with an unidentified impurity which was invisible on TLC (UV visualisation).

2-*N*-(1-Adamantyl)-6-*O*-allyl-2′-deoxyguanosine. 2-*N*-(1-Adamantyl)-6-*O*-allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine **9b** (630 mg, 0.95 mmol) was dissolved in THF (20 cm^3) and the solution was cooled in an ice-bath. TBAF (1.1 M in THF; 2 cm^3) was added. The reaction mixture was allowed to warm to room temperature and, after 45 min, the solvent was removed. The product was isolated by column chromatography using 10% ethanol in ethyl acetate as the eluting solvent. The product was isolated as an oil (359 mg, 86%); δ_H(300 MHz; [$^2H_4$]methanol) 1.70 (6 H, m, adamantyl), 2.05 (3 H, m, adamantyl), 2.12 (6 H, m, adamantyl), 2.28 (1 H, m, 2′-H), 2.75 (1 H, m, 2′-H), 3.63 (2 H, m, 5′-H_2), 3.95 (1 H, m, 4′-H), 4.48 (1 H, m, 3′-H), 4.96 (2 H, d, *J* 5.4, OCH_2), 5.22 (1 H, d, *J* 1.5 and 10.5, CH=C*H*H), 5.39 (1H, dd, *J* 1.5 and 17.3, CH=CH*H*), 6.02–6.16 (1 H, m, C*H*=CH_2), 6.26 (1 H, dd, *J* 6.2 and 7.7, 1′-H) and 8.00 (1 H, s, 8-H); *m/z* (EI) 441 (M$^+$, 16%), 325 ([M + 1 − ribose]$^+$, 100), 284 (49), 268 (83), 135 (72), 93 (23), 79 (32), 67 (19) and 41 (40); *m/z* (FD) 441 (M$^+$).

6-*O*-Allyl-2′-deoxy-2-*N*-(2-hydroxyethyl)guanosine. 6-*O*-Allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-*N*-(2-hydroxyethyl)guanosine **9c** (619 mg, 1.07 mmol) was dissolved in THF (20 cm^3), the solution was cooled in an ice-bath, and TBAF (1.1 M in THF; 2.5 cm^3) was added. On warming to room temperature, the reaction mixture was stored for 30 min, after which time the solvent was removed. The product was purified by column chromatography using 40% ethanol in ethyl acetate as the eluting solvent. The product was an oil (359 mg, 95%); δ_H(300 MHz; [$^2H_4$]methanol) 2.26–2.36 (1 H, m, 2′-H), 2.71–2.84 (1 H, m, 2′-H), 3.49 (2 H, d, *J* 5.6, CH_2), 3.68 (2 H, t, *J* 5.6, CH_2), 3.64–3.80 (2 H, m, 5′-H_2), 3.96 (1 H, m, 4′-H), 4.52 (1 H, m, 3′-H), 4.95 (2 H, d, *J* 4.0, OCH_2), 5.21 (1 H, dd, *J* 1.5 and 10.5, CH=C*H*H), 5.43 (1 H, dd, *J* 1.5 and 17.2, CH=CH*H*), 6.00–6.15 (1 H, m, C*H*=CH_2), 6.28 (1 H, dd, *J* 6.4 and 7.4, 1′-H) and 7.99 (1 H, s, 8-H); δ_C(75 MHz; [$^2H_4$]methanol) 40.3, 44.5, 61.4, 63.0, 67.3, 72.4, 85.6, 88.7, 115.0, 117.8, 133.6, 139.2, 154.0, 160.2 and 161.1; *m/z* (EI) 351 (M$^+$, 5%) and 235 ([M − ribose]$^+$, 20).

6-*O*-Allyl-2′-deoxy-2-*N*-(methoxycarbonylmethyl)guanosine. 6-*O*-Allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-*N*-(methoxycarbonylmethyl)guanosine **9d** (564 mg, 0.93 mmol) was suspended in THF (20 cm^3), the solution was cooled in an ice-bath, and TBAF (1.1 M in THF; 2 cm^3) was added. After 30 min, the solvent was removed and the desired product was isolated by column chromatography using 40% ethanol in ethyl acetate as the eluting solvent (311 mg, 88%); δ_H(300 MHz; [$^2H_4$]methanol) 2.23–2.37 (1 H, m, 2′-H), 2.67–2.83 (1 H, m, 2′-H), 3.66 (3 H, s, OMe), 3.64–3.79 (2 H, m, 5′-H_2), 3.96 (1 H, m, 4′-H), 4.05 (2 H, s, NHCH_2), 4.50 (1 H, m, 3′-H), 4.90 (2 H, d, *J* 5.6, OCH_2), 5.19 (1 H, dd, *J* 1.5 and 10.4, CH=C*H*H), 5.37 (1 H, dd, *J* 1.5 and 17.2, CH=CH*H*), 5.96–6.12 (1 H, m, C*H*=CH_2), 6.27 (1 H, pseudo-t, *J* 7.4, 1′-H) and 8.05 (1 H, s, 8-H); δ_C(75 MHz; [$^2H_4$]methanol) 40.1, 43.9, 51.8, 62.8, 67.3, 72.1, 85.5, 88.6, 115.2, 117.8, 133.4, 139.5, 153.7, 159.4, 160.9 and 172.9; *m/z* (EI) 379 (M$^+$, 1%), 343 (2), 244 (20), 204 (76), 135 (35), 98 (36), 81 (77) and 41 (100).

6-*O*-Allyl-2′-deoxy-2-(phenylthio)inosine. 6-*O*-Allyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2-(phenylthio)inosine **9l** (344 mg, 0.55 mmol) was dissolved in THF (10 cm^3), the solution was cooled in an ice-bath, and TBAF (1.1 M in THF; 1 cm^3) was added. After 30 min the solvent was removed and the desired product was isolated by column chromatography using 10% ethanol in ethyl acetate as the eluting solvent. The *title compound* was isolated as a crystalline solid (197 mg, 90%) (Found: C, 56.96; H, 5.22; N, 13.77. $C_{19}H_{20}N_4O_4S$ requires C, 56.99; H, 5.03; N, 13.99%); δ_H(300 MHz; $CDCl_3$) 2.29–2.39 (1 H, m, 2′-H), 3.01–3.13 (1 H, m, 2′-H), 3.77–4.01 (2 H, m, 5′-H_2), 4.20 (1 H, m, 4′-H), 4.69–4.75 (3 H, m, 3′-H and OCH_2), 5.13–5.22 (2 H, m, CH=CH_2), 5.78–5.93 (1 H, m, C*H*=CH_2), 6.29 (1 H, dd, *J* 5.8 and 8.8, 1′-H), 7.45–7.47 (3 H, m, Ph), 7.66–7.69 (2 H, m, Ph) and 7.87 (1 H, s, 8-H); *m/z* (EI) 323 ([M − Ph]$^+$, 17%), 283 ([M − ribose]$^+$, 85), 269 (27), 255 (100), 193 (41), 142 (31), 117 (60), 98 (36), 73 (32), 57 (53) and 43 (58).

Deallylations

2-*N*-Allyl-2′-deoxyguanosine 10a. 2-*N*,6-*O*-Diallyl-2′-deoxyguanosine (directly from the previous reaction) was dissolved in ethanol (20 cm^3), and water (2 cm^3) and Wilkinson's catalyst (50 mg) were added. The reaction mixture was heated at reflux. After 24 h the solvent was removed and the product was isolated by flash column chromatography on silica gel, using 70% ethanol in ethyl acetate as the eluent. The *title compound* was isolated as a solid (280 mg), which was further purified by crystallisation from ethanol–ethyl acetate, mp 224–226 °C (Found: C, 51.18; H, 5.64; N, 22.41. $C_{13}H_{17}N_5O_4$ requires C, 50.79; H, 5.58; N, 22.80%); δ_H[300 MHz; $(CD_3)_2SO$] 2.15–2.25 (1 H, m, 2′-H), 2.37–2.69 (1 H, m, 2′-H), 3.54–3.62 (2 H, m, 5′-H_2), 3.81 (1 H, m, 4′-H), 3.94 (2 H, m, NHCH_2), 4.36 (1 H, m, 3′-H), 4.87 (1 H, br t, OH), 5.13 (1 H, dd, *J* 1.6 and 10.3, CH=C*H*H), 5.23 (1 H, dd, *J* 1.6 and 17.3, CH=CH*H*), 5.28 (1 H, br d, OH), 5.86–6.01 (1 H, m, C*H*=CH_2), 6.27 (1 H, dd, *J* 6.5 and 8.5, 1′-H), 6.86 (1 H, br t, N*H*allyl), 7.91 (1 H, s, 8-H) and 10.75 (1 H, br s, NH); *m/z* (EI) 191 ([MH − ribose]$^+$, 29%), 176 (45), 117 (21), 98 (39), 81 (100), 68 (21), 53 (37) and 39 (67); *m/z* (FD) 307 (M$^+$).

2-*N*-(1-Adamantyl)-2′-deoxyguanosine 10b. 2-*N*-(1-Adamantyl)-6-*O*-allyl-2′-deoxyguanosine (420 mg, 0.95 mmol) was dissolved in ethanol (20 cm^3), and water (2 cm^3) and Wilkinson's catalyst (50 mg) were added. The reaction mixture was heated at reflux temperature, and after 5 days the solvent was removed. The product was isolated by column chromatography using 40% ethanol in ethyl acetate as the eluting solvent. The *title product* was a solid (159 mg, 42%), which was further purified by crystallisation from ethyl acetate–ethanol, mp >230 °C (Found: C, 60.11; H, 6.79; N, 17.49. $C_{20}H_{27}N_5O_4$ requires C, 59.82; H, 6.78; N, 17.45%); δ_H[300 MHz; $(CD_3)_2SO$] 1.57 (6 H, m, adamantyl), 1.97 (9 H, m, adamantyl), 2.17 (1 H, m, 2′-H), 2.56 (1 H, m, 2′-H), 3.42 (2 H, m, 5′-H_2), 3.71 (1 H, m, 4′-H), 4.23 (1 H, m, 3′-H), 4.83 (1 H, br t, OH), 5.21 (1 H, br d, OH), 6.26 (1 H, pseudo-t, *J* 7.0, 1′-H), 6.18 (1 H, br s, N*H*adamantyl), 7.80 (1 H, s, 8-H) and 10.18 (1 H, br s, NH); δ_C[75 MHz; $(CD_3)_2SO$] 30.2, 36.8, 40.9, 41.9, 52.6, 62.5, 71.8, 84.6, 88.3, 116.8, 137.1, 151.6, 151.9 and 158.9; *m/z* (EI) 285 ([M + 1 − ribose]$^+$, 29%), 135 ([M + 1 − ribose − NHadamantyl]$^+$, 82), 120 (33), 98 (100), 81 (74) and 41 (71).

2′-Deoxy-2-*N*-(2-hydroxyethyl)guanosine 10c. 6-*O*-Allyl-2′-deoxy-2-*N*-(2-hydroxyethyl)guanosine (359 mg, 1.02 mmol) was dissolved in ethanol (20 cm^3) and water (2 cm^3) and Wilkinson's catalyst (50 mg) were added. The reaction mixture was heated at reflux temperature and after 30 min the solvent was removed. The product was isolated by column chromatography using ethanol as the eluent. The *product* was isolated as a solid (73 mg, 23%), which was further purified by crystallisation from ethyl acetate–ethanol, mp 223–225 °C (Found: C, 45.93; H, 5.36; N, 22.70. $C_{12}H_{17}N_5O_5$ requires C, 46.28; H, 5.51; N, 22.50%); δ_H(300 MHz; [$^2H_4$]methanol) 2.33 (1 H, m, 2′-H), 2.70 (1 H, m, 2′-H), 3.48 (2 H, m, 5′-H_2), 3.70 (4 H, m, CH_2CH_2), 3.93 (1 H, m, 4′-H), 4.60 (1 H, m, 3′-H), 6.27 (1 H, m, 1′-H) and 7.94 (1 H, s, 8-H); *m/z* (EI) 195 ([MH − ribose]$^+$, 3%), 177 ([MH − ribose − H_2O]$^+$, 77), 164 (18), 151 (24), 135 (29), 117 ([MH − ribose − $NHCH_2CH_2OH$]$^+$, 22), 98 (94), 81 (100), 68 (32), 53 (41), 44 (53) and 36 (70); *m/z* (FD) 311 (M^+).

2′-Deoxy-2-*N*-(methoxycarbonylmethyl)guanosine 10d. 6-*O*-Allyl-2′-deoxy-2-*N*-(methoxycarbonylmethyl)guanosine (288 mg, 0.76 mmol) was dissolved in ethanol (14 cm^3), and water (2 cm^3) and Wilkinson's catalyst (35 mg) were added. The reaction mixture was heated at reflux temperature and after 30 min the solvent was removed. The product was isolated by column chromatography using ethanol as the eluent. The *product* was isolated as a solid (152 mg, 59%), mp > 230 °C (Found: C, 46.21; H, 5.07; N, 20.96. $C_{13}H_{17}N_5O_6$ requires C, 46.00; H, 5.05; N, 20.65%); δ_H[300 MHz; $(CD_3)_2SO$] 2.22–2.31 (1 H, m, 2′-H), 2.63–2.75 (1 H, m, 2′-H), 3.49–3.67 (2 H, m, 5′-H_2), 3.76 (3 H, s, OMe), 3.89 (1 H, m, 4′-H), 4.17 (2 H, d, *J* 5.7, NHCH_2), 4.41 (1 H, m, 3′-H), 4.98 (1 H, t, *J* 5.5, OH), 5.38 (1 H, d, *J* 4.0, OH), 6.19 (1 H, pseudo-t, *J* 7.3, 1′-H), 6.94 (1 H, br t, N*H*CH_2), 8.02 (1 H, s, 8-H) and 11.13 (1 H, br s, NH); *m/z* (EI) 191 ([M − CH_3O − ribose]$^+$, 3%), 98 (31), 81 (60) and 44 (100).

9-*N*-Substituted-6-*O*-allylguanines

6-*O*-Allyl-9-*N*-(2-cyanoethyl)guanine 12. 6-*O*-Allylguanine (5.05 g, 26.4 mmol) was dissolved in DMF (80 cm^3) and potassium carbonate (180 mg, 1.3 mmol) and acrylonitrile (1.68 g, 31.7 mmol) were added. The mixture was stirred at room temperature (30 °C) for 3 days. The solution was filtered and the DMF was removed *in vacuo*. The residue was recrystallised from ethyl acetate to yield the title compound as a crystalline solid (5.01 g, 78%), mp 147–148 °C (Found: C, 54.19; H, 4.72; N, 34.60; Calc. for $C_{11}H_{12}N_6O$: C, 54.09; H, 4.95; N, 34.33%); δ_H[300 MHz; $(CD_3)_2SO$] 3.20 (2 H, t, *J* 6.3, CH_2CN), 4.39 (2 H, t, *J* 6.3, NCH_2), 5.03 (2 H, d, *J* 5.7, OCH_2), 5.33 (1 H, dd, *J* 1.3 and 10.5, CH=C*H*H), 5.48 (1 H, dd, *J* 1.3 and 17.2, CH=CH*H*), 6.11–6.24 (1 H, m, C*H*=CH_2), 6.59 (2 H, br s, NH_2) and 8.01 (1 H, s, 8-H); δ_C[75 MHz; $(CD_3)_2SO$] 17.8, 38.5, 66.0, 113.6, 118.0, 118.2, 133.2, 139.4, 154.2, 159.8 and 160.0. *m/z* (EI) 244 (M^+, 100%), 215 (29), 204 ([MH − allyl]$^+$, 24), 188 ([MH − Oallyl]$^+$, 21), 54 (24) and 43 (38).

6-*O*-Allyl-9-*N*-(2-cyanoethyl)xanthine 13. 6-*O*-Allyl-9-*N*-(2-cyanoethyl)guanine **12** (1.5 g, 6.15 mmol) was dissolved in dichloromethane (150 cm^3) and *tert*-butyl nitrite (30 cm^3) was added. The solution was stirred at room temperature for 10 min and then was cooled in an ice-bath. A precipitate began to appear, and after 30 min the flask was transferred to the freezer. After a further 30 min, the solid was collected by suction filtration. The solid was taken up into hot ethyl acetate (~500 cm^3) and the orange solid impurities were removed by filtration. Removal of the solvent gave a pale cream solid (635 mg, 42%) (the product may be used at this stage or further purified to give an off-white powder by crystallisation from a minimum amount of ethanol); δ_H[300 MHz; $(CD_3)_2SO$] 3.09 (2 H, t, *J* 6.5, CH_2CN), 4.35 (2 H, t, *J* 6.5, NCH_2), 4.96 (2 H, d, *J* 4.3, OCH_2), 5.25 (1 H, dd, *J* 1.6 and 10.4, CH=C*H*H), 5.39 (1 H, dd, *J* 1.6 and 17.2, CH=CH*H*), 6.01–6.14 (1 H, m, C*H*=CH_2), 8.04 (1 H, s, 8-H) and 11.75 (1 H, br s, NH); *m/z* (EI) 205 ([MH − allyl]$^+$, 12%), 152 ([MH − allyl − CH_2CH_2CN]$^+$, 100), 109 (67) and 53 (89).

6-*O*-Allyl-9-*N*-(2-cyanoethyl)-2-*O*-(trifluoromethylsulfonyl)-xanthine 14. 6-*O*-Allyl-9-*N*-(2-cyanoethyl)xanthine **13** (225 mg, 0.92 mmol) was dissolved in anhydrous dichloromethane (40 cm^3), and triethylamine (0.5 cm^3) and DMAP (~10 mg) were added. The mixture was cooled in an ice-bath and trifluoromethanesulfonyl chloride (186 mg, 1.1 mmol) was added. The reaction mixture was stirred for 30 min, or until none of the starting xanthine derivative remained by TLC. Removal of the solvent, followed by flash column chromatography on silica, using 20% light petroleum in ethyl acetate as the eluting solvent, gave the required product as a pale yellow oil which crystallised in the 'fridge (216 mg, 62%); δ_H(300 MHz; $CDCl_3$) 3.05 (2 H, t, *J* 6.5, CH_2CN), 4.53 (2 H, t, *J* 6.5, NCH_2), 5.13 (2 H, m, OCH_2), 5.38 (1 H, m, CH=C*H*H), 5.52 (1 H, m, CH=CH*H*), 6.10–6.21 (1 H, m, C*H*=CH_2) and 8.10 (1 H, s, 8-H); *m/z* (EI) 377 (M^+, 32%), 244 (44), 189 (100), 81 (28), 69 (32), 54 (28) and 41 (79).

2-*N*,6-*O*-Diallyl-9-*N*-(2-cyanoethyl)guanine 15a. 6-*O*-Allyl-9-*N*-(2-cyanoethyl)-2-*O*-(trifluoromethylsulfonyl)xanthine **14** (343 mg, 0.91 mmol) was dissolved in DMF (8 cm^3), allylamine (207 mg, 3.64 mmol) was added, and the reaction mixture was stirred at room temperature for 90 min. The solvent was removed *in vacuo* and the product was isolated as a solid by flash column chromatography using ethyl acetate as the eluting solvent (201 mg, 78%), mp 103–106 °C; δ_H[300 MHz; $(CD_3)_2SO$] 3.08 (2 H, t, *J* 6.5, CH_2CN), 3.88 (2 H, m, NHCH_2), 4.27 (2 H, t, *J* 6.5, NHCH_2), 4.92 (2 H, d, *J* 5.7, OCH_2), 4.95 (1 H, dd, *J* 1.5 and 10.3, NCH_2CH=C*H*H), 5.13 (1 H, dd, *J* 1.5 and 17.1, $NHCH_2$CH=CH*H*), 5.22 (1 H, dd, *J* 1.3 and 10.3, OCH_2CH=C*H*H), 5.36 (1 H, dd *J* 1.3 and 17.1, OCH_2CH=CH*H*), 5.79–5.95 (1 H, m, $NHCH_2$C*H*), 5.98–6.14 (1 H, m, OCH_2C*H*), 7.12 (1 H, t, *J* 5.8, NH) and 7.86 (1 H, s, 8-H); *m/z* (EI) 284 (M^+, 88%), 269 (70), 243 ([M − allyl]$^+$, 100), 228 ([MH − Oallyl]$^+$, 42), 188 (69), 135 (21), 81 (26), 54 (60) and 41 (53).

6-*O*-Allyl-9-*N*-(2-cyanoethyl)-2-*N*-(2-hydroxyethyl)guanine 15b. 6-*O*-Allyl-9-*N*-(2-cyanoethyl)-2-*O*-(trifluoromethylsulfonyl)xanthine **14** (443 mg, 1.18 mmol) was dissolved in DMF (10 cm^3), ethanolamine (287 mg, 4.70 mmol) was added, and the reaction mixture was stirred at room temperature for 120 min. The solvent was removed *in vacuo* and the product was isolated by flash column chromatography using 10% ethanol in ethyl acetate as the eluting solvent (340 mg, 100%); δ_H(300 MHz; $CDCl_3$) 2.91 (2 H, t, *J* 6.6, CH_2CN), 3.57 (2 H, m, CH_2), 3.81 (2 H, m, CH_2), 4.31 (2 H, t, *J* 6.6, NCH_2), 4.98 (2 H, m, OCH_2), 5.26 (1 H, dd, *J* 1.4 and 10.5, CH=C*H*H), 5.37 (1 H, dd, *J* 1.4 and 17.2, CH=CH*H*), 6.00–6.13 (1 H, m, C*H*=CH_2) and 7.63 (1 H, s, C-8).

2-*N*,6-*O*-Diallylguanine 16a. Sodium (59 mg, 2.56 mmol) was added to dry ethanol (15 cm^3). The resulting solution was added to 2-*N*,6-*O*-diallyl-9-*N*-(2-cyanoethyl)guanine **15a** (182 mg, 0.64 mmol) and the mixture was heated to reflux. After 10 min, the solution was cooled, and neutralised using glacial acetic acid. The solvent was removed and water (20 cm^3) was added. The product was extracted with ethyl acetate (3 × 15 cm^3) and the combined organic extracts were dried over $MgSO_4$. The solvent was removed and the residue was recrystallised from light petroleum–ethyl acetate to afford the required 2-*substituted*-6-O-*allylguanine derivative* **16a** as a crystalline solid (133 mg, 90%), mp 159–161 °C (Found: C, 57.40; H, 5.92; N, 30.45. $C_{11}H_{13}N_5O$ requires C, 57.13; H, 5.67; N, 30.28%); δ_H(300 MHz; $CDCl_3$) 4.17 (2 H, m, NHCH_2), 5.00 (2 H, d, *J* 5.8, OCH_2), 5.12 (1 H, br t, NH), 5.33–5.13 (3 H, 3 × dd, OCH_2CH=C*H*H, and NCH_2-CH=CH_2), 5.42 (1 H, dd, *J* 1.5 and 17.2, OCH_2CH=CH*H*), 6.19–5.91 (2 H, m, OCH_2C*H* and $NHCH_2$C*H*), 7.71 (1 H, s, 8-H) and 11.41 (1 H, br s, NH); *m/z* (EI) 231 (M^+, 76%), 216 (58), 202 (23), 190 ([M − allyl]$^+$, 100), 176 (32), 135 (94), 56 (47) and 41 (27).

6-*O*-Allyl-2-*N*-(2-hydroxyethyl)guanine 16b. Sodium (120 mg,

5.2 mmol) was added to dry ethanol (20 cm^3). The resulting solution was added to 6-*O*-allyl-2-*N*-(2-hydroxyethyl)guanine **15b** (340 mg, 1.18 mmol) and the mixture was heated to reflux. After 20 min, the solution was cooled, and neutralised using glacial acetic acid. The solvent was removed and water (20 cm^3) was added. The product was extracted with ethyl acetate (3 × 15 cm^3) and the combined organic extracts were dried over $MgSO_4$. The solvent was removed and the residue was recrystallised from ethanol–ethyl acetate to afford the required *title product* as a solid (255 mg, 92%), mp 184–185 °C (Found: C, 51.21; H, 5.66; N, 29.71. $C_{10}H_{13}N_5O_2$ requires C, 51.06; H, 5.57; N, 29.77%); δ_H(300 MHz; [$^2H_4$]methanol) 3.48 (2 H, t, *J* 5.7, CH_2), 3.68 (2 H, t, *J* 5.7, CH_2), 4.96 (2 H, m, OCH_2), 5.22 (1 H, m, CH=C*H*H), 5.41 (1 H, m, CH=CH*H*), 6.06–6.15 (1 H, m, C*H*=CH_2) and 7.76 (1 H, s, 8-H); *m/z* (EI) 235 (M^+, 28%), 204 (100), 191 ([MH − CH_2CH_2OH]$^+$, 21), 164 (47), 135 (38) and 41 (39).

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