# An Efficient Regioselective Synthesis of Substituted Purine Analogues of Guanosine and Inosine

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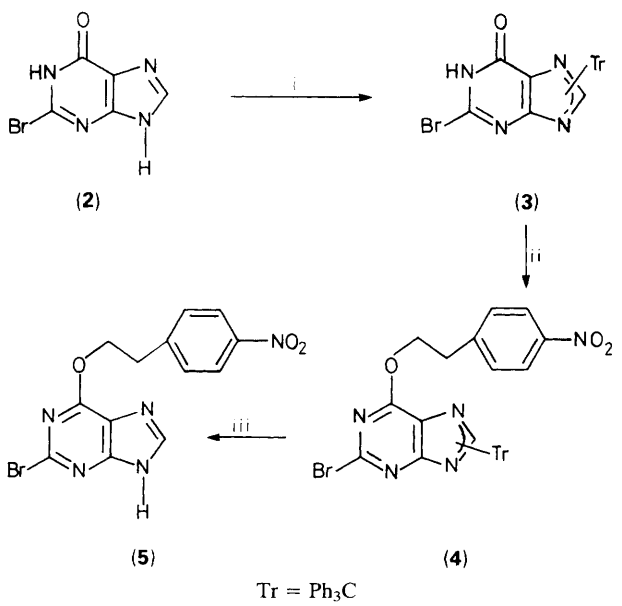
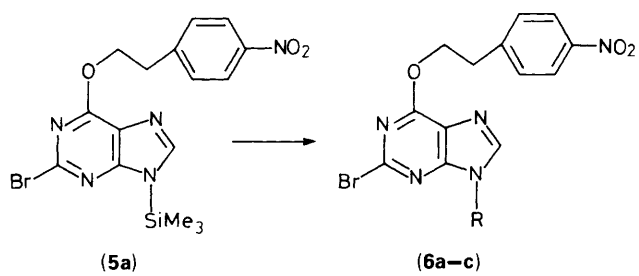
Condensation of 2-bromo-6-(4-nitrophenylethoxy)purine as the trimethylsilyl derivative (**5a**) with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose, 1-*O*-acetyl-2,3-di-*O*-benzoyl-5-deoxy-5-diethoxy-phosphinyl-β-D-ribofuranose, and (2-acetoxyethoxy)methyl bromide resulted in $N^9$-regioselective alkylation to give (**6a–c**), which were then converted to guanine and hypoxanthine nucleosides, nucleotides, and Acyclovir analogues, respectively.

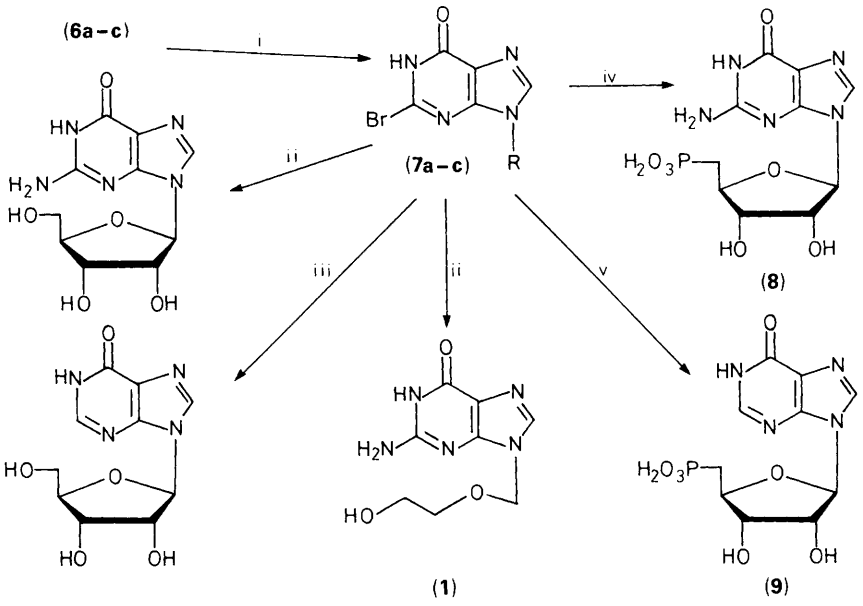
There has been considerable interest in the synthesis of guanine nucleosides following the report of the antiviral properties of 'Acyclovir' [(2-hydroxyethoxy)methylguanine] (**1**) against herpes simplex virus.[1] The synthesis of 9-substituted guanosine analogues has often posed problems such as contamination with $N^7$ substitution.[2] Zou and Robins[3] have reported recently a high-yield regioselective procedure for guanosine synthesis which gives some 3% of the bisriboside as a by-product. However, the diphenylcarbamoyl protecting group used is unstable even towards mildly acidic or basic conditions,[4] which limits further modification of the base moiety. Our attempt to synthesize guanosine 5'-deoxy-5'-phosphonate[5] by Zou's procedure was unsuccessful. In this communication we report an alternative procedure which can be used to synthesize both 9-substituted guanosine and inosine analogues in high yield.

Alkylation of 2-bromo-6-oxopurine (**2**)[6] with trityl (Tr) chloride and triethylamine gave the $N^7/N^9$-trityl derivatives (**3**) in quantitative yield (Scheme 1). Reaction of crude (**3**) with 4-nitrophenylethanol under Mitsunobu conditions, as reported by Himmelsbach *et al.*,[7] gave the corresponding tritylated 2-bromo-6-(4-nitrophenylethoxy)purine (**4**) in 85% yield, crystallized from propan-2-ol. The trityl group was removed with 80% acetic acid to give 2-bromo-6-(4-nitrophenylethoxy)purine (**5**) in quantitative yield. Compound (**5**)




**Scheme 1.** TrCl (2 equiv.), $Et_3N$ (3 equiv.), 100 °C, 2 h, 100%; ii, $PPh_3$ (2 equiv.), diethyl azodicarboxylate (2 equiv.), $p$-$O_2NC_6H_4CH_2CH_2OH$/dioxane (2 equiv.), 80 °C, 6 h, 85%; iii, 80% HOAc, 80 °C,






**Scheme 2.** *Reagents and conditions:* i, MeCN/DBU (1 equiv.), 80—85%; ii, methanolic $NH_3$, 120 °C, 80%; iii, (a) Pd/C (H), 60 psi, room temp., 16 h, (b) methanolic $NH_3$, room temp., 16 h, 81%; iv, (a) $Me_3SiBr$ (3 equiv.), MeCN, room temp., 6 h, (b) methanolic $NH_3$, 120 °C, 16 h, 55%; v, (a) Pd/C (H), 60 psi, room temp., 16 h, (b) $Me_3SiBr$ (3 equiv.), MeCN, room temp., 6 h, (c) methanolic $NH_3$, room temp., 16 h, 57%.

can be prepared on a large scale in 75% overall yield, without requiring chromatographic purification in any step during its preparation.

The base (**5**) was silylated with bistrimethylsilylacetamide to yield (**5a**), which was condensed with the appropriate sugar or alkylating agent according to the conditions shown in Table 1 to provide the $N^9$-alkylated products (**6a—c**).† The 4-nitrophenylethyl moiety was removed[7] by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and after the disappearance of the starting material on t.l.c., the reaction was quenched with Dowex 50 X 8($H^+$), which after filtration gave the intermediates (**7a—c**) in 80—85% yield (Scheme 2).

Conversion of (**7a**) to guanosine and inosine was achieved in excellent yields under the conditions shown in Scheme 2. Compound (**7c**) was converted to 5′-deoxy-5′-phosphonates of guanosine and inosine as reported earlier.[5] Compound (**7b**) was converted to Acyclovir (**1**) as shown in Scheme 2.

† The $N^9$:$N^7$ ratio was determined by the integration of the C-8 $^1$H n.m.r. signal, which for the $N^7$ isomer appears slightly downfield from that of the $N^9$ isomer [*e.g.*, in (**7b**): $N^9$ δ 8.22, $N^7$ δ 8.25, see also ref. 2]. The $N^7$ isomer could not be isolated pure free from the desired $N^9$ isomer. All compounds give satisfactory elemental analysis. $^1$H N.m.r. spectra of the $N^9$ isomer were recorded in $CDCl_3$ on an IBM NR/300 n.m.r. spectrometer unless otherwise stated: (**4**), δ 3.27 (t, *J* 6.7 Hz, 2H), 4.76 (t, *J* 6.7 Hz, 2H), 7.12 and 7.29 (m, 15H), 7.46 (d, *J* 8.5 Hz, 2H), 7.89 (s, 1H), 8.15 (d, *J* 8.5 Hz, 2H); (**5**), $(CD_3)_2SO$, δ 3.28 (t, *J* 6.6 Hz, 2H), 4.78 (t, *J* 6.6 Hz, 2H), 7.63 (d, *J* 8.6 Hz, 2H), 8.17 (d, *J*, 8.6 Hz, 2H), 8.39 (s, 1H), 13.5 (br. s, 1H); (**6a**), m.p. 206—207 °C; δ 2.07, 2.12, 2.14 (3s, COMe), 3.29 (t, *J* 6.7 Hz, $-CH_2$), 4.38 (m, 2H), 4.42 (t, *J* 6.7 Hz, $CH_2$), 5.56 (dd, $J_1$ 4.4 Hz, $J_2$ 5.6 Hz, 1H), 5.75 (dd, $J_1$ 5.6 Hz, $J_2$ 5.5 Hz, 1H), 6.16 (d, *J* 5.5 Hz, 1H), 7.48 and 8.18 (d, *J* 8.7, 4H), 8.02 (s, 1H, H-8); (**6b**), syrup; δ 1.94 (s, Me), 3.24 (t, *J* 6.6 Hz, 2H), 3.67 (dd, $J_1$ 4.78 Hz, $J_2$ 4.43 Hz, 2H), 4.09 (dd, $J_1$ 4.8 Hz, $J_2$ 4.4 Hz, 2H), 4.77 (t, *J* 6.6 Hz, 2H), 5.57 (s, 2H), 7.4 and 8.05 (d, *J* 8.7 Hz, 4H), 8.01 (s, 1H, H-8); (**6c**), syrup; δ 1.23 (m, 6H), 2.56 (m, 2H), 3.24 (t, 2H), 4.0 (m, 4H), 4.5 (m, 1H), 4.77 (m, 2H), 5.97 (t, 1H), 6.16 (t, 1H), 6.13 (d, *J* 5.1 Hz, 1H), 7.3 and 7.9 (m, 14H), 8.23 (s, 1H, H-8); (**7b**), m.p. 144—145 °C; $(CD_3)_2SO$, δ 1.95 (s, COMe, 3H), 3.68 (t, *J* 4.6 Hz, 2H), 4.07 (t, *J* 4.6 Hz, 2H), 5.52 (s, 2H), 8.22 (s, 1H, H-8), 13.25 (br. s, 1H).

**Table 1.**

| Product | Alkylating agent | Catalyst (amount) | Yield $N^9$ /% | Ratio $N^9$:$N^7$ |
|---|---|---|---|---|
| (**6a**) | 1,2,3,5-Tetra-acetylribose[a] | TMSOTf[c] (1.5 equiv) | 95 | 20:1 |
| (**6b**) | $AcOCH_2CH_2OCH_2Br$[a] | None | 76 | 99:1 |
| (**6c**) | 1-*O*-Acetyl-2,3-di-*O*-benzoyl-5-deoxy-5-diethoxyphosphinyl-β-D-ribofuranose[b] | TMSOTf[c] (3 equiv.) | 75 | 19:1 |

[a] *Reaction conditions:* MeCN, reflux, 1 h; room temp., 16 h. [b] MeCN, 0 °C, 4 h; room temp., 16 h. [c] TMSOTf = $CF_3SO_3SiMe_3$.

Thus, by using 2-bromo-6-(4-nitrophenylethoxy)purine (**5**), both guanine and hypoxanthine nucleosides could be prepared *via* a common intermediate. Also, this procedure provides an opportunity to introduce various nucleophiles at C-2, which is currently under investigation in our laboratory.

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