Pergamon

Tetrahedron Letters 42 (2001) 1781–1784

TETRAHEDRON LETTERS

Regioselective alkylation of guanines using 2-acetoxytetrahydrofurans

Graham R. Geen,[a] Peter M. Kincey[a,*] and P. Grant Spoors[b]

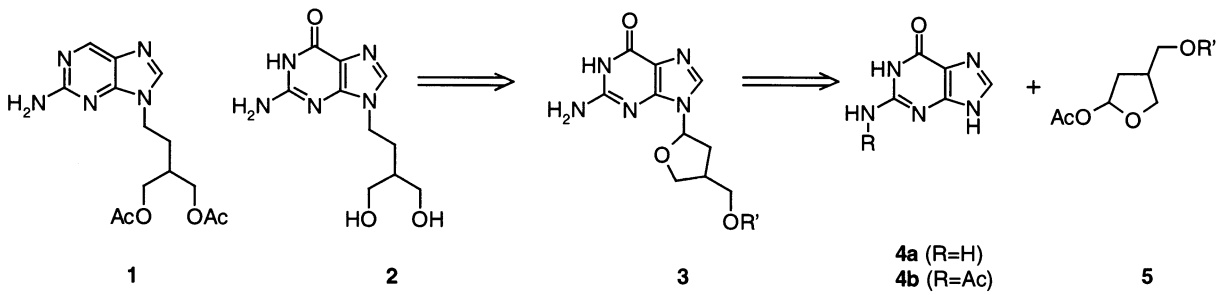
[a]*SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK*
[b]*SmithKline Beecham Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA 19406, USA*

Received 13 December 2000; accepted 20 December 2000

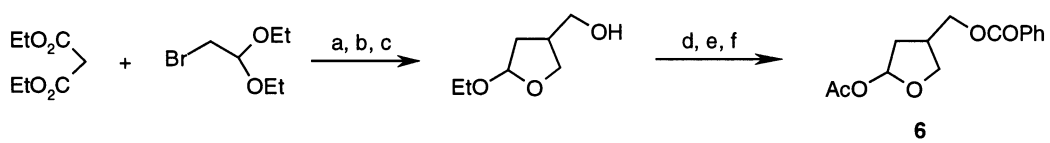
Abstract—Reaction of silylated guanine derivatives with 2-acetoxy-4-benzoyloxymethyltetrahydrofuran in DMF or NMP resulted in selective N-9 alkylation. This was used as the basis for a regioselective synthesis of the anti-viral agents famciclovir and penciclovir.

The N-9 alkylation of purines remains an important synthetic route to pharmaceutically important acyclic nucleoside analogues, however these reactions are rarely regiospecific, giving rise to mixtures of N-9 and N-7 alkylated products.[1] In particular, base-catalysed alkylations of guanine and 2-acylated guanines exhibit very poor regioselectivity, resulting in approximately equal amounts of N-9 and N-7 isomers. Conversely, acid-mediated alkylations of guanines using α-halo or α-acetoxy ether alkylating agents give regioisomeric mixtures initially, but on heating the N-7 isomer rearranges to the thermodynamically more stable N-9.[2]

We have been investigating the possibility of synthesising the anti-viral agents famciclovir **1** and penciclovir **2** from guanine starting materials, but have hitherto been unable to take direct advantage of this rearrangement due to the all carbon backbone of the side-chain. However, we considered that such a rearrangement might be exploited if we employed a tetrahydrofuran-



Scheme 1.



Scheme 2. (a) NaOEt, NaI, EtOH, reflux, 48 h (60%); (b) $LiAlH_4$ (2 equiv.), Et_2O, rt, 18 h, (94%); (c) Dowex 50WX8-H^+ resin, EtOH, reflux, 2 h, (83%); (d) PhCOCl, NEt_3, CH_2Cl_2, 0–5°C 1 h then rt 2 h, (99%); (e) HCl, H_2O, dioxan, rt, 18 h, (47%); (f) Ac_2O, NEt_3, DMAP, powdered 3 Å mol. sieve, CH_3CN, rt, 1 h, (95%).

* Corresponding author.

0040-4039/01/$ - see front matter
PII: S0040-4039(00)02326-1

substituted purine **3**, prepared by alkylation of a guanine with a 2-acetoxytetrahydrofuran **5**.[3] Reductive cleavage of the tetrahydrofuran ring in **3** would then furnish famciclovir and penciclovir (Scheme 1).

The alkylating agent 2-acetoxy-4-benzoyloxymethyltetrahydrofuran **6**[4] was prepared as a 1:1 mixture of diastereoisomers in six steps from diethyl malonate according to Scheme 2.

Initially, 2-*N*-acetylguanine **4b** was silylated using bis(trimethylsilyl)acetamide (BSA), and alkylated with **6** following the glycosylation method of Vorbrüggen (TMS–OTf, acetonitrile, 0°C, 3 h).[2b] Examination of the reaction mixture by reverse-phase HPLC showed complete consumption of **4b** and formation of four products corresponding to the two diastereoisomers of each of the N-9 (**7b**) and N-7 (**8b**) alkylated guanines. The ratio of N-9 to N-7 products was approximately 2:1.[5] Heating the mixture to 60°C did not result in any rearrangement; instead, regeneration of *N*-acetylguanine was observed. In the presence of excess alkylating agent some rearrangement did occur upon heating, but much decomposition was also evident.

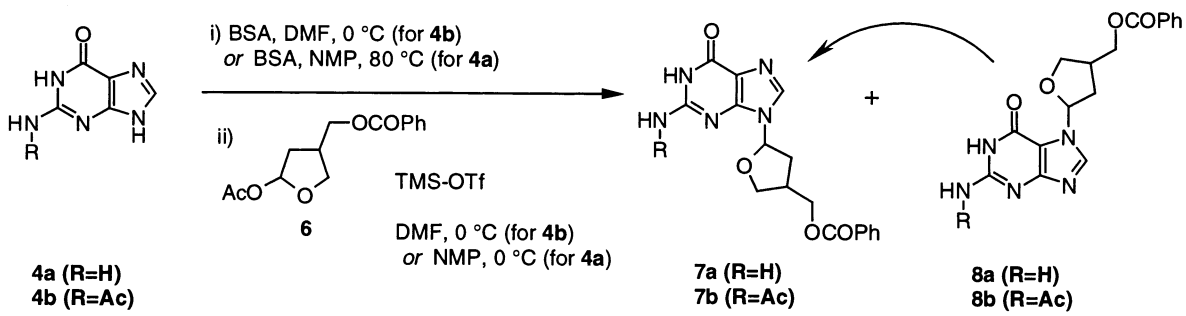
When the alkylation reaction was performed in DMF, however, a remarkable low-temperature rearrangement occurred. After 30 minutes at 0°C, the N-9/N-7 ratio was about 1:1, but on continued stirring this increased to 10:1 after 3 hours, reaching a maximum of 15:1 after 5 hours. Upon quenching the reaction with aqueous sodium bicarbonate, the product crystallised from the reaction mixture giving essentially pure N-9 alkylated purine **7b** in 83% yield. Intriguingly, replacement of DMF by *N*-methyl-2-pyrrolidinone (NMP) resulted in loss of regioselectivity, the N-9/N-7 ratio reaching a maximum of 2.5:1. Other solvents (e.g. 1,2-dichloroethane, dichloromethane, toluene, DMSO) generally gave poor to moderate isomer ratios.

In contrast, the analogous reaction using guanine **4a** as substrate proceeded better in NMP (N-9/N-7 ratio 15:1 after 24 h) than in DMF (ratio 10:1). In this case, quenching the reaction with a small amount of aqueous sodium bicarbonate resulted in preferential crystallisation of the N-7 isomer **8a**. After filtration, further addition of water caused precipitation of pure N-9 alkylated guanine **7a** in 70% yield (Scheme 3).[6]

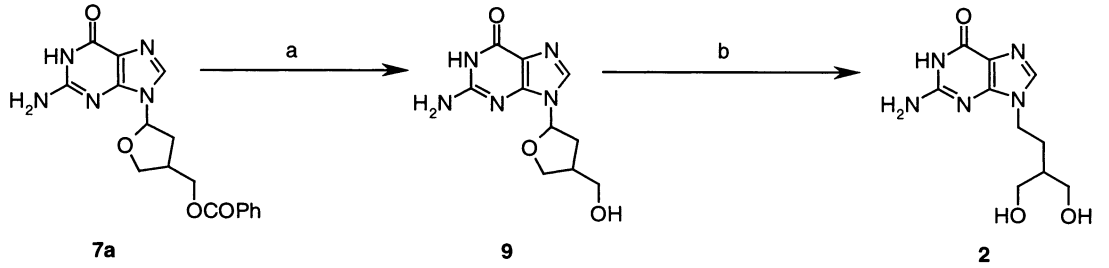
It is noteworthy that these N-7 to N-9 migrations take place at low temperatures, as such rearrangements normally require heating.[2,7] Analogous preparations of compounds such as acyclovir, which entail migration of an acyclic side-chain, may require temperatures of 100°C or more.[8] The use of the polar solvents DMF and NMP is also an unusual feature of this reaction, as non-polar solvents such as 1,2-dichloroethane or toluene are reported to be favoured for N-9 alkylation of silylated purines.[2c,7,9]

Having achieved the desired regioselective alkylations, attention turned to the reductive ring cleavage. Although numerous examples have been reported of the reductive cleavage of acetals, aminals and ethers using reducing agents such as H_2/metal catalysts,[10] $NaBH_4$[11] and $LiAlH_4/AlCl_3$,[12] the only report of such cleavage of the C-1′–O-4′ bond of nucleosides employs diisobutylaluminium hydride (DIBAL-H).[13] Attempted reduction of the tetrahydrofuranyl purines **7** using any of the above reducing agents did not give any ring-opened product. However, upon hydrolysis of the benzoate ester in the alkylated guanine **7a**, the resulting hydroxymethyl-tetrahydrofuranyl guanine **9** succumbed to reductive cleavage using DIBAL-H in THF to yield penciclovir directly. The reaction was slow, and a large excess of DIBAL-H (15 equiv.) was required in order to achieve 50% conversion in 48 h. After quenching the reaction with aqueous potassium sodium tartrate, evaporation to dryness and crystallisation of the product from water, penciclovir was obtained in no more than 10% yield (Scheme 4).

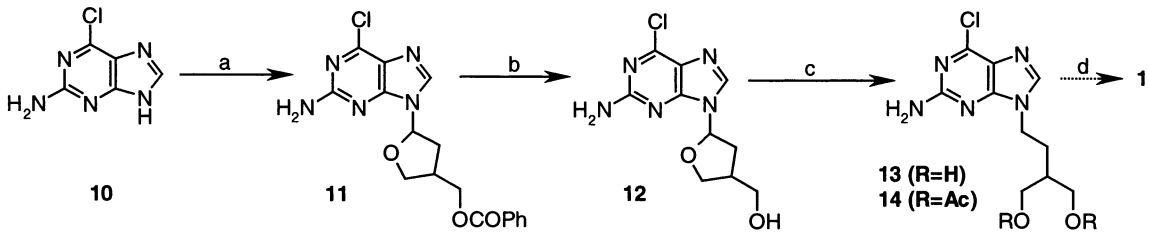
An analogous synthesis of famciclovir **1** was accomplished starting from 2-amino-6-chloropurine (ACP) **10**. Alkylation of **10** with **6** proceeded smoothly in DMF to give a 15:1 ratio of N-9/N-7 alkylated products. Crystallisation of the crude product from diethyl ether gave the N-9 alkylated purine **11** in 81% yield.[14] Once again, reaction of the benzoate **11** with DIBAL-H failed to give any ring-opening, and it was necessary to prepare the free hydroxy-compound **12** as a suitable substrate. Addition of 10 equiv. DIBAL-H to a solution of **12** in THF resulted in formation of the acyclic diol **13**. This material was not isolated, but was acetylated in situ using excess acetic anhydride to give the diacetate **14** in 24% yield (Scheme 5). The diacetate **14** is a known precursor to famciclovir (and penciclovir), and the transformation is effected readily by hydrogenolysis.[15]



Scheme 3.



Scheme 4. (a) 1 M NaOH (aq), rt, 3 h, (87%); (b) DIBAL-H (15 equiv.), THF, rt, 48 h, (10%).



Scheme 5. (a) (i) BSA, DMF, rt, 1.5 h; (ii) **6**, TMS–OTf, DMF, 0–5°C, 3 h, (81%); (b) NaOH, H_2O, dioxan, rt, 4 h, (42%); (c) (i) DIBAL-H (10 equiv.), THF, rt, 24 h; (ii) Ac_2O, NEt_3, DMAP, CH_2Cl_2, reflux, 2 h, (24%); (d) H_2 (1 atm), 5% Pd/C, NEt_3, EtOAc, 50°C, 4 h, (81%) (see ref. 15).

In conclusion, we have developed a highly regioselective alkylation of guanines and 2-aminopurines using 2-acetoxytetrahydrofurans resulting in the formation of intermediates which furnish famciclovir and penciclovir after reductive cleavage of the tetrahydrofuran ring. It appears that the regioselectivity of the alkylation is influenced by both the substrate and the solvent in a rather subtle manner, and is not simply dependent on solvent polarity as has previously been suggested. This work may have further applicability to the synthesis of other purine nucleosides. The yields of acyclic purines obtained from the reductive cleavage reactions are modest at present, and additional work will be required to optimise this stage.

References

1. Kjellberg, J.; Johansson, N. G. *Nucleosides Nucleotides* **1989**, *8*, 225–256.
2. (a) Dudycz, L. W.; Wright, G. E. *Nucleosides Nucleotides* **1984**, *3*, 33–44; (b) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234–1255; (c) Vorbrüggen, H.; Höfle, G. *Chem. Ber.* **1981**, *114*, 1256–1268.
3. Sells, T. B.; Nair, V. *Tetrahedron* **1994**, *50*, 117–138.
4. Selected analytical data for **6**: δ_H (DMSO-d_6) 1.93–2.42 (m, 2H, tetrahydrofuryl CH_2), 1.99, 2.01 (2s, 3H, CH_3), 2.77–2.87 (m, 1H, tetrahydrofuryl CH), 3.80, 4.12 (2dd, 2H, tetrahydrofuryl CH_2O), 4.23–4.29 (m, 2H, CH_2O), 6.23, 6.25 (2dd, 1H, tetrahydrofuryl CHO), 7.53 (dd, 2H, 2×aromatic CH), 7.68 (dd, 1H, aromatic CH), 7.98 (d, 2H, 2×aromatic CH); δ_C (DMSO-d_6) 21.0 (CH_3), 34.5, 34.9 (tetrahydrofuryl CH_2), 36.2, 36.3 (tetrahydrofuryl CH), 65.6 (CH_2O), 70.2, 70.4 (tetrahydrofuryl CH_2O), 98.4 (tetrahydrofuryl CHO), 128.7 (2×aromatic CH), 129.2 (2×aromatic CH), 129.6 (aromatic C), 133.4 (aromatic CH), 169.7 (COPh), 172.0 ($COCH_3$); HRMS (EI) calcd for $[C_{14}H_{16}O_5]^+$: 264.0998; found: 264.0978.
5. The N-9 and N-7 isomers were separated by chromatography and the position of alkylation determined by nmr. Selected analytical data for **7b**: δ_H (DMSO-d_6) 2.13 (s, 3H, CH_3), 2.35–2.72 (m, 2H, tetrahydrofuryl CH_2), 2.92–3.13 (m, 1H, tetrahydrofuryl CH), 3.84, 4.02, 4.12, 4.30 (4dd, 2H, tetrahydrofuryl CH_2O), 4.33–4.47 (m, 2H, CH_2O), 6.14, 6.23 (2dd, 1H, tetrahydrofuryl CHO), 7.54 (dd, 2H, 2×aromatic CH), 7.67 (dd, 1H, aromatic CH), 7.99 (dd, 2H, 2×aromatic CH), 8.08, 8.15 (2s, 1H, H-8); δ_C (DMSO-d_6) 24.7 (CH_3), 33.9 (tetrahydrofuryl CH_2), 37.0, 38.3 (tetrahydrofuryl CH), 65.2, 65.5 (CH_2O), 70.3, 70.5 (tetrahydrofuryl CH_2O), 84.1 (tetrahydrofuryl CHO), 120.1 (C-5), 128.7 (2×aromatic CH), 129.1 (2×aromatic CH), 129.5 (aromatic C), 133.3 (aromatic CH), 136.7, 136.9 (C-8), 148.9, 149.2 (C-4), 150.6 (C-2), 157.5 (C-6), 165.5 (COPh), 174.3 ($COCH_3$); HRMS (ES) calcd for $[C_{19}H_{20}N_5O_5+H]^+$: 398.1464; found: 398.1501.
6. Selected analytical data for **7a**: δ_H (DMSO-d_6) 2.31–2.60 (m, 2H, tetrahydrofuryl CH_2), 2.89–3.10 (m, 1H, tetrahydrofuryl CH), 3.79–4.29 (m, 2H, tetrahydrofuryl CH_2O), 4.29–4.51 (m, 2H, CH_2O), 6.06, 6.14 (2dd, 1H, tetrahydrofuryl CHO), 6.45 (br s, 2H, NH_2), 7.57 (dd, 2H, 2×aromatic CH), 7.67 (dd, 1H, aromatic CH), 7.87, 7.93 (2s, 1H, H-8), 7.99 (dd, 2H, 2×aromatic CH), 10.62 (br s, 1H, NH); δ_C (DMSO-d_6) 33.6, 33.9 (tetrahydrofuryl CH_2), 37.0, 38.3 (tetrahydrofuryl CH), 65.3, 65.5 (CH_2O), 70.2, 70.4 (tetrahydrofuryl CH_2O), 83.6, 83.7 (tetrahydrofuryl CHO), 116.8, 116.9 (C-5), 128.7 (2×aromatic CH), 129.1 (2×aromatic CH), 129.5 (aromatic C), 133.3 (aromatic CH), 135.3 (C-8), 150.6, 150.8 (C-4), 153.4 (C-2), 156.6 (C-6), 165.5 (COPh); HRMS (ES) calcd for $[C_{17}H_{18}N_5O_4+H]^+$: 356.1359; found: 356.1374.
7. Garner, P.; Ramakanth, S. *J. Org. Chem.* **1988**, *53*, 1294–1298.
8. Shiragimi, H.; Koguchi, Y.; Tanaka, Y.; Takamatsu, S.; Uchida, Y.; Ineyama, T.; Izawa, K. *Nucleosides Nucleotides* **1995**, *14*, 337–340.

9. Vorbrüggen, H. *Acta Biochim. Pol.* **1996**, *43*, 25–36.
10. (a) Ashton, W. T.; Brown, R. D. *J. Heterocyclic Chem.* **1980**, *17*, 1709–1712; (b) Vasella, A. *Helv. Chim. Acta* **1977**, *60*, 426–446.
11. (a) Kabat, M. M.; Pankiewicz, K. W.; Sochacka, E.; Watanabe, K. A. *Chem. Pharm. Bull.* **1988**, *36*, 634–640; (b) Mirza, S.; Vasella, A. *Helv. Chim. Acta* **1984**, *67*, 1562–1567.
12. Eliel, E. L.; Nowack, B. E.; Daignault, R. A.; Badding, V. G. *J. Org. Chem.* **1965**, *30*, 2441–2447.
13. (a) Hirota, K.; Monguchi, Y.; Kitade, Y.; Sajiki, H. *Tetrahedron* **1997**, *53*, 16683–16698; (b) Kitade, Y.; Hirota, K.; Maki, Y. *Tetrahedron Lett.* **1993**, *34*, 4835–4836.
14. Selected analytical data for **11**: δ_H (DMSO-d_6) 2.38–2.67 (m, 2H, tetrahydrofuryl CH_2), 2.92–3.15 (m, 1H, tetrahydrofuryl CH), 3.85–4.29 (m, 2H, tetrahydrofuryl CH_2O), 4.32–4.51 (m, 2H, CH_2O), 6.18, 6.26 (2dd, 1H, tetrahydrofuryl CHO), 6.95 (br s, 2H, NH_2), 7.54 (dd, 2H, 2×aromatic CH), 7.67 (dd, 1H, aromatic CH), 7.99 (dd, 2H, 2×aromatic CH), 8.30, 8.36 (2s, 1H, H-8); δ_C (DMSO-d_6) 33.3, 33.7 (tetrahydrofuryl CH_2), 37.0, 38.3 (tetrahydrofuryl CH), 65.2, 65.5 (CH_2O), 70.5, 70.7 (tetrahydrofuryl CH_2O), 84.2, 84.3 (tetrahydrofuryl CHO), 123.6, 123.8 (C-5), 128.7 (2×aromatic CH), 129.1 (2×aromatic CH), 129.5 (aromatic C), 133.3 (aromatic CH), 141.2 (C-8), 149.4 (C-4), 153.4, 153.5 (C-2), 159.6 (C-6), 165.6 (COPh); calcd for $C_{17}H_{16}ClN_5O_3$: C 54.62; H 4.31; N 18.74; Found: C 54.47; H 4.30; N 18.58.
15. Choudary, B. M.; Geen, G. R.; Kincey, P. M.; Parratt, M. J.; Dales, J. R. M.; Johnson, G. P.; O'Donnell, S.; Tudor, D. W.; Woods, N. *Nucleosides Nucleotides* **1996**, *15*, 981–994.