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Practical syntheses of penciclovir and famciclovir from *N*2-acetyl-7-benzylguanine

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Abstract—We have established practical methods for the synthesis of penciclovir (PCV) and famciclovir (FCV) from readily available guanosine via *N*2-acetyl-7-benzylguanine. The alkylation of *N*2-acetyl-7-benzylguanine proceeded selectively at the N9 position to give the desired alkylated product in good yield in salt form. After conventional catalytic hydrogenolysis of the benzyl group and hydrolysis of the resulting acetate, pure PCV was obtained without the need for chromatography. As a side chain precursor, the mesylate was selected rather than a halide since the corresponding halides gave several impurities under the same reaction conditions. Two procedures for the synthesis of FCV from PCV and a derivative are also reported.

1. Introduction

Since Schaeffer et al. discovered that acyclovir is a potent and selective anti-herpes virus agent, several groups have undertaken intensive studies to develop still more potent and effective acyclic nucleoside analogues.[1] As a result, penciclovir (PCV) **1** and its pro-drug famciclovir (FCV) **2** were found to be potent and highly selective anti-viral agents against both the herpes simplex virus (HSV) and the varicella-zoster virus (VZV).[2] It has also been reported that **1** and **2** exhibit anti hepatitis B virus (HBV) activity.[3] PCV **1** and FCV **2** are analogues of acyclovir that have alkyl side chains at the N9 position (Fig. 1).

To synthesize **1** and **2**, 2-amino-6-chloropurine is commonly used as a starting material for coupling with alkyl halide side chains.[4] Normally, alkylation takes place at the N9 position as well as at the N7 position of the purine moiety, and the N9/N7 ratio is less than 6:1.[4a,b,g] To improve this ratio, several approaches have been reported, which involve changing the C-6 substituent of 2-aminopurine.[4h] For example, Geen et al. reported a ratio of 5.5:1 in the alkylation of 2-amino-6-chloropurine and noted that it could be improved to 9:1 using 2-amino-6-iodopurine as the starting material.[4c] On the other hand, this ratio was also improved by changing the structure of the side chains.[4d,e,k] Recently, Toyokuni et al. reported an excellent method using 2-phenyl-5-haloethyl-1,3-dioxolane to give the N9-alkylated compound in 94% yield.[4l] However, in each case the regioselectivity was not perfect, and it was difficult to eliminate N7 compounds from the desired N9 product without column chromatography. When triethyl 3-bromopropane-1,1,1-tricarboxylate was used as an alkyl side chain, the N7-alkylated compound was easily separated by crystallization of the N9-alkylated compound.[4f] Unfortunately, though, this reaction sequence required longer steps than the case of using diacetoxy alkyl halide side chain which is normally used to synthesize **1** and **2** from 2-amino-6-chloropurine. Geen et al. have further developed several interesting methods, which involve the coupling of 2-amino-6-chloropurine with an α-acetoxyfuran derivative under acidic conditions[4j] and Pd-catalyzed N9-selective allylation with an allyl acetate side chain.[4i] However, these sequences again require multiple steps to synthesize **1** and **2**. It should be noted that 2-amino-6-chloropurine is not a desirable compound for use in large-scale synthesis due to its high mutagenicity.[5]

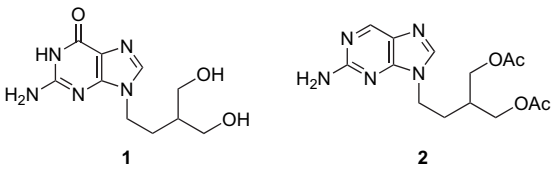

Figure 1. PCV **1** and FCV **2**.

Guanosine **3** is manufactured in very large scale by fermentation. We have previously developed practical methods to

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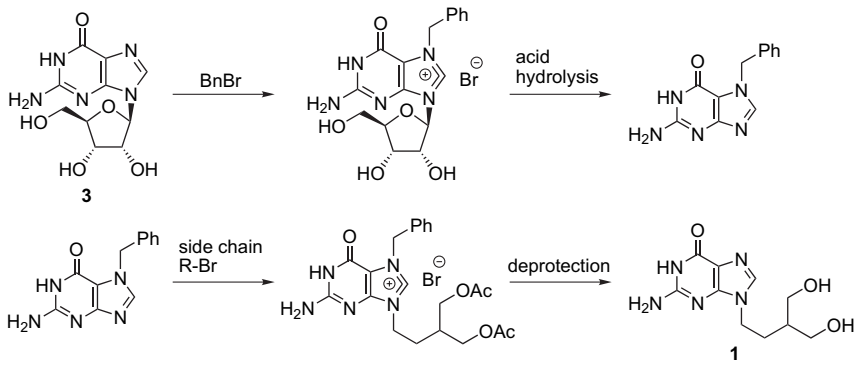
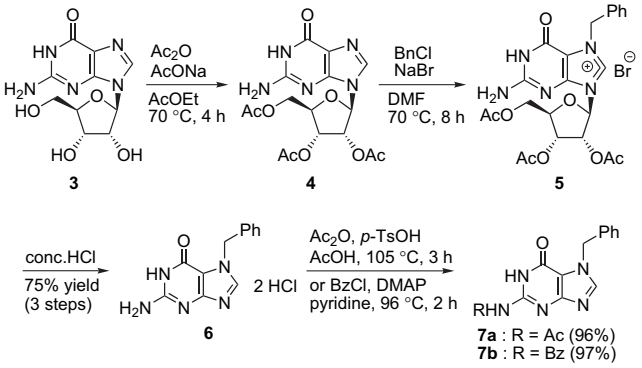


Scheme 1. Synthesis of 7-benzylguanine and selective N9-alkylation.

synthesize first acyclovir by the chemical transpurination of **3**[6a] and then d4T via the enzymatic transglycosylation of **3**.[6b] We considered that it may also be possible to use **3** as a starting material for the synthesis of **1** and **2**: in this respect, **3** may be considered an N9 ribofuranoside-protected guanine. It is known that **3** can be converted to 7-benzylguanine in two steps by conducting benzylation under neutral conditions followed by acidic deglycosylation.[7] We speculated that if 7-benzylguanine could be coupled with the side chains **8a**–**c** at the N9 position under neutral conditions, we might be able to obtain PCV **1** without the formation of the N7-alkylated byproduct after reductive removal of the N7 benzyl group (Scheme 1).[8] We reported here a practical synthesis of PCV **1** using 7-benzylguanine derivatives and also describe two methods for the synthesis of FCV **2** via **1** and its precursor.[9]

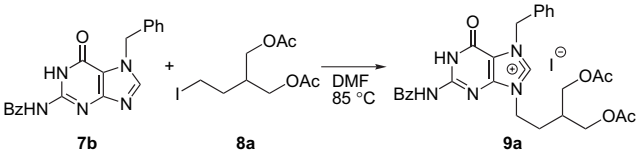
2. Results and discussion

7-Benzylguanine has previously been prepared by treating guanosine **3** with benzyl bromide followed by acid hydrolysis.[7] However, the reaction required dimethyl sulfoxide (DMSO) as a solvent due to the low solubility of **3** in other solvents. Since DMSO is not desirable for use in industrial-scale production for reasons of cost and safety, we searched for other reaction systems to prepare 7-benzylguanine. When we used readily available 2′,3′,5′-tri-*O*-acetylguanosine **4** as a starting material, the benzylation of **4** proceeded well even in *N*,*N*-dimethylformamide (DMF) to give the desired benzylated product as a bromide salt **5** in good yield. In this reaction, the combination of benzyl chloride and sodium bromide can be used instead of expensive benzyl bromide. The benzylation reaction must be carried out below 70 °C, since the deglycosylation of **5** occurs at higher temperatures to generate 7,9-dibenzylated guanine[10] as a byproduct. After the acid hydrolysis of **5**, 7BnG·2HCl **6** was obtained in 75% yield.[11] In addition to the fact that a favorable solvent and inexpensive benzyl chloride can be used, there is another advantage in this reaction sequence, although the reaction requires an additional acetylation step. Specifically, the free form of 7-benzylguanine prepared by the previous method was obtained as very low-density crystals, which were therefore difficult to filter off. On the other hand, upon formation of the HCl salt, compound **6** could be handled more easily in the isolation steps. To improve the solubility of **6** in the reaction solvent, we carried out the acetylation and benzoylation of **6** to give *N*Ac7BnG **7a** and *N*Bz7BnG **7b**, respectively, in good yield (Scheme 2). We considered using *N*-acetyl-2′,3′,5′-tri-*O*-acetylguanosine[12] as a starting material for the synthesis of **7a**, but discounted this idea because deprotection of the *N*-acetyl group is inevitable in the deglycosylation step.



Scheme 2. Preparation of *N*2-protected 7-benzylguanines from guanosine **3**.

First, we examined the coupling reactions of the 7BnG derivatives **7a**,**b** with the diacetate side chains **8a**,**b**. In the case of the coupling of *N*Bz7BnG **7b** with **8a**[4c], the coupling product **9a** could be obtained in crystalline form. After X-ray crystal structural analysis and NMR studies, compound **9a** was unequivocally identified as the N9-alkylated compound (Scheme 3). The coupling product **9a** exists as a rather stable ionic compound under neutral conditions, while acidic or basic hydrolysis produces decomposition products (Fig. 2).[13]



Scheme 3. Preparation of an N9-alkylated 7-benzylguanine derivative.

However, when we used *N*Ac7BnG **7a** and side chains **8a**,**b**, the coupling products **9b**,**c** could not be crystallized, and therefore it was difficult to purify these products in this step. Fortunately, after the debenzylation by catalytic hydrogenolysis of **9b**,**c** followed by alkaline hydrolysis of the acetate, PCV **1** was easily isolated as crystals in respective yields of 74 and 68%. This process did not require any form of chromatographic purification to give pure PCV **1** in good yield (Scheme 4).

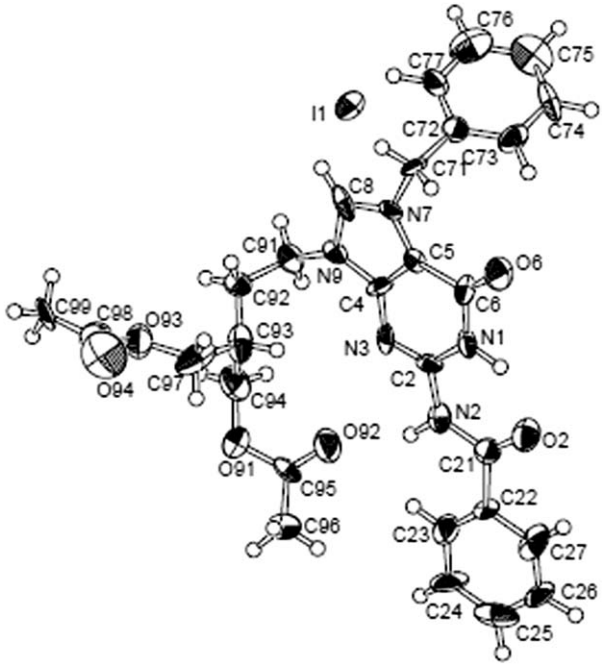
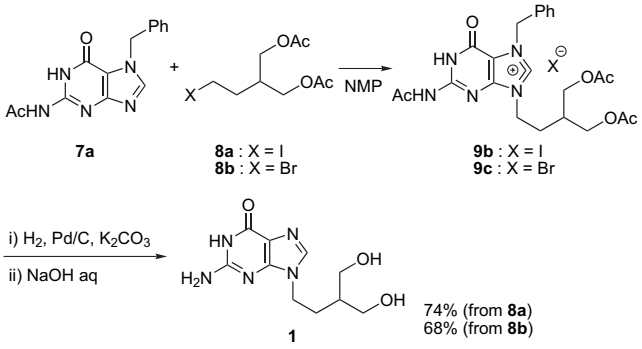


Figure 2. X-ray crystal structure of the coupling product **9a**.



Scheme 4. Preparation of PCV **1** from *N*Ac7BnG **7a**.

Next, we turned our attention to the comparative reactivities with various alkyl side chains (see Table 1). In the case of the bromide **8b**,[14] the yield of PCV **1** was lower than that of the expensive iodide **8a** (68 vs 74%) under the same reaction conditions (80 °C, 20 h). When the temperature in the reaction of *N*Ac7BnG **7a** with **8b** was raised, several byproducts such as Ac_3PCV **10**, the 7,9-dialkylated compound **11**, and NAc-Bn_2G **12**[8b] were detected by HPLC: clearly, the yield of PCV **1** could not be improved simply by raising the reaction temperature, and problematic impurities were also generated. We speculate that the mechanism of the side reaction is that shown in Scheme 5. The coupling of **7a** with the bromide **8b** gives **9c** as a bromide salt. However, the bromide anion of **9c** attacks the benzyl carbon of **9c** itself at a higher temperature to give **10** and benzyl bromide. Ac_3PCV **10** then reacts with extra **8b** to give **11**. NAc-Bn_2G **12** must arise by the reaction of benzyl bromide with remaining **7a**.

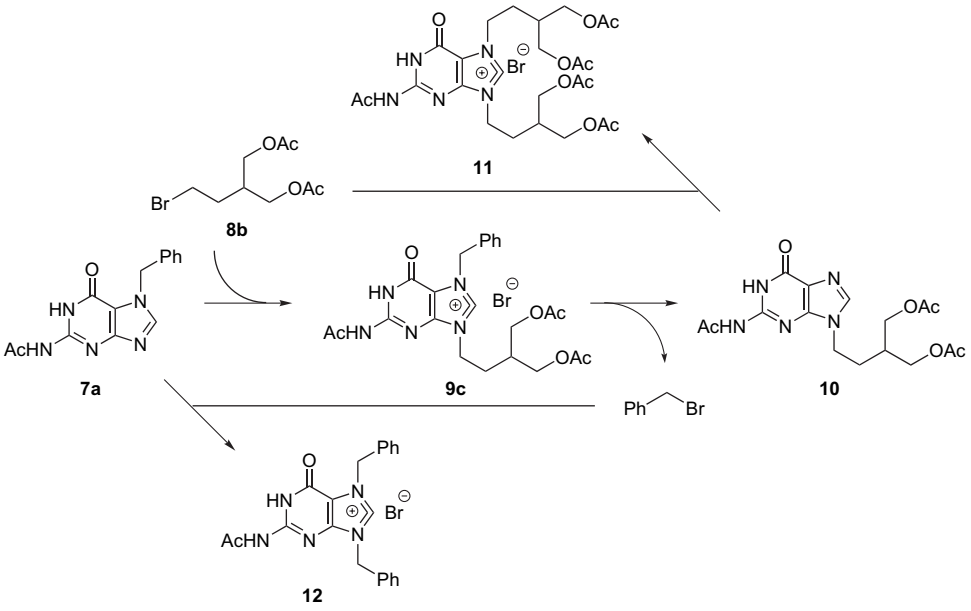
We considered that it may be possible to suppress the side reactions by changing the leaving group of the side chain from halide to the less nucleophilic sulfonate. Thus, we tried the coupling of *N*Ac7BnG **7a** with the mesylate **8c**,[4c] which is a precursor in the synthesis of iodide **8a** and bromide **8b** and therefore less expensive. As we anticipated, the mesylate **8c** was much less reactive than iodide **8a** and bromide **8b**. However, the reaction of *N*Ac7BnG **7a** with mesylate **8c** was complete within 8 h in *N*-methylpyrrolidone (NMP) when the reaction temperature was raised to 120 °C. The reaction proceeded without the formation of any impurities—even at higher temperature. PCV **1** was synthesized by coupling with *N*Ac7BnG **7a** and mesylate **8c**, followed by debenzylation and deacetylation in 76% without isolation of any intermediates from *N*Ac7BnG **7a**. In addition to the use of cheap **8c**, there was another advantage in terms of product purity, although the reaction yield was similar to that using iodide **8a** as a side chain.

6ClFCV **14** has been reported to be a key intermediate for the synthesis of FCV **2**.[4f] We investigated the transformation of PCV **1** to **2**. PCV **1** was converted to Ac_2PCV **13** by selective acetylation of the hydroxy groups.[15] Ac_2PCV **13** was then treated with phosphorus oxychloride, tetraethylammonium chloride, and triethylamine at 80 °C to give the known intermediate **14** in 70% yield, in the same manner as has been reported in the 6-chlorination of *N*-acetyl-2′,3′,5′-tri-*O*-acetyl-guanosine.[16] 6ClFCV **14** was transformed into FCV **2** in 81% yield by the procedure described in the literature (Scheme 6).[4f]

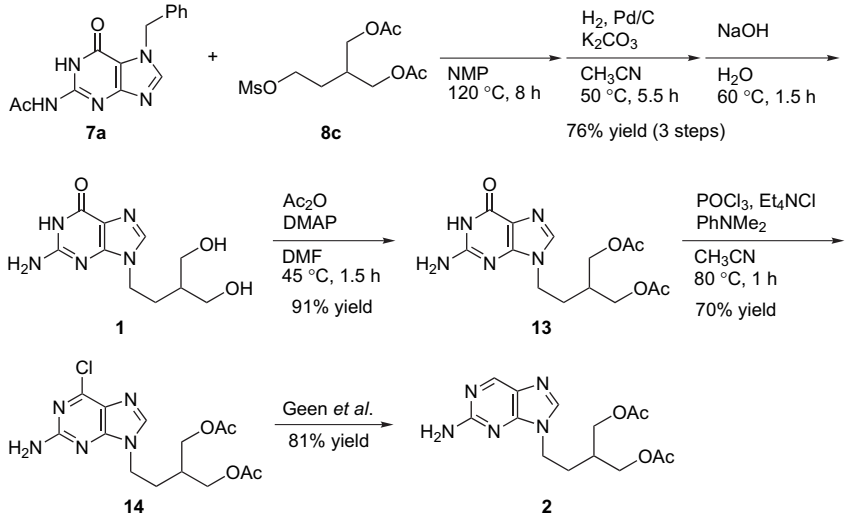
We also established another efficient synthetic route to prepare FCV **2** from **10**. Ac_3PCV **10** was synthesized by coupling with *N*Ac7BnG **7a** and **8c** followed by catalytic debenzylation at 50 °C, in 78% yield based on **7a**. Ac_3PCV **10** was then converted to *N*Ac6ClFCV **15** by chlorination in the same manner as Ac_2PCV **13**. The reaction mixture of **15** was treated under acidic conditions in MeOH, where the *N*-acetyl group of **15** was deprotected selectively to give 6ClFCV **14** (Scheme 7). The overall yield of **14** from Ac_3PCV **10** was 77%, which is better than the yield of **14** (64%) from PCV **1**. Interestingly, the *N*-selective deacetylation of *N*Ac6ClFCV **15** was accomplished under acidic conditions.

Table 1. N-Alkylation of *N*Ac7BnG **7a**

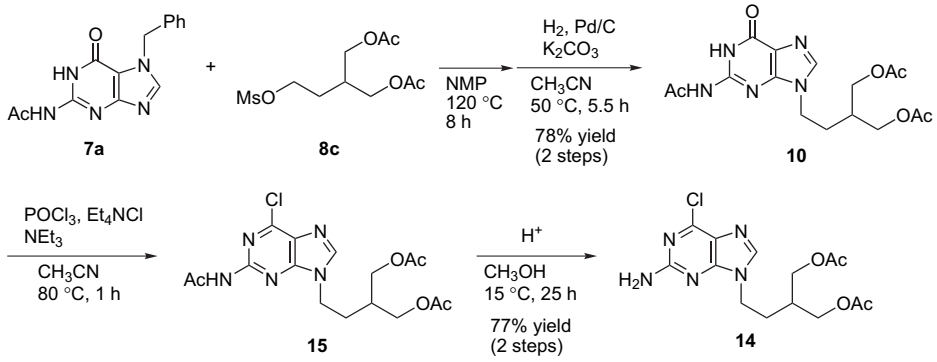
Entry	Side chain leaving group	Temp (°C)	Time (h)	HPLC (area %)				
				9-Alkyl (**9x**)	*N*Ac7BnG (**7a**)	Ac_3PCV (**10**)	7,9-Alkyl (**11**)	NAc-Bn_2G (**12**)
1	**8a** (I)	80	20	75.5	8.1	4.9	2.9	4.7
2	**8b** (Br)	80	20	70.1	20.6	1.6	1.1	2
3	**8b** (Br)	100	8	72.1	3.7	5.6	6.9	8.6
4	**8c** (OMs)	80	20	36.6	58.4	0.1	0.1	N.D.
5	**8c** (OMs)	100	20	79.2	14.8	0.1	0.2	N.D.
6	**8c** (OMs)	120	8	86.2	9.5	0.4	0.3	0.4



Scheme 5. Possible mechanism for the N9-alkylation of *N*Ac7BnG **7a**.



Scheme 6. Preparation of FCV **2** from *N*Ac7BnG **7a**.



Scheme 7. Preparation of 6ClFCV **14** from *N*Ac7BnG **7a**.

3. Conclusion

We have established practical synthetic routes to PCV **1** and FCV **2**. The yields of **1** and **2** were 76 and 49% from *N*Ac7BnG **7a**, respectively; there was no need to purify either by chromatography.

4. Experimental

4.1. General

All reagents were purchased and used without further purification. Thin-layer chromatography (TLC) was conducted on precoated TLC plates (Merck $60F_{254}$). High-performance liquid chromatography (HPLC) was performed with a Hitachi L-6000 pump and L-4000 UV detector system using a YMC-ODS-A column. Melting points were measured with a Büchi B-545. NMR spectra were obtained on a BRUKER Advance-400 MHz spectrometer. All ^{1}H NMR spectra were measured in DMSO-d_6 solvent, and chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.00) as an internal standard. All ^{13}C NMR spectra were measured in DMSO-d_6 solvent, and chemical shifts are reported as δ values in parts per million relative to DMSO-d_6 (δ 39.5) as an internal standard. Infrared (IR) spectra were recorded on an ASI React IR 1000 FTIR spectrometer with an ATR sampling system and are reported in wave number (cm^{-1}). Mass spectra (MS) and High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-700V (JEOL Datum Ltd).

4.1.1. 2′,3′,5′-Tri-*O*-acetylguanosine (4). A mixture of guanosine **3** sodium salt (66.58 g, 0.20 mol) in AcOEt (400 mL) was added to acetic anhydride (79.3 mL, 0.84 mol) and stirred for 2 h at 60 °C. After the mixture was cooled to room temperature, water (200 mL) was added, and the mixture was separated. The organic layer was concentrated in vacuo. To the residue was added water (1.0 L) and 1 M NaOH aq to pH 5.0. The mixture was filtered off and washed with water (1.0 L). After the residue was dried, compound **4** (74.4 g, 91%) was obtained as colorless crystals: mp 224–227 °C (lit.[17] 225–227 °C); IR (neat) 3149, 2738, 1740, 1686, 1212, 1073, 783, 675, 635 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.04 (3H, s, OAc), 2.05 (3H, s, OAc), 2.11 (3H, s, NAc), 4.26 (1H, dd, J=5.6, 11.2 Hz, H5′-a), 4.29–4.34 (1H, m, H-4′), 4.38 (1H, dd, J=3.6, 11.2 Hz, H-5′-b), 5.49 (1H, dd, J=4.1, 5.9 Hz, H-3′), 5.79 (1H, t, J=6.0 Hz, H-2′), 5.98 (1H, d, J=6.1 Hz, H-1′), 6.53 (2H, br s, NH_2), 7.93 (1H, s, H-8), 10.72 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.5, 20.7, 20.9, 63.4, 70.7, 72.4, 79.9, 84.8, 117.2, 136.0, 151.5, 154.3, 157.0, 169.6, 169.8, 170.4; MS (FAB+) *m*/*z* 410 (MH^+), 432 ($M+Na^+$); HRMS (FAB+) calcd for $C_{16}H_{20}N_5O_8$ (MH^+): 410.1312, found, 410.1310.

4.1.2. 7-Benzylguanine dihydrochloride (6).[11] A solution of guanosine **3** (13.9 g, 48.1 mmol) in DMF (28.3 mL) was added to sodium acetate (985.6 mg, 12.0 mmol) and acetic anhydride (19.1 mL, 202 mol) and the mixture was stirred for 4 h at 70 °C. After the mixture was cooled to 30 °C, concd HCl (19.1 mL, 202 mmol), sodium bromide (8.89 g, 86.5 mmol), and benzyl chloride (6.64 mL, 57.7 mmol) were added, and the mixture was stirred for 8 h at 70 °C. After the mixture was cooled to room temperature, concd HCl (40.5 mL, 481 mmol) was added and the mixture was stirred for 3 h at 40 °C. After the mixture was cooled to 0 °C, 8 M NaOH aq (42 mL, 336 mmol) and CH_3OH (50 mL) were added. The mixture was filtered off and washed with 50% CH_3OH aq (40 mL). After the residue was dried, compound **6** (15.1 g, 75%) was obtained as colorless crystals: mp 285 °C (dec); IR (neat) 3406, 3122, 2732, 1706, 1663, 1609, 1520, 1158, 843, 706, 679, 621 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.52 (2H, s, CH_2), 7.32–7.43 (5H, m, aryl), 8.34 (2H, br s, NH_2), 8.91 (1H, s, H-8); ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.6, 107.5, 128.2, 128.6, 129.1, 136.2, 140.5, 150.9, 153.4, 154.5; MS (FAB+) *m*/*z* 242 (7BnG-H^+); HRMS (FAB+) calcd for $C_{12}H_{12}N_5O$ (7BnG-H^+): 242.1031, found, 242.1064; Anal. Calcd for $C_{12}H_{13}Cl_2N_5O$: C, 45.88; H, 4.17; N, 22.29. Found: C, 46.17; H, 4.30; N, 22.69.

4.1.3. *N*2-Acetyl-7-benzylguanine (7a). A mixture of compound **6** (4.37 g, 13.9 mmol) in AcOH (9 mL) was added to acetic anhydride (4.44 mL, 45.1 mmol) and *p*-TsOH·H_2O (132.8 mg, 0.70 mmol) and the resulting solution was stirred for 3 h at 105 °C. After the mixture was cooled to room temperature, water (180 mL), 5% $NaHCO_3$ aq (150 mL) and 1 M NaOH aq (100 mL) were added to give pH 5.3. The slurry was filtered off and washed with water (50 mL). After the residue was dried, *N*Ac7BnG **7a** (3.77 g, 95.7%) was obtained as colorless crystals: mp 237–238 °C (lit.[18] 241 °C); IR (neat) 3141, 1713, 1686, 1619, 1546, 1424, 1364, 1246, 1216, 778, 710, 652 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.15 (3H, s, NAc), 5.51 (2H, s, CH_2), 7.27–7.36 (5H, m, aryl), 8.34 (1H, s, H-8), 11.56 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.5, 49.6, 111.5, 127.9, 128.2, 129.0, 137.7, 144.7, 147.4, 153.0, 157.6, 173.7; MS (FAB+) *m*/*z* 284 (MH^+); HRMS (FAB+) calcd for $C_{14}H_{14}N_5O_2$ (MH^+): 284.1148, found, 284.1147.

4.1.4. *N*2-Benzoyl-7-benzylguanine (7b). A mixture of compound **6** (7.29 g, 23.2 mmol) in pyridine (47 mL) was added to 4-dimethylaminopyridine (145.6 mg, 1.19 mmol). Benzoyl chloride (5.5 mL, 47.4 mmol) was added dropwise and the mixture was stirred for 2 h at 96 °C. After the mixture was cooled to room temperature, AcOEt (95 mL) was added and the mixture was stirred for 0.5 h at room temperature. The precipitated crystals were collected on filter and washed with AcOEt. The crystals were added to water (95 mL) and stirred for 2 h at room temperature. The slurry was filtered off and washed with water. After the residue was dried, *N*Bz7BnG **7b** (7.79 g, 97.0%) was obtained as an off-white powder: mp 265–267 °C; IR (neat) 3089, 1684, 1657, 1609, 1534, 1370, 1268, 1233, 903, 782, 697, 658 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.55 (2H, s, CH_2), 7.28–7.39 (5H, m, aryl), 7.53–7.58 (2H, m, aryl), 7.64–7.69 (1H, m, aryl), 8.03–8.07 (2H, m, aryl), 8.39 (1H, s, H-8), 11.86 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.6, 111.9, 127.9, 128.3, 128.7, 128.9, 129.1, 132.6, 133.4, 137.7, 144.8, 147.5, 153.2, 157.6, 169.1; MS (FAB+) *m*/*z* 346 (MH^+); HRMS (FAB+) calcd for $C_{19}H_{16}N_5O_2$ (MH^+): 346.1304, found, 346.1315.

4.1.5. 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-*N*2-benzoyl-7-benzylguaninium iodide (9a). A mixture of *N*Bz7BnG **7b**

(3.579 g, 10.0 mmol) in DMF (7.5 mL) was added to iodide **8a** (3.25 g, 10.0 mmol), and the mixture was stirred for 18 h at 85 °C. After the mixture was cooled to 75 °C, AcOEt (30 mL) was added and the mixture was cooled to 0 °C. The mixture was filtered off and washed with AcOEt (15 mL). After the residue was dried, compound **9a** (4.41 g, 64%) was obtained as a pale yellowish powder: mp 180–181 °C; IR (neat) 3320, 3160, 2977, 1711, 1596, 1420, 1241, 787, 710 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.96–2.04 (2H, m, H-2′), 2.02 (6H, s, Ac×2), 2.06–2.12 (1H, m, H-3′), 4.06 (4H, d, J=5.7 Hz, H-4′), 4.37 (2H, t, J=7.4 Hz, H-1′), 5.73 (2H, s, CH_2), 7.38–7.47 (3H, m, aryl), 7.50–7.53 (2H, m, aryl), 7.56–7.61 (2H, m, aryl), 7.69–7.74 (1H, m, aryl), 8.03–8.06 (2H, m, aryl), 9.74 (1H, s, H-8); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.0, 27.8, 34.5, 44.1, 52.0, 63.7, 111.1, 128.7, 129.0, 129.0, 129.2, 129.3, 132.1, 134.0, 134.6, 140.4, 148.0, 151.3, 152.1, 169.5, 170.7; MS (FAB+) m/z 532 ($M-I^+$); HRMS (FAB+) calcd for $C_{28}H_{29}N_5O_6$ ($M-I^+$): 532.2191, found, 532.2214.

4.1.6. Penciclovir (1) from iodide 8a. A mixture of *N*Ac7BnG **7a** (20.6 g, 70.5 mmol) in 1-methylpyrrolidone (23.5 mL) was added to iodide **8a** (22.9 g, 70.5 mmol), and the mixture was stirred for16 h at 80 °C. After the mixture was cooled to room temperature, 50% CH_3OH aq (236 mL), 5% Pd–C (50% wet, 6.34 g), and K_2CO_3 (14.9 g, 141 mmol) were added and the mixture was stirred at 45 °C under a hydrogen atmosphere (1 atm) for 21.5 h. After the mixture was cooled to room temperature, 4 M NaOH aq (35.5 mL) was added and filtered off, the residue was washed with 2 M NaOH aq (60 mL), and the filtrate was concentrated. To the residue was added water (20 mL), and this mixture was stirred for 1 h at 60 °C. After the mixture was cooled to room temperature, the pH of the solution was adjusted to 11.5 by 2 M HCl aq and the precipitated 7BnG was filtered off. The pH of the filtrate was adjusted to 6.0 by 6 M HCl aq, and then the temperature was lowered to 0 °C. The mixture was filtered off and washed with cold water (30 mL). After the residue was dried, PCV **1** (13.4 g, 74%) was obtained as colorless crystals: mp 270–272 °C (lit.[4b] 275–277 °C); IR (neat) 3411, 3128, 2881, 2667, 1675, 1602, 1397, 1196, 1054, 992, 781, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.41–1.48 (1H, m, H-3′), 1.67–1.74 (2H, m, H-2′), 3.32–3.38 (2H, m, H-4′-a), 3.39–3.46 (2H, m, H-4′-b), 4.00 (2H, t, J=7.4 Hz, H-1′), 4.41 (2H, t, J=5.2 Hz, OH×2), 6.41 (2H, br s, NH_2), 7.68 (1H, s, H-8), 10.50 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.2, 41.1, 41.4, 61.7, 116.9, 137.7, 151.5, 153.8, 157.2; MS (FAB+) m/z 254 (MH^+); HRMS (FAB+) calcd for $C_{10}H_{16}N_5O_3$ (MH^+): 254.1253, found, 254.1230.

4.1.7. Penciclovir (1) from bromide 8b. A mixture of *N*Ac7BnG **7a** (4.44 g, 15.0 mmol) in 1-methylpyrrolidone (5.0 mL) was added to bromide **8b** (4.23 g, 15.0 mmol) and this mixture was stirred for 18 h at 80 °C. After the mixture was cooled to room temperature, 50% CH_3OH aq (60 mL), 5% Pd–C (50% wet, 1.37 g), and K_2CO_3 (3.18 g, 30.0 mmol) were added and the mixture was stirred at 45 °C under a hydrogen atmosphere (1 atm) for 21.5 h. After the mixture was cooled to room temperature, 25% NaOH aq (4.85 g) was added and filtered off, the residue was washed with 50% CH_3OH aq (20 mL), and the filtrate was concentrated. To the residue was added 25% NaOH aq (1.18 g) to pH over 13.0 and the mixture was stirred for 2 h at 50 °C. After the mixture was cooled to room temperature, the pH of the solution was adjusted to 7.0 by 6 M HCl aq and the solution was cooled to 0 °C. The mixture was filtered off and washed with cold water (5 mL). After the residue was dried, PCV **1** (2.58 g, 68%) was obtained as colorless crystals.

4.1.8. Penciclovir (1) from mesylate 8c. A mixture of *N*Ac7BnG **7a** (1.67 g, 5.84 mmol) in 1-methylpyrrolidone (1.2 mL) was added to mesylate **8c** (1.68 g, 5.84 mmol) and this mixture was stirred for 8 h at 120 °C. After the mixture was cooled to room temperature, CH_3CN (29.2 mL), 5% Pd–C (50% wet, 0.515 g), and K_2CO_3 (0.485 g, 3.50 mmol) were added and the mixture was stirred at 50 °C under a hydrogen atmosphere (1 atm) for 10 h. After the mixture was cooled to room temperature, 4 M NaOH aq (4.4 mL) was added and filtered off, the residue was washed with 2 M NaOH aq (2×3 mL), and the filtrate was concentrated. To the residue was added 2 M NaOH aq (8.5 L) and the mixture was stirred for 1.5 h at 60 °C. After the mixture was cooled to room temperature, the solution was washed with CH_2Cl_2 (10 mL), and the pH of the water layer was adjusted to 6.7 by concd H_2SO_4. The mixture was stirred for 1 h at room temperature and filtered off, and the residue was washed with cold water (3 mL). After the residue was dried, PCV **1** (1.12 g, 76%) was obtained as colorless crystals.

4.1.9. 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-*N*2-acetylguanine (10). A mixture of *N*Ac7BnG **7a** (2.86 g, 10.0 mmol) in 1-methylpyrrolidone (2.0 mL) was added to **8c** (2.87 g, 10.0 mmol) and the mixture was stirred for 8 h at 120 °C. After the mixture was cooled to 50 °C, CH_3CN (50 mL), 5% Pd–C (50% wet, 0.88 g), and K_2CO_3 (0.83 g, 6.02 mmol) were added and the mixture was stirred at 50 °C under a hydrogen atmosphere (1 atm) for 5.5 h. AcOH (20.0 mL) was added and filtered off at 50 °C, and the residue was washed with AcOH (10 mL). After the mixture was cooled to room temperature, the filtrate was concentrated in vacuo, and coevaporated with toluene (10 mL). To the residue was added AcOEt (20 mL), and the mixture was stirred for 1 h at room temperature, filtered off, washed with AcOEt (10 mL). The wet crystals were added to water (40 mL), and then stirred for 0.5 h at 60 °C and for 2 h at room temperature. The mixture was filtered off and washed with water. After the mixture was dried, Ac_3PCV **10** (3.03 g, 78%) was obtained as a pale yellowish powder: mp 226–227 °C (lit.[8c] 222–223 °C); IR (neat) 3267, 3085, 1729, 1663, 1603, 1540, 1262, 1233, 785, 739, 633 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.82–1.88 (2H, m, H-2′), 1.90–1.97 (1H, m, H-3′), 2.00 (6H, s, OAc×2), 2.18 (3H, s, NAc), 4.02 (4H, d, J=5.3 Hz, H-4′), 4.15 (2H, t, J=7.1 Hz, H-1′), 8.02 (1H, s, H-8), 11.66 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.0, 24.2, 28.6, 34.8, 41.4, 63.8, 120.5, 140.1, 148.0, 148.9, 155.3, 170.7, 173.8; MS (FAB+) m/z 380 (MH^+); HRMS (FAB+) calcd for $C_{16}H_{22}N_5O_6$ (MH^+): 380.1570, found, 380.1556.

4.1.10. 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)guanine (13). A mixture of PCV **1** (12.5 g, 48.8 mmol) in DMF (46 mL) was added to 4-dimethylaminopyridine (0.3 g, 2.5 mmol) and acetic anhydride (10.6 mL, 112.2 mmol), and the mixture was stirred for 1.5 h at 45 °C. After the mixture was cooled to room temperature, 2-propanol (115 mL)

was added and the mixture was stirred for 1.5 h at 0 °C. The mixture was filtered off and washed with 2-propanol (2×15 mL). The wet crystals were added to AcOEt (105 mL), warmed to 70 °C, and cooled to room temperature. The mixture was filtered off and washed with AcOEt (2×15 mL). After the residue was dried, Ac_2PCV **13** (15.3 g, 91%) was obtained as colorless crystals: mp 198–202 °C (lit.[15a] 202–205 °C); IR (neat) 3323, 3159, 2730, 1735, 1686, 1605, 1366, 1221, 1036, 785, 691, 639 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.77–1.84 (2H, m, H-2′), 1.88–1.95 (1H, m, H-3′), 2.00 (6H, s, Ac×2), 4.00–4.04 (6H, m, H-1′ and H-4′), 6.40 (2H, br s, NH_2), 7.70 (1H, s, H-8), 10.52 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.5, 28.1, 34.3, 40.3, 63.3, 116.5, 137.2, 151.0, 153.4, 156.7, 170.2; MS (FAB+) *m/z* 338 (MH^+); HRMS (FAB+) calcd for $C_{14}H_{20}N_5O_5$ (MH^+): 338.1464, found, 338.1462.

4.1.11. 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-chloropurine (14), from Ac_2PCV 13. A mixture of Ac_2PCV **13** (5.16 g, 15.0 mmol) and tetraethylammonium chloride (4.97 g, 30.0 mmol) in CH_3CN (30 mL) was cooled to 0 °C and added to *N*,*N*-dimethylaniline (1.0 mL, 7.5 mmol) and phosphorus oxychloride (6.25 mL, 67.5 mmol). The mixture was stirred for 1 h at 70 °C and evaporated. The residue was diluted with CH_2Cl_2 (60 mL) and washed with satd $NaHCO_3$ aq (2×45 mL) and water (30 mL). The CH_2Cl_2 layer was evaporated in vacuo. To the residue was added CH_3OH (7 mL) and H_2O (3.5 mL) and the mixture was stirred for 1.5 h at −5 °C. The mixture was filtered off and washed with 75% CH_3OH aq. After the residue was dried, the crude solid of 6ClFCV **14** (3.96 g) was obtained as an off-white solid. Recrystallization from 2-propanol gave pure 6ClFCV **14** (3.74 g, 70%) as a pale yellowish powder: mp 132–134 °C (lit.[4c] 134–136 °C); IR (neat) 3485, 3301, 3195, 1744, 1729, 1623, 1559, 1472, 1239, 1023, 907, 880, 647 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.83–1.89 (2H, m, H-2′), 1.90–1.95 (1H, m, H-3′), 1.99 (6H, s, Ac×2), 4.01 (4H, d, J=5.6 Hz, H-4′), 4.13 (2H, t, J=7.1 Hz, H-1′), 6.90 (2H, br s, NH_2), 8.16 (1H, s, H-8); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.9, 28.1, 34.8, 41.2, 63.8, 123.7, 143.5, 149.7, 154.4, 160.1, 170.7; MS (FAB+) *m/z* 356 (MH^+); HRMS (FAB+) calcd for $C_{14}H_{19}ClN_5O_4$ (MH^+): 356.1126, found, 356.1131.

4.1.12. 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-chloropurine (14), from Ac_3PCV 10. A mixture of Ac_3PCV **10** (1.93 g, 5.02 mmol) and tetraethylammonium chloride (1.66 g, 10.4 mmol) in CH_3CN (10 mL) was cooled to 0 °C, and triethylamine (0.35 mL, 2.51 mmol) and phosphorus oxychloride (2.09 mL, 22.6 mmol) were added. The mixture was stirred for 1 h at 80 °C and evaporated. The residue was diluted by CH_2Cl_2 (9 mL). After the mixture was cooled to 0 °C, 2 M NaOH aq (6 mL) and 4 M NaOH aq (3 mL) were added dropwise, and the mixture was separated. To the CH_2Cl_2 layer was added satd $NaHCO_3$ aq (4 mL) and water (2 mL), and the mixture was stirred for 0.5 h at room temperature. After layer separation, the CH_2Cl_2 layer was evaporated in vacuo. To the residue was added CH_3OH (6 mL), and the mixture was stirred 25 h at 15 °C, while the progression of deacetylation was confirmed. At that time the pH of the solution was 0.6. After deacetylation, the pH of the mixture was adjusted to 7.0 by satd $NaHCO_3$ aq, and the mixture was stirred for 1.5 h at 0 °C. The mixture was filtered off and washed with water. After the residue was dried, 6ClFCV **14** (1.42 g, 77%) was obtained as a pale yellowish powder.

5. Crystallographic data

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC600088. Copies of the data can be obtained, free of charge, on application on CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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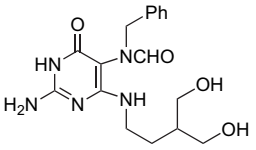

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