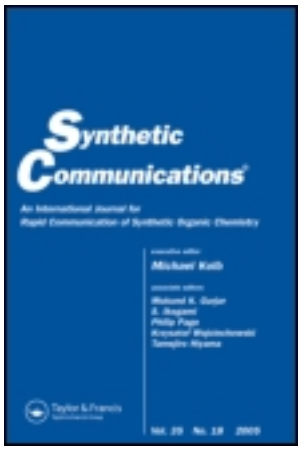

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[a] Crump Institute for Molecular Imaging, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

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Selective and Practical Synthesis of Penciclovir

Tatsushi Toyokuni,* Joseph C. Walsh, Mohammad Namavari, Shirin S. Shinde, Jennifer R. Moore, Jorge R. Barrio, and Nagichettiar Satyamurthy

Crump Institute for Molecular Imaging,
Department of Molecular and Medical Pharmacology,
David Geffen School of Medicine at UCLA, Los
Angeles, California, USA

ABSTRACT

A selective and practical method has been developed for the synthesis of penciclovir (**1**) in gram quantities involving a highly N^9 selective alykylation of 2-amino-6-chloropurine (**9**) with 2-(2-phenyl-1,3-dioxane-5-yl)ethanol (**12**) as a key step.

Key Words: Alkylation; Penciclover; Practical; Selective; Synthesis.

*Correspondence: Tatsushi Toyokuni, LA Tech Center, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, 6140 Bristol Parkway, Culver City, CA 90230, USA; Fax: 310-670-8428; E-mail: ttoyokuni@mednet.ucla.edu.

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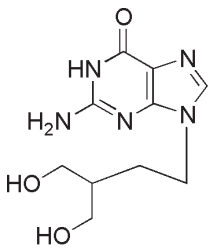
INTRODUCTION

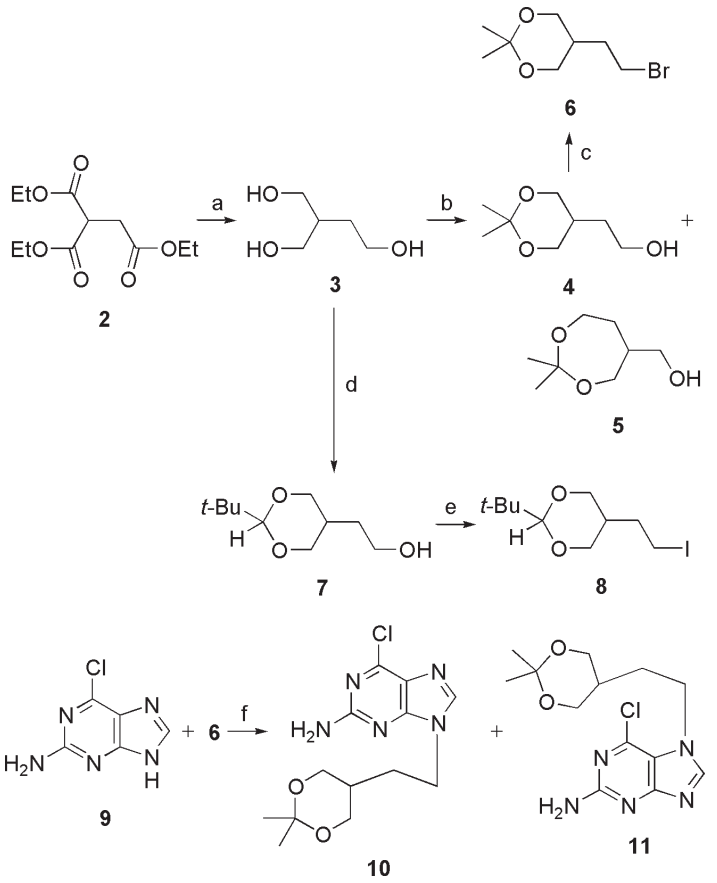
Penciclovir[1] is a widely used drug for the treatment of herpes virus infections[1] (Fig. 1). Since the first synthesis by Pandit et al. in 1972,[2] a number of methods have been developed for the preparation of **1**.[3] Among them the method reported by Harnden et al. in 1985[3a,b] remains the most concise route from commercially available starting compounds. However, two key steps in this method are rather inefficient and make the procedure less attractive. For example, the protection of 1,3-diol functionality in compound **3** (Sch. 1) as the acetonide derivative yields a mixture of products **4** and **5** in a ratio of ~4:1. The required acetonide **4** is separated from the unwanted derivative **5** by column chromatography. Secondly, alkylating agent **6** derived from the alcohol **4** when reacted with the chloropurine **9** also yields a mixture of N^9 and N^7 alkylated products **10** and **11**, respectively, which are separated by column chromatography. To obviate these shortcomings a newer procedure has recently been introduced.[3e] In this method the 1,3-diol function is protected as a cyclic acetal containing a bulky *tert*-butyl group (Sch. 1, products **7** and **8**) to enhance N^9 regioselectivity during the alkylation of **9**. However, in this method also a significant amount (~10%) of the undesirable N^7 alkylation product was formed.

As a part of our on-going research program,[4] we required penciclovir in gram quantities on a regular basis. We have developed an efficient synthesis of **1** involving a highly N^9 selective alkylation procedure. To the best of our knowledge this method provides the highest N^9 regioselectivity for the alkylation to yield **1**. Described herein is a practical method suitable for a large-scale synthesis of penciclovir.



Penciclovir (**1**)

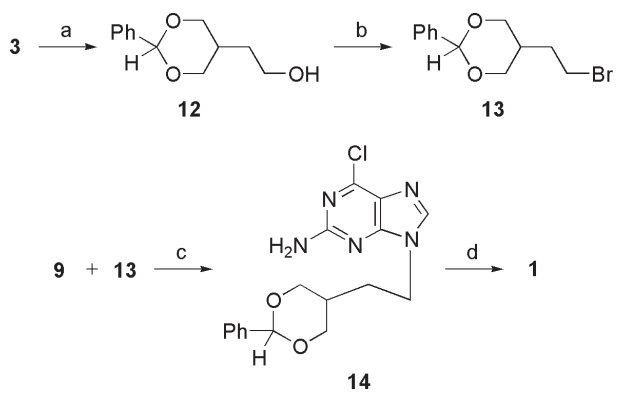
Figure 1.



Scheme 1. (a) $NaBH_4$, *t*-BuOH, MeOH; (b) 2,2-dimethoxypropane, TsOH, THF; (c) CBr_4, PPh_3, DMF; (d) trimethylacetaldehyde, TsOH, THF; (e) (1) MsCl, Et_3N, (2) NaI, acetone; (f) K_2CO_3, DMF.

RESULTS AND DISCUSSION

Scheme 2 delineates the synthesis of penciclovir developed in our laboratories. The triol **3** was synthesized in 79% yield from the triester **2** (Sch. 1) using the $NaBH_4$/*t*-BuOH/MeOH system.[5] The crude product was purified with the aid of anion- and cation exchange resins.[6] Since ion-exchange resins can be regenerated repeatedly, the resin-based purification is particularly suited for the preparative-scale synthesis because of its simplicity.



Scheme 2. (a) Benzaldehyde dimethyl acetal, TsOH, THF; (b) CBr_4, PPh_3, DMF; (c) K_2CO_3, DMF; (d) 2 M HCl.

Benzylidene acetal, which is readily formed in high yields by a reaction with commercially available benzaldehyde dimethyl acetal, is commonly used for selective protection of 1,3-diols in carbohydrate chemistry.[7] The triol **3** was treated with benzaldehyde dimethyl acetal in the presence of TsOH at room temperature to yield the expected 1,3-dioxane **12**[8] as the sole product in 80–85% yields. As expected, the ^{1}H NMR spectrum indicated that **12** was produced as a mixture of cis and trans isomers in a ratio of approximately 1:3. The trans isomer was readily identified based on the splitting patterns of the signals at δ 3.59 (pseudo t, 2H, $J = 11$ Hz) and δ 4.27 (dd, 2H, $J = 11$ and 4 Hz), which are characteristic of two equivalent axial (H-4ax and H-6ax) and two equivalent equatorial protons (H-4eq and H-6eq) having a vicinal axial proton (H-5) in a chair conformation. On the other hand, the proton NMR spectrum of the cis isomer suggested that it probably adopts a distorted or nonchair conformation.

Treatment of the alcohol **12** with CBr_4 and Ph_3P yielded the benzylidene-protected bromide **13** in 81% yield. The ^{1}H NMR spectrum revealed that the product is a 1:1.5 mixture of cis and trans isomers, as a result of equilibration of the cis and trans isomers during the bromination.[9] Because of deterioration during storage, the bromide **13** was used shortly after preparation.

Alkylation of 2-amino-6-chloropurine (**9**) was carried out using 0.9 equivalent of **13** in anhydrous DMF.[10] TLC analysis of the reaction mixture indicated a complete consumption of **13** and the formation of two closely migrating products, which were isolated in ~95% yield as a mixture by silica-gel column chromatography. The ^{1}H NMR spectra

showed that these two products were cis and trans isomers in a ratio of approximately 1:1.5. However, we could not determine the site of alkylation even though ^{1}H NMR has previously been successfully used to characterize the position (N^9 vs. N^7) of alkylation.[11] Since the alkylated product **14** was isolated near quantitatively, the position of the alkylation was determined after its transformation to the final product **1**. Thus, the mixture of cis and trans isomers was hydrolyzed with 2 M HCl to afford a single product in 80–85% yield, whose ^{1}H NMR spectrum in DMSO-d_6 and UV spectrum in H_2O were in good agreement with those reported for penciclovir.[3a,b] This clearly indicates a regioselective alkylation at the N^9 position in **10** to yield the alkylated purine **14** as a mixture of cis and trans isomers. The regioselectivity displayed by **13** also suggests that, in addition to the steric effect as proposed by Geen et al.,[3e] the π–π electronic interaction between the benzylidene phenyl and purine base groups might synergistically contribute to maximize the N^9-alkylation of **9**. The exact origin of this high regioselectivity needs further investigation.

EXPERIMENTAL

General Methods

Melting points were measured on an Electrothermal Digital Melting Point Apparatus IA9300 and are uncorrected. ^{1}H NMR spectra were recorded on a Brucker AM360 in D_2O, $CDCl_3$, or in DMSO-d_6 with acetone (δ 2.22 for D_2O) and TMS (for $CDCl_3$ and DMSO-d_6) as internal standards. High-resolution mass spectra (HRMS) were obtained using a positive mode on a VG 70VSE (AutoSpec) for EI and on a VG ZAB-SE for FAB. Ultra violet spectra were recorded on a Beckman DU-600 spectrophotometer. TLC was performed on precoated POLYGRAM® SIL G/UV$_{254}$ plates. The silica gel used for an open column chromatography was EM Science Silica Gel 40 (0.063–0.200 mm). The starting materials triethyl 1,1,2-ethanetricarboxylate (**2**) and 2-amino-6-chloropurine (**9**), as well as all other reagents and anhydrous solvents, were purchased from Aldrich Chemical Co.

2-Hydroxymethyl-1,4-butanediol[3a,b] (3)

The reaction was carried out using a modification of a procedure previously reported.[3a,b] To a refluxing solution of triethyl

1,1,2-ethanetricarboxylate (**2**) (46 mL, 0.2 mol) and $NaBH_4$ (20 g) in *t*-BuOH (400 mL) was added MeOH (25 mL) in portions over a period of 30 min. Reflux was continued for an additional 30 min, the mixture was cooled and neutralized with 3 M HCl (~65 mL). The resulting precipitate was removed by filtration and the filtrate was evaporated. The residue was dissolved in a minimum amount of H_2O (the solution should not be viscous) and passed successively through anion-exchange resign (Amberlite IRA-400 OH^-; 0.018–0.045 mesh; 30 × 380 mm) and cation-exchange resin (Amberlite IR-120 H^+; 0.014–0.040 mesh; 30 × 380 mm) column chromatography with H_2O as eluent. The vanillin-stain positive fractions were combined and evaporated to give **3** (19 g, 79%) as a clear viscous oil: ^{1}H NMR (D_2O) δ 1.55 (pseudo q, 2H, $J = 7$ Hz, H-3), 1.76 (pseudo septet, 1H, $J = 7$ Hz, H-2), 3.58 (d, 4H, $J = 7$ Hz, H-1), 3.65 (t, 2H, $J = 7$ Hz, H-4). The ^{1}H NMR spectrum was in good agreement with the reported data.[3b]

2-(2-Phenyl-1,3-dioxane-5-yl)ethanol[8] (12)

A solution of **3** (18 g, 0.15 mol) in anhydrous THF (500 mL) was treated with benzaldehyde dimethyl acetal (30 mL, 0.2 mol) in the presence of TsOH monohydrate (3 mg, 15.5 mmol) at room temperature for 1 h. The reaction mixture was poured onto saturated aq $NaHCO_3$ (150 mL) and extracted with Et_2O. The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated to give **12** (26 g, 83%) as a colorless solid. The ^{1}H NMR spectrum indicated that this was a mixture of cis and trans isomers in an approximately 1:3 ratio. For the cis isomer: ^{1}H NMR ($CDCl_3$) δ 1.55 (br s, 1H, H-5), 2.07 (pseudo q, 2H, $J = 7$ Hz, CH_2CH_2OH), 3.83 (pseudo t, 2H, $J = 7$ Hz, CH_2CH_2OH), 4.12 (br d, 2H, $J = 11$ Hz), and 4.17 (br d, 2H, $J = 11$ Hz) (H-4 and H-6), 4.86 (br s, 1H, OH), 5.52 (s, 1H, H-2), 7.3–7.7 (m, 5H, Ar H); for the trans isomer: ^{1}H NMR ($CDCl_3$) δ 1.35 (pseudo q, 2H, $J = 5$ Hz, CH_2CH_2OH), 2.29 (m, 1H, H-5), 3.59 (pseudo t, 2H, $J = 11$ Hz, H-4ax and H-6ax), 3.66 (pseudo t, 2H, $J = 7$ Hz, CH_2CH_2OH), 4.27 (dd, 2H, $J = 11$ and 4 Hz, H-4eq and H-6eq), 4.86 (br s, 1H, OH), 5.43 (s, 1H, H-2), 7.3–7.7 (m, 5H, Ar H). HREIMS: calcd. for $C_{12}H_{16}O_3$ 208.1099. Found: 208.1097.

5-(2-Bromoethyl)-2-phenyl-1,3-dioxane (13)

To an ice-cooled solution of **12** (5.0 g, 24 mmol) and CBr_4 (12.6 g, 37.6 mmol) in anhydrous CH_2Cl_2 (100 mL) was added Ph_3P

(10.0 g, 37.7 mmol) in portions over a period of 10 min with vigorous stirring. Stirring was continued in an ice-bath for 1.5 h, the reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with saturated aq $NaHCO_3$ (2×200 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated to yield a light yellow oil. The crude product was purified by silica-gel column chromatography with hexane–acetone (3:1, v/v) to give **13** (5.3 g, 81%) as a pale yellow oil. The ^{1}H NMR spectrum indicated that this was a mixture of cis and trans isomers in an approximately 1:1.5 ratio. For the cis isomer: ^{1}H NMR ($CDCl_3$) δ 1.80 (br s, 1H, H-5), 2.40 (pseudo q, 2H, $J = 7$ Hz, CH_2CH_2Br), 3.60 (pseudo t, 2H, $J = 7$ Hz, CH_2CH_2Br), 4.07 (br d, 2H, $J = 11$ Hz), and 4.15 (br d, 2H, $J = 11$ Hz) (H-4 and H-6), 5.51 (s, 1H, H-2), 7.3–7.5 (m, 5H, Ar H); for the trans isomer: ^{1}H NMR ($CDCl_3$) δ 1.71 (pseudo q, 2H, $J = 7$ Hz, CH_2CH_2Br), 2.37 (m, 1H, H-5), 3.39 (pseudo t, 2H, $J = 7$ Hz, CH_2CH_2Br), 3.59 (pseudo t, 2H, $J = 11$ Hz, H-4ax and H-6ax), 4.27 (dd, 2H, $J = 11$ and 5 Hz, H-4eq and H-6eq), 5.42 (s, 1H, H-2), 7.3–7.5 (m, 5H, Ar H). Without further characterization the product **13** was used in the next step the same day (see below).

2-Amino-6-chloro-9-[2-(2-phenyl-1,3-dioxane-5-yl)-ethyl]guanine (14)

A mixture of **13** (4.0 g, 14.8 mmol), 2-amino-6-chloropurine (**9**) (2.8 g, 16.3 mmol) and K_2CO_3 (3.4 g, 24.6 mmol) in anhydrous DMF (50 mL) was stirred at room temperature for 3 d. The brown colored reaction mixture was then filtered and the filtrate was evaporated to give a dark orange oil. The crude product was placed on a silica-gel column and eluted first with $CHCl_3$–MeOH (80:1, v/v) to remove less polar impurities and then with $CHCl_3$–MeOH (60:1, v/v) to give **14** (5.0 g, 94% based on **13**). The ^{1}H NMR spectrum indicated that this was a mixture of cis and trans isomers in an approximately 1:1.5 ratio. For the cis isomer: ^{1}H NMR ($CDCl_3$) δ 1.43 (br s, 1H, H-5′), 2.42 (pseudo q, 2H, $J = 7$ Hz, CH_2CH_2N), 4.12 (t, 2H, $J = 7$ Hz, CH_2CH_2N), 4.15 (br s, 4H, H-4′ and H-6′), 5.13 (br s, 2H, NH_2), 5.53 (s, 1H, H-2′), 7.3–7.5 (m, 5H, Ar H), 7.80 (s, 1H, H-8); for the trans isomer: ^{1}H NMR ($CDCl_3$) δ 1.71 (pseudo q, 2H, $J = 7$ Hz, CH_2CH_2N), 2.18 (m, 1H, H-5′), 3.63 (pseudo t, 2H, $J = 11$ Hz, H-4′ax and H-6′ax), 4.12 (t, 2H, $J = 7$ Hz, CH_2CH_2N), 4.30 (dd, 2H, $J = 11$ and 5 Hz, H-4′eq and H-6′eq), 5.13 (br s, 2H, NH_2), 5.44 (s, 1H, H-2′), 7.3–7.5 (m, 5H, Ar H), 7.77 (s, 1H, H-8). HRFABMS: calcd. for $C_{17}H_{19}ClN_5O_2$ (M + H) 360.1227. Found: 360.1216.

9-[4-Hydroxy-3-(hydroxymethyl)butyl]guanine (Penciclovir)[3a,b] (1)

A solution of **14** (4.7 g, 13.4 mmol) in 2 M HCl (15 mL) was heated to 90°C for 3 h. The reaction mixture was cooled to room temperature and neutralized with 10% aq NaOH. The mixture was placed in a refrigerator for 2 d and the resulting precipitate was collected by filtration to yield **1** (2.8 g, 83%) as a colorless crystalline solid: m.p. 268.4–269.2°C [Lit.[3a,b] 275–277°C]. UV (H_2O) λ_{max} 252 and 273 (sh) nm [Lit[3a,b] 253 and 270 (sh) nm]. ^{1}H NMR (DMSO-d_6) δ 1.42 (pseudo septet, 1H, $J = 7$ Hz, H-3′), 1.69 (pseudo q, 2H, $J = 7$ Hz, H-2′), 3.37 (ddd, 2H, $J = 11$, 7 and 7 Hz) and 3.41 (ddd, 2H, $J = 11$, 7 and 7 Hz) (CH_2OH), 3.98 (t, 2H, $J = 7$ Hz, H-1′), 4.42 (t, 2H, $J = 7$ Hz, OH), 6.42 (br s, 2H, NH_2), 7.67 (s, 1H, H-8), 10.50 (br s, 1H, H-1). The ^{1}H NMR spectrum is in good agreement with the literature data.[3a,b]

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10. We have been carrying out this coupling reaction during a weekend. Harnden et al. reported that **6** and **9** were reacted at 4°C overnight, while Geen et al. left the mixture of **8** and **9** at room temperature for 18 h (see Ref. 3b and Ref. 3e, respectively).
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