Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 7009–7013
Tetrahedron

C-4′ Truncated carbocyclic formycin derivatives

Jian Zhou, Minmin Yang, Akin Akdag and Stewart W. Schneller*

Department of Chemistry and Biochemistry, College of Science and Mathematics, Auburn University, Auburn, AL 36849-5319, USA

Received 15 January 2006; revised 12 April 2006; accepted 21 April 2006
Available online 19 May 2006

Abstract—Formycin is a naturally occurring C-glycoside (C-nucleoside) that possesses antitumor, antibacterial, antifungal, and antiviral activity. In connection with our ongoing interest in the design and syntheses of C-nucleoside derived antiviral agents this report describes the preparation of carbocyclic formycin and its 7-hydroxy (oxo) analog lacking the C-4′ hydroxylmethylene moiety in racemic form (**4** and **6**, respectively). An antiviral analysis of (±)-**4** did not disclose any activity.

1. Introduction

Aristeromycin (**1**) and formycin A (**2**) (Fig. 1) are two examples of naturally occurring nucleosides that possess significant antiviral activity.[1] Aristeromycin belongs to the carbocyclic nucleoside class and formycin A and formycin B (**3**) (Fig. 1) are representatives of C-nucleosides. In the former case, the ribofuranose oxygen of the more common nucleosides is replaced by a methylene while, with C-nucleosides, the ribofuranosyl moiety is linked to the heterocyclic base by a carbon–carbon bond at the anomeric center. Both carbocyclic and C-nucleosides are stable to purine nucleoside phosphorylase (PNP),[1a,2] an enzyme that renders typical nucleosides with limited potential as therapeutic agents.[2] However, the high toxicity associated with these compounds has restricted their development.

In our ongoing search for new antiviral agents, we sought compounds that combined the structural features of **1**–**3** that could improve their antiviral profiles and show less cytotoxicity. Compound **4** was chosen as a target because of its isomeric relationship to **5**,[3a] which is an antiviral candidate with activity towards the orthopoxviruses[3b,c] and human cytomegalovirus[3d] by apparent virtue of its inhibition of *S*-adenosylhomocysteine hydrolase.[3a]

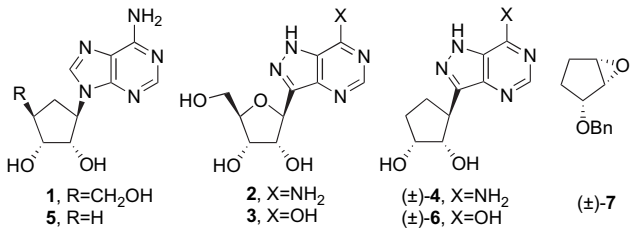


Figure 1.

While the synthesis of carbocyclic C-nucleosides has been challenging[4,5] our laboratory previously communicated a model synthesis for a formycin representative.[6] Herein, we report further progress in this endeavor, leading to a novel and practical synthesis of (±)-**4** and its companion (±)-**6** (Fig. 1).

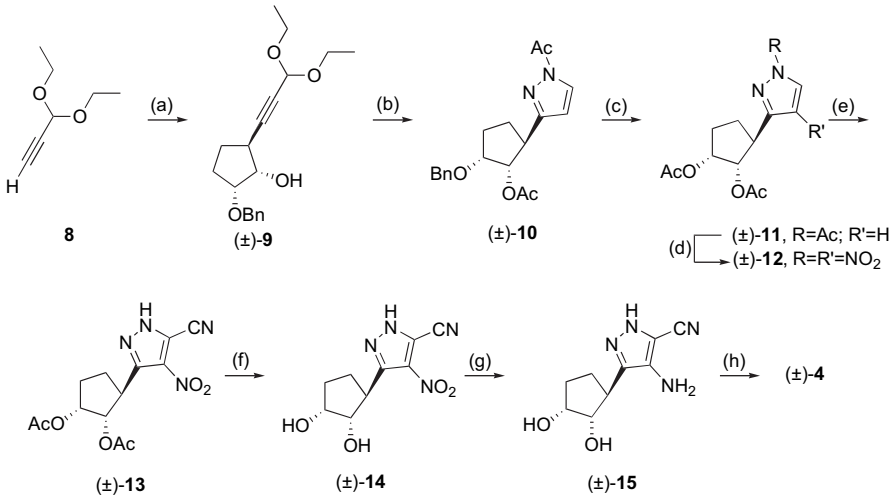
2. Chemistry

The syntheses began with ring opening of the readily available (±)-*cis*-3-(benzyloxy)-1,2-epoxycyclopentane (**7**)[7] by the lithiated derivative of 3,3-diethoxy-1-propyne (**8**, commercially available) in the presence of boron trifluoride etherate[8] to provide (±)-**9** (21%, 71% based on recovered starting material) (Scheme 1). Attempts to improve the yield by using either excess **8** or alternative solvents such as toluene, hexamethylphosphoramide, methylene chloride or co-solvents (such as tetrahydrofuran/hexamethylphosphoramide) were unsuccessful.

Hydrolysis of (±)-**9** with a mixture of acetic acid and 10% aqueous hydrochloric acid followed by treatment of the resulting acetylenic aldehyde with hydrazine monohydrate gave a pyrazole derivative[2,9] that was acetylated to provide the key synthetic intermediate (±)-**10** (Scheme 1). To introduce the fused pyrimidine N-4, nitration of (±)-**10** with ammonium nitrate and trifluoroacetic anhydride in trifluoroacetic acid following literature conditions[10] was attempted. However, the major component in the product mixture (by ^{1}H NMR) possessed a nitrated benzyl unit. Thus, replacing the benzyl protecting group of (±)-**10** with an acetyl to give (±)-**11** led to (±)-**12** that was, in turn, converted into (±)-**13** by a *cine*-substitution reaction with potassium

Keywords: Formycin; Carbocyclic C-nucleosides; Epoxide ring opening; Antiviral testing.
* Corresponding author. Tel.: +1 334 844 5737; fax: +1 334 844 5824; e-mail: schnest@auburn.edu

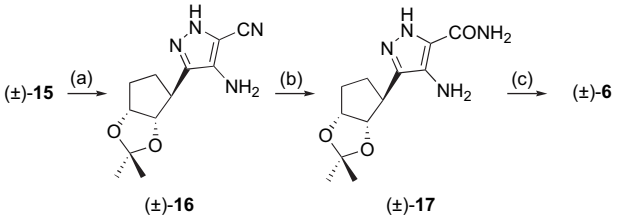
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.04.068



Scheme 1. Reagents and conditions: (a) i. *n*-BuLi/hexanes; ii. (±)-(**7**), $BF_3 \cdot Et_2O$, 71% (based on recovered starting material); (b) i. 10% HCl, AcOH; ii. $N_2H_4 \cdot H_2O$, AcOH; iii. Ac_2O, pyridine, DMAP, 65%; (c) i. 50 psi H_2, 10% Pd/C, MeOH, ii. Ac_2O, Et_3N, DMAP, CH_2Cl_2, 96%; (d) NH_4NO_3, TFA, TFAA; (e) using **12**, KCN, EtOH, EtOAc, 89%; (f) NH_3, MeOH, 95%; (g) 30 psi H_2, 10% Pd/C, MeOH, 92%; (h) $HC(=NH)NH_2 \cdot AcOH$, EtOH, 71%.

cyanide.[11] Deacetylation to (±)-**14** followed by hydrogenation in the presence of palladium/carbon afforded a quantitative amount of (±)-**15**. Treatment of (±)-**15** with formamidine acetate in refluxing ethanol proceeded with ring annulation to (±)-**4**.

Steps towards (±)-**6** (Scheme 2) began with unsuccessful attempts to carry out hydration of (±)-**15** using hydrogen peroxide in methanol to afford a requisite amide. Success was achieved, however, by protecting the hydroxyl groups of (±)-**15** with 2,2-dimethoxypropane (to (±)-**16**) (Scheme 2). Subsequent hydration of (±)-**16** provided amide (±)-**17**. Cyclization of (±)-**17** with formamidine acetate and deprotection yielded (±)-**6**.



Scheme 2. Reagents and conditions: (a) concd HCl, acetone, $Me_2C(OMe)_2$, 98%; (b) H_2O_2, NH_4OH, MeOH, 50%; (c) i. $HC(=NH)NH_2 \cdot AcOH$, EtOH; ii. 1 N HCl, 56% for two steps.

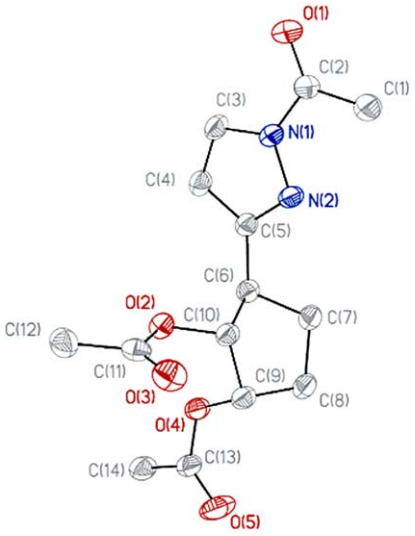


Figure 2. X-ray structure for compound (±)-**11**.[14]

To confirm the stereochemical orientations of the cyclopentyl ring substituents in these reactions an X-ray structure determination of (±)-**11** was obtained (Fig. 2).

3. Antiviral results

Compound (±)-**4** was subjected to broad antiviral analysis and was found to be inactive.[12,13] Weak cellular cytotoxicity was observed towards four of the host cell lines: MA-104, respiratory syncytial virus assay (IC_{50} 54 μg/mL); HeLa Ohio-1, rhinovirus type 2 assay (IC_{50} 80 μg/mL); BS-C-1, Pichinde assay (IC_{50} 53 μg/mL); and CV-1, measles assay (IC_{50} 76 μg/mL).

4. Conclusion

The antiviral potential[3b,c,d] of previously reported chiral **5**[3a] does not extend to isomer **4** in its racemic form. At this time, such an observation does not encourage us to seek an enantiospecific synthesis of the enantiomers represented by (±)-**4**. However, the synthetic process[6] elaborated upon herein opens an accessible means to carbocyclic C-nucleosides of potential usefulness in biochemical studies requiring novel adenosine isomers.

5. Experimental

5.1. General

Melting points were recorded on a Meltemp II melting point apparatus and the values are uncorrected. The combustion analyses were performed at Atlantic Microlab, Norcross,

GA. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker AC 250 spectrometer (250 MHz for proton and 62.5 MHz for carbon) or a Bruker AV 400 spectrometer (400 MHz for proton and 100 MHz for carbon), referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The X-ray analysis was conducted by using a Bruker APEX CCD single crystal X-ray diffractometer. The electrospray ionization mass spectral data were obtained using a Waters Micromass QTOF mass spectrometer. The reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Whatman Diamond silica gel 60-F_{254} precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. Column chromatography was performed on Whatman silica, 230–400 mesh, and 60 Å using elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials.

5.1.1. (±)-(1α,2α,3β)-1-Benzyloxy-2-acetoxy-3-(1-acetyl-1*H*-pyrazol-3-yl)cyclopentane (10). To a solution of 3,3-diethoxy-1-propyne (97%) (6.3 g, 48 mmol) in anhydrous toluene (130 mL) was added *n*-butyllithium (2.5 M solution in hexanes, 20 mL, 50.0 mmol) at −78 °C under an atmosphere of N_2. After the reaction mixture was stirred for ca. 30 min, a solution of epoxide (±)-**7** (7.3 g, 38 mmol) in anhydrous toluene (10 mL) was added via syringe, followed by $BF_3\cdot OEt_2$ (6.3 mL, 50 mmol) over 5 min. The reaction mixture was stirred at −78 °C for 2 h and then at 0–5 °C for additional ca. 5 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl solution and partitioned between EtOAc and H_2O. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and the filtrate evaporated in vacuo to afford a liquid residue. Purification of the residue by flash column chromatography (hexanes/EtOAc, 4:1 to 3:1) led to recovered starting material (5.1 g, 27 mmol) and (±)-(1α,2α,3β)-1-benzyloxy-2-hydroxy-3-(3,3-diethoxy-prop-1-ynyl)cyclopentane (**9**) (2.6 g, 8.2 mmol, 71% based on recovered starting material) as a light yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (m, 6H), 1.64 (m, 1H), 1.78 (m, 1H), 1.96 (m, 1H), 2.16 (m, 1H), 2.83 (m, 2H), 3.56 (m, 2H), 3.72 (m, 2H), 3.95 (m, 1H), 4.03 (m, 1H), 4.50 (d, 1H, *J*=11.7 Hz), 4.60 (d, 1H, *J*=11.7 Hz), 5.28 (d, 1H, *J*=1.5 Hz), 7.29–7.35 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 27.9, 36.2, 59.1, 61.4, 63.4, 72.0, 78.3, 80.1, 88.0, 91.9, 128.1, 128.3, 128.9, 138.3.

To a solution of **9** (2.3 g, 7.2 mmol) in glacial AcOH (72 mL) was added 10% HCl (18 mL), and this mixture was stirred at room temperature for 1 h. To this a solution of hydrazine monohydrate (4.5 g) in glacial AcOH (36 mL) was added dropwise over 20 min. The resulting solution was heated at reflux overnight and concentrated in vacuo to afford dark brown oil. The crude product was dissolved in pyridine (100 mL) and Ac_2O (8 mL) and DMAP were added. The resulting solution was stirred for 16 h at room temperature. The solvent was removed in vacuo, and the crude residue dissolved in EtOAc (800 mL), washed with 10% HCl and brine, dried (Na_2SO_4), concentrated, and the residue chromatographed to afford **10** (1.6 g, 4.7 mmol, 65%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (m, 1H), 1.94 (m, 1H), 2.04 (m, 1H), 2.09 (s, 3H), 2.25 (m, 1H), 2.64 (s, 3H), 3.50 (ddd, 1H, *J*=8.4 Hz), 4.16 (ddd, 1H, *J*=4.9 Hz), 4.55 (s, 2H), 5.20 (dd, 1H, *J*=4.9, 7.6 Hz), 6.30 (d, 1H, *J*=2.9 Hz), 7.26 (m, 1H), 7.30 (m, 4H), 8.16 (d, 1H, *J*=2.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 21.8, 25.9, 28.7, 41.1, 71.9, 78.4, 78.8, 108.8, 127.6, 127.7, 128.5, 129.0, 138.5, 158.5, 169.5, 170.8. Anal. calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.73; H, 6.56; N, 7.96.

5.1.2. (±)-(1α,2α,3β)-1,2-Diacetoxy-3-(1-acetyl-1*H*-pyrazol-3-yl)cyclopentane (11). To a solution of **10** (5.0 g, 12 mmol) in MeOH (60 mL) was added catalytic amount of 10% Pd/C. The mixture was shaken under 50 psi of H_2 at room temperature overnight. After this period, the mixture was filtered, and the filtrate concentrated in vacuo to afford a colorless oil. This crude product was dissolved in CH_2Cl_2 (100 mL) and to this triethylamine (1.4 mL), Ac_2O (2.3 mL), and catalytic amount of DMAP were added. The resulting solution was stirred overnight and then washed with brine, dried (Na_2SO_4), concentrated, and chromatographed (EtOAc/hexanes, 1:3) to afford **11** (3.3 g, 11 mmol, 96%) as a white solid, mp 79–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (m, 2H), 2.03 (s, 3H), 2.09 (s, 3H), 2.31 (m, 2H), 2.66 (s, 3H), 3.48 (ddd, 1H, *J*=8.9 Hz), 5.26 (m, 1H), 5.40 (m, 1H), 6.32 (d, 1H, *J*=2.8 Hz), 8.17 (d, 1H, *J*=2.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 21.2, 21.9, 26.1, 27.0, 28.3, 40.7, 73.4, 77.8, 108.6, 129.3, 157.8, 169.6, 170.5. Anal. calcd for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.52. Found: C, 57.41; H, 6.24; N, 9.50.

5.1.3. (±)-(1α,2α,3β)-1,2-Diacetoxy-3-(5-cyano-4-nitro-1*H*-pyrazol-3-yl)cyclopentane (13). Trifluoroacetic anhydride (15.5 mL) was added dropwise to a stirred solution of **11** (3.3 g, 11 mmol) containing ammonium nitrate (8.9 g) in trifluoroacetic acid (130 mL) at 0 °C. The resulting solution was allowed to warm to room temperature and then stirred overnight. The solvent was evaporated by means of a rotavapor. The residue was placed in CH_2Cl_2 and then washed with H_2O, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo to give the **12** (3.8 g) as a white solid that was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94 (m, 2H), 1.99 (s, 3H), 2.11 (s, 3H), 2.27 (m, 1H), 2.49 (m, 1H), 4.09 (ddd, 1H, *J*=8.5 Hz), 5.42 (m, 1H), 5.52 (m, 1H), 9.12 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 21.0, 26.3, 28.3, 39.6, 73.3, 76.5, 125.3, 134.3, 149.1, 170.2 (2C).

A solution of the **12** (3.8 g) prepared above in EtOH (36 mL) and EtOAc (36 mL) was added dropwise to a stirred solution of KCN (5.2 g, 80 mmol) in EtOH (95 mL) and H_2O (23 mL). Following an additional 5 min at room temperature, the reaction mixture was neutralized with HOAc (8.5 mL). After evaporation of the solvent, the residue was diluted with EtOAc (500 mL), washed with H_2O and brine, dried (Na_2SO_4), concentrated in vacuo, and chromatographed (CH_2Cl_2/MeOH, 20:1) to afford **13** (3.2 g, 10 mmol, 89% based on **11**) as a white solid, mp 129–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 (m, 1H), 2.03 (m, 1H), 2.05 (s, 3H), 2.14 (m, 1H), 2.16 (s, 3H), 2.32 (m, 1H), 2.59 (m, 1H), 4.23 (m, 1H), 5.48 (m, 1H), 5.53 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 21.2, 26.7, 28.2, 38.6, 73.0, 75.8, 110.8, 123.0, 134.1, 144.9, 171.2, 172.1. Anal. calcd for $C_{13}H_{14}N_4O_6$: C, 48.45; H, 4.38; N, 17.38. Found: C, 48.16; H, 4.31; N, 17.42.

5.1.4. (±)-(1α,2α,3β)-1,2-Dihydroxy-3-(5-cyano-4-nitro-1*H*-pyrazol-3-yl)cyclopentane (14). Ammonia gas was introduced to a solution of compound **13** (2.0 g, 6.2 mmol) in MeOH (100 mL). This reaction mixture was allowed to stir at room temperature until TLC analysis indicated starting material was no longer present. The solvent was then removed in vacuo and the residue purified by chromatography (CH_2Cl_2/MeOH, 3:1) to afford **14** (1.4 g, 5.9 mmol, 95%) as a light yellow solid, mp 220–222 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.63 (m, 2H), 1.97 (m, 1H), 2.15 (m, 1H), 3.80 (m, 1H), 3.96 (m, 1H), 4.10 (m, 1H), 4.68 (br s, 1H), 4.91 (br s, 1H), 14.81 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.0, 29.8, 39.2, 71.6, 77.9, 112.0, 121.8, 133.7, 147.7. Anal. calcd for $C_9H_{10}N_4O_4$: C, 45.38; H, 4.23; N, 23.52. Found: C, 45.43; H, 4.32; N, 23.43.

5.1.5. (±)-(1α,2α,3β)-1,2-Dihydroxy-3-(4-amino-5-cyano-1*H*-pyrazol-3-yl)cyclopentane (15). A catalytic amount of 10% Pd/C was added to a solution of **12** (1.23 g, 5.20 mmol) in MeOH (100 mL). The resulting mixture was shaken under 30 psi of H_2 overnight. The solvent was then evaporated in vacuo and the product purified by chromatography (CH_2Cl_2/EtOAc/MeOH, 8:1:0.5) to afford **15** as a white solid (1.0 g, 4.8 mmol, 92%), mp 190–191 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.56 (m, 2H), 1.97 (m, 2H), 3.08 (dd, 1H, J=8.9, 17.8 Hz), 3.79 (m, 1H), 3.88 (br s, 1H), 4.36 (br s, 2H), 4.52 (br s, 1H), 4.69 (d, 1H, J=6.3 Hz), 12.97 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.9, 30.1, 38.2, 71.4, 78.2, 114.1, 115.3, 130.9, 133.1. Anal. calcd for $C_9H_{12}N_4O_2$: C, 51.92; H, 5.81; N, 26.91. Found: C, 52.10; H, 5.93; N, 27.09.

5.1.6. (±)-(1α,2α,3β)-1,2-Dihydroxy-3-[(7-amino-1*H*-pyrazolo[4,3-*d*]pyrimid-3-yl)]cyclopentane (4). A solution of **15** (0.15 g, 0.72 mmol) in EtOH (30 mL) was stirred with formamidine acetate (0.10 g, 0.96 mmol) under reflux for 30 min. The resulting white precipitate was isolated by filtration, washed with EtOH, and dried to afford **4** (0.12 g, 0.51 mmol, 71%) as a white solid, mp 261–262 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.66 (m, 1H), 1.90 (m, 1H), 1.99 (m, 1H), 2.09 (m, 1H), 4.02 (br s, 1H), 4.23 (br s, 1H), 4.40 (m, 2H), 4.91 (br s, 1H), 7.25 (br s, 2H), 8.15 (br s, 1H), 12.4 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.2, 30.3, 41.4, 66.4, 72.0, 77.9, 121.9, 139.5, 147.2, 150.8. HRMS calcd for $C_{10}H_{13}N_5O_2$ $[M+H]^+$ 236.1147, found 236.1141.

5.1.7. (±)-(1α,2α,3β)-1,2-*O*-Isopropylidene-3-(4-amino-5-cyano-1*H*-pyrazol-3-yl)cyclopentane (16). Concentrated HCl (0.21 mL) was added to a stirred suspension of **15** (590 mg, 2.83 mmol) in dry acetone (60 mL) and 2,2-dimethoxypropane (60 mL) causing immediate clarification. After 4 h at room temperature, the solution was neutralized by addition of concentrated NH_4OH and evaporated to dryness. The residue was purified by chromatography (CH_2Cl_2/MeOH, 19:1) to give 690 mg (2.78 mmol, 98%) of **16** as a white solid, mp 148.5–149.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23 (s, 3H), 1.39 (s, 3H), 1.61 (m, 2H), 1.75 (m, 1H), 2.02 (m, 1H), 3.24 (m, 1H), 4.69 (m, 4H), 12.9 (br s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 15.2, 24.2, 26.6, 28.1, 30.9, 40.7, 65.0, 80.3, 83.9, 109.6, 115.0, 132.0. Anal. calcd for $C_{12}H_{16}N_4O_2$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.32; H, 6.85; N, 22.89.

5.1.8. (±)-4-Amino-5-[(1β,2α,3α)-2,3-*O*-isopropylidene-cyclopent-1-yl]-2*H*-pyrazole-3-carboxylic acid amide (17). Hydrogen peroxide (50%, 0.19 mL) was added to a rapidly stirred mixture of **16** (570 mg, 2.30 mmol) in concentrated NH_4OH (10 mL) and MeOH (20 mL) at 0 °C. The solution was allowed to stir at room temperature overnight. After the solvent was evaporated, the residue was purified by chromatography (EtOAc/MeOH, 9:1) to afford **17** (310 mg, 1.16 mmol, 50%) as an off-white solid, mp 191.6–192.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26 (s, 3H), 1.41 (s, 3H), 1.65 (m, 1H), 1.76 (m, 2H), 2.02 (m, 1H), 3.23 (m, 1H), 4.43 (br s, 1H), 4.62 (m, 1H), 4.71 (m, 2H), 7.22 (br s 2H), 12.03 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.0, 26.4, 27.4, 31.0, 41.1, 80.6, 84.0, 108.7, 120.4, 131.3, 141.4, 161.9. Anal. calcd for $C_{12}H_{18}N_4O_3$: C, 54.12; H, 6.81; N, 21.04. Found: C, 53.98; H, 6.98; N, 20.81.

5.1.9. (±)-(1α,2α,3β)-1,2-Dihydroxy-3-[(7-hydroxy-1*H*-pyrazolo[4,3-*d*]pyrimid-3-yl)]cyclopentane (6). A solution of **17** (0.26 g, 0.98 mmol) in EtOH (50 mL) was stirred with formamidine acetate (0.14 g, 1.3 mmol) under reflux for 40 min. The resulting white precipitate was isolated by filtration and washed with EtOH. This white solid was dissolved in 1 N HCl (5 mL). The reaction mixture was allowed to stir at room temperature for 3 h. The quantity of solvent was reduced and the mixture was then neutralized with NH_4OH to afford **6**, upon filtration, as a white solid (0.13 g, 0.55 mmol, 56%), mp 245–246 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.62 (m, 1H), 1.80 (m, 1H), 1.97 (m, 1H), 2.07 (m, 1H), 3.99 (s, 1H), 4.17 (s, 1H), 4.43 (s, 1H), 4.62 (m, 1H), 7.81 (s, 1H), 12.18 (br s, 2H), 13.77 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 26.7, 30.3, 41.2, 72.0, 77.9, 127.3, 137.1, 142.0, 148.2, 153.2. HRMS calcd for $C_{10}H_{12}N_4O_3$ (M^++H) 237.0987, found 237.0980.

5.1.10. X-ray data for compound (±)-11. Crystallographic data (excluding structure factors) for (±)-**11** has been deposited with Cambridge Crystallographic Data Centre as supplementary number CCDC 284037. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

This research was supported by funds from the Department of Health and Human Services (AI 56540), which is appreciated. We thank Dr. Thomas Albrecht-Schmitt, Auburn University, for securing the X-ray data for **11**. We are also indebted to the following individuals for providing the antiviral data[13] following their standard protocols: Dr. Erik De Clercq, the Rega Institute, Leuven Belgium; Dr. Earl Kern, University of Alabama at Birmingham, Birmingham, AL; and Dr. Robert Sidwell, Utah State University, Logan, UT.

References and notes

1. (a) Schneller, S. W. *Curr. Top. Med. Chem.* **2002**, *2*, 1087–1092; (b) Herdewijn, P.; Balzarini, J.; De Clercq, E.; Vanderhaeghe, H. *J. Med. Chem.* **1985**, *28*, 1385–1386; (c)

De Clercq, E. *Biochem. Pharmacol.* **1987**, *36*, 2567–2575; (d) Cools, M.; De Clercq, E. *Biochem. Pharmacol.* **1989**, *38*, 1061–1067; (e) Hori, M.; Ito, E.; Takita, T.; Koyama, G.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1964**, *17A*, 96–99; (f) Koyama, G.; Umezawa, H. *J. Antibiot.* **1965**, *18A*, 175–177.

2. For a leading reference see Evans, G. B.; Furneaux, R. H.; Gainsford, G. J.; Hanson, J. C.; Kicska, G. A.; Sauve, A. A.; Schramm, V. L.; Tyler, P. C. *J. Med. Chem.* **2003**, *46*, 155–160.
3. (a) Wolfe, M. S.; Lee, Y. H.; Bartlett, W. J.; Borcherding, D. R.; Borchardt, R. T. *J. Med. Chem.* **1992**, *35*, 1782–1791; (b) Hasobe, M.; Liang, H.; Ault-Riche, D. B.; Borcherding, D. R.; Wolfe, M. S.; Borchardt, R. T. *Antiviral Chem. Chemother.* **1993**, *4*, 245–248; (c) De Clercq, E.; Neyts, J. *Rev. Med. Virol.* **2004**, *14*, 289–300; (d) Unpublished results from our laboratory [CPE inhibition: EC_{50} 0.17 μg/mL (ganciclovir EC_{50} 0.2 μg/mL), CC_{50} >100 μg/mL; plaque reduction: EC_{50} 0.7 μg/mL (ganciclovir 1.6 μg/mL), CC_{50} >100 μg/mL].[3e] (e) Assay method described in Roy, A.; Schneller, S. W.; Keith, K. A.; Hartline, C. B.; Kern, E. R. *Bioorg. Med. Chem.* **2005**, *13*, 4443–4449.
4. Chun, B. K.; Song, G. Y.; Chu, C. K. *J. Org. Chem.* **2001**, *66*, 4852–4853.
5. Boyer, S. J.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 3976–3980.
6. Zhou, J.; Yang, M.; Schneller, S. W. *Tetrahedron Lett.* **2004**, *45*, 8233–8234.
7. Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Eur. J. Org. Chem.* **1998**, *8*, 1675–1686.
8. (a) Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702–14703; (b) Kita, Y.; Futamura, J.; Ohba, Y.; Sawama, Y.; Ganesh, J. K.; Fujioka, H. *J. Org. Chem.* **2003**, *68*, 5917–5924.
9. (a) Rycroft, A. D.; Singh, G.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2667–2668; (b) Buchanan, J. G.; Quijano, M. L.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1573–1576.
10. Buchanan, J. G.; Jumaah, A. O.; Kerr, G.; Talekar, R. R.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1077–1083.
11. Buchanan, J. G.; Stobie, A.; Wightman, R. H. *Can. J. Chem.* **1980**, *58*, 2624–2627.
12. Viruses subjected (±)-**4** were influenza A (H1N1 and H3N2), influenza B, respiratory syncytial virus, herpes simplex virus 1 and 2, human cytomegalovirus, varicella zoster virus, vaccinia virus, cowpox virus, adenovirus type 1, Punta Toro virus, rhinovirus type 2, Venezuelan equine encephalitis, yellow fever, Pichinde, HIV-1 and HIV-2, Dengue virus, measles, parainfluenza-3, reovirus, Sindbis virus, Coxsackie virus B4, and vesicular stomatitis.
13. For leading references on the procedures used for the assays see (a) Rajappan, V. P.; Schneller, S. W.; Williams, S. L.; Kern, E. R. *Bioorg. Med. Chem.* **2002**, *10*, 883–886; (b) Siddiqi, S. M.; Chen, X.; Schneller, S. W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1994**, *37*, 551–554; (c) http://www.usu.edu/iar/Brochure/brochure.html.
14. To simplify viewing the ORTEP representation in Figure 2 the hydrogen atoms are omitted. However, the hydrogen atom on C(6) is oriented down while hydrogens on C(9) and C(10) are up.