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Palladium-Catalyzed Synthesis of *cis*-2-[4-(9*H*-Purin-9-yl)-2-cyclopenten-1-yl]ethanol Analogues

Lakshmi B. Akella and Robert Vince*

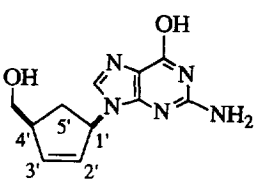
Department of Medicinal Chemistry, College of Pharmacy
University of Minnesota, 308 Harvard Street, S.E.,
Minneapolis, MN 55455-0343

Abstract: A concise 6 -7 step synthesis of the carbocyclic nucleosides *cis*-2-[4-(9*H*-Purin-9-yl)-2-cyclopenten-1-yl]ethanol analogues utilizing palladium chemistry has been described.

INTRODUCTION

Carbocyclic nucleosides[1], where the furanose oxygen of the natural nucleosides is replaced by a methylene group play an important role in antiviral chemotherapy. They have been identified as useful synthetic targets due to their metabolic stability towards phosphorylase enzymes and decreased toxicity[2].

Carbocyclic 2',3'-didehydro-2',3'-dideoxyguanosine (carbovir, **1**) (Fig. 1) is a potential drug for the treatment of AIDS by selective inhibition[3] of HIV-1 reverse transcriptase. In our ongoing search for more potent anti HIV agents we have synthesized the 4' hydroxyethyl substituted cyclopentenyl nucleoside analogues **2** and **3** (Fig. 1). These derivatives are 5'-*homo*-carbocyclic nucleosides structurally related to carbovir.



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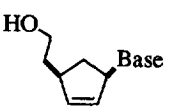


Base = Adenine, **2**
Guanine, **3**

Figure 1

Our retrosynthetic approach is shown in Figure 2.

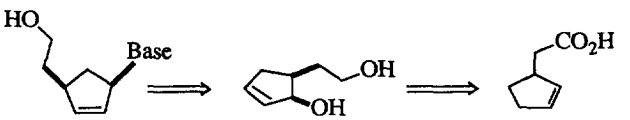
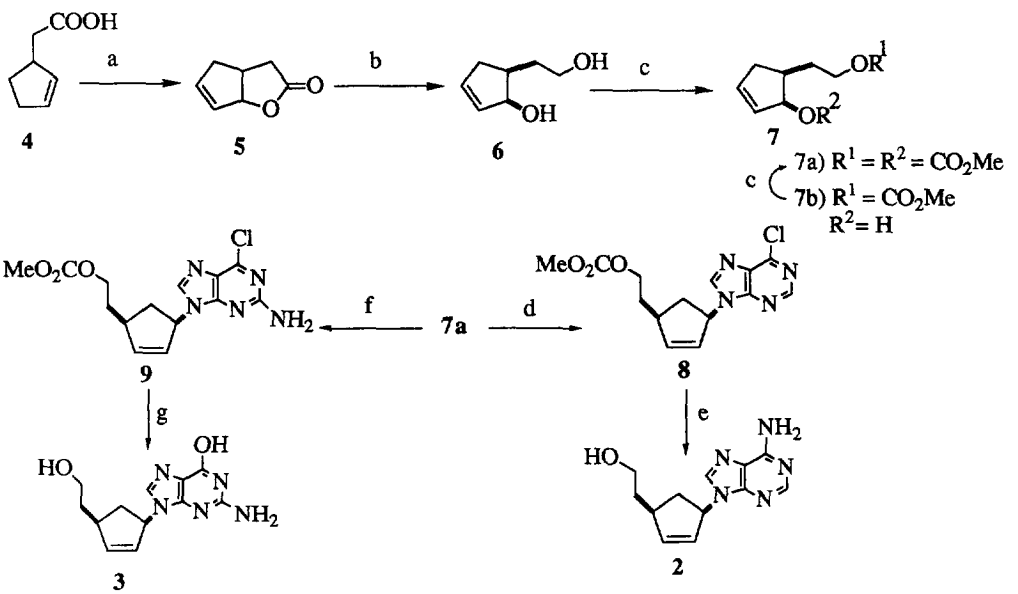


Figure 2

DISCUSSION

Racemic 2-cyclopentene-1-acetic acid **4** was chosen as the starting material for the intramolecular acyloxy palladation reaction. Cyclization of **4** to obtain the unsaturated lactone **5** was accomplished by Larock's procedure[4] using 5 mol% $Pd(OAc)_2$ and 2 equiv. of NaOAc in DMF under argon atmosphere in 85% yield. Reduction of **5** with lithium aluminum hydride afforded the diol **6** in 95% yield. Treatment of diol **6** with dimethyl pyrocarbonate and DMAP led to the formation of the dicarbonate **7a** in 50% yield after chromatography and recycling of the monocarbonate **7b** (Scheme 1).



(a) $Pd(OAc)_2$, NaOAc, O_2 atmos., RT, 12 h, 85%. (b) LAH, ether, O °C to RT, overnight, 95%. (c) DMAP, $O(CO_2CH_3)_2$, 0 °C, 15 min. then RT overnight, 50%. (d) $Pd(PPh_3)_4$, NaH, 6-chloropurine, THF, 60 °C, N_2 atmos., 3 h, 54%. (e) (i) liq. NH_3, sealed tube, 60 °C, 48 h. (ii) 0.5 N NaOH (aq), 4 h, reflux, 2 steps, 55%. (f) $Pd(PPh_3)_4$, NaH, 2-amino-6-chloropurine, THF, 60°C, N_2 atmos., 3h, 56%. (g) (i) CF_3CO_2H/H_2O (2:1) RT, 48 h (ii) 0.5 N NaOH (aq), RT, 2 h, 2 steps 52%.

Scheme 1

The key step to append the purine moiety was based on π allyl-palladium chemistry in an analogous manner to that described previously.[5,6] Thus, 6-chloropurine was deprotonated using NaH in DMF and heated at 60 °C under N_2 atmosphere for 30 min., then **7a** and 5 mol% $Pd(PPh_3)_4$ were added and heated at 60 °C for 3 hours. Attack of the nucleophile proceeded anti to the π-allyl palladium complex from the less hindered side resulting in the stereo and regiospecific formation of **8** in 55% yield.

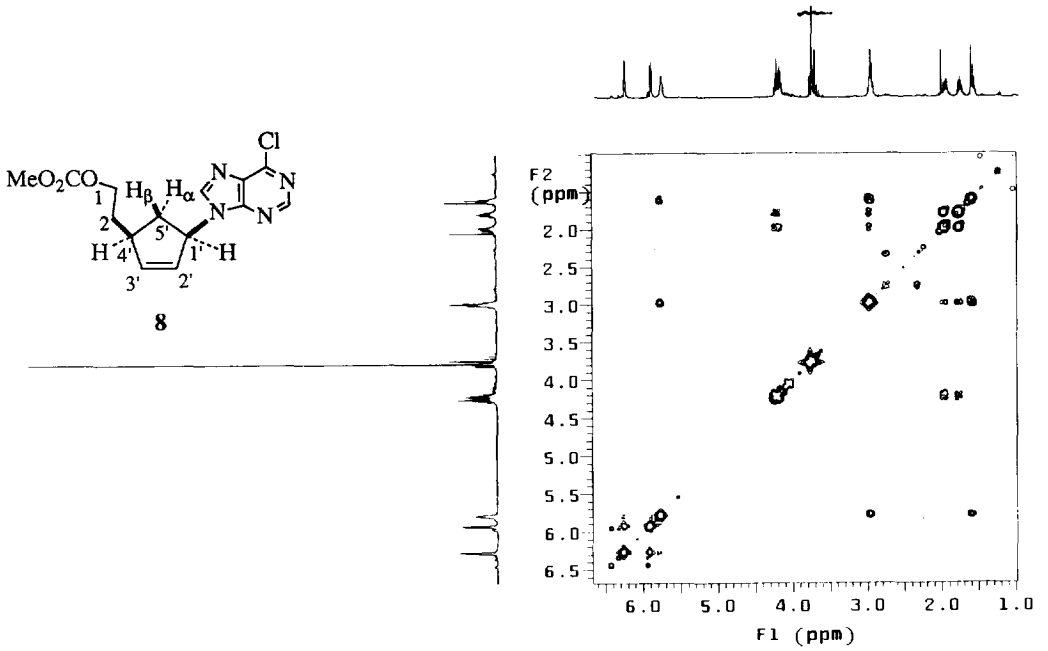


Figure 3. 2D HOMOCOSY spectrum of **8**.

The structure of **8** was unequivocally assigned by NMR spectroscopy. The 500 MHz ^1H NMR spectrum facilitated the analysis of all the interacting spins. The proton at C-1' resonated at 5.7 ppm and the C-5' protons Hα & Hβ appeared at 1.5 ppm and 3 ppm. The difference in chemical shift values is attributed to the proximity of the Hβ proton to the purine base. The vicinal couplings between different protons were confirmed as cross signals in the ^1H-^1H COSY 2D NMR spectrum (Fig. 3). The proton at C-1' (5.7 ppm) showed cross peaks with the protons at C-5' (1.5 ppm and 3 ppm) indicating that the coupling partner is a methylene carbon and the proton at C-4' showed cross signals with C-2 protons (1.7 ppm and 2 ppm) thus confirming the structure **8**. The couplings of C-4' protons with C-5' protons proved to be less informative since the chemical shift values of C-4' proton and C-5'β proton are coincidental.

Treatment of **8** with liquid NH_3 followed by hydrolysis with 0.5 N NaOH under reflux conditions for 3 hours gave **2** in 54% yield. Similarly **7a** was coupled with 2-amino-6-chloropurine to give **9** in 56% yield. Base hydrolysis of **9** to obtain **3** directly proceeded with very low yield. Therefore, **9** was allowed to react with CF_3CO_2H / H_2O (2:1) at room temperature for 48 hours[7] to give the guanine derivative which was then transformed to **3** by treatment with 0.5 N NaOH at room temperature for 2 hours in 52% yield.

In conclusion, the racemic synthesis of the title compounds is reported using palladium chemistry in 6-7 steps. In addition to having potential activity on their own, these homonucleosides will also be excellent sources for the preparation of phosphonate analogs. Initial phosphorylation is the first step in the intracellular activation of carbovir[8,9] and other 2',3'-didehydro-2',3'-dideoxynucleosides.[10] The strategy for using phophonate analogs where the CH_2-O-PO_3H_2 system of activated nucleosides is replaced by the more stable - CH_2-CH_2-PO_3H_2 has recently been discussed.[11] The anti-HIV evaluation of these compounds and the preparation of phosphonate analogs are currently under investigation and will be reported at a later date.

EXPERIMENTAL

General

All reactions involving air sensitive agents were conducted under a N_2 atmosphere. Solvents were dried appropriately wherever required. Melting points were determined on a Mel-Temp II apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Varian 300, 500 and Bruker-300 MHz instruments and NMR values are reported in δ. Thin layer chromatography (TLC) was done on E. Merck silica gel (0.25 mm thickness) 60F-254 glass plates. Plates were visualized in anisaldeyde solution by dipping and heating the plate (anisaldehyde, 25 ml; 97% H_2SO_4, 25 ml; glacial acetic acid, 5 ml; 95% ethanol, 450 ml). Column chromatography was performed on Merck silica gel 60 (230-400 mesh). Organic phases were dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure. Chemical Ionization (CI), Mass spectra (MS) were obtained with a Finnigan 4000 MAT 95, fast atom bombardment (FAB) MS were obtained with a VG 7070E-HF spectrometer. Elemental analyses were performed by M-H-W laboratories, Phoenix, AZ.

(±)-*cis*-5-(2-Hydroxyethyl)-2-cyclopenten-1-ol(6). LAH (3.83 g, 0.1 moles) was suspended in anhydrous ether (100 ml) and stirred at -10 °C. Compound **5** (4.17 g, 33.6 mmoles) in anhydrous ether (30 ml) was added dropwise to the suspension and stirring was continued overnight. The reaction mixture was cooled to -10 °C and quenched cautiously with the minimum amount of H_2O, and diluted with ether (50 ml). The aluminum salts were filtered and washed thoroughly with ether (50 ml). The ether layer was concentrated to give an oil. The oil was flashed over a column using 1:1 hexane / EtOAc as eluent. Fractions containing the desired compound (R_f = 0.23, 1:1 hexane / EtOAc) were removed of solvent by evaporation under reduced pressure to give **6**[12] as an oil (4.08 g, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): 5.8 (m, 1H), 4.8 (d, 1H), 4.6 (m, 1H), 4.0 (broad s, 1H), 3.5-3.8 (m, 3H), 2.4 (m, 1H), 2.0-2.2 (m, 2H), 1.6-1.9 (m, 2H); MS (CI, $M+NH_4^+$, 146, M^+, 128). *Anal.* Calcd for $C_7H_{12}O_2$: C, 65.6; H, 9.44. Found: C, 65.67; H, 9.46.

(±)-*cis*-1-Hydroxyethyl-2-hydroxy-2-cyclopentene-1,2-bis-(methylcarbonate) (7a). Compound **6** (1 g, 7.8 mmoles) was dissolved in anhydrous THF (30 ml), to which was added DMAP (100 mg, 0.78 mmoles) . To the reaction mixture stirred at 0°C, dimethyl pyrocarbonate (8.4 ml, 78 mmoles) was added dropwise. After 15 min., the ice bath was removed and the reaction mixture was stirred overnight. Then, the reaction mixture was concentrated at reduced pressure. The residue was chromatographed on silica gel using 5:1 hexane / EtOAc as eluent. Fractions containing the compound (R_f = 0.75, 5:1 hexane / EtOAc) were

removed of solvent by evaporation under reduced pressure to give an oil **7a** (1.9 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): 6.1 (m, 1H), 5.9 (m, 1H), 5.4 (m, 1H), 4.1 (m, 2H), 3.7 (d, 6H), 2.3-2.5 (m, 2H), 2.1-2.2 (m, 1H), 1.7-2 (m, 2H); MS (CI, $[M+NH_4]^+$, 262). *Anal.* Calcd. for $C_{11}H_{16}O_6$: C, 54.09; H, 6.6. Found: C, 54.30; H, 6.55.

(±)-*cis*-2-[4-(6-Chloro-9H-purin-9-yl)-2-cyclopent-1-enyl]-hydroxyethyl(methyl carbonate) (8). 6-chloropurine (994 mg, 6.4 mmoles) was added to a stirred suspension of NaH (97%, 190 mg, 7.86 mmoles) in dry DMF (5 ml) at RT. The reaction mixture was heated at 60 °C for 30 min., then it was cooled to RT and compound **7a** (1.28 g, 5.24 mmoles) in DMF (10 ml) and $Pd(PPh_3)_4$ (1.514 g, 1.3 mmoles) were added. The flask was covered with aluminum foil to exclude light and the mixture was heated at 60 °C for 2 h. The reaction mixture was diluted with methanol (15 ml) and the salts were filtered. The filtrate was concentrated under reduced pressure to obtain a residue. The residue was flashed over a column, using an elution gradient of hexane / EtOAc (1:1) to EtOAc. The solvent was removed from fractions containing the desired compound (R_f = 0.53, 1:1 hexane / EtOAc) to give a white solid **8** (900 mg, 54%, mp 88-90 °C). ^{1}H NMR (500 MHz, $CDCl_3$): 8.75 (s, 1H), 8.15 (s, 1H), 6.25 (m, 1H), 5.88 (m, 1H), 5.7 (m, 1H), 4.2 (m, 2H), 3.78 (s, 3H), 3.0 (m, 2H), 2.0 (m, 1H), 1.8 (m, 1H), 1.6 (m, 1H); MS (FAB $[M+H]^+$, 323. *Anal.* Calcd for $C_{14}H_{15}ClN_4O_3$: C, 52.1; H, 4.68; N, 17.36. Found: C, 52.30; H, 4.83; N, 17.27.

(±)-*cis*-2-[4-(6-Amino-9H-purin-9-yl)-2-cyclopent-1-enyl]-ethanol (2). Into a stainless steel bomb containing compound **8** (365 mg, 1.1 mmoles) dissolved in methanol (2 ml), was added excess liq. NH_3. The bomb was sealed and heated at 65 °C for 48 h. Ater cooling and evaporation of the ammonia, the contents were diluted with methanol (4 ml) and the salts were filtered. The solvent was removed at reduced pressure to give a residue, to which was added 0.5 N aqueous NaOH (15 ml) and refluxed for 4 h. The reaction mixture was cooled to RT and acidified with 1N HCl (pH 5). The water was removed at reduced pressure, the residue was adsorbed on silica gel and chromatographed. The desired compound (R_f = 0.45, 5:1 CH_2Cl_2 / MeOH) eluted with 10:1 CH_2Cl_2 / MeOH and the fractions were removed of solvent at reduced pressure to obtain **2** as a white solid (150 mg, 55% for 2 steps, mp. 150-152 °C). ^{1}H NMR (500 MHz, DMSO-d_6) 8.18 (s, 1H), 8.05 (s, 1H), 7.2 (s, 2H), 6.2-6.23 (m, 1H), 5.87-5.9 (m, 1H), 5.59-5.63 (m, 1H), 4.53 (t, OH, D_2O exchangeable), 3.57-3.63 (m, 2H), 2.84-2.9 (m, 2H), 1.75-1.8 (m, 1H), 1.5-1.6 (m, 2H); MS (FAB) $[M+H]^+$, 246.2. *Anal.* Calcd for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55. Found: C, 58.80; H, 6.19; N, 28.36.

(±)-*cis*-2-Amino-1,9-dihydro-9-[4-(hydroxyethyl)-2-cyclopenten-1-yl-6H-purine-6-one (3). 2-amino-6-chloropurine was added to a stirred suspension of NaH (95%, 200 mg, 8 mmoles) and heated at 60 °C for 30 min., then cooled to room temperature. The flask was covered with aluminum foil and **7a** (1.29 g, 5.3 mmoles) in DMF (5 ml) and $Pd(PPh_3)_4$ (612 mg, 0.53 mmoles) was added and heated for 3 h. The reaction mixture was cooled and DMF was removed in *vacuo*. The residue was adsorbed to silica gel which was packed onto a column and eluted with 3:2 hexane / EtOAc. The solvent was removed from the fractions by evaporation under reduced pressure to give a white solid **9** (1 g, 56%). To **9** was added CF_3CO_2H / H_2O

(2:1) (15 ml) and stirred at room temperature for 48 h. The solvents were removed under reduced pressure and the reaction mixture was adjusted to pH 6 by the dropwise addition of MeOH / NH_4OH (10:1). The contents were removed of solvents under reduced pressure and passed over a short column of silica gel. The column was eluted with 10:1 CH_2Cl_2 / MeOH and the fractions were removed of solvent under reduced pressure to obtain a white solid. To the white solid was added 0.5 N aq. NaOH (15 ml) and stirred at room temperature for 2 h. then, acidified with 1N HCl (pH-6). The residue was adsorbed to silica gel which was packed onto a column and eluted with CH_2Cl_2 / MeOH (10:1.5). The solvent was removed by evaporation at reduced pressure from fractions with R_f = 0.3 (5:1 CH_2Cl_2 / MeOH) giving **3** as a white solid (240 mg, 52%, mp 220°C (with decomposition). ^1H NMR (300 MHz, $DMSOd_6$) 11 (br. s, NH), 7.65 (s, 1H), 6.5 (s, NH_2), 6.18-6.22 (m,1H), 5.82-5.85 (m, 1H), 5.43-5.48 (m, 1H), 4.5 (t, OH), 3.58-3.64 (m, 2H), 2.78-2.83 (m, 1H), 2.88-2.96 (m, 1H), 1.77-1.83 (m, 1H), 1.49-1.61 (m, 2H). MS HR FAB Calcd. for $C_{12}H_{15}N_5O_2$, 261.1223, Found: $[M+H]^+$, 262.1317.

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