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Enantioselective Synthesis of 2-[5-(9*H*-Purin-9-yl)-2-cyclopenten-1-yl]-ethanol Analogues as Potential Antiviral agents.

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Abstract: The enantioselective synthesis of 2-[5-(9*H*-purin-9-yl)-2-cyclopenten-1-yl]ethanol analogues is described. (1R,5R)-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-cyclopenten-5-ol **4a** and (1S,5S)-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-cyclopenten-5-ol **4b** were coupled with 6-chloropurine and 2-amino-6-chloropurine using Mitsunobu reaction conditions. Compounds **6a & b, 7a & b, 8a & b, 9a & b,** and **10a & b** were tested for antiviral activity.

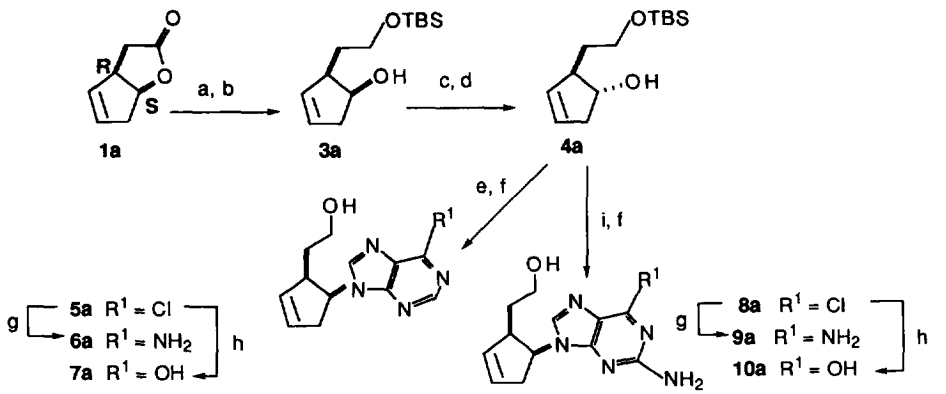
INTRODUCTION

HIV reverse transcriptase (RT) is one of the targets for the development of new drugs for the treatment of AIDS. Carbocyclic nucleosides are attractive targets due to their metabolic stability towards phosphorylase enzymes and their wide range of biological activity.[1] Carbovir[2] and a 6-cyclopropyl analogue of carbovir have emerged as potential drug candidates and are currently in clinical trials.[3]

Despite a number of nucleoside RT inhibitors[4-6] there is still an increasing necessity for less toxic and more effective anti-HIV agents. In this paper, we report the synthesis and biological activity of 2-[5-(9H-purin-9-yl)-2-cyclopentenyl]-ethanol analogues as structural variants of carbovir.

DISCUSSION

Reduction of (-)-cis-2-oxabicyclo[3.3.0]oct-6-en-3-one (**1a**) with lithium aluminum hydride gave the known diol[7] (**2a**) in 95% yield. Selective protection of the primary alcohol was achieved by reacting **2a** with *t*-butyldi-



(a) LAH, ether (anhyd), -10 °C to RT. (b) TBSCl, imidazole, CH_2Cl_2 (anhyd), -20 to 0 °C.
(c) PPh_3, DEAD, $PhCO_2H$. (d) K_2CO_3, MeOH. (e) PPh_3, DEAD, 6-chloropurine, THF (anhyd), RT.
(f) TBAF, CH_2Cl_2, -20 °C. (g) liq. NH_3 (excess) 65 °C, 48 h. (h) 0.5 *N* aq. NaOH, reflux, 3 h.
(i) PPh_3, DEAD, 2-amino-6-chloropurine, THF, RT.

Scheme 1

methylsilylchloride in dichloromethane in the presence of imidazole to give **3a**[7] in quantitative yield (Scheme 1).

The desired stereochemistry in the synthesis of the title compounds was achieved by consecutive Mitsunobu reactions.[8] The first Mitsunobu reaction was performed to invert the hydroxyl group of **3a** and the second to append the purine moiety to the cyclopentene **4a**.

The monoprotected alcohol **3a** was treated with triphenylphosphine, DEAD and benzoic acid at room temperature to obtain a mixture. The resulting mixture was chromatographed to obtain the benzoate ester which was hydrolysed with K_2CO_3 in MeOH to give the inverted alcohol **4a** in 25% yield for the 2 steps after chromatographic purification. The alcohol **4a** was coupled with 6-chloropurine and also with 2-amino-6-chloropurine using standard Mitsunobu conditions.[9] Deprotection of the *t*-butyldimethylsilyl group with TBAF at -20°C gave **5a** & **8a** in yields of 67% and 56% respectively, for the 2 steps. Deprotection at higher temperatures (0 °C and room temperature) led to the elimination of the purine moiety. Attempted deprotection after ammonolysis also led to the elimination of the purine moiety.

The chloropurine **5a** was converted to the adenine analogue **6a** in 42% yield using standard ammonolysis conditions and to the inosine analogue **7a** in 74% yield using 0.5 *N* aq NaOH under reflux conditions. The 2-amino-6-chloropurine derivative **8a** was treated with excess ammonia and heated at 65°C for 48 h to obtain the diamino purine **9a** in 32% yield. **9a** was hydrolysed with refluxing 0.5 *N* aq NaOH to give the guanosine analogue **10a** in 41% yield. The absolute stereochemistry of this series of nucleoside analogs is analogous to the ribose C-1 and C-4 of natural β-D-ribofuranosyl nucleosides.

The same sequence of reactions were performed starting with enantiomerically pure (+)-cis-2-oxabicyclo-[3.3.0]oct-6-en-3-one (**1b**) to obtain the series **6b**, **7b**, **8b**, **9b** & **10b** corresponding to L-ribonucleosides. The reactions were not optimized for yields, except to obtain usable quantities of material.

BIOLOGICAL RESULTS

Compounds **5a** - **10a** and **5b** - **10b** were tested against herpes simplex virus type 1. All compounds were inactive at concentrations below 50 μg/mL except the insosine derivatives **7a** and **7b**. Interestingly, **7a** , which has the same absolute stereochemistry as (-) carbovir and the natural nucleosides, is ten times more active (IC_{50} = 1 μg/mL) than its enantiomer **7b** (IC_{50} = 10 μg/mL). Evaluation for cytotoxicity against P388 mouse leukemia cells in vitro revealed that none of the compounds exhibited antitumor activitiy. None of the compounds demonstrated significant activity against HIV in CEM cell cultures.

EXPERIMENTAL

General

Elemental analyses were performed by M-H-W laboratories, Phoenix, AZ. Melting points were determined on a Mel-Temp II apparatus and are uncorrected. ^1H NMR spectra were recorded on Varian Unity 500 & 300 MHz and GE 300 MHz instruments and chemical shift 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 with 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. Chemical Ionization (CI), mass spectra were obtained with a Finnigan 4000, fast atom bombardment (FAB) mass spectra (MS) low resolution were obtained with a VG 7070E-HF spectrometer and high resolution with Finnigan Mat 95 respectively. Optical rotations were carried out on a Rudolph polarimeter.

(1R,5R)-1-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-2-cyclopenten-5-ol (4a). DEAD (2.9 mL, 18.6 mmoles) was added dropwise to a stirring solution of triphenylphosphine (4.88 g, 18.6 mmoles) in anhyd THF (30 mL) at RT. Then a solution of the monoprotected alcohol **3a** (3.0 g, 12.4 mmoles, NMR data of **3a** obtained from **2a**[7a] match with **3b**) in THF (20 mL) was added dropwise followed by benzoic acid (2.27 g, 18.6 mmoles). After 2 h, an additional 1.5 equiv of triphenylphosphine, DEAD and benzoic acid were added and stirring was continued at RT overnight. The solvents were removed under reduced pressure leaving a syrup. The syrup was flashed over a column to seperate the two uv active spots using 10:1 hexane / EtOAc as eluent. Fractions with R_f 0.73 (5:1 hexane / EtOAc) were concentrated under reduced pressure to obtain the benzoate ester as an oil. ^1H NMR (300 MHz, $CDCl_3$): 8.0 (d, 2H), 7.24-7.55 (m, 3H), 5.70-5.75 (m, 2H), 5.27-5.29 (m, 1H), 3.68-3.73 (t, 1H), 2.88-2.96 (m, 2H), 2.03-2.45 (d, 1H), 1.57-1.77 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H). To the ester in anhyd methanol (30 mL), was added K_2CO_3 (2.6 g, 18.7 mmoles), and the suspension was stirred at RT overnight. The solvent was removed under reduced pressure, diluted with water (15 mL), and extracted with EtOAc (2 x 20 mL). The organic phase was dried and concentrated at reduced pressure leaving an oil. The oil was flashed over a column, eluting with 10:1 hexane / EtOAc. The solvent was removed under reduced pressure from the fractions with R_f 0.35 (5:1 hexane / EtOAc), leaving the inverted alcohol **4a** as an oil (0.735 g, 25% from 3a).

^{1}H NMR (300 MHz, $CDCl_3$): 5.6-5.68 (m, 1H), 5.5-5.58 (m, 1H), 4.04-4.1 (m, 1H), 3.8-3.85 (m, 1H), 3.65-3.75 (m, 1H), 3.5 (s, OH), 2.56-2.66 (m, 2H), 2.22-2.4 (m, 1H), 1.7-1.8 (m, 1H), 1.5-1.6 (m, 1H), 0.86 (s, 9H), 0.02 (s, 6H). MS (CI, $[M+H^+]$), 243. *Anal.* Calcd for $C_{13}H_{26}O_2Si$: C, 64.4; H, 10.81. Found: C, 64.57; H, 10.69. Alcohol **4b** was obtained from **3b**[7b] in 23% yield, using the same conditions. MS (CI, $[M+H^+]$), 243. *Anal.* Calcd for $C_{13}H_{26}O_2Si$: C, 64.4; H, 10.81. Found: C, 64.29; H, 10.71.

(1R,5S)-2-[5-(6-Chloro-9H-purin-9-yl)-2-cyclopentenyl]-ethanol (5a). 6-chloropurine (1.00 g, 6.5 mmoles) was added to a stirring solution of triphenylphosphine (1.72 g, 6.5 mmoles) in anhyd THF (30 mL). The resulting suspension was stirred for 10 min., followed by the dropwise addition of a solution of the alcohol **4a** (0.79 g, 3.3 mmoles) in THF (10 mL). The reaction mixture was stirred at RT overnight and concentrated *in vacuo*. The resulting syrup was chromatographed, using a eluent gradient of 5:1 hexane / EtOAc to 5:3 hexane / EtOAc. The fractions eluting with Rf 0.58 (1:1 hexane / EtOAc) were removed of solvent *in vacuo* giving an oil (0.650 g, 64%). TBAF (1M in THF, 12.4 mL, 12.4 mmoles) was added to the oil (1.17 g, 3 mmoles) in THF (10 mL) and stirred at -20 °C for 3 h. The reaction mixture was quenched with satd. aq NH_4Cl (15 mL) and extracted with EtOAc (2 x 20 mL). The organics were concentrated under reduced pressure and the residue was chromatographed eluting with EtOAc. The solvent was removed from the fractions with R_f 0.16 (EtOAc) giving chloropurine **5a** as a viscous oil (0.574 g, 70%). ^{1}H NMR (300 MHz, CD_3OD): 8.72 (s, 1H), 8.5 (s, 1H), 6.04-6.07 (m, 1H), 5.95-5.97 (m, 1H), 5.46-5.52 (m, 1H), 2.94-3.5 (m, 3H & 1 OH), 0.95-1.7 (m, 4H). MS LRFAB, 265 $[M+H]^+$. MS HR FAB Calcd. for $C_{12}H_{13}ClN_4O$, 264, Found: $[M+H]^+$, 265.
Chloropurine **5b** was obtained in 68% yield (for 2 steps) using the same conditions. MS LRFAB, 265 $[M+H]^+$. MS HR FAB Calcd. for $C_{12}H_{13}ClN_4O$, 264, Found: $[M+H]^+$, 265.

(1R,5S)-2-[5-(6-Amino-9H-purin-9-yl)-2-cyclopentenyl]-ethanol (6a). Excess liq.NH_3 was added to a solution of **5a** (0.2 g, 0.75 mmoles) in methanol (5 mL) in a bomb and the resulting solution was heated at 65 °C for 48 h. After cooling and evaporation of the ammonia, water (3 mL) was added. The compound was filtered and washed thoroughly with hexanes (15 mL) and dichloromethane (10 mL), and dried under vacuum giving the adenine compound **6a** as a light brown solid (0.077 g, 42%, mp 198-199 °C). $[\alpha]^{23}_D$ -164° (c, 0.25, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6) 8.16 (s, 1H), 8.04 (s, 1H), 7.2 (s, NH_2), 5.9-6.0 (m, 2H), 5.2 (m, 1H), 2.8-3.5 (m, 4H & 1OH), 0.95-1.0 (m, 3H). MS LRFAB 246 $[M+H]^+$. *Anal.* Calcd for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55. Found: C, 58.53; H, 6.39; N, 28.13.
(1S,5R)-2-[5-(6-Amino-9H-purin-9-yl)-2-cyclopentenyl]-ethanol (6b). 69%, mp 198-199 °C. $[\alpha]^{23}_D$ +172° (c, 0.25, MeOH).MS LRFAB 246 $[M+H]^+$. *Anal.* Calcd for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55. Found: C, 58.90; H, 6.29; N,2 8.62.
(1S,5R)-1,9-dihydro-9-[5-(hydroxyethyl)-3-cyclopentenyl-6H-purin-6-one (7a). Compound **5a** (0.15 g, 0.568 mmoles) in 0.5 *N* aq NaOH (10 mL) was refluxed for 3 h. Then the reaction mixture was cooled to RT, acidified with 1*N* HCl (pH 5), and allowed to stir at RT overnight. The reaction mixture was concentrated and the residue was chromatographed, eluting with 10:1 CH_2Cl_2 / MeOH. Solvent was removed from the fractions under reduced pressure giving the inosine **7a** as a white solid (0.103 g, 74%, mp 198 °C (with dec).

$[\alpha]^{23}_D$ -134.4° (c, 0.25, MeOH). ^{1}H NMR (300 MHz, CD_3OD) 8.05 (s, 1H), 8.03 (s, 1H), (6.01-6.04 (m,1H), 5.92-5.95 (m,1H), 5.33-5.39 (m, 1H), 3.4-3.55 (m, 2H), 2.8-3.36 (m, 3H), 1.0-1.17 (m, 2H). MS LRFAB 247 $[M+H]^+$. *Anal.* Calcd for $C_{12}H_{14}N_4O_2 \cdot 0.5\ H_2O$: C, 56.46; H, 5.92; N, 21.94. Found: C, 56.46; H, 5.96; N, 21.73.

(1R,5S)-1,9-dihydro-9-[5-(hydroxyethyl)-3-cyclopentenyl-6H-purin-6-one (7b). 44%, mp 200 °C (with dec). $[\alpha]^{23}_D$ +128° (c, 0.25, MeOH).MS LRFAB 247 $[M+H]^+$. *Anal.* Calcd for $C_{12}H_{14}N_4O_2 \cdot 1.5\ H_2O$: C, 52.36; H, 6.22; N, 20.35. Found: C, 52.01; H, 6.76; N, 19.91.

(1R,5S)-2-[5-(2-Amino-6-chloro-9H-purin-9-yl)-2-cyclopentenyl]-ethanol (8a). To a stirring solution of triphenylphosphine (2.6 g, 9.9 mmoles) in anhyd THF (30 mL) was added 2-amino-6-chloropurine (1.68 g, 9.9 mmoles). DEAD (9.9 mmoles, 1.56 ml) was added dropwise to the suspension, followed by **8a** (1.2 g, 4.9 mmoles) in THF (10 mL) at RT. After 2 h, an additional 2 equiv of triphenylphosphine, DEAD and 2-amino-6-chloropurine were added and stirred overnight. The reaction mixture was concentrated giving a residue which was adsorbed on silica gel, flashed over a column and eluted with 1:1 hexane / EtOAc. Solvent was removed from the fractions with R_f 0.7 (EtOAc) giving an oil. TBAF (1 M in THF, 15.3 mmoles, 15.2 mL) was added to the oil in THF (15 mL) and stirred at -20 °C for 4 h. The reaction mixture was quenched with satd. aq NH_4Cl (20 mL) and extracted with EtOAc (2 x 20 mL). The organic phase was dried, solvent removed under reduced pressure giving a residue which was chromatographed using 1:1 hexane / EtOAc and EtOAc. Solvent was removed from fractions under reduced pressure with R_f 0.23 (EtOAc) giving 2-amino-6-chloropurine compound **8a** as a white solid (0.567 g, 54%, mp 64-66 °C). $[\alpha]^{23}_D$ -239.2° (c, 0.25, MeOH).^{1}H NMR (300 MHz, DMSO-d_6) 8.0 (s, 1H), 6.9 (s, NH_2), 5.87-5.92 (m, 2H), 5.04-5.07 (m, 1H), 2.84-3.25 (m, 4H), 1.24-1.55 (m, 2H), 0.85-0.96 (m, 2H). MS LRFAB 280 $[M+H]^+$. *Anal.* Calcd for $C_{12}H_{14}ClN_5O$: C, 51.52; H, 5.04; N, 25.03. Found: C, 51.35; H, 5.35; N, 25.31.

(1S,5R)-2-[5-(2-Amino-6-chloro-9H-purin-9-yl)-2-cyclopentenyl]-ethanol (8b). 35 %, mp 64-66 °C. $[\alpha]^{23}_D$ +231.2° (c, 0.25, MeOH).MS LRFAB 280 $[M+H]^+$. *Anal.* Calcd for $C_{12}H_{14}ClN_5O \cdot 0.2\ H_2O$: C, 50.87; H, 4.98; N, 24.71. Found: C, 50.50; H, 5.34; N, 24.40.

(1R,5S)-2-[5-(2,6-Diamino-9H-purin-9-yl)-2-cyclopentenyl)-ethanol (9a). Excess liq.NH_3 was added to solution of **8a** (0.1 g, 0.358 mmoles) in MeOH (3 ml) in a bomb and was heated at 65 °C for 48 h. After cooling and evaporation of solvent, the residue was chromatographed eluting with a gradient of 10:1 CH_2Cl_2 / MeOH. Solvent was removed from fractions with Rf 0.58 (5:1 CH_2Cl_2 / MeOH) under reduced pressure giving the diamino compound **9a** as a white solid (0.03 g, 32%, mp 211-213 °C). $[\alpha]^{23}_D$ -227.6° (c, 0.25, MeOH).^{1}H NMR (500 MHz, CD_3OD) 8.0 (s, 1H), 6.2-6.35 (m, 2H), 5.4 (m, 1H), 3.6-3.8 (m, 2H), 3.1-3.5 (m, 3H), 1.4 (m, 2H). MS LRFAB 261 $[M+H]^+$. *Anal.* Calcd for $C_{12}H_{16}N_6O$: C, 55.37; H, 6.19; N, 32.28. Found: C, 55.20; H, 6.35; N, 32.18.

(1S,5R)-2-[5-(2,6-Diamino-9H-purin-9-yl)-2-cyclopentenyl)-ethanol (9b). 32%, mp 208-210 °C, $[\alpha]^{23}_D$ +233.6° (c, 0.25, MeOH).MS LRFAB 261 $[M+H]^+$. *Anal.* Calcd for $C_{12}H_{16}N_6O$: C, 55.37; H, 6.19; N, 32.28. Found: C, 55.28; H, 6.30; N, 32.18.

(1S,5R)-2-Amino-1,9-dihydro-9-[5-(hydroxyethyl)-3-cyclopentenyl-6H-purin-6-one (10a). **8a** (0.145 g, 0.5 m moles) in 0.5 *N* aq NaOH (15 mL) was refluxed for 3.5 h. The reaction mixture was cooled to RT, acidified with 1 *N* HCl (pH 5) and concentrated to a residue. The residue was adsorbed on silica gel and chromatographed eluting with 10:1 CH_2Cl_2 / MeOH. Fractions with R_f 0.29 (5:1 CH_2Cl_2 / MeOH) were removed of solvent under reduced pressure giving the guanine compound **10a** as a white solid (0.055 g, 41%, mp 190 °C (with dec). $[\alpha]^{23}_D$ -168° (c, 0.25, MeOH). ^1H NMR (500 MHz, DMSO-d_6) 10.6 (s, NH), 7.6 (s, 1H), 6.5 (s, NH_2), 5.8-6.0 (m, 2H), 5.0 (m, 1H), 4.4 (t, OH), 4.1 (m, 1H), 2.75-3.4 (m, 4H), 0.95-1.0 (m, 2H). MS LRFAB 262[M+H]$^+$. *Anal.* Calcd for $C_{12}H_{15}N_5O_2 \cdot 3.5\ H_2O$: C, 44.44; H, 6.82; N, 21.59. Found: C, 45.05; H, 6.95; N, 21.27.

(1R,5S)-2-Amino-1,9-dihydro-9-[5-(hydroxyethyl)-3-cyclopentenyl-6H-purin-6-one (10b). 47%, mp 180 °C (with dec). $[\alpha]^{23}_D$ +187.2°(c, 0.25, MeOH).MS LRFAB 262[M+H]$^+$. *Anal.* Calcd for $C_{12}H_{15}N_5O_2$: C, 55.16; H, 5.78; N, 26.8. Found: C, 54.96; H, 5.71; N, 26.62.d.

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