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## Nucleosides, Nucleotides and Nucleic Acids

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### 5'-Nor Carbocyclic Ribavirin

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## 5'-Nor Carbocyclic Ribavirin

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### ABSTRACT

An efficient synthesis of 5'-nor carbocyclic ribavirin (**4**) is described in 13 steps from conveniently available (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (**6**). Compound **4** was evaluated against the following viruses: herpes simplex type 1 and 2, vaccinia, cowpox, smallpox, Ebola, hepatitis B, hepatitis C, adenovirus type 1, influenza A (H1N1 and H3N2), influenza B, parainfluenza type 3, Pichinde, Punta Toro A, respiratory syncytial, rhinovirus type 2, Venezuelan equine encephalitis, yellow fever, and West Nile. No activity was found nor was there any cytotoxicity to the viral host cells.

*Key Words:* 1,2,4-Triazole; Carbocyclic nucleoside; Antiviral.

### INTRODUCTION

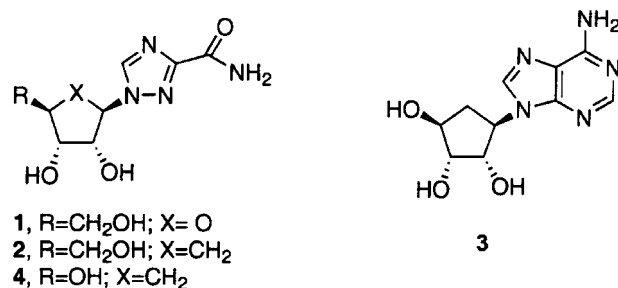
The synthetic nucleoside ribavirin (**1**) has gained prominence as a clinically useful broad-spectrum antiviral agent<sup>[1–8]</sup> and has shown therapeutic potential towards the orthopox viruses.<sup>[9]</sup> The most striking structural feature of **1** is the 1,2,4-triazole ring, which is unique among nucleoside derived medicinal agents. To extend this heterocyclic moiety to other nucleoside analogs, carbocyclic ribavirin (**2**) has been

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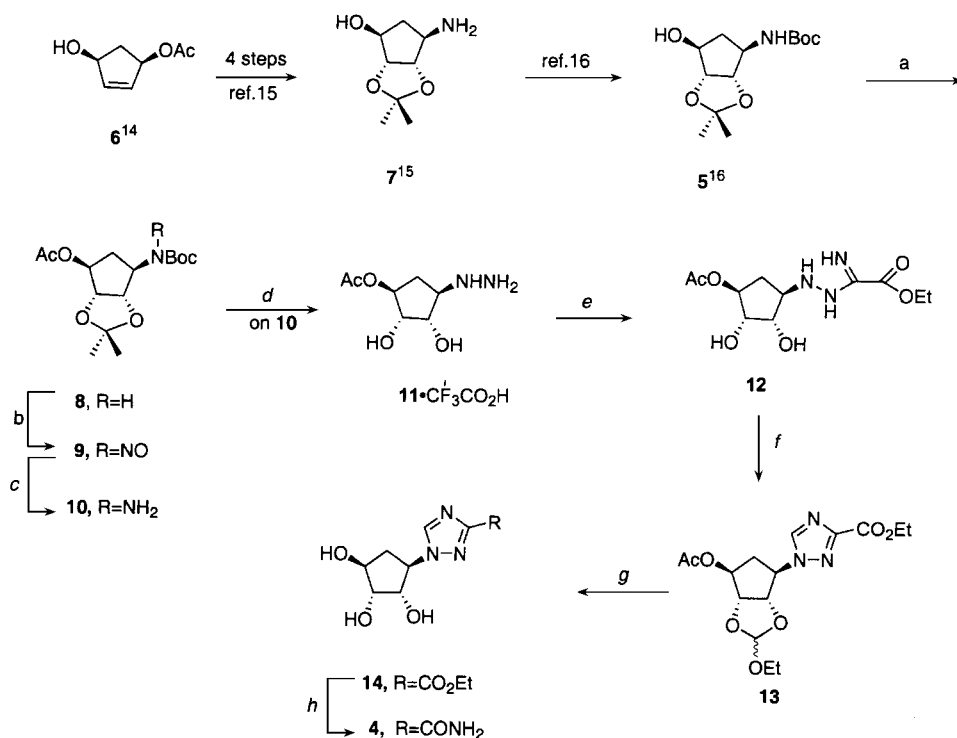
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**Figure 1.** Ribavirin and various carbocyclic nucleosides.

described,<sup>[10]</sup> but, to date, studies on its biological properties have been limited (Fig. 1).<sup>[10a]</sup> As an outgrowth of our investigations of 5'-nor carbocyclic nucleosides, which have displayed significant antiviral activity<sup>[11]</sup> (for example, 5'-noraristeromycin, (**3**)),<sup>[12,13]</sup> we sought 5'-nor carbocyclic ribavirin (**4**). The synthesis and antiviral analysis of **4** is presented here.



**Scheme 1.** Reaction conditions: *a*, Ac<sub>2</sub>O, TEA, DMAP, CH<sub>3</sub>CN, rt; *b*, NOBF<sub>4</sub>, pyridine, CH<sub>3</sub>CN, −30 then to 0°C; *c*, Zn, HOAc, 10°C; *d*, TFA/H<sub>2</sub>O, rt; *e*, ethyl carboethoxyformimidate,<sup>17</sup> NaHCO<sub>3</sub>, MeOH, 0°C; *f*, HC(OEt)<sub>3</sub>, toluene, 110°C; *g*, HCl/THF(1:1), 50°C; *h*, saturated NH<sub>3</sub>/MeOH, rt.

## RESULTS

### Synthesis

In order to adapt a literature procedure<sup>[10]</sup> for the synthesis of **4**, the protected trihydroxycyclopentylamine **5** was identified as the appropriate starting material and, consequently, obtained from the readily available (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (**6**)<sup>[14]</sup> via **7**.<sup>[15]</sup> Protective acetylation of the secondary alcohol of **5** to **8** was followed by nitrosation with nitrosonium tetrafluoroborate to provide **9**. Reduction of **9** led to the protected hydrazine derivative **10**, which was then subjected to acidic deprotection to **11**. Derivatizing **11** for creating the triazole ring was accomplished with ethyl carboethoxyformimidate<sup>[17]</sup> to **12**. Ring closure of **12** triethyl orthoformate to the ethyl 1,2,4-triazole-3-carboxylate **13** as its 2',3'-protected mixed orthoester was easily achieved. Acidic treatment of **13** to **14** was followed by amidation to the desired **4** (Sch. 1).

### Antiviral

Compound **4** was evaluated for the effectiveness towards the following viruses: herpes simplex type 1 and 2, vaccinia, cowpox, smallpox, Ebola, hepatitis B, hepatitis C, adenovirus type 1, influenza A (H1N1 and H3N2), influenza B, parainfluenza type 3, Pichinde, Punta Toro A, respiratory syncytial, rhinovirus type 2, Venezuelan equine encephalitis, yellow fever, and West Nile. No activity was found nor was there any cytotoxicity to the viral host cells.<sup>[18]</sup>

## EXPERIMENTAL SECTION

### General Methods

Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. Combustion analyses were performed by Atlantic Microlab, Inc., Norcross, GA. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker AC 250 spectrometer (operated at 250 and 62.5 MHz, respectively) and are referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), m (multiplet), and br (broad). Optical rotations were measured on a Jasco P-1010 polarimeter. Reactions were monitored by thin-layer chromatography (TLC) using 0.5-mm Whatman Diamond silica gel 60-F<sub>254</sub> precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. Yields refer to chromatographically and spectroscopically (<sup>1</sup>H and <sup>13</sup>C NMR) homogeneous materials.

**(1*S*,2*R*,3*S*,4*R*)-1-Acetoxy-2,3-(isopropylidenedioxy)-4-(tert-butoxycarbonyl amino)-cyclopentane (8).** To a solution of **5** (0.93 g, 3.4 mmol), *p*-(dimethylamino)pyridine (209 mg, 1.71 mmol) and triethylamine (0.95 mL, 6.81 mmol) in dry CH<sub>3</sub>CN (45 mL) was added anhydrous acetic acid (0.8 mL, 8.51 mmol). The reaction mixture was



stirred for 2 h at room temperature, poured into ice H<sub>2</sub>O and extracted with EtOAc. The organic-layer was washed with a saturated sodium bicarbonate solution and H<sub>2</sub>O, dried (MgSO<sub>4</sub>) and filtered. The filtrate was evaporated in vacuo and the residue purified by column chromatography (hexanes-EtOAc, 2.5:1) to give **8** (1.07 g, 100%) as a white solid: mp 69°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.26 (s, 3H, CH<sub>3</sub>), 1.42 (s, 3H, CH<sub>3</sub>), 1.45 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.72 (m, 1H, H-5), 2.10 (s, 3H, CH<sub>3</sub>COO), 2.40 (m, 1H, H-5), 4.13 (m, 1H, H-4), 4.52 (s, 2H, H-1, H-2), 4.80 (br s, 1H, NH), 5.11 (d, 1H, H-2); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 21.4 (C(CH<sub>3</sub>)<sub>3</sub>), 24.0 (C(CH<sub>3</sub>)<sub>2</sub>), 26.4 (OCOCH<sub>3</sub>), 28.5 (C-5), 33.8 (C-4), 56.6 (OC(CH<sub>3</sub>)<sub>3</sub>), 79.9 (C-1), 84.3 (C-3), 85.8 (C-2), 111.0 (C(CH<sub>3</sub>)<sub>2</sub>), 155.0 (NHCO), 169.6 (CH<sub>3</sub>COO). Anal. Calcd. for C<sub>15</sub>H<sub>25</sub>NO<sub>6</sub>: C, 57.13; H, 7.99; N, 4.44. Found: C, 57.17; H, 8.01; N, 4.46.

**(1S,2R,3S,4R)-1-Acetoxy-2,3-(isopropylidenedioxy)-4-[N-nitroso-N-(tert-butoxycarbonyl)amino]cyclopentane (9).** To a stirred solution of **8** (1.43 g, 4.53 mmol), and anhydrous pyridine (0.73 mL, 9.06 mmol) in dry CH<sub>3</sub>CN (60 mL), cooled to -30°C, was added NOBF<sub>4</sub> (1.22 g, 10.44 mmol). The solution was maintained at -30°C under N<sub>2</sub> for 30 min. This was followed by stirring at 0°C for another 1.5 h and the solution then added to CH<sub>2</sub>Cl<sub>2</sub> and ice. The organic layer was further extracted with cold H<sub>2</sub>O and dried (MgSO<sub>4</sub>) and the solvent eliminated in vacuo without heating. The residue was purified by column chromatography (cold hexanes-EtOAc, 3:1) to give **9** (1.56 g, 100%) as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.26 (s, 3H, CH<sub>3</sub>), 1.49 (s, 3H, CH<sub>3</sub>), 1.65 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.91 (m, 1H, H-5), 2.0 (s, 3H, CH<sub>3</sub>COO), 2.46 (m, 1H, H-5), 4.78 (m, 2H, H-1, H-4), 4.98 (m, 2H, H-2, H-3); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 21.1 (C(CH<sub>3</sub>)<sub>3</sub>), 25.2 (C(CH<sub>3</sub>)<sub>2</sub>), 27.9 (OCOCH<sub>3</sub>), 33.5 (C-5), 53.9 (C-4), 78.4 (OCC(CH<sub>3</sub>)<sub>3</sub>), 81.0 (C-1), 83.9 (C-3), 86.1 (C-2), 113.1 (C(CH<sub>3</sub>)<sub>2</sub>), 151.8 (NCO), 170.5 (CH<sub>3</sub>COO). Anal. Calcd. for C<sub>15</sub>H<sub>24</sub>N<sub>2</sub>O<sub>7</sub>: C, 52.32; H, 7.02; N, 8.13. Found: C, 52.01; H, 7.07; N, 7.77.

**(1S,2R,3S,4R)-1-Acetoxy-2,3-(isopropylidenedioxy)-4-[N-(tert-butoxycarbonyl)hydrazino]cyclopentane (10).** Compound **9** (3.76 g, 10.91 mmol) was dissolved in glacial AcOH (100 mL) and the solution brought to 10°C. Zinc dust (6.41 g, 98.19 mmol) was added slowly to the solution. The reaction was stirred at room temperature for 40 min. The precipitate was separated by filtration and washed with EtOAc. The filtrate and the washings were combined and this solution washed with cold saturated sodium carbonate solution (3 × 100 mL) and brine (2 × 100 mL), dried (MgSO<sub>4</sub>), filtered and the filtrate evaporated in vacuo. The residue was purified by column chromatography (hexanes-EtOAc, 2.3:1, 1.5:1, 1:1) to give **10** (3.1 g, 86%) as a colorless syrup: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.30 (s, 3H, CH<sub>3</sub>), 1.47 (s, 3H, CH<sub>3</sub>), 1.54 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.89 (m, 1H, H-5), 2.06 (s, 3H, CH<sub>3</sub>COO), 2.42 (m, 1H, H-5), 3.79 (br s, 2H, NH<sub>2</sub>), 4.45 (m, 1H, H-4); 4.57 (m, 1H, H-1), 4.81 (m, 1H, H-3), 5.0 (m, 1H, H-2); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 21.2 (C(CH<sub>3</sub>)<sub>3</sub>), 25.1 (C(CH<sub>3</sub>)<sub>2</sub>), 27.3 (OCOCH<sub>3</sub>), 28.5 (C-5), 34.3 (C-4), 61.8 (OCO(CH<sub>3</sub>)<sub>3</sub>), 78.0 (C-1), 81.03 (C-3), 84.3 (C-2), 112.3 (C(CH<sub>3</sub>)<sub>2</sub>), 156.8 (NCO), 170.5 (CH<sub>3</sub>COO). Anal. Calcd. for C<sub>15</sub>H<sub>26</sub>N<sub>2</sub>O<sub>6</sub>: C, 54.53; H, 7.93; N, 8.48. Found: C, 54.56; H, 8.04; N, 8.10.

**(1'*R*,2'*S*,3'*R*,4'*S*)-1-[4'-Acetoxy-2',3'-(ethoxymethylidenedioxy)cyclopent-1'-yl]-1*H*-[1,2,4]triazole-3-carboxylic Acid Ethyl Ester (13).** A solution of **10** (1.13 g, 3.42 mmol) in CF<sub>3</sub>COOH-water (9:1, v/v, 20 mL) was stirred for 50 min at room temperature and concentrated. The residue was coevaporated with MeOH (3 × 40 mL) to give a yellowish oil. To the crude amine salt **11** in dry MeOH (50 mL) at 0°C were added NaHCO<sub>3</sub> (0.53 g, 6.3 mmol) and ethyl carboethoxyformimidate (0.94 g, 6.3 mmol). The mixture was stirred at 0°C for 30 min and the solvent was evaporated at room temperature. The residue was chromatographed (EtOAc-MeOH, 12:1) to give 1.46 g (79%) of **12** as a yellowish viscous liquid. To a solution of **12** (1.43 g, 4.94 mmol) in anhydrous toluene (35 mL) was added triethyl orthoformate (11 mL) and the solution was heated at 110°C for 4 h. After removal of the solvent, the residue was purified by column chromatography (hexanes-EtOAc, 2:1, then 1:1) to give **13** (0.85 g, 48%) as a yellow viscous liquid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.27 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.43 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 2.08 (s, 3H, OCOCH<sub>3</sub>), 2.41 (m, 1H, H-5'), 2.92 (m, 1H, H-5'), 3.67 (q, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 4.48 (q, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 4.77 (m, 1H, H-1'), 5.03 (m, 2H, H-2', H-4'), 5.28 (m, 1H, H-3'), 5.93 (s, 1H, OCHOCH<sub>2</sub>CH<sub>3</sub>), 8.28 (s, 1H, H-5); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 14.4 (OCH<sub>2</sub>CH<sub>3</sub>), 15.1 (OCH<sub>2</sub>CH<sub>3</sub>), 21.0 (CH<sub>3</sub>COO), 34.9 (C-5'), 61.8 (OCH<sub>2</sub>CH<sub>3</sub>), 62.2 (OCH<sub>2</sub>CH<sub>3</sub>), 65.0 (C-1'), 76.7 (C-4'), 83.6 (C-2'), 83.9 (C-3'), 118.2 (CHOCH<sub>2</sub>CH<sub>3</sub>), 144.5 (C-5), 155.8 (C-3), 159.8 (CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 170.2 (OCOCH<sub>3</sub>). Anal. Calcd. for C<sub>15</sub>H<sub>21</sub>N<sub>3</sub>O<sub>7</sub>: C, 50.70; H, 5.96; N, 11.83. Found: C, 50.92; H, 6.01; N, 11.60.

**(1'*R*,2'*S*,3'*R*,4'*S*)-1-[2',3',4'-Trihydroxycyclopent-1'-yl]-1*H*-[1,2,4]triazole-3-carboxylic Acid Ethyl Ester (14).** A solution of **13** (0.85 g, 2.39 mmol) in %5 HCl-THF (1:1, v/v, 50 mL) was stirred for 13 h at 50°C and concentrated. The residue was coevaporated with MeOH (3 × 30 mL). The obtained material was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 20:3) to give **14** (0.43 g, 69%) as pale yellow foam: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.30 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.79 (m, 1H, H-5'); 2.56 (m, 1H, 1H-5'), 3.70 (br s, 1H, OH), 3.88 (br s, 1H, OH), 4.31 (m, 3H, H-1', OCH<sub>2</sub>CH<sub>3</sub>), 4.63 (q, 1H, H-4'), 4.94 (m, 1H, H-2'), 5.08 (m, 2H, H-3', OH), 8.69 (s, 1H, H-5); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) 14.1 (OCH<sub>2</sub>CH<sub>3</sub>), 36.1 (C-5'), 60.9 (OCH<sub>2</sub>CH<sub>3</sub>), 63.6 (C-1'), 73.0 (C-4'), 75.6 (C-2'), 76.6 (C-3'), 145.7 (C-5), 153.9 (C-3), 159.5 (CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>). Anal. Calcd. for C<sub>10</sub>H<sub>15</sub>N<sub>3</sub>O<sub>5</sub>•0.3 MeOH: C, 46.31; H, 6.07; N, 15.73. Found: C, 45.98; H, 6.20; N, 15.50.

**(1'*R*,2'*S*,3'*R*,4'*S*)-1-[2',3',4'-Trihydroxycyclopent-1'-yl]-1*H*-[1,2,4]triazole-3-carboxylic Acid Amide (4).** A solution of **14** (0.35 g, 1.36 mmol) in dry MeOH (25 mL) saturated with NH<sub>3</sub> was kept at room temperature for 2 days in a Parr Stainless steel sealed reaction vessel. The solvent was evaporated under reduced pressure and the residue recrystallized from MeOH-EtOAc to give **4** (0.19 g, 61%) as a white solid: mp 141°C; [α]<sub>D</sub><sup>21.9</sup> -67.43° (c 0.294, H<sub>2</sub>O); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.80 (m, 1H, H-5'), 2.56 (m, 1H, H-5'), 3.70 (br s, 1H, OH), 3.86 (br s, 1H, OH), 4.26 (m, 1H, H-1'), 4.63 (q, 1H, H-4'), 4.93 (m, 1H, H-2'), 5.07 (m, 2H, H-3', OH), 7.56 and 7.76 (2 br s, 1H, NH<sub>2</sub>), 8.60 (s, 1H, H-5); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 36.1 (C-5'), 63.3 (C-1'), 73.1 (C-4'), 75.5 (C-2'), 76.7 (C-3'), 144.8 (C-5), 156.9 (C-3), 160.6 (CONH<sub>2</sub>). Anal. Calcd. for C<sub>8</sub>H<sub>12</sub>N<sub>4</sub>O<sub>4</sub>: C, 42.10; H, 5.30; N, 24.55. Found: C, 42.19; H, 5.37; N, 24.59.



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## REFERENCES

1. Sidwell, R.W.; Huffman, J.H.; Khare, G.P.; Allen, L.B.; Witkowski, J.T.; Robins, R.K. Broad-spectrum antiviral activity of virazole: 1- $\beta$ -D-ribofuransyl-1,2,4-triazole-3-carboxamide. *Science* **1972**, *177*, 705–706.
2. Cummings, K.J.; Lee, S.M.; West, E.S.; Cid-Ruzafa, J.; Fein, S.G.; Aoki, Y.; Sulkowski, M.S.; Goodman, S.N. Interferon and ribavirin vs interferon alone in the re-treatment of chronic hepatitis C previously nonresponsive to interferon: A meta-analysis of randomized trials. *JAMA* **2001**, *285*, 193–199.
3. Di Bisceglie, A.M.; Thompson, J.; Smith-Wilkaitis, N.; Brunt, E.M.; Bacon, B.R. Combination of interferon and ribavirin in chronic hepatitis C: Re-treatment of nonresponders to interferon. *Hepatology* **2001**, *33*, 704–707.
4. Anderi, G.; De Clercq, E. Molecular approaches for the treatment of hemorrhagic fever virus infections. *Antiviral Res.* **1993**, *22*, 45–75.
5. Huggins, J.W. Prospects for treatment of viral hemorrhagic fevers with ribavirin, a broad-spectrum antiviral drug. *Rev. Infect. Dis.* **1989**, *11*, S750–S761.
6. Krilov, L.R. Respiratory syncytial virus: Update on infection, treatment, and prevention. *Curr. Infect. Dis. Rep.* **2001**, *3*, 242–246.
7. Huggins, J.W.; Hsiang, C.M.; Cosgriff, T.M.; Guang, M.Y.; Smith, J.I.; Wu, Z.O.; LeDuc, J.W.; Zheng, Z.M.; Meegan, J.M.; Wang, Q.N. Prospective, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. *J. Infect. Dis.* **1991**, *164*, 1119–1127.
8. Mc Junkin, J.E.; Khan, R.; de los Reyes, E.C.; Parsons, D.L.; Minnich, L.L.; Ashley, R.G.; Tsai, T.F. Treatment of severe La Crosse encephalitis with intravenous ribavirin following diagnosis by brain biopsy. *Pediatrics* **1997**, *99*, 261–267.
9. Smee, D.F.; Huggins, J.W. Potential of the IMP dehydrogenase inhibitors for antiviral therapies of poxvirus infections. *Antiviral Res.* **1998**, *37*, A89.
10. (a) Noble, S.A.; Beddall, N.E.; Beveridge, A.J.; Marr, C.L.P.; Mo, C.L.; Myers, P.L.; Penn, C.R.; Storer, R.; Woods, J.M. Synthesis and biological evaluation of carbocyclic analogues of ribavirin. *Nucleosides Nucleotides* **1991**, *10*, 487–490; (b) Kuang, R.; Ganguly, A.K.; Chan, T-M.; Pramanik, B.N.; Blythin, D.J.; McPhail, A.T.; Saksena, A.K. Enantioselective syntheses of carbocyclic ribavirin and its analogs: Linear versus convergent approaches. *Tetrahedron Lett.* **2000**, *41*, 9575–9579.



11. For a leading reference see Rajappan, V.P.; Yin, X.; Schneller, S.W. A flexible synthesis of carbanucleosides and 5'-nor-1'-homo carbanucleosides from a common precursor. *Tetrahedron* **2002**, *58*, 9889–9895.
12. Seley, K.L.; Schneller, S.W.; Korba, B. A 5'-noraristeromycin enantiomer with activity towards hepatitis B virus. *Nucleosides Nucleotides* **1997**, *16*, 2095–2099.
13. Patil, S.D.; Schneller, S.W.; Hosaya, M.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. Synthesis and antiviral properties of ( $\pm$ )-5'-noraristeromycin and related purine carbocyclic nucleosides. A new lead for anti-human cytomegalovirus agent design. *J. Med. Chem.* **1992**, *35*, 3372–3377.
14. Siddiqi, S.M.; Chen, X.; Schneller, S.W. Enantiospecific synthesis of 5'-noraristeromycin and its 7-deaza derivative and a formal synthesis of (–)-5'-homoraristeromycin. *Nucleosides Nucleotides* **1993**, *12*, 267–278.
15. Rajappan, V.P.; Hegde, V.R.; Schneller, S.W. A protected form of (1*S*,2*R*,3*S*,4*R*)-4-aminocyclopentane-1,2,3-triol, a useful precursor to 5'-norcarbocyclic nucleosides. *Syn. Commun.* **2001**, *31*, 2849–2854.
16. Shireman, B.T.; Miller, M.J. Rapid syntheses of either enantiomer of important carbocyclic nucleoside precursors. *Tetrahedron Lett.* **2000**, *41*, 9537–9540.
17. McKillop, A.; Chattopadhyay, S.K.; Henderson, A.; Avendano, C. Applications of ethyl carboethoxyformimidate to heterocyclic synthesis: Preparation of condensed pyrazinones and 1,4-oxazinones. *Synthesis* **1997**, *3*, 301–304.
18. For leading references on the procedures used for the assays see (a) Das, S.R.; Schneller, S.W.; Balzarini, J.; De Clercq, E. A mercapto analogue of 5'-noraristeromycin. *Bioorg. Med. Chem.* **2002**, *10*, 457–460; (b) Barnard, D.L.; Stowell, V.D.; Seley, K.L.; Hegde, V.R.; Das, S.R.; Rajappan, V.P.; Schneller, S.W.; Smee, D.F.; Sidwell, R.W. Inhibition of measles virus replication by 5'-nor carbocyclic adenosine analogues. *Antiviral Chem. Chemother.* **2001**, *12*, 241–250.

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