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# Enantioselective syntheses of carbocyclic ribavirin and its analogs: linear versus convergent approaches†

Rongze Kuang*,[a] Ashit K. Ganguly*,[b] Tze-Ming Chan,[a] Birendra N. Pramanik,[a] David J. Blythin,[a] Andrew T. McPhail[c] and Anil. K. Saksena[a,*]

[a]*Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*
[b]*Department of Chemistry, Stevens Institute of Technology, Castle Point on Hudson, Hoboken, NJ 07030, USA*
[c]*Paul M. Gross Chemical Laboratories, Duke University, Durham, NC 27706, USA*

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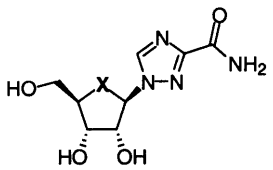
**Abstract**

The first enantioselective syntheses of carbocyclic ribavirin by both convergent and linear approaches are described. The linear approach from chiral nonracemic 2-azabicyclo[2.2.1]hept-5-en-3-one proves to be a highly efficient route to carbocyclic analogs of ribavirin. 

*Keywords:* nucleoside; antiviral; carbocyclic ribavirin; enantioselection; azide; triazole; olefin metathesis.

Ribavirin (**1**) is a broad-spectrum antiviral agent, and the combination of ribavirin and interferon-α has been approved by the FDA as a new therapy for hepatitis C.[1] Structural modification of ribavirin represents a promising approach in the search for new antiviral agents. One strategy is to replace the furanose oxygen in ribavirin with a methylene group, which gives the carbocyclic version of ribavirin. Such a modification is of particular interest, since the resulting carbocyclic ribavirin (**2**) may possess greater metabolic stability to the phosphorylase enzymes which cleave the *N*-glycosidic linkage in normal nucleosides.[2] This communication describes our effort to develop an efficient enantioselective synthesis of chiral carbocyclic ribavirin analogs.




**1**, X = O; **2**, X = $CH_2$

* Corresponding authors. Fax: 908-740-7152; e-mail: anil.saksena@spcorp.com

† Dedicated to Professor Harry H. Wasserman on the happy occasion of his 80th birthday. It is a privilege to recognize his brilliant contributions to organic chemistry.

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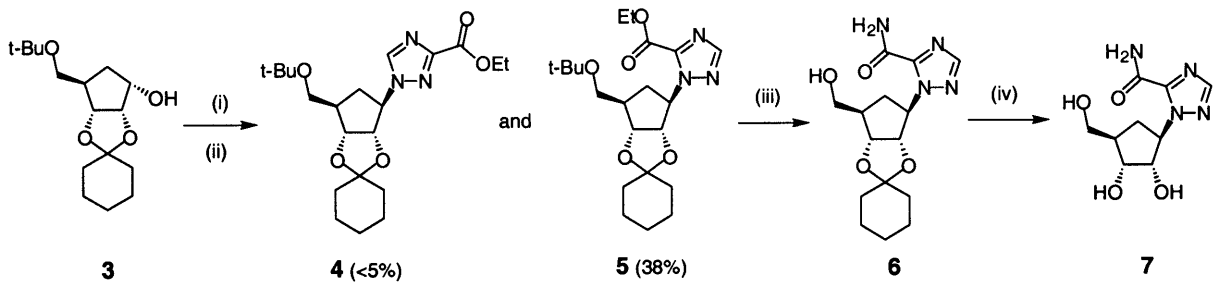
Strategically, carbocyclic ribavirin can be synthesized by both convergent and linear approaches.[3,4] In seeking convergent routes to **2** and its analogs, the key cyclopentyl alcohol **3** was readily synthesized in six steps from ribonolactone.[5] However, attempted nucleophilic displacement of the triflate derived from **3** with the Na-salt of ethyl 1,2,4-triazole-3-carboxylate provided to our surprise **5** as a major product resulting from the alkylation of the more hindered nitrogen. The desired product **4** was estimated to be less than 5% by NMR of the crude reaction mixture. The structure of the major product was confirmed by single-crystal X-ray crystallography of the amide **5**.[13] Deprotection then provided **7**, the 5-carboxamido isomer of **2**. Attempted direct coupling of **3** with 1H-1,2,4-triazol-3-carboxylate under Mitsunobu conditions also failed to provide the desired product **4**. (Scheme 1).

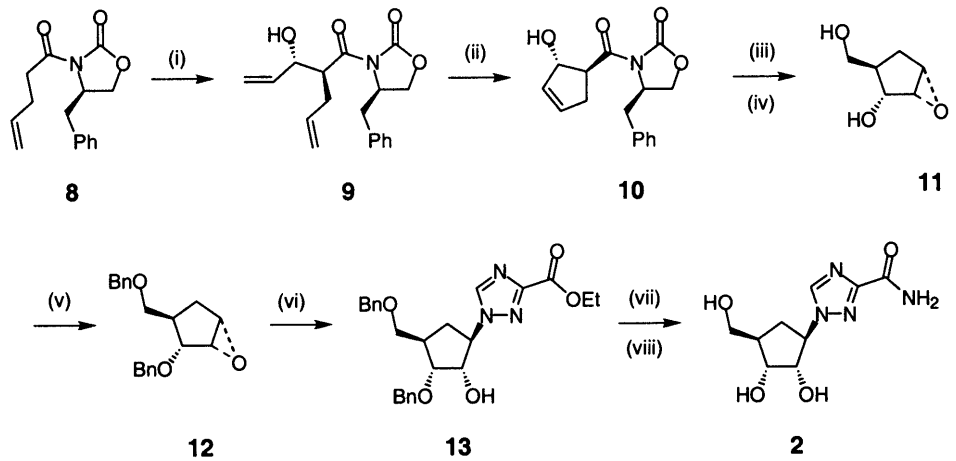



Scheme 1. (i) $(CF_3SO_2)_2O$; (ii) 1,2,4-triazol-carboxylic acid ethyl ester, NaH, DMF, $-10 \sim 0°C$; (iii) $NH_3$/MeOH, 100%; (iv) $CF_3CO_2H/H_2O$, 87%

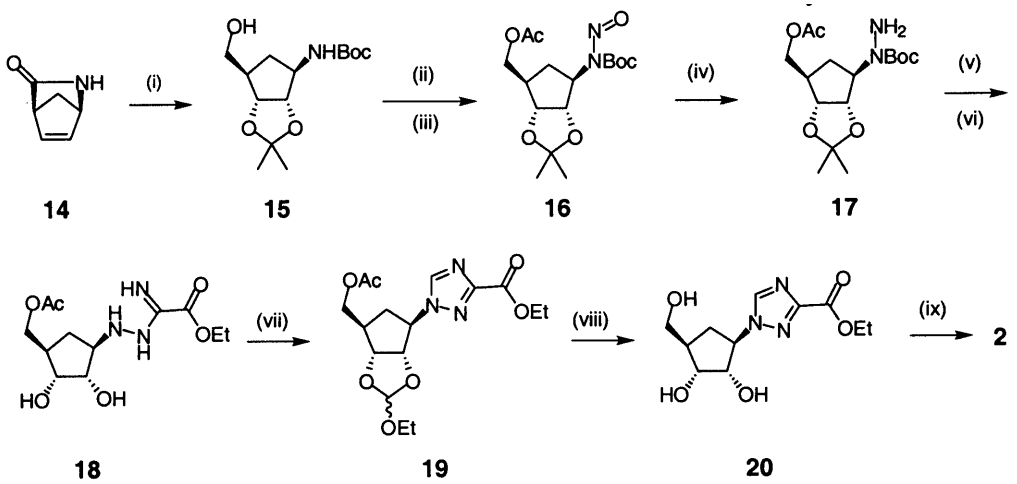
An alternative, convergent strategy required regioselective ring-opening of the chiral epoxide **12**. Since **12** was available from earlier syntheses only in the racemic form,[6] a new enantioselective synthesis of this epoxide was developed based on an *anti*-aldol condensation[7] and ring-closing olefin metathesis. In a similar approach Crimmins et al. have used *syn*-aldol adducts for the construction of other carbocyclic structures.[8] An efficient synthesis of epoxide **12** was achieved in four steps beginning with chiral oxazolidinone **8**. While the *anti*-aldol condensation gave only a moderate yield, all of the other steps proceeded in high yields to provide the non-racemic epoxy diol **11**.[13] After protecting the hydroxyl groups, the resulting epoxide **12** was reacted with the triazole in the presence of NaH to give the desired ring-opening product **13** as the major isomer in 40% yield. Further treatment with ammonia followed by hydrogenolytic deprotection provided carbocyclic ribavirin **2** in 14% overall yield in nine steps. This epoxide route represents a highly concise approach to carbocyclic ribavirin **2**, the major deficiency being the yield in the crucial triazole displacement on **12**. (Scheme 2).

Our linear approach to carbocyclic ribavirin **2** focuses on the application of the commercially available chiral nonracemic building block, 2-azabicyclo[2.2.1]hept-5-en-3-one **14** (Scheme 3). This bicyclic lactam has been used in a number of syntheses of carbocyclic nucleosides, most of which involve the construction of heterocycles from cyclopentylamine intermediates.[3] However, transformations of the lactam **14** into a cyclopentylhydrazine or cyclopentylazide, possible precursors for **2**, have not been reported.

The starting 2-azabicyclo[2.2.1]hept-5-en-3-one **14** was first converted into the protected cyclopentylamine **15** according to a published method.[9] A high-yielding transformation of **15** into the cyclopentylhydrazine **17** was accomplished by modification of a two-step protocol developed by Vilarrasa.[10,11] The *t*-Boc protected amine **16** was first reacted with nitrosonium



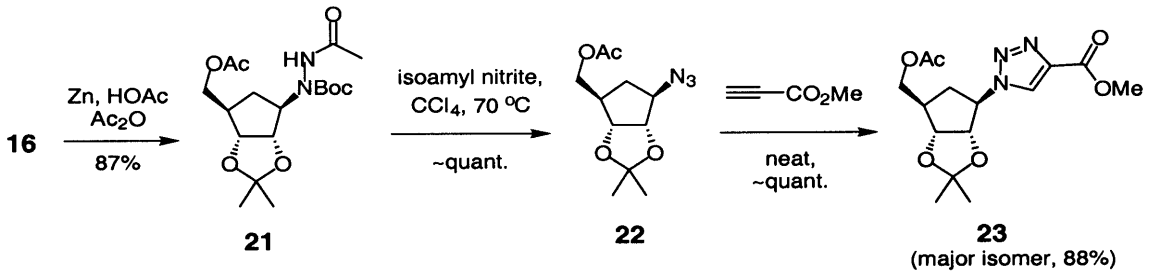

Scheme 2. (i) 2 equiv. $N$-$Bu_2BOTf$, $iPr_2NEt$, acrolein, –78°C, 53%; (ii) Grubb's catalyst, 96%; (iii) $LiBH_4$, MeOH, THF, 0°C, 83%; (iv) $m$CPBA, 97%; (v) $PhCH_2Br$, NaH, THF, 74%; (vi) 1,2,4-triazol-3-carboxylic acid ethyl ester, NaH, DMF, 110°C, 40%; (vii) $NH_3$/MeOH, 100%; (viii) $H_2$, 10% Pd/C




Scheme 3. (i) Four steps, Ref. 9; (ii) $Ac_2O$, TEA, DMAP, $CH_3CN$, rt, 1.5 h,100%; (iii) $NOBF_4$, pyridine, $CH_3CN$, –30°C, 0.5 h, then 0°C, 2 h, 100%; (iv) Zn, HOAc, 8–10°C, 20 min, 95%; (v) TFA/$H_2O$, 1 h; (vi) ethyl carboethoxyformimidate, $NaHCO_3$, MeOH, 0°C, 0.5 h; (vii) excess $HC(OEt)_3$, toluene, 110°C, 4 h, 82% from **17**; (viii) 5% HCl/THF(1:1), 50°C, overnight, 93%; (ix) saturated $NH_3$/MeOH (–15°C), sealed flask, rt, overnight, 100%

tetrafluoroborate in the presence of pyridine in acetonitrile, and the resulting $N$-nitroso compound was then reduced to **17** with zinc powder in glacial acetic acid. After the TFA deprotection, the hydrazine TFA salt was coupled with ethyl carboethoxyformimidate,[12] and the intermediate **18** was heated with triethyl orthoformate in toluene at 110°C for 5 h to give the carbocyclic triazole intermediate **19** with concomitant protection of the 1,2-diol functionality as a cyclic orthoformate. Heating this intermediate in 5% HCl/THF solution provided **20** which upon further treatment with ammonia/methanol gave the carbocyclic ribavirin **2** in 12 steps from the bicyclic lactam **14** in 46% overall yield.

In a further extension of the above linear approach, a high yielding synthesis of the cyclopentylazide **22** was developed by heating the *N*-Boc,*N*′-acetyl cyclopentylhydrazine (**21**) with isoamyl nitrite in $CCl_4$.[10] This efficient approach to the cyclopentylazide now allows us to access structurally diverse analogs of carbocyclic ribavirin through 1,3-dipolar cycloaddition reactions. For example, reaction of **22** with methyl propiolate provided **23**, the 1,2,3-triazolo analog of **2**, in excellent yield (Scheme 4).




Scheme 4.

Compared to the convergent approaches examined in this study, the linear approach is preferred. It is noteworthy that chromatographic purification is necessary only for two intermediates (**19** and **20**), and that the steps (ii)–(v) can be performed on the same day.

In summary, we have developed a highly efficient enantioselective synthesis of carbocyclic ribavirin **2**. The facile syntheses of both the cyclopentylhydrazine and cyclopentylazide intermediates **17** and **22** from the bicyclic lactam **14** attest to the versatility of this readily available chiral building block in the synthesis of carbocyclic nucleosides and other biologically useful compounds. We shall report on the biological activity of these compounds in a future communication.

**Spectroscopic data for key compounds**

Compound **2**: identical NMR and HRMS data were obtained for **2** from both Schemes 2 and 3. Compound **2** is highly hygroscopic. It became a viscous oil upon exposure to the atmosphere. $^1$H NMR ($CD_3OD$): 1.91 (ddd, $J=8.2$, 9.9, 13.2 Hz, 1H), 2.20 (m, 1H), 2.40 (dt, $J=8.6$, 13.2 Hz, 1H), 3.63 (d, $J=6.0$ Hz, 2H), 3.98 (dd, $J=3.1$, 5.3 Hz, 1H), 4.21 (dd, $J=5.3$, 8.4 Hz, 1H), 4.77 (dt, $J=8.5$, 9.5 Hz, 1H), 8.53 (s, 1H); HRMS $[M+1]^+$ found 243.1096, calcd for $C_9H_{15}N_4O_4$ 243.1093. $[\alpha]_D^{20}=-60.2$ (*c* 0.5, MeOH).

Compound **7**: $^1$H NMR ($CD_3OD$): 1.78 (ddd, $J=8.6$, 9.5, 13.0 Hz, 1H), 2.23 (m, 1H), 2.39 (dt, $J=8.5$, 13.0 Hz, 1H), 3.63 (m, 2H), 4.04 (dd, $J=4.0$, 5.4 Hz, 1H), 4.38 (dd, $J=5.6$, 7.8 Hz, 1H), 4.89 (s, br, 5H), 5.81 (dt, $J=8.4$, 9.4 Hz, 1H), 7.98 (s, 1H); HRMS $[M+1]^+$ found 243.1098, calcd for $C_9H_{15}N_4O_4$ 243.1093.

Compound **22**: $^1$H NMR ($CDCl_3$): 1.30 (s, 3H), 1.46 (s, 3H), 1.64 (dt, $J=4.3$, 13.9 Hz, 1H), 2.08 (s, 3H), 2.30 (ddd, $J=$ 6.0, 7.8, 14.0 Hz, 1H), 2.43 (m, 1H), 3.98–4.14 (m, 3H), 4.48 (m, 2H). FTIR: 2104.74 ($-N_3$) cm$^{-1}$.

Compound **23**: $^1$H NMR ($CDCl_3$): 1.30 (s, 3H), 1.54 (s, 3H), 2.07 (s, 3H), 2.32 (dt, $J=11.0$, 12.6 Hz, 1H), 2.55 (m, 1H) 2.63 (dt, $J=7.7$, 12.7 Hz, 1H), 3.93 (s, 3H), 4.18 (d, $J=5.9$ Hz, 2H), 4.59 (dd, $J=4.6$, 7.0 Hz, 1H), 4.77 (m, 1H), 4.85 (dd, $J=5.4$, 7.0 Hz, 1H), 8.19 (s, 1H); HRMS $[M+1]^+$ found 340.1516, calcd for $C_{15}H_{21}N_3O_6$ 340.1509. $[\alpha]_D^{20}=-50.7$ (*c* 1.1, $CH_2Cl_2$).

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