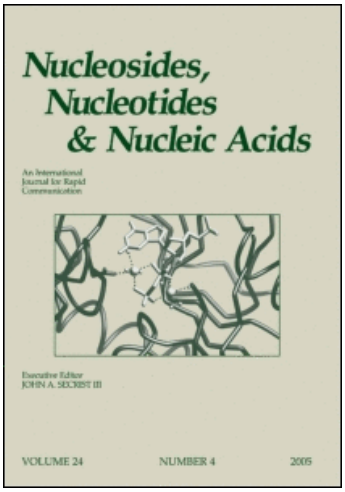


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of 3'-Deoxy-3'-*C*-Hydroxymethyl Analogues of Tiazofurin and Ribavirin

Moon Woo Chun[a]; Myong Jung Kim[a]; Ji Hye Shin[a]; Lak Shin Jeong[b]
[a] Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, Seoul, Korea [b] College of Pharmacy, Ewha Womans University, Seoul, Korea

To cite this Article Chun, Moon Woo , Kim, Myong Jung , Shin, Ji Hye and Jeong, Lak Shin(2005) 'Synthesis of 3'-Deoxy-3'-*C*-Hydroxymethyl Analogues of Tiazofurin and Ribavirin', Nucleosides, Nucleotides and Nucleic Acids, 24: 5, 975 — 977
To link to this Article: DOI: 10.1081/NCN-200059338
URL: http://dx.doi.org/10.1081/NCN-200059338

Nucleosides, Nucleotides, and Nucleic Acids, 24 (5–7):975–977, (2005)

ISSN: 1525-7770 print/ 1532-2335 online
DOI: 10.1081/NCN-200059338

Taylor & Francis
Taylor & Francis Group

SYNTHESIS OF 3′-DEOXY-3′-*C*-HYDROXYMETHYL ANALOGUES OF TIAZOFURIN AND RIBAVIRIN

Moon Woo Chun, Myong Jung Kim, and Ji Hye Shin ▫ *Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, Seoul, Korea*

Lak Shin Jeong ▫ *College of Pharmacy, Ewha Womans University, Seoul, Korea*

▫ *On the basis of potent biological activity of 3′-branched-3′-deoxynucleoside analogues, novel ribavirin and tiazofurin derivatives with 3′-C-hydroxymethyl substituent were synthesized, starting from* D*-xylose.*

INTRODUCTION

Ribavirin[1] is a broad-spectrum antiviral agent through the inhibition of IMPDH which catalyzes an essential step in the de novo biosynthesis of guanine nucleotides, namely, the conversion of inosine-5′-monophosphate (IMP) to xanthosine-5′-monophosphate (XMP) and currently used in combination with interferon-α for the treatment of chronic hepatitis C virus infection. Tiazofurin[2] inhibits the same enzyme after metabolic conversion into thiazole-4-carboxamide adenine dinucleotide (TAD), an analogue of the cofactor NAD, and is currently undergoing clinical trials as an antitumor agent.

The 3′-branched-3′-deoxy nucleoside analogues have received much attention as potential chemotherapeutic agents and some of them have been shown to display antiviral and anticancer activities. Also, it has been known that branched nucleosides are biologically active due to greater recognition of these substrates by DNA polymerase, compared to non-branched nucleoside substrates.[3]

Based on these findings, it was interesting to put the hydroxymethyl group at the C3 position of tiazofurin and ribavirin, respectively, and to compare their biological activities with those of parent nucleosides. Here, we wish to report the asymmetric synthesis of the 3′-deoxy-3′-*C*-hydroxymethyl tiazofurin (**1**) and ribavirin (**2**) derivatives, starting from D-xylose (Figure 1).

Address correspondence to Moon Woo Chun, Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, Seoul 151-742, Korea.

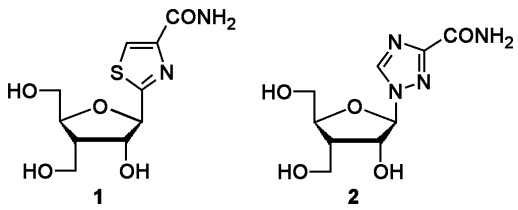
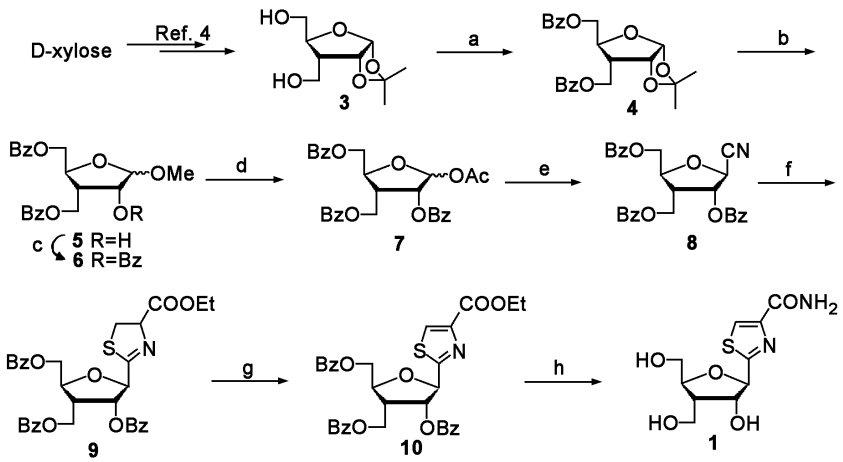


FIGURE 1 Structures of the target nucleosides.

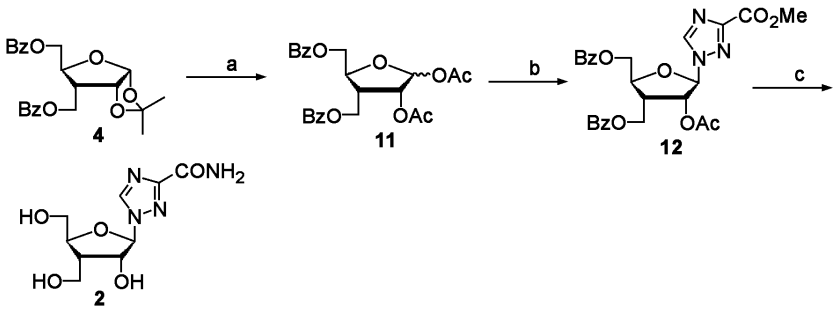
RESULTS AND DISCUSSION

Our synthetic approach to the thiazole nucleoside **1** was fist to synthesize ribofuranosyl cyanide as a key intermediate from D-xylose and then to cyclocondense with L-cysteine ethyl ester hydrochloride.

3-*C*-Hydroxymethyl derivative (**3**) was prepared from D-xylose by known method.[4] Treatment of **3** with benzoyl chloride gave the dibenzoate **4**, in which 1,2-acetonide was removed by acid-catalyzed methanolysis to give the methoxide 5. Compound 5 was treated with benzoyl chloride to afford the tribenzoate **6**, which was treated with $Ac_2O/AcOH/c\text{-}H_2SO_4$ to give the 1-*O*-acetyl derivative **7**. 3-*C*-Benzoyloxymethyl-3-deoxy-2,5-di-*O*-benzoylribofuranosyl cyanide (**8**) was prepared by treating acetate **7** with cyanotrimethylsilane and $SnCl_4$ in dichloromethane. Cyanide **8** was treated with L-cystein ethyl ester hydrochloride in the presence of triethylamine to give the thiazole **9**, which was dehydrogenated by treatment with bromotrichloromethane in combination with DBU to afford the thiazole **10**. Ammonolysis and debenzoylation of the ester **10** using methanolic ammonia yielded 3′-*C*-hydroxymethyl substituted tiazofurin derivative 1 (Scheme 1).



SCHEME 1 Reagents and conditions: (a) BzCl, pyridine, RT, 16 h, 90%; (b) 1%HCl in MeOH, RT, 3 h, 89%; (c) BzCl, pyridine, RT, 16 h, 90%; (d) $AcOH/Ac_2O/c\text{-}H_2SO_4$, 0°C, 0.5 h, 95%; (e) TMSCN, $SnCl_4$, CH_2Cl_2, reflux, 3 h, 81%; (f) L-cysteine ethyl ester hydrochloride, Et_3N, MeOH, 2 h, 75%; (g) DBU, $BrCCl_3$, CH_2Cl_2, 0°C, 16 h, 80%; (h) NH_3/MeOH, RT, 18 h, 80%.



SCHEME 2 Reagents and conditions: (a) i. 85% HCO_2H, 55°C, 2 h; ii. Ac_2O, pyridine, RT, 18 h, 92%; (b) silylated methyl-1,2,4-triazole-3-carboxylate, $SnCl_4$, CH_3CN, RT, 29 h, 45%; (c) NH_3/MeOH, RT, 18 h, 80%.

Synthesis of 3′-deoxy-3′-*C*-hydroxymethylribavirin (**2**) is outlined in Scheme 2. 1,2-*O*-Isopropylidene group of **4** was hydrolyzed with 85% formic acid, followed by acetylation to give the acetate **11**. Condensation of glycosyl donor **11** with silylated methyl-1,2,4-triazole-3-carboxylate in the presence of $SnCl_4$ in acetonitrile gave the protected nucleoside **12**. Treatment of **12** with methanolic ammonia yielded the 3′-*C*-hydroxymethyl substituted ribavirin derivative 2. In summary, we have accomplished the synthesis of novel 3′-deoxy-3′-*C*-hydroxymethyl analogues of tiazofurin and ribavirin *via* cyclocondensation of ribofuranosyl cyanide **8** with L-cysteine ethyl ester hydrochloride and condensation of glycosyl donor **11** with methyl-1,2,4-triazole-3-carboxylate, respectively. The biological assay of the final nucleosides **1** and **2** is in progress in our laboratory and will be reported elsewhere.

REFERENCES

1. Wray, S.K.; Gilbert, B.E.; Noall, M.W.; Knight, V. Mode of action of ribavirin: effect of nucleotide pool alterations on influenza virus ribonucleoprotein synthesis. Antiviral Res. **1985**, *5*, 29.
2. Weber, G.; Prajda, N.; Abonyi, M.; Look, K.Y.; Tricot, G. Tiazofurin: molecular and clinical action. Anticancer Res. **1996**, *16*, 3313.
3. Acton, E.M.; Goerner, R.N.; Uh, H.S.; Ryan, K.J.; Henry, D.W. Improved antitumor effects in 3′-branched homologues of 2′-deoxythioguanosine. Synthesis and evaluation of thioguanine nucleosides of 2,3-dideoxy-3-(hydroxymethyl)-D-erythro-pentofuranose. J. Med. Chem. **1979**, *22*, 518.
4. Lin, T.-S.; Zhu, J.-L.; Dutschmann, G.E.; Cheng, Y.-C.; Prusoff, W.H. Syntheses and biological evaluations of 3′-deoxy-3′-*C*-branched-chain-substituted nucleosides. J. Med. Chem. **1993**, *36*, 353.