Tetrahedron Letters 53 (2012) 1753–1755

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Deoxy derivatives of L-like 5′-noraristeromycin

Shante Hinton, Alecia Riddick, Tesfaye Serbessa *

Department of Chemistry, Geology, and Physics, Elizabeth City State University, Elizabeth City, NC 27909, USA

ARTICLE INFO

Article history:
Received 20 December 2011
Revised 21 January 2012
Accepted 23 January 2012
Available online 2 February 2012

Keywords:
L-like
Carbanucleosides
HBV
Noraristeromycin

ABSTRACT

Several base variations of 2′- and 3′-deoxy derivatives of (+)-4′-deoxy-5′-noraristeromycin have been prepared from enantiomerically pure precursors following standard purine nucleoside construction. These carbocyclic nucleosides were evaluated against hepatitis B virus (HBV) and found to be inactive. No cytotoxicity to the cell line was observed.

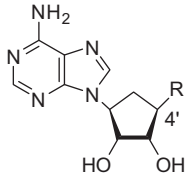
Introduction

Many years ago, the study of carbocyclic nucleosides lacking a methylene group at the 5′-position (5′-norcarbanucleosides) was initiated.[1] Within this series of compounds, (+)-5′-noraristeromycin **1** (L-like) (Fig. 1) was the first to show significant activity toward hepatitis B virus (HBV), while the (−)-enantiomer (D-like) was inactive.[2] Further investigation led to the discovery of (+)-4′-deoxy-5′-noraristeromycin **2**,[3] which is ten times more potent in its activity against HBV. As part of an ongoing effort to determine the structural entities necessary for activity, base and cyclopentyl variations (compounds **3–8**) were designed and synthesized.

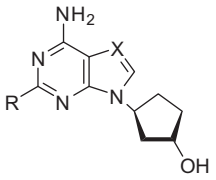
Chemistry

As depicted in Scheme 1, target compounds **3–5** can be derived from the S_N2 reaction of mesylate[4] **9** (prepared from dicyclopentadiene in six steps) and a suitable base. For the preparation of **3**, the mesylate was added to a suspension of adenine **10** and sodium hydride in dimethylformamide (DMF). This resulted in the formation of the protected nucleoside **13**. The acetate group of **13** was then readily cleaved by using ammonia gas in anhydrous methanol to give **3**. A similar procedure was utilized to achieve the synthesis of **4** and **5**. A commercially available base, 2-amino-6-chloropurine **11**, was used for the synthesis of **4**. Compound **5**, however, required the preparation of the 7-deazapurine base **12** prepared from ethyl cyanoacetate and bromoacetaldehyde diethyl acetal in five steps.[5] Ammonolysis was employed to complete the synthesis of both target compounds.

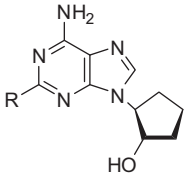
Optically active amino alcohol **16** was used in the synthesis of **6** (Scheme 2). The compound was prepared by utilizing the enantioselective ring opening reaction of cyclopentene oxide (using



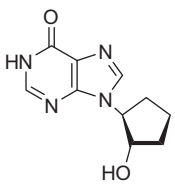
1. R=OH
2. R=H



3 X=N, R=H
4. X=N, R=NH_2
5. X=CH, R=H



6 R=H
7 R=NH_2

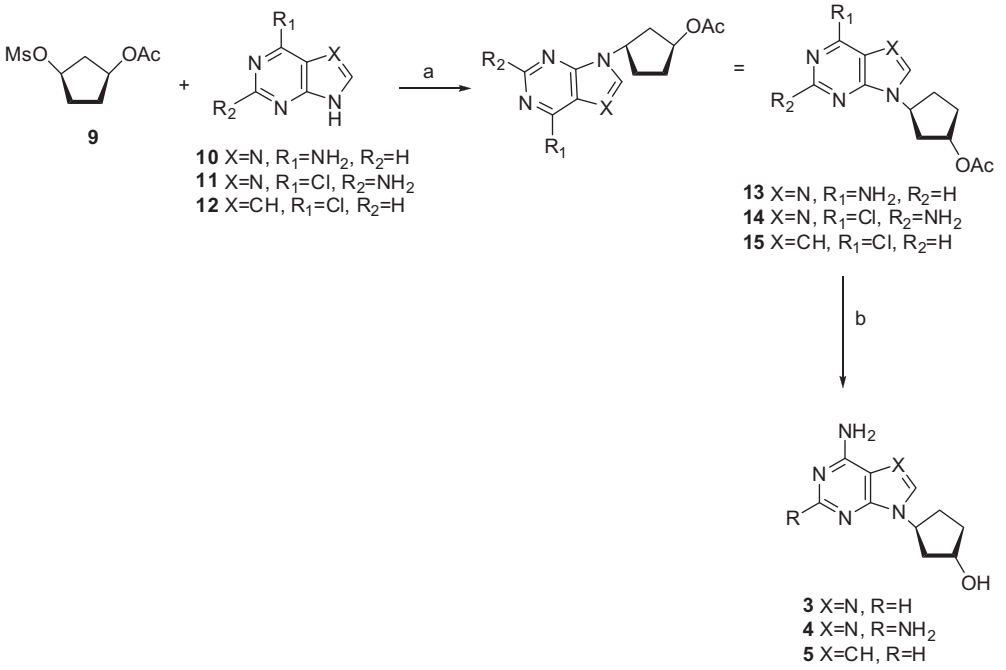


8

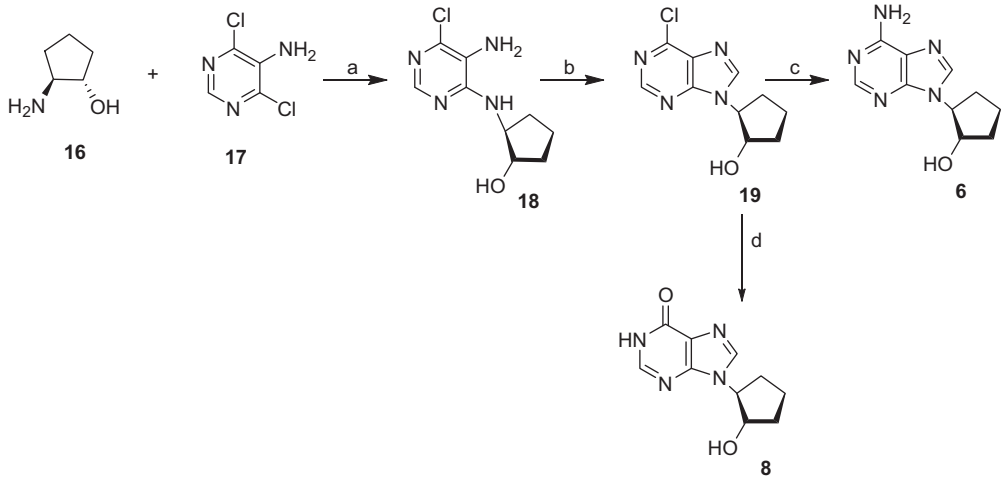
Figure 1. Lead and target compounds.

* Corresponding author. Tel.: +1 252 335 3438; fax: +1 252 335 3508.
E-mail address: tserbessa@mail.ecsu.edu (T. Serbessa).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2012.01.101



Scheme 1. Preparation of 2′-deoxy derivatives. Reagents and conditions: (a) NaH, DMF; (b) NH_3/MeOH.



Scheme 2. Preparation of 3′-deoxy derivatives. Reagents and conditions: (a) 1-BuOH, Et_3N; (b) $(EtO)_2CHOAc$, 90 °C; (c) NH_3/MeOH, 120 °C; (d) 1N HCl.

trimethylsilyl azide) followed by desilylation and reduction as shown by Jacobsen.[6] Under nucleophilic aromatic substitution conditions, displacement of one of the chlorine substituents of 5-amino-4,6-dichloropyrimidine **17** by the amino group of **16** yielded the purine nucleoside precursor **18**. Heating **18** in diethoxymethyl acetate resulted in ring closure to give **19**. Ammonolysis of **19** led to **6**, while refluxing **19** in 1N hydrochloric acid yielded **8**.

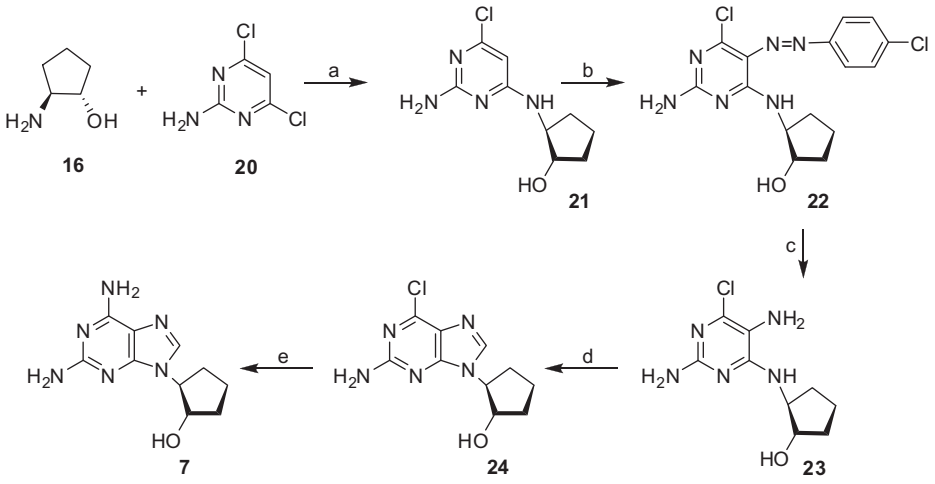
Scheme 3 shows that compound **7** was accessible via the standard carbocyclic ring construction[7] using 2-amino-4,6-dichoropyrimidine **20** and amino alcohol **16**. Refluxing these starting materials in 1-butanol in the presence of triethylamine afforded **21**. Installation of the C-5 amino group on the pyrimidine ring began with a diazonium coupling reaction of **21** with 4-chlorobenzenediazonium chloride to yield **22**. The azo compound **22** was reduced with zinc and acetic acid and then cyclized using diethoxymethyl acetate to give **24**. The C-6 chlorine of **24** was replaced by an amino group in the final step.

Antiviral analysis

To investigate their biological potential, compounds **3–8** were subjected to antiviral screening versus hepatitis B virus. No activity was found. Furthermore, no cytotoxicity arose in the cell lines used in the antiviral assays.

Conclusion

The synthesis of several 2′- and 3′-deoxy derivatives of (+)-4′-deoxy-5′-noraristeromycin has been achieved. The use of amino



Scheme 3. Preparation of **7**. Reagents and conditions: (a) 1-BuOH, Et_3N; (b) 4-benzenediazonium chloride, NaOAc, HOAc; (c) zinc powder, HOAc, EtOH, H_2O; (d) $(EtO)_2CHOAc$, 90 °C; (e) NH_3/MeOH, 120 °C.

alcohols such as **16** provides a convenient approach to enantiomerically pure modified nucleosides. The absence of antiviral activity suggests the importance of both 2′ and 3′ hydroxyl groups in the interaction with the biological target macromolecule.

Acknowledgment

This research was supported by funds from the Department of Health and Human Services (AI 083926). This support is greatly appreciated.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.101.

References and notes

1. Koga, M.; Schneller, S. W. *Tetrahedron Lett.* **1990**, *31*, 5861.
2. Seley, K. L.; Schneller, S. W.; Korba, B. *Nucleosides Nucleotides* **1997**, *16*, 2095.
3. Seley, K. L.; Schneller, S. W.; Korba *J. Med. Chem.* **1998**, *41*, 2168.
4. Borcherding, D. R.; Peet, N. P.; Munson, H. R.; Zhang, H.; Hoffman, P. F.; Bowlin, T. L.; Edwards, C. K. *J. Med. Chem.* **1996**, *39*, 2615.
5. Davol, J. *J. Chem. Soc.* **1960**, 131.
6. Martinez, L. E.; Leighton, 1. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897.
7. Siddiqui, S. M.; Jacobsen, K. A.; Esker, J. L.; Olah, M. E.; Melman, N.; Tiwari, K. N.; Secrist, J. A., III; Schneller, S. W.; Cristalli, G.; Stiles, G. L.; Johnson, C. R.; Ijzerman, A. P. *J. Med. Chem.* **1995**, *38*, 1174.