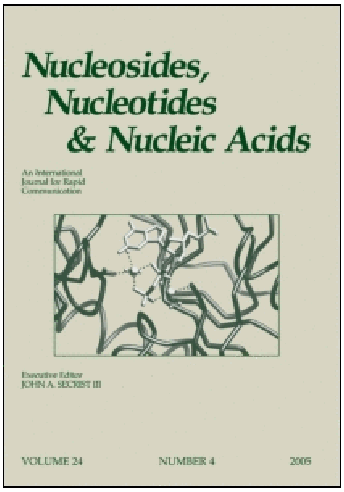


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

ASYMMETRIC SYNTHESIS OF CARBOCYCLIC PYRIMIDINE NUCLEOSIDES VIA π-ALLYLPALLADIUM COMPLEX

Junxing Shi[a]; Raymond F. Schinazi[b]
[a] Pharmasset, Inc., Tucker, Georgia [b] Veterans Affairs Medical Center, Decatur, Georgia

To cite this Article Shi, Junxing and Schinazi, Raymond F.(2001) 'ASYMMETRIC SYNTHESIS OF CARBOCYCLIC PYRIMIDINE NUCLEOSIDES VIA π-ALLYLPALLADIUM COMPLEX', Nucleosides, Nucleotides and Nucleic Acids, 20: 4, 1367 — 1370

To link to this Article: DOI: 10.1081/NCN-100002557

URL: http://dx.doi.org/10.1081/NCN-100002557

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 20(4–7), 1367–1370 (2001)

ASYMMETRIC SYNTHESIS OF CARBOCYCLIC PYRIMIDINE NUCLEOSIDES VIA π-ALLYLPALLADIUM COMPLEX

Junxing Shi[1] and Raymond F. Schinazi[2,3,*]

[1]Pharmasset, Inc., Tucker, Georgia, 30084
[2]Veterans Affairs Medical Center, Decatur, Georgia, 30033
[3]Emory University, Atlanta, Georgia, 30322

ABSTRACT

Racemic and enantiomerically pure carbocyclic pyrimidine nucleosides were synthesized efficiently by a convergent approach using *Trost* nucleophilic addition of π-allylpalladium complexes.

INTRODUCTION

In the last two decades, nucleoside analogues have been investigated with renewed interest in the search for effective anticancer and/or antiviral agents in general, and in particular against human immunodeficiency virus (HIV). Such efforts have resulted in the discovery of certain nucleoside analogues possessing potent antiviral activity, with several of these becoming clinically successful agents. Recent examples are carbocyclic nucleosides abacavir (Ziagen) [1], which has been approved for clinical use against HIV, and entecavir in clinical development for hepatitis B virus [2]. Carbocyclic nucleosides continue to be studied intensively chemically and biologically. In contrast to carbocyclic purine nucleosides that have been the major focus due to their discovery in nature, carbocyclic pyrimidine nucleosides have not drawn much attention. Previously, we reported the synthesis and evaluation of racemic carbocyclic pyrimidine nucleosides, and demonstrated

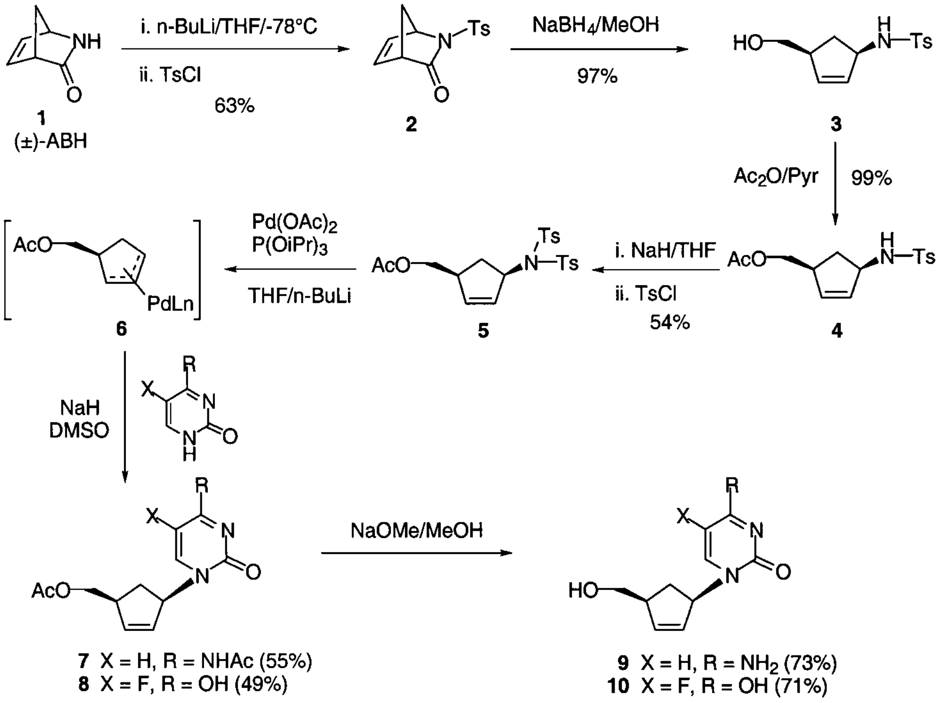
---

[*]Corresponding author.

that their triphosphates possess potent inhibitory activity against HIV reverse transcriptase [3]. Given the vast potential for these analogues, a synthetic method for the development of enantiomerically enriched carbocyclic pyrimidine nucleosides is warranted. In our continued search for anticancer and antiviral agents, we embarked on the development of efficient, versatile approaches to the synthesis of enantiomerically pure carbocyclic pyrimidine nucleosides.

RESULTS AND DISCUSSION

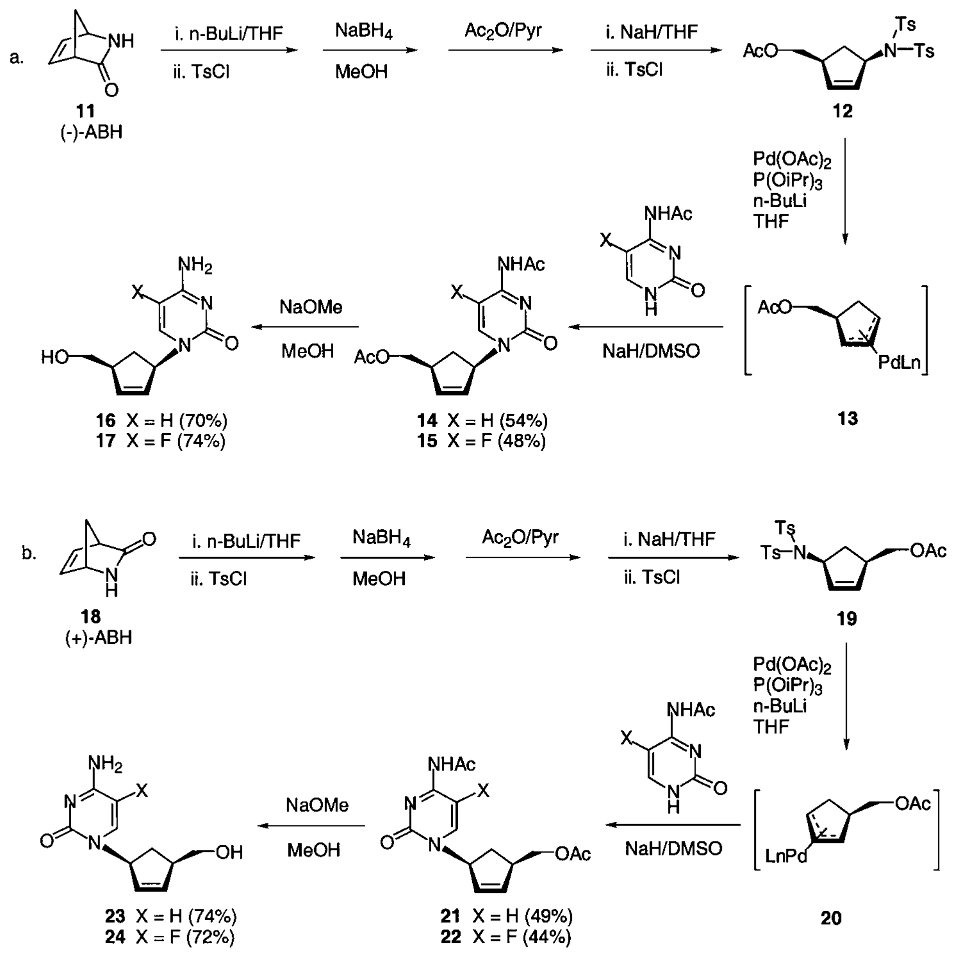
To date, the methods used in the synthesis of carbocyclic pyrimidine nucleosides, especially for chiral compounds, are lengthy or require special chiral synthons that are not commercially available. Among the current synthetic methods, a convergent approach using *Trost* nucleophilic addition of π-allylpalladium complexes was found to be attractive [4]. This approach allows for the attachment of different nucleobases to a suitable cyclopentenyl moiety. The substrates previously used in this condensation are reported as being predominately cyclopentenyl esters and carbonates that require multistep synthesis. Recently, it has been reported that allylic nitrogen functionality can be used in the *Trost* reaction, and some cyclopentenyl amides were used as starting blocks in the synthesis of racemic carbocyclic purine



Scheme 1. Synthesis of racemic carbocyclic pyrimidine nucleosides.

nucleosides [5,6]. We applied this same strategy for the synthesis of carbocyclic pyrimidine nucleosides.

This approach was initially evaluated for the synthesis of racemic carbocyclic pyrimidine nucleosides. The cylcopentenylditosylimde **5** was prepared by adapting *Jung*'s procedure [4] with a minor modification. Starting from (±)-2-azabicyclo[2.2.1]hept-5-en-3-one [**1**, (±)-ABH, also called *Vince lactam*], after tosylation with n-BuLi/TsCl, the N-tosylated lactam **2** was prepared. Reduction with $NaBH_4$ gave the ring-opening product **3**, which was acetylated to monosulfonamide **4**. Upon further tosylation, cyclopentenylditosylimide **5** was obtained. Under *Trost* conditions [4], reaction of **5** with Pd(0) catalyst formed the π-allylpalladium complex **6** as an intermediate. Condensation of the latter with N^4-acetylcytosine afforded the carbanucleoside **7**. In a similar manner, reaction of complex **6** with 5-fluorouracil produced the acetylated uracil carbanucleoside **8**. After deprotection



Scheme 2. Synthesis of enantiomerically pure carbocyclic pyrimidine nucleosides.

of **7** and **8**, the desired pyrimidine carbanucleosides **9** and **10**, respectively, were obtained (Scheme 1).

Using this strategy in the synthesis of enantiomerically pure carbocyclic nucleosides, the chiral cyclopentenylditosylimide **12** was prepared, starting from chiral lactam **11**, (1*R*)-(−)-ABH, *via* tosylation, reduction, acetylation, and a second tosylation. Under *Trost* conditions [4], the ditosylimide **12**, through the π-allylpalladium complex **13**, was condensed with N^4-acetylcytosine and N^4-acetyl-5-fluorocytosine to give the protected carbanucleosides **14** and **15**. Upon saponification, compounds **14** and **15** gave rise to chiral carbocyclic nucleosides **16** and **17**, respectively (Scheme 2a).

The enantiomeric counterparts of these carbanucleosides were also prepared in a similar manner. Conversion of (1*S*)-(+)-ABH **18** into chiral cyclopentenylditosylimide **19**, followed by coupling with N^4-acetylcytosine and N^4-acetyl-5-fluorocytosine, through π-allylpalladium complex **20**, yielded the protected nucleosides **21** and **22**. Upon deprotection, the enantiomerically pure carbocyclic cytosine nucleosides **23** and **24**, respectively, were obtained (Scheme 2b). These nucleosides were characterized by NMR, high-resolution mass spectra, and HPLC.

In summary, a facile and efficient method for the synthesis of carbocyclic pyrimidine nucleosides was successfully developed. Starting with readily available chiral building blocks, both enantiomers of carbocyclic pyrimidine nucleosides were synthesized by the procedure that requires fewer steps, and produced a better overall yield compared to other methods. More importantly, it provides a simple and concise route to the enantiomerically pure carbocyclic pyrimidine nucleosides that previously were not easily attainable.

RFS is supported by NIH grant R01-AI-41980 and the Department of Veterans Affairs.

REFERENCES

1. Daluge, S.M. U.S. Patent 5,034,394, 1991.
2. Furman, P.A.; Schinazi, R.F. *Therapies for Viral Hepatitis*, Schinazi, R.F.; Sommadossi, J.-P.; and Thomas, H.C. Eds.; International Medical Press, London, (1998), pp. 273–283.
3. Shi, J.; McAtee, J.J.; Schlueter-Wirtz, S.; Tharnish, P.; Juodawlkis, A.; Liotta, D.C.; Schinazi, R.F. *J. Med. Chem.*, **1999**, *42*, 859–867.
4. Trost, B.M. *Angew. Chem., Int. Ed. Engl.*, **1986**, *25*, 1–20.
5. Jung, M.E.; Rhee, H. *J. Org. Chem.*, **1994**, *59*, 4719–4720.
6. Katagiri, N.; Takebayashi, M.; Kokufuda, H.; Kaneko, C.; Kanehira, K.; Torihara, M. *J. Org. Chem.*, **1997**, *62*, 1580–1581.

Downloaded At: 12:28 26 January 2011

Request Permission or Order Reprints Instantly!

Interested in copying and sharing this article? In most cases, U.S. Copyright Law requires that you get permission from the article's rightsholder before using copyrighted content.

All information and materials found in this article, including but not limited to text, trademarks, patents, logos, graphics and images (the "Materials"), are the copyrighted works and other forms of intellectual property of Marcel Dekker, Inc., or its licensors. All rights not expressly granted are reserved.

Get permission to lawfully reproduce and distribute the Materials or order reprints quickly and painlessly. Simply click on the "Request Permission/Reprints Here" link below and follow the instructions. Visit the U.S. Copyright Office for information on Fair Use limitations of U.S. copyright law. Please refer to The Association of American Publishers' (AAP) website for guidelines on Fair Use in the Classroom.

The Materials are for your personal use only and cannot be reformatted, reposted, resold or distributed by electronic means or otherwise without permission from Marcel Dekker, Inc. Marcel Dekker, Inc. grants you the limited right to display the Materials only on your personal computer or personal wireless device, and to copy and download single copies of such Materials provided that any copyright, trademark or other notice appearing on such Materials is also retained by, displayed, copied or downloaded as part of the Materials and is not removed or obscured, and provided you do not edit, modify, alter or enhance the Materials. Please refer to our Website User Agreement for more details.

Order now!

Reprints of this article can also be ordered at
http://www.dekker.com/servlet/product/DOI/101081NCN100002557