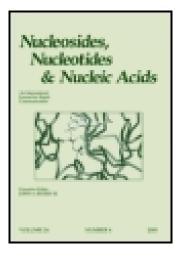
This article was downloaded by: [Georgia Tech Library] On: 10 November 2014, At: 18:45 Publisher: Taylor & Francis Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



# Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lncn20

## Stereospecific Synthesis of (-)-Neplanocin F

Sergio Rodriguez Ropero<sup>a</sup>, Dolorès Edmont<sup>a</sup>, Christophe Mathé<sup>a</sup> & Christian Périgaud<sup>a</sup> <sup>a</sup> UMR 5625 CNRS-UM II, Université Montpellier II, Montpellier, France Published online: 10 Dec 2007.

To cite this article: Sergio Rodriguez Ropero, Dolorès Edmont, Christophe Mathé & Christian Périgaud (2007) Stereospecific Synthesis of (-)-Neplanocin F, Nucleosides, Nucleotides and Nucleic Acids, 26:8-9, 1111-1114, DOI: 10.1080/15257770701521284

To link to this article: <u>http://dx.doi.org/10.1080/15257770701521284</u>

### PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at <a href="http://www.tandfonline.com/page/terms-and-conditions">http://www.tandfonline.com/page/terms-and-conditions</a>



#### STEREOSPECIFIC SYNTHESIS OF (-)-NEPLANOCIN F

Sergio Rodriguez Ropero, Dolorès Edmont, Christophe Mathé,

and Christian Périgaud D UMR 5625 CNRS-UM II, Université Montpellier II, Montpellier, France

 $\Box$  The stereospecific synthesis of (-)-neplanocin F was achieved in 15 steps from 2,3-Oisopropylidene-D-1,4-ribonolactone. The synthetic methodology can give an access through appropriate modifications to new series of carbanucleosides.

Keywords Neplanocin; carbanucleoside; stereospecific synthesis

#### INTRODUCTION

The neplanocin derivatives are an important class of naturally occurring carbanucleosides isolated from *Ampullariella regularis*.<sup>[1]</sup> The neplanocin family includes five distinct components such as (–)-neplanocin A, (–)-neplanocin B, (–)-neplanocin C, (–)-neplanocin D, and (–)-neplanocin F (Figure 1).

Among them, (-)-neplanocin A has received great attention due to its interesting biological properties<sup>[2]</sup> and numerous syntheses of neplanocin A as well as of its analogues have been reported.<sup>[3]</sup> Conversely, only two syntheses of neplanocin F, a minor component of the neplanocin family, have been reported including the total synthesis as a racemate of (+/-)-neplanocin  $F^{[4]}$  as well as the enantioselective synthesis of its unnatural (+) enantiomer.<sup>[5]</sup> Although (-)-neplanocin F does not present antiviral activity, the stereospecific synthesis of such a carbanucleoside which is an allylic rearranged isomer of (-)-neplanocin A, can give an access, through appropriate chemical modifications, to new series of carbanucleosides.

S.R.R. and D.E. are particularly grateful to The Ministerio de Educion y Ciencia, (Spain) and Sidaction (France), respectively, for postdoctoral fellowships.

Address correspondence to Christophe Mathé, UMR 5625 CNRS-UM II, Case courier 008, place E, Bataillon, Université Montpellier II, 34095 Montpellier Cedex, France. E-mail: cmathe@univ-montp2.fr

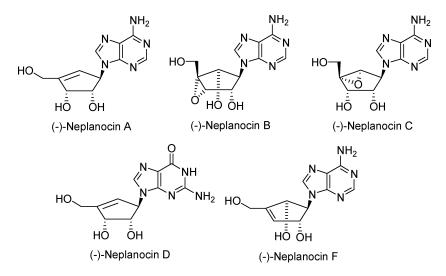
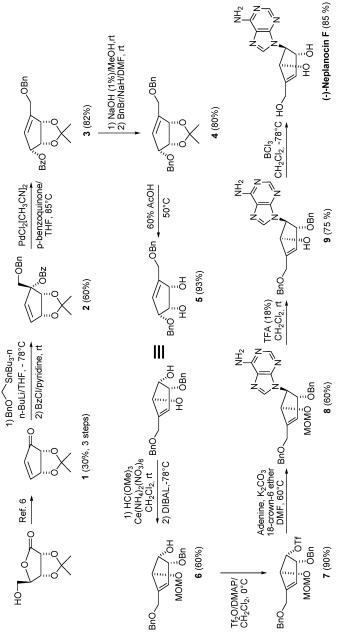


FIGURE 1 Naturally occurring carbocyclic nucleosides from the neplanocin family.

#### **SYNTHESIS**

The synthesis of (–)-neplanocin F was stereospecifically achieved from the known cyclopentenone 1 (Scheme 1) which was obtained from commercially available 2,3-O-isopropylidene-D-1,4-ribonolactone according to literature protocols.<sup>[6]</sup> Briefly, treatment of 1 with [(benzyloxy)methyl] (tributyl)stannane<sup>[7]</sup> in the presence of n-BuLi in THF at  $-78^{\circ}$ C yielded stereoselectively the 1,2-addition product which upon benzoylation provided compound **2**.

Palladium-catalyzed rearrangement of **2** gave the corresponding isomeric allylic benzoate **3** with good yield. Saponification of **3** and protection of the resulting alcohol with benzyl group afforded cyclopentenol **4**. After acetonide cleavage, regioselective protection of the allylic hydroxyl position<sup>[5]</sup> on compound **5** with a methoxymethyl (MOM) protecting group led to intermediate **6** with the homoallylic secondary alcohol free at the required position. Introduction of the heterocyclic base was achieved via the preparation of the triflate **7**, which upon reaction with adenine, potassium carbonate and a catalytic amount of 18-crown-6 ether in DMF gave solely the N-9 alkylated product. The N-9 alkylated position was unambigously established by NMR and UV spectra. Removal of the MOM group by treatment with TFA/CH<sub>2</sub>Cl<sub>2</sub> and well as the two benzyl ethers by treatment with BCl<sub>3</sub>/CH<sub>2</sub>Cl<sub>2</sub> at  $-78^{\circ}$  provided the target molecule (–)-neplanocin F. <sup>1</sup>H NMR spectrum was identical with that previously reported for the unnatural enantiomer<sup>[5]</sup> and the optical rotation agreed with literature data.<sup>[8]</sup>



**SCHEME 1** Synthetic pathway for (-)-neplanocin F.

#### CONCLUSION

The efficient stereospecific synthesis of (-)-neplanocin F was realized from 2,3-O-isopropylidene-D-1,4-ribonolactone in 15 steps. The synthetic methodology can give an access, through appropriate functionalizations to new series of carbanucleosides.

#### REFERENCES

- Hayashi, M.; Yaginuma, S.; Muto, N.; Tsujino, M. Structures of neplanocins, new antitumor antibiotics. Nucl. Acids Res. Symp. Ser. 1980, 8, s65–s67.
- De Clercq, E. Antiviral and antimetabolic activities of neplanocins. Antimicrob. Agents Chemother. 1985, 28, 84–89.
- For recent references, see: a) Ono, M.; Nishimura, K.; Tsubouchi, H.; Nagaoka, Y.; Tomioka, K. Total Synthesis of (-)-Neplanocin A by Using Lithium Thiolate-Initiated Michael-Aldol Tandem Cyclization Reaction., J. Org. Chem. 2001, 66, 8199–8203; b) Moon, H.R.; Lee, H.J.; Kim, K.R.; Lee, K.M.; Lee, S.K.; Kim, H.O.; Chun, M.W.; Jeong, L.S. Synthesis of 5'-substituted fluoro-neplanocin A analogues: importance of a hydrogen bonding donor at 5'-position for the inhibitory activity of S-adenosylhomocysteine hydrolase. Bioorg. Med. Chem. Lett. 2004, 14, 5641–5644.
- Bodenteich, M.; Marquez, V.E.; Hallows, W.H.; Goldstein, B.M. Synthesis and structural determination of (.+-.)-neplanocin F. J. Org. Chem. 1992, 57, 2071–2076.
- Comin, M.J.; Leitofuter, J.; Rodríguez, J.B. Enantioselective synthesis of (+)-neplanocin F. *Tetrahedron* 2002, 58, 3129–3136.

1114