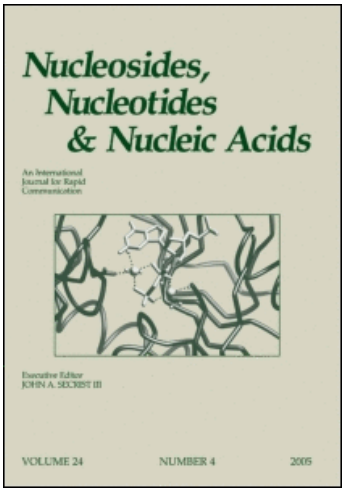

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STEREOSPECIFIC SYNTHESIS OF (−)-NEPLANOCIN F

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□ *The stereospecific synthesis of (−)-neplanocin F was achieved in 15 steps from 2,3-O-isopropylidene-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*.[1] 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[2] and numerous syntheses of neplanocin A as well as of its analogues have been reported.[3] 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.[5] 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.

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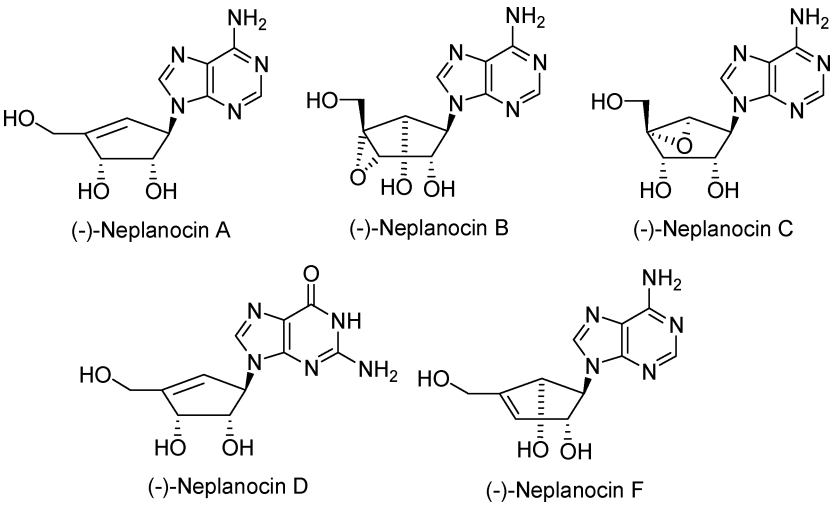
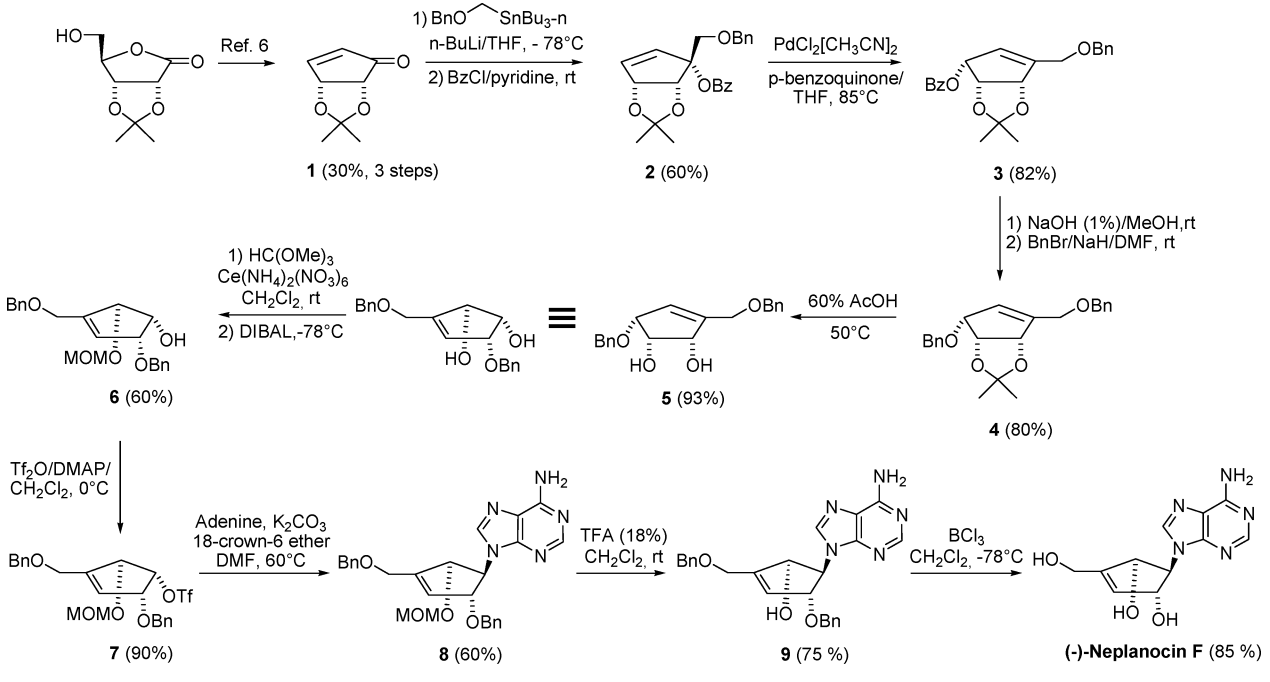


FIGURE 1 Naturally occurring carbocyclic nucleosides from the neplanocin family.

SYNTHESIS

The synthesis of (−)-neplanocin F was stereospecificaly 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.[6] Briefly, treatment of **1** with [(benzyloxy)methyl] (tributyl)stannane[7] in the presence of n-BuLi in THF at −78°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[5] 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_2Cl_2 and well as the two benzyl ethers by treatment with BCl_3/CH_2Cl_2 at −78° provided the target molecule (−)-neplanocin F. ^1H NMR spectrum was identical with that previously reported for the unnatural enantiomer[5] and the optical rotation agreed with literature data.[8]



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.

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