Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 2, pp. 373-374, 1996
Copyright © 1996 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0957-4166/96 $15.00 + 0.00

S0957-4166(96)00009-2

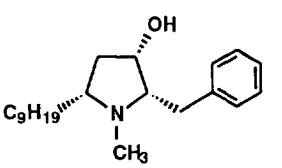
A Novel Stereoselective Synthesis of Enantiomerically Pure Antifungal Agent, (+)-Preussin

Hidemi Yoda,* Hiroyasu Yamazaki, and Kunihiko Takabe*

Department of Molecular Science, Faculty of Engineering,
Shizuoka University, Hamamatsu 432, Japan

Abstract: An efficient and novel process is described for the asymmetric synthesis of (2*S*,3*S*,5*R*)-1-methyl-5-nonyl-2-(phenylmethyl)-3-pyrrolidinol, (+)-preussin employing reductive deoxygenation of a functionalized quaternary α-hydroxy *N*-Boc pyrrolidine obtained by stereocontrolled elaboration of tri-*O*-benzyl-β-D-arabino-furanose. The synthetic strategy involves no separation of stereoisomers through the entire sequence.

(+)-Preussin (L-657,398) **1**, an antifungal antibiotic first isolated in 1988 from fermentation broths of *Aspergillus ochraceus* ATCC 22947, has attracted considerable attention since this compound was shown to inhibit growth of the bacteria, *Candida*, and filamentous fungi, including *Trichophyton menta* and *Microsporum canis*.[1] The relative and absolute stereochemistry of **1** was determined from ^{1}H and ^{13}C NMR spectra and nuclear Overhauser effect experiments.[1b] Due to its interesting activities as well as unique structural features, to our knowledge, five approaches to the total synthesis of **1** have been elaborated to date,[2] some of which required multistep reactions or have included a nonstereoselective route with stereoisomer separation.

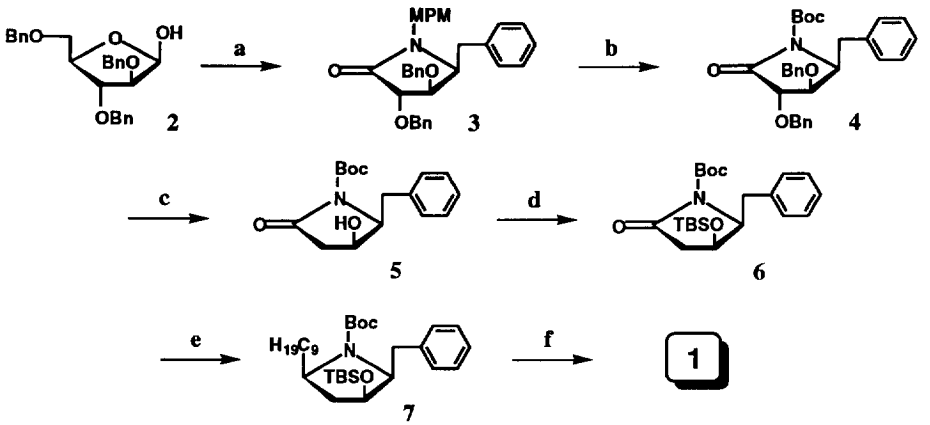


Preussin 1

On the other hand, recently we reported a novel and short synthetic strategy for the preparation of enantiomerically pure (-)-anisomycin[3] employing the *cis*-selective lactam formation protocol.[4] In this connection it is noteworthy that (+)-preussin **1** and its acetate ester show a broader spectrum of antifungal activity against both filamentous fungi and yeasts than the structurally related anisomycin.[1a]

With these considerations in mind, we wish to communicate the details of a novel synthetic process for the preparation of **1** without separation of stereoisomers. This method features the stereocontrolled elaboration of the functionalized *N*-Boc lactam derivative according to our preceding report[5] in which asymmetric deoxygenation of the quaternary α-hydroxy compound is an essential step for introducing a stereogenic center.

As shown in Scheme 1, functionalized diastereomerically pure *N*-*p*-methoxybenzyl (MPM) lactam **3**, obtained from commercially available 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose **2**[3,4,5] in high yield, was treated with CAN followed by the Boc-protection to give *N*-Boc lactam **4**. After removal of the protecting groups from **4** with Pd(black), highly regioselective acylation with PhOCSCl followed by radical deoxygenation with



Scheme 1. Reagents and conditions: (a) 1 $MPMNH_2$, Benzene, MS 4A, reflux; quant.; 2 BnMgCl, -78 °C, THF; 3 PCC, MS 4A, CH_2Cl_2; 59% (2 steps); (b) 1 $Ce(NH_4)_2(NO_3)_6$, CH_3CN-H_2O; 76%; 2 $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; quant.; (c) 1 Pd(black), HCOOH, MeOH; quant.; 2 PhOCSCl, pyridine, DMAP, CH_3CN; 3 Bu_3SnH, AIBN, toluene, 90 °C; 72% (2 steps); (d) TBSCl, imidazole, DMF; 91%; (e) 1 $C_9H_{19}MgBr$, -78 °C, THF; 2 Et_3SiH, BF_3•OEt_2, -40~-30 °C, CH_2Cl_2; 67% (2 steps); (f) 1 Bu_4NF, THF; 97%; 2 $LiAlH_4$, THF, 50 °C; 92%.

Bu_3SnH[6] resulted in the preparation of **5**, $[\alpha]^{24}_D$ +25.1 (*c* 0.85, $CHCl_3$) in high yield. This was then silylated to give **6**, $[\alpha]^{23}_D$ +37.9 (*c* 1.20, $CHCl_3$). Nucleophilic addition of nonylmagnesium bromide to the key compound **6** provided the labile quaternary α-hydroxy *N*-Boc intermediate. This was readily submitted to reductive deoxygenation with Et3SiH in the presence of BF_3•OEt_2, cleanly leading to the pyrrolidine derivative **7**, $[\alpha]^{25}_D$ -46.4 (*c* 1.50, $CHCl_3$) as a single stereoisomer[5] in 67% yield (2 steps) with the desired ***R*** configuration.[7] Accompanying formation of small amounts of ketone (5%) derived from equilibrium of the quaternary intermediate was observed. Finally, **7** was reduced effectively with LiAlH4 in THF in 92% yield after desilylation to complete the total synthesis of (+)-preussin **1**, $[\alpha]^{24}_D$ +28.2 (*c* 1.00, $CHCl_3$) [natural **1**, $[\alpha]^{25}_D$ +22.0 (*c* 1.0, $CHCl_3$)[1b]]. The spectral data of the synthetic amorphous solid **1** were completely identical with those of the reported natural[1] and synthetic[2] compound.

This process, in which (+)-preussin is synthesized from 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose, involves no separation of stereoisomers throughout the entire sequence and provides a new synthetic strategy.

References and notes

1. (a) Schwartz, R. E.; Liesch, J.; Hensens, O.; Zitano, L.; Honeycutt, S.; Garrity, G.; Fromtling, R. A.; Onishi, J.; Monaghan, R. *J. Antibiot.* **1988**, *41*, 1774. (b) Johnson, J. H.; Phillipson, D. W.; Kahle, A. D. *J. Antibiot.* **1989**, *42*, 1184.
2. (a) Pak, C. S.; Lee, G. H. *J. Org. Chem.* **1991**, *56*, 1128. (b) Shimazaki, M.; Okazaki, F.; Nakajima, F. Ishikawa, T.; Ohta, A. *Heterocycles* **1993**, *36*, 1823. (c) McGrane, P. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1993**, *115*, 11485. (d) Overhand, M.; Hecht, S. M. *J. Org. Chem.* **1994**, *59*, 4721. (e) Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241.
3. Yoda, H.; Nakajima, T.; Yamazaki, H.; Takabe, K. *Heterocycles* **1995**, *41*, 2423.
4. (a) Lay, L.; Nicotra, F.; Paganini, A.; Pangrazio, C.; Panza, L. *Tetrahedron Lett.* **1993**, *34*, 4555. (b) Hashimoto, M.; Terashima, S. *Chem. Lett.* **1994**, 1001.
5. Yoda, H.; Yamazaki, H.; Kawauchi, M.; Takabe, K. *Tetrahedron: Asymmetry* in press.
6. Sharma, R.; Marquez, V. E. *Synth. Commun.* **1994**, *24*, 1937.
7. The absolute configuration of the generated stereogenic center was determined based on its spectral data of synthetic (+)-**1**.

(*Received in Japan* 20 *November* 1995)