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

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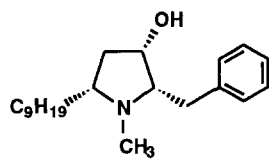
Abstract: An efficient and novel process is described for the asymmetric synthesis of (2*S*,3*S*,5*R*)-1-methyl-5-nonyl-2-(phenylmethyl)-3-pyrrolidinol, (+)-preussin employing reductive deoxygenation of a functionalized quaternary α-hydroxy *N*-Boc pyrrolidine obtained by stereocontrolled elaboration 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.

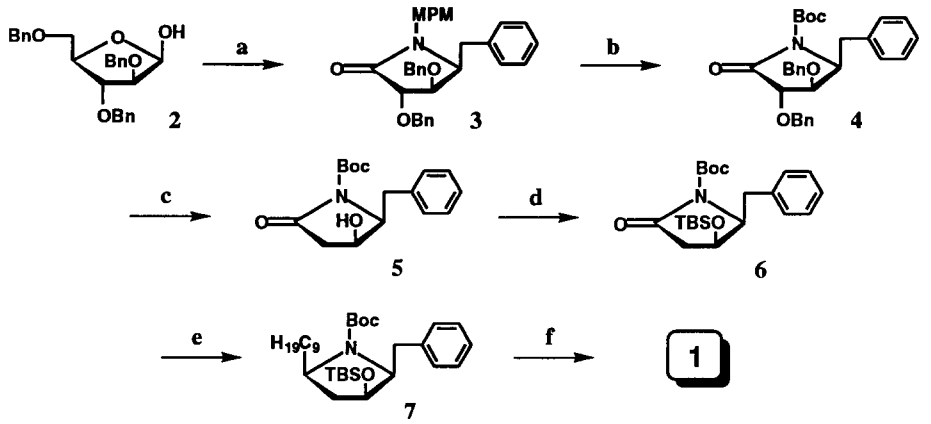


Preussin 1

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 Et_3SiH 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 $LiAlH_4$ 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.

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7. The absolute configuration of the generated stereogenic center was determined based on its spectral data of synthetic (+)-**1**.

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