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Facile and Efficient Total Synthesis of (+)-Preussin

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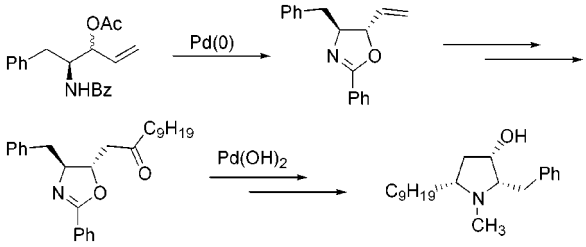
ABSTRACT



The enantioselective total synthesis of (+)-preussin, a potent antifungal agent, has been achieved. The key steps are a Pd(0)-catalyzed oxazoline-forming reaction from L-phenylalanine, hydrogenolysis, and subsequent diastereoselective reductive cyclization of the intermediate aminoketone to pyrrolidine using Pearlman's catalyst.

(+)-Preussin (**1**, Figure 1), a potent antifungal agent possessing a pyrrolidine skeleton, was isolated from fermentation broths of both *Aspergillus ochraceus* and *Preussia* sp. in the late 1980s.[1,2] Both **1** and its acetate ester **2** possess significant activity as broad-spectrum antibiotics against yeasts and filamentous fungi.[2] A number of its synthetic approaches have been reported due to its novel pyrrolidine structure and its interesting biological activity.[3]

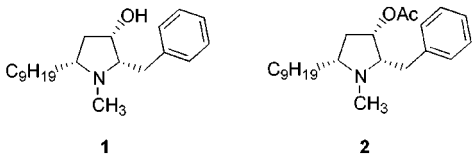
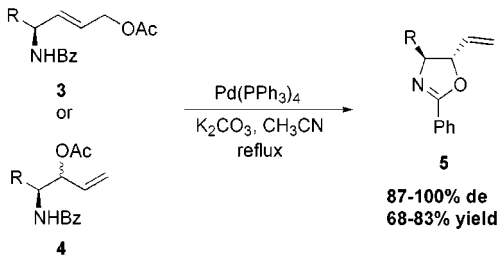


Figure 1.

In a previous paper,[4] we described a new Pd(0)-catalyzed procedure for the stereoselective formation of an oxazoline ring from an acyclic allylic and homoallylic amide having a benzoyl substituent as an *N*-protection group. The most significant point of this method is that it is based on the *trans*-oxazoline ring formation in palladium(0)-catalyzed conditions (Scheme 1). We envisioned that this method could be utilized to set the vicinal amino alcohol stereochemistry of the preussin. The pendant vinyl group could be converted to the appropriate ketone which could be employed in the stereoselective installation of the nonyl group by catalytic hydrogenation of oxazoline.

Scheme 1



(1) Schartz, R. E.; Liesch, J.; Hensens, O.; Zitano, L.; Honeycutt, S.; Garrity, G.; Fromtling, R. A.; Onishi, J.; Monaghan, R. *J. Antibiot*. **1988**, 1744.

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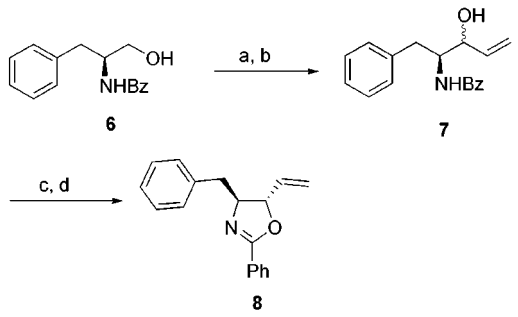
The synthesis of **1** began with the protected L-*N*-benzoyl phenylalaninol **6** as shown in Scheme 2. Oxidation of alcohol

Scheme 2[a]

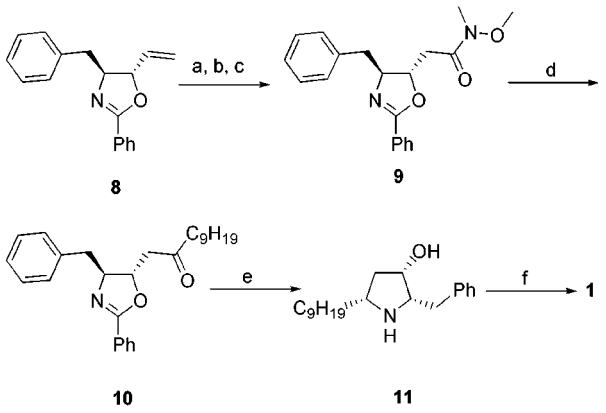


[a] (a) Dess−Martin periodinane, CH_2Cl_2; (b) CH_2═$CHMgBr$, THF, 70% for 2 steps; (c) Ac_2O, pyr, CH_2Cl_2, 99%; (d) $Pd(PPh_3)_4$, K_2CO_3, CH_3CN, 83%.

6 with Dess−Martin periodinane[4b,5] gave the corresponding aldehyde without racemization,[4b,5b] which was reacted with vinylmagnesium bromide in THF at 0 °C to afford the corresponding allyl alcohol **7** as an ca. 1.1:1 mixture of syn/anti isomers (^{1}H NMR) in 70% yield.[6] Acetylation of the hydoxyl group yielded the secondary allylic acetate. A standard oxazoline ring formation reaction [$Pd(PPh_3)_4$, K_2CO_3, in CH_3CN] of the allylic acetate of **7** gave the desired *trans*-oxazoline **8** as the major compound with high diastereoselectivity (14:1) and in good yield (83%).[5]

Oxidation of alkene **8** with 9-BBN[7] gave the corresponding alcohol in 82% yield. This alcohol was further oxidized to the corresponding acid with ruthenium chloride.[8] The resulting carboxylic acid was converted to its Weinreb amide[9] **9** via DCC-mediated condensation with *N*,*O*-dimethylhydroxylamine in 85% yield. Treatment of the amide with nonylmagnesium bromide (THF, −30 → 0 °C, 1 h) provided ketone **10** in 80% yield. Hydrogenolysis of oxazoline[10] **10** in 1:10 AcOH/MeOH was performed under 70 psi of H_2 and ambient temperature. Under these conditions, we achieved not only hydrogenolysis of oxazoline moiety but also cyclization of the intermediate aminoketone to pyrrolidine **11**, a known precursor of preussin,[3i] as a single isomer in 50% yield. Spectroscopic data and the specific rotation of **11** were in good agreement with the literature values reported.[3i] Finally, pyrrolidine **11** was methylated conventionally[11] to produce (+)-preussin in 78% yield (Scheme 3).

Scheme 3[a]



[a] (a) 9-BBN, THF, 82%; (b) $RuCl_3$, $NaIO_4$, $NaHCO_3$, CCl_4/CH_3CN/H_2O; (c) DCC, DMAP, $NH(CH_3)OCH_3$−HCl, Et_3N, CH_2Cl_2, 85% for 2 steps; (d) $C_9H_{19}MgBr$, THF, −30 °C, 80%; (e) $Pd(OH)_2$/H_2, AcOH/MeOH (1:9), 50%; (f) HCHO, $NaBH_3CN$, AcOH, 78%.

In summary, we report a new asymmetric synthetic method for (+)-preussin utilizing oxazoline **8**. The key features in this strategy are the diastereoselective oxazoline formation reaction catalyzed by palladium(0) and pyrrolidine formation by catalytic hydrogenation of oxazoline.

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Supporting Information Available: Experimental procedure and characterization data for compounds **1** and **9**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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