A Concise Synthesis of the Antifungal Agent (+)-Preussin

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Summary: The antifungal agent (+)-preussin (**1**) was synthesized in five efficient transformations from *t*-Boc-(*S*)-phenylalanine. The key step involved the Hg(II)-mediated ring closure of ynone **4**, a 5-*endo-dig* process.

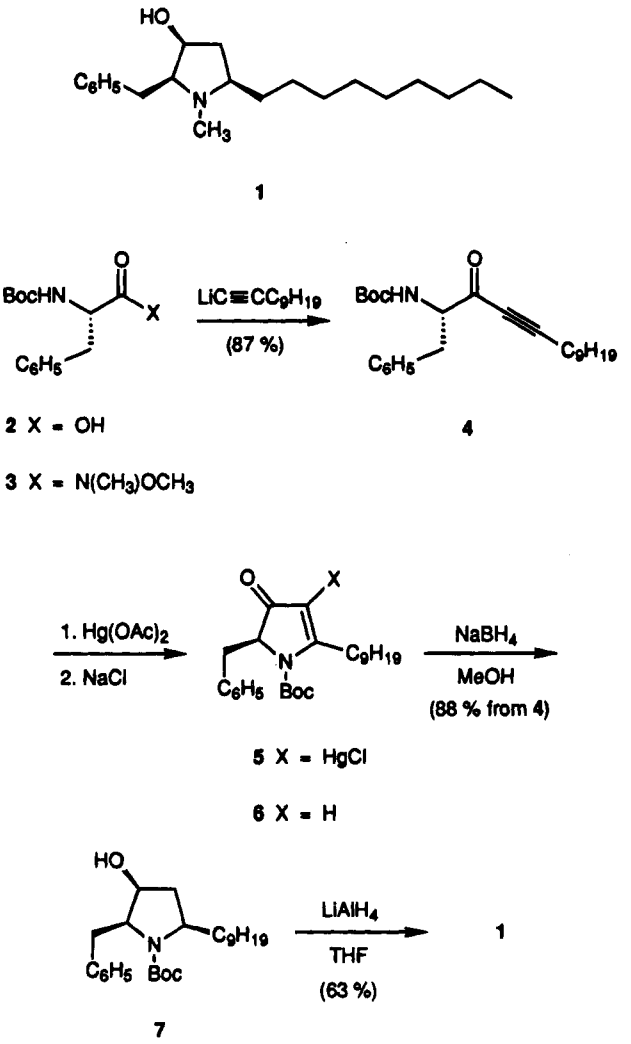
The pyrrolidinol alkaloid (+)-preussin (**1**) has been isolated from the microorganisms *Preussia* sp. and *Aspergillus ochraceus*.[1] Preussin is strongly inhibitory to the growth of bacteria, *Candida*, and filamentous fungi, including *Trichophyton menta* and *Microsporum canis*.[1] (+)-Preussin was first synthesized starting from D-glucose.[2a] More recently, a shorter nonstereoselective route was reported from (*R*)-phenylalanine.[2b] Presently, we describe a short, highly efficient and stereoselective synthesis of (+)-preussin.

The strategy employed for the synthesis of (+)-preussin is outlined in Scheme 1. The Weinreb amide[3] **3** was accessible in 77% yield from commercially available *t*-Boc-(*S*)-phenylalanine via DCC-mediated condensation with *N*,*O*-dimethylhydroxylamine. Treatment of **3** with undecynyllithium[4] (THF, −23 °C, 1 h) provided ynone **4** as a colorless oil in 87% yield.

When treated with $Hg(OAc)_2$ in CH_3NO_2,[5] ynone **4** underwent 5-*endo-dig* cyclization[6] affording pyrrolinones **5** and **6** in an 8:1 ratio and in overall yields ranging from 80 to 92%. Although the mechanism of formation of enone **6** is uncertain, it seems likely that it is formed by protodemercuration[5a] of **5** which constitutes the primary product of cyclization.[7]

Pyrrolinones **5** and **6** could be separated readily by chromatography on silica gel, but partial racemization occurred as a consequence. Accordingly, the mixture of **5** and **6** was treated directly with $NaBH_4$ (CH_3OH, −10 °C);[8] *N*-Boc-pyrrolidinol **7** was obtained as the sole stereoisomer in 88% overall yield from ynone **4**. The highly stereoselective formation of **7** must result from enone reduction from the less hindered face, i.e., oppposite the benzyl group. The stereochemistry of pyrrolidinol **7** was secured by NOE NMR experiments, as well as

Scheme 1



preparation and characterization of each of the possible diastereomers.[9] The optical purity of compound **7** was shown to be >95% ee, as judged from the ^1H NMR spectrum of the corresponding Mosher ester derivative. Treatment of carbamate **7** with $LiAlH_4$ (THF, 67 °C, 4 h) afforded (+)-preussin (**1**) as a colorless, amorphous solid in 63% yield.[10] The optical rotation determined for **1** ($[\alpha]_D$ +32.8° (*c* 1.0, $CHCl_3$)) and the NMR spectra were in good agreement with the reported value for synthetic (+)-preussin prepared by stereospecific synthesis from D-glucose.[2a]

Synthetic (+)-preussin was tested in a strain of *Saccharomyces cerevisiae* deficient in recombinational DNA repair.[11] (+)-Preussin was a potent inhibitor of this yeast

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(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. (c) Schwartz, R. E.; Onishi, J. C.; Monaghan, R. L.; Liesch, J. M.; Hensens, O. D. U. S. Patent 4,847,284, 1989.

(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.

(3) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Fehrentz, J.-A.; Castro, B. *Synthesis* **1983**, 676.

(4) Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5320.

(5) (a) Larock, R. C.; Harrison, L. W. *J. Am. Chem. Soc.* **1984**, *106*, 4218. (b) Harding, K. E.; Tiner, T. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon; New York, 1990; Vol. 6, p 363.

(6) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(7) Consistent with this thesis, treatment of **5** with a 7:1 mixture of ethyl acetate–concd HCl (0 °C, 5 min) effected its quantitative conversion to **6** (with concomitant racemization).

(8) (a) Whitesides, G. M.; San Filippo, J., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 6611. (b) Mehta, G.; Murthy, A. N.; Reddy, D. S.; Reddy, A. V. *J. Am. Chem. Soc.* **1986**, *108*, 3443.

(9) Irradiation of the benzylic H's at 2.95 ppm in a NOE experiment gave a 3.8% enhancement of the resonance at 1.7 ppm (corresponding to the first CH_2 of the nonyl substituent), indicating a *cis*-2,5-dialkyl relationship.

(10) Preussin was also accessible from compound **6** in a single step by treatment with $LiAlH_4$ in THF (0 °C for 1 h, then 67 °C for 4 h), albeit only in modest (11%) yield.

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strain (IC_{12} 2.5 nM) as compared with its lack of effect on an otherwise isogenic strain proficient in DNA repair (no inhibition observed at 63 μM preussin); this finding identifies preussin as a putative DNA damaging agent in yeast.

By application of the synthetic strategy described herein, we have been able to prepare congeners of (+)-preussin having extraordinary potency toward a strain of *Saccharomyces cerevisiae* deficient in recombinational repair ($IC_{12} \sim 25$ pM).[12]

(11) Eng, W.-K.; Faucette, L.; Johnson, R. K.; Sternglanz, R. *Mol. Pharmacol.* **1988**, *34*, 755.

(12) The preparation and biological evaluation of both enantiomers of preussin, as well as the diastereomers and a number of structural analogs, will be reported elsewhere. Overhand, M.; Short, G.; Hecht, S. M.; Hofmann, G. A.; Johnson, R. K. Manuscript in preparation.

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Supplementary Material Available: Experimental procedures and characterization data for **1**, **3**, **4**, and **7** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.