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A concise and efficient synthesis of (+)-preussin

Abstract: A novel and efficient synthesis of (+)-preussin (**7**) starting from *N*-butoxycarbonyl-L-phenylalaninal (**1**) is described. This natural product was synthesized under mild conditions and with good overall yield.

Keywords: cyclization; phenylalanine; pyrrolidines; vinylation.

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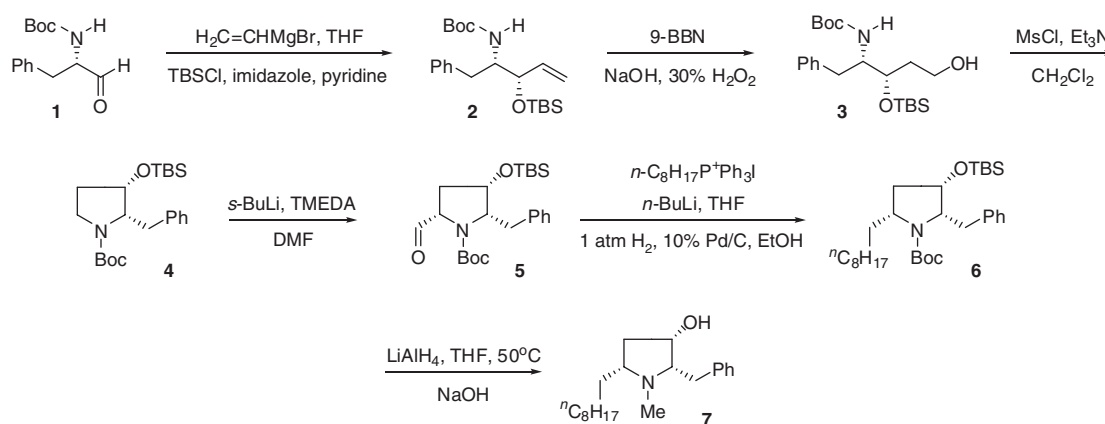
Compound **7** is a naturally occurring pyrrolidine alkaloid isolated from the fermentation of *Aspergillus ochraceus* [14, 15]. It has been shown to possess a potent antifungal activity [16]. Its interesting structural features and remarkable biological activity have made preussin an attractive target for synthetic chemists, and several approaches to the preparation of **7** have been reported [17–33]. To demonstrate the synthetic utility of the methodology of Arévalo-García and Colmenares [34], the details of a novel synthetic process leading to the preparation of this natural product, (2*S*,3*S*,5*R*)-(+)-preussin (**7**) are communicated here.

Introduction

The pyrrolidine ring is a significant motif found in many natural and unnatural bioactive molecules. It occurs in a range of pheromones, alkaloids, drug candidates, and other important compounds [1–4] that are antibacterial and neuroexcitatory agents, venoms, or fungicides [5–9]. Consequently, molecules which possess the pyrrolidine motif are often promising drug candidates for use in the pharmaceutical industry, and enantomerically pure pyrrolidines are excellent chiral building blocks in asymmetric synthesis [8, 10–13]. Accordingly, there is continuous research towards the stereocontrolled access to functionalized pyrrolidines. One of those important compounds is preussin (structure **7** in Scheme 1).

Results and discussion

From the retrosynthetic analysis (not shown), it was clear that the target compound **7** could be acquired from the readily available precursor **1** [35] (Scheme 1). Thus, the synthesis of **7** started with the reaction of aldehyde **1** (1 eq.) in THF with vinylmagnesium bromide (4 eq.) at 0°C affording a *syn*-amino alcohol [36, 37] as the major product (*syn:anti*=94:6) in 76% yield. Protection of the hydroxy group of this adduct (1 eq.) with *tert*-butyldimethylsilyl chloride (2.2 eq.) in pyridine afforded protected alcohol **2** [38] in 90% overall yield. Hydroboration of **2** with 9-borabicyclo[3.3.1]nonane (1.4 eq.) in the presence of hydrogen peroxide and sodium hydroxide at room temperature afforded alcohol **3** in 81% yield [38].



Scheme 1 Synthesis of (+)-preussin (**7**).

Next, the primary hydroxyl group in **3** was activated by the reaction with MeSO_2Cl (2.9 eq.) in the presence of Et_3N in dichloromethane. This reaction proceeded smoothly and was followed by an intramolecular $\text{S}_{\text{N}}2$ displacement affording the cyclized product **4** in 71% yield. Following Beak's methodology [39–42], lithiation of **4** with *s*-BuLi (1.3 eq.) in the presence of TMEDA followed by the reaction of the resultant 2-lithiopyrrolidine with *N,N*-dimethylformamide (1.5 eq.) provided a mixture of aldehydes (*cis:trans*=93:7) from which the major product **5** was obtained in 78% yield by flash chromatography. Treatment of aldehyde **5** with the Wittig reagent generated *in situ* from *n*-octyltriphenylphosphonium iodide (1.5 eq.) and *n*-butyllithium (1.6 eq.) afforded an olefin (83%), which was rapidly hydrogenated (1 atm. H_2 , 10% Pd/C, rt, EtOH) obtaining **6** [43] in quantitative yield. The end-game was accomplished through the one-pot reported procedure, leading to the deprotection/reduction ($\text{LiAlH}_4/\text{NaOH}$) [44] of **6**, completing the synthesis of (+)-preussin (**7**), in 91% yield (Scheme 1). Its ^1H NMR and ^{13}C NMR spectra are virtually identical to literature data [14, 15, 24, 26, 27, 29]. Its specific optical rotation $[\alpha]_{\text{D}}^{25}=+26.8^\circ$ (*c* 1.1, CHCl_3) that is greater than the literature value $[\alpha]_{\text{D}}^{25}=+22.0^\circ$ (*c* 1.0, CHCl_3) demonstrates that product **7** of high optical purity was obtained. The high chemical purity is strongly supported by the excellent results of elemental analysis.

Conclusions

A new efficient, stereoselective route to biologically important (+)-preussin was developed. The strategy can be extended to the synthesis of other members of this class of biologically active products, and further studies in this field are currently underway.

Experimental

Solvents and all other reagents were obtained from Aldrich, Fluka or Avocado. Solvents were dried using common laboratory methods [45], and their evaporation was performed in a rotary evaporator under reduced pressure. Analytical thin-layer chromatography (TLC) was performed on a pre-coated Merck silica-gel 60 F₂₅₄ TLC plate. Purification was performed by flash column chromatography [46] on silica gel (Kieselgel-60, Merck, 230–400 mesh). The NMR spectra were recorded with a Bruker Avance spectrometer in CDCl_3 at 300 MHz (^1H NMR) and 75 MHz (^{13}C NMR). The IR spectra were recorded on a Jasco FT/IR-430 spectrophotometer. Yields refer to chromatographically and spectroscopically pure compounds.

(2*S*,3*S*)-1-(*tert*-Butoxycarbonyl)-3-*tert*-butyldimethylsiloxy-2-(phenylmethyl)pyrrolidine (**4**)

A solution of alcohol **3** [38] (900 mg, 2.19 mmol) and Et_3N (0.88 mL, 6.35 mmol) in dichloromethane (5 mL) at -5°C was treated with MeSO_2Cl (0.49 mL, 6.35 mmol). The mixture was stirred at -5°C to 0°C for 20 min and then warmed to ambient temperature. Stirring was continued for another 1 h and then the mixture was quenched by addition of saturated NH_4Cl (6 mL) and H_2O (3 mL). The aqueous layer was extracted with dichloromethane (3×10 mL), and the extract was washed with brine and dried over anhydrous Na_2SO_4 . The solvent was then removed under reduced pressure and the product was purified by flash column chromatography eluting with 10% EtOAc in petroleum ether to afford **4** (610 mg, 71%) as a colorless oil; ^1H NMR: δ 7.08 (m, 5H), 4.10 (dt, $J = 7.0$ Hz and 7.0 Hz, 1H), 4.0 (dt, $J = 6.1$ Hz and 6.0 Hz, 1H), 3.68 (m, 2H), 3.01 (m, 2H), 1.95 (m, 2H), 1.35 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR: δ 154.9, 139.5, 129.6, 128.3, 126.0, 79.5, 71.0, 61.9, 43.4, 34.5, 31.3, 28.4; 20.1, -5.0, -5.1; IR (film): 1720, 1600, 1405, 1352, 1255, 837 cm^{-1} . Anal. Calcd for $\text{C}_{22}\text{H}_{37}\text{NO}_3\text{Si}$: C, 67.47; H, 9.52; N, 3.58. Found: C, 67.39; H, 9.51; N, 3.61.

(2*S*,4*S*,5*S*)-1-(*tert*-Butoxycarbonyl)-4-*tert*-butyldimethylsiloxy-5-(phenylmethyl)pyrrolidine-2-carbaldehyde (**5**)

To a stirred solution of **4** (0.962 g, 2.45 mmol) in ether (10 mL) under nitrogen atmosphere was added TMEDA (0.482 mL, 3.19 mmol). The solution was cooled to -65°C and *s*-BuLi (1.38 M in cyclohexane, 2.46 mL, 3.19 mmol) was added dropwise. The solution was allowed to warm to -30°C and was stirred for another 30 min. It was then cooled to -78°C and treated with DMF (0.284 mL, 3.68 mmol). After 10 min the mixture was quenched with saturated NH_4Cl (3 mL), allowed to warm to room temperature, and diluted with ether (30 mL). The aqueous layer was extracted with ether (3×6 mL) and the combined ether solutions were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/ethyl acetate, 90:10) to afford **5** (0.803 g (78%), (diastereoselectivity, 93:7) of **5**, as a colorless oil; ^1H NMR: δ 9.25 (br s, 1H), 7.15 (m, 5H), 4.18 (dt, $J = 6.1$ Hz and 7.2 Hz, 1H), 4.09 (m, 1H), 3.85 (dt, $J = 2.0$ Hz and 7.4 Hz, 1H), 2.90 (m, 2H), 2.1 (m, 2H), 1.44 (s, 9H), 0.90 (s, 9H), 0.05 (s, 3H), -0.04 (s, 3H); ^{13}C NMR: δ 201.0, 156.6, 139.0, 136.0, 129.0, 128.2, 71.0, 68.0, 61.0, 60.3, 33.3, 27.0, 26.1, 21.3, 18.3, -4.0; IR (film): 2730, 1730, 1705, 1570, 815 cm^{-1} . Anal. Calcd for $\text{C}_{23}\text{H}_{37}\text{NO}_4\text{Si}$: C, 65.83; H, 8.89; N, 3.34. Found: C, 65.79; H, 8.85; N, 3.43.

(2*S*,3*S*,5*R*)-(+)-Preussin (**7**)

A solution of **6** (500 mg, 0.97 mmol) in THF (5 mL) was stirred at 0°C under nitrogen atmosphere and treated dropwise using a syringe with a solution of LiAlH_4 (5.85 mL, 5.85 mmol, 1 M in THF). The resulting mixture was heated under reflux until the starting material was consumed as determined by TLC analysis (approx. 10 h). The reaction mixture was then cooled to 0°C , quenched with water (2 mL),

and diluted with diethyl ether (10 mL). Aqueous NaOH (5 mL, 10 M) and water (1 mL) were then added and an insoluble white precipitate was formed. The organic supernatant was decanted to an Erlenmeyer flask and the precipitate was washed with diethyl ether. The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The oily residue was subjected to flash chromatography eluting with hexane/ethyl acetate, 5:1, to afford 280.2 mg (91%) of (+)-preussin as a colorless oil; ^1H NMR: δ 7.21 (m, 5 H), 3.5 (m, 1 H), 2.86 (m, 2 H), 2.3 (s, 3H), 2.23 (m, 1H), 1.69 (m, 1 H), 1.46 (m, 1 H), 2.66–2.60 (m, 2 H), 1.30–1.18 (m, 16 H), 0.88 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR: δ 138.5, 129.2, 128.4, 126.0, 71.5, 68.7, 53.4, 38.6, 35.0, 33.5, 31.8, 29.9, 29.5, 29.3, 29.0, 26.3, 22.7, 14.1; IR (film): 3400,

2935, 2900, 1457, 1400, 1170 cm^{-1} . Anal. Calcd for $\text{C}_{21}\text{H}_{35}\text{NO}$: C, 79.4; H, 11.1; N, 4.41. Found: C, 79.1; H, 10.9; N, 4.39.

Acknowledgments: The author is grateful to Mrs Agnieszka Chilicka for proofreading this paper and to EARTH University and the Educational Research Institute for partial support of this work.

Received December 12, 2013; accepted January 9, 2014

References

- [1] Hanessian, S.; Bayrakdarian, M.; Luo, X. Total synthesis of A-315675: a potent inhibitor of influenza neuraminidase. *J. Am. Chem. Soc.* **2002**, *124*, 4716–4721; Erratum: *J. Am. Chem. Soc.* **2003**, *125*, 4958.
- [2] Ma, D.; Yang, J. Total synthesis of kaitocephalin, the first naturally occurring AMPA/KA receptor antagonist. *J. Am. Chem. Soc.* **2001**, *123*, 9706–9707.
- [3] Michael, J. P. Indolizidine and quinolizidine alkaloids. *Nat. Prod. Rep.* **2005**, *22*, 603–626.
- [4] Watanabe, H.; Okue, M.; Kobayashi, H.; Kitahara, T. The first synthesis of kaitocephalin based on the structure revision. *Tetrahedron Lett.* **2002**, *43*, 861–864.
- [5] Attygalle, A. B.; Morgan, D. E. Chemicals from the glands of ants. *Chem. Soc. Rev.* **1984**, *13*, 245–278.
- [6] Flanagan, D. M.; Jouilli, M. M. Synthetic strategies for the construction of 3-pyrrolidinol, a versatile nitrogen. *Heterocycles* **1987**, *26*, 2247–2265.
- [7] Maesiot, G.; Delaude, C. In *The Alkaloids*; Brosei, A., Ed.; Academic Press: New York, 1986; Vol. 27, Chapter 3. Pyrrolidine Alkaloids, pp. 269–322.
- [8] Numata, A.; Ibuka, T. In *The Alkaloids*; Broesi, A., Ed.; Academic Press: New York, 1987; Vol. 31, Chapter 6. Alkaloids from Ants and Other Insects, pp. 193–315.
- [9] Pedder, D. J.; Fales, H. M.; Jaouni, T.; Blum, M.; MacConnell, J.; Crewe, R. M. Constituents of the venom of a South African fire ant (*Solenopsis punctaticeps*): 2,5 dialkylpyrrolidines and -pyrrolines, identification and synthesis. *Tetrahedron* **1976**, *32*, 2275–2279.
- [10] O'Hagan, D. Pyrrole, pyrrolidine, pyridine, piperidine and tropane alkaloids. *Nat. Prod. Rep.* **2000**, *17*, 435–446.
- [11] Hanessian, S.; Yun, H.; Tintelnot-Blomley, M. Stereoselective synthesis of constrained azacyclic hydroxyethylene isosteres as aspartic protease inhibitors: dipolar cycloaddition and related methodologies toward branched pyrrolidine and pyrrolidinone carboxylic acids. *J. Org. Chem.* **2005**, *70*, 6746–6756.
- [12] Huryn, D. M. In *Comprehension Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991, Vol. 1, pp 64–71.
- [13] Schomaker, J. M.; Bhattacharjee, J. Y.; Borhan, B. Diastereomerically and enantiomerically pure 2,3-disubstituted pyrrolidines from 2,3-aziridin-1-ols using a sulfoxonium ylide: a one-carbon homologative relay ring expansion. *J. Am. Chem. Soc.* **2007**, *129*, 1996–2003 (and references cited therein).
- [14] Johnson, J. H.; Phillipson, D. W.; Khale, A. D. The relative and absolute stereochemistry of the antifungal agent preussin. *J. Antibiot.* **1989**, *42*, 1184–1185.
- [15] Schwartz, R. E.; Liesch, J.; Hensens, O.; Zitano, L.; Honeycutt, S.; Garrity, G.; Fromtling, R. A.; Onishi, J.; Monaghan, R. L-657,398, A novel antifungal agent: fermentation, isolation, structural elucidation and biological properties. *J. Antibiot.* **1988**, *41*, 1774–1779.
- [16] Canova, S.; Bellosta, V.; Cossy, J. Total synthesis of (+)-preussin: control of the stereogenic centers by enantioselective allyltitanations. *Synlett* **2004**, *10*, 1811–1813.
- [17] Armas, P. D.; Tellado-Garcia, F.; Tellado-Marrero, J. J.; Robles, J. Diastereoselective formal synthesis of the antifungal agent, (+)-preussin. A new entry to chiral pyrrolidines. *Tetrahedron Lett.* **1998**, *39*, 131–134.
- [18] Bach, T.; Brummerhop, H. Unprecedented facial diastereoselectivity in the Paternò-Büchi reaction of a chiral dihydropyrrole – a short total synthesis of (+)-preussin. *Angew. Chem. Int. Ed.* **1998**, *37*, 3400–3402.
- [19] Davis, F. A.; Deng, J. Asymmetric synthesis of (+)-preussin from *N*-sulfinyl δ -amino β -ketoesters. *Tetrahedron* **2004**, *60*, 5111–5115.
- [20] Deng, W.; Overman, L. E. Enantioselective total synthesis of either enantiomer of the antifungal antibiotic preussin (L-657,398) from (*S*)-phenylalanine. *J. Am. Chem. Soc.* **1994**, *116*, 11241–11250.
- [21] Kadota, I.; Saya, S.; Yamamoto, Y. Novel route to the synthesis of hydroxylated pyrrolidine derivatives via the intramolecular reaction of γ -aminoallylstannane with aldehyde. Total synthesis of (+)-preussin. *Heterocycles* **1997**, *46*, 335–348.
- [22] Kanazawa, A.; Gillet, S.; Delair, P.; Greene, A. E. Practical asymmetric approach to pyrrolidinones: efficient synthesis of (+)-preussin and (–)-AHPA. *J. Org. Chem.* **1998**, *63*, 4660–4663.
- [23] Krasinski, A.; Gruza, H.; Jurczak, J. Efficient stereoselective synthesis of (2*S*,3*S*,5*R*)-(+)-preussin. *Heterocycles* **2001**, *54*, 581–584.
- [24] Lee, K.-Y.; Kim, Y.-H.; Oh, C.-Y.; Ham, W.-H. Facile and efficient total synthesis of (+)-preussin. *Org. Lett.* **2000**, *2*, 4041–4042.
- [25] McGrane, P. L.; Livinghouse, T. Synthetic applications of imidotitanium-alkyne [2+2] cycloadditions. A concise, stereo-

- controlled total synthesis of the antifungal agent (+)-preussin. *J. Am. Chem. Soc.* **1993**, *115*, 11485–11489.
- [26] Okue, M.; Watanabe, H.; Kitahara, T. A concise synthesis of (+)-preussin. *Tetrahedron* **2001**, *57*, 4107–4110.
- [27] Overhand, M.; Hecht, S. M. A concise synthesis of the antifungal agent (+)-preussin. *J. Org. Chem.* **1994**, *59*, 4721–4722.
- [28] Pak, C. S.; Lee, G. H. Total synthesis of (+)-preussin, a novel antifungal agent. *J. Org. Chem.* **1991**, *56*, 1128–1133.
- [29] Raghavan, S.; Rasheed, M. A. A novel and stereospecific synthesis of (+)-preussin. *Tetrahedron* **2003**, *59*, 10307–10312.
- [30] Schaumann, E.; Beier, C. An epoxide-based enantioselective synthesis of the antifungal antibiotic (+)-preussin. *Synthesis* **1997**, *11*, 1296–1300.
- [31] Shimazaki, M.; Okazaki, F.; Nakajima, F.; Ishikawa, T.; Ohta, A. Synthesis of (+)-preussin. *Heterocycles* **1993**, *36*, 1823–1836.
- [32] Verma, R.; Ghosh, S. K. A silicon controlled total synthesis of the antifungal agent (+)-preussin. *Chem. Commun.* **1997**, *17*, 1601–1602.
- [33] Yoda, H.; Yamazaki, H.; Takabe, K. A novel stereoselective synthesis of enantiomerically pure antifungal agent, (+)-preussin. *Tetrahedron Asymm.* **1996**, *7*, 373–374.
- [34] Arévalo-García, E. B.; Colmenares, J. C. A versatile synthesis of (+) deoxoprosopinine and (–) deoxoprosophylline. *Tetrahedron Lett.* **2008**, *49*, 6972–6973.
- [35] Alfaro, R.; Yuste, F.; Ortiz, B.; Sánchez-Obregón, R.; Ruano, J. L. G. γ -Amino vinyl sulfoxides in asymmetric synthesis. Synthesis of optically pure α -substituted β -amino nitriles. *Tetrahedron* **2009**, *65*, 357–363.
- [36] Datta, A.; Veeresa, G. A stereoselective route to hydroxyethylamine dipeptide isosteres. *J. Org. Chem.* **2000**, *65*, 7609–7611.
- [37] Spaltenstein, A.; Leban, J. J.; Huang, J. J.; Reinhardt, K. R.; Viveros, O. H.; Sigafos, J.; Crouch, R. Design and synthesis of novel protease inhibitors. Tripeptide α',β' -epoxyketones as nanomolar inactivators of the proteasome. *Tetrahedron Lett.* **1996**, *37*, 1343–1346.
- [38] Pais, G. C. G.; Maier, E. M. Efficient synthesis of the γ -amino- β -hydroxy acid subunit of hapalosin. *J. Org. Chem.* **1999**, *64*, 4551–4554.
- [39] Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. Regioselective, diastereoselective, and enantioselective lithiation-substitution sequences: reaction pathways and synthetic applications. *Acc. Chem. Res.* **1996**, *29*, 552–560.
- [40] Beak, P.; Lee, W. K. α -Lithioamine synthetic equivalents: syntheses of diastereoisomers from the Boc-piperidines. *J. Org. Chem.* **1990**, *55*, 2578–2580.
- [41] Beak, P.; Lee, W. K. α -Lithioamine synthetic equivalents: syntheses of diastereoisomers from Boc derivatives of cyclic amines. *J. Org. Chem.* **1993**, *58*, 1109–1117.
- [42] Wilkinson, T. J.; Stehle, N. W.; Beak, P. Enantioselective syntheses of 2-alkyl- and 2,6-dialkylpiperidine alkaloids: preparations of the hydrochlorides of (–)-coniine, (–)-solenopsin A, and (–)-dihydropinidine. *Org. Lett.* **2000**, *2*, 155–158.
- [43] Huang, P. Q.; Wu, T. J.; Ruan, Y. P. A flexible approach to (S)-5-alkyl tetramic acid derivatives: application to the asymmetric synthesis of (+)-preussin and protected (3S,4S)-AHPPA. *Org. Lett.* **2003**, *5*, 4341–4344.
- [44] Beaudoin, M.; Wolfe, J. P. A concise stereoselective synthesis of preussin, 3-epi-preussin and analogues. *Org. Lett.* **2006**, *8*, 2353–2356.
- [45] Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford, 1996.
- [46] Still, W. C.; Kahn, M.; Mitra, A. Rapid chromatographic techniques for preparative separation with moderate resolution. *J. Org. Chem.* **1978**, *43*, 2923–2925.