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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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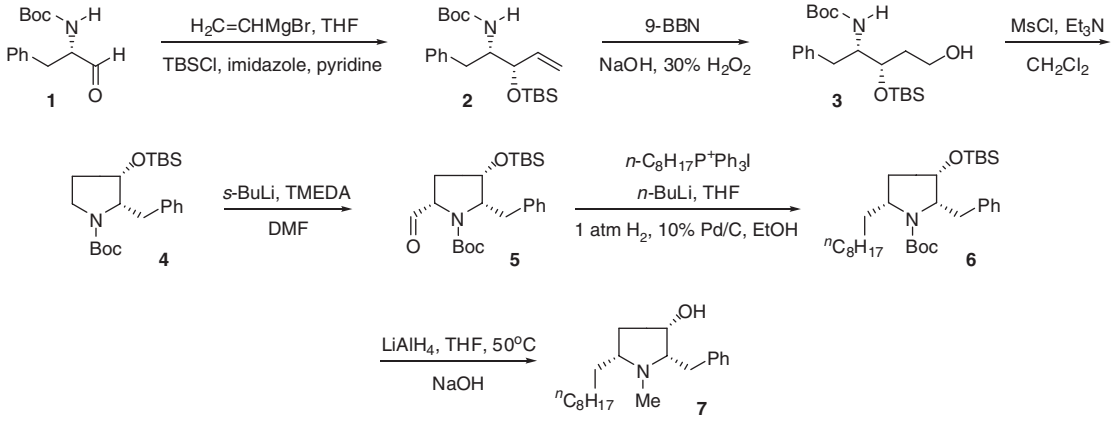
Introduction

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).

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.

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 S_N2 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 ($LiAlH_4$/NaOH) [44] of **6**, completing the synthesis of (+)-preussin (**7**), in 91% yield (Scheme 1). Its ^{1}H NMR and ^{13}C NMR spectra are virtually identical to literature data [14, 15, 24, 26, 27, 29]. Its specific optical rotation $[\alpha]_D^{25}$=+26.8° (*c* 1.1, $CHCl_3$) that is greater than the literature value $[\alpha]_D^{25}$=+22.0° (*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 F_{254} 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 (^{1}H 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; ^{1}H 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 $C_{22}H_{37}NO_3Si$: 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 0.803 g (78%), (diastereoselectivity, 93:7) of **5**, as a colorless oil; ^{1}H 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 $C_{23}H_{37}NO_4Si$: 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; ^{1}H 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 $C_{21}H_{35}NO$: C, 79.4; H, 11.1; N, 4.41. Found: C, 79.1; H, 10.9; N, 4.39.

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