DOI: 10.1002/ejoc.200500833

A Concise Total Synthesis of Antifungal Antibiotic (+)-Preussin

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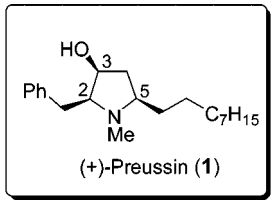
Keywords: Preussin / Asymmetric synthesis / Allylation / Asymmetric nitro-aldol / Binaphthol-derived catalysts

A short synthesis of the pharmacologically important natural product (+)-preussin is described. Two asymmetric C–C bond-formation reactions mediated by binaphthol-derived asymmetric catalysts have been applied to control the stereochemistry of its three stereocenters.

Introduction

In 1988 researchers at Merck Sharp & Dohme isolated (+)-preussin (L-657, 398) (**1**), a pyrrolidine alkaloid, from the fermentation broth of *Aspregillius ostraceus* (ATCC 29947) and subsequently from that of *Preussia* sp.[1] In preliminary biological studies (+)-preussin was shown to inhibit growth of the bacteria *Candida* and filamentous fungi, including *Trichophyton menta* and *Microsporum canis*.[2] Later on, Yoshida and co-workers rediscovered (+)-preussin as a selective inhibitor of cell growth of the fission yeast *ts* mutants defective on *cdc*2-regulatory genes.[3] Detailed biological studies by Muller and co-workers revealed that (+)-preussin induces apoptosis in human tumor cells.[4] It was also found in vitro to be a potent inhibitor of cyclin E kinase (CDK2-cyclin E) with a 50% inhibitory concentration of around 500 nM.



(+)-Preussin (**1**)

(+)-Preussin inhibits cell-cycle progression into the S phase. Remarkably, the induction of apoptosis is not blocked by a high level of B cell lymphoma-2 (Bcl-2), which usually confers resistance to chemotherapeutic agents. More recent reports disclosed that (+)-preussin inhibits programed-1 ribosomal frameshifting.[5]

In view of these observations, it has become clear that it is imperative to provide synthetic access to this compound to deconvolute its biological activity.

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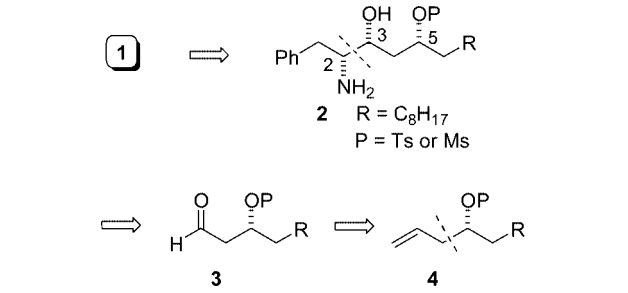
Despite a plethora of syntheses,[6] interest in the synthesis of (+)-preussin remains undiminished. The development of methods with enough flexibility to allow the construction of non-natural analogs continues to be an important topic, particularly with a view to investigating structure–activity relationships.

Investigations in our laboratory over the past few years have demonstrated the utility of nitroaliphatics in the syntheses of pharmacologically important natural products.[7a–7e] In this context we report here a total synthesis of **1** by a route that has inherent flexibility enabling access to analogs with various substituents as well as stereochemistry at the C-2 and C-5 atoms.

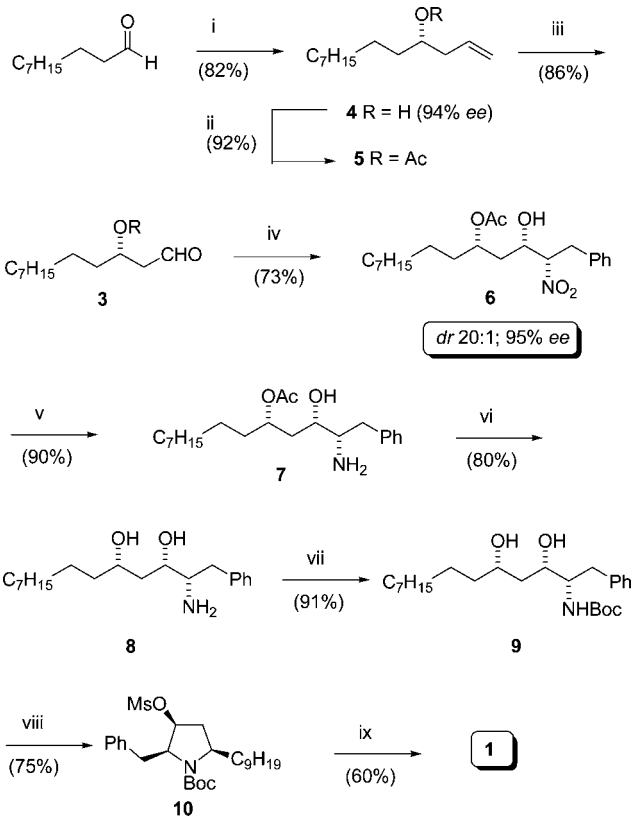
Results and Discussions

Recently we recorded excellent stereoselectivity during the synthesis of (+)-boronolide[7e] by an asymmetric nitro-aldol reaction of an α-hydroxy aldehyde catalyzed by a La-BINOL complex. This result encouraged us to explore the synthesis of **1**. In formulating a synthetic route to **1** (Scheme 1), the displacement of an activated alcohol moiety (tosylate, mesylate or triflate) by an amine appeared to be the most convenient route for the construction of the 2,5-disubstituted pyrrolidine core. We contemplated that the stereochemistry at the C-2 and C-3 positions could be secured by applying the asymmetric nitro-aldol reaction. To install the stereochemistry at the C-5 position, we relied on asymmetric allylation.

The present synthesis (Scheme 2) was initiated by employing the catalytic asymmetric allylstannation protocol developed by Keck and co-workers.[8] In the presence of a catalytic system comprising of 1 equiv. of (*S*)-BINOL, 1 equiv. of Ti(O-*i*Pr)$_4$ and 4-Å molecular sieves, which had been premixed at reflux temperature in CH_2Cl_2, the reaction of *n*-decanal and allyltributylstannane provided the homoallylic alcohol **4**[9a] in 82% yield and 94% *ee*[10] {$[\alpha]_D^{20}$ = –13.2 (*c* = 1.1, CH_2Cl_2); ref.[9b]: $[\alpha]_D^{20}$ = –10.4 (*c* = 6.7, C_6H_6)}.



Scheme 1.



Scheme 2. Reagents and conditions: (i) (*S*)-BINOL, Ti(O-*i*Pr)$_4$, allyltributylstannane, CH_2Cl_2, –78 to –20 °C, 36 h; (ii) acetic anhydride, iodine, room temp., 10 min; (iii) OsO_4, 2,6-lutidine, $NaIO_4$, dioxane/H_2O, room temp., 30 min; (iv) 2-phenyl-1-nitroethane, La-(*R*)-BINOL complex, THF, –50 °C, 60 h; (v) 10% Pd/C, H_2 (1 atm.), MeOH, room temp., 3 h; (vi) 5% aq. HCl, room temp., 2 h; (vii) $(Boc)_2O$, sat. $NaHCO_3$ soln. EtOAc, room temp., 3 h; (viii) MsCl, Et_3N, CH_2Cl_2, 0 °C to room temp., 6 h; (ix) $LiAlH_4$, THF, reflux, 8 h.

Acetylation of the hydroxy function with acetic anhydride catalyzed by iodine[11] followed by oxidative cleavage of the olefinic bond using OsO_4 and $NaIO_4$ in the presence of 2,6-lutidine in dioxane/water[12] furnished the corresponding aldehyde **3**. This aldehyde without further purification was subjected to Shibasaki's asymmetric nitro-aldol reaction[13] with 2-phenyl-1-nitroethane in the presence of the La-(*R*)-BINOL complex in THF at –50 °C to deliver the nitro alcohol **6** in 73% yield with a satisfactory diastereoselectivity (diastereomeric ratio = 20:1, as determined by ^{1}H NMR spectroscopy). Preparative TLC (9% ethyl acetate in hexane) allowed the mixture to be separated and the diastereomerically pure **6** (95% *ee*) was used for the rest of the synthesis.

The catalytic hydrogenation of **6** with 10% Pd/C in MeOH at 1 atm provided the corresponding amino alcohol **7** in 90% yield. Hydrolytic removal of the acetate group with 5% aqueous HCl led to the amino diol **8**. Boc-protection of the amino group followed by exposure to methanesulfonyl chloride in the presence of Et_3N in THF, directly afforded the pyrrolidine derivative **10**. Finally, treatment of *N*-Boc-pyrrolidine **10** with LAH under reported conditions[14] furnished the target molecule. The physical and spectral properties of our synthetic material closely matched those published for the natural product.[1]

Thus, we have achieved a remarkably simple and very economical synthesis of the target molecule. The noteworthy feature of this synthesis is that it is an exception to most other chiral-auxillary-based approaches[6] with excellent stereocontrol resulting from Shibasaki's nitro-aldol reaction of a chiral β-hydroxy aldehyde.[13]

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded using a Bruker DPX-300 NMR machine. IR spectra were recorded with a Perkin–Elmer 1640 FT-IR spectrometer. Optical rotations were measured with a Perkin–Elmer 343 polarimeter. Elemental analyses were carried out using a Perkin–Elmer series II CSNS/O Model 2400 analyzer. Mass spectra were recorded with a Bruker Daltonic Data Analysis 2.0 spectrometer. Column chromatography was performed with Merck silica gel (60–120 mesh) and preparative TLC was carried out using plates prepared with Merck silica gel G. Moisture-sensitive reactions were conducted under nitrogen. Diethyl ether and THF were distilled from benzophenone ketyl prior to use. Dichloromethane was distilled from P_2O_5 and stored over molecular sieves. All solvents were distilled at their boiling points and other commercially available reagents were used as received unless otherwise noted. PE: petroleum ether.

(4*S*)-Tridec-1-en-4-ol (4): A mixture of (*S*)-BINOL (0.24 g, 0.84 mmol) and Ti(O-*i*Pr)$_4$ (0.24 g, 0.84 mmol) in CH_2Cl_2 (15 mL) in presence of 4-Å molecular sieves (2.4 g) was stirred under reflux. After 1 h the reaction mixture was cooled to room temperature, *n*-decanal (1.3 g, 8.3 mmol) was added and the resulting mixture was stirred for 10 min. The reaction mixture was then cooled to –78 °C and allyltributylstannane (3.02 g, 9.1 mmol) was then added and the stirring was continued at –20 °C for 36 h. Saturated $NaHCO_3$ solution (1.5 mL) was added to quench the reaction and then the mixture was stirred for an additional 30 min and extracted with CH_2Cl_2 (30 mL). The extract was washed with water (10 mL), dried (Na_2SO_4), the solvent evaporated and the residue purified by chromatography on SiO_2 (EtOAc/PE, 1:10) to give 1.35 g (6.8 mmol, 82%, 94% *ee*) of **4** as a clear liquid. $[\alpha]_D^{20}$ = –12.3 (*c* = 0.9, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3410 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 6.7 Hz, 3 H), 1.30–1.62 (m, 16 H), 2.06–2.13 (m, 2 H), 2.35 (br. s, 1 H), 3.54–3.61 (m, 1 H), 5.05 (dd, *J* = 16.1, 11.3 Hz, 1 H), 5.13 (dd, *J* = 16.1, 1.5 Hz, 1 H), 5.74–5.77 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.07, 22.81, 25.07, 28.94, 29.5, 32.0, 36.8, 40.6, 71.0, 116.7, 135.2 ppm. MS (ESI): *m*/*z* = 221.0 [M + Na]$^+$. $C_{13}H_{26}O$ (198.4): calcd. C, 78.72, H 13.20; found C 78.80, H 13.14.

(1*S*)-1-Allyldecyl Acetate (5): Iodine (75 mg, 0.59 mmol) was added to a stirred solution of homoallylic alcohol **4** (1.3 g, 6.6 mmol) and acetic anhydride (1.35 g, 13.2 mmol) and the reaction mixture was then stirred at room temperature for 10 min. 10% $Na_2S_2O_3$ solution (10 mL) was added and the mixture was extracted with diethyl ether (60 mL) and then washed successively with 10% $NaHCO_3$ solution (3×10 mL) and H_2O (20 mL). The organic phase was dried (Na_2SO_4), the solvent evaporated and the residue was purified by chromatography on SiO_2 (EtOAc/PE, 1:20) to give 1.46 g (6.08 mmol, 92%) of **5** as a clear liquid. $[\alpha]_D^{20}$ = –13.2 (*c* = 1.1, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 1734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 6.7 Hz, 3 H), 1.30–1.61 (m, 16 H), 2.02–2.10 (m, 2 H), 2.13 (s, 3 H), 4.88–4.92 (m, 1 H), 5.05 (dd, *J* = 16.1, 11.3 Hz, 1 H), 5.14 (dd, *J* = 16.1, 1.5 Hz, 1 H), 5.74–5.79 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.07, 20.08, 22.8, 25.0, 28.6, 29.6, 32.1, 36.7, 74.0, 116.7, 135.2 ppm. MS (ESI): *m*/*z* = 240.3 $[M]^+$. $C_{15}H_{28}O_2$ (240.4): calcd. C 74.95, H 11.74; found C 75.01, H 11.69.

(3*S*)-3-Acetoxydodecanal (3): 2,6-Lutidine (1.28 g, 11.9 mmol), OsO_4 (4% solution in *i*-PrOH, 0.012 mL) and $NaIO_4$ (5.1 g, 23.9 mmol) were added to a solution of the acetate **5** (1.46 g, 6.08 mmol) in dioxane/H_2O (60 mL, 3:1). The mixture was stirred at room temperature and upon completion H_2O (30 mL) was added and the solution extracted with CH_2Cl_2 (3×20 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated to give 1.27 g (5.25 mmol, 86%) of **3** as a pale yellow liquid which, without further purification, was applied in the next step.

(1*S*,2*S*,3*S*)-1-(2-Hydroxy-3-nitro-4-phenylbutyl)decyl Acetate (6): The La-(*R*)-BINOL catalyst (3.7 mL) was gradually added using a syringe to a mixture of aldehyde **3** (1.25 g, 5.2 mmol) and 2-phenyl-1-nitroethane (1.6 g, 10.6 mmol) in THF (15 mL) cooled to –50 °C. The reaction mixture was stirred at –50 °C for 60 h and then quenched by the addition of 1 N HCl (1 mL). The reaction mixture was then extracted with diethyl ether (30 mL), washed with a 10% $NaHCO_3$ solution (3×10 mL) and then with H_2O (15 mL). The organic phase was dried (Na_2SO_4), the solvent evaporated and the residue purified by preparative TLC (9% EtOAc in PE) to give 1.5 g (3.8 mmol, 73%, 95% *ee*) of **6** as a pale yellow oil. $[\alpha]_D^{20}$ = –11.7 (*c* = 0.6, CH_2Cl_2). IR ($CHCl_3$): $\tilde{\nu}$ = 3410, 1734, 1557 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 6.7 Hz, 3 H), 1.22–1.34 (m, 14 H), 1.42–1.46 (br. s, 2 H), 2.06 (m, 2 H), 2.16 (s, 3 H), 2.45 (br. s, 1 H), 2.81 (d, *J* = 7.3 Hz, 2 H), 3.28 (dt, *J* = 3.2, 4.6 Hz, 1 H), 4.77 (m, 1 H), 4.84 (dt, *J* = 3.4, 4.6 Hz, 1 H), 7.11–7.24 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.07, 20.8, 22.7, 25.0, 28.8, 29.5, 29.6, 32.0, 33.7, 39.5, 41.0, 54.2, 72.7, 74.2, 126.8, 128.1, 128.8, 138.7 ppm. MS (ESI): *m*/*z* = 393.1 $[M]^+$. $C_{22}H_{35}NO_5$ (393.5): calcd. C 67.15, H 8.96, N 3.56; found C 67.23, H 9.05, N 3.64.

(1*S*,2*S*,3*S*)-1-(3-Amino-2-hydroxy-4-phenylbutyl)decyl Acetate (7): A mixture of the nitro alcohol **6** (1.45 g, 3.7 mmol) and 10% Pd/C (0.3 g) in anhydrous MeOH (40 mL) was stirred vigorously under hydrogen for 3 h. The reaction mixture was then filtered, the solvent removed and the residue purified by chromatography on SiO_2 (EtOAc/PE, 1:5) to give 1.2 g (3.33 mmol, 90%) of **7** as a clear liquid. $[\alpha]_D^{20}$ = –11.7 (*c* = 0.6, CH_2Cl_2). IR ($CHCl_3$): $\tilde{\nu}$ = 3410, 1734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 6.7 Hz, 3 H), 1.19–1.34 (br. s, 14 H), 1.42–1.50 (br. s, 2 H), 2.06–2.13 (m, 2 H), 2.16 (s, 3 H), 2.70 (br. s, 2 H), 2.84 (d, *J* = 7.3 Hz, 2 H), 2.96–3.03 (m, 1 H), 3.22 (m, 1 H), 4.77–4.81 (m, 1 H), 7.10–7.24 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 20.9, 22.8, 25.1, 28.8, 29.5, 29.6, 32.0, 33.7, 38.5, 41.4, 55.0, 71.7, 126.9, 127.9, 128.8, 141.0 ppm. MS (ESI): *m*/*z* = 363.0 $[M]^+$. $C_{22}H_{37}NO_3$ (363.5): calcd. C 72.69, H 10.26, N 3.85; found C 72.76, H 10.33, N 3.91.

(2*S*,3*S*,5*S*)-2-Amino-1-phenyltetradecane-3,5-diol (8): The amino alcohol **7** (0.9 g, 2.47 mmol) was stirred with 5% aqueous HCl (2 mL) at room temperature for 2 h. The reaction mixture was then extracted with Et_2O (20 mL), washed with 20% $NaHCO_3$ solution and then with water. The organic phase was then dried (Na_2SO_4). The solvent was evaporated and the residue purified by chromatography on SiO_2 (EtOAc/PE, 1:3) to give 0.636 g (1.98 mmol, 80%) of the amino diol **8** as a clear liquid. $[\alpha]_D^{20}$ = –11.7 (*c* = 0.6, CH_2Cl_2). IR ($CHCl_3$): $\tilde{\nu}$ = 3410, 3300 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 6.7 Hz, 3 H), 1.20–1.33 (br. s, 14 H), 1.48–1.50 (br. s, 2 H), 2.07–2.15 (m, 2 H), 2.68 (br. s, 2 H), 2.81 (d, *J* = 7.3 Hz, 2 H), 2.95–3.07 (m, 1 H), 3.22–3.28 (m, 1 H), 3.73–3.80 (m, 1 H), 7.10–7.24 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 21.9, 25.8, 28.7, 29.5, 29.6, 36.9, 38.1, 40.8, 54.5, 72.1, 126.8, 128.1, 128.9, 141.1 ppm. MS (ESI): *m*/*z* = 344.1 $[M + Na]^+$. $C_{20}H_{35}NO_2$ (321.5): calcd. C 74.72, H 10.97, N 4.36; found C 74.80, H 10.88, N 4.30.

***tert*-Butyl (1*S*,2*S*,4*S*)-(1-Benzyl-2,4-dihydroxytridecyl)carbamate (9):** A saturated $NaHCO_3$ solution (10 mL) followed by $(Boc)_2O$ (0.37 g, 1.72 mmol) were added to a well stirred solution of amino diol **8** (0.59 g, 1.72 mmol) in AcOEt (10 mL) and the resulting mixture was continued to be stirred at room temperature. After completion, the layers were separated and the organic phase dried (Na_2SO_4), the solvent evaporated and the residue purified by chromatography on SiO_2 (EtOAc/PE, 1:15) to give 0.66 g (1.57 mmol, 91%) of **9** as a clear liquid. $[\alpha]_D^{20}$ = –13.2 (*c* = 1.1, CH_2Cl_2). IR ($CHCl_3$): $\tilde{\nu}$ = 3410, 3300, 1734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.7 Hz, 3 H), 1.18–1.30 (br. s, 14 H), 1.39 (s, 9 H), 1.46–1.48 (s, 2 H), 2.07–2.13 (m, 2 H), 2.81 (d, *J* = 7.3 Hz, 2 H), 3.23 (dt, *J* = 3.1, 4.6 Hz, 1 H), 3.73–3.78 (m, 1 H), 3.98 (dt, *J* = 3.2, 4.8 Hz, 1 H), 6.27 (br. s, 1 H), 7.19–7.28 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.9, 25.8, 28.2, 28.6, 29.5, 29.6, 36.7, 38.2, 41.1, 54.3, 70.6, 72.0, 79.7, 126.8, 128.1, 128.9, 140.9, 155.8 ppm. MS (ESI): *m*/*z* = 421.1 $[M]^+$. $C_{25}H_{43}NO_4$ (421.6): calcd. C 71.22, H 10.28, N 3.32; found C 71.28, H 10.34, N 3.27.

***tert*-Butyl (2*S*,3*S*,5*R*)-2-Benzyl-3-methylsulfonyloxy-5-nonylpyrrolidine-1-carboxylate (10):** Triethylamine (0.21 g, 2.12 mmol) and methanesulfonyl chloride (0.244 g, 2.13 mmol) were added to a well-stirred solution of *N*-Boc-protected diol **9** (0.6 g, 1.42 mmol) in dry CH_2Cl_2 (14 mL) cooled to 0 °C under N_2. The reaction mixture was then stirred for 4 h at room temperature. After completion, the reaction mixture was extracted with Et_2O and washed with water and brine. The organic phase was dried (Na_2SO_4), the solvent evaporated and the residue purified by chromatography on SiO_2 (EtOAc/PE, 1:10) to give 0.52 g (1.07 mmol, 75%) of **10** as a clear liquid. $[\alpha]_D^{20}$ = +11.2 (*c* = 1.1, CH_2Cl_2). IR ($CHCl_3$): $\tilde{\nu}$ = 3410, 3300, 1734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.7 Hz, 3 H), 1.19–1.28 (m, 14 H), 1.42 (s, 9 H), 1.46–1.53 (m, 2 H), 1.78–1.81 (m, 1 H), 1.96–2.00 (m, 1 H), 2.20–2.29 (m, 2 H), 2.66 (dd, *J* = 14.0, 6.7 Hz, 1 H), 2.98 (dd, *J* = 14.0, 6.1 Hz, 1 H), 3.15 (s, 3 H), 3.38 (ddd, *J* = 9.2, 5.5, 3.7 Hz, 1 H), 7.18–7.25 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 24.2, 25.0, 28.8, 29.5, 29.7, 33.1, 37.6, 54.2, 58.2, 71.1, 82.0, 126.9, 128.1, 137.9, 153.6 ppm. MS (ESI): *m*/*z* = 481.3 $[M]^+$. $C_{26}H_{43}NO_5S$ (481.2): calcd. C 64.83, H 9.00, N 2.91; found C 64.89, H 9.15, N 2.84.

(2*S*,3*S*,5*R*)-2-Benzyl-3-hydroxy-1-methyl-5-nonylpyrrolidine (1): $LiAlH_4$ (0.36 g, 9.3 mmol) was added to a solution of *N*-Boc-pyrrolidine **9** (0.45 g, 0.93 mmol) in THF (10 mL) and the mixture was refluxed. Upon completion the mixture was cooled to 0 °C and a saturated NH_4Cl solution (15 mL) was added slowly followed by water (30 mL). The resulting solution was then extracted with diethyl ether (3×50 mL), the combined extracts were washed with brine and dried (Na_2SO_4). The solvent was then evaporated and

the residue purified by chromatography on SiO_2 (EtOAc/PE, 1:3) to give 0.176 g (0.55 mmol, 60%) of preussin as a colored wax. $[\alpha]_D^{20}$ = +13.2 (*c* = 1.1, CH_2Cl_2); ref.[2b] $[\alpha]_D^{25}$ = +22.0 (*c* = 1.0 $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3410, 2910, 1490 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.9 Hz, 3 H), 1.20–1.28 (m, 14 H), 1.33 (dd, *J* = 14.0, 5.9 Hz, 1 H), 1.56–1.64 (m, 2 H), 1.76–1.81 (m, 1 H), 1.99–2.05 (m, 1 H), 2.19 (dt, *J* = 14.0, 6.1 Hz, 1 H), 2.25 (ddd, *J* = 10.8, 7.6, 5.1 Hz, 1 H), 3.19 (s, 3 H), 3.32 (ddd, *J* = 9.0, 5.2, 3.9 Hz, 1 H), 3.42 (dd, *J* = 13.1, 7.9 Hz, 1 H), 3.87 (m, 1 H), 7.17–7.25 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 23.0, 25.6, 28.9, 29.4, 29.7, 30.2, 32.0, 33.1, 34.6, 40.2, 47.8, 66.1, 71.1, 72.8, 126.9, 128.1, 132.9, 138.9 ppm. MS (ESI): *m*/*z* = 317.5 $[M]^+$. $C_{21}H_{35}NO$ (317.5): calcd. C 79.44, H 11.11, N 4.41; found C 79.52, H 11.17, N 4.37.

Acknowledgments

The authors are thankful to the Director, RRL Jorhat, for providing facilities. J.B. also thanks CSIR (New Delhi) for a Research Fellowship.

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Received: October 24, 2005
Published Online: February 3, 2006

