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Stereoselective Synthesis of the Antifungal Antibiotic (+)-Preussin

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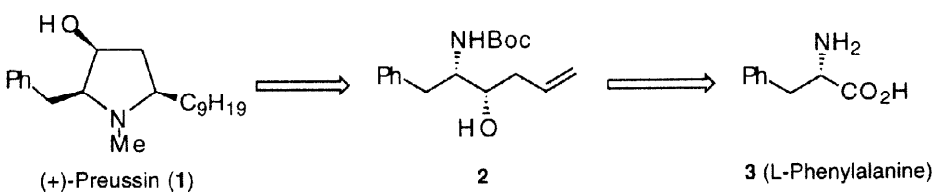
Abstract : A concise total synthesis of enantiopure (+)-preussin (**1**) from L-phenylalanine (**3**) is described. The key steps involve i) *syn*-selective formation of the 1,2-amino alcohol fragment **2**, *via* chelation controlled addition of allylmagnesium bromide to *N*-Boc-phenylalaninal, and ii) L-selectride® mediated stereoselective reduction of the ketone **8** to the alcohol derivative **9** with the required stereochemistry for final cyclization.

Keywords : antibiotic; chelation control; Grignard reaction; stereoselection.

The naturally occurring pyrrolidine alkaloid (+)-preussin **1** (L659, 398) was isolated from the fermentation broths of *Preussia sp.* and *Aspergillus ochraceus.*[1] Preussin and its acyl derivatives exhibit significant activity as broad-spectrum antibiotics against both filamentous fungi and yeasts. The impressive biological activity and interesting structural features have thus made preussin an attractive target for synthesis.[2]

Chelation controlled addition of Grignard reagents to chiral α-aminoaldehydes, resulting in *syn*-selective formation of 1,2-aminoalcohols,[3] has been shown to be a versatile tool for the asymmetric synthesis of this important structural motif of wide occurrence. Recent work from our laboratory has demonstrated the utility of the above approach for the synthesis of biologically important hydroxy aminoacids, statine,[4a] polyoxamic acid,[4b] and 3-hydroxyglutamic acid.[4c] In continuation of these studies we undertook a total synthesis of preussin, following the retrosynthetic strategy as shown in Scheme 1. We contemplated that, applying the aforementioned protocol, an advanced intermediate **2**, comprising the aminoalcohol functionalites of required stereochemistry as present in **1**, can be easily assembled by reacting L-*N*-Boc-phenylalaninal with allylmagnesium bromide. Subsequent transformations involving the alkene moiety would then lead to the title compound. Details of the studies thus initiated are described herein.



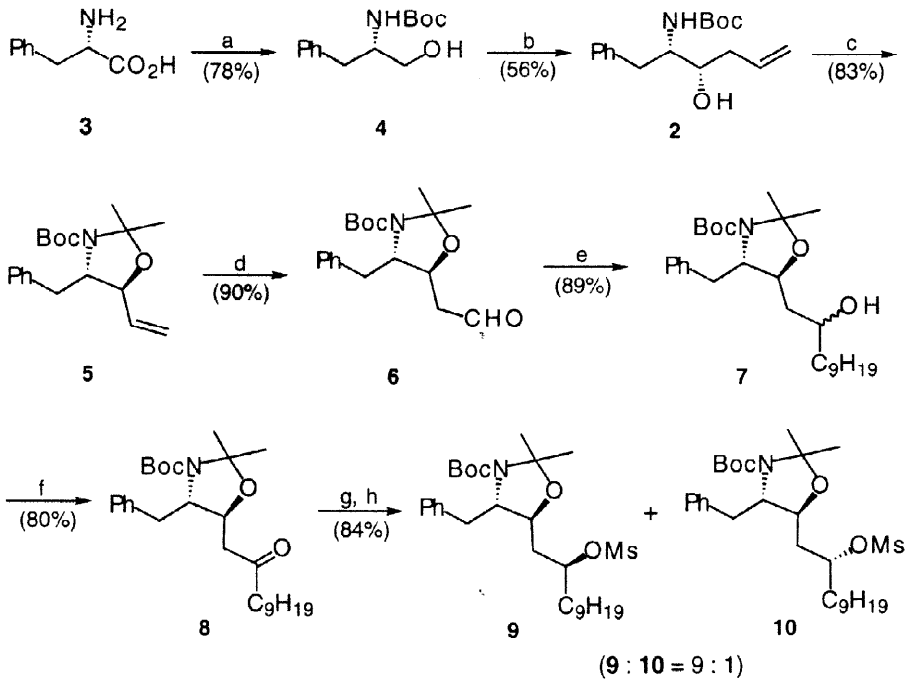
(+)-Preussin (**1**) **2** **3** (L-Phenylalanine)

Scheme 1

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00981-8

Results and Discussion

N-Boc-phenylalaninol (**4**) was prepared in a one-pot reaction by lithium aluminium hydride reduction and derivatization of L-phenylalanine **3** (Scheme 2). Swern oxidation of **4** followed by *in-situ* reaction of the resulting aldehyde with allylmagnesium bromide, following an established procedure,[3a] yielded the homoallylic alcohol **2** with good diastereoselection (6:1, diastereoisomers separated by column chromatography) in favour of the *syn* isomer,[5] which is in agreement with the reported observations.[3,4]

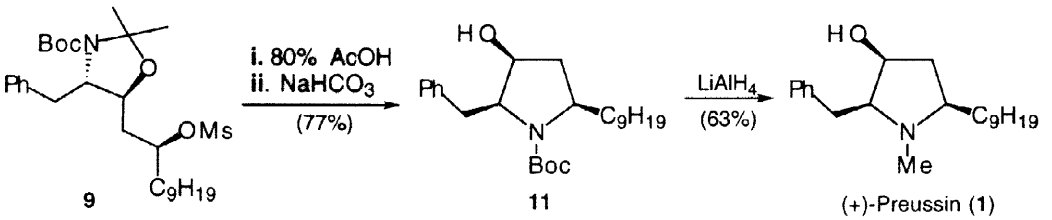


a. $LiAlH_4$ then Boc_2O. **b.** Swern oxidation then $H_2C{=}CH\text{-}CH_2MgBr$. **c.** $Me_2C(OMe)_2$, PPTS. **d.** OsO_4, NMO, then $NaIO_4$ (on silica gel). **e.** $H_{19}C_9MgBr$, Et_2O. **f.** 2-Iodoxybenzoic acid. **g.** L-Selectride (1M soln. in THF). **h.** MsCl, Et_3N.

Scheme 2

Having synthesized the pivotal amino alcohol intermediate, introduction of the nonyl side chain was next investigated. Acetonide protection of the amino alcohol functionality of **2** afforded the corresponding oxazolidine derivative **5.** Subsequent oxidative cleavage of the olefin to aldehyde **6** and its reaction with the Grignard reagent derived from 1-bromononane resulted in the corresponding alcohol **7** as an inseparable mixture of isomers (7:3, by HPLC) at the newly formed center. However, oxidation of this alcohol to its corresponding ketone **8**, followed by stereoselective reduction of the carbonyl group using L-selectride® (lithium tri-*sec* -butyl- borohydride) and subsequent mesylation of the hydroxy group thus formed, yielded the mesylates **9** and **10** in a 9:1 ratio of diastereoisomers which could be easily separated by column chromatography. The assigned stereochemistry for the isomers **9** and **10** was confirmed by the subsequent reactions. Thus, acetonide deprotection of the major product **9** under standard conditions directly afforded the pyrollidine derivative **11** (Scheme 3), a known precursor of (+)-preussin.[2g] Spectroscopic data and the specific rotation of **11**{$[\alpha]_D$ = -56.9 (c = 1.1, CH_2Cl_2): lit.[2g] $[\alpha]_D$ = -56.6 (c = 1.0, CH_2Cl_2)} were in good agreement with the literature reported values, which also conclusively proved the stereochemical assignments

for the mesylates **9** and **10**. Finally, treatment of the *N*-Boc-pyrrolidine **11** with lithium aluminium hydride under reported conditions[2g] completed the intended synthesis of (+)-preussin (**1**), the spectral data [2g] and the specific rotation of which {[α]$_D$ = +21.6 (c = 0.7, $CHCl_3$) : Natural **1** [1b] [α]$_D$ = +22.0 (c = 1.0, $CHCl_3$)} are in excellent agreement with the reported values.



Scheme 3

In conclusion, a concise synthesis of natural (+)-preussin was accomplished in ten steps (8.7% overall yield), starting from the readily available amino acid L-phenylalanine, following a simple and efficient reaction sequence. The synthesis demonstrates the utility of chelation controlled Grignard reactions on chiral α-amino aldehydes for the stereoselective formation of the *syn*-1,2-aminoalcohol unit. The strategy and the approach described can also be easily adapted to synthesize various C-1 and C-4 modified analogues of preussin. The above route thus offers a viable alternative to the existing methodologies for synthesizing this biologically important title compound and its modified analogues in search of improved activity.

Experimental Section

General. Reagents and solvents were obtained from commercial suppliers and used as received, unless otherwise noted. Moisture or air sensitive reactions were conducted under a nitrogen atmosphere in oven dried (120°C) glass apparatus. Diethyl ether and THF were distilled from sodium benzophenone ketyl prior to use. Toluene was dried over sodium, whereas dichloromethane and triethylamine were distilled from CaH_2 and stored over molecular sieves and anhydrous KOH respectively. All yields reported refer to isolated material judged to be homogeneous by tlc and NMR spectroscopy. Column chromatography was performed on silica gel 60 (60-120 mesh), using ethyl acetate/hexane mixture as eluent, unless specified otherwise. The NMR spectra were recorded in $CDCl_3$ on a 200 MHz spectrometer with TMS as the internal standard. Elemental analyses were carried out in the Indian Association for the Cultivation of Science, Jadavpur, Calcutta.

(*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-phenyl-1-propanol (4). L-Phenylalanine (6.3 g, 38.13 mmol) was added in small portions to a suspension of lithium aluminium hydride (2.89 g, 76.26 mmol) in refluxing THF (125 mL) and refluxing continued for another 7 h. The reaction mixture was then cooled to 0°C (ice-bath) and excess reagent quenched by careful addition of an aqueous 15% NaOH solution (3 mL) and water (9 mL). After stirring at room temperature for 10 min, a solution of di-*tert*- butyl dicarbonate (8.31 g, 38.13 mmol) in CH_2Cl_2 (40 mL) was added to the mixture and stirred at 60°C for 6 h, cooled to room temperature, filtered through a pad of anhydrous Na_2SO_4 and the filtrate concentrated under vacuum. Purification of the oily residue by column chromatography (ethyl acetate/hexane = 1/3) afforded the pure *N*-Boc-amino alcohol **4** (6.72 g, 70%) as a white solid, similar in all respects to the commercially available sample (Aldrich Chemical Company, Inc.).

(4*S*, 5*S*)-5-[(*tert*-Butoxycarbonyl)amino]-4-hydroxy-6-phenyl-1-hexene (2). To a stirred solution of oxalyl chloride (2.4 mL, 27.88 mmol) and CH_2Cl_2 (50 mL) at -78°C under nitrogen atmosphere

was added DMSO (2.26 mL, 31.86 mmol) dropwise. After stirring for 30 min, a solution of the amino alcohol **4** (4 g, 15.93 mmol) in CH_2Cl_2 (100 mL) was added over 30 min. The mixture was warmed to -35°C and stirred for 30 min at this temperature, followed by addition of diisopropylethyl amine (19 mL, 111.55 mmol) over 5 min. The reaction mixture was then warmed to 0°C in 15 min and transferred through a cannula to a room temperature solution of allylmagnesium bromide [prepared from Mg (5 g, 0.2 mol) and allyl bromide (10.1 mL, 0.12 mol) in ether (100 mL)] over 30 min. After stirring for 2 h at room temperature the reaction mixture was poured into aqueous saturated NH_4Cl solution (100 mL) and acidified to pH 4 by adding 10% aqueous HCl solution. The organic layer was separated, aqeous layer extracted with $CHCl_3$ (3x100 mL) and the combined organic extracts were washed sequentially with water and brine. After drying over Na_2SO_4, solvent was removed under vacuum and the residue purified by flash column chromatography (ethyl acetate/hexane = 1/12) to yield the amino alcohol **2** (2.6 g, 56%) as a viscous semi solid: $[\alpha]_D$ = -26.4 (c=1, $CHCl_3$); IR (neat) 3443, 3401, 1690 cm^{-1}; ^1H NMR δ 1.39 (br s, 9H), 2.15-2.3 (m, 2H), 2.8-2.92 (m, 2H), 3.49-3.61 (m, 1H), 3.64-3.80 (m, 1H), 4.8 (d, *J* = 8.8 Hz, 1H), 5.1 (br d, *J* = 13.3 Hz, 2H), 5.62-5.85 (m, 1H), 7.1-7.35 (m, 5H); ^{13}C NMR δ 178.3, 156.0, 138.3, 134.4, 129.3, 128.3, 126.2, 118.2, 79.2, 70.1, 55.1, 39.2, 38.7, 28.2 ; HRMS (CI) calcd. for $C_{17}H_{26}NO_3$ 292.1912 (MH^+); found 292.1892; Anal. Calcd for $C_{17}H_{25}NO_3$ (291.4): C, 70.07; H, 8.65; N, 4.81. Found : C, 69.81; H, 8.28; N, 4.78.

(4*S*,5*S*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-benzyl-5-(2-propenyl)-1,3-oxazolidine (5) A solution of **2** (3 g, 10.3 mmol), 2,2-dimethoxypropane (19.5 mL, 123.7 mmol) and a catalytic amount of pyridinium p-toluenesulfonate (50 mg) in toluene (35 mL) was stirred at 80°C for 4 h. Removal of solvent under vacuum and purification of the residue by column chromatography (ethyl acetate/hexane = 1/19) afforded the pure oxazolidine **5** (2.83 g, 83%) as a light yellow viscous liquid: $[\alpha]_D$ = -10.3 (c = 1.1, $CHCl_3$); IR (neat) 1698 cm^{-1}; ^1H NMR δ 1.46 (s, 3H), 1.54 (br s, 12H), 1.97-2.18 (m, 2H), 2.18 (m, 2H), 2.60-2.89 (m, 1H), 3.23 (dd, *J* = 4.5 and 12.7 Hz, 1H), 3.68-3.86 (m, 1H), 3.9 (dd, *J* = 5.3 and 11.2 Hz,1H), 4.8-5.0 (m, 2H), 5.42-5.68 (m, 1H), 7.1-7.35 (m, 5H); ^{13}C NMR δ 170.2, 137.7, 133.7, 129.7, 129.3, 128.4, 126.4, 117.4, 79.7, 77.8, 62.6, 39.2, 39.1, 37.5, 28.5, 26.9 ; HRMS (FAB+) calcd. for $C_{20}H_{30}NO_3$ 332.2225 (MH^+); found 332.2233; Anal. Calcd for $C_{20}H_{29}NO_3$ (331.46): C, 72.47; H, 8.82; N, 4.23. Found : C, 72.51; H, 8.57; N, 4.51.

(4*S*,5*S*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-benzyl-5-formylmethyl-1,3-oxazolidine (6). To a stirred solution of the allyl oxazolidine **5** (1.35 g, 4.08 mmol) and N-methylmorpholine-N-oxide (2.38 g, 20.35 mmol) in acetone (10 mL) and water (2 mL) at room temperature was added a catalytic amount of OsO_4 solution in toluene (5% solution, 5 mol%). After stirring for 8 h, a saturated aqueous solution of Na_2SO_3 (5 mL) was added to the mixture and extracted with ethylacetate (3x50 mL). The combined extracts were dried over Na_2SO_4 and solvent removed thoroughly under vacuum affording the crude dihydroxylated compound (1.5 g) which was dissolved in CH_2Cl_2 (20 mL) and added in one lot to a vigourously stirred suspension of $NaIO_4$ supported in silica gel (8 g, 20% $NaIO_4$)[6] in CH_2Cl_2 (20 mL) maintained at 0°C. After stirring at the same temperature for 1 h, the solid was removed by filtration, washed with $CHCl_3$ (3x25 mL), combined filtrate concentrated under vacuum and the residue purified by column chromatography (ethyl acetate/hexane = 1/6) yielding the pure aldehyde **6** (1.23 g, 90% two steps) as a viscous liquid: $[\alpha]_D$ = -3.4 (c = 1, $CHCl_3$); IR (neat) 1725, 1694 cm^{-1}; ^1H NMR δ 1.42 (br s, 15H), 2.13 (dd, *J* = 5.4 and 12.1 Hz, 1H), 2.45 (m, 1H), 2.73 (br s, 1H), 3.32 (br d, *J* = 12.4 Hz,1H), 3.37 (br s, 1H), 4.40 (m, 1H), 7.22 (m, 5H), 9.64 (br s, 1H); MS (FAB+) 334 (MH^+); Anal. Calcd for $C_{19}H_{27}NO_4$ (333.43): C, 68.44; H, 8.16; N, 4.20. Found : C, 68.79; H, 8.03; N, 4.44.

(4*S*,5*S*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-benzyl-5-(2-hydroxyundecyl)-1,3-oxazolidine (7). To an ice-cooled solution of nonylmagnesium bromide (5.93 mmol) [prepared from Mg (0.29 g, 11.9 mmol) and nonyl bromide (1.13 mL, 5.93 mmol)] in ether (50 mL) was added dropwise over 15 min, a solution of the aldehyde **6** (1g, 2.98 mmol) in ether (15 mL) under nitrogen atmosphere. The mixture was then stirred at room temperature for 4 h and poured into a saturated aqueous NH_4Cl solution (50 mL). The organic layer was separated, aqueous layer extracted with ethylacetate (2x50 mL), combined extracts washed with brine, dried (Na_2SO_4) and solvent removed under vacuum. The residue on column chromatography (ethyl acetate/hexane = 1/7) afforded **7** (1.09 g, 89%) as a colourless oil: IR (neat) 3477, 1700 cm^{-1}; ^1H NMR δ 0.85 (br t, J = 6.8 Hz, 3H), 1.2 (br s, 18H), 1.34-1.61 (m, 13H), 1.73-1.92 (m, 2H), 2.61-2.9 (br s, 1H), 3.18-3.22 (m, 1H), 3.42-3.82 (m, 3H), 3.95-4.18 (m, 1H), 7.1- 7.32 (m, 5H); MS (FAB+) 462 (MH^+); Anal. Calcd for $C_{28}H_{47}NO_4$ (461.69): C, 72.84; H, 10.26; N, 3.03. Found : C, 73.02; H, 9.97; N, 3.28.

(4*S*,5*S*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-benzyl-5-(2-oxoundecyl)-1,3-oxazolidine (8). To a room temperature solution of 2-iodoxybenzoic acid (1.21 g, 4.33 mmol) in DMSO (6 mL) was added a solution of the secondary alcohol **7** (1g, 2.16 mmol) in THF (10 mL) and stirred for 2 h. The reaction was quenched by addition of water (10 mL), the precipitated solid was filtered, filtrate extracted with ether (3x50 mL) and the combined extracts dried over Na_2SO_4. Evaporation of solvent and purification of the crude product by column chromatography (ethyl acetate/hexane = 1/8) afforded the pure ketone **8** (796 mg, 80%) as a colorless oily liquid: $[\alpha]_D$ = -2.3 (c = 1.1, $CHCl_3$); IR (neat) 1693 (br) cm^{-1}; ^1H NMR δ 0.86 (br t, J = 6.1 Hz, 3H), 1.2 (br s, 14H), 1.31-1.62 (m, 15H), 2.1 (dd,J = 4.25 and 10.6 Hz, 1H), 2.2 (br t,J = 6.8 Hz, 2H), 2.51 (dd,J = 7.6 and 8.9 Hz, 1H), 2.63-2.84 (m, 1H), 3.25 (br d, J = 13.1 Hz,1H), 3.66-3.78 (m, 1H), 4.28-4.37 (m, 1H), 7.1-7.3 (m, 5H); ^{13}C NMR δ 207.9, 168.2, 137.3, 129.5, 128.4, 126.5, 80.0, 63.1, 47.8, 43.2, 31.7, 29.2, 28.4, 26.6, 23.3, 22.5; 14.0; MS (FAB+) 459 (M^+); Anal. Calcd for $C_{28}H_{45}NO_4$ (459.68): C, 73.16; H, 9.87; N, 3.05. Found : C, 73.07; H, 9.73; N, 3.15.

(4*S*, 5*S*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-benzyl-5-[(2*S*)-2-(methanesulfonyloxy)-undecyl]-1,3-oxazolidine (9) and (4*S*, 5*S*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-benzyl-5-[(2*R*)-2-(methanesulfonyloxy)undecyl]-1,3-oxazolidine (10). To a solution of the ketone **8** (500 mg, 1.08 mmol) in THF (10 mL) at - 78°C was added dropwise L-selectride® (1 M soln. in THF, 2.16 mL, 2.16 mmol) and stirred for 45 min. The reaction was quenched by sequential addition of MeOH (1.5 mL) and aqueous 10% NaOH (2mL). After stirring at room temperature for 10 min, the mixture was extracted with ether (3x40 mL), combined extracts washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4) and solvent was removed thoroughly under vacuum. The crude alcohol (500 mg) thus obtained was dissolved in CH_2Cl_2 (15 mL), cooled to 0°C (ice-bath) and a catalytic amount of DMAP (20 mg) and Et_3N (1.5 mL, 10.8 mmol) added to it followed by dropwise addition of methanesulfonyl chloride (0.42 mL, 5.42 mmol). After stirring for 15 min at 0°C and 14 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed sequentially with water, saturated aqueous $NaHCO_3$ and brine. Drying (Na_2SO_4), removal of solvent and column chromatography (ethyl acetate/hexane = 1/9 ---> 1/7) of the crude mixture yielded the pure mesylates **9** (452 mg, 77%) and **10** (43 mg, 7%) as colorless liquids : **9** (major isomer): $[\alpha]_D$ = -12.1 (c = 1, $CHCl_3$); IR (neat) 1697, 1161 cm^{-1}; ^1H NMR δ 0.9 (br t, J = 6.4 Hz, 3H), 1.28 (br s, 14H), 1.35-1.71 (m, 18H), 1.80-1.97 (m, 1H), 2.63-2.71 (m, 1H), 2.88 (s, 3H), 3.29 (br d, J = 11.3 Hz,1H), 3.69-3.84 (m, 1H), 3.88-4.0 (m, 1H), 4.59-4.75 (m, 1H), 7.09-7.36 (m, 5H); MS (FAB+) 541 (M^+) . **10** (minor isomer): $[\alpha]_D$ = -3.81 (c = 1.1, $CHCl_3$); ^1H NMR δ 0.85 (br t, J = 6.5 Hz, 3H), 1.20 (br s, 14H), 1.35-

1.68 (m, 18H), 1.80-2.01 (m, 1H), 2.72 (br s, 1H), 2.86 (s, 3H), 3.07-3.28 (m, 1H), 3.61-3.80 (m, 1H), 3.84-4.02 (m, 1H), 4.53-4.72 (m, 1H), 7.06-7.3 (m, 5H). The above mesylates were found to decompose on storage and were used immediately for the next reaction.

(2*S*, 3*S*, 5*R*)-2-Benzyl-1-(*tert*-butoxycarbonyl)-5-nonyl-3-pyrrolidinol (11). A solution of **9** (400 mg, 0.74 mmol) in 80% aqueous AcOH (30 mL) was stirred at room temperature for 24 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL), cooled to 0^0C and neutralized to pH 7 by adding solid $NaHCO_3$ in small portions. The layers were then separated, aqueous layer extracted with CH_2Cl_2 (2 x 25 mL) and the combined organic extracts were washed sequentially with water and brine. After drying over Na_2SO_4 and removal of solvent under vacuum, the residue was column chromatographed (ethyl acetate/hexane = 1/4) to afford the pure product **11** (230 mg, 77%) as a colorless liquid, the spectral and analytical data of which are in good agreement with the reported values.[2g]

(2*S*, 3*S*, 5*R*)-2-Benzyl-1-methyl-5-nonyl-3-pyrrolidinol (1). To a solution of the *N*-Boc-pyrrolidine **11** (100 mg, 0.24 mmol) in THF (8 mL) was added lithium aluminium hydride (95 mg, 2.4 mmol) and the mixture refluxed for 7 h. After cooling to 0^0C, saturated aqueous NH_4Cl (15 mL) and water (30 mL) was added to the reaction mixture, the resulting solution extracted with ether (3x50 mL), combined extract washed with brine, dried over Na_2SO_4, solvent removed under vacuum and the residue purified by column chromatography (ethyl acetate/hexane = 1/3) to yield (+)-preussin (**1**) (51 mg, 63%) as a colorless waxy solid, the spectral and analytical data of which is consistent with those reported in the literature.[2g]

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References and Notes

IICT communication No. 3959

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5. Assignment of *syn* stereochemistry to the major isomer **2**, initially based on analogy (ref. 3,4), was proved conclusively by comparing the spectral and analytical data of the subsequent reaction products **11** and **1** with their literature reported values (*vide infra*).
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