Practical Asymmetric Approach to Pyrrolidinones: Efficient Synthesis of (+)-Preussin and (−)-AHPPA†

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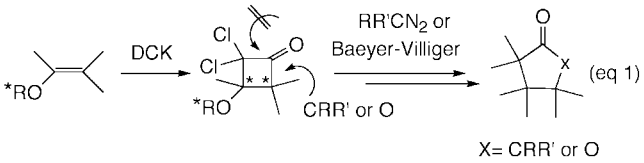
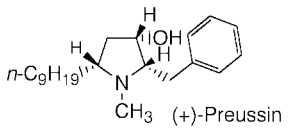
A novel, dichloroketene−chiral enol ether cycloaddition-based synthesis of enantiopure (+)-preussin and (−)-AHPPA has been realized. The efficient, highly stereoselective approach, which involves a Beckmann ring expansion reaction to access the key pyrrolidinone, proceeds in ca. 16% overall yield for each of the compounds.

Pyrrolidines are naturally ubiquitous, biologically important substances that display diverse structural and stereochemical features.[1] Not surprisingly, these alkaloids have been accorded considerable attention from synthetic chemists, and an impressive range of new methodology has resulted, most recently in the area of asymmetric synthesis.

Over the past several years, we have developed a conceptually simple, yet quite effective, asymmetric approach to cyclopentane and γ-butyrolactone-containing natural products based on diastereofacially selective 2 + 2 cycloaddition of dichloroketene (DCK) with chiral *O*-alkyl enol ethers, followed by regioselective ring expansion of the resulting α,α-dichlorocyclobutanones (eq 1).[2] In this paper, the potential of this methodology for



providing efficient access also to pyrrolidines, by way of the corresponding pyrrolidinones,[3] is illustrated through a synthesis of (+)-preussin (**1**).[4] In addition, a new chiral pyrrolidinone-based route to (3*S*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA, **2**)[5] is described.



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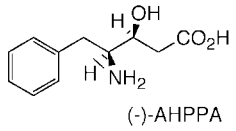

2

(+)-Preussin (L-657,398) was first isolated in 1988 from fermentation broths of *Aspergillus ochraceus*[4a] and shortly after from those of *Preussia* sp.[4b] It has been found to possess a broad spectrum of potent antifungal activity

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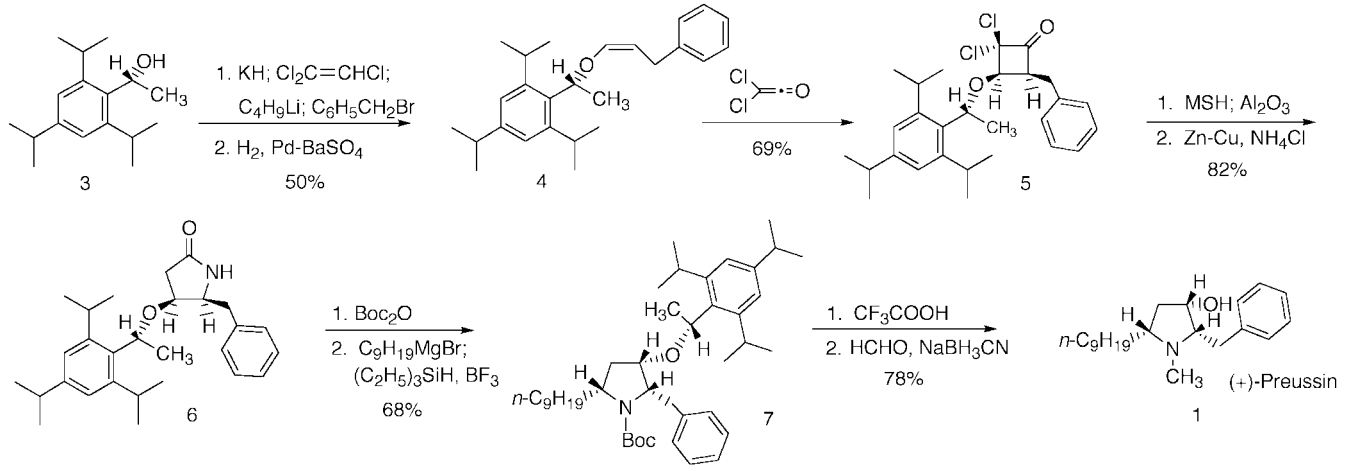
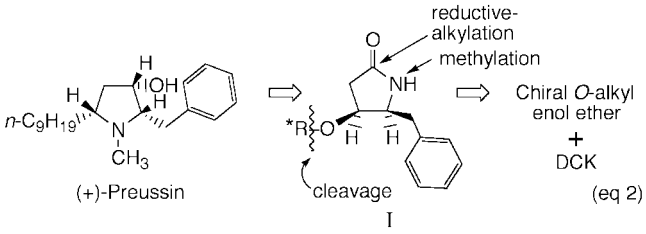
Scheme 1



against both filamentous fungi and yeasts, significantly broader than that displayed by the structurally related pyrrolidine anisomycin.[4a,b] Although several approaches to (+)-preussin have been reported over the past decade, they almost invariably involve construction of the natural product from chiral pool starting material, most often (*S*)-phenylalanine.[4c−j]

Our approach to this alkaloid is outlined retrosynthetically in eq 2. We envisioned that (+)-preussin would be obtained from the pyrrolidinone I by reductive alkylation, inductor cleavage, and *N*-methylation and that pyrrolidinone I in turn would be derived by reduction of the ring-expanded 2 + 2 cycloadduct formed from a chiral enol ether and dichloroketene.[3e] The successful route based on this strategy is described below.



(eq 2)

Readily available, enantiomerically pure (*R*)-1-(2,4,6-triisopropylphenyl)ethanol (**3**, Scheme 1)[6] was converted in a one-pot procedure to the sensitive benzylated ynol ether, which was partially reduced with hydrogen in the presence of palladium on barium sulfate in pyridine[7] to afford the pure *Z*-enol ether **4** in 50% overall yield (70%/step). Dichloroketene, generated in situ from trichloroacetyl chloride with zinc−copper couple, added smoothly and with pleasingly high facial selectivity to enol ether **4** to provide the dichlorocyclobutanone **5** as the major diastereomer (94:6 by ^{1}H NMR) in high yield.[2] A single recrystallization of this material from acetone−water served to remove efficiently the small amount of diastereomeric contamination and afforded the pure cyclobutanone **5** in 69% yield. The indicated stereochemistry in this adduct was provisionally assigned on the basis of molecular modeling studies, which clearly indicated the Cα-*si* face of enol ether **4** to be the more accessible, and was subsequently confirmed by the preparation of (+)-preussin.

The desired cyclobutanone−pyrrolidinone conversion of **5** was readily accomplished and apparently with complete regiocontrol through application of Tamura's Beckmann reagent, *O*-(mesitylenesulfonyl)hydroxylamine (MSH), to provide the ring-expanded derivative in high yield.[3e,8] Exposure of this material at room temperature to zinc−copper couple in methanol saturated with ammonium chloride,[9] an excellent, but strangely seldom-used reducing system, cleanly gave pyrrolidinone **6** in 82% overall yield (90%/step).

The stereoselective installation of the nonyl group, in place of the carbonyl oxygen, proved to be somewhat challenging. For example, while the imino methyl ether could be prepared from **6** with trimethyloxonium tetrafluoroborate, clean conversion of this substrate to the desired imine intermediate with the organomagnesium or lithium reagent could not be accomplished.[10] Similarly, the *N*-trimethylsilyl derivative of **6** failed to provide more than trace amounts of the expected imine on treatment with the organolithium reagent.[11] Fortunately, however, the corresponding *N*-*tert*-butoxylcarbonyl (Boc) derivative underwent smooth addition of nonylmagnesium bromide, and in situ the resulting α-hydroxy carbamate experienced stereoselective reduction with triethylsilane−boron trifluoride etherate[4h] to provide the all-cis pyrrolidine **7** as the unique product in 68% yield.

Pyrrolidine **7** suffered double cleavage in the presence of trifluoroacetic acid to afford in quantitative yield norpreussin, which was then *N*-methylated conventionally[12] to produce (+)-preussin in 78% yield. The identity of the synthetic material, enantiopure by HPLC, was unambiguously confirmed through comparison of its spectral data with those reported for the naturally

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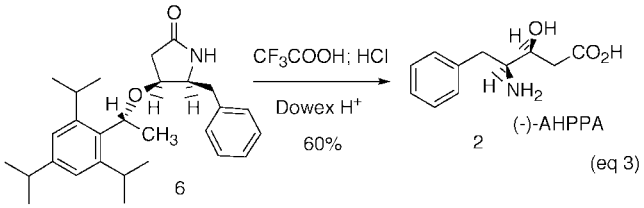
derived substance and by direct comparison with a sample kindly provided by Professor Hecht of independently prepared[4g] synthetic (+)-preussin, previously compared directly with natural preussin.

Pyrrolidinone **6** also proved to be a direct precursor of (3*S*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA, **2**), an unusual amino acid that is found in several ahpatinin acid protease inhibitors from *Streptomyces* sp. WK-142[5a] and that has been used for a variety of purposes.[5b−n] Lactam **6** was treated first with trifluoroacetic acid and then, in the same pot, with concentrated hydrochloric acid to effect inductor cleavage-ring opening (eq 3).[3e] Ion-exchange column chromatography of the



resulting salt then afforded AHPPA, identified through comparison of its spectral data with those reported in the literature and shown to be enantiopure by HPLC.

In summary, enantiopure (+)-preussin and (−)-AHPPA have been prepared in 15% (ten steps) and 17% (six steps) overall yields, respectively, through chiral enol ether−dichloroketene diastereofacially selective 2 + 2 cycloaddition. The syntheses are competitive with most previously recorded in the literature of these natural products, in particular those that eschew chiral pool material, and bode well for future extension to pyrrolizidine and indolizidine preparation.

Experimental Section

Isolation of the crude product was generally accomplished by pouring the reaction mixture into water and then thoroughly extracting the separated aqueous phase with the specified solvent. After being washed with 10% aqueous HCl and/or $NaHCO_3$ (if required), water, and saturated aqueous NaCl, the combined organic phases were dried over anhyd Na_2SO_4 or $MgSO_4$ and then filtered and concentrated under reduced pressure on a Büchi Rotovapor to yield the crude reaction product. Tetrahydrofuran and ether were distilled from sodium−benzophenone, and methanol was distilled from magnesium. Pentane, dichloromethane, acetonitrile, *N*,*N*-diisopropylethylamine, HMPA, and triethylamine were distilled from calcium hydride.

(−)-2-[(1*R*)-1-[((1*Z*)-3-Phenyl-1-propenyl)oxy)ethyl]-1,3,5-triisopropylbenzene (4). An argon-flushed flask was charged with 2.80 g (24.4 mmol) of a 35% suspension of potassium hydride in mineral oil. The mineral oil was removed by washing with hexane, and the flask was capped with a rubber septum and connected to a Nujol-filled bubbler by means of a syringe needle. A solution of 3.00 g (12.1 mmol) of alcohol **3**[6] in 24 mL of anhydrous tetrahydrofuran was then added dropwise by syringe. The mixture was stirred until hydrogen evolution was complete, cooled to −50 °C, and treated dropwise over 15 min with a solution of trichloroethylene (1.10 mL, 1.62 g, 12.4 mmol) in 15 mL of anhydrous tetrahydrofuran, after which the reaction mixture was allowed to warm to 20 °C over 1 h. The resulting brown solution was then cooled to −70 °C and treated dropwise with 12.1 mL (30.2 mmol) of 2.5 M *n*-butyllithium in hexanes. After being stirred for 30 min at −70 °C, the reaction mixture was warmed to −40 °C over 30 min and treated dropwise with a solution of 5.80 mL (8.34 g, 48.8 mmol) of benzyl bromide (filtered over 1:1 Al_2O_3/P_2O_5) in 9.2 mL of hexamethylphosphoramide. The solution was stirred at 20 °C for 2 h, whereupon it was poured into cold saturated aqueous ammonium chloride. The crude product was isolated with pentane in the usual way and partially purified by rapid filtration through silica gel (120 mL, pretreated with 2.5% triethylamine, v/v) with pentane containing 1% of triethylamine to afford crude 2-[(1*R*)-1-[(3-phenyl-1-propynyl)oxy]ethyl]-1,3,5-triisopropylbenzene: IR 3068, 3028, 2272, 1607 cm^{-1}.

A mixture of the above crude acetylenic ether and 530 mg of 10% palladium on barium sulfate in 40 mL of pyridine was stirred under hydrogen for 5 h, whereupon the hydrogen was replaced with argon and the reaction mixture was filtered with the aid of ether. The solvents were washed with saturated aqueous copper sulfate, water, and saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel (pretreated with 2.5% triethylamine, v/v) with pentane to afford 2.22 g (50% overall) of enol ether **4**: mp 41−41.5 °C (pentane); $[\alpha]^{20}_D$ −40.2° (*c* 1.0, chloroform); IR 3051, 1662, 1607, 1384, 1271, 1115, 1077, 742 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.20−1.35 (m, 18 H), 1.63 (d, J = 6.9 Hz, 3 H), 2.86 (hept, J = 6.9 Hz, 1 H), 3.30−3.60 (m, 4 H), 4.49 (dt, J = 7.2, 6.5 Hz, 1 H), 5.38 (q, J = 6.9 Hz, 1 H), 6.07 (dt, J = 6.2, 1.4 Hz, 1 H), 7.01 (s, 2 H), 7.1−7.3 (m, 5 H); ^{13}C NMR (50.3 MHz) δ 22.6, 24.0, 24.7, 29.2, 30.5, 34.1, 75.4, 104.9, 121.9, 125.5, 128.2, 128.3, 132.9, 141.9, 144.4, 147.7; mass spectrum (CI) *m*/*z* 382 (M^+ + 18), 248, 231 (100).

Anal. Calcd for $C_{26}H_{36}O$: C, 85.65; H, 9.96. Found: C, 85.59; H, 9.96.

(+)-(2*S*,3*R*)-2-Benzyl-4,4-dichloro-3-[(1*R*)-1-(2,4,6-triisopropylphenyl)ethoxy]cyclobutanone (5). To a stirred mixture of 1.67 g (4.58 mmol) of enol ether **4** and 4.30 g (ca. 66 mmol) of Zn−Cu couple in 40 mL of ether under argon was added over 1.5 h 0.770 mL (1.25 g, 6.90 mmol) of freshly distilled trichloroacetyl chloride in 16 mL of ether. After an additional 1 h, the ether solution was separated from the excess couple and added to hexane, and the resulting mixture was partially concentrated under reduced pressure in order to precipitate the zinc chloride. The supernatant was decanted and washed successively with a cold aqueous solution of sodium bicarbonate, water, and brine and then dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure left crude cyclobutanone **5** (containing ca. 6% of its diastereomer (δ 5.47 ppm)) as a white solid. Recrystallization of this material from acetone−water gave 1.50 g (69%) of pure **5**: mp 115−116 °C (methanol−water); $[\alpha]^{20}_D$ +41.2° (*c* 1, chloroform); IR 3092, 3068, 3037, 1808, 1610, 1382, 1166, 1073 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.00−1.40 (m, 18 H), 1.70 (d, J = 6.9 Hz, 3 H), 2.91 (hept, J = 6.9 Hz, 1 H), 3.11 (d, J = 7.9 Hz, 2 H), 3.26 (hept, J = 6.9 Hz, 1 H), 3.65−3.90 (m, 2 H), 4.37 (d, J = 9.3 Hz, 1 H), 5.49 (q, J = 6.9 Hz, 1 H), 7.0−7.4 (m, 7 H); ^{13}C NMR (50.3 MHz) δ 22.2, 23.4, 23.5, 24.5, 24.8, 25.0, 27.9, 28.8, 30.5, 31.0, 33.6, 59.9, 73.1, 77.0, 88.0, 120.5, 123.0, 126.2, 128.1, 128.5, 130.0, 137.9, 146.7, 147.9, 148.5, 195.2; mass spectrum (EI) *m*/*z* 492 (M^+ + 18), 248, 231 (100).

Anal. Calcd for $C_{28}H_{36}O_2Cl_2$: C, 70.73; H, 7.63. Found: 70.43; H, 7.70.

(+)-(4*S*,5*S*)-5-Benzyl-4-[(1*R*)-1-(2,4,6-triisopropylphenyl)-ethoxy]-2-pyrrolidinone (6). A solution of 546 mg (1.15 mmol) of cyclobutanone **5** in 5 mL of dichloromethane was treated with 1.19 g (5.53 mmol) of *O*-(mesitylenesulfonyl)hydroxylamine and stirred at 20 °C for 40 min. The solvent was then removed under reduced pressure, and the resulting material in 2 mL of toluene was placed on a column of basic alumina (20 g, Merck activity 1) and eluted rapidly with methanol. The resulting crude (4*R*,5*S*)-5-benzyl-3,3-dichloro-4-[(1*R*)-1-(2,4,6-triisopropylphenyl)ethoxy]-2-pyrrolidinone (IR 1730 cm^{-1}) was used below.

The crude dichloro lactam in 40 mL of methanol previously saturated with ammonium chloride was stirred at 20 °C with 2.0 g (ca. 30 mmol) of zinc−copper couple under argon for 2 h, whereupon the mixture was filtered to remove the excess couple. The filtrate was concentrated under reduced pressure, and the residue was then processed with dichloromethane in

the usual way and purified by silica gel chromatography with 10% ether in dichloromethane to give 398 mg (82% overall) of lactam **6**: mp 126−127 °C (pentane−ether); $[\alpha]^{20}_D$ +34.4° (*c* 1.0, chloroform); IR 3236, 1707, 1615, 1374, 1115, 1087 cm^{-1}; ^1H NMR (200 MHz) δ 1.1−1.4 (m, 18 H), 1.60 (d, J = 6.5 Hz, 3 H), 2.50 (dd, J = 7.2, 1.7 Hz, 2 H), 2.60−2.80 (m, 1 H), 2.86 (hept, J = 6.9 Hz, 1 H), 3.00−3.25 (m, 2 H), 3.70−4.00 (m, 2 H), 4.23 (pseudo q, J = 7.2 Hz, 1 H), 5.12 (q, J = 6.9 Hz, 1 H), 5.78 (br s, 1 H), 6.95−7.35 (m, 7 H); ^{13}C NMR (50.3 MHz) δ 23.1, 23.8, 24.2, 24.9, 25.0, 28.0, 29.1, 33.9, 36.2, 36.3, 59.1, 71.3, 72.4, 120.3, 123.2, 126.4, 128.6, 129.2, 132.0, 138.2, 145.8, 147.7, 148.6, 174.3; mass spectrum (CI) *m*/*z* 439 (M^+ + 18), 422 (MH^+, 100).

Anal. Calcd for $C_{28}H_{39}NO_2$: C, 79.76; H, 9.32; N, 3.32. Found: C, 79.66; H, 9.51; N, 3.56.

(−)-(2*S*,3*S*,5*R*)-2-Benzyl-1-[(1,1-dimethylethoxy)carbonyl]-5-nonyl-3-[(1*R*)-1-(2,4,6-triisopropylphenyl)ethoxy]-pyrrolidine (7). To a solution of lactam **6** (217 mg, 0.52 mmol) in 2.8 mL of dry dichloromethane was added 0.450 mL (334 mg, 2.58 mmol) of *N*,*N*-diisopropylethylamine, 0.640 mL (608 mg, 2.79 mmol) of di-*tert*-butyl dicarbonate, and 34 mg (0.28 mmol) of 4-(dimethylamino)pyridine. The resulting mixture was stirred at 20 °C for 3 h, after which time the crude product was isolated with dichloromethane in the usual manner and purified by column chromatography on silica gel with 10% ethyl acetate in hexane to give 269 mg (100%) of (+)-(4*S*,5*S*)-5-benzyl-1-[(1,1-dimethylethoxy)carbonyl]-4-[(1*R*)-1-(2,4,6-triisopropylphenyl)ethoxy]-2-pyrrolidinone: mp 137−138 °C; $[\alpha]^{20}_D$ +91.5° (*c* 1.5, chloroform); IR 3086, 3062, 3030, 1794, 1764, 1718, 1610, 1257, 1218, 1166, 1114, 1079, 1027 cm^{-1}; ^1H NMR (200 MHz) δ 1.0−1.30 (m, 18 H), 1.40 (s, 9 H), 1.57 (d, J = 6.9 Hz, 3 H), 2.42 (AB of ABX, δ_a = 2.29, δ_b = 2.55, J_{ab} = 16.7 Hz, J_{ax} = 10.4 Hz, J_{bx} = 7.7 Hz, 2 H), 2.75−3.25 (m, 4 H), 3.69 (m, 1 H), 4.07 (dt, J = 10.3, 7.9 Hz, 1 H), 4.40 (dt, J = 6.9, 5.8 Hz, 1 H), 5.02 (q, J = 6.8, 1 H), 6.92 (br s, 1 H), 7.00 (br s, 1 H), 7.16−7.28 (br s, 5 H); ^{13}C NMR (62.5 MHz) δ 170.7, 149.4, 148.8, 147.8, 145.9, 137.7, 131.5, 130.4, 128.1, 126.3, 123.4, 120.6, 82.9, 71.3, 69.6, 61.1, 37.0, 34.6, 33.9, 29.0, 27.8, 25.0, 24.9, 24.2, 23.8, 23.1; mass spectrum (CI) *m*/*z* 422 (MH^+ − Boc), 231 (100).

Anal. Calcd for $C_{33}H_{47}NO_4$: C, 75.97; H, 9.08; N, 2.68. Found: C, 75.89; H, 9.21; N, 2.68.

To a stirred solution of this derivative (90 mg, 0.17 mmol) in 1.8 mL of THF at −80 °C under argon was added dropwise 1.45 mL (0.42 mmol) of a 0.29 M solution of nonylmagnesium bromide in THF. The resulting solution was stirred for 30 min at −80 °C, and then the THF was eliminated under under reduced pressure while the temperature of the reaction mixture was maintained below −20 °C. The residue was dissolved in 2 mL of CH_2Cl_2 and cooled to −90 °C. To this solution were added 0.320 mL (233 mg, 2.00 mmol) of triethylsilane and, after 5 min, 0.380 mL (426 mg, 3.00 mmol) of boron trifluoride etherate. The reaction mixture was allowed to warm slowly to −40 °C, stirred for 1 h at this temperature, and then quenched by the addition of aqueous sodium bicarbonate solution. The crude product was isolated with dichloromethane in the normal manner and purified by column chromatography on silica gel with 2% ethyl acetate in hexane to afford 74 mg (68%) of pyrrolidine **7** as a white solid: mp 78−79 °C; $[\alpha]^{20}_D$ −3° (*c* 3, chloroform); IR 3092, 3063, 3035, 1700, 1615, 1374, 1184, 1144, 1081 cm^{-1}; ^1H NMR (200 MHz, C_6D_6, 72 °C) δ 0.90 (deformed t, J = 6.9 Hz, 3 H), 1.15−1.50 (m, 42 H), 1.56 (d, J = 6.5 Hz, 3 H), 1.55−1.80 (m, 1 H), 2.15−2.45 (m, 1 H), 2.32 (dt, J = 12.0, 7.2 Hz, 1 H), 2.70−2.90 (m, 1 H), 2.97 (AB of ABX, δ_a = 3.15, δ_b = 2.79, J_{ab} = 13.5 Hz, J_{ax} = 5.5 Hz, J_{bx} = 7.2 Hz, 2 H), 3.20−3.90 (m, 3 H), 3.85 (dt, J = 10.3, 7.2 Hz, 1 H), 4.33 (dt, J = 6.8, 5.8 Hz, 1 H), 5.11 (q, J = 6.7 Hz, 1 H), 7.0−7.4 (m, 7 H); ^{13}C NMR (50.3 MHz) δ 154.8, 148.8, 147.4, 145.4, 139.9, 133.3, 130.1, 127.9, 125.5, 123.3, 120.5, 78.8, 72.0, 61.1, 55.7, 37.5, 36.5, 35.3, 34.0, 31.9, 29.7, 29.6, 29.3, 29.1, 27.9, 26.6, 24.9, 24.4, 23.9, 23.4, 22.7, 14.1; mass spectrum (CI) *m*/*z* 634 (MH^+), 231 (100).

Anal. Calcd for $C_{42}H_{67}NO_3$: C, 79.57; H, 10.65; N, 2.21. Found: C, 79.65; H, 10.82; N, 2.32.

(+)-(2*S*,3*S*,5*R*)-2-Benzyl-3-hydroxy-1-methyl-5-nonylpyrrolidine ((+)-Preussin (1)). A mixture of 52 mg (0.08 mmol) of **7** and 0.5 mL of trifluoroacetic acid was stirred at 20 °C for 1 h and then evaporated to dryness under reduced pressure. The residue was processed with dichloromethane in the usual way, and the crude product was purified by silica gel chromatography with 30% ethyl acetate in hexane containing 2% of methanol saturated with NH_3 to give 25 mg (100%) of (−)-(2*S*,3*S*,5*R*)-2-benzyl-3-hydroxy-5-nonylpyrrolidine as a white solid: mp 101−102 °C; $[\alpha]^{20}_D$ −15.6° (*c* 1, methanol); IR 3425, 1638, 1340, 1161 cm^{-1}; ^1H NMR (200 MHz) δ 0.85 (t, J = 6.3 Hz, 3 H), 1.20−1.60 (m, 18 H), 1.90 (br s, 1 H), 2.17−2.34 (ddd, J = 14.0, 8.5, 6.1 Hz, 1 H), 2.77−3.07 (m, 4 H), 4.0 (m, 1 H), 7.1−7.3 (m, 5 H); ^{13}C NMR (50.3 MHz) δ 139.8, 128.9, 128.5, 126.1, 72.2, 65.7, 57.0, 42.0, 37.5, 35.6, 31.9, 29.7, 29.6, 29.3, 27.2, 22.6, 14.1; mass spectrum (CI) *m*/*z* 304 (MH^+), 212 (100). Anal. Calcd for $C_{20}H_{33}NO$: C, 79.15; H, 10.96; N, 4.61. Found: C, 78.99; H, 11.06; N, 4.73.

To a solution of 16 mg (0.05 mmol) of the above pyrrolidine in 0.70 mL of acetonitrile was added 0.23 mL of 37% aqueous formaldehyde, 17 μL of acetic acid, and 16 mg (0.25 mmol) of sodium cyanoborohydride. The resulting solution was stirred at 20 °C for 4 h and then concentrated under reduced pressure. The crude product was isolated with dichloromethane in the normal manner and purified by silica gel chromatography with 20% ethyl acetate in hexane to afford 13 mg (78%) of (+)-preussin (**1**): $[\alpha]^{25}_D$ +32° (*c* 1.1, chloroform); IR 3454, 3087, 3064, 3030, 1615, 1355, 1148, 1038, 923 cm^{-1}; ^1H NMR (300 MHz) δ 0.87 (t, J = 6.5 Hz, 3 H), 1.16−1.45 (m, 16 H), 1.70 (m, 1 H), 1.90−2.30 (m, 4 H), 2.32 (s, 3 H), 2.75−2.95 (m, 2 H), 3.79 (m, 1 H), 7.10−7.35 (m, 5 H); ^{13}C NMR (75.5 MHz) δ 139.5, 129.3, 128.3, 126.0, 73.6, 70.5, 65.8, 39.3, 38.6, 34.9, 33.7, 31.9, 29.9, 29.6, 29.5, 29.3, 26.2, 22.6, 14.0; mass spectrum (EI) *m*/*z* 317 (M^+), 226 (100); HRMS *m*/*e* calcd for $C_{21}H_{35}NO$ (M^+) 317.2719, found 317.2701; HPLC (Chiracel OD-H, 5 mm, 2-propanol/hexane = 2:98, 0.5 mL/min, t_R 11.80 min (vs 11.18 min)) indicated an enantiopurity of ≥99%.

(−)-(3*S*,4*S*)-4-Amino-3-hydroxy-5-phenylpentanoic Acid ((3*S*,4*S*)-AHPPA (2)). A 67-mg (0.16 mmol) sample of lactam **6** was stirred with 0.20 mL of trifluoroacetic acid at 20 °C under argon for 1.5 h, whereupon 11 mL of 12 N HCl was added, and the reaction mixture was heated at 80 °C for 3 h. The mixture was then concentrated under reduced pressure and the resulting material was passed down a column of 8 g of Dowex 50W (X8 50/100 mesh, H^+ form) ion-exchange resin, eluting with water (discarded) and then 2 N aqueous ammonium hydroxide. Evaporation of the latter provided 20 mg (60%) of (−)-AHPPA (**2**): IR (Nujol) 3342, 3149, 3045, 1620, 1551, 1407, 1160, 1119 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 2.17−2.47 (m, 2 H), 2.61−2.99 (ABX, J = 14.3, 9.3, 5.0 Hz, 2 H), 3.32 (m, 1 H), 3.86 (m, 1 H), 7.20 (m, 5 H); ^{13}C NMR (50.3 MHz, D_2O) δ 38.3, 44.2, 59.7, 70.5, 130.3, 132.0, 132.1, 138.1, 181.3; mass spectrum (CI) *m*/*z* 210 (MH^+), 192 (100%). The *N*-Boc methyl ester derivative: mp 97 °C (lit.[5c] mp 97−98 °C); $[\alpha]^{20}_D$ −35° (*c* 0.8, methanol) (lit.[5c] $[\alpha]^{20}_D$ −36° (*c* 1.0, methanol)); IR 3390, 3034, 1724, 1701, 1374, 1259, 1173, 1092, 1058 cm^{-1}; NMR (200 MHz) δ 1.40 (s, 9 H), 1.62 (s, 1 H), 2.3−2.7 (m, 2 H), 2.91 (d, J = 7.5 Hz, 2 H), 3.45 (s, 1 H), 3.68 (s, 3 H), 4.00 (br d, 1 H), 4.94 (m, 1 H), 7.15−7.25 (m, 5 H); ^{13}C NMR (50.3 MHz) δ 28.3, 38.4, 38.5, 51.8, 55.4, 67.0, 79.4, 126.3, 128.4, 129.4, 138.1, 155.8, 173.8; HPLC (Chiracel OD-H, 5 mm, 2-propanol/hexane = 1:99, 0.5 mL/min, t_R 13.38 min (vs 11.31 min)) indicated an enantiopurity of ≥99%.

Anal. Calcd for $C_{17}H_{25}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 61.98; H, 7.74; N, 4.26.

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