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# Asymmetric synthesis of (+)-preussin from *N*-sulfinyl δ-amino β-ketoesters

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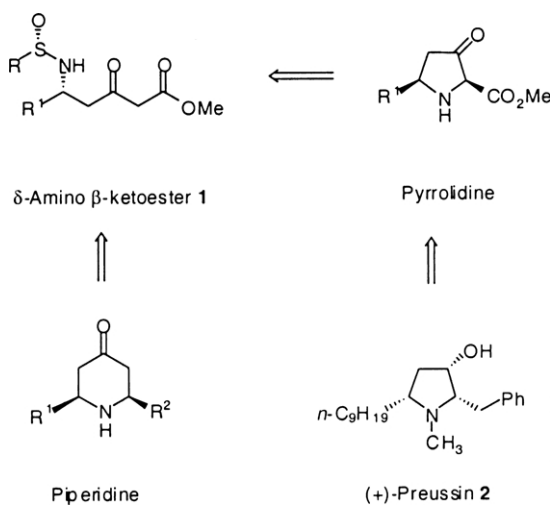
**Abstract**—The efficient asymmetric synthesis of the antifungal pyrrolidine alkaloid (+)-preussin (**2**) was accomplished via the stereoselective reduction of a 5-substituted 3-oxo proline. The oxo proline was prepared from an *N*-sulfinyl δ-amino β-ketoester, a sulfinimine derived polyfunctionalized chiral building block.


## 1. Introduction

Recent results in our laboratory have demonstrated the utility of *N*-sulfinyl δ-amino β-ketoesters as valuable chiral building blocks for the concise asymmetric synthesis of polysubstituted piperidine[1] and pyrrolidine alkaloids[2] (Scheme 1).[3] The piperidine structure is rapidly assembled via an intramolecular Mannich reaction of the amine salt of **1** and diverse carbonyl compounds.[1] Construction of the pyrrolidine framework (5-substituted 3-oxo prolines) involves a novel intramolecular metal carbenoid NH insertion reaction of the α-diazo δ-amino β-ketoester corresponding to **1**.[2] The fact that the NH insertion reaction is highly stereoselective and exclusively affords the *cis*-2,5-disubstituted product suggested the possibility of efficient asymmetric syntheses of 2,3,5-trisubstituted pyrrolidines such as (+)-preussin (**2**).[2a]




**Scheme 1.**

(+)-Preussin (**2**) has been the subject of a number of asymmetric syntheses[4] of varying degrees of conciseness because it is a potent antifungal agent with significant broad-spectrum antibiotic activity against yeast and filamentous fungi.[5] To prepare (+)-**2** from the oxo proline requires (i) a stereoselective reduction of the 3-oxo unit, (ii) conversion of the carbomethoxy group into a benzyl group, and (iii) *N*-methylation. We describe here the realization of this objective with a highly efficient asymmetric synthesis of (+)-preussin (**2**) from a sulfinimine derived δ-amino β-ketoester.

The δ-amino β-ketoester ($R_S$,5*S*)-(−)-**5** was prepared as previously described except that the sulfinimine (*R*)-(−)-**3** was prepared from commercially (Scheme 2) available (*R*)-(−)-*p*-toluenesulfinamide and 2,4-*trans*,*trans*-decadienal.[1d] The deprotection/protection sequence performed on (−)-**5** gave the *N*-Boc derivative (*S*)-(+)-**6** in 86% yield, and hydrogenation afforded (*S*)-(+)-**7** in nearly quantitative yield.

With the requisite *N*-Boc δ-amino β-ketoester (*S*)-(+)-**7** in hand, treatment with commercially available 4-carboxybenzenesulfonylazide (4-CBSA)[2] in the presence of $Et_3N$ gave the key α-diazo derivative (*S*)-(+)-**8** in 94% isolated yield (Scheme 3). On treatment of (+)-**8** with 5 mol% $Rh_2(OAc)_4$ at rt in DCM the oxo proline **9** was isolated as a single diastereoisomer in 96% crude yield.[2] A concerted or nearly concerted metal carbenoid N–H insertion reaction mechanism was proposed earlier for the high stereoselectivity of this reaction.[2b] The crude $^1H$ NMR exhibits

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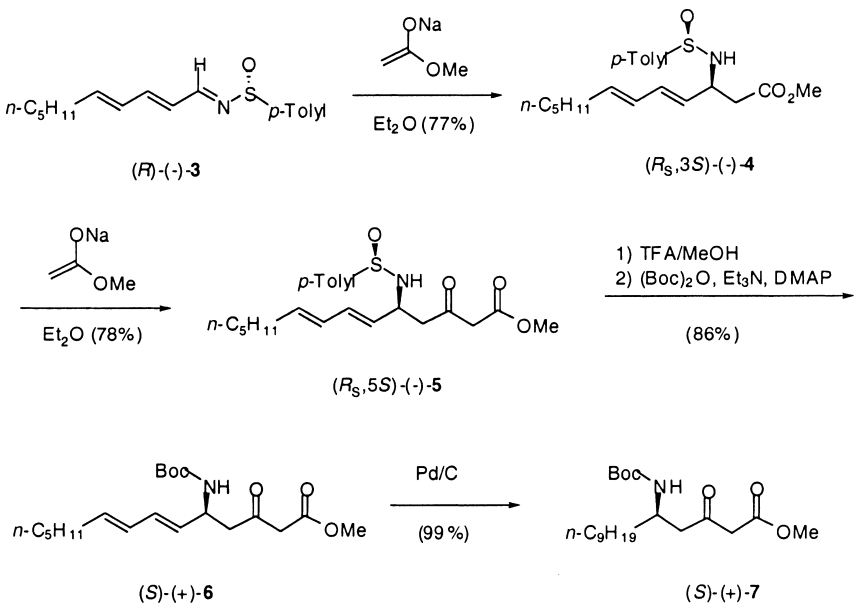
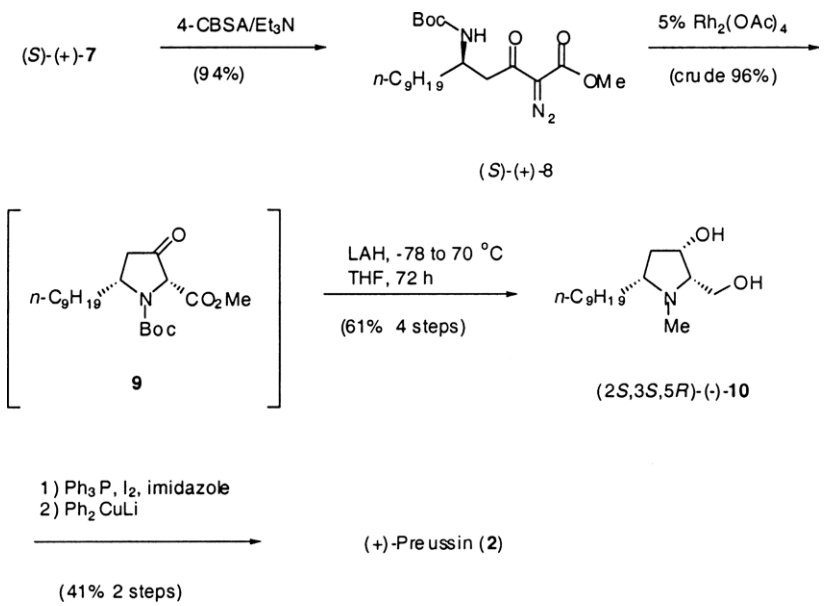



**Scheme 2.**

broadening of peaks due, we believe, to the presence of rotomers at the Boc group. However, attempts at purification by silica gel chromatography resulted in epimerization at C-2 to give **9** as 6:1 mixture of inseparable *cis*/*trans* isomers as suggested by $^1$H NMR of the carboxyl methyl group. The presence of rotomers and peak broadening made the spectra quite complex to analyze. Facile epimerization at C-2 on purification was noted earlier for the 5-phenyl substituent,[2a] but not the 5-*tert*-butyl derivative,[2b] and may be due to the larger sized of the *tert*-butyl group. To avoid having to separate the diastereoisomers later in the synthesis, the crude oxo proline was taken on to the next step without purification. The fact at crude **9** was stable in solution for several hours suggest that epimerization occurs under acidic, silica gel, conditions.

Because lithium aluminum hydride (LAH) reduces ketones to alcohols, carboxylic esters to hydroxy methylene groups, and *N*-Boc to *N*-methyl groups[6] the possibility that all three reductions could be carried out stereoselectivity in one pot to give (−)-**10** was next explored. Initial studies with 10.0 equiv. of LAH at rt for 12 h resulted in reduction of both the oxo and carbomethoxy groups; however, poor stereoselectivity for the reduction of the 3-oxo group afforded a 4:1 mixture of isomers. Furthermore, the *N*-Boc group was not reduced. When the reduction was carried out at −78 °C for 4 h with slow warming to room temperature the oxo group was reduced with complete *cis* selectivity. Continued heating of the reaction mixture for 72 h at 70 °C afforded the desired dihydroxy *N*-methyl pyrrolidine (−)-**10**, in one pot, in 61% isolated yield for the four steps.

Conversion of diol (−)-**10** to (+)-preussin (**2**) requires selective conversion of the primary alcohol, in the presence




**Scheme 3.**

of the secondary alcohol, into a leaving group that will facilitate coupling with the phenyl group. Initial attempts to tosylate the primary alcohol in the presence of the secondary alcohol using *p*-toluenesulfonyl chloride and various bases (pyridine, $Et_3N$, and *i*-$Pr_2NEt$) resulted in extensive decomposition. Iodination with 4 equiv. of $I_2$, $Ph_3P$ and imidazole appeared to be successful, but the product decomposed on work-up. For this reason, the crude iodide was immediately treated with 10 equiv. $Ph_2CuLi$ at −78 °C and warmed to rt and stirred for 8 h, which afforded, following chromatography, (+)-preussin (**2**) in 40% yield for the two steps. This material had properties consistent with literature values.[4e]

In summary, a concise asymmetric synthesis of the pyrrolidine antifungal agent (+)-preussin (**2**) was accomplished from the sulfinimine derived δ-amino β-ketoester (+)-**7** with an overall yield of 23% for the seven steps, a number of steps being carried out in one pot.

## 2. Experimental

### 2.1. General procedures

Column chromatography was performed on silica gel, Merck grade 60 (230–400 mesh). TLC plates were visualized with UV, in an iodine chamber, or with phosphomolybdic acid, unless noted otherwise. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 341 polarimeter and IR spectra were recorded, using NaCl plates or as KBr disks, on a Mattson 4020 FTIR. $^1H$ NMR and $^{13}C$NMR spectra were recorded on a GE Omega 500, operating at 500 and 125 MHz, respectively. HR-MS was performed in the Department of Chemistry, Drexel University, Philadelphia, PA, using a Fissions ZAB HF double-focusing mass spectrometer. Elemental analyses were performed in the Department of Chemistry, University of Pennsylvania, Philadelphia, PA.

Solvents were purified using the Glass Contour solvent dispensing system. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification.

**2.1.1. (*R*)-(−)-*N*-(2,4-Decaylidene)-*p*-toluenesulfinamide (3).** In an oven-dried, 25-mL one-necked, round-bottomed flask equipped with a magnetic stirring bar was placed *E*,*E*-2,4-decadienal (0.360 mL, 2.0 mmol, Aldrich) in $CH_2Cl_2$ (10 mL). Titanium(IV) ethoxide (0.22 mL, 1.0 mmol) and (*R*)-(−)-*p*-toluenesulfinamide (0.283 g, 2.0 mmol, Aldrich) were added and the reaction mixture was stirred at rt for 12 h.[7] At this time, the reaction was quenched by addition of ice-$H_2O$ (4 mL) and filtered through Celite. The organic phase was washed with brine (4 mL), dried ($Na_2SO_4$), and concentrated. Flash chromatography (30% EtOAc/hexanes) afforded 0.435 g (75%) of (*R*)-(−)-**3** as an oil; $[\alpha]_D^{20}=-820.0$ (*c* 1.2, $CHCl_3$); IR (neat): 2927, 2857, 1608, 1560, 1094 $cm^{-1}$; $^1H$ NMR ($CHCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.29 (m, 4H), 1.42 (m, 2H), 2.16 (dd, *J*=7.0, 14.0 Hz, 2H), 2.39 (s, 3H), 6.11 (m, 1H), 6.19 (m, 1H), 6.37 (dd, *J*=10.0, 16.0 Hz, 1H), 6.87 (dd, *J*=10.0, 16.0 Hz, 1H), 7.28 (d, *J*=8.0 Hz, 2H), 7.55 (d, *J*=8.0 Hz, 2H), 8.35 (d, *J*=8.5 Hz, 1H); $^{13}C$ NMR δ 14.4, 21.8, 22.9, 28.8, 31.8, 33.5, 125.0, 127.2, 129.6, 130.2, 142.0, 142.5, 145.3, 147.9, 162.1. HR-MS calcd for $C_{17}H_{23}NOSNa$ (M+Na): 312.1398. Found: 312.1396.

**2.1.2. ($R_S$,3*S*)-(−)-Methyl-3-*N*-(*p*-toluenesulfinyl)amino-3-dodeca-4,6-dienoate (4).** In a 50-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and an argon balloon was placed NaHMDS (1.80 mL, 1.0 M solution in THF) in ether (20 mL) and the solution was cooled to −78 °C. Anhydrous methyl acetate (0.15 mL, 1.80 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 50 min. At this time, sulfinimine (*R*)-(−)-**3** (0.35 g, 1.22 mmol) in ether (5 mL) was added dropwise and the reaction mixture was stirred for 4 h and quenched at −78 °C with sat. $NH_4Cl$ solution (6 mL). The aqueous phase was washed with EtOAc (2×8 mL) and the combined organic phases were washed with brine (8 mL), dried ($Na_2SO_4$), and concentrated. Chromatography (50% EtOAc/hexanes) afforded 0.34 g (77%) of an oil; $[\alpha]_D^{20}=-114.0$ (*c* 1.1, $CHCl_3$); IR (KBr): 3198, 2927, 1734, 1437 $cm^{-1}$; $^1H$ NMR ($CHCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.27 (m, 4H), 1.38 (m, 2H), 2.05 (dd, *J*=7.5, 15.0 Hz, 2H), 2.39 (s, 3H), 2.61 (m, 2H), 3.63 (s, 3H), 4.27 (m, 1H), 4.75 (d, *J*=6.0 Hz, 1H), 5.58 (dd, *J*=8.0, 16.5 Hz, 1H), 5.73 (m, 1H), 6.01 (m, 1H), 6.28 (dd, *J*=10.5, 15.0 Hz, 1H), 7.28 (d, *J*=8.0 Hz, 2H), 7.55 (d, *J*=8.0 Hz, 2H); $^{13}C$ NMR δ 14.4, 20.9, 21.8, 22.9, 29.2, 31.8, 33.0, 41.2, 52.2, 53.4, 125.9, 126.8, 129.4, 129.6, 130.0, 133.7, 137.2, 141.7, 142.6, 171.8. HR-MS calcd for $C_{20}H_{29}NO_3SNa$ (M+Na): 386.1766. Found: 386.1756.

**2.1.3. ($R_S$,5*S*)-(−)-Methyl-3-oxo-5-(*p*-toluenesulfinyl-amino)-tetradeca-6,8-dienoate (5).** In a 25-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed NaHMDS (2.60 mL, 1.0 M solution in THF) in THF (6 mL) and the solution was cooled to −78 °C. Methyl acetate (0.21 mL, 2.60 mmol) was added and the reaction mixture was stirred for 1 h and ($R_S$,3*S*)-(−)-**4** (0.23 g, 0.60 mmol) in THF (4 mL) was added. The reaction mixture was stirred at −78 °C for 2.0 h, for 50 min at −15 °C or until completed (monitored by TLC), and quenched by the addition of sat. $NH_4Cl$ (4.0 mL). The aqueous phase was extracted with EtOAc (3×8 mL), the combined organic phases were dried ($Na_2SO_4$), and concentrated.

Chromatography (20% EtOAc/hexane) gave 0.195 g (78%) of an oil; $[\alpha]_D^{20}=-91.6$ (*c* 1.0, $CHCl_3$); IR (neat): 3211, 2926, 1718, 1653 $cm^{-1}$; $^1H$ NMR ($CHCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.27 (m, 4H), 1.38 (m, 2H), 2.05 (dd, *J*=7.5, 15.0 Hz, 2H), 2.39 (s, 3H), 2.88 (d, *J*=6.0 Hz, 2H), 3.40 (s, 2H), 3.70 (s, 3H), 4.31 (m, 1H), 4.63 (d, *J*=6.0 Hz, 1H), 5.58 (dd, *J*=8.0, 16.5 Hz, 1H), 5.73 (m, 1H), 6.01 (m, 1H), 6.22 (dd, *J*=10.5, 15.0 Hz, 1H), 7.28 (d, *J*=8.0 Hz, 2H), 7.57 (d, *J*=8.0 Hz, 2H); $^{13}C$ NMR δ 14.4, 21.8, 22.9, 29.2, 31.8, 33.1, 49.4, 49.9, 52.8, 52.9, 125.9, 129.3, 129.6, 130.0, 133.7, 137.2, 141.8, 142.6, 167.6, 201.2. HR-MS calcd for $C_{22}H_{31}NO_4SNa$ (M+Na): 428.1872. Found: 428.1871.

**2.1.4. (*S*)-(+)-Methyl-3-oxo-5-(*tert*-butyloxycarbonyl-amino)-tetradeca-6,8-dienoate (6).** In a 25-mL,

one-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon-filled balloon was placed ($R_S$,5*S*)-(−)-**5** (0.170 g, 0.40 mmol) in MeOH (8 mL). The reaction mixture was cooled to 0 °C, TFA (0.156 mL, 2.0 mmol) was added, and the reaction mixture was stirred at rt for 2 h. At this time the solution was concentrated, the residue was dissolved in THF (8 mL), cooled to 0 °C, and $Et_3N$ (0.330 mL, 2.4 mmol), DMAP (ca. 0.005 g), and di-*tert*-butyldicarbonate (0.132 g (0.60 mmol) were added. The reaction mixture was stirred for 2 h at 0 °C and quenched by the addition of sat. $NH_4Cl$ (3.0 mL). The aqueous phase was extracted with EtOAc (2×8 mL), and the combined organic phases were washed with $H_2O$ (8 mL), brine (8 mL), dried ($Na_2SO_4$), and concentrated. Chromatography (5–30% EtOAc/hexanes) gave 0.130 g (86%) of a yellow solid; mp 57.0–58.0 °C; $[\alpha]_D^{20}$=+3.60 (*c* 0.7, $CHCl_3$); IR (KBr): 3349, 2924, 1751, 1684, 1525 $cm^{-1}$; $^1H$ NMR ($CHCl_3$) $\delta$ 0.87 (t, *J*=7.0 Hz, 3H), 1.24 (m, 4H), 1.38 (m, 2H), 1.43 (s, 9H), 2.05 (dd, *J*=7.5, 15.0 Hz, 2H), 2.86 (d, *J*=5.0 Hz, 2H), 3.46 (dd, *J*=20.0, 16.0 Hz, 2H), 3.73 (s, 3H), 4.50 (m, 1H), 5.01 (bs, 1H), 5.53 (dd, *J*=8.0, 16.5 Hz, 1H), 5.69 (m, 1H), 5.98 (m, 1H), 6.12 (dd, *J*=10.5, 15.0 Hz, 1H); $^{13}C$ NMR $\delta$ 14.4, 23.0, 29.0, 29.4, 32.0, 33.0, 48.4, 49.5, 50.0, 52.8, 80.2, 91.7, 129.8, 129.9, 132.2, 136.5, 155.7, 167.8, 201.1. Anal calcd for $C_{21}H_{37}NO_5$: C, 65.77; H, 9.72; N, 3.65. Found: C, 65.55; H, 9.29; N, 3.72.

**2.1.5. (*S*)-(+)-Methyl-3-oxo-5-(*tert*-butyloxycarbonylamino)-5-nonylpentanoate (7).** In a 50-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and rubber septum was placed (*S*)-(+)-**6** (0.40 g, 1.04 mmol) in MeOH (20 mL). To the solution was added 10% Pd/C and the reaction mixture was stirred under an $H_2$ balloon for 2 h. At this time, the solution was filtered through Celite and concentrated to give 0.404 g (100%) of a white solid; mp 48.0–49.0 °C; $[\alpha]_D^{20}$=+27.2 (*c* 1.1, $CHCl_3$); IR (KBr): 3353, 2923, 1684 $cm^{-1}$; $^1H$ NMR ($CHCl_3$) $\delta$ 0.87 (t, *J*=7.0 Hz, 3H), 1.24 (b, 14H), 1.41 (b, 9H), 1.50 (b, 2H), 2.74 (m, 2H), 3.47 (m, 2H), 3.73 (s, 3H), 3.89 (m, 1H), 4.79 (d, *J*=8.0 Hz, 1H); $^{13}C$ NMR $\delta$ 14.5, 23.1, 26.6, 28.8, 29.7, 29.9, 32.3, 35.0, 47.8, 48.0, 49.7, 52.8, 79.7, 91.4, 155.8, 167.9, 202.2. Anal calcd for $C_{21}H_{41}NO_5$: C, 65.08; H, 10.66; N, 3.61. Found: C 64.83; H, 10.24; N, 4.01.

**2.1.6. (*S*)-(+)-Methyl-2-diazo-3-oxo-5-(*tert*-butyloxycarbonylamino)-5-nonylpentanoate (8).** In a 25-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed (*S*)-(+)-**7** (0.400 g, 1.08 mmol) and *p*-carboxybenzenesulfonyl azide (*p*-CBSA) (0.277 g, 1.18 mmol) in acetonitrile (8 mL). The reaction mixture was cooled to 0 °C and $Et_3N$ (0.44 mL, 3.24 mmol) was added and the reaction mixture was stirred for 2 h. At this time, the white precipitate was removed by filtration, the filtrate was concentrated, and EtOAc (20 mL) was added to the residue. The organic phase was washed with $H_2O$ (2×8 mL), 1 N NaOH (2×8 mL), brine (10 mL), dried ($Na_2SO_4$), and concentrated to give 0.400 g (94%) of a gel; $[\alpha]_D^{20}$=+26.4 (*c* 1.0, $CHCl_3$); IR (KBr): 3376, 2928, 2855, 2135, 1718, 1172 $cm^{-1}$; $^1H$ NMR ($CHCl_3$) $\delta$ 0.87 (t, *J*=7.0 Hz, 3H), 1.24 (b, 14H), 1.41 (b, 9H), 1.50 (b, 2H), 3.00 (m, 2H), 3.73 (s, 3H), 3.89 (m, 1H), 4.79 (d, *J*=8.0 Hz, 1H); $^{13}C$ NMR $\delta$ 14.5, 23.1, 26.6, 29.8, 29.9, 30.0, 32.4, 36.1, 45.7, 49.0, 52.6, 76.9, 79.6, 156.0, 162.3, 191.3. HR-MS calcd for $C_{20}H_{35}NO_5Na$ (M+Na): 420.2474. Found: 420.2468.

**2.1.7. Methyl-*N*-(*tert*-butyloxycarbonyl)-3-oxo-5-nonylpyrrolidine-2-carboxylate (9).** In a 50-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon-filled balloon was placed (*S*)-(+)-**8** (0.250 g, 0.63 mmol) in DCM (20 mL). To the solution was added $Rh_2(OAc)_4$ (0.028, 5 mol%) and the reaction mixture was stirred for 2 h at rt. At this time, the solution was concentrated. The $^1H$ NMR spectra indicated the presence of a single isomer as a mixture of rotomers suggested by peak broadening; major rotomer: $^1H$ NMR ($CHCl_3$) $\delta$ 0.87 (t, *J*=7.0 Hz, 3H), 1.29 (m, 24H), 1.95 (b, 1H), 2.40 (b, 1H), 2.80 (b, 1H), 3.80 (s, 3H), 4.28 (b, 1H), 4.60 (b, 1H); minor rotomer: $\delta$ 0.87 (t, *J*=7.0 Hz, 3H), 1.29 (m, 24H), 1.95 (b, 1H), 2.38 (b, 1H), 2.82 (b, 1H), 3.80 (s, 3H), 4.28 (b, 1H), 4.68 (b, 1H). Chromatography (10% EtOAc/hexanes) resulted in a 6:1 mixture of isomers; major isomer: $^1H$ NMR ($CHCl_3$) $\delta$ 0.87 (t, *J*=7.0 Hz, 3H), 1.29 (m, 24H), 1.95 (b, 1H), 2.40 (b, 1H), 2.80 (b, 1H), 3.80 (s, 3H), 4.28 (b, 1H), 4.60 (b, 1H); minor isomer: $\delta$ 0.87 (t, *J*=7.0 Hz, 3H), 1.29 (m, 24H), 1.82 (b, 1H), 2.38 (b, 1H), 2.90 (b, 1H), 3.76 (s, 3H), 4.40 (b, 1H), 4.60 (b, 1H).

**2.1.8. (2*S*,3*S*,5*R*)-(−)-*N*-Methyl-2-hydroxymethyl-3-hydroxy-5-nonylpyrrolidine (10).** To crude **9** was added THF (20 mL), the solution was cooled to −78 °C, LAH (0.120 g, 3.15 mmol) was added, and the reaction mixture was stirred for 4 h. At this time, the solution was slowly warmed to 0 °C, stirred at this temperature for 2 h, cooled to −78 °C, and LAH (0.120 g, 3.15 mmol) was added. The reaction mixture was heated at 70 °C for 72 h at which time the reaction was quenched by the addition of $H_2O$ (0.24 mL) and 10% NaOH (0.72 mL), and $H_2O$ (0.24 mL). The solution was stirred for 1 h, passed through Celite, the organic phase was washed with brine (5 mL), and ($Na_2SO_4$), and concentrated. Chromatography (2% MeOH/EtOAc) afforded 0.099 g (61%) of an oil $[\alpha]_D^{20}$=−37.8 (*c* 0.7, $CHCl_3$); IR (KBr): 3379, 2925, 2854, 2791, 1030 $cm^{-1}$; $^1H$ NMR ($CHCl_3$) $\delta$ 0.87 (t, *J*=7.0 Hz, 3H), 1.29 (b, 16H), 1.41 (b, 9H), 1.70 (m, 1H), 2.25 (m, 1H), 2.27 (s, 3H), 2.39 (m, 1H), 2.44 (m, 1H), 3.11 (b, 2H), 3.73 (dd, *J*=3.5, 11.5 Hz, 1H), 3.80 (dd, *J*=2.0, 11.5 Hz, 1H), 4.29 (dd, *J*=7.0, 14.0 Hz, 1H); $^{13}C$ NMR $\delta$ 14.5, 23.1, 26.5, 29.7, 29.98, 30.02, 30.4, 32.3, 34.1, 39.0, 42.3, 59.5, 64.4, 70.1, 72.3. HR-MS calcd for $C_{15}H_{31}NO_2Na$ (M+Na): 280.2252. Found: 280.2260.

**2.1.9. (2*S*,3*S*,5*R*)-(+)-Preussin (2).** In a 10-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed (−)-**10** (0.031 g, 0.120 mmol) in DCM (5 mL), the solution was cooled to 0 °C, $Ph_3P$ (0.160 g, 0.60 mmol), imidazole (0.041 g, 0.60 mmol), and $I_2$ (0.150 g, 0.60 mmol) were added. The reaction mixture was stirred at this temperature for 4 h and the solution was filtered. The filtrate was concentrated, dissolved in THF (3 mL), and cooled to −78 °C. In a separate 10-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed CuI (0.230 g, 1.20 mmol) in THF (2 mL). The solution was cooled to 0 °C, and PhLi (1.5 mL, 2.40 mmol, 1.6 M in cyclohexane and ether) was

added dropwise. The suspension, which turned to a clear green solution after stirring at 0 °C for 10 min, was cooled to −78 °C, and the $I_2$ solution mixture was added dropwise. After stirring the reaction mixture at rt for 8 h the solution was cooled to −78 °C, stirred for 30 min, and poured into sat. aq. $NH_4Cl$ (4 mL). The aqueous phase was extracted with EtOAc (2×10 mL), the combined organic phases were washed with brine (8 mL), dried ($Na_2SO_4$), and concentrated. Chromatography (30% EtOAc/hexane) afforded 0.016 g (41%) of an oil; $[\alpha]_D^{20}=+30.8$ (*c* 0.7, $CHCl_3$) [lit.[4e] +31.5 (*c* 1.0, $CHCl_3$)]. Spectral properties were consistent with literature values.[4e]

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## References and notes

1. (a) Davis, F. A.; Chao, B.; Fang, T.; Szewczyk, J. M. *Org. Lett.* **1999**, *1*, 1041. (b) Davis, F. A.; Chao, B. *Org. Lett.* **2000**, *2*, 2623. (c) Davis, F. A.; Fang, T.; Chao, B.; Burns, D. M. *Synthesis* **2000**, 2106. (d) Davis, F. A.; Chao, B.; Rao, A. *Org. Lett.* **2001**, *3*, 3169. (e) Davis, F. A.; Zhang, Y.; Anilkumar, G. *J. Org. Chem.* **2003**, *68*, 8061. (f) Davis, F. A.; Rao, A.; Carroll, P. J. *Org. Lett.* **2003**, *5*, 3855.
2. (a) Davis, F. A.; Fang, T.; Goswami, R. *Org. Lett.* **2002**, *4*, 1599. (b) Davis, F. A.; Yang, B.; Deng, Y. *J. Org. Chem.* **2003**, *68*, 5147.
3. For a review see Davis, F. A.; Chao, B.; Andemichael, Y. W.; Mohanty, P. K.; Fang, T.; Burns, D. M.; Rao, A.; Szewczyk, J. M. *Heteroto. Chem.* **2002**, *13*, 486.
4. For earlier asymmetric synthesis of (+)-preussin see (a) Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241. (b) Overhand, M.; Hecht, S. M. *J. Org. Chem.* **1994**, *59*, 4721. (c) Bach, T.; Brummerhop, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 3400. (d) Kanazawa, A.; Gillet, S.; Delair, P.; Greene, A. E. *J. Org. Chem.* **1998**, *63*, 4660. (e) Lee, K.-Y.; Kim, Y.-H.; Oh, C.-Y.; Ham, W.-H. *Org. Lett.* **2000**, *2*, 4041. (f) Okue, M.; Watanabe, H.; Kitahara, T. *Tetrahedron* **2001**, *57*, 4107.
5. (a) Schartz, R. E.; Liesch, J.; Hensens, O.; Zitano, L.; Honeycutt, S.; Garrity, G.; Fromtling, R. A.; Onishi, J.; Monaghan, R. *J. Antibiot.* **1988**, 1774. (b) Johnson, J. H.; Phillipson, D. W.; Kahle, A. D. *J. Antibiot.* **1989**, 1184.
6. Clapham, B.; Cho, C.; Janda, K. D. *J. Org. Chem.* **2001**, *66*, 868.
7. (a) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1043. (b) Fanelli, D. L.; Szewczyk, J. M.; Zhang, Y.; Reddy, G. V.; Burns, D. M.; Davis, F. A. *Org. Synth.* **1999**, *77*, 50.