its intensity was much greater than that of any other ion. Minimal fragmentation in the mass spectrum suggests unusual stability of the diamantane structure and its anion. The ^{19}F NMR spectrum of *F*-diamantane consists of three resonances at −117.32, −209.68, and −223.68 ppm relative to internal $CFCl_3$ with ratio of 6:3:1 (Figure 1). This is consistent with the structure of *F*-diamantane which has three groups of chemically equivalent fluorine atoms. The chemical shifts of the secondary fluorine (F_s) and the axial tertiary fluorine (F_a) are close to those of *F*-adamantane[5] since they are in a similar magnetic environment (Figure 2). Also like *F*-adamantane a very simple infrared spectrum reflects the high symmetry of the *F*-diamantane structure. Besides the C–C and C–F stretching bands (at 1300 vs, 1272 w, 1052 m, 968 s cm^{-1}), there is only one other absorption of very weak intensity (at 822 cm^{-1}). The Raman spectrum has bands at 1336 w, 1327 w, 1314 m, 1292 s, 1200 w, 685 m, and 544 s cm^{-1}. Diamantane belongs to D_{3d} point group which has a center of symmetry, vibrations that are infrared active are not Raman active, and vice versa.[10] This was confirmed by our infrared and Raman spectral analysis of perfluorodiamantane. A detailed analysis and calculations relating to the infrared and Raman spectra will be reported later.

Experimental Section

The perfluorination was carried out on an improved reactor, and detailed procedures have been described elsewhere.[9] The products were characterized by a vapor-phase infrared spectrum recorded on a Bio-Rad FTS-7 SPC 3200 spectrometer and a Raman spectrum recorded on a Ramanor HG-2S Spectrophotometer manufactured by Jobin Yvon Instrument, SA. The negative chemical ionization (electron attachment) mass spectrum was recorded on a VG.ZAB-EQ mass spectrometer. Samples were introduced into the source via the reference inlet to a pressure of 10^{-6} Torr and diluted with nitrogen gas to 10^{-5}–10^{-4} Torr and bombarded with 70 eV electrons. The ^{19}F FTNMR spectrum was recorded on a JEOL FX90Q (omniprobe) in $CFCl_3$ as both solvent and internal standard; elemental analyses were performed by E+R Microanalytical Laboratory, Inc., Corona, NY.

Diamantane was prepared according to literature procedures[11] and purified by column chromatography using hexane as eluant and alumina as stationary phase. The product (mp 230 °C, lit.[6] mp 236–237 °C) was contaminated with an isomeric material comprising approximately 22% by GLC. DSC of the unsealed diamantane sample shows sublimation (heat flow) begins about 62 °C and increases almost linearly to 125 °C where rapid heat gain occurs. Sublimation at 85 °C gives slow steady sublimation of about 0.08 g/h.

Aerosol Fluorination of Diamantane. Diamantane 77% (0.50 g, 2.66 mmol) was loaded into the hydrocarbon evaporator. Referring to the aerosol fluorinator components described in Figure 1 in ref 9, the following specific fluorination conditions were used: preaerosol furnace (>1050 °C), main carrier, 500 mL/min He; hydrocarbon evaporator (85 °C), primary hydrocarbon carrier, 170 mL/min He, secondary hydrocarbon carrier, 500 mL/min He; module 1 (−18 °C), inlet 1-1, 170 mL/min He, 8 mL/min F_2; inlet 1-2, 170 mL/min He, 52 mL/min F_2; module 2 (−10 °C), inlet 2-1, 170 mL/min He, 38 mL/min F_2; inlet 2-2, 170 mL/min He, 6 mL/min F_2. All helium carrier gas flows were initiated except the primary hydrocarbon carrier gas. When the preaerosol (NaF) furnace reached 1050 °C, fluorine flow was initiated. When all gas flows were stable and required temperatures were reached, the dewar around the product trap was filled with liquid N_2. The valve controlling the primary hydrocarbon carrier gas was opened, and the evaporator was heated to 85 °C at which temperature diamantane sublimes slowly. After 5 h, the reaction was stopped. The product trap was connected to the vacuum line and pumped for 18 h to effect maximum transfer. Following trap to trap fractionation, 0.12 g of crude product was collected as a white solid in the −22 °C trap. About 0.10 g of starting material was recovered from the evaporator of the reactor. Pure perfluorodiamantane (0.10 g, 8.0 % yield) was obtained by dissolving the fractionated product (77.2% GLC purity) in $CF_2ClCFCl_2$ (R-113) and separating on a Fluorosilicone QF-1 column (7 m × $^3/_8$ in.). The column temperature was 180 °C and retention time was 17.5 min. Anal. Calcd for $C_{14}F_{20}$: C, 30.68; F, 69.32; H, 0.00. Found: C, 30.75; F, 69.78; H, 0.00.

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Synthesis of Ant Venom Alkaloids from Chiral β-Enamino Lactones: (3*S*,5*R*,8*S*)-3-Heptyl-5-methylpyrrolizidine

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A large number of substituted piperidines and pyrrolidines have been reported as constituents from the venoms of ants in the related genera *Monomorium* and *Solenopsis*, many of which display significant biological activity.[1] Although the relative configurations of these compounds have been determined by racemic syntheses, their absolute configurations have not been yet established, probably owing to the scarcity of natural material. We report here the enantiospecific synthesis of (3*S*,5*R*,8*S*)-3-heptyl-3-methylpyrrolizidine (1), which is the only known bicyclic alkaloid from a *Solenopsis* species, as well as being the only known natural 3,5-dialkylpyrrolizidine.[2]

The first asymmetric synthesis was described by Takano et al.[3a] from a chiral epoxide, the second by Husson et al.,[3b] by utilizing a chiral 2-cyano-6-oxazolopiperidine synthon, and the third by Momose et al.[3c] from alanine. The relative stereochemistries at C-3, C-5, and C-8 of pyrrolizidine 1 have been well established in both syntheses, yet the reported optical rotations are contradictory: the synthetic alkaloid 1 was stated to be levorotatory in the work of Takano and dextrorotatory in the syntheses of Husson and Momose for the same reported absolute configurations. Here we present a new strategy for the synthesis of such compounds.

Results and Discussion

Our approach includes the reductions of the iminium **2** to induce the formation of the last asymmetric carbon C-3 and of the imino alcohol **3** to form the C-8 atom with a *S*-configuration from the chiral pyrrolidinone **4d** (Scheme I).

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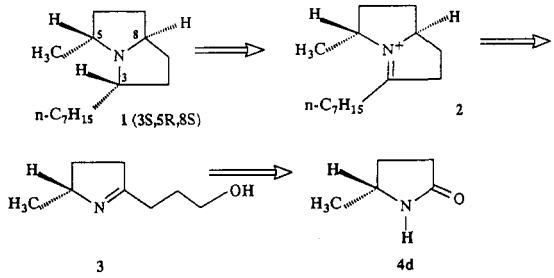
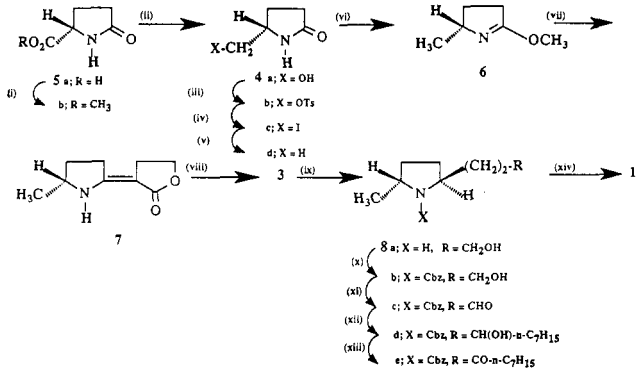
Scheme I



Scheme II[a]



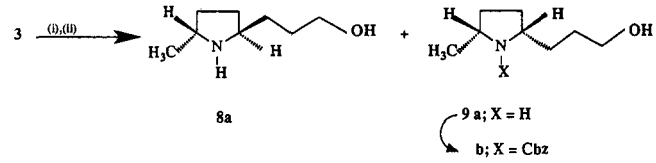
[a] Reagents: (i) MeOH, $SOCl_2$ (86%); (ii) $NaBH_4$, EtOH, −15 °C to room temperature (90%); (iii) TsCl, $N(Et)_3$, CH_2Cl_2, (72%); (iv) NaI, CH_3CN reflux (97%); (v) H_2 atm pressure, PtO_2, N(Et) MeOH (67%); (vi) $MeSO_4$, 60 °C (78%); (vii) 2-acetylbutyrolactone, $Ni(acac)_2$, 110 °C, 110 h (63%); (viii) 3 N HCl, 60 °C, 12 h (92%); (ix) $NaBH_4$, EtOH, (90%); (x) CbzCl, $NaHCO_3$, H_2O, 80 °C (65%); (xi) PCC, CH_2Cl_2 (83%); (xii) n-$C_7H_{15}MgBr$, ether (62%); (xiii) PCC, CH_2Cl_2 (59%); (xiv) H_2 atm pressure, $Pd/BaSO_4$, MeOH (80%).

Attention was directed first toward the synthesis of the (*R*)-5-methylpyrrolidinone (**4d**), which was prepared from the readily available natural (*S*)-pyroglutamic acid (**5a**). The acid **5a** was esterified, then reduced to the alcohol **4a**, and transformed to the tosylate **4b**, according to the reported method.[4] Nucleophilic substitution of **4b** with sodium iodide followed by hydrogenolysis afforded the pyrrolidinone **4d**. These preliminary steps permit us to elaborate a new synthesis of (3*S*,5*R*,8*S*)-3-heptyl-5-methylpyrrolizidine (**1**) (Scheme II).

The key feature of our strategy is based upon a new condensation reaction between 2-acetylbutyrolactone and lactim ether **6** (prepared by reaction of lactam **4d** with dimethyl sulfate) which affords the chiral β-enamino lactone **7**. This reaction is base catalyzed by $Ni(acac)_2$[5] and allows direct introduction of a protected alcohol, which is a carbonyl equivalent that can be transformed to iminium **2**. This is the first example reported of monosubstituted β-keto ester condensation with lactim ether.[6] The reaction requires a deacylation step, with liberation of methanol to lead to the thermodynamically stable β-enamino ester (Scheme II).

With 3 N hydrochloric acid **7** hydrolyzes and decarboxylates cleanly to give the imino alcohol **3**. Reduction of **3** with sodium borohydride in ethanol affords a mixture (ca. 1:1) of pyrrolidines **8a** and **9a**. This reduction had been observed under other experimental conditions[7] to give

Scheme III[a]



[a] Reagents: (i) $NaBH_4$, EtOH, **8a** + **9a** (90%); (ii) CbzCl, $NaHCO_3$, H_2O, 0 °C, **9b** (92%) + unchanged **8a** (90%).

stereoselective trans reduction of unfunctionalized pyrrolidines, but in the present study a separation of isomers was required.

Before oxidizing alcohol **8a** to carbonyl derivative, the secondary amine had to be protected as a carbamate **8b**[8] to avoid a ring-closure reaction. Benzyl chloroformate reacted with the diastereoisomeric mixture of amino alcohols **8a** and **9a**, but kinetic control was observed leading to an easy chemical separation of compounds **8a** and **9a**. At 0 °C, only the cis isomer is transformed into the carbamate **9b**. This reaction is another key step which permits isolation of the pure trans amino alcohol **8a** (Scheme III).

Upon treatment with benzyl chloroformate at 80 °C, the trans heterocycle **8a** affords the carbamate **8b**. Oxidation of **8b** with pyridinium chlorochromate gives the aldehyde **8c**. Further carbon-chain elongation of **8c** was carried out by addition of a Grignard reagent. Corey–Suggs[9] oxidation of the resulting alcohol **8d** affords ketone **8e**, and final hydrogenation over $Pd/BaSO_4$ in methanol gives stereospecifically (+)-(3*S*,5*R*,8*S*)-3-heptyl-5-methylpyrrolizidine (**1**), $[\alpha]^{22}_D$ +6.60 (*c* = 2.35, chloroform). The infrared and ^1H and ^{13}C NMR spectra of synthetic material **1** are identical with those reported for the natural product.[2]

The stereochemical determination of carbamates **8b** and **9b** was fully established after examination of their ^1H NMR spectra. The diastereotopic protons of the methylene benzylic group gave a characteristic AB pattern in the trans isomer **8b** while they do not show significant nonequivalence in the cis isomer **9b**. The two diasteroisomeric pyrrolidines **8a** and **9a** can also be distinguished in their ^{13}C NMR spectra. The four chemical shifts δ = 58.8, 57.7, 54.1, and 52.7 ppm are assigned to the tertiary carbons C-α and C-α′ of the heterocycles **8a** and **9a** from the mixture obtained by $NaBH_4$ reduction of cyclic imine **3**. The chemical shifts δ = 57.7 ppm for C-α with the hydroxypropyl substituent and δ = 52.7 for C-α′ bearing the methyl substituent were assigned to the pure *trans*-pyrrolidine **8a**, compared with those of the cis isomer **9a**, which are always upfield ($\delta_{C\text{-}\alpha}$ = 58.8 and $\delta_{C\text{-}\alpha'}$ =. 54.1).[10]

For compounds **8b**, **8c**, **8d**, **8e**, and **9b**, peak doubling is observed. A ^1H NMR variable-temperature experiment carried out with **8c** showed coalescence of split peaks, which proved the existence of conformers and the absence of epimers.

The last reductive annelation yields a pure diasteroisomer of compound **1** whose relative sterochemistry has already been established.[2a] ^1H NMR spectrum of compound **1** exhibits single-proton multiplets centered at δ 3.60, 2.78, and 2.62, which are characteristic of cis-fused pyrrolizidines with the 3- and 5-H trans to the nitrogen lone pair.[11] Characteristic ^{13}C NMR resonances at δ 66.5,

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(6) This reaction is still in study and seems to be general.
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64.8, and 61.6 ppm for the C-8, C-3, and C-5 are in complete accord with these described for the natural product.[2a]

Conclusion

The present work is the first entry to the synthesis of pyrrolizidine alkaloids starting from (*S*)-pyroglutamic acid. This synthesis permits unambiguous assignment of the absolute configuration 3*S*,5*R*,8*S* to the dextrorotatory isomer.

Experimental Section

All melting points were determined with a Büchi apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter in a 1-dm cell. IR spectra were recorded on a Philips PU 9700 spectrometer. ^{1}H NMR spectra were measured with a Bruker WP 80 (80 MHz), Bruker AC 200 (200 MHz), and Bruker WM 500 (500 MHz). ^{13}C NMR spectra were determined on a Bruker WM 80 (20 MHz) and Bruker AC 200 (50 MHz). ^{1}H chemical shifts are reported in ppm from an internal standard Me_4Si or of residual chloroform (7.27 ppm). ^{13}C chemical shifts are reported in ppm from the central peak of deuteriochloroform (77.1 ppm). Mass spectra were measured with a Nermag R-10-10 spectrometer. Analytical TLC was performed on Merck precoated silica gel 60F plates. Merck silica gel 60 (230–400 mesh) was used for column chromatography.

Methyl (*S*)-pyroglutamate (5b) was prepared from (*S*)-pyroglutamic acid (**5a**) according to Maeda's method[12] in 86% yield.

(*S*)-5-(Hydroxymethyl)pyrrolidin-2-one (4a) was prepared by $NaBH_4$ reduction of **5b** in 90% yield.[12]

(*S*)-5-[(Tosyloxy)methyl]pyrrolidin-2-one (4b) was obtained by reaction of **4a** with tosyl chloride in presence of triethylamine[13] to afford **4b** in 72% yield.

(*S*)-5-(Iodomethyl)pyrrolidin-2-one (4c). A solution of **4b** (50 g, 185 mmol) and sodium iodide (85 g, 570 mmol) in dry CH_3CN (650 mL) were refluxed for 4 h. After filtration, the solution was concentrated in vacuo, acidified with 1 N HCl (150 mL), and extracted with $CHCl_3$ (3 × 100 mL). The extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residual crystals were washed with hexane (250 mL) and recrystallized from benzene/acetone (99:1) to afford **4c** (40.4 g, 97% yield): mp 81 °C [lit.[3] mp 78–80 °C]; $[\alpha]^{22}_D$ −63° (*c* = 1.24, ethanol) [lit.[14] $[\alpha]^{20}_D$ −55° (*c* = 1.24, ethanol)]; IR ($CHBr_3$) 3400, 1705 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ 7.00–6.80 (m, 1 H), 3.95–3.75 (m, 1 H), 3.25 (d, 2 H, *J* = 8 Hz), 2.55–2.20 (m, 3 H), 1.95–1.70 (m, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.0, 55.3, 30.3, 27.4, 11.2. Anal. Calcd for C_5H_8NOI: C, 26.68; H, 3.58; N, 6.22. Found: C, 26.75, H, 3.59; N, 6.06.

(*R*)-5-Methylpyrrolidin-2-one (4d). A solution of **4c** (22.5 g, 100 mmol) and triethylamine (20.2 g, 200 mmol) in methanol (80 mL) was hydrogenated, at atmospheric pressure, in the presence of PtO_2 (30 mg). After filtration the solution was concentrated under reduced pressure. The residue was acidified with 1 N HCl (30 mL) and extracted with $CHCl_3$ (3 × 100 mL). The organic layers were dried over Na_2SO_4, evaporated, and then distilled under reduced pressure to give **4d** (6.6 g, 67% yield): bp 138 °C (35 mmHg) [lit.[12] bp 89 °C (6 mmHg)]; $[\alpha]^{22}_D$ +24.6° (*c* = 0.9, water) [lit.[12] $[\alpha]^{22}_D$ +17.2° (*c* = 1.02, ethanol)]; IR (neat) 3250, 1690 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 7.00–6.80 (m, 1 H), 3.90–3.70 (m, 1 H), 2.50–1.85 (m, 3 H), 1.70–1.20 (m, 1 H), 1.15 (d, 3 H, *J* = 6 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) δ 170.4, 50.0, 30.5, 28.9, 21.9. Anal. Calcd for C_5H_9NO: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.75, H, 9.20; N, 14.11.

(*R*)-2-Methoxy-5-methyl-5*H*-3,4-dihydropyrrole (6). A mixture of lactam **4d** (9.9 g, 100 mmol) and dimethyl sulfate (12.6 g, 100 mmol) were heated at 60 °C overnight. The reaction mixture is basified to pH 9 with aqueous potassium carbonate, extracted with ether (6 × 50 mL), dried over Na_2SO_4, and concentrated. The crude product was distilled under reduced pressure to afford **6** (8.8 g, 78% yield): bp 38 °C (35 mmHg); $[\alpha]^{22}_D$ +46.7° (*c* = 0.96, ethanol); IR (neat) 1640 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 4.20–3.80 (m, 1 H), 3.90 (s, 3 H), 2.75–2.00 (m, 3 H), 1.75–1.30 (m, 1 H), 1.25 (d, 3 H, *J* = 7 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) δ 172.1, 61.4, 55.0, 31.6, 22.8. Anal. Calcd for $C_6H_{11}NO$:C, 63.68; H, 9.80; N, 12.39. Found: C, 63.42, H, 9.95; N, 12.05.

(*R*)-3-(5-Methyl-2-pyrrolidinylidene)furan-2-one (7). Lactim ether **6** (10.2 g, 90 mmol), 2-acetylbutyrolactone (12.8 g, 100 mmol), and $Ni(acac)_2$ (0.5 g, 2 mmol) were heated at 110 °C for 110 h. The reaction mixture was concentrated and recrystallized from cyclohexane/acetone (98:2) to obtained **7** (9.5 g, 63% yield): mp 98 °C; $[\alpha]^{22}_D$ +17.6° (*c* = 1.08, dichloromethane); IR($CHBr_3$) 1690, 1615 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55–7.30 (m, 1 H), 4.25 (t, 2 H, *J* = 7 Hz), 4.00–3.80 (m, 1 H), 2.75 (t, 2 H, *J* = 7 Hz), 2.60–2.40 (m, 2 H), 2.25–2.05 (m, 1 H), 1.70–1.40 (m, 1 H), 1.20 (d, 3 H, *J* = 7 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) δ 174.4, 160.40, 80.5, 65.8, 52.1, 31.0, 30.1, 25.8, 21.7. Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.61; H, 7.79; N, 8.36.

(*R*)-2-(1-Hydroxypropyl)-5-methyl-5*H*-3,4-dihydropyrrole (3). Enamino lactone **7** (3.35 g, 20 mmol) and 3 N HCl (30 mL) were heated at 60 °C for 12 h. An aqueous potassium carbonate solution was then slowly added until pH = 9. The reaction mixture was extracted with $CHCl_3$ (3 × 15 mL), dried over Na_2SO_4, concentrated, and distilled under reduced pressure to give **3** (2.6 g, 92% yield): bp 134 °C (25 mmHg); $[\alpha]^{22}_D$ +73° (*c* = 1, ethanol); IR (neat) 3600, 3200, 1640 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.25–5.10 (br s, 1 H), 3.95–3.75 (m, 1 H), 3.50 (t, 2 H, *J* = 6 Hz), 2.50–2.25 (m, 4 H), 2.05–1.85 (m, 1 H), 1.70 (q, 2 H, *J* = 6 Hz), 1.35–1.15 (m, 1 H), 1.05 (d, 3 H, *J* = 6 Hz); ^{13}C NMR (20 MHz, $CDCl_3$), δ 177.8, 67.3, 62.2, 38.0, 31.7, 30.5, 28.7, 21.8. Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.02; H, 10.70; N, 9.83.

Reduction of Imino Alcohol 3. Sodium borohydride (11.4 g, 300 mmol) was added by small portions to a solution of **3** (14.1 g, 100 mmol) in absolute EtOH (100 mL) with stirring for 48 h. The reaction was acidified with 6 N HCl until pH = 1. Stirring was continued 1 h, and then EtOH was removed under reduced pressure and the resulting aqueous solution saturated with K_2CO_3. The mixture was extracted with $CHCl_3$ (5 × 50 mL). Organic layers were dried over Na_2SO_4, concentrated, and then distilled under reduced pressure to afford a mixture of **8a** and **9a** (1:1) (12.9 g, 90% yield): bp 138 °C (25 mmHg) [lit.[15] bp 113–114 °C (5 mmHg)]. Then benzyl chloroformate (14.15 g, 83 mmol) was added drop by drop to a solution containing the mixture of amino alcohols **8a** and **9a** (11.9 g, 83 mmol) and $NaHCO_3$ (7 g, 83 mmol) in water (140 mL), maintained at 0 °C. The reaction mixture was stirred 30 min at 0 °C and 1.5 h at room temperature, extracted with $CHCl_3$ (5 × 30 mL), dried over Na_2SO_4, and concentrated in vacuo, and the crude product was distilled under reduced pressure to give the carbamate **9b** (92% yield). Then the aqueous layer was saturated with solid K_2CO_3, extracted with $CHCl_3$ (6 × 60 mL), dried over Na_2SO_4, concentrated in vacuo, and distilled under reduced pressure to afford the amino alcohol **8a** (6.4 g, 90% yield).

(2*S*,5*R*)-2-(1-Hydroxypropyl)-5-methylpyrrolidine (8a): bp 138 °C (25 mmHg); $[\alpha]^{22}_D$ −25.1° (*c* = 1, dichloromethane); IR (neat) 3300 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18–3.76 (m, 2 H), 3.49–3.42 (m, 1 H), 3.41–3.35 (m, 1 H), 3.10–3.01 (m, 2 H), 1.86–1.77 (m, 2 H), 1.55–1.38 (m, 3 H), 1.37–1.28 (m, 1 H), 1.27–1.16 (m, 1 H), 1.15–1.04 (m, 1 H), 0.97 (d, 3 H, *J* = 7 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) δ 62.0, 57.7, 52.8, 34.3, 34.2, 32.4, 30.1, 20.8. Anal. Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 67.02; H, 11.91; N, 9.81.

(2*R*,5*R*)-1-(Carbobenzyloxy)-2-(1-hydroxypropyl)-5-methylpyrrolidine (9b): bp 180 °C (0.5 mmHg); $[\alpha]^{22}_D$ + 10.0° (*c* = 0.89, chloroform); IR (neat) 3600–3200, 1670 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30 (br, s, 5 H), 5.15 (s, 2 H), 4.05–3.80 (m, 2 H), 3.70–3.50 (m, 2 H), 2.15 (s, 1 H), 2.10–1.35 (m 8 H), 1.20 (d, 3 H, *J* = 7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.3, 136.9, 128.4, 127.8, 66.5, 62.4, 58.7, 54.1, 32.4, 22.0. Anal. Calcd for $C_{16}H_{23}NO_3$:

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C, 69.28; H, 8.36; N, 5.05. Found: C, 69.09; H, 8.37; N, 5.24.

(2*S*,5*R*)-1-(Carbobenzyloxy)-2-(1-hydroxypropyl)-5-methylpyrrolidine (8b). To the *trans*-amino alcohol **8a** (2.7 g, 19 mmol) in water (35 mL) containing $NaHCO_3$ (2 g, 24 mmol) was added benzyl chloroformate (3.22 g, 19 mmol). The reaction mixture was heated at 80 °C for 24 h, cooled, and extracted with $CHCl_3$ (3 × 30 mL). To the aqueous layer was added benzyl chloroformate (3.22 g, 19 mmol), and the mixture was heated at 80 °C for 24 h. The reaction mixture was then extracted with $CHCl_3$ (3 × 30 mL). The organic layers were joined, dried over Na_2SO_4, concentrated in vacuo, and distilled under reduced pressure to give **8b** (3.4 g, 65% yield): bp 175 °C (0.05 mmHg); $[\alpha]^{22}_D$ −55° (c = 1.36, chloroform); IR (neat) 3500, 1680 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.50–7.20 (m, 5 H), 5.20–5.00 (m, 2 H), 4.05–3.70 (m, 2 H), 3.70–3.40 (m, 2 H), 2.70–2.50 (m, 1 H), 2.20–1.10 (m, 8 H), 1.15 (d, 1 H, *J* = 7 Hz), 1.10 (d, 2 H, *J* = 7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.7, 154.2, 136.9, 128.4, 127.9, 66.6, 62.4, 62.1, 57.4, 53.5, 30.5, 30.3, 29.60, 29.4, 29.1, 27.5, 26.9, 20.4, 19.3. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.28; H, 8.31; N, 5.14.

(2*S*,5*R*)-1-(Carbobenzyloxy)-2-(1-oxopropyl)-5-methylpyrrolidine (8c). Carbamate **8b** (2.77 g, 10 mmol) in CH_2Cl_2 (30 mL) was added to a solution of pyridinium chlorochromate (3.45 g, 16 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then 3 h at room temperature. The solution was filtered over Celite, and the solvent was removed in vacuo. The brown residue was triturated with ether (4 × 30 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo to give **8c** (2.28 g, 83% yield). An analytical sample was distilled under reduced pressure: bp (Kugelrohr) 220 °C (0.1 mmHg); $[\alpha]^{22}_D$ −56° (c = 0.95, chloroform); IR (neat) 1720, 1680 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.85–9.75 (m, 0.7 H), 9.55–9.45 (m, 0.3 H), 7.35–7.15 (br s, 5 H), 5.20–5.00 (m, 2 H), 4.10–3.70 (m, 2 H), 2.50–1.40 (m, 6 H), 1.20 (d, 1 H, *J* = 7 Hz), 1.15 (d, 2 H, *J* = 7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.5, 201.0, 154.2, 154.1, 136.8, 128.4, 127.8, 66.5, 57.4, 53.6, 41.0, 40.9, 30.5, 29.6, 27.9, 27.5, 26.7, 26.5, 25.6, 20.4, 19.2. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.95; H, 7.74; N, 5.10.

1-(Carbobenzyloxy)-2-(3-hydroxydecyl)-5-methylpyrrolidine (8d). Grignard reagent was prepared from Mg (2.9 g, 120 mmol) and heptyl bromide (19.7 g, 110 mmol) and then added to a cold (0 °C) solution of aldehyde **8c** (27.5 g, 100 mmol) in dry ether (100 mL). The reaction mixture was stirred 30 min at 0 °C then 3 h at room temperature, dropped to ice containing NH_4Cl, extracted with ether (4 × 60 mL), dried over Na_2SO_4, concentrated in vacuo, and purified by chromatography on silica gel (eluted with ether:pentane = 60:40, R_f = 0.2) to give alcohol **8d** (22.5 g, 62% yield): bp 204 °C (0.05 mmHg); IR (neat) 3500, 3200, 1680 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35–7.15 (m, 5 H), 5.15 (s, 2 H), 4.10–3.40 (m, 3 H), 2.40–1.70 (m, 4 H), 1.70–1.10 (m, 20 H). 0.95–0.75 (m, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.0, 137.0, 128.3, 127.7, 66.4, 52.9, 37.2, 31.7, 30.4, 29.6, 29.2, 27.4, 26.9, 25.6, 22.6, 20.4, 19.2, 14.0. Anal. Calcd for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.73. Found: C, 73.51; H, 9.54; N, 3.39.

(2*S*,5*R*)-1-(Carbobenzyloxy)-2-(3-oxodecyl)-5-methylpyrrolidine (8e). Alcohol **8d** (3.75 g, 10 mmol) in CH_2Cl_2 (30 mL) was added to a solution of pyridinium chlorochromate (3.45 g, 16 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then 3 h at room temperature. The solution was filtered over Celite and solvent removed in vacuo. The brown residue was triturated with ether (4 × 30 mL). The organic layers were dried over Na_2SO_4, concentrated in vacuo, and purified by chromatography on silica gel (eluted with ether:pentane = 20:80, R_f = 0.20) to isolate ketone **8e** (2.2 g, 59% yield): bp 194 °C (0.05 mmHg); IR (neat) 1700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.45–7.22 (m, 5 H), 5.25–5.03 (m, 2 H), 4.20–3.70 (m, 2 H), 2.55–2.18 (m, 4 H), 2.18–1.80 (m, 2 H), 1.75–1.40 (m, 4 H), 1.38–1.05 (m, 13 H), 1.00–0.80 (m, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.0, 155.1, 137.0, 128.5, 127.9, 66.5, 57.5, 57.2, 53.6, 53.3, 42.6, 39.9, 31.7, 31.0, 29.9, 29.2, 29.1, 28.5, 27.5, 27.2, 23.7, 22.6, 20.8, 19.6, 14.1. Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 73.85; H, 9.41; N, 3.74.

(3*S*,5*R*,8*S*)-3-Heptyl-5-methylpyrrolizidine (1). Carbamate **8e** (0.75 g, 2 mmol) in methanol (30 mL) was hydrogenated at atmospheric pressure over Pd–$BaSO_4$ (20 mg). When 2 equiv were absorbed, the solution was filtered and the solvent removed in vacuo. The crude product was distilled under reduced pressure to give **1** (0.36 g, 80% yield): bp 190 °C (25 mmHg); $[\alpha]^{22}_D$ +6.60° (c = 2.35, chloroform); IR (neat) 2860, 2790 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.65–3.55 (m, 1 H), 2.85–2.70 (m, 1 H), 2.70–2.55 (m, 1 H), 2.05–1.80 (m, 4 H), 1.55–1.15 (m, 16 H), 1.10 (d, 3 H, *J* = 7 Hz), 0.85 (t, 3 H, *J* = 7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 66.5, 64.8, 61.6, 37.1, 34.4, 32.3, 32.0, 31.8, 31.6, 29.8, 29.3, 27.2, 22.6, 21.7, 13.9. MS (70 ev) *m/z* 223 (6) [$M^{+\cdot}$], 208 (9), 194 (3), 180 (2.5), 166 (1), 152 (1.5), 124 (100), 110 (4), 81 (21), 55 (10), 31 (7). Anal. Calcd for $C_{15}H_{29}N$: C, 80.64, H, 13.09; N, 6.27. Found: C, 80.52; H, 13.08; N, 6.22. The data show 2% less of the epimeric isomer at C-3.

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Supplementary Material Available: Spectra of **4c**, **4d**, **6**, **7**, **3**, **8a**, **8b**, **8c**, **9b**, **8d**, **8e**, and **1** (27 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; seen any current masthead page for ordering information.

CsF-Promoted Esterification of Carboxylic Acids. A Practical Alternative to the Diazomethane Method and Direct Conversion of Organotin Carboxylates

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Esterification of carboxylic acids by reaction with alkyl halides is a fundamental transformation in organic synthesis.[1] Potassium and cesium salts have proved useful for this purpose. Clark et al., in their extensive studies, revealed KF to be effective, but unfortunately, the reaction usually required high temperature (110–130 °C).[2] In addition, KF[3] and $CsHCO_3$[4] were reported to promote solid-phase peptide synthesis. More recently, Cs_2CO_3 was employed in macrolactonization[5] and peptide synthesis.[6] However, little attention has been directed toward CsF[7]

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