First Synthesis of Nonracemic (*R*)-(+)-Myrmicarin 217

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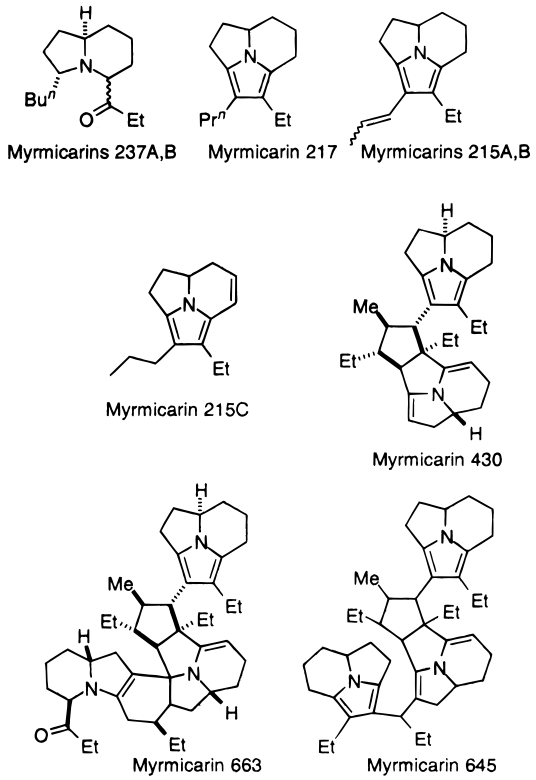
Although ants (Formicidae) have been known to produce various monocyclic and bicyclic alkaloids for a long time,[1] it is only recently that tricyclic and oligocyclic alkaloids were found in their poison glands. Such compounds were discovered by Schröder et al. in the secretions of *Myrmicaria* ants, a genus of african Myrmicinae (*M. striata*, *M. eumenoides*, and *M. opaciventris*), and named myrmicarins (Chart 1). Myrmicarins 217 and 215A−C are simple pyrrolo[2,1,5-*cd*]indolizidines. In myrmicarin 217 (M217) the substituents on the pyrrole ring are an ethyl and a propyl group.[2] For M215A,B the propyl group is replaced by a propenyl substituent ((*Z*) for M215A, (*E*) for M215B). M215C is probably formed by air oxidation of M217. M430 can be regarded as a dimer of M215.[3] It is composed of a complex four-ring system and a pyrroloindolizidine subunit. M663 possesses a trimeric structure, also including a pyrroloindolizidine moiety.[4] Another compound, M645, has been tentatively assigned a trimeric structure containing two pyrroloindolizidine moieties. All these compounds can be postulated to derive biochemically from two other myrmicarins, M237A,B, which are epimers at position 5, but in which position 8a is known to be (*R*). Thus, even though the absolute configuration of M215A−C, M217, M430, and M663 are not known, it is probable that stereogenic centers of these pyrroloindolizidines also have a (*R*) configuration.

Syntheses of M237A,B have been reported,[5,6] as well as a synthesis of racemic M217.[7] Here we present the first synthesis of nonracemic (*R*)-(+)-myrmicarin 217 and of its enantiomer.

We choose L and D glutamic acids to introduce the stereogenic center of (*R*)-M217 and of its enantiomer. According to a procedure described by Jefford et al.,[8] the diethyl ester of D-glutamic acid was condensed with tetrahydro-2,5-dimethoxyfuran to give the pyrrole **1** (Scheme 1) which when treated by BBr_3 gave the bicyclic compound **2**. A first attempt to reduce simultaneously the two carbonyl groups of this ketoester, using $LiAlH_4$, failed. A two-step strategy was then envisaged using

Chart 1



$NaBH_3CN$ in the presence of ZnI_2 to reduce the ketone function into a methylene group[9] and $LiAlH_4$ in THF to reduce the ester function into an alcohol. Using these conditions, compound **3** was obtained in 72% yield from **2**. At this stage, one further carbon atom was to be introduced. The alcohol **3** was transformed into a sulfonate, which upon treatment with cyanide anions gave nitrile **4**. Interestingly, when this nucleophilic substitution was carried out with a triflate group, the yield of this two-step homologation was 55%, while a 90% yield was obtained when the leaving group was a mesylate. Chiral GC analysis of compound **4** showed that it was 97% enantiomerically pure. Hydrolysis of the nitrile group was performed in 90% yield using an aqueous sodium hydroxide solution in methanol. Cyclization of the corresponding acid **5** to the tetrahydro-1*H*-pyrroloindolizine **6** was achieved in poor yield (20%) with phosphorus pentaoxide in toluene.[10] A more efficient process (57% yield) involved the formation of a mixed anhydride followed by ring closure at 40 °C in CH_2Cl_2 in the presence of $BF_3{\cdot}OEt_2$. Afterward, a Friedel−Crafts acylation was carried out to introduce an acetyl group on C4 of the pyrrole ring,[11] and as expected, due to the carbonyl group at the C2 position, the reaction was totally regioselective. Once more, two carbonyl groups had to be reduced. To our surprise, the substrate **7** underwent polymerization when the previously used conditions ($NaBH_3CN$, ZnI_2) were employed. Attempts using the

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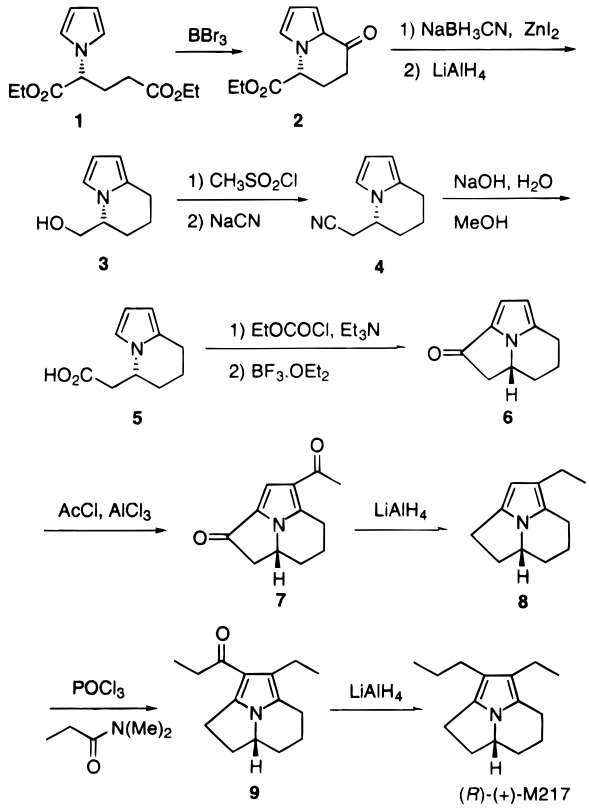
Scheme 1



Wolff−Kishner reduction also failed. Finally, it was found that $LiAlH_4$ efficiently reduced simultaneously the two ketone functions into methylene groups (60% yield). Introduction of a propionyl substituent in the last free position of the pyrrole ring was necessary to complete the synthesis. The best result was obtained with a Vilsmeier-type reagent (prepared by the reaction of *N*,*N*-dimethylpropionamide with $POCl_3$) which reacted with compound **8** to provide the ketone **9** in reasonable yield.[12] The last step of the synthesis was the reduction of the ketone function by $LiAlH_4$ (yield: 60%).

As previously noticed by Schröder et al., we observed that M217 is readily oxidized by air into M215C. However, M217 can be preserved from oxidation by storing under a nitrogen atmosphere. The overall yield of (*R*)-M217 from pyrrole **1** was 7.5%. Its ee, determined by chiral gas chromatography, was found to be 98% and its $[\alpha]_D$ was +88 (*c* 1, CH_2Cl_2). Similarly, (*S*)-*ent*-M217 was obtained from L-glutamic acid.

Experimental Section

All commercial solvents were distilled before use. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen atmosphere. Column chromatography purifications were carried out using silica gel (70−230 mesh).^{1}H NMR and ^{13}C NMR were recorded at 200 and 50 MHz, respectively. Peak assignments were determined using DEPT and two-dimensional experiments.

(5*R*)-(5,6,7,8-Tetrahydroindolizin-5-yl)methanol (3). A solution of **2** (2.03 g, 10 mmol) in dry CH_2Cl_2 (30 mL) was added to a suspension of $NaBH_3CN$ (0.628 g, 15 mmol) and ZnI_2 (10 mmol) in dry CH_2Cl_2 (30 mL). The resulting mixture was refluxed for 150 min and then poured onto crushed ice. After decantation the organic layer was dried over $MgSO_4$ and concentrated to give the corresponding indolizine which was characterized by ^{1}H and ^{13}C NMR spectroscopy.^{1}H NMR (200 MHz; $CDCl_3$) δ (ppm) 1.26 (t, 3H, J = 6.8 Hz, Me), 1.78 (m, 2H, H-6), 2.19 (m, 2H, H-7), 2.79 (m, 2H, H-8), 4.21 (q, 2H, J = 6.8 Hz, O−CH_2), 4.70 (m, 1H, H-5), 5.84 (m, 1H, H-2), 6.13 (m, 1H, H-1), 6.49 (m, 1H, H-3); ^{13}C NMR (50 MHz; $CDCl_3$) δ 14.1 (Me), 18.8, 23.1, 27.2, 57.2, 61.3, 104.3 (C-2), 108.2 (C-1), 119.2 (C-3), 128.6, 170.8 (CO).

The previous crude ester was then dissolved in dry THF (50 mL) and stirred under N_2 at 0 °C. A suspension of $LiAlH_4$ (0.608 g) in THF (40 mL) was then added, and the resulting mixture was allowed to warm to room temperature. After stirring for 2 h at room temperature, the solution was cooled to 0 °C and quenched with a saturated aqueous solution of Na_2SO_4. After filtration, the organic layer was dried over $MgSO_4$ and concentrated. Column chromatography on silica gel (CH_2Cl_2/AcOEt, 9:1) of the residue yielded 1.09 g (72% from **2**) of **3**. $[\alpha]^{20}_D = -33.7$ (*c* 1.00, CH_2Cl_2); IR (NaCl) 3485 (OH) cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ (ppm) 1.65−2.06 (m, 4H, H-6 and H-7), 2.71 (m, 2H, H-8), 3.77 (m, 3H, CH_2O and OH), 4.08 (m, 1H, H-5), 5.81 (m, 1H, H-2), 6.10 (m, 1H, H-1), 6.70 (m, 1H, H-3); ^{13}C NMR (50 MHz; $CDCl_3$) δ (ppm) 18.7 (C-7), 23.1 (C-8), 25.3 (C-6), 55.2 (CH_2O), 65.1 (C-5), 103.5 (C-2), 107.2 (C-1), 117.1 (C-3), 129.3. MS (EI) 151 ($M^{\cdot+}$). Anal. Calcd for $C_9H_{13}NO$: C, 71.48; H, 8.66; N, 9.26. Found: C, 71.50; H, 8.81; N, 9.11.

(5*R*)-(5,6,7,8-Tetrahydroindolizin-5-yl)acetonitrile (4). A solution of methanesulfonyl chloride (1.53 mL, 20 mmol) was gradually added to a stirred solution of **3** (1.51 g, 10 mmol) in dry dichloromethane (20 mL) and pyridine (5.6 mL) at 0 °C. After 13 h at room temperature, the mixture was poured into ice−water and stirred for an additional 30 min at room temperature. The two-phase system was extracted with CH_2Cl_2. The combined organic layers were washed subsequently with aqueous HCl (1 N), $NaHCO_3$ (5%), and brine and then dried, filtered, and evaporated to yield quantitatively the corresponding methanesulfonate as a colorless oil. ^{1}H NMR (200 MHz; $CDCl_3$) δ (ppm) 1.76−2.12 (m, 4H, H-6 and H-7), 2.71 (m, 2H, H-8), 2.82 (s, 3H, CH_3), 4.30 (m, 3H, CH_2O, and H-5), 5.79 (m, 1H, H-2), 6.09 (m, 1H, H-1), 6.64 (m, 1H, H-3).

The obtained crude methanesulfonate and sodium cyanide (1.47 g, 30 mmol) were dissolved in DMF (20 mL). The resulting mixture was heated for 15 h at 90 °C, cooled, and then poured into water (20 mL). Extraction with ether followed by washing, drying ($MgSO_4$), and evaporation of the solvent gave a residue which was purified by column chromatography on silica gel (CH_2Cl_2). The nitrile (1.44 g, 90% from **3**) was obtained. $[\alpha]^{20}_D = +54.5$ (*c* 0.20, CH_2Cl_2); IR (NaCl) 2242 (CN), 2843, 2928, 3105 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ (ppm) 1.72−2.31 (m, 4H, H-6 and H-7), 2.28 (m, 4H, CH_2CN and H-8), 4.38 (m, 1H, H-5), 5.83 (m, 1H, H-2), 6.16 (m, 1H, H-1), 6.63 (m, 1H, H-3); ^{13}C NMR (50 MHz; $CDCl_3$) δ (ppm) 18.3, 23.1, 24.7, 28.5, 50.6 (C-5), 104.7 (C-2), 108.8 (C-1), 116.8 (C-3), 116.9 (CN), 129.1. MS (EI) 160 ($M^{\cdot+}$). Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.96; H, 7.54; N, 17.48. Found: C, 74.66; H, 7.53; N, 17.11. The ee's of isolated nitrile **4** (97%) and of its enantiomer (96%) were determined by gas chromatography on a chiral capillary column (hydrodex b cyclodextrin Type 3 (neutral) 25 m × 0.25 mm Macherey Nagel A.G.).

(5*R*)-(5,6,7,8-Tetrahydroindolizin-5-yl)acetic Acid (5). Nitrile **4** (1.6 g, 10 mmol) was added to a mixture of aqueous sodium hydroxide (25%, 70 mL) and methanol (200 mL). The solution was stirred under reflux for 6 h, cooled to 0 °C, and then washed twice with CH_2Cl_2. The aqueous layer was acidified to pH 5 with 2 N aqueous hydrochloric acid. Ethyl acetate and brine were then added. The organic layer was separated, dried over $MgSO_4$, and evaporated to give the desired acid as a yellow oil (1.61 g, 90% yield). $[\alpha]^{20}_D = +12.5$ (*c* 0.2, CH_2Cl_2); IR (NaCl) 3420 (OH) cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ (ppm) 1.71−2.20 (m, 4H, H-6 and H-7), 2.68−3.09 (m, 4H, CH_2CO and H-8), 4.52 (m, 1H, H-5), 5.80 (m, 1H, H-2), 6.12 (m, 1H, H-1), 6.59 (m, 1H, H-3), 10.05 (bs, 1H, OH); ^{13}C NMR (50 MHz; $CDCl_3$) δ (ppm) 18.5, 23.2, 28.9, 41.1, 50.6 (C-5), 104.7 (C-2), 108.1 (C-1), 117.1 (C-3), 129.2, 176.7 (CO_2H). MS (EI) 179 ($M^{\cdot+}$).

(7a*R*)-5,6,7,7a-Tetrahydro-1*H*-pyrrolo[2,1,5-*cd*]indolizin-2-one (6). Triethylamine (6.95 mL, 50 mmol) was added to a solution of compound **5** (1.79 g, 10 mmol) in dry THF (20 mL). The solution was cooled to 0 °C, and ethyl chloroformate (1.92 mL, 20 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 40 min. The solvent was removed, and the

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crude solid was dissolved in dry ether. Triethylamine hydrochloride was removed by filtration. The filtrate was then evaporated to give the crude mixed anhydride which was characterized by ^{1}H NMR spectroscopy. ^{1}H NMR (200 MHz; $CDCl_3$) δ (ppm) 1.37 (t, 3H, J = 7.2 Hz, CH_3), 1.79−2.17 (m, 4H, H-6 and H-7), 2.73−3.12 (m, 4H, H-8 and CH_2CO), 4.29 (q, 2H, J = 7.2 Hz, CH_2O), 4.38 (m, 1H, H-5), 5.82 (m, 1H, H-2), 6.13 (m, 1H), 6.58 (m, 1H, H-3).

The obtained anhydride was dissolved in dry CH_2Cl_2 (20 mL) and added dropwise (40 min) at 40 °C to a solution of $BF_3{\cdot}OEt_2$ (6.33 mL, 50 mmol) in dry CH_2Cl_2 (100 mL). The solution was stirred under reflux for 3 h and then cooled. Water was added, and after decantation and separation, the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated. The crude residue was purified by chromatography on silica gel (CH_2Cl_2/AcOEt, 9:1) to yield compound **6** (0.917 g, 57%). $[\alpha]^{20}_D = +83.8$ (c 0.50, CH_2Cl_2); IR (NaCl) 1673 (CO) cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ (ppm) 1.46−1.60 (m, 1H, H-7), 1.76−2.08 (m, 1H, H-6), 2.14−2.25 (m, 2H, H-6 and H-7), 2.69−3.11 (m, 4H, H-1 and H-5), 4.29 (m, 1H, H-7a), 6.17 (d, 1H, J = 4.1 Hz, H-4), 6.67 (d, 1H, J = 4.1 Hz, H-3). ^{13}C NMR (50 MHz; $CDCl_3$) δ (ppm) 20.3 (C-6), 20.4 (C-5), 27.8 (C-7), 47.0 (C-1), 51.2 (C-7a), 108.3 (C-4), 111.9 (C-3), 127.4, 132.3, 186.3 (CO). MS (EI) 161($M^{\cdot+}$). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.50; H, 6.87; N, 8.68. Found: C, 74.75; H, 6.81; N, 8.65.

(7a*R*)-4-Acetyl-5,6,7,7a-tetrahydro-1*H*-pyrrolo[2,1,5-*cd*]-indolizin-2-one (7). A solution of ketone **6** (500 mg, 3.10 mmol) in CH_2Cl_2 (5 mL) was added to a suspension of aluminum chloride (1.53 g, 11.49 mmol) in dry CH_2Cl_2 (20 mL) and acetyl chloride (0.288 mL, 4.037 mmol). The resulting mixture was refluxed for 2 h, poured onto crushed ice, and stirred until melted. The layers were separated, and the aqueous one was extracted three times with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (CH_2Cl_2/AcOEt, 9:1) of the residue gave pure compound **7** (584 mg, yield: 93%). $[\alpha]^{20}_D = +38.1$ (c 1, CH_2Cl_2); IR (NaCl) 1665 and 1663 (CO) cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ (ppm) 1.46−1.65 (m, 1H, H-7), 1.88−2.09 (m, 1H, H-6), 2.20−2.33 (m, 2H, H-6 and H-7), 2.40 (s, 3H, CH_3), 2.72−2.84 (m, 1H, H-1), 2.87−3.07 (m, 1H, H-5), 3.10−3.18 (m, 1H, H-1), 3.20−3.34 (m, 1H, H-5), 4.25−4.34 (m, 1H, H-7a), 7.00 (s, 1H, H-3). ^{13}C NMR (50 MHz; $CDCl_3$) δ (ppm) 20.5 (C-6), 22.9 (C-5), 27.5 (C-7), 28.1 (CH_3), 47.3 (C-1), 52.2 (C-7a), 110.0 (C-3), 127.1 (C-4), 127.6 (C-3a), 137.1 (C-4a), 188.4 (CO), 194.7 (CH_3CO). MS (EI) 203 ($M^{\cdot+}$). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.44; N, 6.89. Found: C, 70.64; H, 6.35; N, 6.80.

(7a*R*)-4-Ethyl-1,2,5,6,7,7a-hexahydro-1*H*-pyrrolo[2,1,5-*cd*]indolizine (8). A suspension of $LiAlH_4$ in dry 1,4-dioxane was added to a stirred solution of compound **7** (500 mg, 2.46 mmol) in the same solvent (20 mL) under N_2 at room temperature. The resulting mixture was heated under reflux for 40 h and then cooled to 0 °C and quenched slowly with a saturated aqueous Na_2SO_4 solution. After filtration the organic layer was dried and evaporated. Column chromatography on silica gel (pentane/CH_2Cl_2, 9:1) of the residue gave **8** (259 mg, yield: 60%). $[\alpha]^{20}_D = +82.2$ (c 0.50, CH_2Cl_2). ^{1}H NMR (200 MHz; $CDCl_3$) δ (ppm) 1.17 (t, 3H, J = 7.5 Hz, CH_3), 1.21−1.44 (m, 1H, H-7), 1.68−1.86 (m, 1H, H-6), 1.89−2.17 (m, 3H, H-1, H-6 and H-7), 2.36−2.67 (m, 4H, CH_2Me, H-5 and H-1), 2.70−2.83 (m, 3H, H-5 and 2 H-2), 3.85 (m, 1H, H-7a), 5.68 (s, 1H, H-3). ^{13}C NMR (50 MHz; $CDCl_3$) δ (ppm) 15.6 (CH_3), 19.6 (CH_2), 20.1 (C-5), 22.3 (C-6), 25.2 (C-2), 29.7 (C-7), 37.2 (C-1), 55.2 (C-7a), 98.7 (C-3), 118.6 (C-2a), 122.7 (C-4), 130.8 (C-4a). MS (EI) 175 ($M^{\cdot+}$). Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.77; N, 7.99. Found: C, 82.12; H, 9.44; N, 7.68.

(4a*R*)-1-(1-Ethyl-3,4,4a,5,6,7-hexahydropyrrolo[2,1,5-*cd*]-indolizin-2-yl)propanone (9). A solution of **8** (200 mg, 1.14 mmol) in dry toluene (10 mL) was added at 90 °C to a mixture of *N*,*N*-dimethylpropionamide (0.136 mL, 1.254 mmol) and $POCl_3$ (0.117 mL, 1.254 mmol) in toluene (5 mL). The resulting mixture was stirred for 3 h. Sodium acetate (3 g) in water (10 mL) was then added at 90 °C, and the reaction was carried on for 15 min. The solution was cooled to room temperature, diluted with water, and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel (CH_2Cl_2) to give compound **9** (179 mg, 68% yield). $[\alpha]^{20}_D = +64.8$ (c 0.50, CH_2Cl_2). IR (NaCl) 1648 (CO) cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ (ppm) 1.10−1.17 (m, 6H, 2 CH_3), 1.25−1.38 (m, 1H, H-5), 1.70−1.77 (m, 1H, H-6), 2.02−2.18 (m, 3H, H-4, H-5 and H-6), 2.45−2.73 (m, 7H, 2 H-7, H-4 and 2 CH_2), 2.90−3.05 (m, 2H, H-3) 3.80−3.90 (m, 1H, H-4a). ^{13}C NMR (50 MHz; $CDCl_3$) δ (ppm) 8.5 (CH_3), 15.2 (CH_3), 19.1, 19.4 (C-7), 22.1 (C-6), 28.1 (C-2), 29.4 (C-5), 34.0 (CH_2), 35.9 (C-4), 55.9 (C-4a), 115.9, 121.0, 124.7, 137.7, 196.3 (CO). MS (EI) 231 ($M^{\cdot+}$). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.62; H, 9.19; N, 6.05.

(4a*R*)-1-Ethyl-3,4,4a,5,6,7-hexahydro-2-propylpyrrolo-[2,1,5-*cd*]indolizine M217. Ketone **9** (100 mg, 0.433 mmol) was reduced with $LiAlH_4$ in refluxing dioxane for 3 h. The crude product was purified by column chromatography (silica gel) to yield 56 mg of M217 (60%). The obtained ^{1}H and ^{13}C NMR spectra were in agreement with ref 2. $[\alpha]^{20}_D = +88$ (c 1, CH_2Cl_2).

(4a*S*)-1-Ethyl-3,4,4a,5,6,7-hexahydro-2-propylpyrrolo-[2,1,5-*cd*]indolizine. The enantiomer of M217 was obtained by the same series of reaction starting with L-glutamic acid.

The ee's of isolated M217 (97.9%) and of its enantiomer (88.5%) were determined by gas chromatography with a chiral capillary column (hydrodex b cyclodextrin Type 3 (neutral) 25 m ×0.25 mm Macherey Nagel A.G.)

Supporting Information Available: Copies of ^{1}H NMR spectra of compounds **3**−**9** and M217. Chiral GC chromatograms of (*R*)-M217 and (*S*)-*ent*-M217. This material is available free of charge via the Internet at http://pubs.acs.org.

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