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General Synthesis of Pyrroloquinolizidines: Synthesis of an Unnatural Homologue of the Pyrroloindolizidine Myrmicarin Alkaloid 215B

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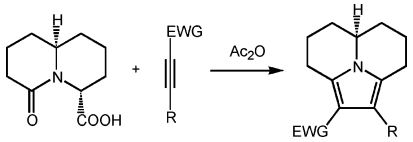
Received November 1, 2006



A general synthesis approach to pyrroloquinolizidines (3,4,5,5a,6,7,8-heptahydropyrrolo[2,1,5-*de*]-quinolizines) via a münchnone 1,3-dipolar cycloaddition is reported. The approach was applied to the synthesis of an unnatural pyrroloquinolizidine homologue of myrmicarin 215B.

Introduction

The myrmicarin alkaloids are a structurally novel group of oligocyclic indolizidine-derived alkaloids and are the major constituent of the poison gland secretion of the African ant species *Myrmicaria opaciventris* (Figure 1).[1] These ants are an ecologically dominant species and a significant anthropoid predator.[1d] Myrmicarins 217 (**1**)[1a] and 215A/B (**2**, **3**)[1a] were isolated by Schröder, Francke, and co-workers, and the structures were assigned on the basis of spectroscopic studies. Myrmicarin 430A, **4**, is a structurally novel heptacyclic bisenamine that could not be isolated or purified due to its instability.[1b] The structure of myrmicarin 430A was determined by NMR studies directly on poison gland secretions.

The combination of the unique structure and promising biological activity of the myrmicarin alkaloids inspired significant interest in the synthesis of these air- and temperature-sensitive compounds. Schröder and Francke[2] reported the first synthesis of racemic myrmicarin 217, **1**, by the conversion of an indolizine derivative to myrmicarin 217 via an unsaturated derivative of myrmicarin 237A (**5**). Vallee and co-workers[3a] described the total synthesis of (+)-(*R*)-myrmicarin 217 and its enantiomer from D-glutamic acid. This same group also reported the synthesis of a mixture of myrmicarin 215A and 215B via a regioselective Vilsmeier—Haack acylation of pyrroloindolizidines from the same starting material.[3b] Recently, Movassaghi

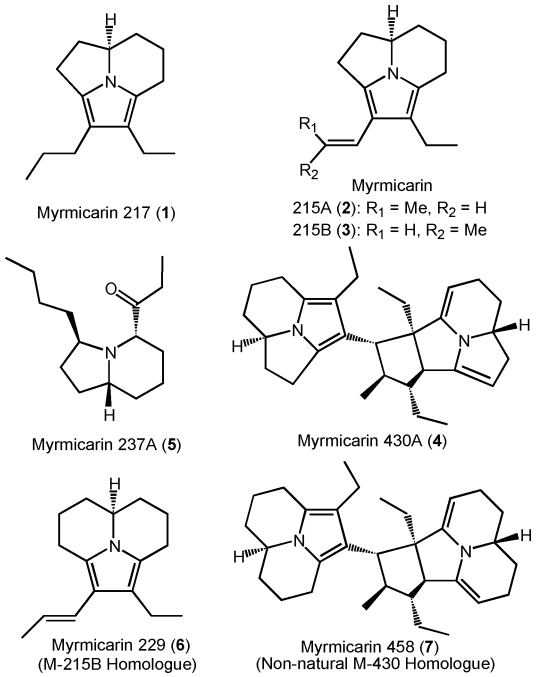


FIGURE 1. Structure of natural and unnatural myrmicarins.

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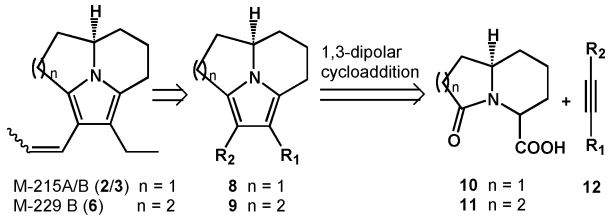
10.1021/jo062262a CCC: $37.00
Published on Web 02/22/2007

SCHEME 1. Retrosynthesis of M-215 A/B and 6



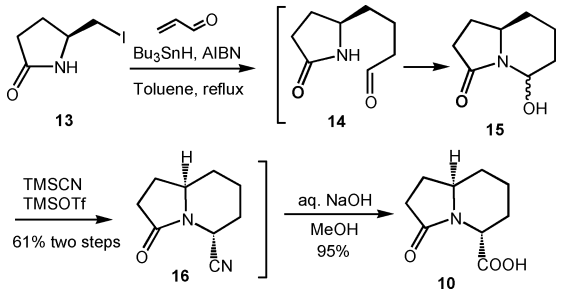
and Ondrus[4a] reported the enantioselective total synthesis of tricyclic myrmicarin alkaloids via stereospecific palladium-catalyzed coupling of a *Z*-vinyl triflate and a pyrrole followed by a copper-catalyzed enantioselective conjugate reduction. They also studied the possible dimerization of (+)-myrmicarin 215B to myrmicarin 430A.[4b] Their studies showed that myrmicarin 215B does react to afford dimeric compounds upon treatment with acid; however, they were unable to provide direct evidence for the formation of myrmicarin 430A. The sensitive nature of myrmicarin 215A/B, and the instability of myrmicarin 430A,[1,4b] led us to consider the synthesis of related compounds that might be more stable and have biological activity similar to the natural products. Accordingly, we examined **6** and **7** which are unnatural homologues of myrmicarin 215 (**2**/**3**) and myrmicarin 430 (**4**). It may be that **7** would be more stable than **4** because of decreased ring strain realized upon moving from an indolizidine to a quinolizidine skeleton.[5] Our initial goal was to develop an efficient route to **6** that would allow sufficient quantities of compound to be prepared so that the acid-mediated dimerization of **6** to **7** could be studied. We report here our studies on the attempted synthesis of myrmicarin 215A/B and the synthesis of **6**, which could be viewed as myrmicarin 229B, an unnatural homologue of myrmicarin 215B.

Results and Discussion

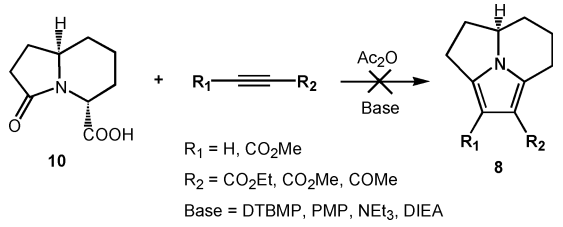
Retrosynthetic analysis of myrmicarin 215A/B (**2**/**3**) and homologue **6** shows that carboxylic acids **10** and **11** might provide rapid access to the tricyclic skeleton (**8**/**9**; Scheme 1). Cyclodehydration of **10**/**11** to a münchnone[6−8] intermediate followed by 1,3-dipolar cycloaddition[9] and retro-Diels−Alder reaction would afford tricyclic pyrroles **8**/**9** which might easily be transformed to the target compounds.

We first set out to prepare indolizidine carboxylic acid **10**. The known[10] iodide **13**, prepared in four steps from (*S*)-pyroglutamic acid,[11−13] was reacted with acrolein in the presence of tributyltin hydride and AIBN to afford hemiaminal **15** in 37% yield (Scheme 2).[14] The corresponding open-chain aldehyde **14** was not observed. The low yield of **15** was likely due to instability upon silica gel chromatography. To circumvent this problem, crude **15** was treated with trimethylsilyl cyanide and trimethylsilyl triflate[15] to afford nitrile **16** in 61% yield for the two steps (Scheme 2). Nitrile **16** appeared to be a single diastereomer by ^{1}H NMR analysis. Hydrolysis of the nitrile afforded acid **10** in 95% yield. Again, the compound was a single diastereomer by ^{1}H NMR analysis. The peak multiplicity and H−H coupling constant corresponding to the hydrogen adjacent to the carboxylic acid (δ 4.82, doublet, J = 5.7 Hz) lead to the conclusion that the carboxylic acid is in a pseudoaxial orientation and is consistent with the expected conformation due to A-strain.[16]

SCHEME 2. Synthesis of Indolizidine Acid 10



SCHEME 3. Attempted 1,3-Dipolar Reaction



We were now in a position to examine the key 1,3-dipolar cycloaddition. Treatment of acid **10** with acetic anhydride to induce cyclodehydration to a münchnone intermediate[7] followed by a 1,3-dipolar cycloaddition reaction with an acetylene should afford tricyclic pyrrole **8** (Scheme 3). Unfortunately, many attempts to effect this transformation using a variety of conditions were unsuccessful.

It appeared the problem was the generation of the münchnone intermediate. This might not be surprising because of the expected strain in the rigid, tricyclic münchnone. In contrast, molecular models and modeling studies showed the higher

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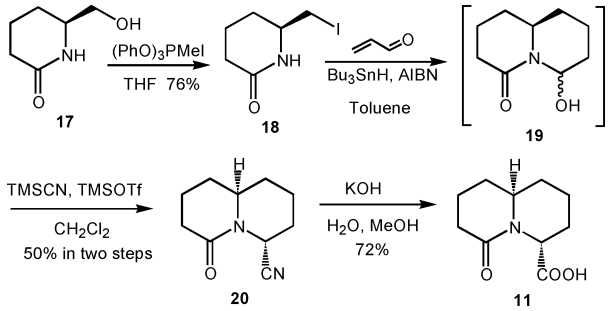
SCHEME 4. Synthesis of Quinolizidine 11

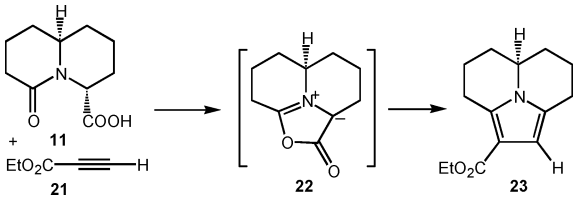


homologue, the 6,6-membered quinolizidine ring, **11**, should provide a much less strained münchnone intermediate. Thus, in spite of the failed approach with acid **10**, we elected to prepare quinolizidine homologue **11** and to examine the münchnone 1,3-dipolar cycloaddition.

Quinolizidine carboxylic acid **11** was prepared from the known[17] 6-hydroxymethyl-2-piperidinone **17** which was in turn derived from L-lysine methyl ester dihydrochloride.[18] Conversion of alcohol **17** to the iodide using triphenylphosphine, imidazole, and iodine[19] afforded **18** in modest yield, but we were unable to adequately purify it due to the fact that small amounts of triphenylphosphine oxide coeluted with the product. Alternatively, treatment of alcohol **17** with methyl triphenoxy phosphonium iodide in DMF[20] gave iodide **18** in 58% yield. In an effort to improve the yield of **18**, we examined the same reaction in the less polar solvent THF[21] and were pleased to obtain **18** in 76% yield (Scheme 4). Reaction of **18** with acrolein in the presence of tributyltin hydride[14] and AIBN afforded hemiaminal **19**, which was treated with trimethylsilyl cyanide and trimethylsilyl triflate[15] to afford nitrile **20** in 50% overall yield. Hydrolysis of **20** afforded acid **11** in 72% yield. This radical reaction appears to be a general method for the annulation of six-membered rings onto lactam iodides such as **13** and **18**.

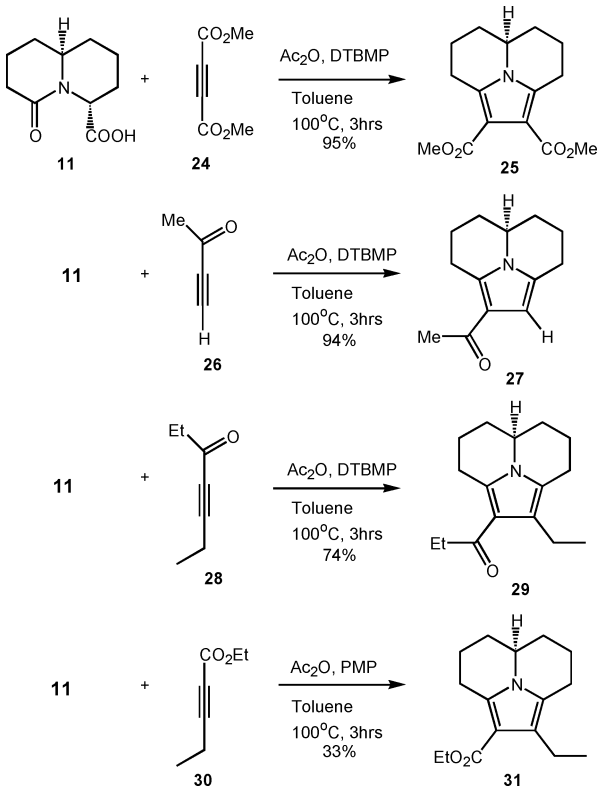
With quinolizidine carboxylic acid **11** in hand, we turned our attention to the formation of münchnone **22** and the subsequent 1,3-dipolar cycloaddition (Table 1). To our knowledge, there is no report of a cycloaddition carried out on a tricyclic münchnone.[6−8] Ethyl propiolate was selected as our "test" dipolarophile, and a variety of conditions were explored for the transformation (Table 1). Carrying out the reaction in acetic anhydride (solvent) at 130 °C in the absence of a base (entry 1) or with a relatively strong, unhindered amine base (TEA, DBU; Table 1, entries 2 and 3) failed to afford any of the desired pyrrole **23**. Using the more hindered tertiary amines, *N*,*N*-diisopropylethylamine (DIEA) and 1,2,2,6,6-pentamethylpiperidine (PMP), afforded **23** in low to modest yield (Table 1, entries 4 and 5). Using 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in acetic anhydride provided **23** in 58% yield (entry 6), and using a solvent of 10% acetic anhydride in toluene and lowering the temperature to 100 °C afforded **23** in 80% yield (entry 7).

TABLE 1. Cycloaddition with Ethyl Propiolate



	rxn conditions	base	solvent	**23** (%)
1	5 h, 130 °C	none	Ac_2O	none
2	5 h, 130 °C	Et_3N	Ac_2O	none
3	5 h, 130 °C	DBU	Ac_2O	none
4	5 h, 130 °C	DIEA	Ac_2O	trace
5	5 h, 130 °C	PMP	Ac_2O	37
6	5 h, 130 °C	DTBMP	Ac_2O	58
7	3 h, 100 °C	DTBMP	10% Ac_2O in toluene	80

SCHEME 5. Synthesis of Pyrroloquinolizidines



We then studied the generality of the 1,3-dipolar cycloaddition using the optimized reaction conditions in Table 1, entry 7. To our delight, the münchnone cycloadditions proceeded very well (Scheme 5). Reaction of quinolizidine **11** and dimethyl acetylenedicarboxylate, **24**, in acetic anhydride gave pyrroloquinolizidine **25** in 95% yield. When 3-butyn-2-one, **26**, was used as the dipolarophile, the corresponding pyrroloquinolizidine **27** was obtained in 94% yield. Carrying out the reaction with disubstituted alkyne **28** resulted in the formation of pyrroloquinolizidine **29** in 74% yield. This is a surprisingly good yield for a disubstituted alkyne in this type of cycloaddition. The related alkyne, **30**, with an ester rather than a ketone afforded **31** in 28% yield using 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as the base and in 33% yield using pentamethylpiperidine (PMP) as the base.

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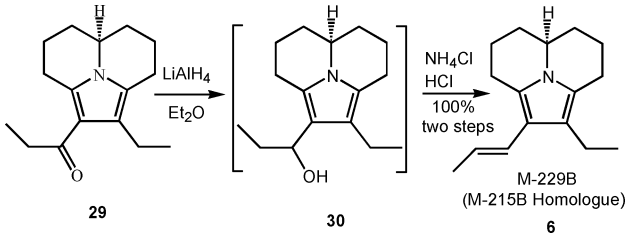
SCHEME 6. Synthesis of 6, M-229B



Traditionally, münchnone cycloadditions exhibit modest to very good regioselectivity.[22] In the case of symmetrical pyrroloquinolizidine **25**, which is achiral, the regioselectivity is irrelevant. However, the other pyrroloquinolizidines in Scheme 5 were derived from unsymmetrical alkynes, and thus the regioselectivity of the cycloaddition determines the optical purity of these products. If the cycloaddition is highly regioselective, products with high optical purity would be obtained, whereas low or no regioselectivity would afford pyrrole products of low or zero optical purity. Compounds **27** and **29** are optically active, indicative of some degree of regioselectivity in the cycloaddition reaction. Determination of the optical purity of these two compounds required the synthesis of racemic **27** and **29** from racemic **11**. Chiral HPLC showed the ratio of the two enantiomers of **27** to be 1.65:1 (24% ee), whereas the ratio of the two enantiomers of **29** was 3.20:1 (52% ee). Thus, the münchnone cycloaddition exhibits only modest regioselectivity. The absolute stereochemistry of the major enantiomer of **27** and **29** could not be determined. Because of the low yield, the optical purity of **31** was not determined.

The factors governing the regiochemistry of münchnone cycloadditions are not fully understood. Whereas some 1,3-dipolar cycloadditions are rationalized in terms of simple FMO theory, this does not correctly predict the results in other cases.[22] A combination of steric, electronic, dipole, and other ground-state and transition-state interactions play a role in determining the regiochemistry; no single criterion successfully predicts the regioselectivity of münchnone cycloaddition reactions.[23]

With an efficient route to pyrroloquinolizidines, we returned to the synthesis of nonnatural myrmicarin 229B, **6**. Pyrroloquinolizidine **29** contains all the carbons found in **6** and is the ideal intermediate to complete the synthesis. Using a modification of conditions employed by Ondrus and Movassaghi in the synthesis of myrmicarin 215B,[4a] we treated **29** with $LiAlH_4$ at −78 °C followed by workup with acid (HCl/NH_4Cl) to afford *trans*-alkene **6** (M-229B) in quantitative yield (Scheme 6). The synthesis of nonnatural M-229B, **6**, was accomplished in seven steps and in 20% overall yield from the known alcohol **17** (11 steps, 17% yield from commercially available L-lysine methyl ester dihydrochloride).

Conclusion

We developed an efficient synthesis of pyrroloquinolizidines via a 1,3-dipolar cycloaddition reaction and also achieved the synthesis of **6**, myrmicarin 229B. Studies on the dimerization of **6** (myrmicarin 229B) to **7** (myrmicarin 430A homologue) are currently under investigation.

Experimental Section

General Information. HPLC was carried out on a Chiralcel OD00CE-GL072 column (4.6 × 250 mm). Flow rate = 0.5 mL/min. The appropriate mixture of hexanes/methanol was used.

(−)-(4*R*,8a*R*)-6-Oxo-4-indolizidinecarboxylic Acid (10). A suspension of AIBN (0.10 g, 0.60 mmol) in toluene (3 mL) was stirred for 10 min at room temperature, and then tributyltin hydride (1.3 mL, 4.8 mmol) was added. The mixture was added to a solution of (−)-(*S*)-5-iodomethyl-2-pyrrolidinone **13** (0.90 g, 4.0 mmol) and acrolein (1.34 mL, 20.0 mmol) in toluene (25 mL) at 110 °C via a syringe pump at the rate of 0.07 mL/min. The resulting solution was refluxed for 15 min. The mixture was cooled, concentrated, dissolved in CH_3CN, and washed with hexanes. The solvent was removed in vacuo to afford a yellow oil. To a solution of the above yellow residue in CH_2Cl_2 (25 mL) at −78 °C were added dropwise trimethylsilyl cyanide (2.7 mL, 20 mmol) and trimethylsilyl trifluoromethanesulfonate (2.17 mL, 12.0 mmol). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was then poured into a stirring saturated aqueous solution of $NaHCO_3$ (100 mL). After 15 min, the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were dried ($MgSO_4$). Concentration afforded crude product as a yellow oil. Flash chromatography (ethyl acetate) gave (4*R*,8a*R*)-(+)-4-cyano-6-oxoindolizine **16** (0.401 g, 61%) as a light yellow oil (single diastereomer by ^1H NMR analysis): $[\alpha]^{20}_D$ = +126.8 (*c* 1.5, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 5.17 (d, J = 4.6 Hz, 1H), 3.68 (m, 1H), 2.40 (m, 2H), 2.31 (m, 1H), 2.01−1.75 (m, 4H), 1.71−1.59 (m, 2H), 1.25−1.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 117.4, 54.6, 40.7, 33.0, 30.2, 28.3, 25.8, 20.8; IR ($CDCl_3$) 2945, 2865, 2232, 1699, 1456, 1409 cm^{-1}. To a solution of nitrile **16** (0.80 g, 4.87 mmol) in methanol (100 mL) was added 25% aqueous NaOH (20 mL). The resulting mixture was refluxed for 6 h and then concentrated. The remaining solution was cooled to 0 °C, acidified to pH 5 (pH paper) by the addition of concentrated HCl, and then extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated to give acid **10** (0.86 g, 95%) as a white solid: mp = 148−150 °C; $[\alpha]^{20}_D$ = −48.5 (*c* 2.56, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (bs, 1H), 4.82 (d, J = 5.7 Hz, 1H), 3.77 (m, 1H), 2.44 (m, 2H), 2.25 (m, 2H), 1.92 (dd, J = 2.6, 12.8 Hz, 1H), 1.80 (dt, J = 3.6, 13.1 Hz, 1H), 1.61 (m, 2H), 1.44 (m, 1H), 1.14 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 174.0, 55.5, 51.5, 32.9, 30.5, 26.4, 26.2, 20.7; IR ($CDCl_3$) 2945, 1718, 1676, 1421, 1314 cm^{-1}; MS (EI) *m*/*z* 182 ($M - H^+$, 100), 113 (25); HRMS (EI) *m*/*z* calcd for $C_9H_{12}NO_3$ ($M - H^+$) 182.0822, found 182.0821.

(−)-(*S*)-6-Iodomethyl-2-piperidinone (18). Using Triphenylphosphine and Iodine. To a solution of alcohol **17**[17] (33.0 mg, 0.255 mmol) in benzene/acetonitrile (2:1, 3 mL/1.5 mL) at 0 °C were added triphenylphosphine (167 mg, 0.638 mmol), imidazole (52.1 mg, 0.765 mmol), and iodine (129.4 mg, 0.510 mmol). The resulting solution was stirred at room temperature overnight. The solvent was removed in vacuo, and the mixture was dissolved in CH_2Cl_2 (3 mL). The mixture was washed with 10% aqueous $Na_2S_2O_3$ (3 mL) and saturated aqueous $NaHCO_3$ (3 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL), and the combined organic extracts were dried ($MgSO_4$). Concentration afforded crude product (200 mg) as a yellow oil. Flash chromatography (10% ethanol/ethyl acetate) gave iodide **18** (34.2 mg, 56%) as a white solid.

Using Triphenoxy Phosphonium Iodide. To a solution of **17**[17] (0.991 g, 7.68 mmol) in tetrahydrofuran (THF, 76.8 mL) at 0 °C was added methyl triphenoxy phosphonium iodide (6.94 g, 15.3 mmol) in one portion. The solution was stirred for 2 h at room temperature. Methanol was added, and the solution was stirred

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another 20 min at room temperature. The solvent was removed in vacuo, and the mixture was dissolved in chloroform ($CHCl_3$, 40 mL). The resulting solution was washed with 10% aqueous $Na_2S_2O_3$ and H_2O. The aqueous layer was extracted with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$). Concentration afforded crude product (7.63 g) as a yellow oil. Flash chromatography (10% ethanol/ethyl acetate) gave iodide **18** (1.40 g, 76%) as a white needle solid: mp = 175−177 °C; $[\alpha]^{20}_D = -13.7$ (*c* 1.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 1H), 3.51 (m, 1H), 3.26 (dd, *J* = 5.3, 10.1 Hz, 1H), 3.14 (dd, *J* = 10.1, 7.0 Hz, 1H), 2.44−2.26 (m, 2H), 2.03 (m, 1H), 1.89 (m, 1H), 1.72 (m, 1H), 1.50 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 53.8, 31.4, 29.1, 19.5, 11.4; IR ($CDCl_3$) 3368, 2957, 1663, 1450, 1418, 1346, 1300 cm^{-1}; MS (EI) *m*/*z* 240 (MH^+, 22), 127 (7), 98 (100); HRMS (EI) *m*/*z* calcd for $C_6H_{11}NOI$ (MH^+) 239.9885, found 239.9879. (±)-6-Iodomethyl-2-piperidinone (±)-**18**: mp = 153.7−156.2 °C; lit.[24] mp = 157−158 °C.

(+)-(4*R*,9a*R*)-Octahydro-6-oxo-4-(cyano)quinolizidine (20). A suspension of AIBN (56.8 mg, 0.346 mmol) in toluene (1.5 mL) was stirred for 10 min at room temperature, and then tributyltin hydride (0.744 mL, 2.77 mmol) was added. The mixture was added to a solution of (−)-(*S*)-6-iodomethyl-2-piperidinone **18** (0.413 g, 1.73 mmol) and acrolein (0.579 mL, 8.64 mmol) in toluene (11 mL) at 100 °C via a syringe pump at the rate of 0.07 mL/min. The resulting solution was stirred at 100 °C for another 2 h. The mixture was cooled, concentrated, dissolved in CH_3CN, and washed with hexanes. The solvent was removed in vacuo to afford a yellow oil. To a solution of the above yellow oil in CH_2Cl_2 (13 mL) at −78 °C was added trimethylsilyl cyanide (1.84 mL, 13.8 mmol) and trimethylsilyl trifluoromethanesulfonate (1.49 mL, 8.64 mmol) dropwise. The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was then poured into a stirring saturated aqueous solution of $NaHCO_3$ (10 mL). After 15 min, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried ($MgSO_4$). Concentration afforded crude product (0.707 g) as a yellow oil. Flash chromatography (3:1 hexanes/ethyl acetate) gave cyanide **20** (0.153 g, 50%) as a light yellow oil (single diastereomer by ^{1}H NMR analysis): $[\alpha]^{20}_D = +25.2$ (*c* 2.7, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (d, *J* = 3.1 Hz, 1H), 3.53 (m, 1H), 2.45 (td, *J* = 4.4, 17.2 Hz, 1H), 2.30 (ddd, *J* = 5.3, 10.6, 16.3 Hz, 1H), 2.07−1.91 (m, 2H), 1.85−1.41 (m, 7H), 1.39−1.22 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 117.8, 54.4, 40.9, 33.0, 30.5, 28.2, 20.5, 19.1; IR ($CDCl_3$) 2953, 2251, 1643, 1445, 1414, 1346 cm^{-1}; MS (EI) *m*/*z* 178 (MH^+, 33), 151 (82), 82 (100); HRMS (EI) *m*/*z* calcd for $C_{10}H_{14}N_2O$ (MH^+) 178.1106, found 178.1110.

(−)-(4*R*,9a*R*)-6-Oxo-4-quinolizidinecarboxylic Acid (11). To a solution of nitrile **20** (43.1 mg, 0.242 mmol) in H_2O (4.8 mL) and methanol (1.2 mL) was added potassium hydroxide (0.271 g, 4.84 mmol). The mixture was refluxed overnight, then allowed to cool to room temperature. Methanol was removed under reduced pressure. The remaining solution was acidified to pH = 3−4 by the addition of concentrated HCl and then extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated to give acid **11** (34.4 mg, 72%) as a white solid: mp = 209−212 °C; $[\alpha]^{20}_D = -11.9$ (*c* 0.6, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50 (d, *J* = 4.8 Hz, 1H), 3.49 (m, 1H), 2.54 (d, *J* = 17.6 Hz, 1H), 2.43−2.30 (m, 2H), 2.01−1.19 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 172.2, 55.0, 51.9, 33.4, 33.0, 31.1, 26.6, 21.1, 19.4; IR ($CDCl_3$) 2948, 1714, 1628, 1414, 1261 cm^{-1}; MS (EI) *m*/*z* 197 (M^+, 11), 152 (100); HRMS (EI) *m*/*z* calcd for $C_{10}H_{15}NO_3$ (M^+) 197.1052, found 197.1053. (±)-6-Oxo-4-quinolizidinecarboxylic acid (±)-**11**: mp = 176−179 °C.

General Experimental Procedure for Pyrroloquinolizidine Synthesis. To a solution of (−)-(4*R*,9a*R*)-6-oxo-4-quinolizidinecarboxylic acid **11** (1.0 equiv) in 10% acetic anhydride in toluene (0.01 M) were added 2,6-di-*tert*-butyl-4-methylpyridine (8.0 equiv) and the appropriate alkyne (16.0 equiv). The reaction mixture was stirred 3 h at 100 °C and concentrated to dryness, and the residue was purified by flash column chromatography to give tricyclic pyrroloquinolizidine.

(−)-1-(Carboethoxy)-(3,4,5,5a,6,7,8-heptahydro)pyrrolo[2,1,5-*de*]quinolizine (23). Using the general experimental procedure, acid **11** (5.8 mg, 0.029 mmol) and alkyne **21** afforded **23** (5.5 mg, 80%) as a light yellow oil: $[\alpha]^{20}_D = -0.99$ (*c* 0.71, CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 6.64 (s, 1H), 4.30 (q, *J* = 7.0 Hz, 2H), 3.52 (dd, *J* = 6.4, 18.7 Hz, 1H), 2.96−2.84 (m, 2H), 2.57 (dd, *J* = 6.3, 15.8 Hz, 1H), 2.41 (m, 1H), 1.56 (m, 1H), 1.45 (m, 1H), 1.22 (m, 4H), 1.16 (t, *J* = 7 Hz, 3H), 1.00−0.95 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 165.9, 134.4, 126.6, 111.7, 106.9, 59.3, 55.6, 30.7, 30.4, 24.3, 23.1, 21.9, 21.5, 15.2; IR (C_6D_6) 2944, 1696, 1521 cm^{-1}; MS (EI) *m*/*z* 233 (M^+, 54), 204 (100), 188 (16), 160 (19); HRMS (EI) *m*/*z* calcd for $C_{14}H_{19}NO_2$ (M^+) 233.1416, found 233.1415.

1,2-Bis(carbomethoxy)-(3,4,5,5a,6,7,8-heptahydro)pyrrolo-[2,1,5-*de*]quinolizine (25). Using the general experimental procedure, acid **11** (5.5 mg, 0.028 mmol) and alkyne **24** afforded **25** (7.3 mg, 95%) as a white solid: mp = 148−150 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 3.69 (s, 6H), 3.16 (dd, *J* = 5.9, 18.0 Hz, 2H), 2.66 (m, 3H), 1.40 (m, 2H), 1.10 (m, 4H), 0.78 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 166.2, 133.6, 112.1, 55.7, 51.2, 30.0, 23.4, 20.3; IR (C_6D_6) 2947, 2870, 1700, 1530, 1439, 1402 cm^{-1}; MS (FAB) *m*/*z* 278 (MH^+, 16), 246 (16); HRMS (FAB) *m*/*z* calcd for $C_{15}H_{20}NO_4$ (MH^+) 278.1392, found 278.1402.

(−)-1-Acetyl-(3,4,5,5a,6,7,8-heptahydro)pyrrolo[2,1,5-*de*]quinolizine (27). Using the general experimental procedure, acid **11** (45.9 mg, 0.233 mmol) and alkyne **26** gave **27** (44.5 mg, 94%) as a light yellow oil: ee = 24% (Chiral HPLC); $[\alpha]^{20}_D = -1.66$ (*c* 0.36, CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 6.12(s, 1H), 3.54 (dd, *J* = 6.2, 18.5 Hz, 1H), 2.90 (m, 2H), 2.59 (dd, *J* = 5.3, 14.9 Hz, 1H), 2.44 (dd, *J* = 5.3, 11.4 Hz, 1H), 2.35 (s, 3H), 1.51 (m, 2H), 1.30−1.15 (m, 4H), 0.92 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 193.3, 133.8, 126.2, 121.0, 106.9, 55.6, 30.7, 30.2, 28.5, 24.9, 23.2, 21.8, 21.4; IR (C_6D_6) 2945, 2867, 1651, 1511 cm^{-1}; MS (EI) *m*/*z* 203 (M^+, 62), 188 (100), 160 (81); HRMS (EI) *m*/*z* calcd for $C_{13}H_{17}NO$ (M^+) 203.1310, found 203.1316.

(−)-1-(2-Ethyl)-(3,4,5,5a,6,7,8-heptahydro)pyrrolo[2,1,5-*de*]-quinolizin-1-yl)propanone (29). Using the general experimental procedure, acid **11** (14.3 mg, 0.0725 mmol) and alkyne **28** afforded **29** (13.2 mg, 74%) as a light yellow oil: ee = 52% (Chiral HPLC); $[\alpha]^{20}_D = -6.65$ (*c* 0.14, CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 3.10 (dd, *J* = 6.4, 18.2 Hz, 1H, C8-H), 2.93 (partially obscured tt, *J* = 2.9, 6.7 Hz, 1H) 2.85 (m, 2H), 2.71 (dd, *J* = 6.4, 11.7 Hz, 1H), 2.66 (q, *J* = 7.6 Hz, 2H), 2.56 (dd, *J* = 5.8, 17.5 Hz, 1H), 2.29 (ddd, *J* = 6.4, 12.3, 17.3 Hz, 1H), 1.54 (m, 2H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.25 (m, 4H), 0.98 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 196.2, 132.7, 123.5, 121.9, 120.4, 55.6, 36.0, 31.1, 30.2, 25.6, 21.9, 21.7, 21.5, 19.6, 16.5, 9.3; IR (C_6D_6) 2939, 2870, 1645, 1494, 1427, 1345 cm^{-1}; MS (CI, NH_3) *m*/*z* 246 (MH^+, 100), 216 (21); HRMS (CI, NH_3) *m*/*z* calcd for $C_{16}H_{24}NO$ (MH^+) 246.1858, found 246.1859.

(−)-1-(Carboethoxy)-2-ethyl-(3,4,5,5a,6,7,8-heptahydro)pyrrolo[2,1,5-*cd*]quinolizine (31). To a solution of acid **11** (5.8 mg, 0.029 mmol) in 10% acetic anhydride in toluene (2.5 mL) was added pentamethylpiperidine (42.5 μL, 0.235 mmol) and ethyl 2-pentynoate (62.0 μL, 0.471 mmol). The reaction mixture was stirred for 3 h at 95 °C and concentrated to dryness, and the residue was purified directly by flash column chromatography (10:1 hexanes/ethyl acetate) to give **31** (2.5 mg, 33%) as a light yellow oil: $[\alpha]^{20}_D = -6.67$ (*c* 0.48, CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 4.29 (q, *J* = 7.0 Hz, 2H), 3.47 (dd, *J* = 6.2, 18.0 Hz, 1H), 2.96 (m, 4H), 2.60 (dd, *J* = 5.7, 16.3 Hz, 1H), 2.33 (m, 1H), 1.55 (m, 2H), 1.43 (t, *J* = 7.0 Hz, 3H), 1.29 (m, 4H), 1.15 (t, *J* = 7.0 Hz, 3H), 1.01 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 166.3, 134.3, 123.1, 122.8, 109.8, 59.0, 55.5, 31.0, 30.5, 24.8, 21.9, 21.6, 21.5, 19.3, 16.6, 15.1; IR (C_6D_6) 2943, 2867, 1692, 1572, 1515, 1457 cm^{-1};

(24) Knapp, S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4006−4014.

MS (FAB) *m*/*z* 261 (MH^+, 100), 232 (20); HRMS (FAB) *m*/*z* calcd for $C_{16}H_{23}NO_2$ (M^+) 261.1729, found 261.1716.

(+)-*E*-2-Ethyl-(3,4,5,5a,6,7,8-heptahydro)-1-(1′-propenyl)pyrrolo[2,1,5-*cd*]quinolizine (6). Using a modification of a procedure by Movassaghi and Ondrus,[4a] lithium aluminum hydride (7.1 mg, 0.19 mmol) was added in one portion to a stirring solution of tricyclic ketone **29** (7.7 mg, 0.031 mmol) and diethyl ether (0.63 mL) at −78 °C. The mixture was stirred for 40 min at 0 °C, and then the suspension was cooled to −78 °C again for 5 min. The excess hydride was quenched by careful addition of water (0.7 mL) via syringe. The mixture was allowed to warm to room temperature. Argon-purged diethyl ether (6 mL) was added, and the organic layer was separated. The organic solution was stirred for 2−3 min in a sealed round-bottom flask under argon, with a pH 2 (pH paper) solution prepared from 1.0 M aqueous ammonium chloride and concentrated hydrochloric acid (3 mL). The aqueous layer was removed by syringe. This was repeated twice at which time TLC showed no starting material left. The organic solution was washed with brine (3 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give myrmicarin 229B, **6** (7.2 mg, 100%), as an oily white solid. Flash chromatography of a similar sample failed to separate the desired compound from oxidized impurities. The melting point could not be obtained due to extreme air sensitivity and the oily nature of the compound: $[\alpha]^{20}_D = +13.1$ (*c* 0.60, CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 6.64 (dq, J = 15.8, 1.8 Hz, 1H), 5.85 (dq, J = 15.8, 6.4 Hz, 1H), 3.09 (tt, J = 2.9, 11.7 Hz, 1H), 2.85 (dd, J = 5.9, 16.4 Hz, 1H), 2.71−2.63 (partially obscured m, 1H), 2.65 (dq, J = 2.92, 7.61 Hz, 2H), 2.61−2.40 (m, 2H), 1.95 (dd, J = 1.8, 6.4 Hz, 3H), 1.63 (m, 2H), 1.36 (m, 3H), 1.29 (t, J = 7.6 Hz, 3H), 1.20−0.99 (m, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 125.9, 123.9, 122.1, 120.1, 119.2, 116.0, 55.4, 31.4, 31.0, 23.6, 22.6, 22.5, 21.9, 20.1, 18.7, 16.4; IR (C_6D_6) 2960, 1646, 1434, 1347, 1260 cm^{-1}; MS (EI) *m*/*z* 229 (M^+, 100), 214 (93), 200 (50); HRMS (EI) *m*/*z* calcd for $C_{16}H_{23}N$ (M^+) 229.1831, found 229.1835.

Acknowledgment. We thank UC Riverside for partial support of this research. We would like to thank Dr. Dan Borchardt and Dr. Yi Meng at the UCR NMR facility for assistance with NMR and Dr. Richard Kondrat and Mr. Ron New for mass spectra.

Supporting Information Available: Experimental procedures for the synthesis of alcohol **17** from (*S*)-lysine methyl ester dihydrochloride and copies of ^{1}H and ^{13}C NMR spectra for these intermediates and compounds **10**, **11**, **16**−**18**, **20**, **23**, **25**, **27**, **29**, **31**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062262A