

Enantioselective Total Synthesis of
Tricyclic Myrmicarins Alkaloids

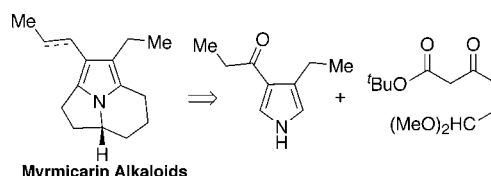
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ABSTRACT



An enantioselective gram-scale synthesis of a key dihydroindolizine intermediate for the preparation of myrmicarins alkaloids is described. Key transformations in this convergent approach include a stereospecific palladium-catalyzed N-vinylation of a pyrrole with a vinyl triflate, a copper-catalyzed enantioselective conjugate reduction of a β -pyrrolyl enoate, and a regioselective Friedel–Crafts reaction. The synthesis of optically active and isomerically pure samples of (4a*R*)-myrmicarins 215A, 215B, and 217 in addition to their respective C4a-epimers is presented.

The myrmicarins are a family of structurally fascinating alkaloids isolated from the poison gland secretions of the African ant species *Myrmecaria opaciventris* (Figure 1).¹ Despite significant isolation and purification challenges due to air and temperature sensitivity, elegant spectroscopic studies have revealed their molecular structures.² The pyrroloindolizine core of myrmicarins 215A (**1**), 215B (**2**), and 217 (**3**) is a common structural motif within many of these alkaloids. Within the family, only the absolute stereochemistry of myrmicarins 237A (**4**) has been secured through an enantioselective synthesis.^{1a,3} Interestingly, the conversion of an unsaturated derivative of **4** to myrmicarins 217 (**3**) suggests the possible biogenesis of other myrmicarins from simpler indolizine derivatives.^{1b,4} The synthesis of (*R*)-myrmicarins 217 (**3**) and (*R*)-myrmicarins 215 as a mixture of olefin isomers has been reported starting with D-glutamic

acid.⁵ The intriguing molecular structures of these poisonous alkaloids combined with challenges associated with their sensitivity provide an exciting arena to test and discover new methodologies for organic synthesis. Herein we describe a convergent synthesis of all naturally occurring tricyclic myrmicarins alkaloids employing an efficient approach to a

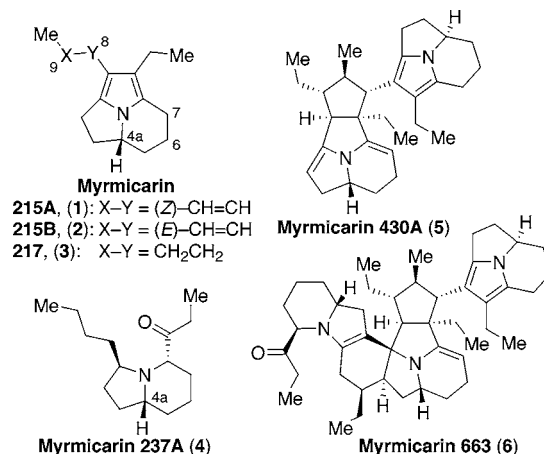


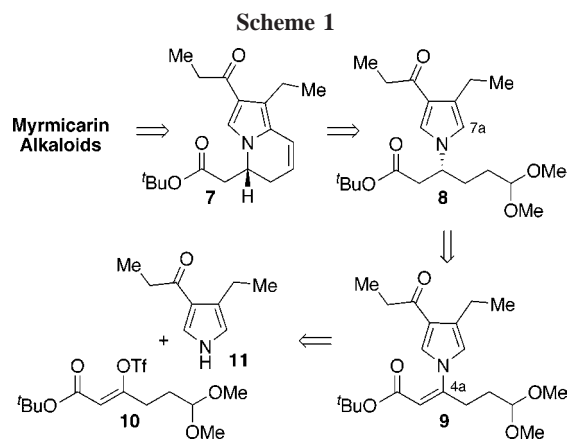
Figure 1. Representative myrmicarins alkaloids.

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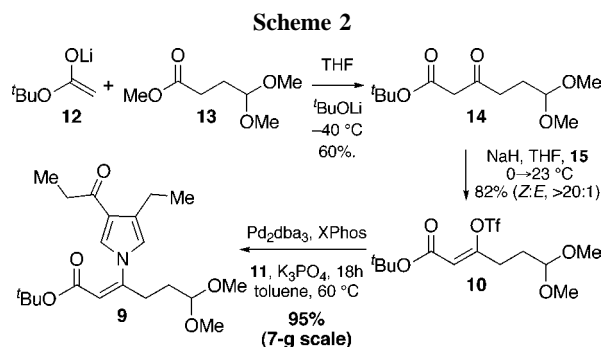
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pivotal optically active dihydroindolizine intermediate. The first preparation of isomerically pure samples of myrmicarins 215A and 215B is discussed. Key steps of the synthesis include an efficient palladium-catalyzed fragment coupling reaction, a copper-catalyzed asymmetric conjugate reduction, and a regioselective Friedel–Crafts reaction.

We envisioned utilization of the optically active dihydroindolizine **7** as a key intermediate for the preparation of myrmicarins alkaloids (Scheme 1). A regioselective Friedel–Crafts reaction of the pyrrole ring (C7a-alkylation) upon Brönsted acid activation of the dimethoxyacetal **8** and elimination of methanol was expected to afford the bicyclic vinyl pyrrole **7**. We planned to use a metal-catalyzed enantioselective conjugate reduction of the β -pyrrolyl enoate **9** to introduce the C4a-stereochemistry.^{6,7} A convergent synthesis of the pyrrolylenoate **9** was envisioned via a metal-catalyzed union of pyrrole **11** and readily available Z-vinyl triflate **10** (Scheme 1).

The synthesis of the required β -pyrrolylenoate **9** began with the Claisen condensation of the lithium enolate **12** and methyl 4-(dimethoxy)-butyrate (**13**)⁸ to give the β -ketoester **14** (Scheme 2). The lithium *tert*-butoxide additive was crucial to ensure rapid deprotonation of product **14**, thus preventing the addition of a second equivalent of the lithium enolate **12**.⁹ The trapping of the sodium enolate of β -ketoester **14** with Comins reagent (2-[*N,N*-bis(trifluoromethylsulfonyl)-amino]-5-chloropyridine, **15**, Scheme 2) gave the vinyl



triflate **10** in 82% yield with high Z-alkene selectivity (Z:E, >20:1).¹⁰ Early in our studies, we relied on the use of a copper-catalyzed N-vinylation of pyrroles for the synthesis of the requisite β -pyrrolyl enoates.^{7,11} However, because of difficulties associated with the synthesis of the necessary Z- β -iodoenates¹² containing acid-sensitive functional groups, we turned our attention to the use of configurationally defined vinyl triflates.¹³ Although copper-based catalyst systems were not effective, the use of palladium dibenzylideneacetone ($\text{Pd}_2(\text{dba})_3$) and 2-dicyclohexyl-phosphino-2',4',6'-triisopropyl-1,1'-biphenyl (XPhos)¹⁴ provided a highly active catalyst system for the desired coupling reaction.¹⁵ Under optimal conditions, stereospecific coupling of pyrrole **11** and Z-vinyl triflate **10** provided the desired Z- β -pyrrolyl enoate **9** in 95% yield on a multigram scale (Scheme 2). This represents the first example of a palladium-catalyzed N-vinylation of an azaheterocycle by a vinyl triflate. The convergent assembly of enoate **9** provides all of the carbons necessary for preparation of the tricyclic myrmicarins.

We planned to introduce the C4a-stereochemistry of the myrmicarins alkaloids through an enantioselective conjugate reduction of enoate **9** (Scheme 3). Recently, a variety of efficient catalytic methods have been reported for the synthesis of optically active β -amino acid derivatives.¹⁶ In particular, we were interested in the utilization of a recently reported methodology for the catalytic asymmetric reduction of β -azaheterocyclic enoates.⁷ Gratifyingly, the copper-catalyzed reduction of enoate **9** in the presence of (*S*)-2,2'-

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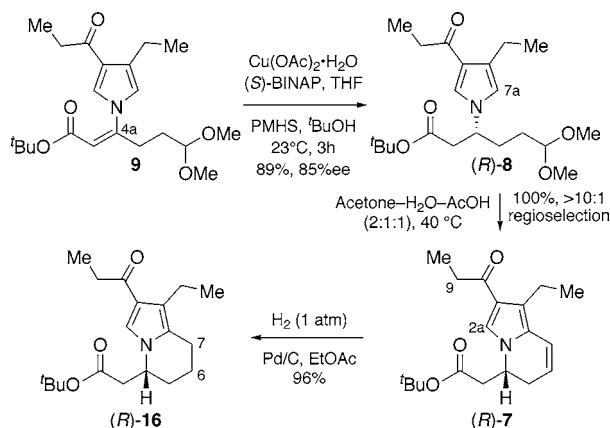
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Scheme 3^a

^a The use of (*R*)-BINAP in the above sequence afforded the corresponding tetrahydroindolizidine (*S*)-**16** on a multigram scale.

bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) and the stoichiometric reductant polymethylhydrosiloxane (PMHS) proceeded efficiently to provide the optically active β -pyrrolyl ester **8**. After minor optimization for the isolation of the substrate at hand, the reduction of enoate **9** proceeded to give the (*R*)- β -pyrrolyl ester **8** in 89% yield and 85% ee on a 2-g scale (Scheme 3).^{17,18} It should be noted that, upon completion of our total synthesis of myrmicarins **217** from the β -pyrrolyl ester **8** prepared using (*R*)-BINAP, we discovered that the conjugate reduction of enoate **9** had proceeded unexpectedly⁷ to give the (*S*)- β -pyrrolyl ester **8**.¹⁹

With a multigram enantioselective synthesis of both enantiomers of β -pyrrolyl ester **8** at hand, we turned our attention to the synthesis of the dihydroindolizidine **7**, a key intermediate for the synthesis of the myrmicarins alkaloids (Scheme 1). Optimal conditions (acetone–acetic acid–water, 2:1:1, 40 °C) were identified for the quantitative conversion of the β -pyrrolyl ester **8** to the bicyclic vinyl pyrrole with good regioselectivity (>10:1) for the desired C7a-cyclization product **7** (Scheme 3).²⁰ The formation of the desired dihydroindolizidine **7** as the major regioisomer was confirmed by a 9.2% NOE between the C9-methylene of the propanoyl group and the pyrrole C2a-methine upon irradiation of the C2a-methine (Scheme 3). Compared to earlier studies employing *N*-alkylpyrrole derivatives, the use of the acyl

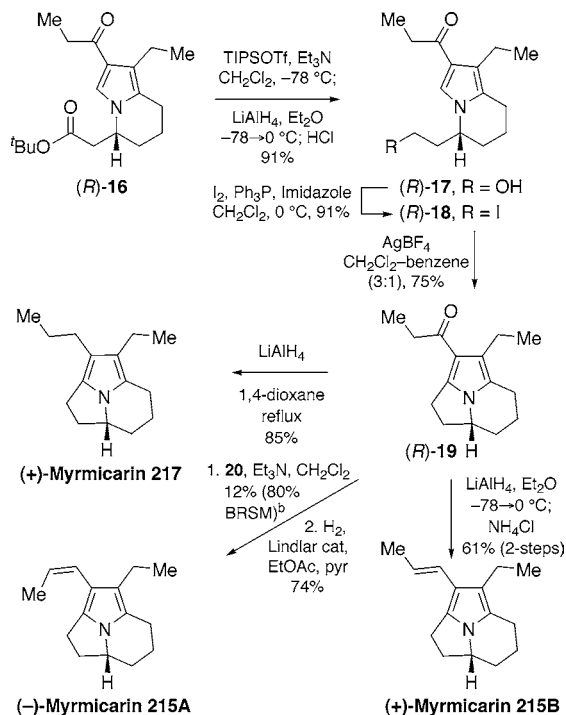
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(17) The ee was determined by chiral HPLC analysis of a more advanced intermediate.

(18) Please see Supporting Information for details.

(19) The absolute stereochemical assignment of the conjugate reduction is made by comparison of the sign of optical rotation of our synthetic myrmicarins **217** (**3**) and *ent*-**3** with that reported for an optically active sample of **3** prepared from D-glutamic acid.⁵

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Scheme 4^a

^a The use of (*S*)-**16** in the above sequence provided the enantiomeric ketone (*S*)-**19** in 55% (3 steps) yield. Ketone (*S*)-**19** was converted to *ent*-myrmicarins (+)-**215A**, (–)-**215B**, and (–)-**217** in 50% BRSM (2 steps), 74%, and 99% yield, respectively.

^b The dehydration reaction is stopped at <30% conversion as a result of sensitivity of the C8-alkyne.¹⁸

pyrrole **11** in the preparation of **7** not only provided a more convergent synthesis, but the C8-carbonyl also afforded greater stability for isolation and storage of key intermediates toward myrmicarins alkaloids.²¹ Hydrogenation of the dihydroindolizidine (*R*)-**7** gave the tetrahydroindolizidine (*R*)-**16** in 96% yield. The corresponding tetrahydroindolizidine (*S*)-**16** was prepared with the same efficiency starting with (*S*)-**8**.

The introduction of the third ring of the pyrroloindolizidine structure required the reduction of the C3-ester **16** to the corresponding C3-alcohol **17** (Scheme 4). Selective reduction of the C3-ester **16** was accomplished in a single operation by transiently protecting the C8-ketone as a silyl enol ether. In this sequence, conversion of the C8-ketone (*R*)-**16** to the corresponding triisopropylsilyl enol ether derivative, reduction of the *tert*-butyl ester by lithium aluminum hydride and protodesilylation by addition of aqueous hydrochloric acid (pH 1) provided the desired alcohol (*R*)-**17** in 91% yield. That this sequence could be executed in a single flask greatly simplified the preparation of alcohol **17**.¹⁸ Treatment of the alcohol (*R*)-**17** with a mixture of triphenylphosphine, iodine, and imidazole led to the conversion of the primary alcohol to the primary iodide (*R*)-**18** in 91% yield. Based on prior literature precedent²² for cyclization of *N*-(ω -alkyl) radicals

(21) Compounds not containing the C8-carbonyl in this series were found to be less stable toward storage as a result of decomposition and polymerization.

onto pyrroles containing an electron-withdrawing group, we first chose to explore free-radical cyclization strategies for the conversion of the iodide **18** to the tricyclic ketone **19**. Accordingly, treatment of the iodide **18** with tri-*n*-butyltin hydride and 2,2'-azobisisobutyronitrile (AIBN) in toluene at reflux did provide tricycle **19**, albeit in low yields and with poor mass recovery (ca. 30–40%). Further attempts using oxidative radical cyclization²³ conditions did not lead to a significant improvement. Ultimately, the optimal conditions for the synthesis of tricyclic ketone **19** were found to involve an intramolecular C2-alkylation of the pyrrole nucleus by activation of the primary iodide **18**.²⁴ Under strictly anhydrous conditions, treatment of (*R*)-**18** with silver tetrafluoroborate in a dichloromethane–benzene (3:1) solvent mixture at ambient temperature furnished the tricyclic ketone (*R*)-**19** in 75% yield (Scheme 4). The identical sequence starting with ketoester (*S*)-**16** furnished the corresponding alcohol (*S*)-**17**, primary iodide (*S*)-**18**, and the ketone (*S*)-**19** in 87%, 86%, and 73% yield, respectively.

The enantiomerically enriched tricyclic ketone **19** provided expedient access to isomerically pure samples of tricyclic myrmicarins **1–3** (Scheme 4). As noted during isolation studies,^{1b} myrmicarins **1–3** were found to be sensitive to air oxidation, giving the corresponding C6–C7 alkene derivatives²⁵ followed by rapid decomposition.¹⁸ It should be noted that the propensity toward air oxidation in these pyrroloindolizine derivatives is higher in the absence of the C8-carbonyl. According to literature precedent, heating a mixture of ketone (*R*)-**19** and lithium aluminum hydride in 1,4-dioxane gave (+)-(*R*)-myrmicarin 217 ((+)-**3**, $[\alpha]^{20}_{\text{D}} = +72.1$ (*c* 0.050, CH₂Cl₂), lit. $[\alpha]^{20}_{\text{D}} = +88$ (*c* 1, CH₂Cl₂), Scheme 4) in 85% yield.^{5a} The enantiomeric (–)-(*R*)-myrmicarin 217 ((–)-**3**, $[\alpha]^{20}_{\text{D}} = -67.4$ (*c* 0.074, CH₂Cl₂)) was prepared via the same procedure in 99% yield.¹⁸

The synthesis of the sensitive myrmicarin 215A (**1**) was achieved via a two-step sequence from the ketone **19** (Scheme 4). Dehydration of the C8-ketone (*R*)-**19** using 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (**20**)²⁶ gave the corresponding C8–C9 alkyne, which proved to be a particularly sensitive intermediate.²⁷ Successful isolation of pure material was only possible by an immediate isolation

and purification of the alkyne at less than 30% conversion (12–19%, 75–80% based on recovered starting material). Partial reduction with Lindlar catalyst under an atmosphere of dihydrogen provided exclusively (–)-(*R*)-myrmicarin 215A ((–)-**1**, $[\alpha]^{20}_{\text{D}} = -53.8$ (*c* 0.045, CH₂Cl₂), Scheme 4) in 74% yield. Similarly, the ketone (*S*)-**19** was converted to the (+)-(*S*)-myrmicarin 215A ((+)-**1**, $[\alpha]^{20}_{\text{D}} = +49.8$ (*c* 0.090, CH₂Cl₂)).

Synthesis of (+)-(*R*)-myrmicarin 215B commenced with the reduction of the ketone (*R*)-**19** with lithium aluminum hydride to the corresponding C8-alcohol as a mixture of diastereomers (~1:1.5). Acid-catalyzed dehydration then afforded isomerically pure (+)-(*R*)-myrmicarin 215B ((+)-**2**, $[\alpha]^{20}_{\text{D}} = +60.4$ (*c* 0.044, CH₂Cl₂), Scheme 4) in 61% yield.²⁸ Starting with ketone (*S*)-**19** the corresponding (–)-(*S*)-myrmicarin 215B ((–)-**2**, $[\alpha]^{20}_{\text{D}} = -58.5$ (*c* 0.085, CH₂Cl₂)) was prepared in 74% yield. Interestingly, (4a*R*)-myrmicarins 215A (**1**) and 215B (**2**) rotate plane-polarized light in opposite directions. Although myrmicarins 215A (**1**) and 215B (**2**) were isolated and characterized as a mixture, our analysis of the isomerically pure samples has confirmed the previously reported ¹H and ¹³C NMR assignments of the mixture.¹⁸

A convergent gram-scale synthesis of the key dihydroindolizine **7** for the synthesis of myrmicarin alkaloids in optically active form is described. The enantioselective synthesis of myrmicarins (–)-215A (**1**), (+)-215B (**2**), and (+)-217 (**3**) in addition to their respective enantiomers is described. Central to the success of this approach was the use of an efficient and stereospecific palladium-catalyzed fragment coupling of a *Z*-vinyl triflate and a pyrrole, a copper-catalyzed enantioselective conjugate reduction, and two Friedel–Crafts reactions to form the pyrroloindolizine core of myrmicarins. The chemistry described here sets the stage for the synthesis of more complex members of this family of alkaloids, and our studies in this area will be reported in due time.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ¹H and ¹³C NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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