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Enantioselective Total Synthesis of Tricyclic Myrmicarin Alkaloids

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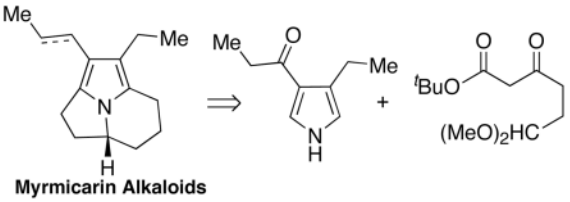
Abstract



An enantioselective gram-scale synthesis of a key dihydroindolizine intermediate for the preparation of myrmicarin 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 *Myrmicaria 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 myrmicarin 237A (**4**) has been secured through an enantioselective synthesis.[1a,3] Interestingly, the conversion of an unsaturated derivative of **4** to myrmicarin 217 (**3**) suggests the possible biogenesis of other myrmicarins from simpler indolizine derivatives.[1b,4] The synthesis of (*R*)-myrmicarin 217 (**3**) and (*R*)-myrmicarin 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 myrmicarin alkaloids employing an efficient approach to a 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.

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

We envisioned utilization of the optically active dihydroindolizine **7** as a key intermediate for the preparation of myrmicarin 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, due to difficulties associated with the synthesis of the necessary *Z*-β-iodoenoates[12] containing acid sensitive functional groups, we turned our attention to the use of configurationally defined vinyl triflates.[13] While copper-based catalyst systems were not effective, the use of palladium dibenzylideneacetone ($Pd_2(dba)_3$) 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 multi–gram 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 myrmicarin 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′-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-gram scale (Scheme 3).[17,18] It should be noted that upon completion of our total synthesis of myrmicarin 217 from the β-pyrrolyl ester **8** prepared using (*R*)-BINAP, we discovered that the conjugate reduction of enoate **9** had proceeded unexpectedly[7] to give the (*S*)-β-pyrrolyl ester **8**.[19]

With a multi-gram enantioselective synthesis of both enantiomers of β-pyrroly ester **8** at hand, we turned our attention to the synthesis of the dihydroindolizine **7**, a key intermediate for the synthesis of the myrmicarin 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 dihydroindolizine **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 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 towards myrmicarin alkaloids.[21] Hydrogenation of the dihydroindolizine (*R*)-**7** gave the tetrahydroindolizine (*R*)-**16** in 96% yield. The corresponding tetrahydroindolizine (*S*)-**16** was prepared with the same efficiency starting with (*S*)-**8**.

The introduction of the third ring of the pyrroloindolizine 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 ^{t}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 precedent[22] for cyclization of *N*-(ω-alkyl) radicals 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 provided tricycle **19**, albeit in low yields and with poor mass recovery (ca. 30–40%). Further attempts using oxidative radical cyclization[23] 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 derivatives[25] 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**, $[\alpha]^{20}_{D}$ = +72.1 (*c* 0.050, CH_2Cl_2), lit.: $[\alpha]^{20}_{D}$ = +88 (*c* 1, CH_2Cl_2), Scheme 4) in 85% yield.[5a] The enantiomeric (−)-(*R*)-myrmicarin 217 ((−)-**3**, $[\alpha]^{20}_{D}$ = −67.4 (*c* 0.074, CH_2Cl_2)) was prepared via the same procedure in 99% yield.[18]

The stereospecific 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**, $[\alpha]^{20}_{D}$ = −53.8 (*c* 0.045, CH_2Cl_2), Scheme 4) in 74% yield. Similarly, the ketone (*S*)-**19** was converted to the (+)-(*S*)-myrmicarin 215A ((+)-**1**, $[\alpha]^{20}_{D}$ = +49.8 (*c* 0.090, CH_2Cl_2)).

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**, $[\alpha]^{20}_{D}$ = +60.4 (*c* 0.044, CH_2Cl_2), Scheme 4) in 61% yield.[28] Starting with ketone (*S*)-**19** the corresponding (−)-(*S*)-myrmicarin 215B ((−)-**2**, $[\alpha]^{20}_{D}$ = −58.5 (*c* 0.085, CH_2Cl_2)) was prepared in 74% yield. Interestingly, (4a*R*)-myrmicarins 215A (**1**) and 215B (**2**) rotate plane–polarized light in opposite directions. While 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 ^{1}H and ^{13}C 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. (a) Francke W, Schröder F, Walter F, Sinnwell V, Baumann H, Kaib M. Liebigs Ann 1995:965–977. (b) Schröder F, Franke S, Francke W, Baumann H, Kaib M, Pasteels JM, Daloze D. Tetrahedron 1996;52:13539–13546.
2. (a) Schröder F, Sinnwell V, Baumann H, Kaib M. J Chem Soc, Chem Commun 1996:2139–2140. (b) Schröder F, Sinnwell V, Baumann H, Kaib M, Francke W. Angew Chem, Int Ed Engl 1997;36:77–80.
3. Thanh GV, Celerier JP, Lhommet G. Tetrahedron Lett 1999;40:3713–3716.
4. Schröder F, Francke W. Tetrahedron 1998;54:5259–5264.
5. (a) Sayah B, Pelloux-Léon N, Vallée Y. J Org Chem 2000;65:2824–2826. [PubMed: 10808465] (b) Sayah B, Pelloux-Léon N, Milet A, Pardillos-Guindet J, Vallée Y. J Org Chem 2001;66:2522–2525. [PubMed: 11281803] For a formal synthesis of **3** starting with D-glutamic acid, see: (c) Settambolo R, Guazzelli G, Lazzaroni R. Tetrahedron: Asymmetry 2003;14:1447–1449.
6. For recent reports on CuH-catalyzed asymmetric conjugate reduction, see: (a) Lipshutz BH, Servesko JM. Angew Chem, Int Ed 2003;42:4789–4792. (b) Hughes G, Kimura M, Buchwald SL. J Am Chem Soc 2003;126:11253–11258. [PubMed: 16220945] and references sited therein. For related references, see: (c) Mahoney WS, Stryker JM. J Am Chem Soc 1989;111:8818–8823.and (d) Mori A, Fujita A, Kajiro H, Nishihara Y, Hiyama T. Tetrahedron 1999;55:4573–4582.
7. Rainka MP, Aye Y, Buchwald SL. Proc Nat Acad Sci, USA 2004;101:5821–5823. [PubMed: 15067136]

8. Ester **13** is commercially available and can be prepared on >30-g scale; see: Drinan MA, Lash TD. J Heterocyclic Chem 1994;31:255–257.
9. Ohta S, Shimabayashi A, Hayakawa S, Sumino M, Okamoto M. Synthesis 1985:45–48.
10. Comins DL, Dehghani A. Tetrahedron Lett 1992;33:6299–6302.
11. For reviews, see: (a) Wolfe JP, Wagaw S, Marcoux JF, Buchwald SL. Acc Chem Res 1998;31:805–818. (b) Hartwig JF. Acc Chem Res 1998;31:852–860. (c) Hartwig JF. Angew Chem, Int Ed 1998;37:2046–2067. (d) Muci AR, Buchwald SL. Top Curr Chem 2002;219:131–209.
12. For the synthesis of Z-β-iodoenoates, see: (a) Piers E, Wong T, Coish PD, Rogers C. Can J Chem 1994;72:1816–1819.and (b) Rossi R, Bellina F, Mannina L. Tetrahedron 1997;53:1025–1044.
13. For reviews on the preparation and use of vinyl triflates, see: (a) Ritter K. Synthesis 1993:735–762.and (b) Baraznenok IL, Nenajdenko VG, Balenkova ES. Tetrahedron 2000;56:3077–3119.
14. Tomori H, Fox JM, Buchwald SL. J Org Chem 2000;65:5334–5341. [PubMed: 10993363] (b) XPhos is available from Strem Chemicals, Inc.
15. For palladium-catalyzed N-vinylation of lithiated azoles, see: (a) Lebedev AY, Izmer VV, Kazyul'kin DN, Beletskaya IP, Voskoboynikov AZ. Org Lett 2002;4:623–626. [PubMed: 11843607] For recent reports on palladium catalyzed N-vinylation, see: (b) Wallace DJ, Klauber DJ, Chen C-y, Volante RP. Org Lett 2003;5:4749–4752. [PubMed: 14627431] and (c) Klapars A, Campos KR, Chen C-y, Volante RP. Org Lett 2005;7:1185–1188. [PubMed: 15760170]
16. For reviews on the synthesis of β-amino acids, see: (a) Juaristi, E., editor. Enantioselective Synthesis of β-Amino Acids. Wiley-VCH; New York: 1997. (b) Liu M, Sibi MP. Tetrahedron 2002;58:7997–8035. (c) Ma JA. Angew Chem, Int Ed 2003;42:4290–4299. (d) Drexler HJ, You J, Zhang S, Fischer C, Baumann W, Spannenberg A, Heller D. Org Process Res Dev 2003;7:355–361. (e) Córdova A. Acc Chem Res 2004;37:102–112. [PubMed: 14967057]
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 myrmicarin 217 (**3**) and *ent*-**3** with that reported for an optically active sample of **3** prepared from D-glutamic acid.[5]
20. For reviews on the chemistry of pyrroles, see: (a) Jones, A., editor. Pyrroles. Wiley; New York: 1990. (b) Alan, JR.; Bean, GP. The Chemistry of Pyrroles. Academic Press; London: 1977. (c) Baltazzi E, Krimen LI. Chem Rev 1963;63:511–556.
21. Compounds not containing the C8-carbonyl in this series were found to be less stable toward storage due to decomposition and polymerization.
22. (a) Aldabbagh F, Bowman WR, Mann E. Tetrahedron Lett 1997;38:7937–7940. (b) Miranda LD, Cruz-Almanza R, Pavón M, Alva E, Muchowski JM. Tetrahedron Lett 1999;40:7153–7157. (c) Allin SM, Barton WRS, Bowman R, McInally T. Tetrahedron Lett 2001;42:7887–7890.
23. (a) Nakamura E, Inubushi T, Aoki S, Machii D. J Am Chem Soc 1991;113:8980–8982. (b) Menes-Arzate M, Martínez R, Cruz-Almanza R, Muchowski JM, Osonio YM, Miranda LD. J Org Chem 2004;69:4001–4004. [PubMed: 15153044]
24. Merlic CA, Miller MM. Organometallics 2001;20:373–375.
25. The immediate air oxidation product of myrmicarins 215A, 215B, and 217 corresponds to myrmicarins 213A, 213B, and 215C, respectively.
26. Tsuji T, Watanabe Y, Mukaiyama T. Tetrahedron Lett 1979:481–482.
27. More forcing dehydration conditions and longer reaction times resulted in lower mass recovery and complications involving C6-C7 oxidation.
28. Direct acidification of the reaction mixture can also provide myrmicarin 215B. See Supporting Information for details.

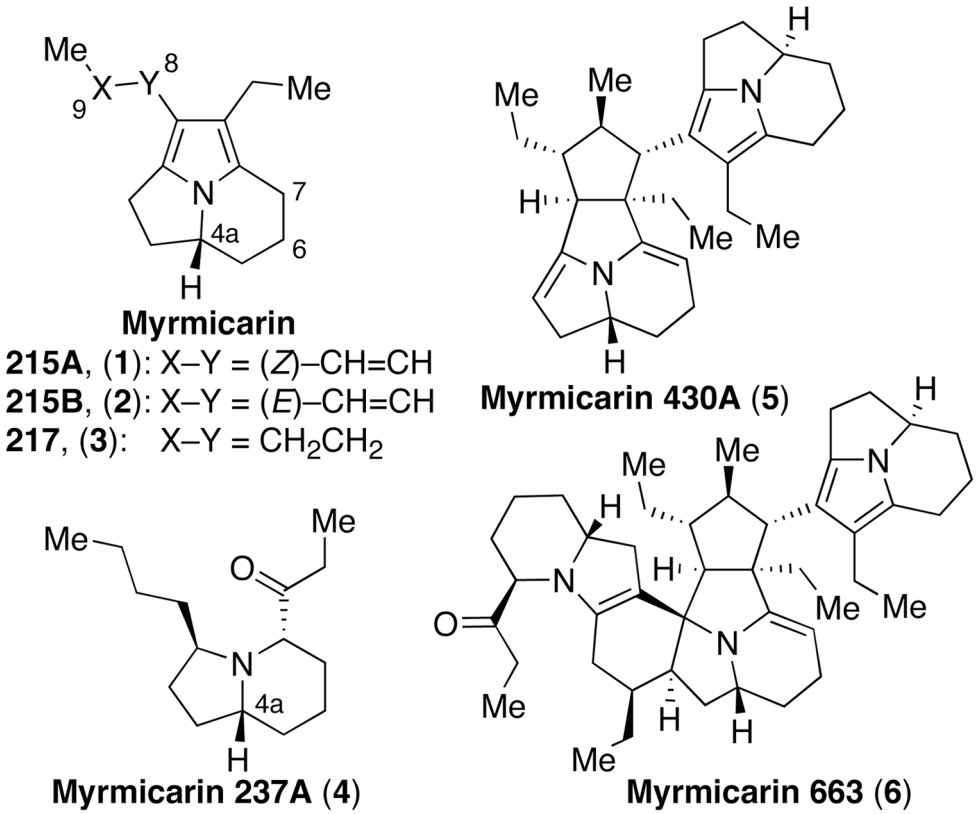
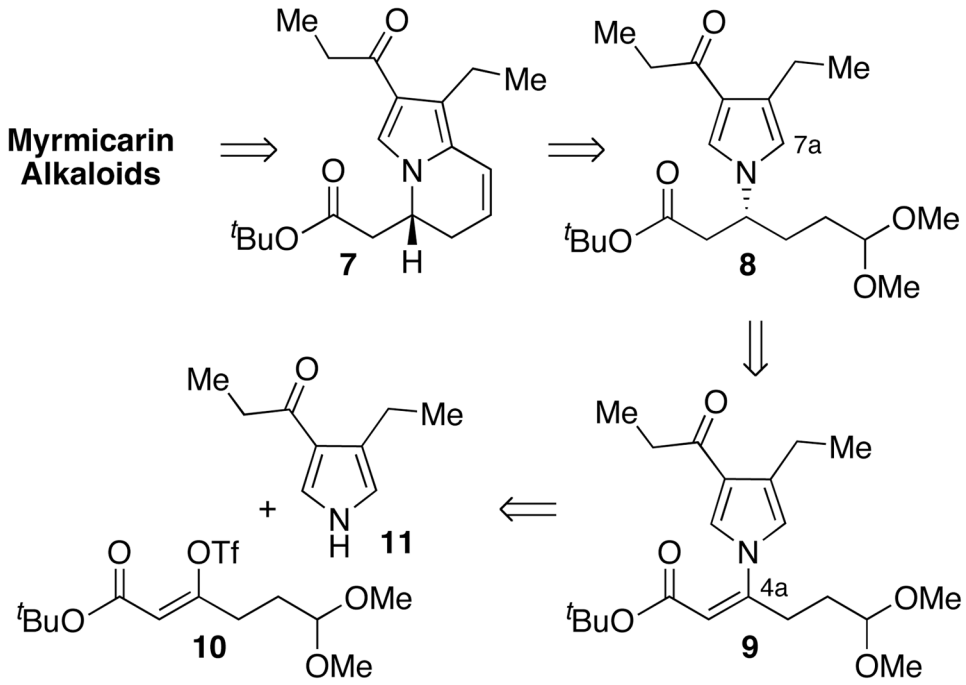
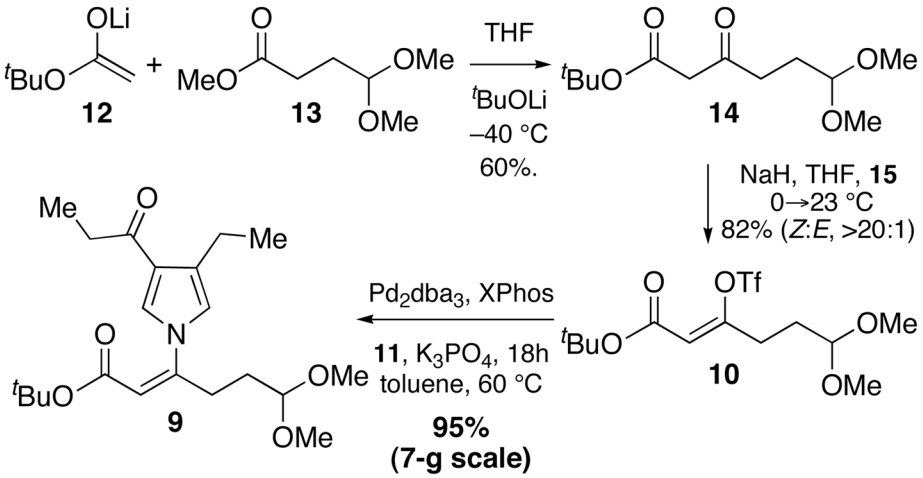


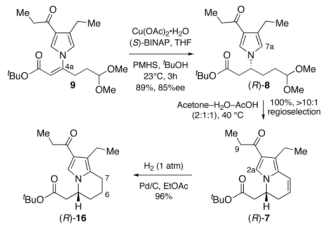
Figure 1.
Representative myrmicarin alkaloids.



Scheme 1.

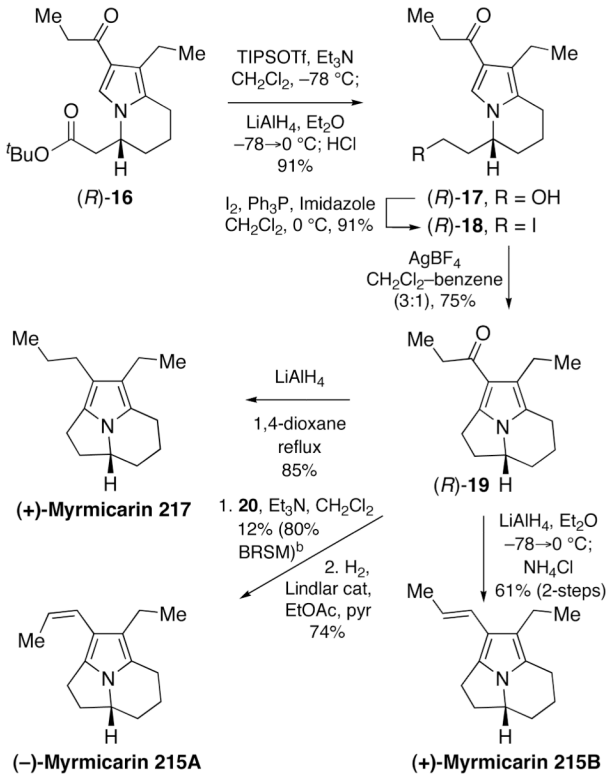


Scheme 2.



Scheme 3a.

[a] The use of (*R*)-BINAP in the above sequence afforded the corresponding tetrahydroindolodizine (*S*)-**16** on multi–gram scale.



Scheme 4a.

[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 due to sensitivity of the C8-alkyne.[18]