

Reversible Dimerization of
(+)-Myrmicarin 215B

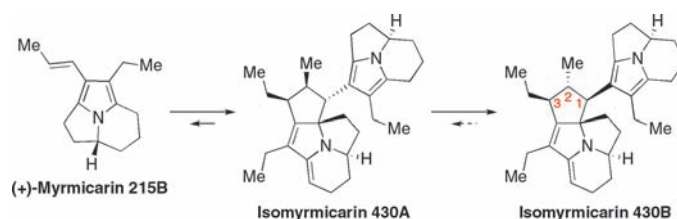
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ABSTRACT



Brønsted acid promoted reversible dimerization of myrmicarin 215B leads to formation of a new heptacyclic product, isomyrmicarin 430B, that possesses a C1,C2-*trans*,C2,C3-*trans*-substituted cyclopentane ring. Mechanistic studies illustrate that isomyrmicarin 430B arises by isomerization of isomyrmicarin 430A via fragmentation to tricyclic azafulvenium ions. Factors influencing the structure of heptacyclic isomyrmicarins and potential relevance of this reversible vinyl pyrroloindolizine dimerization to the biosynthesis of complex myrmicarins are discussed.

The myrmicarins are a family of air-sensitive alkaloids isolated from the poison gland of the African ant species *Myrmecaria opaciventris*. Detailed spectroscopic studies by Schröder, Francke, and co-workers have revealed the relative stereochemistry of myrmicarins 430A and 663 (**M430A** and **M663**, Figure 1), while the stereochemistry of myrmicarin 645 (**M645**) remains unknown.¹ Significantly, the extreme air sensitivity of **M430A** required its characterization as a *crude* isolation mixture using phase-sensitive 2D-NMR techniques.² The challenges offered by their elaborate and highly air-sensitive structures and the lack of information regarding their specific mode of biological action inspired us to embark on their study. Specifically, we envisioned that the complex myrmicarins could be assembled through potentially biomimetic dimerization or trimerization of the tricyclic myrmicarins. Herein, we report the first experimental evidence for the

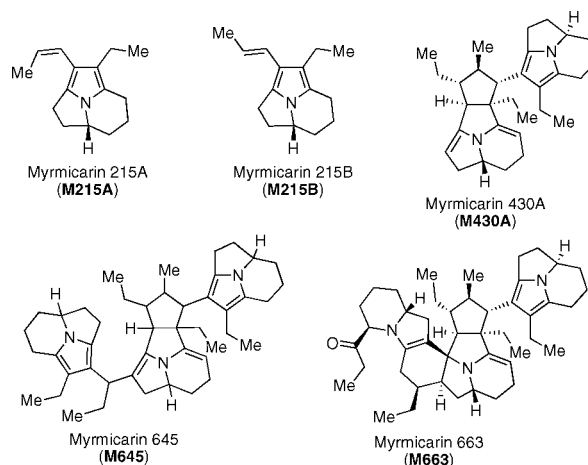
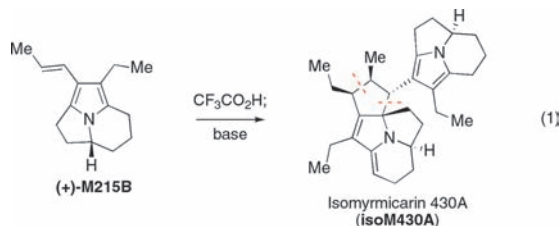


Figure 1. Representative myrmicarins alkaloids.

reversible dimerization of (+)-myrmicarin 215B (**M215B**) and discuss mechanistic studies that provide a more detailed understanding of the reactivity of this natural alkaloid toxin.

(1) **M430A**: (a) Schröder, F.; Sinnwell, V.; Baumann, H.; Kaib, M. *Chem. Commun.* **1996**, 18, 2139–2140 **M663** and **M645**: (b) Schröder, F.; Sinnwell, V.; Baumann, H.; Kaib, M.; Francke, W. *Angew. Chem., Int. Ed.* **1997**, 36, 77–80. **M217**, **M215A**, and **M215B**: (c) Schröder, F.; Francke, S.; Francke, W.; Baumann, H.; Kaib, M.; Pasteels, J. M.; Daloze, D. *Tetrahedron* **1996**, 52, 13539–13546.

(2) An isomeric myrmicarins 430 was identified during these studies, but no structural data was reported (ref 1a).

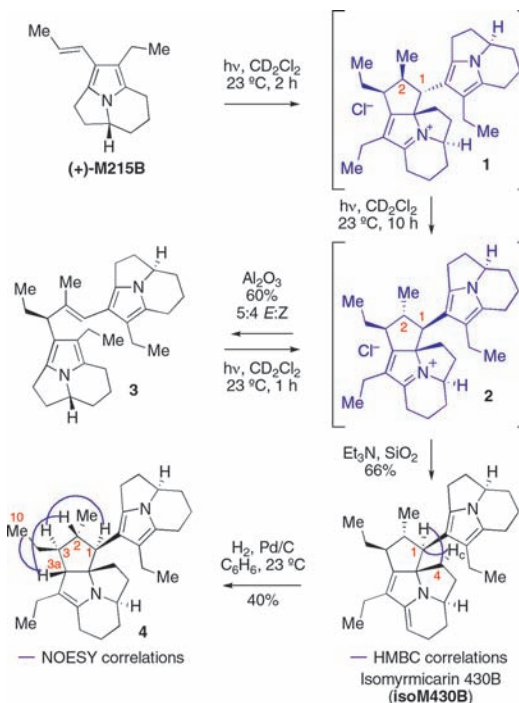


In 2005, we disclosed a highly efficient and diastereoselective Brønsted acid promoted dimerization of (+)-**M215B** to yield the heptacyclic structure of isomyrmicaridin 430A (**isoM430A**, eq 1).³ To determine the influence of the reaction conditions on the rate, reversibility, and products of this dimerization, we examined the acid-promoted chemical reactivity of (+)-**M215B** in a range of different Brønsted acids, solvents, and additives.⁴ The rapid formation of **isoM430A** as the sole product without visible intermediacy of other dimeric or tricyclic compounds motivated us to identify a gradual, noninvasive method of introducing the Brønsted acid that would be compatible with in situ analysis of highly air-sensitive dimeric compounds. Reports describing slow photochemical generation of hydrochloric acid from dichloromethane upon ultraviolet irradiation suggested a possible technique that would satisfy these requirements.⁵ Use of deuterated dichloromethane as solvent would enable us to use in situ ¹H NMR monitoring and deuterium incorporation as mechanistic probes to study the Brønsted acid promoted dimerization of (+)-**M215B**.

An initial experiment demonstrated that irradiation of a sample of water–dichloromethane (7% v/v) using a medium-pressure mercury UV lamp afforded an aqueous layer at a pH of approximately 3, indicating the presence of photochemically generated acid.⁶ When we applied this technique in our own study, in situ monitoring by ¹H NMR revealed that irradiation of a rigorously degassed dichloromethane-*d*₂ solution of (+)-**M215B** yielded the **isoM430A** precursor **1** (Scheme 1) as the sole product after 2 h of irradiation. Irradiation for an additional 10 h caused gradual conversion to the C1, C2 isomeric heptacycle **2**.⁷

In order to perform rigorous structural analysis of this new dimeric compound, we attempted to isolate a neutral derivative. We anticipated that use of our reported techniques for isolation and derivatization of highly air-sensitive dimeric pyrroloindolizines would provide samples for comparison

Scheme 1. Dimerization of **M215B** upon Photochemical Generation of HCl



with reported myrmicaridin and isomyrmicaridin structures.⁸ Rapid filtration of the reaction mixture containing **2** through triethylamine-pretreated silica gel furnished a new heptacyclic structure (Scheme 1). While this exceptionally fragile compound underwent complete decomposition within approximately 4 h,⁹ analysis of freshly prepared samples using two-dimensional NMR techniques revealed that the heptacycle had the same connectivity as **isoM430A**. Specifically, reciprocal C1/C4-H_c and C4/C1-H HMBC correlations established the regiochemistry of the cyclopentannulation. To emphasize the analogy between the connectivity of this dimer and that of **isoM430A**, we termed this heptacyclic diene isomyrmicaridin 430B (**isoM430B**). To confirm the stereochemistry of this exceedingly unstable compound, a freshly generated sample was immediately treated with dihydrogen in the presence of catalytic palladium on carbon, a procedure that we had developed for derivatization of the similarly unstable **isoM430A**.^{3a} The resulting enamine **4** could be purified by chromatography and was stable over a period of days in degassed benzene-*d*₆. Strong C3a-H/C2-H and C1-H/C3-H NOESY correlations revealed that the configuration of the C1 and C2 positions was inverted relative to **isoM430A**, while a C3a-H/C10-H NOESY correlation showed that the **isoM430A** stereochemistry at C3 was maintained.

(8) Attempts to prepare neutral or salt derivatives of complex myrmicaridin and isomyrmicaridin structures for X-ray crystallographic analysis have been unsuccessful (refs 1a and 3b).

(9) Although samples of iminium salt **2** could be stored for up to 3 days without visible decomposition, the corresponding heptacyclic diene (**isoM430B**, Scheme 1) was subject to more rapid decomposition.

(3) (a) Ondrus, A. E.; Movassaghi, M. *Tetrahedron* **2005**, 62, 5287–5297. For our enantioselective synthesis of **M215A**, **M215B**, and **M217**, see: (b) Movassaghi, M.; Ondrus, A. E. *Org. Lett.* **2005**, 7, 4423–4426.

(4) Movassaghi, M.; Ondrus, A. E.; Chen, B. *J. Org. Chem.* **2007**, 72, 10065–10074.

(5) For selected studies on the generation of hydrochloric acid from chlorinated solvents upon ultraviolet irradiation, see: (a) Scolaro, L. M.; Romeo, A.; Castriciano, M. A.; De Luca, G.; Patane, S.; Micali, N. *J. Am. Chem. Soc.* **2003**, 125, 2040–2041. (b) Semeluk, G. P.; Unger, I. *Nature* **1963**, 198, 853–855. (c) Alapi, T.; Dombi, A. *Chemosphere* **2007**, 67, 693–701.

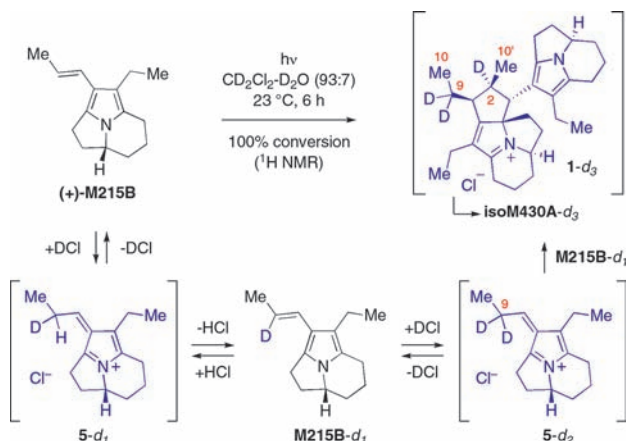
(6) Water was added to dissolve photochemically generated hydrochloric acid and maximize its capture.

(7) Irradiation of **M215B** in nonchlorinated solvents resulted in partial isomerization to **M215A**. See the Supporting Information for details.

By contrast, filtration of the reaction mixture containing the iminium ion **2** through basic alumina gel caused fragmentation to alkene **3** as a variable (1:0 to 1:1) mixture of *E/Z* isomers in yields of 40–60% (Scheme 1). Interestingly, irradiation of a dichloromethane solution of **3** as a mixture of isomers in any proportion directly produced **2** within 1 h (Scheme 1).⁷

As an additional probe to study the mechanism of formation of **isoM430B**, we sought to perform deuterium incorporation studies. For this purpose, known quantities of deuterium oxide (D₂O) were included in the reaction medium to override the effect of exchange between photochemically generated deuterium chloride and adventitious protium sources.¹⁰ Under these conditions, irradiation of a D₂O–dichloromethane-*d*₂ (7% v/v) solution of (+)-**M215B** for 6 h yielded a dimeric structure showing three sites of deuterium incorporation (Scheme 2).¹¹ While the remainder of the ¹H

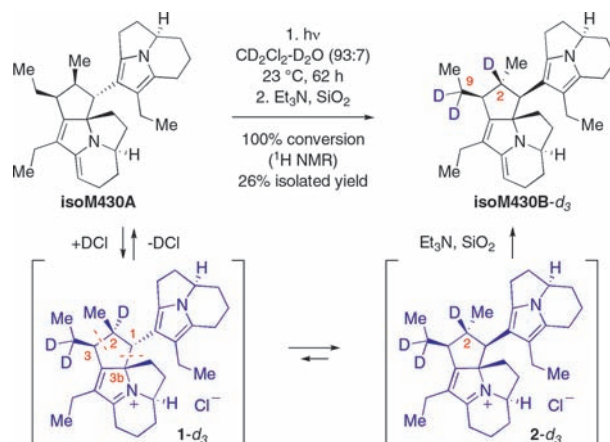
Scheme 2. Deuterium Incorporation in **isoM430A**



NMR spectrum matched that of the undeuterated iminium ion **1**, the splitting pattern induced by coupling to the C2 and C9 protons in the C10' and C10 methyl signals, respectively, was absent. This result indicated that rapid equilibrium between (+)-**M215B** and the tricyclic azafulvenium ion **5** had resulted in full deuterium incorporation at C9 in both of the tricyclic dimerization partners, which appeared as deuterium incorporation at the corresponding C2 and C9 positions in the **isoM430A** heptacycle.

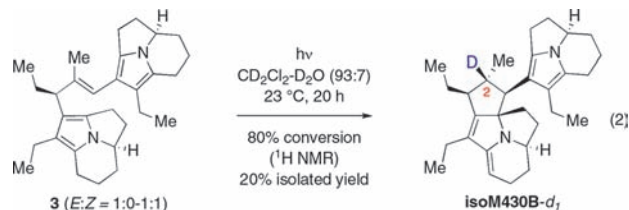
Interestingly, irradiation of **isoM430A** in D₂O–dichloromethane-*d*₂ (7% v/v) for 62 h resulted in the formation of the **isoM430B** heptacycle showing three sites of deuteration (Scheme 3). In this case, full deuterium incorporation had again occurred at C2 and at both positions of the C9

Scheme 3. Deuterium Incorporation in **1** and **isoM430B**



methylene group.¹² Monitoring of the reaction in situ by ¹H NMR showed that the **isoM430A** stereochemistry was maintained throughout full deuterium incorporation at C2 and C9, whereupon slow isomerization yielded **isoM430B**. Deuterium incorporation at C9 in these heptacycles is consistent with fragmentation of the dimeric structure to tricyclic azafulvenium ions, which would again be subject to rapid H/D exchange at C9 (Scheme 2). Significantly, this provided the first evidence that an equilibrium process involving formation of the **isoM430A** heptacycle may encompass reversible formation of both the first and the second bond of the dimerization.

By contrast, irradiation of a dichloromethane-*d*₂ solution of hexacyclic alkene **3** for 20 h in the presence of D₂O directly produced the **isoM430B** heptacycle exhibiting complete deuterium incorporation at C2 only (eq 2). The failure of **3** to incorporate deuterium at C9 suggests that it did not detectably interconvert with tricyclic azafulvenium ions over the period of irradiation.



Furthermore, irradiation of a D₂O–dichloromethane-*d*₂ solution of **isoM430B** for 67 h effected no deuterium incorporation at C2 or C9, suggesting that it did not appreciably fragment to either hexacyclic or tricyclic azafulvenium ions on this time scale.

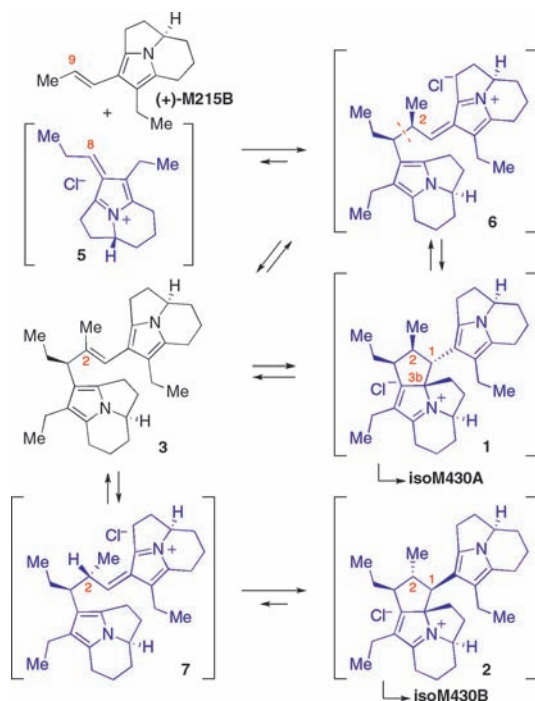
Cumulatively, these results suggest a mechanism in which trace quantities of photochemically generated hydrochloric acid promote reversible dimerization of (+)-**M215B** (Scheme 4). Initial dimerization produces hexacyclic azafulvenium ion

(10) H/D exchange between photochemically generated DCl and trace moisture or acidic protons in dimeric azafulvenium or iminium structures prevented detectable deuterium incorporation in reactions conducted in dichloromethane-*d*₂ alone.

(11) Rapid H/D exchange at C8 in **isoM430A** and **isoM430B** with trace water during filtration through silica gel prevented observation of potential deuterium incorporation.

(12) Potential intermediacy of **2** possessing deuterium incorporation at C2 alone could not be detected by ¹H NMR due to signal overlap.

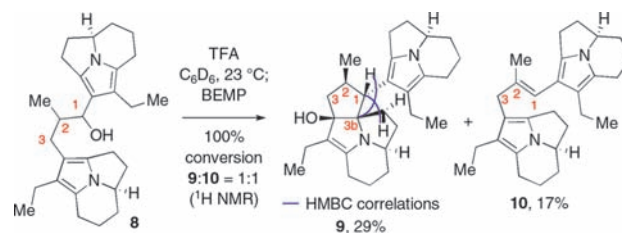
Scheme 4. Proposed Mechanism for Reversible Dimerization of **M215B** in the Presence of Photochemically Generated H(D)Cl



6 with the **isoM430A** stereochemistry at C2, which cyclizes to heptacycle **1**. Rupture of the C1–C3b bond of the iminium ion could regenerate azafulvenium ion **6**, and fragmentation of this structure would produce tricyclic azafulvenium ion **5**. Alternatively, **6** may undergo deprotonation at C2 to form alkene **3**. Protonation of this alkene from the opposite face would provide azafulvenium ion **7** with the **isoM430B** configuration at C2. Significantly, the failure of **3** to detectably interconvert with tricyclic azafulvenium ions suggests that fragmentation is slow relative to interconversion between dimeric structures.¹³ Rapid cyclization of **7** would generate the C1,C2-*trans*,C2,C3-*trans*-substituted heptacycle **2** as the thermodynamic product. Interestingly, the cyclopentane substituents in **M430A** also exhibit a C1,C2-*trans*,C2,C3-*trans* substitution pattern, consistent with a possibility that **M430A** may also be a thermodynamic product in an equilibrium process.

Although the C1 and C2 stereocenters in **isoM430B** were inverted relative to those in **isoM430A**, neither the stereochemistry at C3 nor the connectivity of the cyclopentane ring was altered. The invariance of the **isoM430A** configuration at C3 and the **isoM430A** connectivity raised the possibility that the C3 stereochemistry established in the first bond formation may influence the regiochemistry of subsequent pyrrole alkylation. To examine this possible relationship, we prepared the C3 unsubstituted hexacyclic alcohol **8** as a 1:1 mixture of C2 epimers (Scheme 5). In situ monitoring by

Scheme 5. Cyclization of **8**



¹H NMR demonstrated that ionization of the C1 alcohol upon treatment of a benzene-*d*₆ solution of **8** with 1.10 equiv of trifluoroacetic acid followed by addition of 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) under inert atmosphere afforded a 1:1 mixture of the **isoM430A** derivative **9** and the alkene **10**. Careful chromatographic separation of these highly sensitive compounds provided pure samples of **9** and **10** for full structural analysis. The generation of a single heptacyclic structure and the failure to observe products with the **M430A** connectivity in the absence of a C3 substituent strongly indicate that the **isoM430A** configuration at the C3 ethyl group is not necessary to direct C3b alkylation.

Mechanistic investigation into the formation of **isoM430B** yielded the first experimental evidence for fully reversible dimerization of (+)-**M215B**. In situ ¹H NMR monitoring of the chemistry of highly sensitive dimeric structures, complemented by isolation of pure samples and derivatives for full spectroscopic analysis, provided detailed information about the intermediates involved in this process. Deuterium incorporation studies indicate that interconversion between isomycarins structures can occur via fragmentation to tricyclic intermediates and establish that (+)-**M215B** dimerizes to afford distinct kinetic and thermodynamic products. Studies on the chemistry of these alkaloids provide insight into the factors that influence the structure and relative stereochemistry of dimeric myrmicarins relevant to a synthetic strategy based on dimerization of pyrroloindolizine derivatives and may provide key information regarding plausible biogenesis and activity of myrmicarin alkaloids.

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Supporting Information Available: Experimental procedures and spectroscopic data for **isoM430B**, **3**, **4**, **9**, and **10**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) Although we did not observe evidence for fragmentation of **3**, this possibility (e.g., via **6** or **7**) cannot be ruled out.