# Total Synthesis and Study of Myrmicarin Alkaloids

**Alison E. Ondrus** and **Mohammad Movassaghi**[a]

[a]Massachusetts Institute of Technology, Department of Chemistry, 77 Massachusetts Avenue 18-292, Cambridge, MA 02139-4307, USA; movassag@mit.edu

## Abstract

The myrmicarins are a family of air and temperature sensitive alkaloids that possess unique structural features. Our concise enantioselective synthesis of the tricyclic myrmicarins enabled evaluation of a potentially biomimetic assembly of the complex members *via* direct dimerization of simpler structures. These studies revealed that myrmicarin 215B undergoes efficient and highly diastereoselective Brønsted acid-induced dimerization to generate a new heptacyclic structure, isomyrmicarin 430A. Mechanistic analysis demonstrated that heterodimerization between myrmicarin 215B and a conformationally restricted azafulvenium ion precursor afforded a functionalized isomyrmicarin 430A structure in a manner that was consistent with a highly efficient, non-concerted ionic process. Recent advancement in heterodimerization between tricyclic derivatives has enabled the preparation of strategically functionalized hexacyclic structures. The design and synthesis of structurally versatile dimeric compounds has greatly facilitated manipulation of these structures *en route* to more complex myrmicarin derivatives.

## Introduction

The myrmicarins are a family of structurally fascinating alkaloids found in the poison gland secretion of the African ant species *Myrmicaria opaciventris* (Figure 1).[1,2] Of the alkaloids produced by ants of the *myrmicinae* group, the higher molecular weight myrmicarins display an unprecedented level of complexity.[3] In addition to challenges presented by their elaborate molecular architectures, the isolation and structure elucidation of the complex myrmicarins has been complicated by their air sensitivity.[4] While the bicyclic and tricyclic myrmicarins can be purified chromatographically, myrmicarin 663 (**M663**) is the only complex member that has been isolated and characterized as a single component.[5] By contrast, the extreme sensitivity of myrmicarin 430A (**M430A**) necessitated its characterization as a mixture with the tricyclic myrmicarins in a sample taken directly from the poison gland. Structural assignments for both **M430A** and **M663** have been achieved using a combination of phase-sensitive two-dimensional NMR techniques. Although submilligram samples of myrmicarin 645 (**M645**) have been obtained, the scarcity and oxidative sensitivity of this compound have prevented assignment of its relative stereochemistry.[1,6] Interestingly, while another alkaloid with a molecular weight of 430 was identified during mass spectrometric analysis of the poison gland secretion, no structural information on this compound was obtained.

The fascinating structures of these alkaloids, combined with the opportunities and challenges associated with their sensitivity and chemistry, inspired us to develop methods for their total synthesis. Specifically, we envisioned a concise assembly of the highly sensitive complex members through potentially biomimetic dimerization or trimerization of the tricyclic members. Herein we report our studies in this area, encompassing a succinct enantioselective

Correspondence to: Mohammad Movassaghi.

synthesis of the tricyclic myrmicarins and the discovery of an unprecedented, highly efficient vinyl pyrroloindolizine dimerization to yield heptacyclic products. Mechanistic analysis of this dimerization using functionalized pyrroloindolizine derivatives revealed that the corresponding heptacyclic products are formed in a highly efficient, non-concerted ionic process. This unique reactivity has enabled us to employ strategic heterodimerization of functionalized pyrroloindolizines to prepare versatile dimeric structures for elaboration to more complex myrmicarin derivatives.

## Hypothesis for biosynthesis of the complex myrmicarins

Shortly after their isolation of the tricyclic myrmicarins, Schröder and Francke reported the racemic synthesis of myrmicarin 217 (**M217**, Figure 1) through dehydrative cyclization of an unsaturated derivative of myrmicarin 237B (**M237B**, Figure 1).[7] This result was consistent with a proposal that the complex myrmicarins may arise through oligomerization of bicyclic structures (Figure 2).[8]

As an alternative to this biosynthetic hypothesis, we proposed that the complex myrmicarins may originate *via* dimerization or trimerization of the tricyclic members. Specifically, **M430A** may arise directly from dimerization of **M215B** (Figure 3).[9] According to this proposal, we envisioned three potentially biomimetic dimerization strategies for the formation of **M430A** (Figure 4).[10] In the first we envisioned an ionic mode of dimerization involving the generation of the highly electrophilic azafulvenium ion **1** (Figure 4A). Nucleophilic addition of neutral **M215B** to this azafulvenium ion would furnish the hexacyclic azafulvenium ion **2**, which could undergo intramolecular alkylation by the neutral pyrrole to establish the **M430A** heptacycle.

Alternatively, we considered that dimerization may occur in a single-step cyclopentannulation event involving a concerted $[6\pi_a+2\pi_s]$ cycloaddition between **M215B** and the *Z*-azafulvenium ion **1** (Figure 4B).[11] In this event, both bonds of the cyclopentane ring would be formed simultaneously *via* an antarafacial interaction between the $6\pi$ unit of the azafulvenium ion and one face of the **M215B** $2\pi$ alkene.[12] Significantly, molecular orbital analysis establishes that the resulting stereochemistry at all of the contiguous stereocenters of the cyclopentane ring would match that of **M430A**. Finally, we considered that the dimerization may proceed through a pathway involving generation of the stabilized radical **4** (Figure 4C).[13] Addition of **4** to the alkene of **M215B** and subsequent 5-*exo* trig radical cyclization of a C1 radical in **5** onto the pyrrole would provide the stabilized heptacyclic radical **6**, which would be subject to oxidation. As dimerization of vinyl pyrroloindolizines *via* any of these approaches was without precedent at the onset of our studies, each of these manifolds represented an attractive means of accessing **M430A**. To identify conditions to achieve the desired dimerization, we began by probing the reactivity of the tricyclic myrmicarin structures.

## Prior syntheses of bicyclic and tricyclic myrmicarins

Motivated by the prominent role of the poison gland secretion in the ecology of the *Myrmicaria* ants and the potent toxicity of the previously unidentified alkaloid constituents, Francke and coworkers embarked on elegant studies to identify the alkaloid poisons produced by *Myrmicaria eumenoides*. In 1995, they reported the first isolation, structure elucidation, and enanioselective synthesis of **M237A** and **M237B** (Figure 1).[1b] Mass spectrometric assisted analysis of the poison gland reservoir of this species revealed that the secretion consisted predominantly of (+)-limonene and two alkaloids with masses of 237. Although pure samples of each alkaloid could be obtained by chromatographic separation on neutral alumina gel, attempted storage at ambient temperature resulted in their rapid interconversion. Analysis of the mixture using a combination of two-dimensional NMR techniques revealed that the alkaloids were diastereomeric 3-butyl-5-(1-oxopropyl)indolizidines.

As the relative stereochemistry of each alkaloid could not be determined by NMR analysis of the mixture, Francke performed a series of structure correlation studies (Schemes 1 and 2). In all of these 5-(1-oxopropyl)-indolizine structures the C5 stereocenter could be readily epimerized under basic conditions to provide separable C5 stereoisomers, thus first considerations focused on controlling the relative stereochemistry of C3 and C9. Synthesis of the C3,C9-*cis* indolizine diastereomers commenced with conjugate addition of nitroester **8** to enone **7** to provide nitroketone **9** (Scheme 1). Stereoselective *cis*-pyrrolodine formation in the presence of palladium in ethanol provided the C3,C9-*cis* diastereomer (±)-**10**. One-pot α-iodination of the ester and intramolecular displacement by the pyrrolidine nitrogen provided the indolizine bicycle. Saponification of the ester and addition of ethyllithium provided a separable mixture of diastereomers (±)-**11** and (±)-**12**. Comparison of the NMR spectra of these compounds to those of the poison gland alkaloids showed that neither matched **M237A** or **M237B**.

To confirm the *trans* disposition of the C3 and C9 methines in **M237A** and **M237B**, Francke synthesized the requisite trans pyrrolidine diastereomer (Scheme 2). Sequential alkylation of *N-tert*-butoxycarbonylpyrroline furnished the intermediate **15**, whereupon employment of the previous synthetic sequence provided C3,C9-*trans* indolizine diastereomers. Comparison of the $^1$H NMR spectra of these compounds to those of the natural isolates revealed that the spectrum of the C5-(*S*) isomer matched that of **M237A**, while the spectrum of the C5-(*R*) isomer matched that of **M237B**.

After confirming the relative stereochemistry of the C3 and C9 stereocenters through synthesis of racemic samples of each diastereomer, Francke achieved the enantioselective syntheses of both **M237A** and M237B (Scheme 3). Lithiation of pyridine **18** and alkylation with enantioenriched epoxide **17** provided the advanced intermediate **19**. Hydrogenation of the pyridine ring provided the desired piperidine **20** with 3:2 selectivity. Tosylation of the C3 alcohol and invertive displacement by the piperidine nitrogen in this mixture furnished the corresponding diastereomeric indolizidines, which were separated to provide the desired bicycle as a single stereoisomer. Acid-induced ketone deprotection occurred without epimerization at C5, exclusively providing (−)-**M237A**. To access (+)-**M237B**, silica gel-induced epimerization at C5 provided a 1:1 mixture of (−)-**M237A** and (+)-**M237B**, which were separated by alumina gel chromatography to provide (+)-**M237B**. This synthesis established the C9-(*R*) configuration in the **M237A** and **M237B** structures.[14]

In 1999, Lhommet *et al* reported an enantioselective synthesis of **M237A** (Scheme 4).[15] To obtain the enantioenriched *trans*-pyrrolidine **22** they employed a highly diastereoselective reduction of β-enaminoester **21** derived from (*S*)-pyroglutamic acid. Horner-Wadsworth-Emmons reaction with a functionalized phosphonate provided the enone **23**. After careful optimization of the reduction sequence, nitrogen deprotection and concomitant alkene reduction under hydrogenation conditions provided the corresponding free amino ketone **24**. Trifluoroacetic acid-induced condensation of the pyrrolidine amine and the pendant ketone produced enone **25**. Stereoselective iminium ion reduction using sodium cyanoborohydride in the presence of hydrochloric acid provided a 92:8 mixture of (−)-**M237A** and (+)-**M237B**, which were separated chromatographically to provide (−)-**M237A** as a single stereoisomer.

The first total synthesis of racemic **M217** was reported by Schröder and Francke in 1998, two years after its isolation (Scheme 5).[7] In line with a biomimetic proposal presented in the isolation paper, the key step of this very interesting synthesis involved dehydrative cyclization of an unsaturated derivative of **M237A** to provide **M217**. Commencing with piperidine **26**, available in four steps from their reported intermediate **19** (Scheme 3), gentle heating in benzene under nitrogen atmosphere resulted in efficient conversion to **M217**. *In situ* $^1$H NMR monitoring revealed that condensation between the amine and the C3 ketone initially produced

the C5,C9-*cis* indolizidine **27**, the proposed unsaturated derivative of **M237**. Rapid epimerization at C5 provided a mixture of stereoisomers. In a slower process, intramolecular addition of the C3-C1″ enamine to the C1′ ketone and dehydration of the resulting alcohol afforded the pyrroloindolizine structure of **M217**.

Schröder and Francke note that formation of **M237A**, **M237B** and **M217** from related monocyclic precursors provides support for an analogous biosynthetic relationship. They postulate that **M215A** and **M215B** might likewise arise *via* cyclization of a doubly unsaturated analogue of **M237**, citing the presence of trace amounts of alkaloids with mass 233 in the poison gland secretion as potential evidence for the existence of this intermediate. The corresponding bicyclic and tricyclic substructures in the complex myrmicarins prompt them to propose a doubly unsaturated derivative of **M237** as a common biogenetic precursor to these alkaloids.

The first enantioselective synthesis of (+)-(*R*)-**M217** was disclosed by Vallée *et al* in 2000 (Scheme 6).[16] Condensation between the D-glutamic acid diethyl ester and tetrahydro-2,5-dimethoxyfuran furnished the enantioenriched *N*-alkylpyrrole **29**. Lewis acid-induced intramolecular Friedel-Crafts cyclization of diester **29** yielded bicycle **30**.[17] Exhaustive reduction of the C7 ketone with sodium cyanoborohydride in the presence of zinc diiodide followed by ester reduction with lithium aluminum hydride generated alcohol **31**. Elaboration to the mixed anhydride **32** and boron trifluoride-induced cyclization yielded the tricyclic ketone **33**. Under the directing influence of the C3 carbonyl substituent, completely regioselective acylation at C1 provided diketone **34**. Reduction of both carbonyl groups using lithium aluminum hydride and Vilsmeier-Haak acylation at the remaining unsubstituted pyrrole position generated the fully substituted **M217** core. Finally, lithium aluminum hydride reduction of the C8 carbonyl substituent furnished (+)-(*R*)-**M217**.

Intercepting Vallée's synthesis at intermediate **31** (Scheme 6), in 2000 Lazzaroni *et al* reported a formal synthesis of (−)-(*S*)-*ent*-**M217** (Scheme 7).[18] Cyclodehydration of the aldehyde **37**[19] provided bicycle **38**, whereupon hydrogenation of the alkene and ester reduction provided alcohol *ent*-**31**.

In 2001 Vallée reported the synthesis of **M215A** and **M215B** as a mixture of geometric isomers (Scheme 8).[20] For the purpose of investigating the inherent selectivity for the position of acylation in **39**, they employed lithium aluminum hydride reduction to remove the electron withdrawing C3 ketone in **33**. Careful optimization of acylating agent, reaction solvent, and reaction temperature revealed that formylation of **39** under Vilsmeier conditions in toluene at 83 °C afforded **40** as the exclusive monoformylation product in 53% yield. Elaboration to **35** followed by a second Vilsmeier-Haack reaction and Wittig homologation of the resulting C8 aldehyde provided **M215A** and **M215B** as a 4:1 mixture.

## Our enantioselective total synthesis of tricyclic myrmicarins

In order to explore our proposed dimerization strategies we required a succinct, convergent, and enantioselective route to the pyrroloindolizine core of the tricyclic myrmicarins.[21] As a strategic element in designing our route we noted that use of a catalytic enantioselective method for introducing the C4a stereocenter (Figure 5) would enable us to efficiently access either antipode of the tricycles, and thus of the complex myrmicarins. Additionally, identification of air- and acid-stable intermediates would allow preparation of a range of derivatives for our proposed dimerization pathways. With these considerations, our strategy entailed rapid assembly of the advanced enantiomerically enriched intermediate **45** through *N*-vinylation of the substituted pyrrole **43** with a vinyl halide or the vinyl triflate **42** followed by an enantioselective conjugate reduction (Figure 5). Successive Friedel-Crafts cyclizations would then yield the pyrroloindolizine substructure. Critically, we envisioned that the acyl substituent

of the pyrrole would direct the successive cyclizations and attenuate the electron rich nature of the pyrrole nucleus, conferring stability to these intermediates.

Inspiration for our *N*-vinylation/asymmetric conjugate reduction sequence arose from a report by Buchwald *et al* in 2004, in which they disclosed an efficient method for enantioselective copper-catalyzed reduction of β-azaheterocyclic enoates to the corresponding β-azaheterocyclic esters.[22] In their report, the necessary β-azaheterocyclic enoates were prepared by copper-catalyzed *N*-vinylation of the corresponding β-iodoenoates. We initially envisioned the use of a vinyl iodide as our *N*-vinylation substrate, however reported conditions for formation of the *Z* vinyl iodide were incompatible with the acid-sensitive dimethoxyacetal functional group of our desired substrate.[23] Furthermore, few methods were available for the direct stereoselective synthesis of *E*-β-iodoenoates. By contrast, several mild methods existed for the stereoselective formation of *E* or *Z* vinyl triflates from the corresponding β-ketoesters. Thus we sought to develop conditions for stereoselective *N*-vinylation of configurationally defined vinyl triflates that would be applicable to a range of nitrogen heterocycles, providing the resulting *N*-azaheterocyclic enoates as versatile compounds.[24]

While several methods were available for the copper-catalyzed *N*-arylation of amines, amides, azoles, and carbamates, far fewer systems had been developed for the corresponding *N*-vinylation reactions. Additionally, few reported methods for the *N*-vinylation of dialkylamines and azoles existed relative to those involving *N*-vinylation of amides and carbamates. At the time of our study, a single report of palladium-catalyzed *N*-vinylation of lithiated azoles with vinyl bromides had been described.[25] While our initial studies showed that copper-based catalyst systems were ineffective, we discovered that the use of palladium catalysts in the presence of a phosphine ligand and an inorganic base efficiently yielded the desired *N*-vinylation products under mild conditions. Optimization of the catalyst system revealed that palladium dibenzylideneacetone (Pd$_2$(dba)$_3$), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (XPhos),[26] and rigorously dry potassium phosphate tribasic in toluene or dioxane at 60 to 100 °C successfully effected *N*-vinylation of a range of heterocycles with both *E*- and *Z*-vinyl triflates, in each case with complete retention of the vinyl triflate geometry (Table 1). Importantly, use of rigorously dry base significantly reduced the formation of alkyne and ketone byproducts. Best results were obtained in *N*-vinylation of electron deficient azoles with β-ketoester derived vinyl triflates, however these conditions were also successfully applied to *N*-vinylation of unsubstituted pyrrole (Table 1, **44a** and **44d**) and indole (Table 1, **44b**), and could be employed for simple ketone-derived vinyl triflates (Table 1, **44l**).

This method was applied on multigram scale to *N*-vinylation of the readily accessible *Z*-vinyl triflate **42** with pyrrole **43** to provide the β-pyrrolyl enoate **44** in 95% yield with complete retention of vinyl triflate geometry (Scheme 9). Copper-catalyzed asymmetric conjugate reduction employing copper acetate dihydrate and *S*-bis(diphenylphosphino)-1,1'-binaphthyl (*S*-BINAP) in the presence of polymethylhydrosiloxane (PMHS) according to Buchwald's protocol smoothly afforded the (*R*)-β-pyrrolyl ester **45**,[27] establishing the absolute stereochemistry at the C4a stereocenter. Subsequent acid-induced Friedel-Crafts cyclization occurred with greater than 10:1 selectivity in favor of the desired regioisomer under the directing influence of the C8 carbonyl. Hydrogenation of the resulting alkene, one-pot reduction of the *tert*-butyl ester through transient *in situ* protection of the C8 ketone, and conversion of the resulting C3 alcohol to the primary iodide **47** provided the precursor to the pyrroloindolizine core. Although radical-mediated cyclization of the primary iodide proceeded in the presence of tri-*n*-butyltin hydride and 2,2'-azobisisobutyronitrile (AIBN) in refluxing toluene, optimal yields were obtained by silver(I)-promoted cyclization under strictly anhydrous conditions. This sequence readily affords multigram quantities of the tricyclic ketone (*R*)-**36** as an air stable solid.

This synthesis of the enantiomerically enriched ketone **36** allowed expedient access to each antipode of all three of the tricyclic myrmicarin alkaloids, providing the first geometrically pure samples of myrmicarin 215A (**M215A**, Scheme 1) and **M215B**. Commencing with (*R*)-**36**, exhaustive lithium aluminum hydride reduction of the C8 carbonyl group provided (+)-(*R*)-**M217** in quantitative yield (Scheme 10). By contrast, **M215B** was prepared by low temperature lithium aluminum hydride reduction of the ketone **36** to yield an inseparable 1:1 mixture of C8 alcohol epimers, which underwent facile elimination under mildly acidic conditions to provide (+)-(*R*)-**M215B** as a single isomer. Stereoselective synthesis of the exceedingly air and acid sensitive (−)-(*R*)-**M215A** was achieved in a two-step sequence through 2-chloro-3-ethylbenzoxazolium tetrafluoroborate-induced dehydration of the C8 carbonyl followed by careful reduction of the intermediate alkyne under Lindlar conditions.[28]

Notably, exposure of **M215A** to mildly acidic conditions, including brief exposure to silica gel, effects partial conversion to **M215B**, requiring its manipulation under strictly neutral or basic conditions. Consistent with their isolation report, all three of the tricyclic myrmicarins undergo gradual conversion to their corresponding C6-C7 oxidized derivatives, accompanied by decomposition. Bubbling oxygen through a sample of pure **M217** in benzene-$d_6$ and monitoring of the mixture by ^{1}H NMR shows almost complete conversion to myrmicarin 215C within 24 hours, accompanied by a complex mixture of minor decomposition products



(1)

(Equation 1). Importantly, ketone **36** does not undergo this mode of oxidation or decomposition, highlighting the advantage of the electron withdrawing carbonyl substituent in the manipulation and long term storage of these tricyclic derivatives.

## Ionic dimerization of tricyclic myrmicarins

Investigation into our proposed ionic mode of dimerization *via* formation of azafulvenium ion intermediates (Figure 4A) commenced by gathering evidence for the existence of tricyclic azafulvenium species. As noted, completely stereoselective formation of **M215B** could be achieved by exposure of a diastereomeric mixture of the alcohols **48** to acidic aqueous work up. Likewise, treatment of a benzene solution of **48** with acetic acid resulted in gradual conversion of the epimers to **M215B** exclusively (Scheme 11). ^{1}H NMR monitoring revealed that the elimination proceeded *via* an approximately 1:1 mixture of the C8 acetate adducts **49**, which were both slowly consumed to provide **M215B**. Although the intermediacy of the C8 acetate adduct and the transformation of both acetate epimers to **M215B** was consistent with the existence of an azafulvenium ion intermediate, this species was not directly observed by ^{1}H NMR, which may be anticipated as a result of its high reactivity and short lifespan.

By contrast, *in situ* ^{1}H NMR monitoring revealed that treatment of a benzene-$d_6$ solution of **M215B** with trifluoroacetic acid (TFA, 1.10 equiv) resulted in quantitative and highly stereoselective dimerization to the heptacyclic iminium ion **50a** within 45 minutes (Scheme 11).[29] Likewise, *in situ* ^{1}H NMR analysis showed that upon treatment with TFA (1.10 equiv) the epimeric alcohols **48** immediately generated **M215B**, which proceeded to exclusively furnish **50a**. When **M215B** was subjected to substoichiometric quantities of TFA, **50a** was produced to approximately the extent of the added acid, whereas addition of a large excess of TFA instead generated a mixture of ring-protonated **M215B** salts, which did not undergo dimerization. Compellingly, exposure of **M215A** to TFA (1.10 equiv) resulted in formation of the same heptacyclic structure. Under the latter conditions, while trace amounts of **M215B** were observed in the reaction mixture throughout the course of dimerization, the predominant

tricyclic species was **M215A**, suggesting that the rate of isomerization of **M215A** was slower than the rate of dimerization of **M215B**. Cumulatively, these observations suggested an acid-promoted formation of a tricyclic azafulvenium ion and subsequent trapping by available **M215B**, consistent with our proposed ionic mode of dimerization. Although subsequent studies have established the reversibility of this dimerization, reversion of the heptacycle **50a** to tricyclic intermediates was *not* observed under these conditions.

Initial efforts to isolate this heptacyclic iminium ion failed due to its extreme sensitivity. The oxidative instability of these alkaloids compelled us to consider chemical modifications that would provide a derivative more stable toward a robust means of characterization, such as X-ray crystallography or two-dimensional NMR analysis of a pure sample.[30] In order to fully characterize the compounds *en route* to these isolable derivatives and to garner information about the reactivity of this dimeric species, we developed techniques that were compatible with *in situ* ^{1}H NMR analysis of these reactions. In particular, use of resin-bound reagents enabled manipulation of the observed intermediates without obscuring the ^{1}H or ^{13}C NMR spectral regions of interest. Gratifyingly, direct addition of the resin-bound base 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP) to a benzene solution of **50a** under inert atmosphere cleanly effected conversion to a heptacyclic diene, which we named isomyrmicarin 430A (**isoM430A**, Scheme 12). While this compound was stable as an argon-purged solution in benzene-$d_6$ for approximately 12 hours, attempts at isolation resulted in decomposition, in line with the high oxidative sensitivity of an electron rich diene.

To enhance the stability of this compound we speculated that mild hydrogenation of this diene may provide a more stable derivative. Indeed, addition of catalytic palladium on carbon and saturation of the mixture with dihydrogen at atmospheric pressure provided the heptacyclic enamine **51** as a single diastereomer (Scheme 12). This compound was sufficiently stable to be purified through a short plug of triethylamine-pretreated silica gel and could be stored for 24 hours as an argon-purged solution in benzene-$d_6$ without significant decomposition. Assignments based on a full complement of two-dimensional NMR data corroborated the structure of the heptacyclic enamine **51** and were in agreement with the assignments for the structures of **50a** and **isoM430A** based on the corresponding two-dimensional NMR data.

The structure of the heptacyclic diene **isoM430A** differed from the **M430A** structure in the connectivity of the C1-C3b bond and the stereochemistry of the C3 substituent on the cyclopentane ring (Figure 6). The stereochemistry of the substituents on the cyclopentane ring were consistent with an ionic dimerization mechanism involving association of **M215B** and azafulvenium ion **1** from the convex face of each tricycle (Figure 7). Nucleophilic addition of **M215B** to **1** would provide the hexacyclic azafulvenium **2**, which could undergo alkylation by the pyrrole in the same relative orientation. This sequence would generate the observed configuration at each of the cyclopentane stereocenters. The approach of **M215B** and the azafulvenium ion may be facilitated by π-stacking between the electron-rich and electron-deficient π systems, which is maintained throughout the proposed mechanism. Indeed, the generation of **isoM430A** as a single diastereomer was compelling evidence for our proposed ionic dimerization of **M215B**, representing an unprecedented mode of reactivity for vinyl pyrroloindolizines.

## Scope of Brønsted acid-promoted dimerization

The charged and highly electrophilic nature of the tricyclic and heptacyclic azafulvenium ions in this ionic mechanism suggested that varying the reaction medium may have a pronounced effect on the rate or reversibility of each step. As such, we reasoned that use of solvents of different polarity, dielectric constant, and nucleophilicity, or introduction of additives may alter the observed regio- or stereoselectivity of the dimerization. To assess the influence of the

reaction conditions on the rate and selectivity of the dimerization process we examined the acid-promoted behavior of the alcohol **48** and **M215B** in the presence of different solvents, acid promoters, inorganic salts, and nucleophilic additives. Due to the known sensitivity of **isoM430A** and the reported sensitivity of **M430A**, these reactions were monitored *in situ* by ^{1}H NMR spectroscopy and the identity of the products was confirmed by conversion to previously prepared and characterized derivatives.

The nature of the solvent had a marked effect on the rate of dimerization. In hydrocarbon solvents such as benzene-$d_6$ and cyclohexane-$d_{12}$, trifluoroacetic acid (TFA)-induced dimerization of **M215B** was complete within 30 minutes, while in tetrahydrofuran-$d_8$ dimerization of **M215B** was only 80% complete within 24 hours (Table 2, entries 1 and 2). In contrast, treatment of an acetonitrile-$d_3$ solution of the alcohol **48** with TFA effected conversion to **50a** within 5 minutes without visible accumulation of **M215B** (Table 2, entry 3). Addition of TFA to a methanol-$d_4$ solution of the alcohol **48** resulted in methanolysis to afford a corresponding 1:1 mixture of C8 methanol adducts (**52**), which were slowly consumed to form **50a** without observable persistence of **M215B** (Table 2, entry 4). In all of these experiments, the rate of addition and number of equivalents of acid used were crucial, as rapid addition or the use of large excess of acid resulted in protonation of the pyrrole ring (*i.e.* **54**, Table 2), which prevented dimerization.

Introduction of salt additives also had a pronounced effect on the dimerization. Addition of stoichiometric strong acid (1.10 equiv) to tetrahydrofuran-$d_8$ or methanol-$d_4$ solutions of the alcohol **48** or **M215B** saturated with lithium perchlorate ($LiClO_4$) led to protonation of the pyrrole ring, inhibiting dimerization (Table 2, entries 6 and 7). While dimerization proceeded in the presence of saturating lithium chloride (LiCl) in tetrahydrofuran-$d_8$, the rate was reduced six-fold relative to that in tetrahydrofuran-$d_8$ alone. Treatment of a methanol-$d_4$ solution of the alcohol **48** with TFA in the presence of the nucleophilic additive *p*-methylbenzenethiol led to formation of C8 thiol adducts of the tricycle (**53**), which did not undergo dimerization (Table 2, entry 8). Significantly, none of these conditions yielded dimeric structures arising from trapping of hexacyclic azafulvenium or heptacyclic iminium intermediates.

While the rate of dimerization of **M215B** varied significantly in solvents of different polarity and in the presence of additives, the dimeric structure produced was exclusively the heptacycle **50**. Dimerization proceeded rapidly in non-nucleophilic and hydrocarbon solvents, while polar and protic solvents reduced the rate of dimerization. Nucleophilic additives likewise retarded or inhibited dimerization by intercepting tricyclic azafulvenium ions to form C8 adducts. The inability to directly identify dimeric species other than **50** or to observe dimeric trapping products suggested that hexacyclic azafulvenium intermediates such as **2** (Figure 4A), if produced, were exceedingly fleeting species that underwent facile intramolecular capture to provide the heptacyclic structure **50**.

## Investigation of a potential [6π$_a$+2π$_s$] cycloaddition mechanism

The insensitivity of the structure of the heptacyclic product to the dimerization conditions prompted us to examine an alternative mechanism for its formation. Specifically, we considered that the exclusive formation of **50** as a single diastereomer may be the consequence of a concerted [6π$_a$+2π$_s$] cycloaddition that generated all of the new stereocenters and both bonds in a single event (Figure 8A).[10,11] In this process, interaction between the 6π component of the azafulvenium ion **1** and the 2π component of **M215B** in a manner that was antarafacial with respect to the 6π component and suprafacial with respect to the 2π component would generate the heptacycle **50**. This analysis requires the reactive azafulvenium ion *E*-**1** to adopt the *E* alkene geometry, which molecular orbital calculations indicate to be 1.3 kcal/mol higher in energy than the *Z*-azafulvenium ion *Z*-**1**.[31] A [6π$_a$+2π$_s$] cycloaddition would proceed through

the higher energy azafulvenium ion *E*-**1** *via* approach of the **M215B** alkene to the sterically accessible side of the azafulvenium π system (Figure 8A). Critically, an analogous [6π$_a$+2π$_s$] cycloaddition involving the sterically accessible sites of the isomeric *Z*-azafulveniun ion *Z*-**1** and the **M215B** alkene would provide a heptacycle possessing the **M430A** connectivity and stereochemistry (Figure 8B).

As a means to investigate this mechanistic hypothesis we designed the conformationally restricted azafulvenium precursor **60** that would yield a *Z*-azafulvenium ion upon activation. To achieve this, we employed a sterically encumbered [1,3,2]-dioxasilocine tether between C3 and C9 of the tricycle to lock the azafulvenium ion *Z*-**61** in the *Z* geometry (Figure 9). In this case, formation of the undesired *E*-azafulvenium ion *E*-**61** would require introduction of a prohibitively strained *trans* alkene. As a further refinement to this design, we noted that the significant steric interaction between the C10 methyl group and the C11 methylene protons in the C9-(*R*) azafulvenium ion *E*-**61**, which were absent in the C9-(*S*) epimer, would more strongly favor formation of the *Z*- azafulvenium ion.

The tethered azafulvenium precursor **60** was readily accessed from the alcohol **55**, an intermediate available from our synthesis of the tricyclic myrmicarins (Scheme 13).[10] After examining a number of conditions to avoid oxidation of the electron rich pyrrole nucleus, conversion of the primary alcohol to the corresponding aldehyde was achieved using 2-iodoxybenzoic acid in dimethylsulfoxide. Triethylsilyl trifluoromethanesulfonate-promoted cyclization of **56** provided the protected alcohol **57** as a 4:1 mixture of diastereomers, which were separated chromatographically after desilylation. Reprotection of the oxidatively sensitive alcohol and hydroxylation using Davis oxaziridine provided the diol **58** as a 4:1 mixture of separable C9 epimers. Mitsunobu inversion of the C9 alcohol with *p*-nitrobenzoic acid and hydrolysis to the free alcohol provided the desired C9 epimer. Deprotection of the C3 alcohol, installation of the siloxy tether,[32] and reduction of the C8 ketone afforded the conformationally restricted azafulvenium precursor **60**.

To investigate our [6π$_a$+2π$_s$] cycloaddition mechanism we required selective ionization of the C8 alcohol in **60** under conditions that would avoid Brønsted acid-induced dimerization of **M215B**. On the basis of this consideration we explored conditions for Lewis acid activation of the C8 alcohol in **60** that would be compatible with **M215B**. After optimization we found that treatment of an acetonitrile solution of the alcohol **48** with scandium trifluoromethanesulfonate (Sc(OTf)$_3$) in the presence of the *E*-thiolketene acetal **62** provided the thiolester **63** without visible Brønsted acid-promoted reactivity (Equation 2). A control experiment demonstrated that addition of Sc(OTf)$_3$ to a solution of **M215B** in acetonitrile did not induce homodimerization.



(2)

With these results, we employed our optimal conditions to effect selective formation of the azafulvenium *Z*-**61** in the presence of **M215B** as an electron rich π nucleophile (Figure 9).[33] *In situ* monitoring by ^{1}H NMR during portion-wise addition of 0.40 equivalents of Sc(OTf)$_3$ to a 1:1 mixture of azafulvenium precursor **60** and **M215B** in acetonitrile-*d$_3$* showed complete and selective formation of the heptacycle **64**, with no visible formation of other tricyclic or dimeric derivatives. This air and acid sensitive compound was sufficiently stable to be isolated and purified by flash column chromatography using triethylamine-pretreated silica gel. Exhaustive structural analysis using a combination of two-dimensional NMR techniques revealed that the obtained product possessed a connectivity and stereochemistry analogous to that of **isoM430A**.

The exclusive formation of heptacycle **64** provided strong evidence for a stepwise mechanism for heterodimerization involving **M215B** and the conformationally restricted azafulvenium precursor **60**. Importantly, participation of the severely strained *E*-azafulvenium ion *E*-**61** in a [$6\pi_a+2\pi_s$] cycloaddition manifold is unlikely, while a [$6\pi_a+2\pi_s$] reaction involving the corresponding *Z*-azafulvenium ion Z-**61** would engender a C3 stereochemistry in the resulting heptacycle opposite to that of **isoM430A**. While these observations did not preclude a concerted [$6\pi_a+2\pi_s$] pathway for homodimerization of **M215B** to produce **M430A** or **isoM430A**, they did implicate two discrete bond forming events in the formation of the heterodimer **64**.

## Directed heterodimerization of functional pyrroloindolizines

The propensity of vinyl pyrroloindolizine derivatives to undergo ionic modes of dimerization inspired us to exploit this behavior to prepare functionalized dimeric derivatives. Data supporting the stepwise nature of these heterodimerizations prompted us to consider tricyclic structures that may enable us to capitalize on the efficiency of the first C2-C3 bond formation (Figure 10). In this vein, we envisioned introduction of a functional group at C8 of the nucleophilic partner in the dimerization that would allow us to secure the C2-C3 bond, then act as a 'blocking' group at C1 in the dimer. Ideally, this functional group would prevent formation of the **isoM430A** heptacycle by either inhibiting C3b alkylation or making it reversible. In this manner we could use a highly selective and efficient ionic dimerization to provide hexacyclic derivatives possessing a handle at C1 to investigate alternative means of accessing **M430A** heptacycle.

We identified the silyl enol ether **73** (Scheme 14) as a suitable tricyclic nucleophile for this proposed heterodimerization manifold. Nucleophilic addition to a tricyclic azafulvenium ion would provide the oxonium intermediate **69** (Figure 10, B=O), which could either desilylate directly or undergo alkylation to yield a labile C3b aminal that would be subject to fragmentation. In an initial attempt, we drew analogy to our previous mechanistic studies and employed the conformationally restricted azafulvenium precursor **72** as an electrophile (Scheme 14A). Significantly, it was necessary to establish conditions that would effect ionization of the C8 alcohol of this azafulvenium precursor without promoting desilylation of the electron-rich silyl enol ether nucleophile. Gratifyingly, *in situ* monitoring by $^1$H NMR showed that subjection of a mixture of the triisopropylsilyl enol ether **73** and the tethered azafulvenium precursor **72** (1.56:1) to catalytic Sc(OTf)$_3$ in acetonitrile-*d$_3$* smoothly yielded the tethered hexacycle **74** as a 5:1 mixture of diastereomers in 73% yield (Scheme 14A). After rapid filtration through triethylamine-pretreated silica gel, a combination of NMR studies on the major diastereomer in the mixture enabled full structural assignment. One-dimensional nOe analysis established that the major diastereomer possessed the **isoM430A** configuration at both C2 and C3. While this tethered heterodimer was sufficiently stable to be stored for brief periods, the enhanced sensitivity of the C4 alcohol toward ionization in the absence of an electron-withdrawing pyrrole substituent hampered further manipulations.

Having established this heterodimerization with the conformationally restricted azafulvenium precursor **72**, we began to examine the scope of tricyclic structures that could function as electrophiles in this manifold. Activation of the simple alcohol **48** by catalytic Sc(OTf)$_3$ in the presence of **73** provided the hexacyclic ketone **75** in 77% yield, which showed a moderately enhanced stability relative to the tethered heterodimer (Scheme 14B). To assign the stereochemistry at C2 and C3 in this hexacyclic dimer we relied on derivatization to a more rigid heptacyclic structure. Low temperature reduction of the C1 ketone using lithium aluminum hydride and treatment of the sensitive hexacyclic alcohol with acetic acid resulted in cyclization to the **isoM430A** heptacycle with greater than 80% stereoselectivity (Scheme 14B).[34] While the success of these heterodimerization reactions confirmed our ability to access

functionalized hexacyclic structures, the persistent formation of the **isoM430A** stereochemistry at C3 prompted refinement of our approach.

To introduce additional flexibility in our heterodimeric structures, we sought conditions that would enable us to employ azafulvenium precursors at the C8 ketone oxidation state (Figure 10). Control over the C3 stereochemistry in the resulting dimeric structures would be facilitated by the corresponding increase in oxidation state at C3. Existing precedent for the addition of π nucleophiles to amides upon activation by trifluoromethanesulfonic anhydride developed in our laboratory[35] suggested that the electron rich ketone in these pyrroloindolizine derivatives may likewise be subject to activation under these conditions. Activation of the C8 carbonyl in **36** with trifluoromethanesulfonic anhydride would generate a substituted azafulvenium ion that may be sufficiently electrophilic to undergo nucleophilic addition by the silyl enol ether **73** (Figure 11). We anticipated that loss of silyl triflate and elimination of trifluoromethanesulfonic acid would yield an enone structure, providing a handle for introduction of the desired stereochemistry at C3. In an initial attempt at this transformation, addition of 1.00 equivalent of trifluoromethanesulfonic anhydride (Tf$_2$O) to a dichloromethane solution of **36** and **73** in the presence of 5.00 equivalents of 2-chloropyridine at −78 °C provided the desired heterodimer **76**, albeit in approximately 10% yield. In this sequence, elimination of trifluoromethanesulfonic acid occurred *via* deprotonation at C9 to provide the β,γ-enone **76** as a mixture of alkene isomers. After careful investigation of the base additive, order of addition, and reaction temperature, an optimized procedure involving portion-wise addition of 1.50 equivalents Tf$_2$O to a dichloromethane solution of **36** and **73** (1:1) at −78 °C in the presence of 5.00 equivalents of 2,6-di-*tert*-butyl-4-methylpyridine afforded the desired dimer **76** in 84% yield as a 3:2 mixture of olefin isomers.

As the C2 stereocenter in all of the previously obtained heterodimers possessed the **M430A** configuration, we focused on preparation of a structure that would maintain this selectivity and allow for alternative stereocontrol at C3.[36] In this vein, we reasoned that use of an α-methoxy ketone as an electrophile in our trifluoromethanesulfonic anhydride dimerization protocol would afford a C9 methyl vinyl ether, which after hydrolysis to the C9 ketone would provide a handle for epimerization to the thermodynamic C2,C3-*trans* diastereomer after closure of the cyclopentane ring (Scheme 15). According to our optimized conditions, Tf$_2$O-mediated heterodimerization of **73** and **77** smoothly provided the methyl vinyl ether **78** as a 3:2:1 mixture of stereoisomers in 84% yield. Upon treatment with mild aqueous acid the C3-C9 vinyl ether reacted rapidly to produce the desired diketone **79**.[37] Notably, as the lower pyrrole unit in this structure lacked an electron withdrawing substituent, it exhibited sensitivity comparable to that of **M217**, and as a result this compound and its derivatives had to be manipulated in the strict absence of oxygen. Investigation of a variety of proton sources revealed that optimal yields were obtained employing an aqueous solution of pyridinium *p*-toluenesulfonate in degassed acetonitrile-benzene. Differentiation between the C9 and C1 carbonyl groups was readily achieved *via* selective deprotonation at the C10 methyl group and trapping of the potassium enolate with triisopropylsilyl chloride to give **80**. After extensive optimization to avoid over reduction at C1 and desilylation of the silyl enol ether, careful reduction of the C1 carbonyl using diisobutylaluminum hydride provided the hexacyclic alcohol **81** as a precursor to C1-functionalized structures.

Preparation of corresponding vinyl halide, triflate, and related derivatives provides substrates for alternative cyclization reactions (Figure 12). Cyclization of a stabilized C1 radical in a 5-*exo*-trig fashion followed by oxidation of the resulting α-amino radical could provide the heptacyclic structure **86**. These derivatives may also allow us to investigate transition metal-mediated cyclization.[38] Oxidative addition into the C1-X bond in **83** and β-migratory insertion would generate the desired C1-C8b bond, whereupon β-hydride elimination from C8 would likewise furnish the heptacycle **86** (Figure 12). Generation of a strained 4-membered ring from

potential β-migratory insertion involving the C3a-C3b bond suggests that this process may proceed with regioselectivity for formation of the desired C1-C8b bond. In addition to providing functional groups in the C1-C3 linkage relevant to radical- and transition metal-mediated cyclization, preparation of hexacyclic structures possessing electronically distinct pyrrole units also provides opportunities for alternative electrophilic activation.

The broad scope, efficiency, and high level of diastereoselection in these heterodimerization reactions enable preparation of a range of hexacyclic cyclization substrates. Refinement of this strategy has led to the design of dimers that display enhanced stability and propensity for elaboration to advanced intermediates. Current efforts are focused on identifying the most concise sequence for derivatization and cyclization of the versatile dimer **83** and related structures. The advanced intermediates accessed *via* the proposed chemistry are expected to be subject to mild conversion to the highly sensitive naturally occurring complex myrmicarins.

## Conclusions

The myrmicarins are a family of alkaloids that exhibit unique structural features and chemical reactivity. Substructure analysis of the complex members suggests that they may be assembled biosynthetically through succinct dimerization and trimerization of the simpler myrmicarin structures. Guided by this hypothesis, we proposed a potentially biosynthetic approach to **M430A** involving dimerization of **M215B**. Our convergent enantioselective route to a stable ketone intermediate possessing the pyrroloindolizine core of the tricyclic myrmicarins enabled us to access enantiomerically enriched samples of the highly sensitive myrmicarins **M217**, **M215A**, and **M215B**. Early investigations on formation of **M430A** through an ionic dimerization pathway established that **M215B** undergoes efficient and highly stereoselective homodimerization in the presence of Brønsted acid to produce the heptacyclic structure of **isoM430A**. Analysis of a potential $[6\pi_a+2\pi_s]$ cycloaddition mechanism employing a conformationally restricted azafulvenium precursor indicated that the corresponding functionalized **isoM430A** heptacycle was formed in an ionic process involving two sequential bond forming events.

Studies on the reactivity of these heterodimeric structures have guided the strategic design of the tricyclic substrates to furnish functionalized dimeric derivatives. Hexacyclic structures possessing a functional group at C1 provide derivatives relevant to diverse modes of cyclization. This approach, based on a proposed biomimetic assembly of tricyclic myrmicarin structures, enables concise synthesis of complex structures and may provide key insight regarding the biosynthesis of this structurally fascinating family of alkaloids.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

## Notes and references

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4. Exposure of a pure sample of **M663** to air for two hours results in 50% decomposition, while exposure of fresh poison gland secretion containing **M430A** to air for one hour results in greater than 90% decomposition of **M430A** (see refs. 1c and 1d). Due to overlap with the crosspeak signals of the tricyclic myrmicarins, the relative stereochemistry of C4a′ in **M430A** could not be determined from the NOESY spectrum (see ref. 1d).

5. **M237A**, **M237B**, and **M217** were isolated as pure components by neutral alumina gel chromatography (see refs. 1a and 1b). **M215A** and **M215B** were isolated as a 2:1 mixture by neutral alumina gel chromatography (see ref. 1a).

6. The stereochemistry illustrated for **M645** in Figure 1 is based on analogy to the other complex myrmicarin structures.

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27. While initial studies employed (*S*)-BINAP as a ligand according to the model for stereoinduction (see ref. 22), comparison of the optical rotation of **36** to the reported value (ref. 16) clarified the opposite sense of stereoinduction.

28. Following our initial report, an alternative synthesis of **M215A** involving formation of the C8 triisopropylbenzenesulfonylhydrazone followed by *n*-butyllithium-induced Shapiro reaction was developed, which provided **M215A** as a single diastereomer in 56% yield from the ketone **36**.

29. Heptacycle **50a** may be in equilibrium with a corresponding trifluoroacetate adduct derivative.

30. Due to the oxidative sensitivity of these heptacyclic structures, attempts to prepare crystalline derivatives of **isoM430A** or protonated salts of the enamine **51** failed to yield samples suitable for X-ray analysis.

31. DFT calculations performed using Spartan 2006, B3LYP/6-31G; gas phase, energy minimized structure of the free azafulvenium ions.

32. Whereas tether introduction had proceeded smoothly with the C9-epimeric diol, iterative silylation, deprotection of partially silylated material, and resubjection of the free diol was necessary to obtain significant quantities of the [1,3,2]-dioxasilocine product.

33. When an acetonitrile solution of the C9-epimeric azafulvenium precursor was subjected to substoichiometric $Sc(OTf)_3$ (0.30 equiv) in the absence of **M215B**, 50% epimerization of the C8 alcohol occurred suggesting reversible ionization and trapping.

34. Notably, **M215B** does not undergo homodimerization in the presence of acetic acid, suggesting that intramolecular alkylation of the hexacyclic azafulvenium ion **14** is more facile than intermolecular trapping of the tricyclic azafulvenium ion **1** by **M215B**.

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36. Attempts to tautomerize the C3-C9 alkene in **76** to the C2-C3 alkene under acidic or basic conditions or through the use of transition metal catalysts were unsuccessful.

37. Efforts to rigorously assign the stereochemistry of rotamers and/or diastereomers of **79** using variable temperature ^{1}H NMR analysis were unsuccessful. Heating to temperatures above 80°C led to decomposition.

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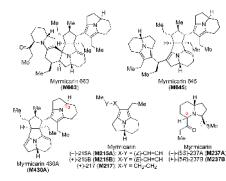
**Fig. 1.**
The Myrmicarin alkaloid family.
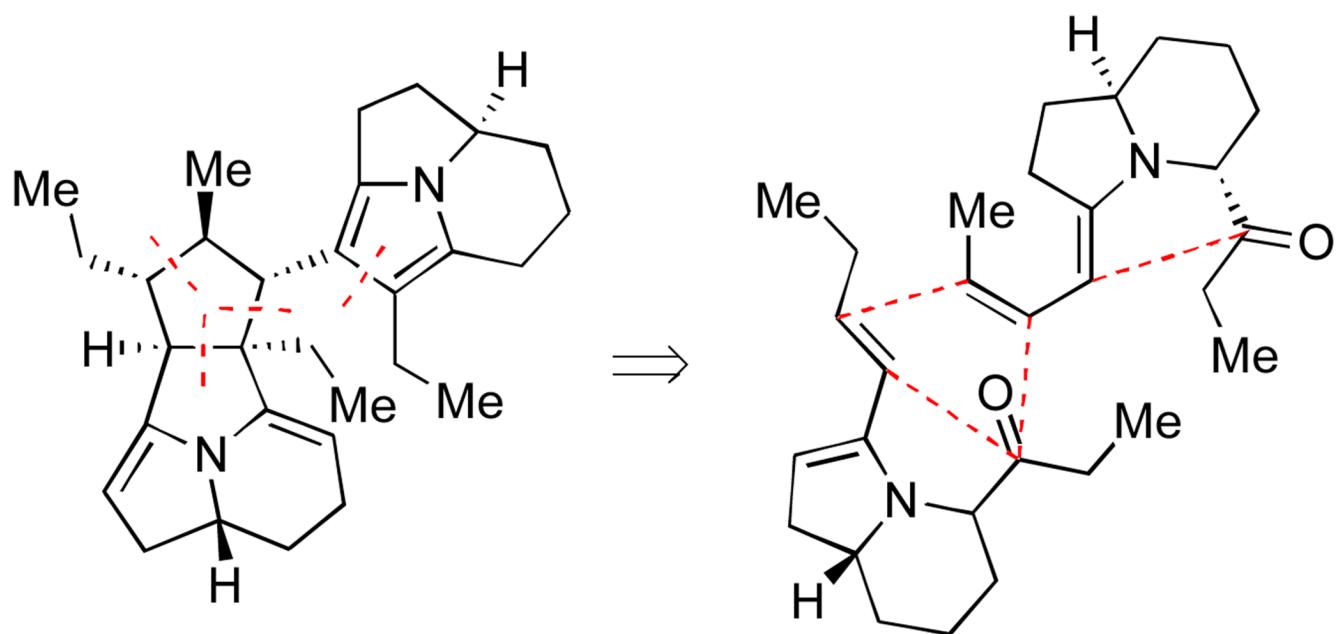
**Fig. 2.**
Schröder and Francke's proposed biosynthesis of **M430A** from unsaturated indolizidine derivatives.
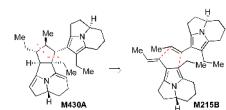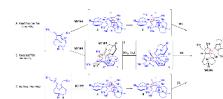
**Fig. 3.**
Our proposed biosynthesis of **M430A** from **M215B**.

**Fig. 4.**
Modes of potentially biomimetic dimerization of **M215B** for the synthesis of **M430**.
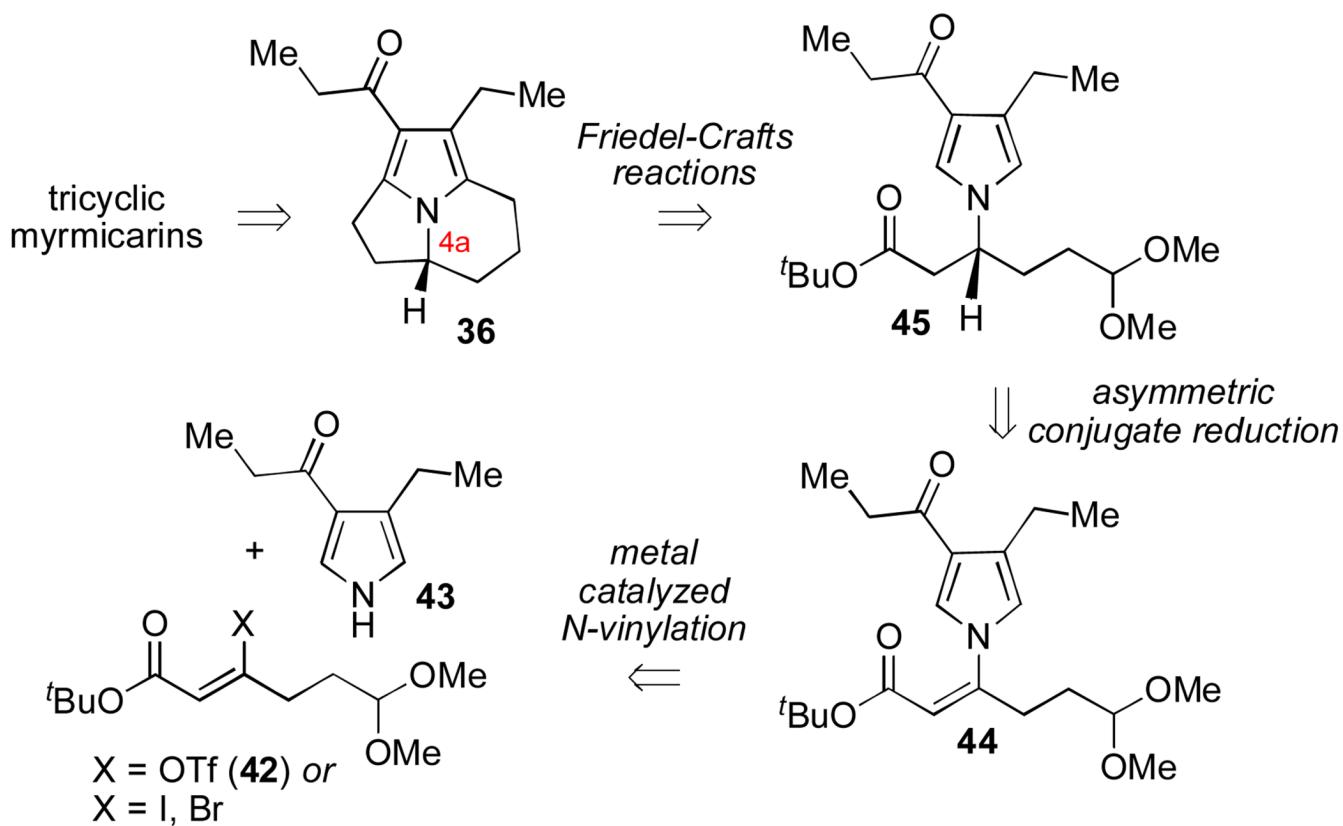
**Fig. 5.**
Our retrosynthetic analysis of tricyclic myrmicarin alkaloids.
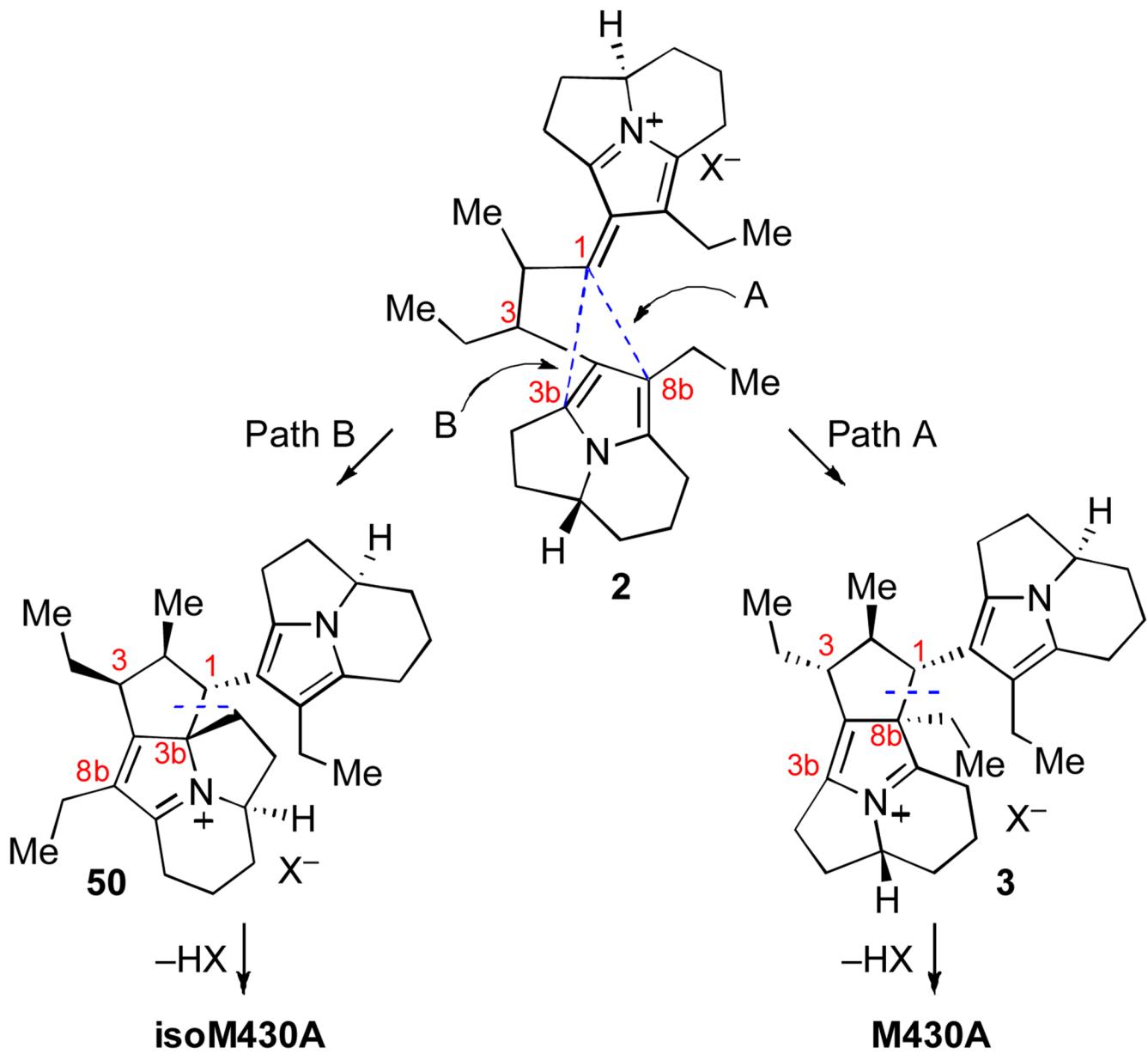
**Fig. 6.**
Regioselectivity of intramolecular Friedel-Crafts alkylation of hexacyclic azafulvenium ion
**2** leading to the **M430A** precursor **3** (Path A) or the **isoM430A** precursor **50** (Path B).
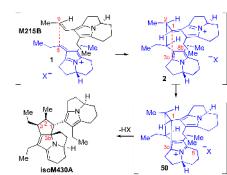
**Fig. 7.**
Proposed mechanism for ionic dimerization of **M215B**.
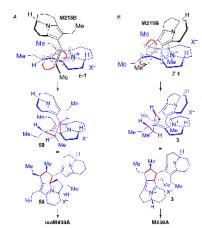
**Fig. 8.**
Potential $[6\pi_a + 2\pi_s]$ cycloaddition mechanisms.
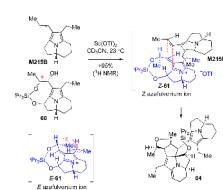
**Fig. 9.**
Selective activation of **60** and nucleophilic addition of **M215B**.
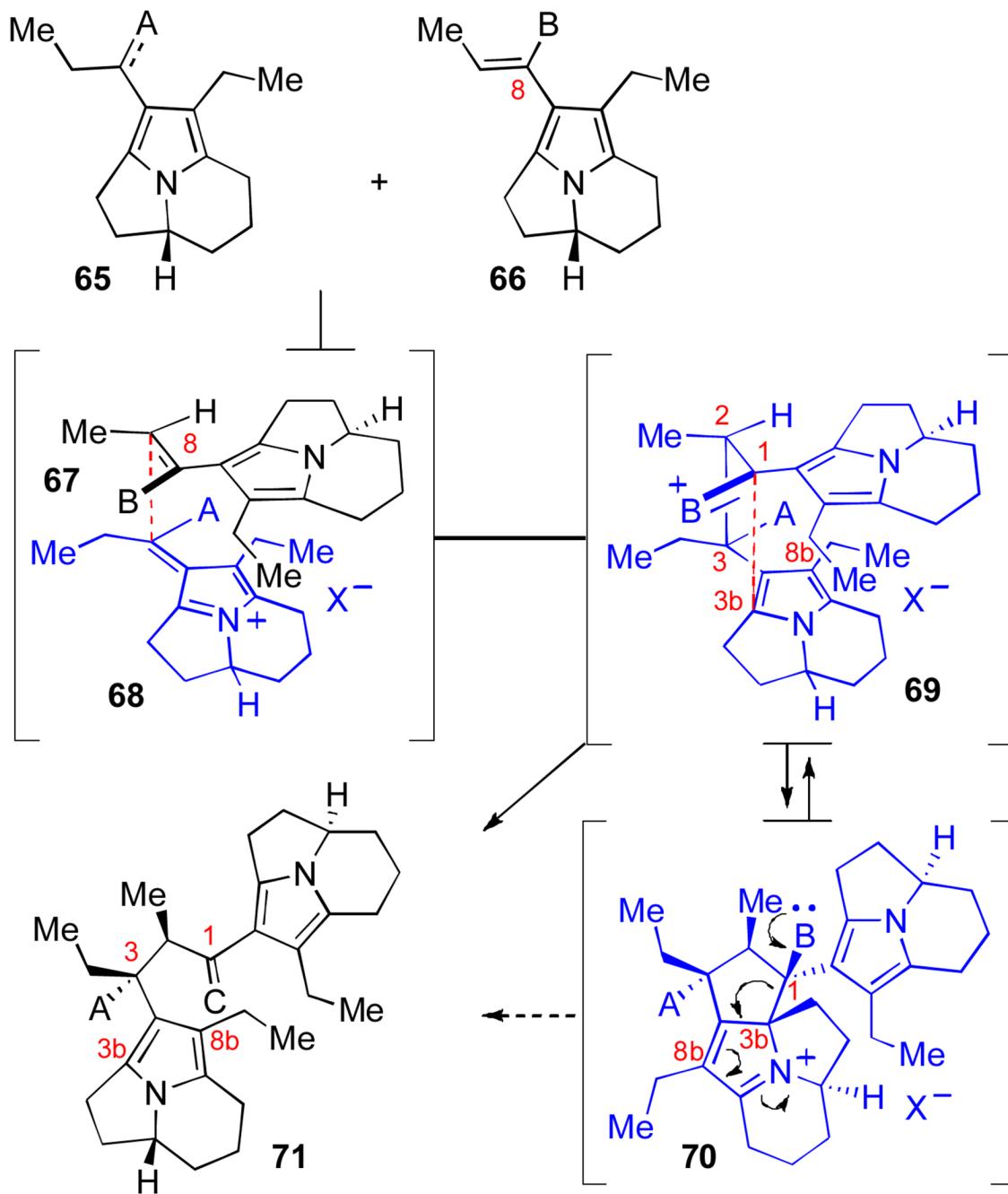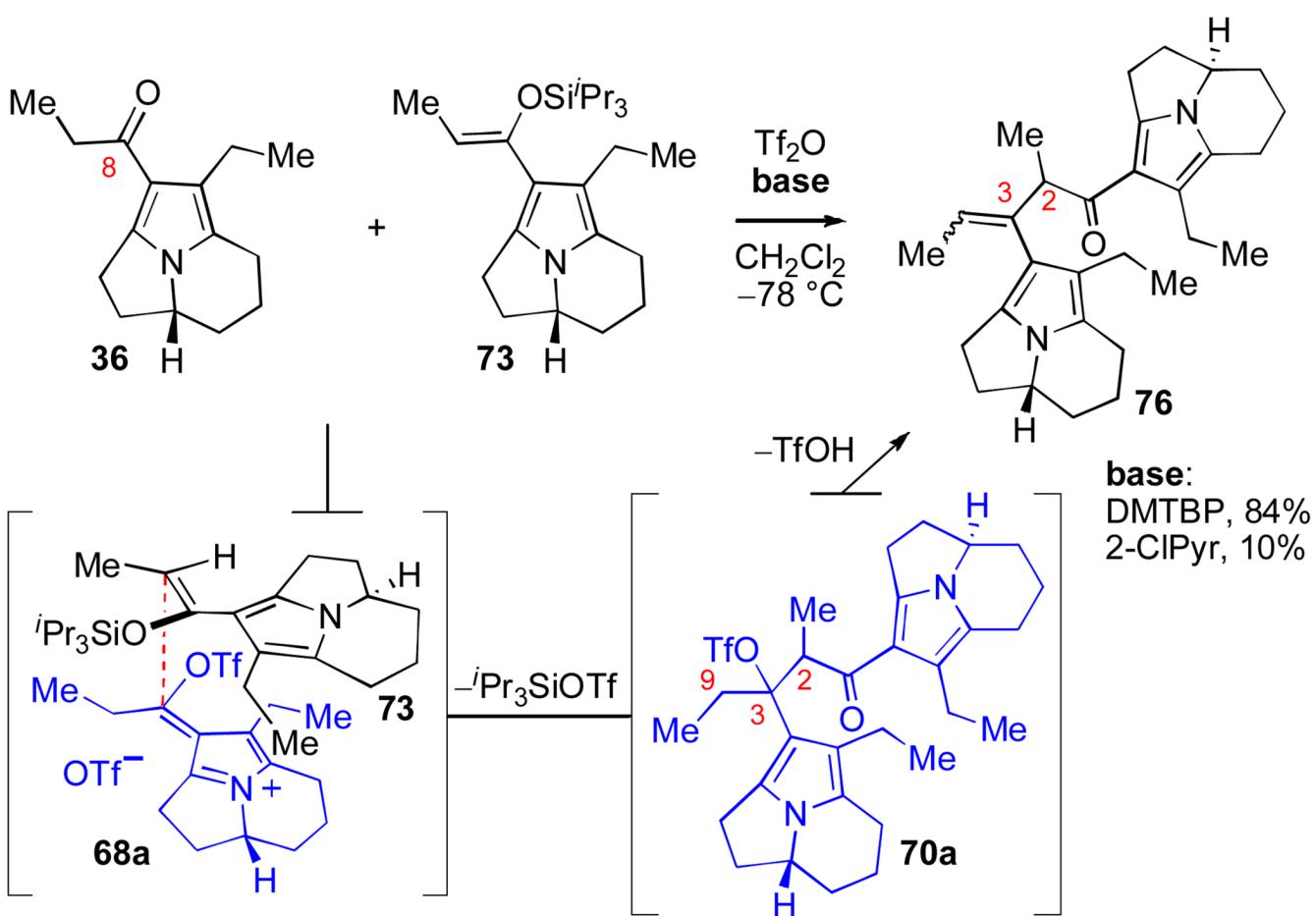
**Fig. 10.**
Heterodimerization of pyrroloindolizine derivatives to functionalized hexacyclic structures.

**Fig. 11.**
Activation of **36** by trifluoromethanesulfonic anhydride and nucleophilic addition of **73** (DMTBP = 2,6-di-*tert*-butyl-4-methylpyridine, 2-ClPyr = 2-chloropyridine).
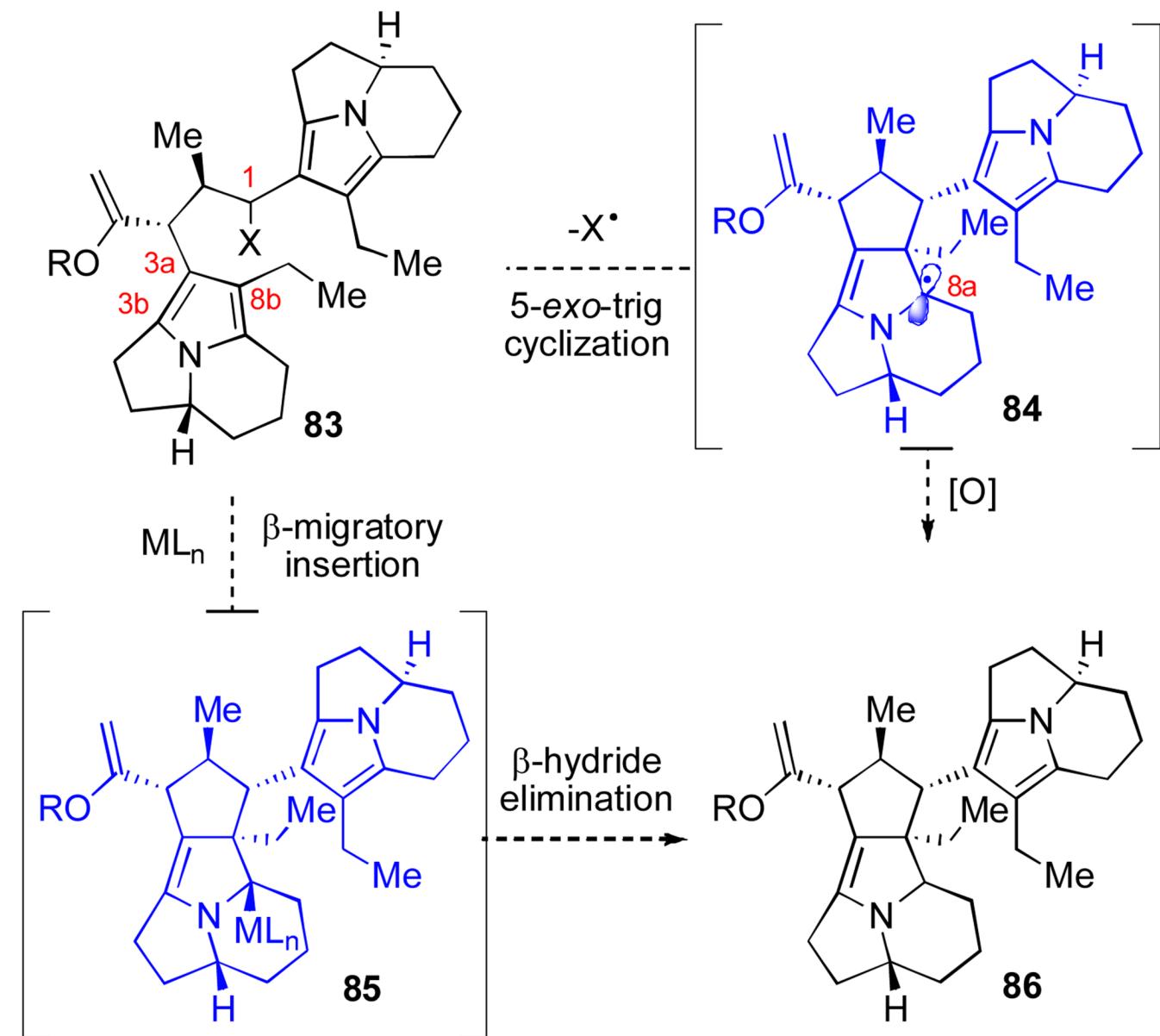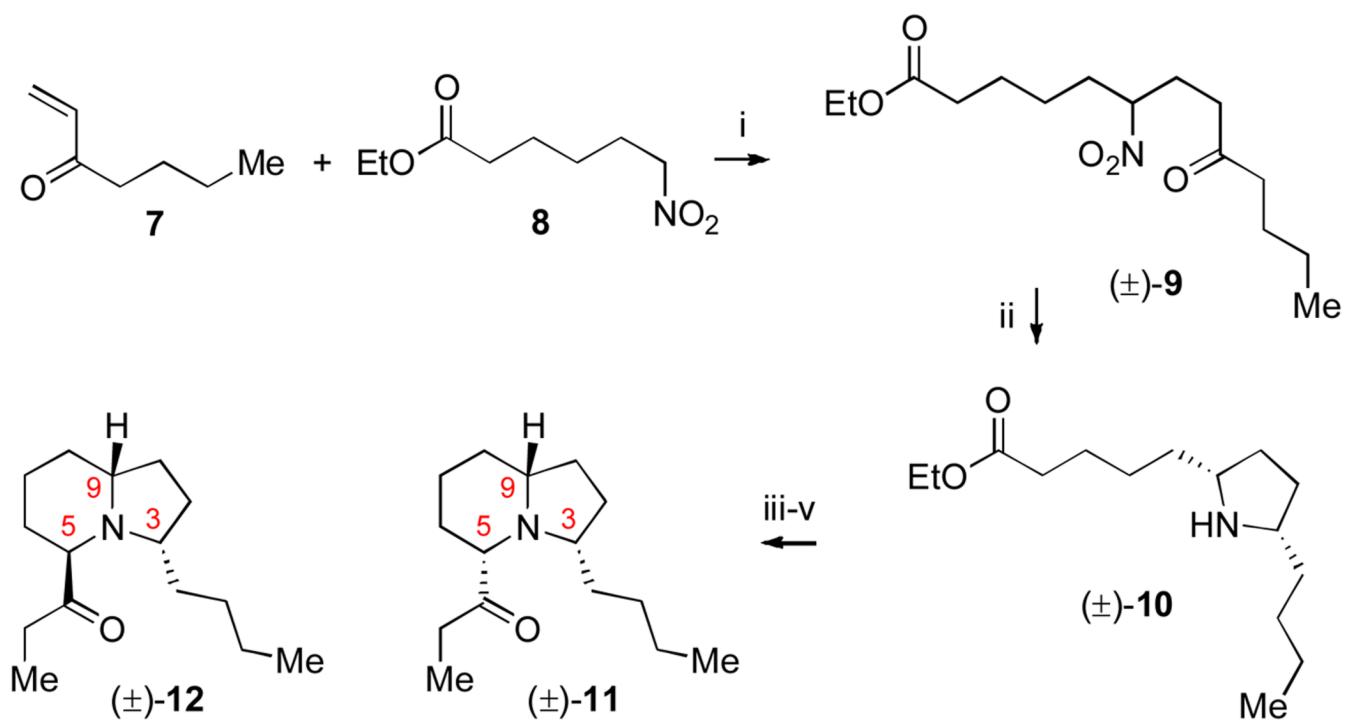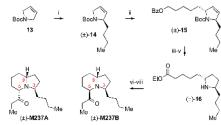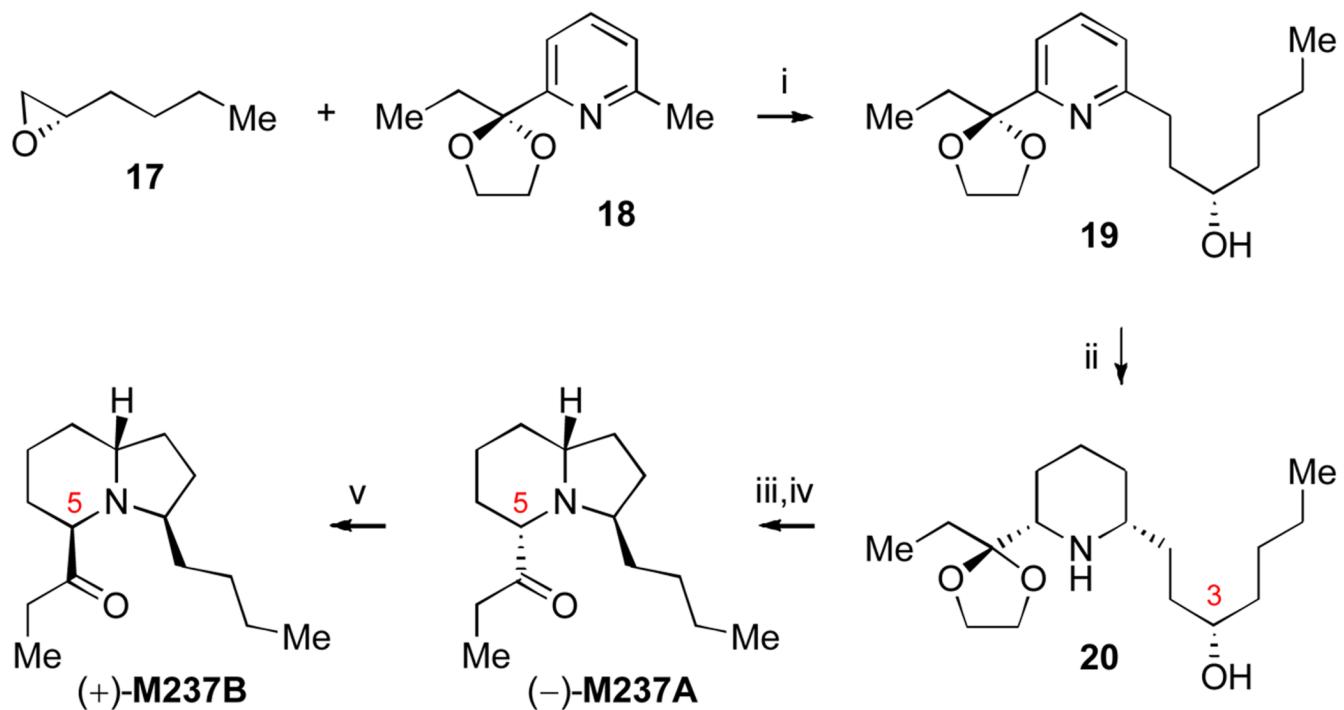
**Fig 12.**
Approaches for cyclization of **83**.
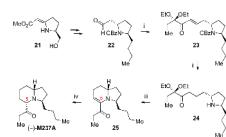
**Scheme 1.**
Francke's synthesis of indolizidines (±)-**11** and (±)-**12**. Reagents and conditions: i, NaOEt, EtOH, 0 °C (80%); ii, $H_2$ (50 atm), Pd/C, $Na_2SO_4$, EtOH, 23 °C (90%, 99:1 dr); iii, $^i Pr_2 NLi$, THF; $I_2$, −78→0 °C; $NaHCO_3$ (65%); iv, KOH, EtOH, $H_2O$, 60 °C; HCl (89%); v, EtLi, $Et_2O$, 0→20 °C (61%); separation by $Al_2O_3$ gel chromatography ((±)-**11**, 43%; (±)-**12**, 18%).
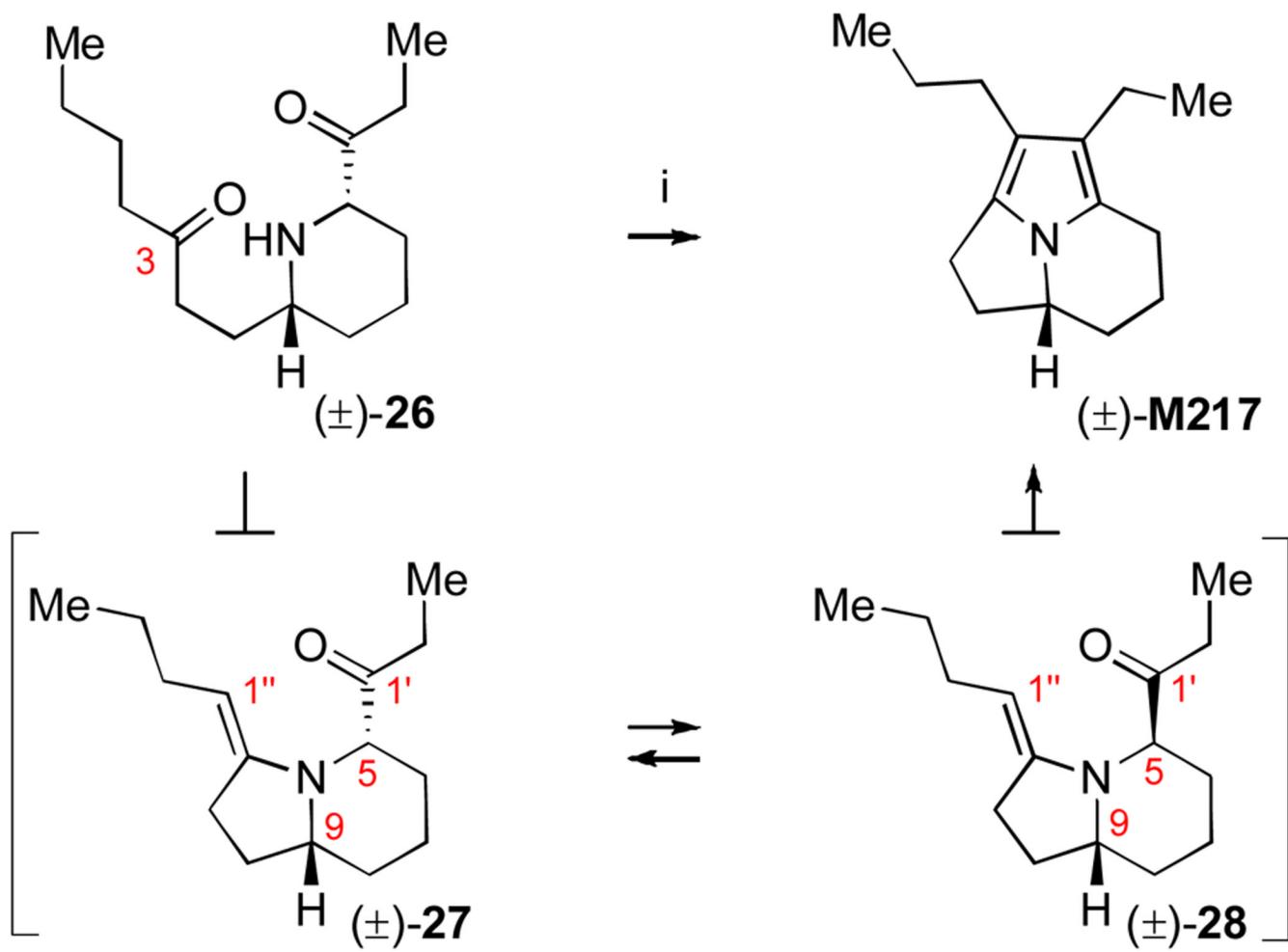
**Scheme 2.**
Francke's synthesis of racemic **M237A** and **M237B**. Reagents and conditions: i, $^i$Pr$_2$NLi, THF; BuBr, −78→0 °C (70%); ii, $^i$Pr$_2$NLi, THF; BzO(CH$_2$)$_5$Br, −78→0 °C (67%, 1 diastereomer); iii, H$_2$ (80 atm), Pd/C, H$_2$O, MeOH, 23 °C (88%); iv, pyridinium dichromate, DMF, 35 °C (79%); v, HCl, EtOH, 78 °C (83%); vi, $^i$Pr$_2$NLi, THF; I$_2$, −78→0 °C; NaHCO$_3$ (65%); vii, KOH, EtOH, 60 °C (89%); viii, EtLi, Et$_2$O, 0→20 °C (61%); separation by Al$_2$O$_3$ chromatography ((±)-**M237A**, 40%; (±)-**M237B**, 26%).
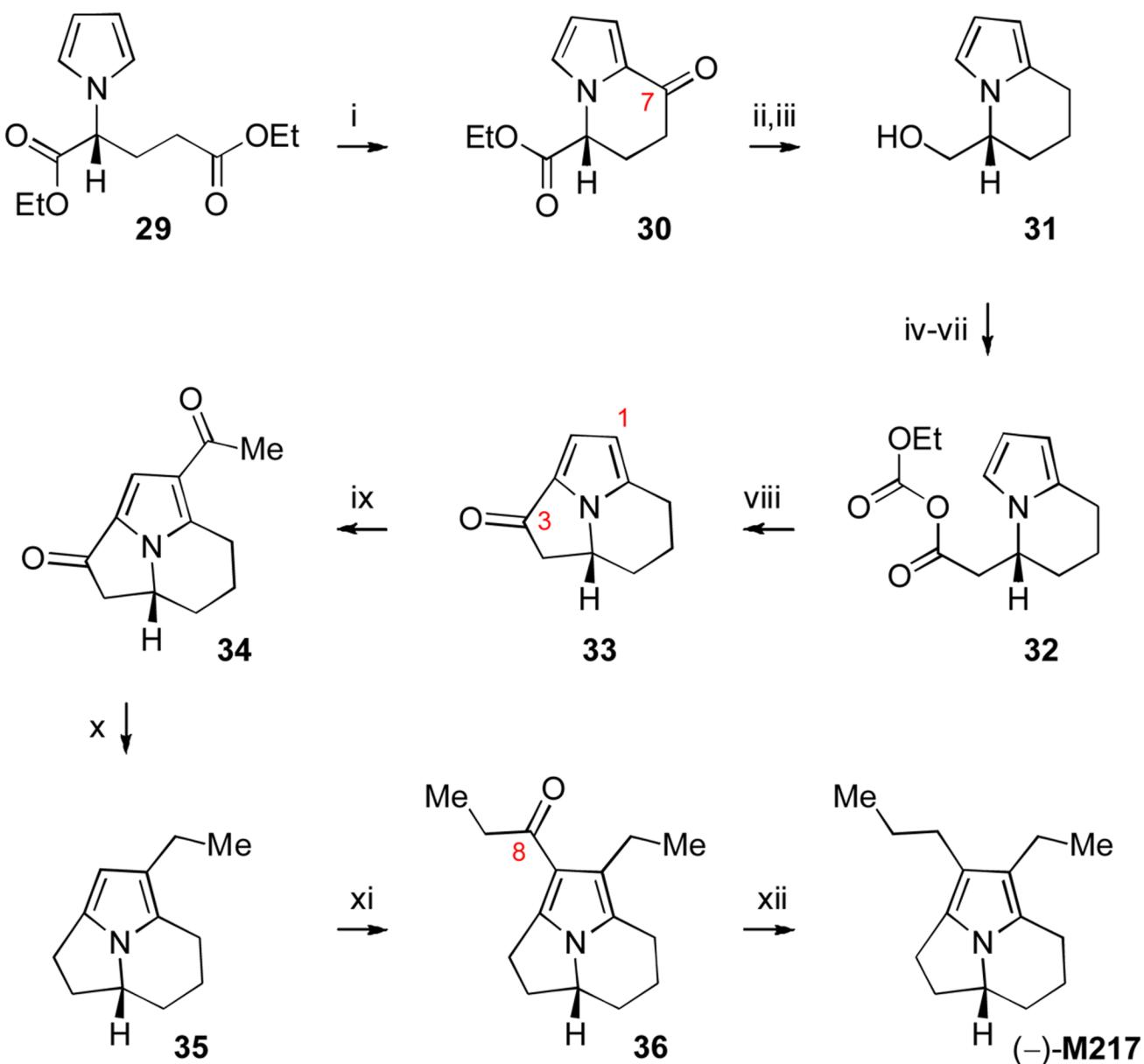
**Scheme 3.**
Francke's synthesis of (−)-**M237A** and (+)-**M237B**. Reagents and conditions: i, $^n$BuLi, **17**, DMPU, THF, −50→0 °C (86%); ii, $H_2$ (50 atm), Pd/C, EtOH, 23 °C (99%, 3:2 dr); iii, TsCl, DMAP, pyridine, −10→0 °C (56%); iv, HCl, $H_2O$, acetone, 57 °C (86%, 98% ee); v, SiO$_2$; separation by Al$_2$O$_3$ chromatography (42%, 98% ee).

**Scheme 4.**
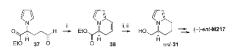
Lhommet's synthesis of (−)-**M237A**. Reagents and conditions: i, (EtO)$_2$P(O)CH$_2$C(O)C(OEt)$_2$Et, KHMDS, THF, 0 °C (85%); ii, H$_2$ (1 atm), Pd/C, MeOH, 23 °C; iii, TFA, H$_2$O; K$_2$CO$_3$ (98% (2-steps)); iv, NaBH$_3$CN, HCl (84%, 92:8 dr).
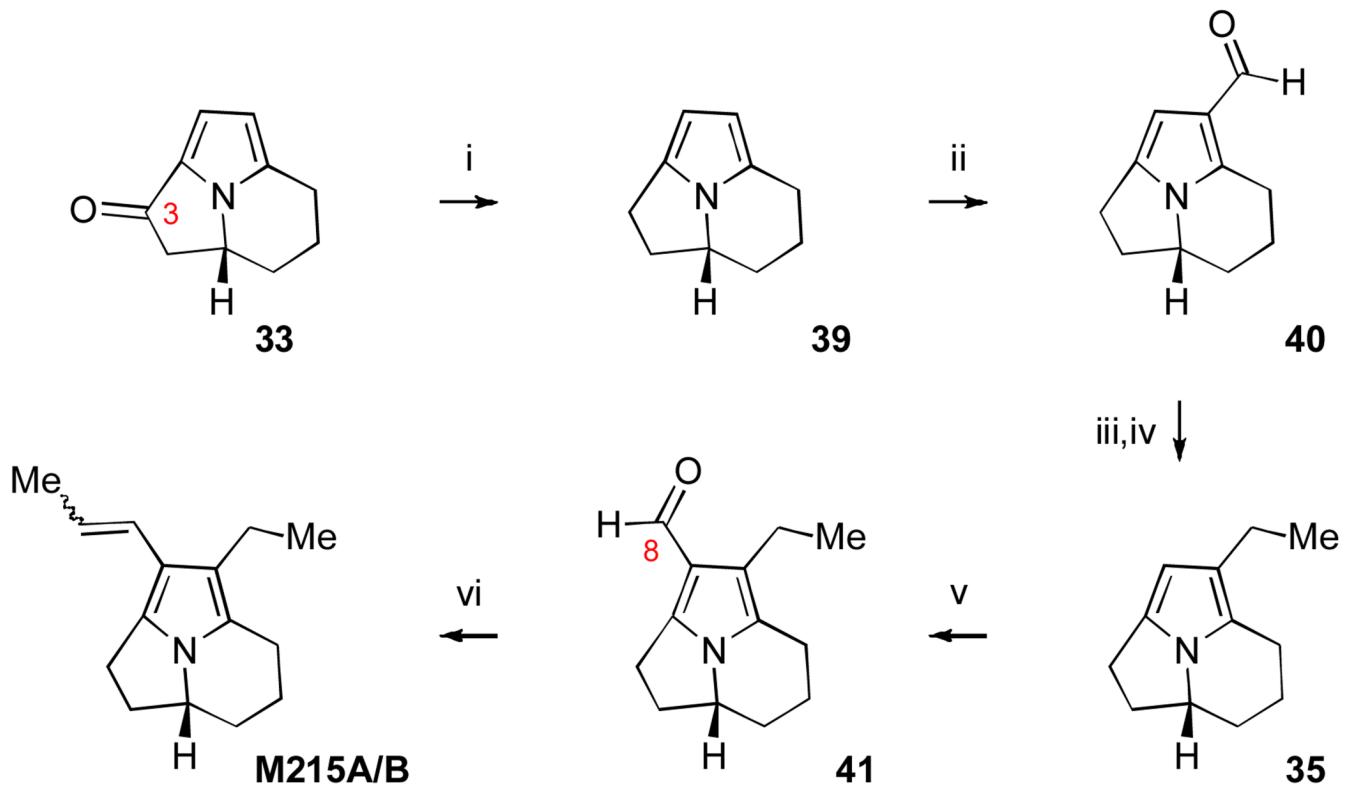
**Scheme 5.**
Schröder and Francke's synthesis of racemic **M217**. Reagents and conditions: i, $C_6H_6$, 40 °C (53%).
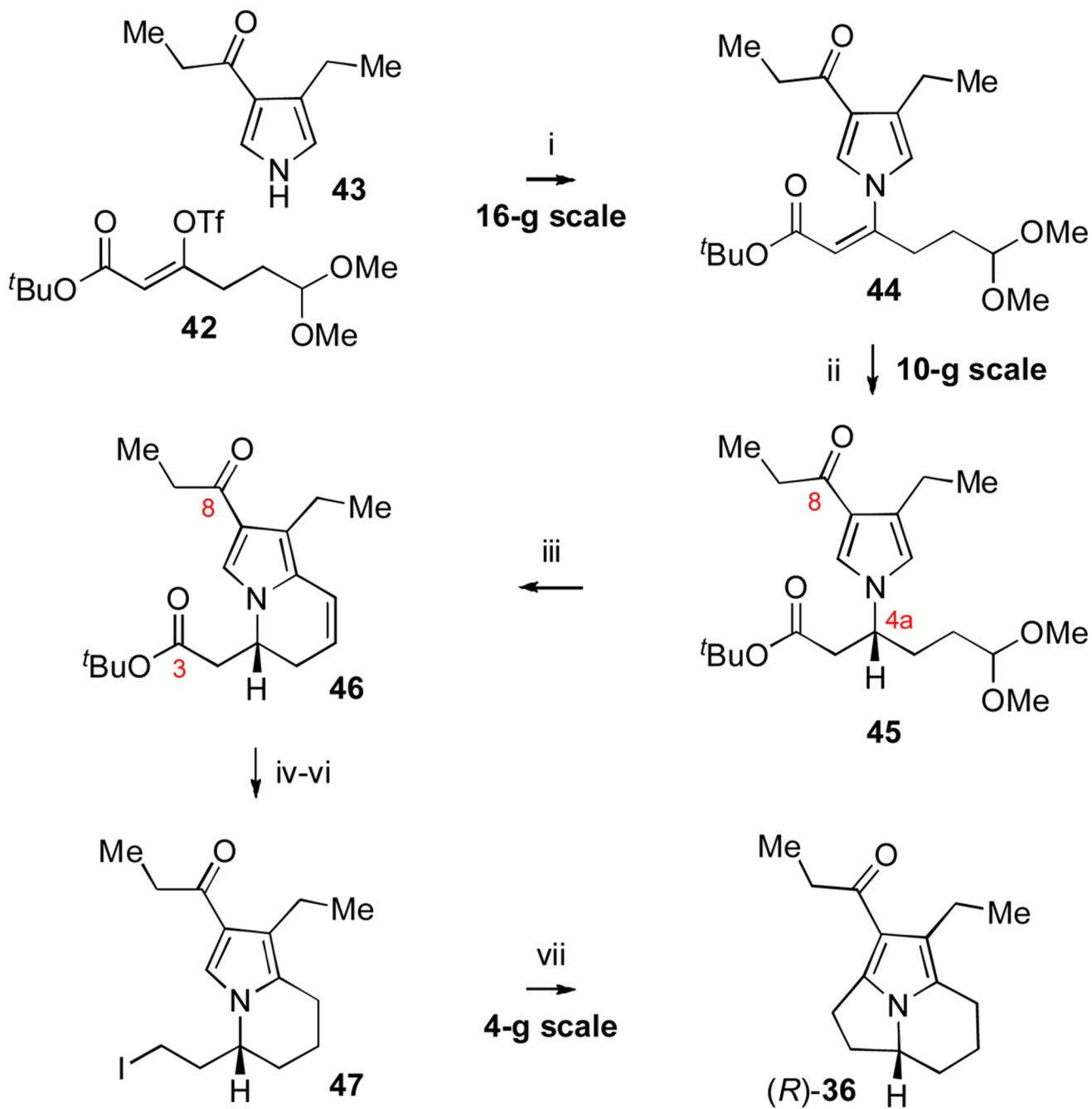
**Scheme 6.**
Vallée's synthesis of (+)-**M217**. Reagents and conditions: i, BBr$_3$, CH$_2$Cl$_2$, 5→23 °C;[17] ii, NaBH$_3$CN, ZnI$_2$, CH$_2$Cl$_2$, 40 °C; iii, LiAlH$_4$, THF, 0→23 °C (72% (2-steps)); iv, MsCl, pyridine, CH$_2$Cl$_2$, 0 °C; v, NaCN, DMF, 90 °C (90% (2-steps)); vi, NaOH, H$_2$O, MeOH, 65 °C (90%); vii, EtOC(O)Cl, Et$_3$N, THF, 0 °C; viii, BF$_3$OEt$_2$, CH$_2$Cl$_2$, 40 °C (57% (2-steps)); ix, MeC(O)Cl, AlCl$_3$, CH$_2$Cl$_2$, 40 °C (93%); x, LiAlH$_4$, THF, 65 °C (60%); xi, MeCH$_2$C(O)NMe$_2$, POCl$_3$, toluene, 90 °C (68%); xii, LiAlH$_4$, 1,4-dioxane, 100 °C (60%).
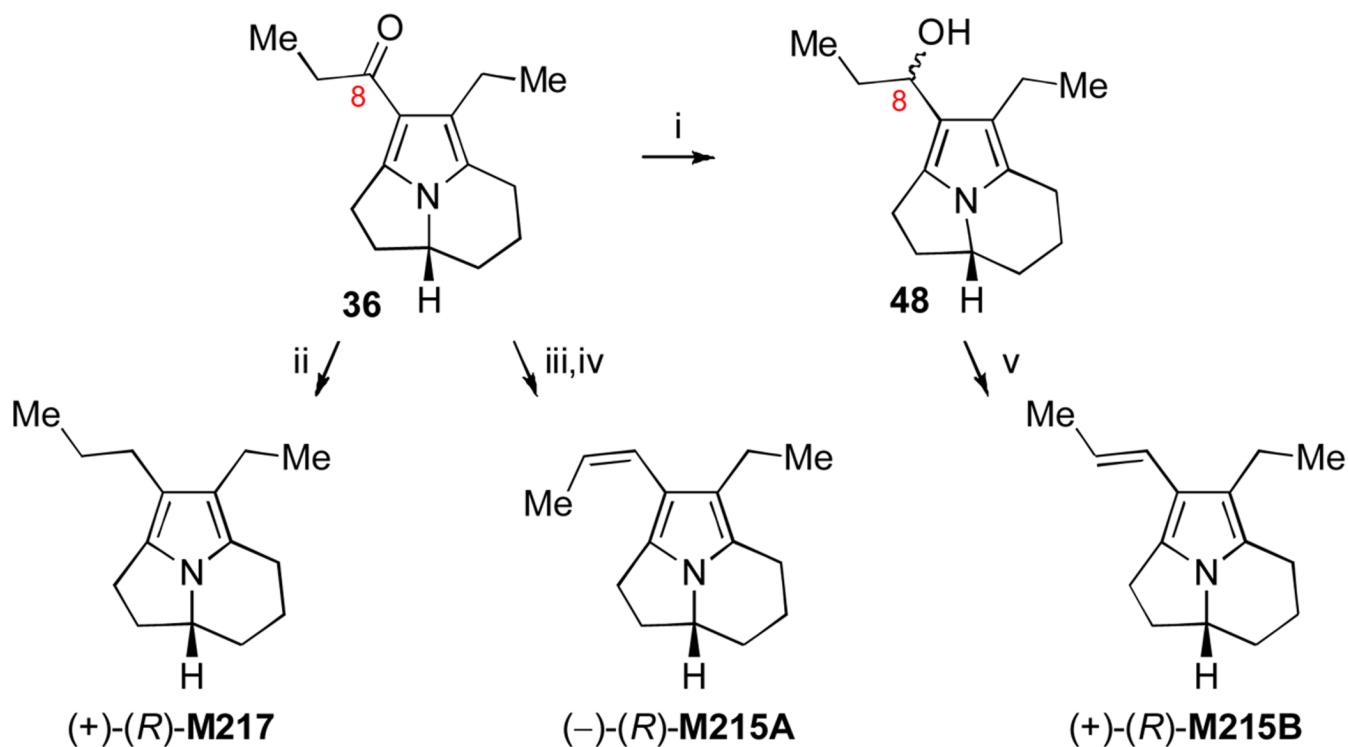
**Scheme 7.**
Lazzaroni's formal synthesis of (−)-*ent*-**M217**. Reagents and conditions: i, DMSO, 100 °C, 2h (55%); ii, H$_2$, Rh/C, Et$_2$O (75%); iii, LiAlH$_4$, THF, 23 °C (80%).
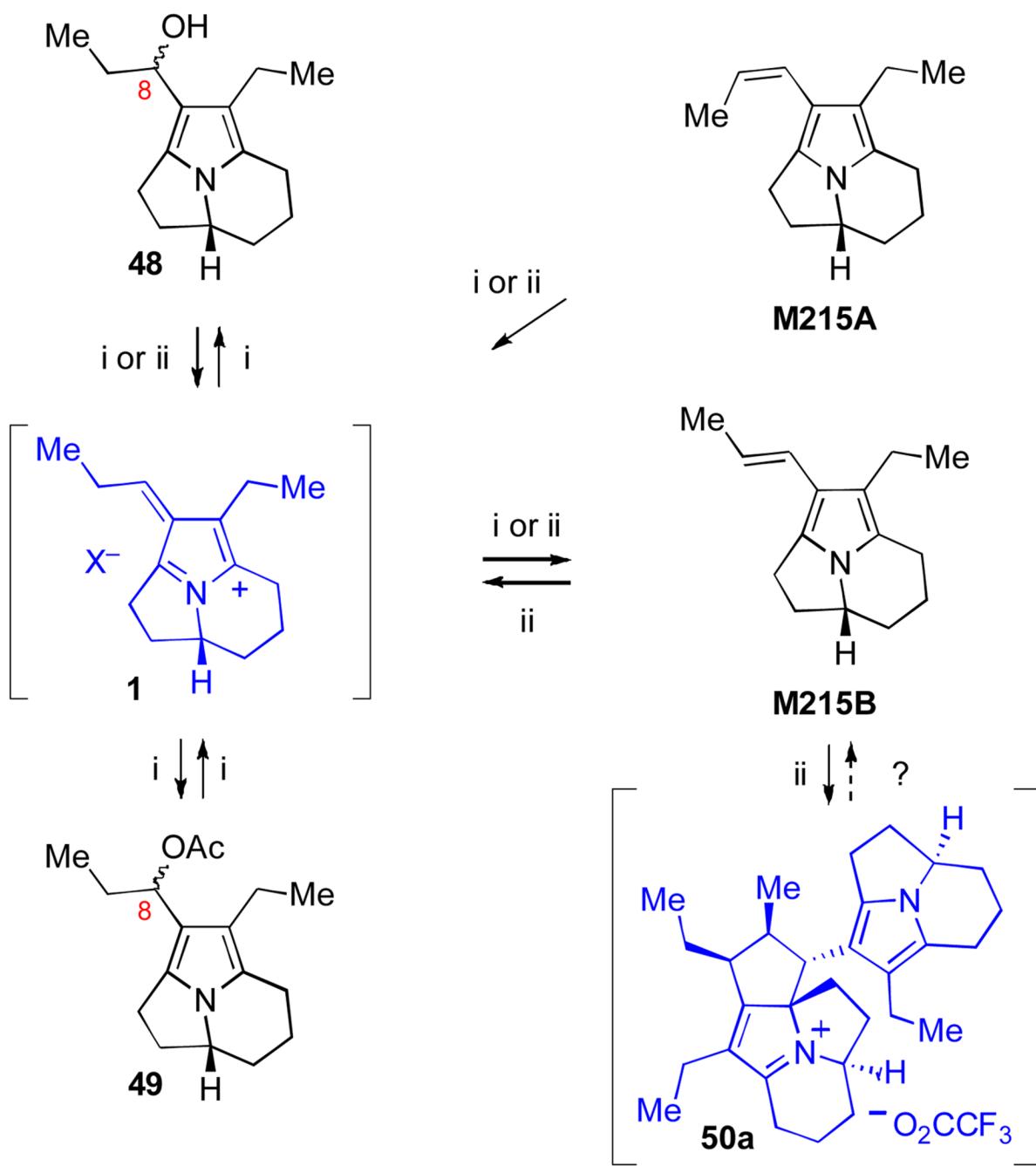
**Scheme 8.**
Vallée's synthesis of enantioenriched **M215A** and **M215B** as a mixture of alkene isomers.
Reagents and conditions: i, LiAlH$_4$, 1,4-dioxane, 100 °C (86%); ii, DMF, POCl$_3$, toluene, 83 °C, 2h (53%); iii, MeLi, THF, 0 °C; iv, LiAlH$_4$, 1,4-dioxane, 88 °C (72% (2-steps)); v, DMF, POCl$_3$, CH$_2$Cl$_2$, 40 °C (80%); vi, Ph$_3$PEtBr, NaH, THF, 65 °C (78%, 4:1 **M215A**:**M215B**).
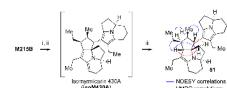
**Scheme 9.**
Our enantioselective synthesis of pyrroloindolizine **36**. Reagents and conditions: i, Pd$_2$dba$_3$, X-Phos, K$_3$PO$_4$, toluene, 60 °C, 18 h (95%); ii, 15% Cu(OAc)$_2$•H$_2$O, (*S*)-BINAP, PMHS, THF, $^t$BuOH, 23 °C, 3 h (89%, 85% ee); iii, acetone, H$_2$O, AcOH, 40 °C; iv, H$_2$, Pd/C, EtOAc, 23 °C (>98% (2-steps)); v, Et$_3$N, TIPSOTf, THF, −78→0 °C; LiAlH$_4$; HCl, 23 °C (87%); vi, I$_2$, Ph$_3$P, imidazole, CH$_2$Cl$_2$, 0 °C (82%); vii, AgBF$_4$, CH$_2$Cl$_2$, C$_6$H$_6$, 23 °C (80%).

**Scheme 10.**
Our enantioselective synthesis of tricyclic myrmicarins. Reagents and conditions: i, LiAlH$_4$, Et$_2$O, −78→0 °C (100%, 1:1 dr); ii, LiAlH$_4$, 1,4-dioxane, 100 °C (92%); iii, 2-chloro-3-ethylbenzoxazolium tetrafluoroborate, Et$_3$N, CH$_2$Cl$_2$, 23 °C (12% (+ 80% SM)); iv, H$_2$, Lindlar cat., EtOAc, Pyr, 23 °C (74%); v, HCl (aq), Et$_2$O, 23 °C (61%).
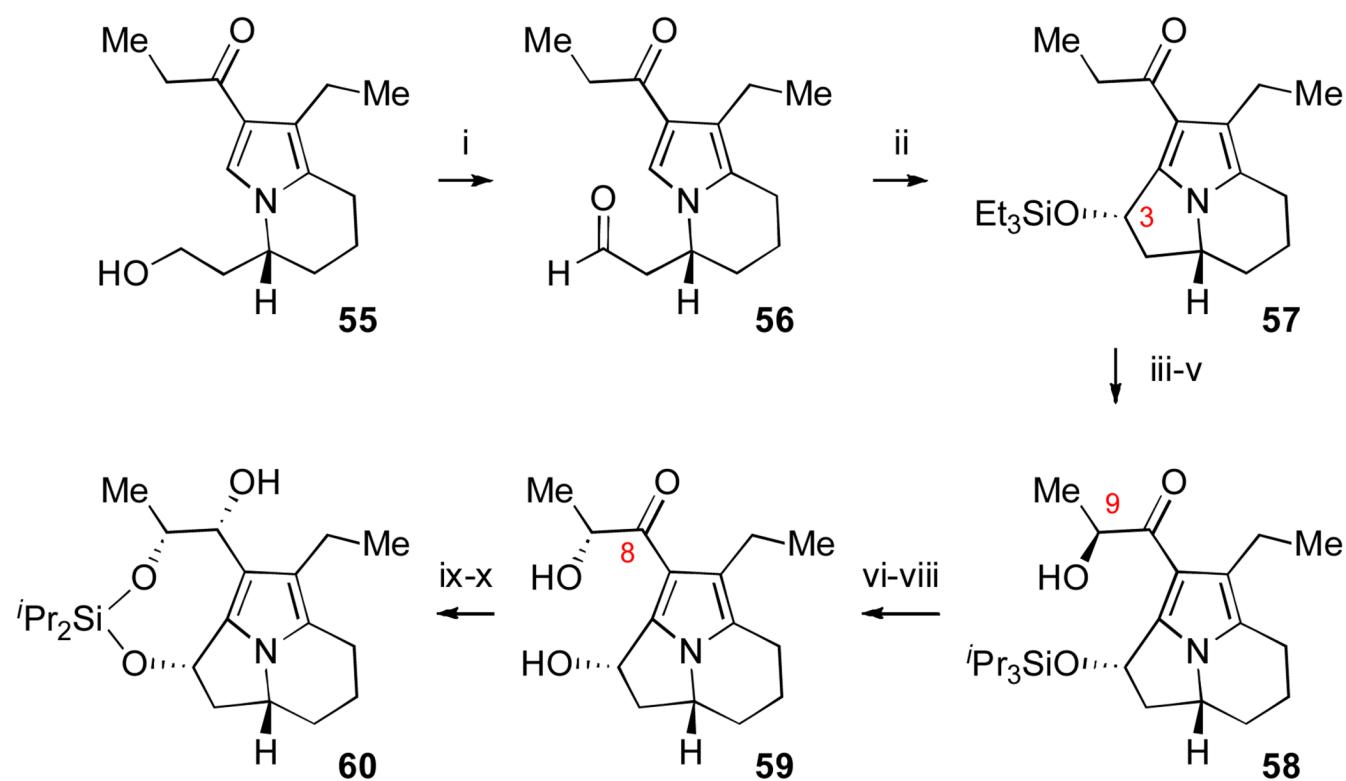
**Scheme 11.**
Acid-induced behavior of tricyclic myrmicarin derivatives. Reagents and conditions: i, AcOH, $C_6D_6$, 23 °C (X = OAc); ii, TFA, $C_6D_6$, 23 °C (X = $F_3CCO_2$).
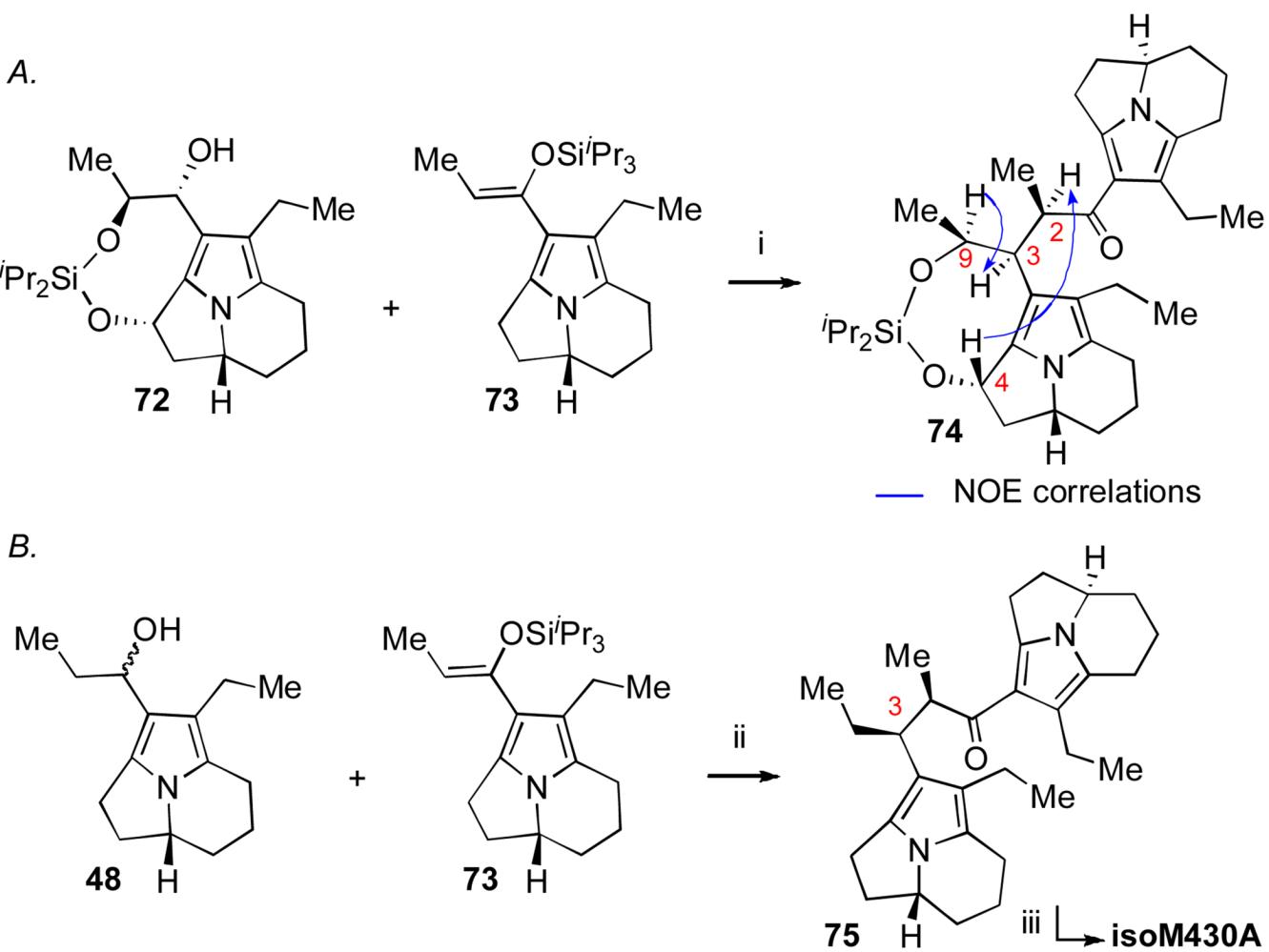
**Scheme 12.**
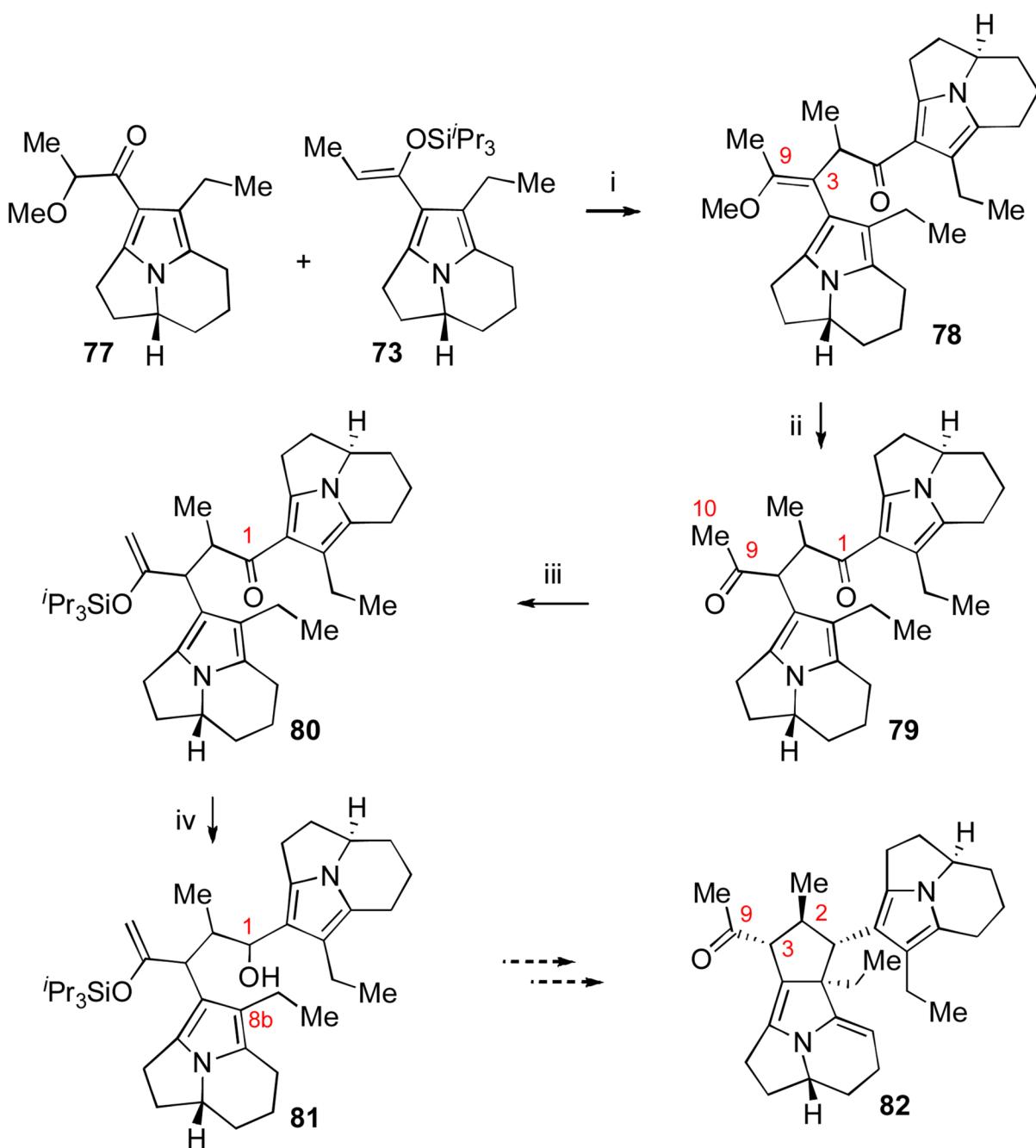
Derivatization and structure verification of the **M215B** dimer. Reagents and conditions: i, TFA, $C_6D_6$, 23 °C, 3 h (90% by $^1H$ NMR); ii, resin bound-BEMP, $C_6D_6$, 23 °C, 30 min (100% by $^1H$ NMR); iii, Pd/C, $H_2$, 23 °C (87% from **M215B**).

**Scheme 13.**
Synthesis of conformationally restricted azafuvenium precursor **60**. Reagents and conditions:
i, IBX, DMSO, 23 °C (82%); ii, TESOTf, 2,6-lutidine, benzene, 23 °C; HCl, 23 °C; iii, TBAF,
THF, 0 °C (81% (2-steps)); iv, TIPSOTf, 2,6-lutidine, $CH_2Cl_2$, −40 °C (82%); v, KHMDS,
Davis oxaziridine, THF, −78 °C (85%, 4:1 dr); vi, PPh$_3$, DEAD, $p$-NO$_2$C$_6$H$_4$CO$_2$H, THF,
23→50 °C (61% (+ 11% SM)); vii, LiOH, THF-H$_2$O, 50 °C (100%); viii, TBAF, THF, 0 °C
(92%); ix, $^i$Pr$_2$SiCl$_2$, DMAP, DMF, 23 °C (29%); x, LAH, Et$_2$O, −78 °C (16% (+8% SM)).

**Scheme 14.**
Selective activation of azafulvenium precursors and nucleophilic addition of **73**. Reagents and conditions: i, Sc(OTf)$_3$, CD$_3$CN, 23 °C (73%); ii, Sc(OTf)$_3$, CD$_3$CN, 23 °C (77%); iii, LiAlH$_4$, Et$_2$O, −78→0 °C; AcOH, 23 °C (90%, >4:1 dr (2 steps)).

**Scheme 15.**
Synthesis of radical cyclization precursor **81**. Reagents and conditions: i, Tf$_2$O, 2,6-di-*t*-butyl-4-methylpyridine, CH$_2$Cl$_2$, −78 °C (84%); ii, PPTS, H$_2$O, MeCN, C$_6$H$_6$, 23 °C (73%); iii, TIPSCl, KHMDS, THF, 0 °C (95%); iv, $^i$Bu$_2$AlH, CH$_2$Cl$_2$, −78→0 °C (73%).

**Table 1**

*N*-Vinylation of substituted pyrroles and indoles with configurationally defined vinyl triflates.



**44a**, 84%

**44b**, 74%

**44c**, 74%

**44d**, 79%

**44e**, 91%

**44f**, 60%

**44g**, 91%

**44h**, 70%

**44i**, 73%

**44j**, 50%

**44k**, 62%

**44l**, 72%
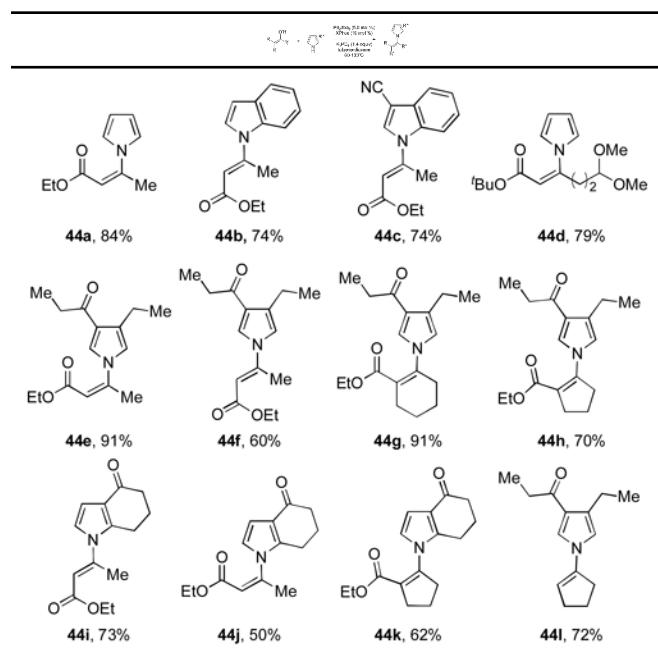
**Table 2**

Brønstead acid-promoted reactivity of **M215B** and tricyclic alcohol **48**.



| entry | substrate | solvent | acid (equiv) | additive | product(s)[a] |
|---|---|---|---|---|---|
| 1 | **M215B** | $C_6D_{12}$ | TFA (<1.00) | none | **50a** |
| 2 | **48** | THF-$d_8$ | TFA (2.20) | none | **50a** |
| 3 | **48** | $CD_3CN$ | TFA (1.10) | none | **50a** |
| 4 | **48** | $CD_3OD$ | TFA (1.10) | none | **52, 50a** |
| 5 | **48** | THF-$d_8$ | TFA (1.10) | LiCl (sat.) | **M215B, 50a** |
| 6 | **M215B** | THF-$d_8$ | TFA (1.10) | $LiClO_4$ (sat.) | **54** |
| 7 | **48** | THF-$d_8$ | $HClO_4$ (1.10) | $LiClO_4$ (sat.) | **54** |
| 8 | **48** | $CD_3OD$ | TFA (1.10) | $p$-MePhSH (0.60 equiv) | **53+50a** (80:20) |

[a]Reactions performed at 23 °C and monitored *in situ* by ^{1}H NMR.