Oligomeric Natural Products

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Synthetic and Theoretical Investigations of Myrmicarin Biosynthesis**

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Isolated as the active components of the poison gland secretion from various *Myrmicaria* ant species found in Africa and characterized by the Francke group over a decade ago, the myrmicarin alkaloids[1] (**1**–**6**, Figure 1) provide a truly unique array of synthetic challenges. Indeed, myrmicarins 215A and B (**1** and **2**) as well as myrmicarin 217 (**3**) are the first examples of naturally occurring pyrrolo-[2,1,5*cd*]indolizidines, while the higher-order structures (**4**–**6**) constitute some of the most complex alkaloids isolated from any insect to date with formidable stereochemical complexity displayed across up to ten ring systems. Enhancing this synthetic challenge is their marked fragility. For example, myrmicarin 430A (**4**) proved sensitive not only to air but also to silica gel and alumina, requiring that its structure be deduced from a series of two-dimensional NMR experiments performed on the crude isolation mixture.[1c]

To date, a number of total syntheses of the simplest members (i.e. **1**–**3**) have been achieved,[2] some of which are enantioselective;[2d–f] however, none of the higher-order members has been synthesized in the laboratory despite the existence of several reasonable biosynthetic hypotheses for how structures **4**–**6** might be formed in nature.[1b,3b] In all cases, efforts to reduce these ideas to practice have led to materials that are stereo- and regioisomeric to the natural isolates. For instance, extensive efforts by the Movassaghi group[3] to effect acid-promoted dimerizations of myrmicarin 215B (**2**) have afforded isomers **8a** and **8b** through a synthetic pathway that sets the incorrect C-3 stereochemistry (the highlighted center; Figure 1) in the opening C–C bond-forming operation. As such, access to **4** is prevented; unclear is whether this stereochemistry also induces the final cyclization to proceed from the incorrect carbon of the pyrrole

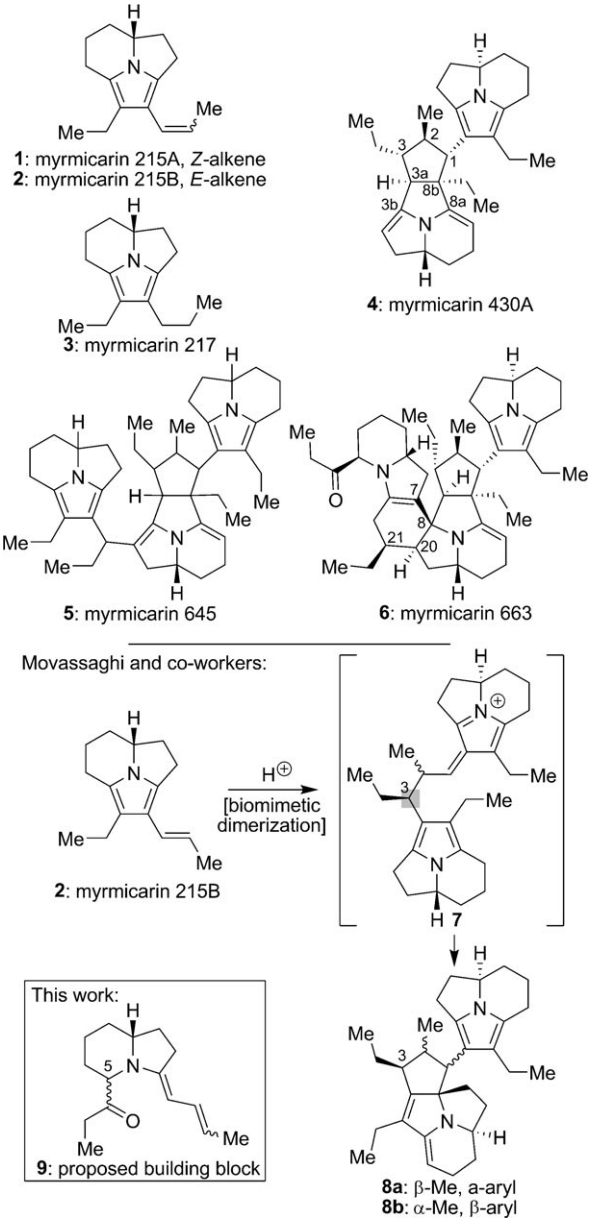

Figure 1. Structures of the myrmicarin alkaloids, previous work towards the dimeric structures, and a proposed building block to accomplish the selective synthesis of the entire family of natural products.

within **7**. Here we present our biomimetic synthetic studies towards these targets, efforts that have led to the most efficient syntheses of the monomeric members to date as well as provided the means to access the correct ethyl group stereochemistry at the critical C-3 position. These studies, in combination with a series of quantum chemical calculations,

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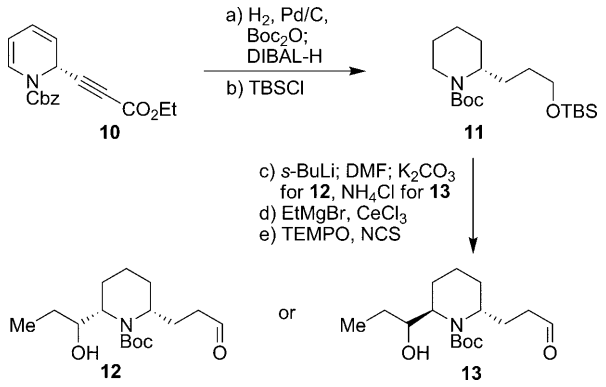
question whether the higher-order structures can be obtained ex vivo through acid-promoted biomimetic synthesis.

Given the consistently reported failure of structures of general architecture **1**–**3** to afford the dimeric members of the family, our synthetic approach was predicated on the idea that an alternate starting material was required if a biomimetic synthesis was to prove successful. In our past efforts seeking to achieve the controlled synthesis of members of other oligomeric natural product families,[4] we have often identified such unique building blocks by searching for anomalous structural features within the higher-order members; here, we wondered if the structure of myrmicarin 663 (**6**) might provide the needed design clues since one-third of its architecture is inconsistent with direct oligomerization of myrmicarin 215-type monomers. Indeed, retrosynthetic cleavage of its C-7/C-8 and C-20/C-21 bonds suggested a structure of type **9** as a possible alternate building block.[5] Its cyclodehydration was anticipated to afford monomers **1**–**3**, while the influence of both its olefin geometry and C-5 ketone stereochemistry was hoped capable of setting the critical C-3 ethyl stereocenter and ultimately leading to **4**. Despite the appeal of this idea, literature precedent regarding the stability of compounds with structures similar to **9** was discouraging,[2a] and even if they could be prepared, it was not obvious which combination of isomers would give rise to the desired product stereochemistry. We thus set out to answer these questions, hoping to selectively synthesize all four possible diastereomers of generalized starting material **9**.

We began by elaborating compound **10** (Scheme 1), prepared in one step in 84% yield and 86% *ee* using a method developed by Ma et al.[6] (see Supporting Information).

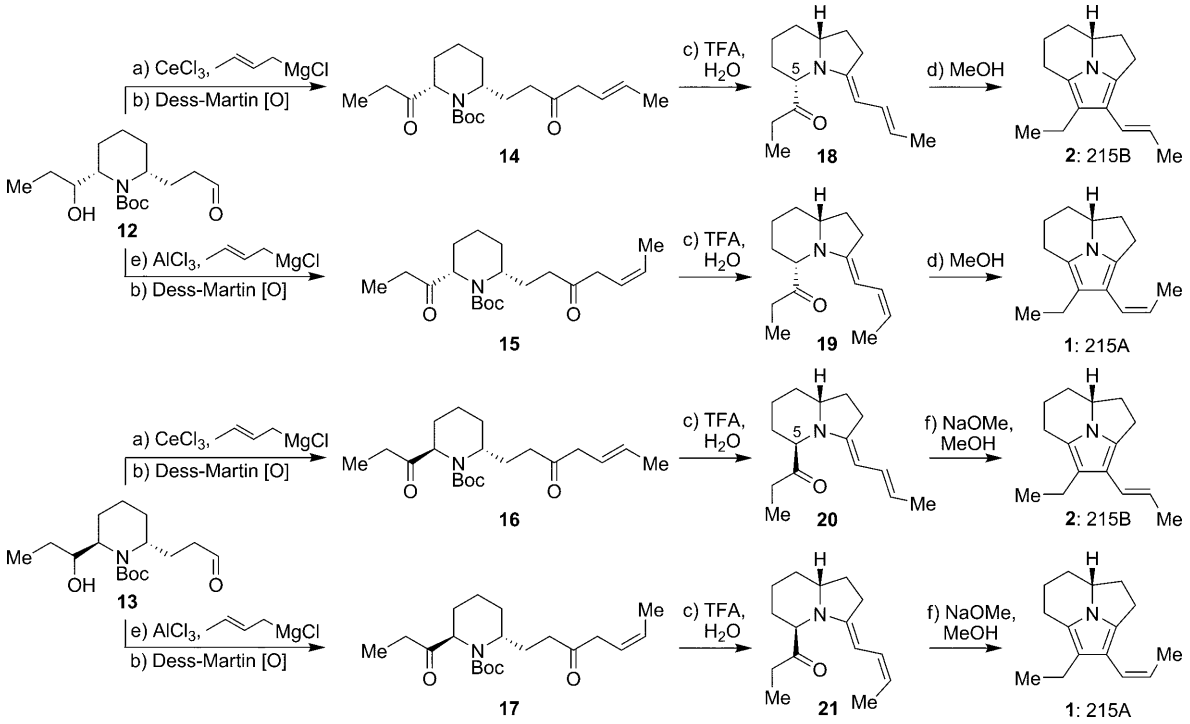


Scheme 1. Synthesis of key intermediates **12** and **13**: a) H_2 (1 atm), Pd/C (10%, 0.05 equiv), Boc_2O (1.3 equiv), EtOAc, 23 °C, 16 h, 84%; concentrate; DIBAL-H (1.1 equiv), THF, −78 °C, 45 min; 0 °C, 15 min, 98%; b) TBSCl (1.3 equiv), imidazole (2.0 equiv), CH_2Cl_2, 23 °C, 12 h, 98%; c) *s*BuLi (1.8 equiv), TMEDA (2.2 equiv), Et_2O, −78→−40 °C, 1 h; DMF (10 equiv), −78→−40 °C, 1.5 h; K_2CO_3/MeOH or NH_4Cl, 90% for **12**, 97% for **13**; d) $CeCl_3$ (1.5 equiv), EtMgBr (1.5 equiv), THF, −40→0 °C; HCl (2.0 equiv), 3 h, 70% for **12**, 89% for **13**; e) TEMPO (0.05 equiv), NCS (1.0 equiv), nBu_4NCl (0.1 equiv), NaBr (1.0 equiv), CH_2Cl_2, pH 8.6 aqueous buffer, 0 °C, 1.5 h, 93% for **12**, 96% for **13**. Boc_2O = di-*tert*-butyldicarbonate, DIBAL-H = diisobutylaluminum hydride, TBS = *tert*-butyldimethylsilyl, DMF = *N*,*N*-dimethylformamide, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy free radical, NCS = *N*-chlorosuccinimide, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

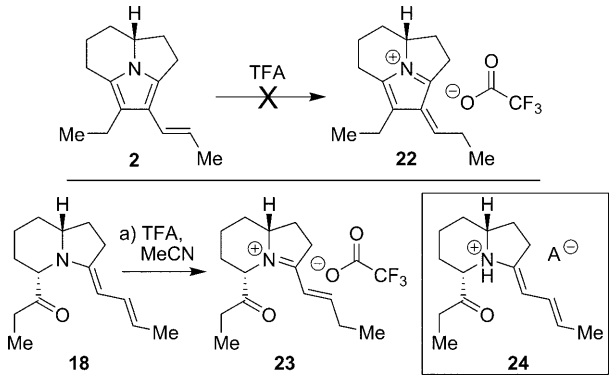
tion), into key intermediates **12** and **13**. This process required five operations, and their critical relative configurations were established with greater than 20:1 selectivity by either basic (**12**) or acidic (**13**) work-up following formylation.[7] With this key stereodivergence secured, we then directed our attention towards stereoselectively adding the linear crotyl chains needed to obtain the target alkene isomers. Among available methods, Lewis acid promoted variants appeared the most appealing since a simple switch in the Lewis acid used could potentially enable selective access to the respective *E*- and *Z*-isomers.

As shown in Scheme 2, this approach proved successful, as the exposure of **12** and **13** to the crotylcerium reagent prepared from $CeCl_3$[8] and 2-butenylmagnesium chloride afforded selective access to the linear *E*-isomers (6:1 α:γ, 8:1 *E*/*Z*), while use of the crotylaluminum reagent from $AlCl_3$[9] furnished the linear *Z*-isomers (4:1 α:γ, >15:1 *Z*/*E*). Subsequent Dess–Martin oxidation of the resultant diastereomeric mixture of diols and separation of the minor branched isomer through silica gel chromatography afforded rapid and highly selective access to **14**–**17** in 26–36% overall yield from commercial materials. Finally, *N*-Boc deprotection of each of these four isomers with TFA in the presence of H_2O,[10] followed by a cold aqueous NaOH quench,[11] afforded dienamines **18**–**21** as stable and fully characterizable compounds.[12] This outcome is in stark contrast to previous studies on myrmicarin 217 (**3**, Figure 1). Indeed, unlike their monoenamine counterparts that have been shown to both spontaneously epimerize at the C-5 position (as noted within **9**) and cyclize to myrmicarin 217 (albeit in low yields),[2a] these compounds are both configurationally stable[13] and do not undergo spontaneous cyclization in aprotic solvents. When exposed to protic solvents, however, **18**–**21** were readily converted into the monomeric myrmicarin alkaloids 215A (**1**) and 215B (**2**) through Knorr pyrrole condensation. For **18** and **19**, simple dissolution in argon-purged MeOH at 23 °C proved sufficient, while **20** and **21** required stirring in NaOMe/MeOH at 50 °C for 1 h (through presumed epimerization at C-5 prior to cyclodehydration). Overall, these natural products were synthesized in ten linear steps from commercial materials in 29% and 31% overall yield, respectively. A similar sequence also enabled access to myrmicarin 217 (**3**) as well as myrmicarin 237B (see Supporting Information for full details). More significantly, with **18**–**21** in hand and the means to arrest or effect their cyclodehydration through solvent control, explorations into unique biomimetic dimerizations could begin.

Initial efforts commenced by exposing **18**–**21** to a series of acidic and aqueous buffers, hoping for a direct, biomimetic synthesis of myrmicarin 430A (**4**, Figure 1). Unfortunately, despite the ease with which **1** and **2** were formed under some of these conditions, we never observed the formation of characterizable dimeric materials.[14] Thus, we shifted to stepwise approaches, hoping to identify a method to stoichiometrically protonate dienamines **18**–**21** and generate their corresponding extended iminium ions as a prelude to adding more **18**–**21** (to serve as nucleophile).[15] As indicated in Scheme 3, previous work by Movassaghi and Ondrus demonstrated that myrmicarin 215 (**2**) does not undergo stoichiometric protonation to give a stable *Z*-azafulvenium (**22**),[3ab]



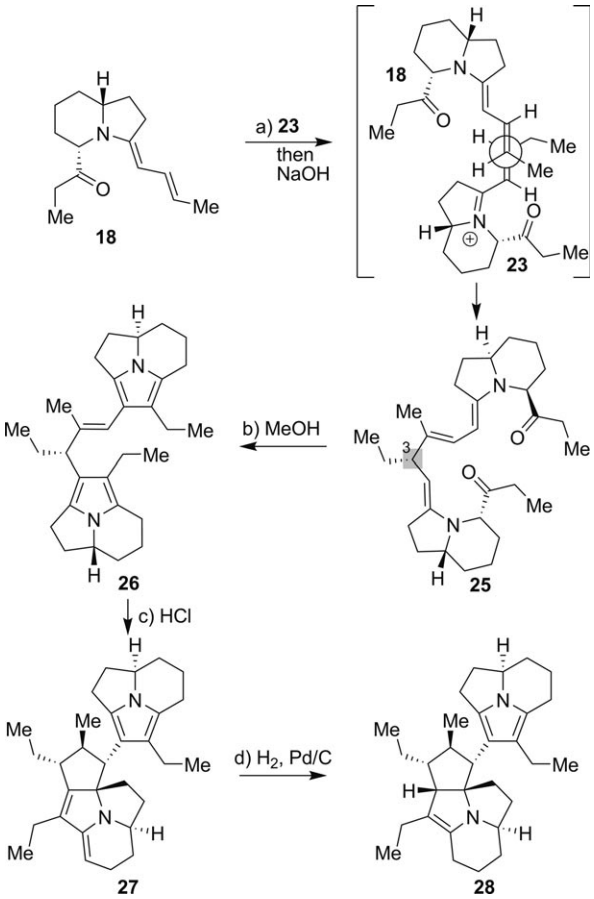
Scheme 2. Synthesis of dimerization precursors **18**–**21** and the total syntheses of myrmicarins 215A (**1**) and 215B (**2**): a) $CeCl_3$ (3.0 equiv), 2-butenylmagnesium chloride (3.0 equiv), THF, −78→−40 °C, 3 h; b) Dess–Martin periodinane (3.0 equiv), CH_2Cl_2, −10 °C, 1.5 h, 71% over 2 steps, E/Z = 8:1 for **14**, 66% over two steps, E/Z = 8:1 for **16**; c) TFA/CH_2Cl_2/H_2O (4:4:1), 0 °C, 1 h, 99%; d) MeOH, 23 °C, 1 h, 99%; e) $AlCl_3$ (6.0 equiv), 2-butenylmagnesium chloride (3.0 equiv), THF, −78→0 °C, 1 h, 62% [two steps, (e) and (b)], E/Z > 15:1 for **15**, 72% [two steps, (e) and (b)], E/Z > 15:1 for **17**; f) NaOMe (10 equiv), MeOH, 50 °C, 1 h, 85%. TFA = trifluoroacetic acid.



Scheme 3. Regiospecific protonation to form iminium ion **23**: a) TFA (1.0 equiv), MeCN, 23 °C, 99%.

though it is a presumed intermediate en route to dimerization with residual **2** in the synthesis of **8a** and **8b** shown within Figure 1. After much experimentation, we found that dienamines **18**–**21** could be stoichiometrically protonated regioselectively at the γ-position with TFA in MeCN to give stable iminium ions such as **23** (Scheme 3). Key nOe correlations (see Supporting Information) revealed that this protonated species exists exclusively as the *E*-isomer in an s-*trans* conformation in solution, which is the conformational equivalent to a prohibitively strained *E*-azafulvenium ion. We note that TFA was unique among the more than ten acid sources screened in effecting this transformation; weaker acids led only to olefin isomerization while stronger acids led exclusively to protonation at nitrogen to afford **24**. Furthermore, if less polar solvents (such as benzene or CH_2Cl_2) were used during the protonation step, various degrees of decomposition were observed.

With the means to prepare extended iminium ions secured, we then began probing dimerizations. Scheme 4 presents the optimized sequence following dozens of experimental variations. In the event, dienamine **18** was added to a solution of iminium ion **23** that had been formed in MeCN at 23 °C as described above. After stirring for 30 min, the reaction contents were quenched with cold aqueous NaOH, affording **25** as a complex diastereomeric mixture that was immediately treated with degassed MeOH to effect biscyclization. This operation afforded, after purification on neutral alumina, hexacycle **26** as a 2:1 mixture of diastereomers (54% combined yield) which could be separated by semi-preparative reverse-phase HPLC.[16] Extensive NMR analysis, particularly 2D nOe experiments, firmly established that these compounds were diastereomers about the C-3 position, with the minor component assigned as the undesired C-3 β-ethyl stereoisomer upon comparison with data previously reported by the Movassaghi group.[3d] In accordance with direct dimerizations of myrmicarin 215[3a,d] (**1** or **2**), the stereochemical outcome of this reaction can be rationalized as resulting from the preferred approach of the nucleophile onto the convex face of the electrophile wherein the difference in the solution conformation of electrophile **23** compared to the presumed protonated form of myrmicarin 215 (**22**) leads to



Scheme 4. Dimerization of monomer and acid mediated cyclization: a) **23** (1.0 equiv), CH_3CN, 23 °C, 1 h; 1 M NaOH, 0 °C; b) MeOH, 23 °C, 3 h, 54% over 2 steps; c) HCl (1.0 M in Et_2O, 20 equiv), CH_2Cl_2, 23 °C, 1 h, 60%; d) H_2, Pd/C (10%, 0.8 equiv), C_6D_6, 0.5 h, 40%.

the reversed stereochemical outcome. Efforts to optimize the diastereomeric ratio of this dimerization through the change of solvent, temperature, and electrophile/nucleophile combinations led either to no improvement or a reversal of selectivity. Indeed, the d.r. for this reaction ranges from 2:1 to 1:1.5.[17] Furthermore, attempts to dimerize compounds **18**–**21** with myrmicarin 215A or B (**1** or **2**) were unproductive. Thus, the overall success of this sequence in delivering the correct C-3 stereochemistry within **26** was wholly dependent on our ability to access all building blocks of type **9**, form stable iminium species from them, effect regioselective dimerization, and use solvent changes to control the timing of the Knorr cyclodehydration.

The question now was what effect would the previously unattainable C-3 stereochemistry have on the regiochemistry of the final ring closure. When hexacycle **26** was treated with an ethereal solution of HCl in CH_2Cl_2 at 23 °C for 1 h and then worked up with base, ^{1}H NMR analysis of the crude reaction mixture showed the exclusive formation of compound **27**, the regio- and stereochemistry of which was determined from nOe correlations in **27** and reduced product **28** (see Supporting Information). Thus, the central cyclopentane in **27** displays the correct *trans-trans* C-1/C-2, C-2/C-3 disposition of myrmicarin 430A (**4**), but reflects regioisomeric pyrrole attack onto the presumed azafulvenium, similar to **7**→**8** (cf. Figure 1).[18] Given that the generally preferred alkylation of pyrroles at either the C-2 or C-5 position is usually a kinetic outcome,[19] attempts were then made to isomerize **27** into myrmicarin 430A (**4**) under strongly acidic conditions, both with and without heating. However, all such experiments led to either complete decomposition or recovered starting material. In addition, efforts were made to cyclize hexacycle **26** with HCl at both elevated temperatures and at −20 °C, but these experiments led to decomposition and variable mixtures of starting material and **27**, respectively. Though the observed decomposition cannot rule out the possibility of initial isomerization to myrmicarin 430A (**4**) followed by decomposition, these results, coupled with the extensive studies by Movassaghi and co-workers, led us to wonder if these collective observations were the result of both a thermodynamic and kinetic preference for C-3b attack. To probe this hypothesis, a series of ab initio quantum chemical calculations were performed.[20]

Figure 2 depicts an energy plot of equilibrium geometries from B3LYP[21]/6-31G(d) optimizations of the hexacyclic iminium ion **29** (its two rotameric isomers about the C-3/C-3a bond, **29a** and **29b**), the two competing C-3b and C-8b alkylation transition states **30** and **32**, and the cyclized iminium products **31** and **33**. The results of these calculations indicate that the two transition states are essentially isoenergetic, though isomer **30** is consistently lower at all levels of theory examined. In addition, these results predict that though rotamer **29b** is more stable than its counterpart, **31** should be the thermodynamic product by 2.9 kcal mol^{-1} from this reaction. It is worth noting that the geometric distortion associated with rotamers **29a** and **29b** is very small, with the

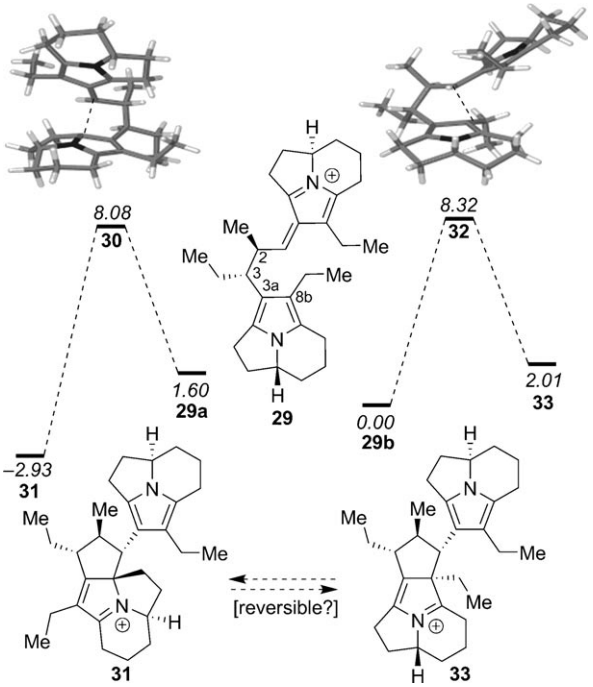


Figure 2. Potential energy surface of the acid catalyzed cyclization of **26**. All values are ΔG in kcal mol^{-1}.

major difference due to the dihedral angle defined by C-2/C-3/C-3a/C-8b (84° vs 69°, respectively). Furthermore, the effects of solvation do not affect the qualitative description of the potential energy surface.

Overall, these results indicate that the cyclization to form compound **27** is not only thermodynamically favored, but there is also no kinetic or thermodynamic preference for the formation of the desired heptacycle **4**. In other words, it does not appear to be possible to access **4** from intermediate **26** under protic conditions. Thus, the combination of our experimental results and theoretical calculations strongly suggest either that intermediates such as **26** are not biomimetic, that enzyme participation plays an important role in preventing rotation about the C-3/C-3a bond, and/or that the alkylation event is coupled to an irreversible deprotonation leading to myrmicarin 430B,[22] a compound that is known to spontaneously isomerize to myrmicarin 430A (**4**). The latter explanation is particularly appealing given that our calculations indicate that **27** and myrmicarin 430A (**4**) are isoenergetic and once formed, myrmicarin 430A (**4**) would require isomerization to the thermodynamically less stable myrmicarin 430B prior to protonation at C-8. Thus, once formed, **4** is not likely to equilibrate to **27** under acidic conditions.

In conclusion, we have completed the shortest and most efficient total syntheses of four of the members of the myrmicarin family, including myrmicarins 215A (**1**), 215B (**2**), and 217 (**3**). Using the key dienamine intermediates **18**–**21**, we were able to achieve dimerizations that selectively accessed the required C-3 ethyl stereochemistry and the all-*trans* cyclopentane backbone of myrmicarin 430A (**4**) for the first time. Experimental results also imply that the tricyclic members of this class are formed spontaneously under biological conditions from oxidized myrmicarin 237 congeners **18** and **19**, though efforts to form the desired dimeric materials have thus far been thwarted. As such, if **26** is indeed a biosynthetic intermediate, reactivity modes other than direct acid catalysis would appear necessary if the higher-order myrmicarins are to be forged from it in a reaction flask.

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[11] Cold NaOH was critical to obtaining high yields in this reaction.

[12] Although we use the term "stable", these compounds cannot be purified on deactivated silica gel, neutral alumina, or basic alumina and must be used directly following extraction without further purification.

[13] The natural product myrmicarin 237 (the fully saturated form of **9**) also lacks configurational stability at the α-position. Calculations suggest that the level of pyramidalization about nitrogen in **18**–**21** is less than in either their monoenamine counterparts or myrmicarin 237, which may account for their observed configurational stability.

[14] We found that dissolving **18** and **19** in either pH 7.4 or 8.6 aqueous buffers also led to the clean formation of myrmicarin 215A and B (**1** and **2**), suggesting that **1**–**3** are spontaneously formed upon oxidation of the *n*-butyl sidechain in myrmicarin 237-like structures. Although these experiments cannot rule out the possibility of other biosynthetic precursors, the above hypothesis is strengthened by the structural features found in the natural isolates myrmicarin 237 and 663 (**6**).

[15] For a review on dienamines, see: P. W. Hickmott, *Tetrahedron* **1984**, *40*, 2989 – 3051.

[16] A number of experiments demonstrated that the desired ethyl epimer cyclizes to **26** faster than the undesired epimer. Performing the reaction in isopropyl alcohol allowed for a sufficiently low overall rate of cyclization to achieve a kinetic resolution leading to up to a 5:1 d.r., albeit in reduced yield (12%).

[17] The reduced d.r. observed in these reactions compared to myrmicarin 215 dimerizations may be a reflection of the conformational flexibility in the dienamine sidechain as well as the less sterically demanding environment of the electrophilic site, thereby allowing for some approach from the concave face of the electrophile to occur. The Supporting Information section contains a listing of various combinations and the resultant product ratios.

[18] Extended reaction times for this final cyclization result in the exclusive formation of compound **8b**, in accordance with the reversibility reported by Movassaghi (Ref. [3d]). In addition, theoretical calculations indicate that **8b** is more stable than **27** by 2.9 kcal mol^{-1}.

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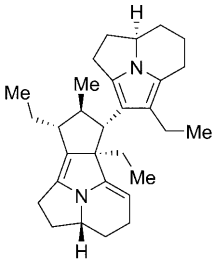
[22] The proposed structure of myrmicarin 430B is shown below; it was found to convert spontaneously to myrmicarin 430A upon standing: F. Schröder, Ph.D. Thesis, University of Hamburg (Germany), **1996**.



myrmicarin 430B (proposed)

