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Biomimetic Entry to the Sarpagan Family of Indole Alkaloids: Total Synthesis of (+)-Geissoschizine and (+)-*N*-Methylvellosimine

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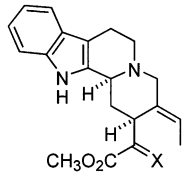
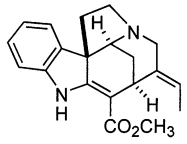
Abstract: A concise synthesis of (+)-geissoschizine (**1**), a biosynthetic precursor of a variety of monoterpenoid indole alkaloids, from D-tryptophan (**19**) was performed as a critical prelude to achieving the first biomimetic, enantioselective synthesis of the sarpagine alkaloid (+)-N_a-methylvellosimine (**5**). The approach to (+)-geissoschizine was designed to address the dual problems of stereocontrolled formation of the *E*-ethylidene moiety and the correct relative configuration at C(3) and C(15). Key steps in the synthesis involve a vinylogous Mannich reaction to prepare the carboline **22**, which has the absolute stereochemistry at C(3) corresponding to that in **1** and **5**, and an intramolecular Michael addition that leads to the tetracyclic corynantheane derivative **24**, which possesses the correct stereochemical relationship between C(3) and C(15). Compound **24** was then transformed into **27**, the pivotal intermediate in the syntheses of **1** and **5**, by a sequence that allowed the stereospecific introduction of the *E*-ethylidene moiety. Selective reduction of the lactam in **27** followed by removal of the C(5) carboxyl group by radical decarbonylation gave deformylgeissoschizine (**2**) that was converted into (+)-geissoschizine (**1**) by formylation. The common intermediate **27** was then converted via a straightforward sequence of reactions into the α-amino nitrile **39**. The derived silyl enol ether **40** underwent ionization upon exposure to $BF_3{\cdot}OEt_2$ to give the intermediate iminium ion **41** that then cyclized in a biomimetically inspired intramolecular Mannich reaction to deliver (+)-N_a-methylvellosimine (**5**). This transformation provides experimental support for the involvement of such a cyclization as one of the key steps in the biosynthesis of the sarpagine and ajmaline alkaloids.

Introduction

The alkaloids of the indole family have arguably been subject to more structural, pharmacological, biosynthetic, and synthetic investigations than any other group of alkaloid natural products.[1] The intense interest in the indole alkaloids derives from the structural diversity and complexity of many of its members coupled with the important physiological properties and medicinal applications of some of these natural bases. As part of our ongoing efforts to develop general strategies for the efficient synthesis of members of the various subgroups of this family, we have completed the total syntheses of a number of structurally different indole alkaloids, including reserpine, tetrahydroalstonine, geissoschizine, rugulovasines A and B, setoclavine, akuammicine, strychnine, and manzamine A.[2] In designing approaches to several of these, key steps for skeletal construction were inspired by proposals for their biogenesis.[3] For example, geissoschizine (**1**) is a known biosynthetic precursor



1: X = CHOH
2: X = H_2



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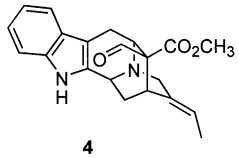

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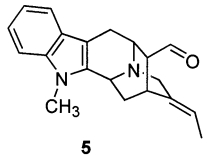

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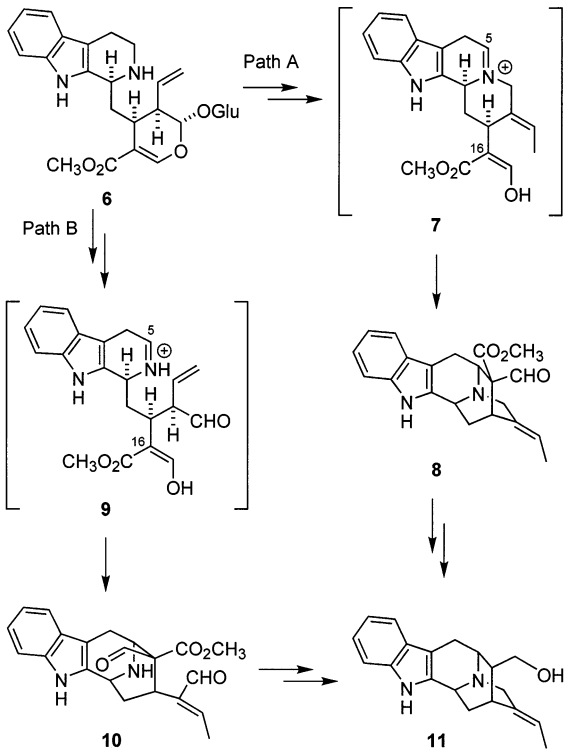
of akuammicine (**3**) and strychnine,[4] and the pivotal step in our synthesis of **3** involved the sequential oxidation and base-

(1) For reviews, see: (a) Herbert, R. B. In *The Monoterpenoid Indole Alkaloids*; supplement to Vol. 25, Part 4 of *The Chemistry of Heterocyclic Compounds*; Saxton J. E., Ed.; Wiley: Chichester, 1994; Chapter 1. (b) Saxton, J. E. In *The Monoterpenoid Indole Alkaloids*; supplement to Vol. 25, Part 4 of *The Chemistry of Heterocyclic Compounds*; Saxton J. E., Ed.; Wiley: Chichester, 1994; Chapter 8. (c) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 50. (d) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, Chapter 1. (e) Toyota, M.; Ihara, M. *Nat. Prod. Rep.* **1998**, 327−340 and references therein.

(2) (a) Martin, S. F.; Rüeger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124. (b) Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161. (c) Martin, S. F.; Clark, C. C.; Corbett, J. W. *J. Org. Chem.* **1995**, *60*, 3236. (d) Ito, M.; Clark, C. C.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003. (e) Liras, S.; Lynch, C. L.; Fryer, A. M.; Vu, B. T.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 5918. (f) Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584.

(3) For a review of some examples of biomimetic alkaloid synthesis, see: Scholz, U.; Winterfeldt, E. *Nat. Prod. Rep.* **2000**, *17*, 349.

Scheme 1

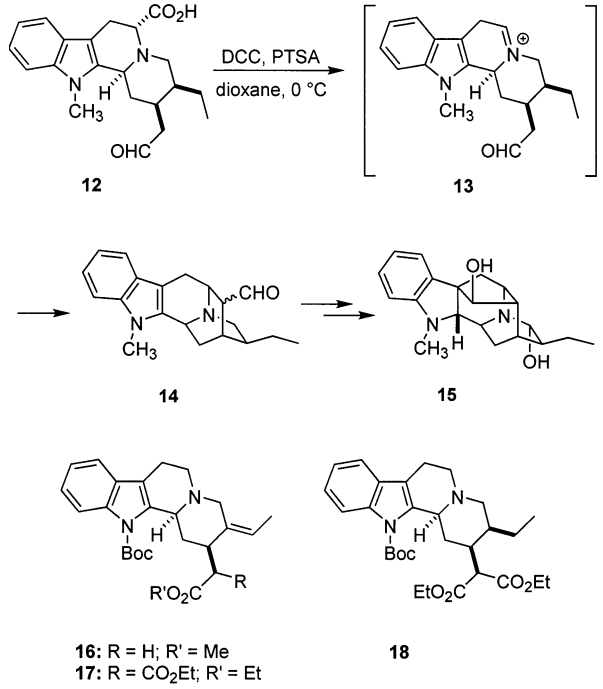


induced skeletal reorganization of the closely related corynanthe-type derivative **2**.[2d]

The successful implementation of a biomimetic transformation as the last step in our synthesis of akuammicine led us to examine the feasibility of preparing alkaloids of the sarpagine family such as polyneuridine aldehyde (**4**) or N_a-methylvellosimine (**5**) from **1** along biogenetic lines. N_a-Methylvellosimine has been isolated from the root bark of *Rauwolfia nitida*, which has been used in indigenous medicine as an emetic and cathartic.[5] Precedent for such a transformation derived from the extensive work of Stöckigt and co-workers, who elucidated many of the details in the enzymatic transformation of strictosidine (**6**), a key intermediate in the biosynthesis of monoterpenoid indole alkaloids, into sarpagan-17-ol (**11**) via the akuammidine aldehyde **8** (Scheme 1),[6] This is a complex sequence of reactions involving more than 10 steps that are catalyzed by a number of different enzymes.

Although these studies elucidated many of the details of indole alkaloid biosynthesis, the question of the timing of bond construction between C(5) and C(16) to produce the sarpagan skeleton remained,[6f,7] and two different proposals have been

Scheme 2



advanced to address this crucial issue. The first of these was set forth in 1968 by van Tamelen, who suggested that the bond between C(5) and C(16) was formed via an intramolecular Mannich reaction of an intermediate such as 4,5-dehydrogeissoschizine **7** (Scheme 1, path A).[8] In support of this novel hypothesis, van Tamelen and Olivier shortly thereafter reported a biogenetic-type synthesis of ajmaline (**15**) in which the key step was the conversion of **12** into a mixture of the epimeric aldehydes **14** (Scheme 2).[9] This remarkable cyclization to give the pentacyclic sarpagan skeleton proceeded via the putative iminium ion **13**, which was produced by decarbonylation of an activated form of the carboxyl group in **12**. Compound **14** was then elaborated into ajmaline (**15**) in a series of transformations.

Some 25 years after van Tamelen's original report, the cyclization of several 4,5-dehydrocorynantheane analogues of **13** was reinvestigated by Lounasmaa and co-workers.[10] Although they were able to transform compounds **16**−**18** into the derived $\Delta^{4(5)}$-iminium ions via a Polonovski−Potier protocol, they did not observe the expected "biogenetic-type" cyclization of any of these iminium ions. On the basis of these findings, Lounasmaa proposed an alternate biosynthetic pathway for forming the sarpagan skeleton that would proceed via an intramolecular Mannich reaction of the conformationally more flexible iminium ion **9** (Scheme 1, path B). Cyclization of the resultant aldehyde **10** would then furnish a pentacyclic intermediate that would be converted into **11**. If this proposal is correct, then the biogenesis of the corynanthe and the sarpagine alkaloids must follow different pathways.

The diametrically opposed observations of van Tamelen and Lounasmaa provided considerable impetus to our efforts to explore a biomimetic synthesis of **5** and related compounds from

(4) (a) Battersby, A. R.; Hall, E. S. *Chem. Commun.* **1969**, 793. (b) Scott, A. I.; Cherry, P. C.; Qureshi, A. A. *J. Am. Chem. Soc.* **1969**, *91*, 4932. (c) Heimberger, S. I.; Scott, A. I. *J. Chem. Soc., Chem. Commun.* **1973**, 217.
(5) Isolation of N_a-methylvellosimine: Amer, M. A.; Court, W. E. *Phytochemistry* **1981**, *20*, 2569.
(6) For reviews, see: (a) Stöckigt, J. In *The Alkaloids*; Cordell G. A., Ed., Academic: San Diego, 1995; Vol. 47, p 115. (b) Stöckigt, J. In *Natural Product Analysis*; Schreiner, P., Herderich, M., Humpf, H.-M., Schwab, W., Eds.; Vieweg: Braunschweig-Wiesbaden, 1998; p 313. See also: (c) Pfitzner, A.; Stöckigt, J. *Tetrahedron Lett.* **1983**, *24*, 1695. (d) Pfitzner, A., Stöckigt, J. *Planta Med.* **1983**, *48*, 221. (e) Pfitzner, A.; Stöckigt, J. *J. Chem. Soc., Chem. Commun.* **1983**, 459. (f) Pfitzner, A.; Krausch, B.; Stöckigt, J. *Tetrahedron* **1984**, *40*, 1691. (f) Herbert, R. B. In *The Biosynthesis of Secondary Metabolites*, 2nd ed; Chapman and Hall: London, 1989; 133. (g) Schmidt, D.; Stöckigt, J. *Planta Med.* **1995**, *61*, 254.
(7) The atoms are numbered according to the "biogenetic numbering" of Le Men and Taylor: Le Men, J.; Taylor, W. I. *Experimenta* **1965**, *21*, 508.
(8) (a) van Tamelen, E. E.; Haarstad, V. B.; Orvis, E. L. *Tetrahedron* **1968**, *24*, 687. (b) van Tamelen, E. E.; Yardley, J. P.; Miyano, M.; Hinshaw, W. B., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 7349.
(9) (a) van Tamelen, E. E.; Olivier, L. K. *J. Am. Chem. Soc.* **1970**, *92*, 2136. (b) van Tamelen, E. E.; Olivier, L. K. *Bioorg. Chem.* **1976**, *5*, 309.
(10) Lounasmaa, M.; Hanhinen, P. *Tetrahedron* **1996**, *52*, 15225.

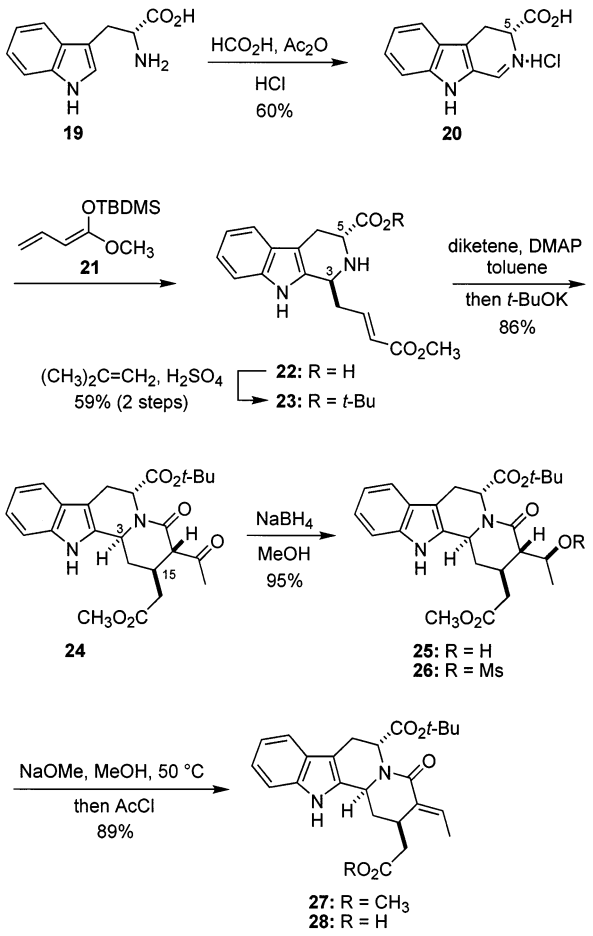
intermediates such as deformylgeissoschizine (**2**). There are, of course, significant differences between the iminium ion **13** of van Tamelen and the iminium ions of Lounasmaa that were generated from **16**−**18**, and we reasoned that these dissimilarities might account for the divergent observations. In particular, the nucleophilic sites on **13** and on the iminium ions derived from **16**−**18** are electronically and sometimes sterically different. Moreover, we believed that the *Z*-ethylidene group in **16** and **17** would not favor conformations that could undergo cyclization, whereas the *E*-ethylidene moiety in compounds related to **2** would clearly favor those conformations.[11,12]

To explore new strategies for the enantioselective syntheses of indole alkaloids of the corynanthe and sarpagine families, we initiated a series of studies that culminated first in an efficient synthesis of (+)-geissoschizine (**1**) and then in a biomimetic synthesis of (+)-N_a-methylvellosimine (**5**). Significantly, this synthesis of **5** represents the first example of a biomimetic, enantioselective synthesis of a member of the sarpagine alkaloid family, and it also provides compelling support for van Tamelen's original proposal for the biogenesis of these and the related ajmaline alkaloids. We now report the details of these investigations.[13]

Results and Discussion

Geissoschizine (**1**), an indole alkaloid belonging to the corynanthe family, has been isolated from a variety of plant species.[14] It is a known intermediate in the biogenesis of a number of monoterpene indole alkaloids.[6] Although **1** may also be envisioned as a precursor of **5**, there is presently no evidence to support this conjecture. Inasmuch as **1** occupies a central position in the area of indole alkaloids, it has been the subject of numerous investigations that have culminated in its synthesis.[15,16] Our first approach to geissoschizine featured a vinylogous Mannich reaction[17,18] and an intramolecular hetero-Diels−Alder reaction as key constructions.[15e,g] In this synthesis, the challenging stereochemical problems of controlling the geometry of the ethylidene side chain and the relative configuration at C(3) and C(15) were effectively controlled. However, the strategy could not be readily modified for an enantioselective synthesis of **1** nor could it be adapted to provide intermediates related to geissoschizine that could be chemically transformed along biogenetic pathways into representative indole alkaloids of the sarpagine and ajmaline groups. A novel entry to geissoschizine that provided simultaneous solutions to both of these problems was therefore developed.

Scheme 3



Synthesis of the Key Corynantheane Intermediate 27. On the basis of prior experience,[2c] we knew that vinylogous Mannich reactions involving iminium ions related to the dihydrocarboline **20**, which was prepared from D-tryptophan (**19**) in a single operation by modification of a known procedure,[19] would proceed preferentially from the face opposite the carboxyl moiety at C(5). Hence, **20** was allowed to react with the vinyl ketene acetal **21** to produce **22** as the only isolable product (Scheme 3). As expected, the nucleophilic attack of **21** onto **20** occurred with high diastereoselectivity from the *si* face, establishing the correct absolute stereochemistry at C(3) of the indole alkaloid targets. Although it was not necessary to esterify the carboxyl function in **20** prior to executing the vinylogous Mannich reaction, subsequent transformations would require such protection of that group. Crude **22** was thus treated directly

(11) For a review, see: Lounasmaa, M.; Hanhinen, P. *Heterocycles* **1999**, *51*, 649.
(12) (a) Tamminen, T.; Jokela, R.; Tirkkonen, B.; Lounasmaa, M. *Tetrahedron* **1989**, *45*, 2683. (b) Jokelar, R.; Halonen, M.; Lounasmaa, M. *Tetrahedron* **1993**, *49*, 2567.
(13) For a preliminary account of the synthesis of (+)-geissoschizine, see: Martin, S. F.; Chen, K.; Eary, C. T. *Org. Lett.* **1999**, *1*, 79.
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(17) For a review of recent applications of vinylogous Mannich reactions to alkaloid synthesis, see: Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895.
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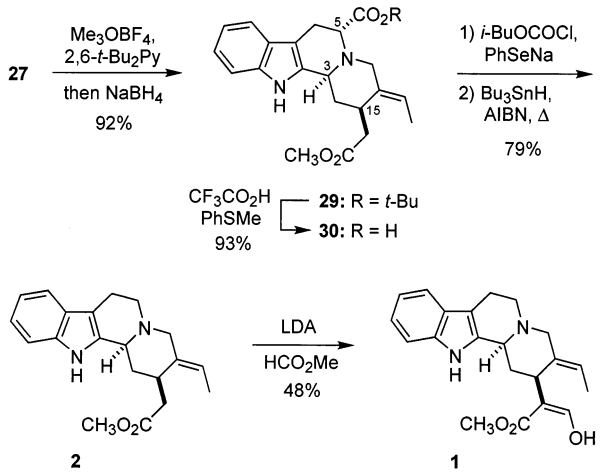
(19) Previero, A.; Coletti-Previero, M.-A.; Barry, L.-G. *Can. J. Chem.* **1968**, *46*, 3404.

with isobutylene in the presence of sulfuric acid to give **23** in 59% overall yield from **20**. N_b-Acylation of **23** with diketene furnished an intermediate β-keto amide that underwent facile cyclization via an intramolecular Michael reaction upon addition of potassium *tert*-butoxide to give **24** (86%). This reaction presumably proceeded under thermodynamic control to establish the correct relative stereochemistry at C(3) and C(15).

The synthesis of **24** completed assembly of the corynantheane framework, so the next phase of the endeavor required introducing the *E*-ethylidene side chain to enable access to **27**. Toward this end, hydride reduction of the C(19) carbonyl function in **24** gave the alcohol **25**, the stereochemistry of which was unambiguously proven by X-ray crystallographic analysis. The stereochemical outcome of this reduction is also consistent with that observed in closely related systems.[2c,20] Stereoselective dehydration of **25** proved to be somewhat more difficult than anticipated. For example, several efforts to effect direct dehydration of **25** by base-induced β-elimination gave only small amounts of **27** together with the corresponding *Z*-isomer. Elimination of the derived mesylate **26** with DBU produced a mixture (ca. 1:1) of **27** and its *Z*-isomer, albeit in modest yield. Preliminary attempts to equilibrate these *E*- and *Z*-geometric isomers with iodine in refluxing benzene led to extensive decomposition. On the other hand, heating a mixture of the isomeric alkenes at 100 °C in the presence of DBU did improve the *E*/*Z*-ratio up to 3.5:1, but again decomposition pathways led to poor material balance. Eventually we discovered that warming a solution of **25** and methanolic NaOMe at 50 °C led to stereoselective elimination to give the desired ester **27** bearing the *E*-ethylidene side chain together with variable amounts of the corresponding acid **28**, although none of the *Z*-isomer was isolated. While the high stereoselectivity observed in this process was somewhat surprising in light of our earlier results, we have observed similar selectivities in related eliminations.[21] The acid **28** was likely produced by saponification of the ester moiety in either **25** or **27** by hydroxide ions generated in the elimination step. Esterification of this acid could be simply performed in situ by adding excess acetyl chloride to the basic reaction mixture, thereby producing **27**, a compound that would serve as the common intermediate for the syntheses of (+)-geissoschizine (**1**) and (+)-N_a-methylvellosimine (**5**), in 85% overall yield from **24**.

Enantioselective Synthesis of (+)-Geissoschizine (1). The transformation of **27** into (+)-geissoschizine (**1**) was initiated with the selective reduction of the lactam function according to the Borch protocol to furnish **29** in 92% yield (Scheme 4).[22] Cleavage of the *tert*-butyl ester moiety was conducted using trifluoroacetic acid in the presence of thioanisole,[23] an essential cation scavenger, to provide the acid **30**. Having served its role as a stereochemical control element to set the absolute stereochemistry at C(3) and C(15), it was now time to remove the carboxyl group from C(5) of **30**. This task, however, proved to be more difficult than anticipated. We first explored the radical decarboxylation of **30** according to several of the classical Barton protocols,[24] but **2** was obtained in only low and inconsistent yields ranging up to 25%. The radical decarboxylation of the benzophenone oxime ester derived from **30** was then examined,[25] but this procedure was unsuccessful, as were alternate methods involving generation and reduction of the iminium ion formed by the reaction of **30** with phosphorus oxychloride.[26] Finally, we discovered that the acyl selenide that was formed by the sequential reaction of **30** with isobutyl chloroformate and then sodium phenylselenide,[27] underwent facile and efficient radical decarbonylation to give deformylgeissoschizine **2** in 79% overall yield from **30**.[28,29] Formylation of **2** according to the procedure of Winterfeldt[16a] then delivered (+)-geissoschizine (**1**) in 48% yield (96% yield based upon recovered starting material) via a sequence requiring only 11 chemical operations from D-tryptophan (**19**). The synthetic (+)-geissoschizine thus obtained was spectroscopically identical with a sample of racemic **1** previously prepared in our group,[15g] and its optical rotation corresponded closely with that reported for natural **1** {$[\alpha]_{20}^{D} = +109$ ($c = 0.58$, EtOH); $[\alpha]_{20}^{D} = +113$ ($c = 0.43$, EtOH)[16b]}.

Scheme 4



Biomimetic Synthesis of (+)-N_a-Methylvellosimine (5). At this juncture, we reasoned that N_a-methylated iminium ions of the general form **31** would constitute potentially viable intermediates in a biomimetic synthesis of (+)-N_a-methylvellosimine. Such iminium ions differ structurally in two important ways from those generated by Lounasmaa, who was unsuccessful in efforts to induce the intramolecular Mannich reaction of iminium ions generated from **16**−**18**.[10] Perhaps most importantly, iminium ions **31** all possess an *E*-ethylidene side chain that should favor those conformations of the DE-ring system in which the substituent at C(15) is approximately

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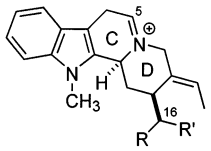
(27) For leading references to acyl selenides, see: (a) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, *57*, 1429. (b) Evans, P. A.; Roseman, J. D.; Garber, L. T. *J. Org. Chem.* **1996**, *61*, 4880.
(28) (a) Pfenninger, J.; Heuberger, C.; Graf, W. *Helv. Chim. Acta* **1980**, *63*, 2328. (b) Ireland, R. E.; Norbeck, D. W.; Mandel, G. S.; Mandel, N. S. *J. Am. Chem. Soc.* **1985**, *107*, 3285.
(29) For other examples of the radical decarbonylation of acyl selenides, see: (a) Quirante, J.; Escolano, C.; Bonjoch, J. *Synlett* **1997**, 179. (b) Stojanovic, A.; Renaud, P. *Synlett* **1997**, 181.

axially oriented. Such a disposition of this side chain would minimize the distance between C(5) and C(16) in the ground state, thereby favoring cyclization.[11] The iminium ions **31**, like van Tamelen's putative iminium ion intermediate **13**,[8] also bear a N_a-methyl group rather than the N_a-Boc group that is found in **16**−**18**. Following the lead of van Tamelen, we would employ the carboxyl moiety at C(5), which had already served as a stereochemical control device to set the absolute stereochemistry in intermediates leading to **1**, as a functional handle for the regioselective formation of the requisite $\Delta^{4(5)}$-iminium ions **31**.



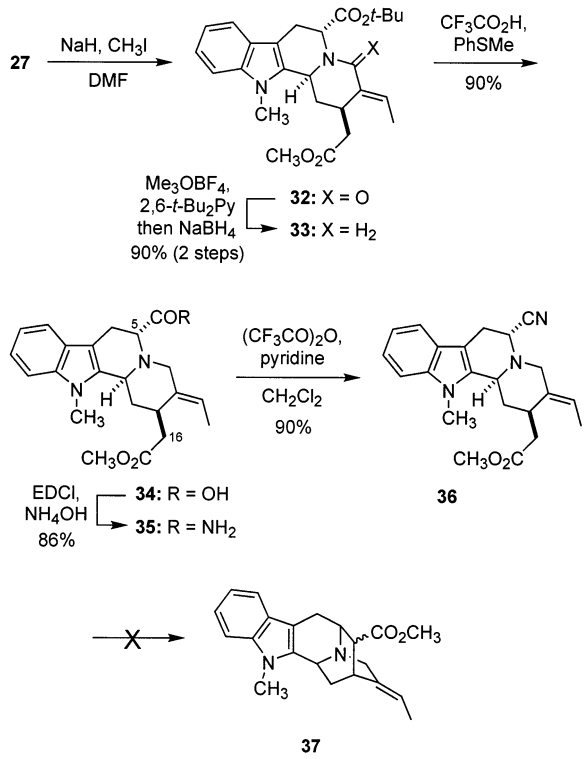
31: R, R' = CO_2CH_3, CHO, H, etc

Toward setting the stage for the key biomimetic cyclization step, the lactam **27** was first reacted with NaH in DMF in the presence of methyl iodide to give the N_a-methylated lactam **32**, which was immediately reduced to the amine **33** in 90% overall yield using the Borch procedure (Scheme 5).[22] An alternative route to **33** was briefly examined in which we attempted to effect the selective alkylation of the N_a-atom of **29**; however, concomitant methylation of the N_b-atom was observed as a significant and unavoidable side reaction. Acid-catalyzed cleavage of the *tert*-butyl ester in **33** in the presence of methylthioanisole proceeded smoothly as before to give the acid **34** in excellent yield.

The synthetic plan now required a suitable tactic for generating a $\Delta^{4(5)}$-iminium ion that would undergo efficient cyclization to the sarpagine framework. The precedent of van Tamelen notwithstanding,[9] it occurred to us that the C(5) carboxylic acid moiety might not be the optimal precursor function as the somewhat harsh conditions required for generating the requisite iminium ion did not seem compatible with the presence of an enol derivative of the ester at C(16). This concern was validated in several exploratory experiments. On the other hand, it was well-known that α-amino nitriles could be transformed into iminium ions under mild conditions.[30] Consequently, **34** was transformed by an 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) mediated coupling with NH_4OH into the corresponding amide **35** in 86% yield.[31] Dehydration of **35** with trifluoroacetic acid anhydride then provided the nitrile **36** in 90% yield. With **36** in hand, we performed several experiments directed toward cyclizing the ester enolate and ketene acetal derived from **36**, but these experiments did not yield detectable amounts of N_a-methyl-16-*epi*-pericyclivine (**37**).[32]

Our inability to cyclize **36** inspired us to modify the nature of the activating function attached to C(16). Toward this goal, the carboxyl group in **36** was selectively reduced in the presence

Scheme 5

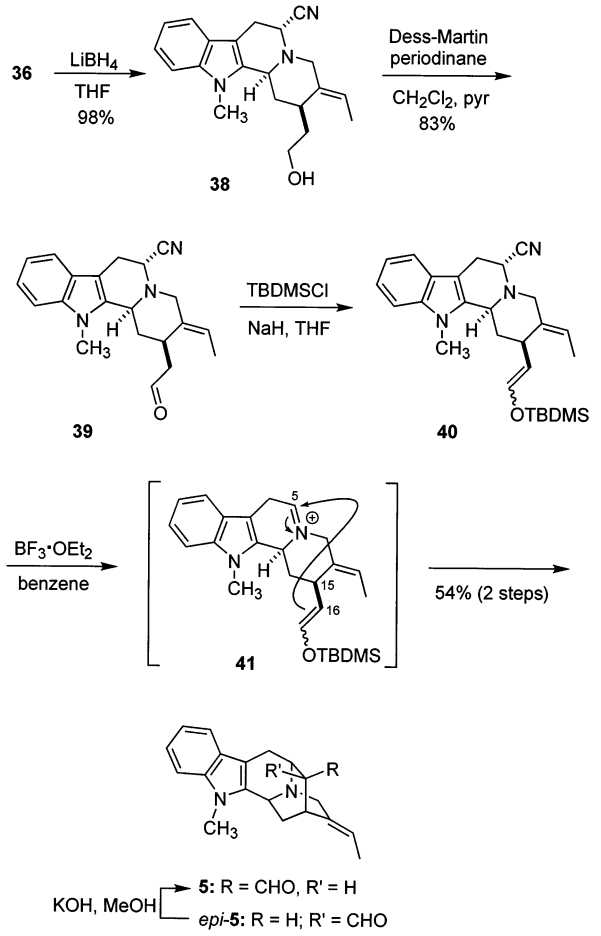


of the cyano group by reaction with $LiBH_4$ in THF (Scheme 6).[33] When a large excess (10 molar equiv) of reducing agent was used and the reaction was conducted in dilute solution (7.5 mM) for an extended period of time (43 h), the alcohol **38** was obtained in a nearly quantitative yield. Attempts to accelerate this reaction by heating, adding MeOH, or using Et_2O as the solvent merely led to decreased yields.[34] Oxidation of the primary alcohol group in **38** using the Dess−Martin periodinane reagent buffered with pyridine gave the aldehyde **39** in 83% yield.[35]

In contrast to our expectations, **39** exhibited no propensity toward cyclization under (Lewis) acidic conditions (CF_3CO_2H, TIPSOTf), even in the presence of silver salts (like $AgBF_4$).[36] We therefore decided to explore a modified tactic that involved subjecting a preformed nucleophilic derivative of the aldehyde to conditions that were known to lead to ionization of α-amino nitriles. Hence, the morpholine enamine of **39** was prepared first and treated with $AgBF_4$ and (Lewis) acid (CF_3CO_2H, TIPSOTf), but we were unable to isolate any of the cyclized products **5** or *epi*-**5**.[37] We then synthesized the silyl enol ether **40** (*E*:*Z* = 61:39) by reacting **39** with TBDMSCl in the presence of NaH. Gratifyingly, when **40** was treated with freshly distilled $BF_3{\cdot}OEt_2$ in degassed benzene at room temperature, a diastereomeric mixture (7:3) of (+)-N_a-methylvellosimine (**5**) and 16-*epi*-(+)-N_a-methylvellosimine (*epi*-**5**) was isolated, presumably

(30) Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ed.; Pergamon Press: 1991, *2*, p 1007 and references therein. See also ref 18a.
(31) Waldmann, H.; Schmidt, G.; Jansen, M.; Geb, J. *Tetrahedron* **1994**, *50*, 11865.
(32) Isolation of **37**: Pinchon, T.-M.; Nuzillard, J.-M.; Richard, B.; Massiot, G.; Le Men-Olivier, L.; Sevenet, T. *Phytochemistry* **1990**, *29*, 3341.
(33) *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, 2nd ed.; Seyden-Penne, J., Ed.; John Wiley & Sons: New York, 1997.
(34) For a review of aspects of borohydride reductions, see: (a) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567. (b) Periasamy, M.; Thirumalaikumar, M. *J. Organomet. Chem.* **2000**, *609*, 137.
(35) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.
(36) Daub, G. W.; Heerding, D. A.; Overman, L. E. *Tetrahedron* **1988**, *44*, 3919.
(37) Attempts of an intramolecular nucleophilic displacement of the cyano group by metal enolates derived from **36** and **39** also failed. For a similar cyclization, see: Herlem, D.; Florés-Parra, A.; Khuong-Huu, F.; Chiaroni, A.; Riche, C. *Tetrahedron* **1982**, *38*, 271.

Scheme 6



via cyclization of the iminium ion **41**. This mixture was simply exposed to aqueous KOH in MeOH to furnish the more stable **5** as the exclusive product in 54% yield (68% based upon recovered aldehyde) from **39**,[38] thereby completing the first biomimetic, enantioselective synthesis of a sarpagine alkaloid. Other Lewis acids including TMSOTf or TBDMSOTf also led to the formation of **5** and *epi*-**5**, albeit with diminished yields. Upon treatment of **40** with $AgBF_4$ in acetonitrile, no cyclization product **5**/*epi*-**5** was detected. The synthetic (+)-N_a-methylvellosimine (**5**) was identical (TLC, ^1H and ^{13}C NMR, MS) with a sample of *ent*-**5**, generously provided by Prof. James M. Cook.[39] The optical rotation of synthetic **5** {$[\alpha]_{20}^{D} = +91$ (c = 0.10, $CHCl_3$)} was higher than that of natural **5** {$[\alpha]_{20}^{D} = +23$ (c = 0.01, $CHCl_3$)[5]} but corresponded well with that of synthetic *ent*-**5** {$[\alpha]_{20}^{D} = -99$ (c = 0.40, $CHCl_3$)[39a]}.

Our original belief that **40** would be transformed into **5** and *epi*-**5** was based upon the prediction that the intermediate iminium ion **41** would reside preferentially in a ground state conformation that was favorable for cyclization. Namely, owing to $A^{1,3}$ strain with the adjacent *E*-ethylidene side chain, the enol ether substituent at C(15) in **41** should occupy an axial position on the D-ring, as had been observed previously for **2** and related compounds.[11,12] One would also then anticipate the D-ring of **41** to reside in a boat-like conformation with a *cis*-fusion of

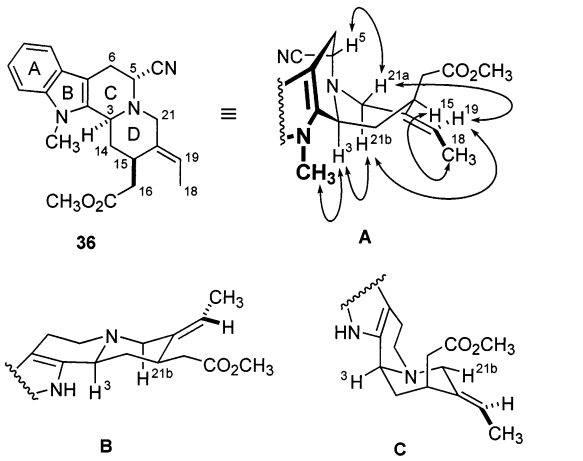


Figure 1. NOESY experiment on **36** with the strong and illustrative NOEs shown for the preferred conformation **A**. The preferred ground state conformation of the C and D rings of (*Z*)-**2** is shown in **B**, and the chair conformation of the D ring of (*E*)-**2** is shown in **C**.

the CD quinolizidine ring system, thus placing C(5) and C(16) in close proximity for the cyclization.

To evaluate the correctness of this structural hypothesis, the solution conformation of the closely related compound **36** was studied in a series of IR and ^1H NMR experiments, including a NOESY experiment in which a number of close contacts were observed (Figure 1). That the quinolizidine CD-ring is likely cis-fused is supported by the absence of Wenkert−Bohlmann absorption bands in the IR spectrum of **36**.[40] These bands should be visible if the nitrogen lone pair were antiperiplanar to both H(3) and H(21b), as is the case for the *trans*-quinolizidine system of (*Z*)-deformylgeissoschizine [(*Z*)-**2**] as shown in **B** (Figure 1).[41] The cis-fusion is further supported by the NOE between N_a-CH_3 and H(3) (see **A** in Figure 1); it is also consistent with the preferred conformation of deformylgeissoschizine (**2**).[11a] The strong NOE contacts between H(5) and H(21a) and the two small coupling constants of $J_{5,6a} = 2.1$ Hz and $J_{5,6b} = 5.1$ Hz suggest that H(5) occupies an equatorial position on the C-ring.

The assignment of a boatlike conformation for the D-ring of **36**, which positions the ester side chain at C(15) in an axial orientation, is consistent with the observed pairwise NOEs between H(3)−H(21b), H(15)−H(18), H(19)−H(21a), and H(19)−H(21b), as shown in **A**. The absence of any NOEs to the methylene group of C(16) suggests that the D-ring has some twist boat character. There is the possibility that the side chain appended to C(15) is axial on a *cis*-quinolizidine system in which the D-ring is a chair (see **C**, Figure 1).[11,12a] However, this conformation is not in accord with the observed NOE between H(3) and H(21b) that are both equatorial in **C**. Chair conformations for D-rings in related N_a-Boc-protected indoloquinolizidines have been previously discounted owing to the steric interactions that would then result between the N_a-CH_3 and the C(14) methylene moieties.[12b] The available spectral evidence and literature precedent thus support our hypothesis that the D-ring of **36** resides in a boat-like conformation with

(38) Bartlett, M. F.; Sklar, R.; Taylor, W. I.; Schlittler, E.; Amai, R. L. S.; Beak, P.; Bringi, N. V.; Wenkert, E. *J. Am. Chem. Soc.* **1962**, *84*, 622.
(39) (a) Total synthesis of *ent*-**5**: Liu, X.; Wang, T.; Xu, Q.; Ma, C.; Cook, J. M. *Tetrahedron Lett.* **2000**, *41*, 6299. (b) Total synthesis of **5**: Yu, J.; Wearing, X. Z.; Cook, J. M. *Tetrahedron Lett.* **2003**, *44*, 543.
(40) (a) Bohlmann, F. *Angew. Chem.* **1957**, *69*, 641. (b) Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157. (c) Wenkert, E.; Roychaudhuri, D. K. *J. Am. Chem. Soc.* **1956**, *78*, 6417.
(41) (a) Wenkert, E.; Guo, M.; Pestchanker, M.; Shi, Y.-J.; Vankar, Y. *J. Org. Chem.* **1989**, *54*, 1166. (b) Takayama, H.; Watanabe, T.; Seki, H.; Aimi, N.; Sakai, S. *Tetrahedron Lett.* **1992**, *33*, 6831.

the C(15) substituent in an axial orientation; it then seems reasonable to surmise that a low-energy conformation for the iminium ion **41** is similar.

Conclusion

A unified strategy for the enantioselective syntheses of the corynanthe alkaloid (+)-geissoschizine (**1**) and the sarpagine alkaloid (+)-N_a-methylvellosimine (**5**) from D-tryptophan (**19**) has been developed. The stereocenter in **19** sets the absolute and relative stereochemistry at all stereocenters in **1** and **5**. Moreover, the carboxyl group in **19** enables the eventual, regioselective generation of the requisite $\Delta^{4(5)}$-iminium ion for the cyclization leading to **5**. In these syntheses, the relative and absolute stereochemistry between C(3) and C(15) and the *E*-ethylidene double bond geometry in both **1** and **5** are completely controlled, thereby addressing several important problems in the area. Furthermore, the synthesis of (+)-N_a-methylvellosimine (**5**) features a biomimetic, intramolecular Mannich reaction that provides persuasive support for a key step in the proposed biosynthesis of the sarpagine and ajmaline alkaloids from corynantheane intermediates. The absolute stereochemistry at C(3) of both **1** and **5** was established at the outset by a vinylogous Mannich reaction in which **22** was produced as the only isolable product. A subsequent intramolecular Michael reaction provided **24**, thereby setting the correct relative stereochemistry between C(3) and C(15). Base-induced dehydration of the derived alcohol **25** cleanly introduced the requisite *E*-ethylidene group and provided the pivotal intermediate **27**. Conversion of **27** into (+)-geissoschizine (**1**) completed a concise enantioselective synthesis of this alkaloid by a sequence that involved only 11 chemical operations from commercially available D-tryptophan and proceeded in 17% overall yield, based upon recovered **2** in the final step. Compound **27** was also converted in eight steps into the key intermediate **40**, which underwent a facile intramolecular Mannich reaction to give (+)-N_a-methylvellosimine (**5**). Further applications of vinylogous Mannich and biomimetic reactions as key steps in the syntheses of complex alkaloids will be reported in due course.

Experimental Section

General Methods. Unless otherwise noted, solvents and reagents were reagent grade and used without purification. CH_2Cl_2, *i*-Pr_2NH, and Et_3N were freshly distilled from CaH_2. THF and Et_2O were passed through two columns of neutral alumina. MeOH, CH_3CN, and DMF were passed through two columns of molecular sieves. Toluene was passed through a column of neutral alumina and a column of Q5 reactant. Reactions involving air- or moisture-sensitive reagents or intermediates were performed under an inert atmosphere of argon in glassware that had been flame dried. Melting points are uncorrected. Infrared (IR) spectra were recorded either neat on sodium chloride plates or as solutions in CH_2Cl_2, as indicated, and are reported in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were obtained as solutions in $CDCl_3$ or C_6D_6, and chemical shifts are reported in parts per million (ppm) downfield from $(CH_3)_4Si$ (TMS). Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as follows: s, singlet; br, broad; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; and comp, complex multiplet. Signals in the ^{13}C NMR that could not be assigned are separated by slashes. Flash column chromatography was performed using Merck silica gel 60 (230−400 mesh ASTM) according to the method of Still.[42]

(42) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(3*S*,5*R*)-3,4,5,6-Tetrahydro-3-(3-methoxycarbonylallyl)-1*H*-pyrido[3,4-*b*]indole-5-carboxylic Acid (22). A mixture of imine hydrochloride **20** (5.12 g, 20.5 mmol) and the vinyl ketene acetal **21** (13.2 g, 61.5 mmol) in anhydrous MeCN (100 mL) was stirred at 0 °C for 30 min and then at room temperature for 4 h, during which time a clear yellow solution resulted. The solvent was removed under reduced pressure to give a thick yellow oil that was purified by flash chromatography eluting with CH_2Cl_2 and MeOH/CH_2Cl_2 (1:9→4:6) to give **22** (6.50 g) as a yellow solid, which was used in the next reaction without further purification. An analytical sample was obtained by flash chromatography eluting with MeOH/CH_2Cl_2 (15:85→20:80): ^1H NMR (250 MHz, MeOH-d_4) δ 7.88 (s, 1 H), 7.46 (d, J = 7.7 Hz, 1 H), 7.32 (d, J = 8.1 Hz, 1 H), 7.16−6.89 (comp, 3 H), 6.07 (d, J = 15.7 Hz, 1 H), 5.12−5.01 (m, 1 H), 4.12 (t, J = 7.6 Hz, 1 H), 3.70 (s, 3 H), 3.37−2.94 (comp, 4 H); ^{13}C NMR (62 MHz, MeOH-d_4) δ 173.5, 167.9, 143.2, 138.5, 129.2, 127.4, 126.5, 123.5, 120.5, 119.2, 112.3, 107.7, 55.8, 52.2, 52.0, 36.4, 23.6; IR (neat) ν 3378, 2950, 1709, 1628 cm^{-1}; HRMS (CI) m/z 315.1333 [$C_{12}H_{19}N_2O_4$ (M + 1) requires 315.1345).

(3*S*,5*R*)-*tert*-Butyl 3,4,5,6-Tetrahydro-3-(3-methoxycarbonylallyl)-1*H*-pyrido[3,4-*b*]indole-5-carboxylate (23). The crude acid **22** (6.5 g) from the preceding experiment was dissolved in 1,4-dioxane (150 mL) containing concentrated H_2SO_4 (10 mL), and isobutylene gas was bubbled for 3 h at room temperature into the mixture through a dispersion tube fitted with a glass frit; the volume of the solution increased by about 20 mL during this period. The solution was maintained at room temperature overnight, and then isobutylene gas was bubbled into the mixture as before for 1 h. The mixture was again allowed to stand overnight, whereupon it was slowly poured into a mixture of ice (100 g), ammonium hydroxide (20 mL), and CH_2Cl_2 (300 mL). The pH of the aqueous phase was adjusted to 9 by the slow addition of additional ammonium hydroxide. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were dried ($MgSO_4$), and the solvents were removed under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (3:7→1:1) to give 4.45 g (59% from **20**) of **23** as a yellow foam: ^1H NMR (250 MHz) δ 7.89 (s, 1 H), 7.50 (d, J = 7.3 Hz, 1 H), 7.30 (d, J = 7.4 Hz, 1 H), 7.19−7.01 (comp, 3 H), 5.97 (d, J = 15.7 Hz, 1 H), 4.38 (t, J = 6.7 Hz, 1 H), 3.81 (dd, J = 7.8, 5.1 Hz, 1 H), 3.75 (s, 3 H), 3.07 (dd, J = 15.4, 5.0 Hz, 1 H), 2.89 (dd, J = 15.3, 6.9 Hz, 1 H), 2.67 (t, J = 6.8 Hz, 2 H), 2.15 (br s, 1 H), 1.46 (s, 9 H); ^{13}C NMR (62 MHz) δ 172.7, 166.6, 145.3, 136.0, 134.0, 127.0, 123.9, 121.9, 119.5, 118.2, 110.8, 108.0, 81.4, 52.9, 51.6, 49.7, 38.8, 28.0, 25.1; IR (neat) 3358, 2977, 1723, 1657 cm^{-1}; HRMS (CI) m/z 371.1965 [$C_{21}H_{27}N_2O_4$ (M + 1) requires 371.1971].

(3*S*,5*R*,15*R*,20*S*)-*tert*-Butyl 3,4,5,6,14,15,20-Heptahydro-20-acetyl-15-methoxycarbonylmethyl-21-oxoindolo[2,3-*a*]quinolizine-5-carboxylate (24). A solution of the amino ester **23** (10.0 g, 27.0 mmol), DMAP (200 mg, 1.64 mmol), and diketene (2.80 mL, 36.3 mmol) in anhydrous toluene (200 mL) was stirred at room temperature for 2.5 h. The solution was diluted with toluene (150 mL) and cooled to −10 °C. Potassium *tert*-butoxide (5.80 g, 51.7 mmol) was added, and the resulting suspension was vigorously stirred at −10 to −5 °C for 70 min. The reaction was quenched by adding 0.5 N HCl (100 mL), and the resulting solution was diluted with EtOAc (300 mL) and water (100 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organic fractions were dried ($MgSO_4$), and the solvents were evaporated under reduced pressure. The product was purified by flash chromatography eluting with CH_2Cl_2 and EtOAc/hexane (3:7) to give 10.5 g (86%) of **24** as a yellow solid: mp 80−82 °C; ^1H NMR (250 MHz) δ 8.07 (s, 1 H), 7.52 (d, J = 7.1 Hz, 1 H), 7.31 (dd, J = 6.9, 1.1 Hz, 1 H), 7.22−7.09 (comp, 2 H), 5.86 (dd, J = 6.1, 1.3 Hz, 1 H), 5.09 (d, J = 10.4 Hz, 1 H), 3.69 (s, 3 H), 3.46−3.38 (comp, 2 H) 2.96 (ddd, J = 8.4, 6.1, 2.1 Hz, 2 H), 2.62 (dt, J = 12.9, 3.6 Hz, 1 H), 2.52−2.26 (comp, 3 H), 2.40 (s, 3 H), 1.28 (s, 9 H); ^{13}C NMR (62 MHz) δ 204.0, 171.9, 169.2, 166.4, 136.5,

131.1, 126.7, 122.4, 119.4, 118.4, 110.9, 107.1, 82.2, 61.5, 51.9, 51.2, 51.1, 38.5, 34.8, 30.3, 29.7, 27.9, 22.6; IR (CH_2Cl_2) 3312, 2976, 1731, 1633, 1621 cm^{-1}; HRMS (CI) *m*/*z* 455.2174 [$C_{25}H_{31}N_2O_6$ (M + 1) requires 455.2182].

(3*S*,5*R*,15*R*,19*S*,20*S*)-*tert*-Butyl 3,4,5,6,14,15,20-Heptahydro-20-(1-hydroxyethyl)-15-methoxycarbonylmethyl-21-oxoindolo[2,3-*a*]-quinolizine-5-carboxylate (25). A mixture of **24** (1.70 g, 3.86 mmol) and $NaBH_4$ (293 mg, 7.72 mmol) in anhydrous MeOH (60 mL) was stirred at −10 °C for 25 min. Saturated $NaHCO_3$ (40 mL) and CH_2Cl_2 (80 mL) were added, and the mixture was stirred at 0 °C for 5 min. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give 1.68 g (95%) of **25** as a white solid: mp 190−192 °C; ^{1}H NMR (250 MHz) δ 7.90 (s, 1 H), 7.52 (d, J = 7.2 Hz, 1 H), 7.31 (d, J = 7.4 Hz, 1 H), 7.21−7.09 (comp, 2 H), 5.90 (d, J = 4.4 Hz, 1 H), 5.04 (d, J = 10.3 Hz, 1 H), 4.27 (br s, 1 H), 3.71 (s, 3 H), 3.44 (d, J = 15.7 Hz, 1 H), 3.28 (br s, 1 H), 2.98 (ddd, J = 15.7, 6.0, 3.8 Hz, 1 H), 2.81−2.31 (comp, 5 H), 1.41 (d, J = 6.4 Hz, 3 H), 1.25 (s, 9 H); ^{13}C NMR (62 MHz) δ 172.6, 170.9, 170.0, 136.5, 131.5, 126.7, 122.3, 119.8, 118.3, 110.9, 107.1, 82.4, 70.7, 53.5, 51.7, 51.4, 50.6, 40.4, 36.7, 31.0, 27.8, 22.6, 21.3; IR (CH_2Cl_2) 3295, 2977, 1732, 1716, 1614 cm^{-1}; HRMS (CI) *m*/*z* 457.2327 [$C_{25}H_{33}N_2O_6$ (M + 1) requires 457.2339].

***tert*-Butyl (20*E*)-[3*S*-(3α,5*β*,15α)]-3,4,5,6,14,15-Hexahydro-15-methoxycarbonylmethyl-20-ethylidene-21-oxoindolo[2,3-*a*]quinolizine-5-carboxylate (27)**. A cold solution of freshly prepared 0.1 M NaOMe (20 mL, 2.09 mmol) was added to a flask containing crude alcohol **25** (288 mg, 0.63 mmol) at 0 °C. After 20 min the mixture was allowed to warm to room temperature and then heated at 50 °C for 1.5 h. The solution was recooled to 0 °C and acetyl chloride (0.54 mL, 7.6 mmol) was slowly added. After 30 min the mixture was allowed to warm to room temperature and stirred for a additional 2.5 h. Saturated $NaHCO_3$ (30 mL) and CH_2Cl_2 (30 mL) were added, and the organic layer was removed. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. The crude concentrate was purified by flash chromatography eluting with 30% EtOAc/hexane to give 239 mg (89%) of **27** as a colorless oil that formed a foam under vacuum: ^{1}H NMR (300 MHz) δ 7.89 (s, 1 H), 7.55 (d, J = 7.2 Hz, 1 H), 7.32 (d, J = 7.2 Hz, 1 H), 7.15 (comp, 2H), 6.87 (q, J = 6.1 Hz, 1 H), 5.81 (d, J = 4.4 Hz, 1 H), 4.88 (d, J = 10.5 Hz, 1 H), 3.68 (s, 3 H), 3.65 (d, J = 15.4 Hz, 1 H), 3.45 (br s, 1 H), 3.1 (dd, J = 5.9, 1.6 Hz, 1 H), 2.81−2.74 (m, 1 H), 2.63 (ddd, J = 16.3, 10.6, 3.5 Hz, 2 H), 1.85 (d, J = 7.3 Hz, 3 H), 1.75−1.65 (m, 1 H), 1.24 (s, 9 H); ^{13}C NMR (75 MHz) δ 172.3, 170.1, 168.5, 136.6, 135.9, 133.5, 132.2, 126.7, 122.0, 119.6, 118.0, 110.9, 106.6, 81.7, 52.0, 51.6, 49.5, 40.0, 36.8, 29.6, 27.8, 23.2, 14.0; IR (neat) 3268, 2976, 1732, 1652, 1608 cm^{-1}; HRMS (CI) *m*/*z* 439.2225 [$C_{25}H_{31}N_2O_5$ (M + 1) requires 439.2233].

(3*S*,5*R*,15*R*,20*E*)-*tert*-Butyl 3,4,5,6,14,15,21-Heptahydro-15-methoxycarbonylmethyl-20-ethylideneindolo[2,3-*a*]quinolizine-5-carboxylate (29). A slurry of **27** (0.843 g, 1.92 mmol) and trimethyloxonium tetrafluoroborate (0.752 g, 5.08 mmol) in CH_2Cl_2 (60 mL) containing 2,6-di-*tert*-butylpyridine (1.27 mL, 5.60 mmol) was stirred at room temperature for 22 h, during which time a homogeneous yellow solution was produced. The reaction mixture was cooled to 0 °C, and anhydrous MeOH (20 mL) was added. After 15 min, $NaBH_4$ (0.750 g, 19.8 mmol) was added, and the mixture was stirred at 0 °C for another 20 min. Saturated $NaHCO_3$ (50 mL) and CH_2Cl_2 (100 mL) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 60 mL). The combined organic fractions were dried ($MgSO_4$), and the solvents were removed under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (2:8→3:7) to give 0.75 g (92%) **29** as a foam: ^{1}H NMR (250 MHz) δ 8.37 (s, 1 H), 7.45 (d, J = 6.9 Hz, 1 H), 7.31−7.28 (m, 1 H), 7.13−7.02 (comp, 2 H), 5.42 (q, J = 6.8 Hz, 1 H), 4.64 (br s, 1 H), 3.71 (dd, J = 6.7, 4.6 Hz, 1 H), 3.65 (s, 3 H), 3.45 (br d, J = 12.1 Hz, 1 H), 3.31−3.01 (comp, 4 H), 2.36−1.99 (comp, 4 H), 1.61 (d, J = 6.8 Hz, 3 H), 1.34 (s, 9 H); ^{13}C NMR (62 MHz) δ 173.7, 171.8, 136.0, 135.8, 134.1, 127.5, 121.3, 120.8, 119.2, 117.9, 110.9, 105.4, 81.8, 61.2, 55.1, 51.7, 49.0, 38.0, 32.4, 31.8, 28.1, 21.9, 12.7; IR (neat) 3377, 2975, 1729 cm^{-1}; HRMS (CI) *m*/*z* 425.2431 [$C_{25}H_{33}N_2O_4$ (M + 1) requires 425.2440].

(3*S*,5*R*,15*R*,20*E*)-3,4,5,6,14,15,21-Heptahydro-15-methoxycarbonylmethyl-20-ethylideneindolo[2,3-*a*]quinolizine-5-carboxylic Acid (30) To a solution of the ester **29** (0.709 g, 1.67 mmol) and thioanisole (3.5 mL) in CH_2Cl_2 (4.0 mL) at 0 °C was added trifluoroacetic acid (4.0 mL), and the solution was then stirred at room temperature for 5 h. The volatiles were removed under vacuum, and the residue was purified by flash chromatography eluting with MeOH/CH_2Cl_2 (5:95→20:80) to give 0.752 g (93%) of **30** as a foam: ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.47 (d, J = 7.7 Hz, 1 H), 7.35 (d, J = 9.7 Hz, 1 H), 7.19−7.03 (comp, 2 H), 5.77 (q, J = 6.8 Hz, 1 H), 5.27 (br s, 1 H), 4.12 (br s, 1 H), 3.88 (AB q, J = 13.5 Hz, 2 H), 3.60 (s, 3 H), 3.54−3.31 (comp, 3 H), 2.49 (br s, 2 H), 2.36 (dd, J = 15.5, 7.6 Hz, 1 H), 2.10 (dd, J = 15.5, 7.9 Hz, 1 H), 1.70 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (62 MHz, MeOH-d_4) δ 173.6, 138.4, 131.0, 130.3, 128.5, 127.5, 123.6, 120.7, 119.2, 112.4, 105.5, 54.3, 53.6, 52.2, 37.4, 31.4, 28.0, 27.7, 21.6, 13.3; IR (neat) 3364, 3233, 2954, 1732, 1682, 1633 cm^{-1}; HRMS (CI) *m*/*z* 369.1799 [$C_{21}H_{25}N_2O_4$ (M + 1) requires 369.1814].

(3*S*,5*R*,15*R*,20*E*)-3,4,5,6,14,15,21-Heptahydro-15-methoxycarbonylmethyl-20-ethylideneindolo[2,3-*a*]quinolizine (2) To a solution of acid **30** (240 mg, 0.652 mmol) in anhydrous THF (25 mL) at −10 °C were added isobutyl chloroformate (0.10 mL, 0.771 mmol) and *N*-methylmorpholine (85 μL, 0.771 mmol). The reaction mixture was stirred at −10 °C for 15 min and at room temperature for 15 min, whereupon it was recooled to −10 °C. A solution of sodium phenylselenide in THF, which was prepared by reaction of benzeneselenol (82 μL, 0.771 mmol) and sodium hydride (32 mg, 60% dispersion in mineral oil, 0.80 mmol) in THF (10 mL) at 0 °C, was then added through a cannula. The resulting mixture was stirred at −10 °C for 20 min and at room temperature for 30 min. The volatiles were removed under reduced pressure, and the residue was dissolved in benzene (20 mL). Neat Bu_3SnH (0.70 mL, 2.60 mmol) and AIBN (20 mg, 0.12 mmol) were added, and the mixture was heated at 80 °C (oil bath temp) with stirring for 4 h. The solvents were removed under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexane (4:6) to give 167 mg (79%) of **2**, which gave spectroscopic data (^{1}H and ^{13}C NMR, IR, and MS) consistent with those reported in the literature.[16]

(3*S*,5*R*,15*R*,20*E*)-*tert*-Butyl *N*-Methyl-3,4,5,6,14,15-hexahydro-15-methoxycarbonylmethyl-20-ethylideneindolo[2,3-*a*]quinolizine-5-carboxylate (33). A mixture of the indole **27** (615 mg, 1.40 mmol), CH_3I (105 μL, 1.68 mmol), NaH (60% suspension in mineral oil, 67 mg, 1.68 mmol), and DMF (15 mL) was stirred at 0 °C for 3 h and then at room temperature overnight. H_2O (20 mL) was added, and the aqueous phase was extrated with CH_2Cl_2 (4 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The ^{1}H NMR spectrum of the crude product indicated a complete conversion to **32**. Hence, the residue was dissolved in CH_2Cl_2 (45 mL), and Me_3OBF_4 (627 mg, 4.20 mmol) and 2,6-di-*tert*-butylpyridine (1.04 mL, 4.62 mmol) were added. The reaction mixture was stirred at room temperature for 20 h and cooled to 0 °C. MeOH (15 mL) was added, and stirring continued for 15 min. $NaBH_4$ (530 mg, 14.0 mmol) was added and stirring was continued for 30 min. Saturated $NaHCO_3$ (aqueous, 20 mL) was added, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure, and the crude product was purified by flash chromatography on silica gel eluting first with hexane and then with EtOAc/hexane (50:50) to give 550 mg (90% over two steps) of **33** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.04 (comp, 4 H), 5.51 (q, J = 7.5 Hz, 1 H), 4.36 (dd, J = 4.1 Hz, 10.8 Hz, 1 H), 3.72 (d, J = 12.6 Hz, 1 H), 3.64 (s, 3 H), 3.61 (s, 3 H), 3.63−3.55 (comp, 2 H), 3.34 (quin,

J = 6.5 Hz, 1 H), 3.15−3.03 (comp, 2 H), 2.72 (dd, J = 7.2, 15.3 Hz, 1 H), 2.58 (dd, J = 8.4, 15.3 Hz, 1 H), 2.41−2.33 (m, 1 H), 1.70 (d, J = 6.3 Hz, 3 H), 1.59−1.50 (m, 1 H), 1.32 (s, 9 H);^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 172.6, 137.65, 137.0, 135.4, 126.6, 121.0, 120.9, 118.9, 117.9, 108.6, 104.8, 80.9, 60.4, 57.0, 51.5, 50.6, 40.1, 36.0, 31.8, 30.4, 28.1, 25.9, 13.0; IR (neat) 2922, 1731, 1470, 1368, 1152, 1011, 845 cm^{-1}; HRMS (CI) m/z 439.2604 [$C_{36}H_{25}N_2O_8$ (M + 1) requires 439.2597].

(3*S*,5*R*,15*R*,20*E*)-*N*-Methyl-3,4,5,6,14,15-hexahydro-15-methoxycarbonylmethyl-20-ethylideneindolo[2,3-*a*]quinolizine-5-carboxylic Acid (34). CF_3CO_2H (0.7 mL) was added dropwise to a stirred solution of the ester **33** (125 mg, 0.29 mmol) and thioanisole (0.6 mL) in CH_2Cl_2 (0.7 mL) at 0 °C. Stirring was continued for 3.5 h, while the solution was allowed to warm to room temperature. The solvents were removed under reduced pressure, and the residue was purified by flash chromatography on silica gel eluting with MeOH/CH_2Cl_2 (10:90) to furnish 100 mg (90%) of the acid **34** as a yellow solid: mp 170−171 °C (from CH_2Cl_2); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.40 (d, J = 7.8 Hz, 1 H), 7.34 (d, J = 8.1 Hz, 1 H), 7.10 (t, J = 7.8 Hz, 1 H), 6.99 (t, J = 7.8 Hz, 1 H), 5.46 (q, J = 7.0 Hz, 1 H), 4.37 (d, J = 10.8 Hz, 1 H), 3.81−3.74 (comp, 2 H), 3.66−3.52 (comp, 2 H), 3.60 (s, 3 H), 3.55 (s, 3 H), 3.27 (quin, J = 6.5 Hz, 1 H), 3.10−2.94 (comp, 2 H), 2.68−2.52 (comp, 2 H), 2.44−2.36 (m, 1 H), 1.64 (d, J = 6.9 Hz, 3 H), 1.58−1.48 (m, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.2, 172.2, 137.2, 134.7, 125.8, 120.9, 118.7, 117.7, 109.2, 104.1, 59.2, 56.3, 51.2, 50.3, 34.8, 31.3, 30.3, 24.8,12.8; IR (CH_2Cl_2) 3401, 2918, 1731, 1681, 1199, 1017, 748 cm^{-1}; HRMS (CI) m/z 383.1971 [$C_{22}H_{27}N_2O_4$ (M + 1) requires 383.1971].

(3*S*,5*R*,15*R*,20*E*)-*N*-Methyl-3,4,5,6,14,15-hexahydro-15-methoxycarbonylmethyl-20-ethylideneindolo[2,3-*a*]quinolizine-5-carboxamide (35). 1-Hydroxybenzotriazole (HOBt) (244 mg, 1.81 mmol) and EDCI (346 mg, 1.81 mmol) were added to a stirred solution of the acid **34** (276 mg, 0.72 mmol) in DMF (15 mL). The reaction mixture was stirred for 1 h, and NH_4OH (2 mL) was added. Stirring was continued overnight, whereupon brine (30 mL) and H_2O (5 mL) were added. The aqueous phase was extracted with EtOAc (3 × 20 mL), and the combined organic phases were dried ($MgSO_4$) and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel eluting with EtOAc to furnish 237 mg (86%) of the amide **35** as a white solid: mp 152−154 °C (from EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.06 (comp, 4 H), 6.47 (br s, 1 H), 5.82 (brs, 1 H), 5.55 (q, J = 7.0 Hz, 1 H), 4.25 (d, J = 8.4 Hz, 1 H), 3.64 (s, 3 H), 3.61 (s, 3 H), 3.60−3.49 (comp, 2 H), 3.41 (d, J = 12.3 Hz, 1 H), 3.29−3.33 (m, 1 H), 3.18 (dd, J = 5.5, 15.9 Hz, 1 H), 3.05 (dd, J = 7.2, 15.9 Hz, 1 H), 2.51 (dd, J = 5.4, 15.3 Hz, 1 H), 2.38 (dd, J = 9.3, 15.3 Hz, 1 H), 2.18 (ddd, J = 2.7, 8.4, 13.8 Hz, 1 H), 1.82−1.72 (m, 1 H), 1.70 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 172.7, 137.8, 135.4, 134.9, 126.2, 123.3, 121.5, 119.2, 118.2, 108.8, 105.2, 62.0, 56.7, 51.6, 51.0, 38.3, 34.0, 33.1, 30.3, 24.3, 13.2; IR (CH_2Cl_2) 2952, 2860, 1732, 1691, 1568, 1470, 1160, 1012 cm^{-1}; HRMS (CI) m/z 382.2140 [$C_{22}H_{28}N_3O_3$ (M + 1) requires 382.2131].

(3*S*,5*R*,15*R*,20*E*)-*N*-Methyl-3,4,5,6,14,15-hexahydro-15-methoxycarbonylmethyl-20-ethylideneindolo[2,3-*a*]quinolizine-5-cyanide (36). $(CF_3CO)_2O$ (133 μL, 0.94 mmol) was added to a stirred solution of **35** (180 mg, 0.47 mmol) and Et_3N (0.66 mL, 4.72 mmol) in CH_2Cl_2 (15 mL) at 0 °C, and the mixture was stirred for 75 min. The volatiles were removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel eluting with EtOAc/hexane (30:70) to give 155 mg (90%) of **36** as a pale yellow solid: mp 178−179 °C (from EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.08 (comp, 4 H), 5.23 (q, J = 6.7 Hz, 1 H), 4.03 (dd, J = 2.1, 5.1 Hz, 1 H), 3.84 (dd, J = 5.7, 10.5 Hz), 3.76 (dt, J = 2.1, 13.2 Hz, 1 H), 3.64 (s, 3 H), 3.63 (s, 3 H), 3.48 (d, J = 13.2, 1 H), 3.39−3.43 (m, 1 H), 3.24 (dd, J = 5.1, 15.3 Hz, 1 H), 3.06 (d, J = 15.3 Hz, 1 H), 2.77 (dd, J = 7.5, 15.3 Hz, 1 H), 2.68−2.55 (comp, 2 H), 1.70 (d, J = 6.7 Hz, 3 H), 1.60 (ddd, J = 2.7, 10.5 Hz, 12.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 137.9, 136.0, 133.5, 126.1, 121.6, 121.2, 119.3, 118.0, 117.3, 108.9, 103.7, 57.6, 51.5, 51.1, 50.8, 40.6, 35.9, 31.1, 30.4, 26.0, 12.9; IR (CH_2Cl_2) 2922, 1732, 1470, 1378, 1149, 742 cm^{-1}; HRMS (CI) m/z 364.2019 [$C_{22}H_{26}N_3O_2$ (M + 1) requires 364.2025].

(3*S*,5*R*,15*R*,20*E*)-*N*-Methyl-3,4,5,6,14,15-hexahydro-20-ethylidene-15-(2-hydroxyethyl)indolo[2,3-*a*]quinolizine-5-cyanide (38). $LiBH_4$ (8 mg, 0.38 mmol) was added to a stirred solution of **36** (20 mg, 0.06 mmol) in THF (8 mL). After 23 h, another portion of $LiBH_4$ (5 mg, 0.23 mmol) was added and stirring was continued for 20 h. Saturated aqueous $NaHCO_3$ (1 mL) and brine (1 mL) were then added, and the mixture was stirred for 15 min. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 2 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with Et_2O to yield 18 mg of **38** (98%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 7.8 Hz, 1 H), 7.26 (d, J = 7.8 Hz, 1 H), 7.21 (dt, J = 1.2, 8.4 Hz, 1 H), 7.11 (dt, J = 1.2, 7.4 Hz, 1 H), 5.55 (q, J = 7.8 Hz, 1 H), 4.01 (dd, J = 2.1, 5.1 Hz, 1 H), 3.87−3.72 (comp, 2 H), 3.66 (s, 3 H), 3.65−3.55 (m, 1 H), 3.48 (d, J = 16.2 Hz, 1 H), 3.23 (ddd, J = 2.1, 5.3 Hz, 15.0 Hz, 1 H), 3.16−3.00 (comp, 2 H), 2.58 (ddd, J = 5.4, 9.6, 12.9 Hz, 1 H), 2.14−2.02 (m, 1 H), 1.79−1.59 (comp, 2 H), 1.70 (dd, J = 1.2, 6.9 Hz), 1.63 (ddd, J = 2.7, 10.2, 10.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 136.2, 134.7, 126.2, 121.5, 120.9, 119.3, 117.9, 117.4, 108.9, 103.7, 61.3, 57.7, 51.2, 50.7, 39.1, 36.1, 31.1, 30.1, 25.9, 13.0; IR (neat) 3388 (br), 2920, 1470, 1378, 1326, 1150, 1055, 910, 7.39 cm^{-1}; HRMS (CI) m/z 336.2069 [$C_{21}H_{26}N_3O$ (M + 1) requires 336.2076].

(3*S*,5*R*,15*R*,20*E*)-*N*-Methyl-3,4,5,6,14,15-hexahydro-15-(2-oxoethyl)-20-ethylideneindolo[2,3-*a*]quinolizine-5-cyanide (39). Dess−Martin reagent (**34**, 0.08 mmol) was added to a stirred solution of the alcohol **38** (18 mg, 0.05 mmol) and pyridine (9 μL) in CH_2Cl_2 (4 mL) at 0 °C. The ice bath was removed, and stirring was continued for 40 min. Saturated aqueous $NaHCO_3$ (1 mL) and saturated aqueous $Na_2S_2O_3$ (1 mL) were then added, and the mixture was stirred for 10 min. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 2 mL). The combined organic phases were dried ($MgSO_4$) and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel eluting with EtOAc/hexane (30:70) to give 15 mg of **39** (83%) as a colorless foam: ^{1}H NMR (300 MHz, C_6D_6) δ 9.27 (s, 1 H), 7.50−7.48 (m, 1 H), 7.29−7.20 (comp, 2 H), 6.98 (d, J = 9.0 Hz, 1 H), 5.19 (q, J = 6.9 Hz, 1 H), 3.64 (m, 1 H), 3.67−3.20 (comp, 3 H), 3.08 (q, J = 7.7 Hz, 1 H), 2.80 (dd, J = 5.3, 15.6 Hz, 1 H), 2.72 (s, 3 H), 2.68 (d, J = 15.6 Hz, 1 H), 2.38 (ddd, J = 1.8, 6.8, 16.5 Hz, 1 H), 2.22 (dd, J = 7.2, 16.5 Hz, 1 H), 2.05 (ddd, J = 6.0, 9.0, 13.4 Hz), 1.48 (d, J = 6.9 Hz, 3 H), 1.19 (ddd, J = 2.1, 9.9, 13.4 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 199.8, 138.5, 136.1, 134.3, 126.8, 122.0, 119.8, 118.5, 117.1, 109.5, 104.1, 120.4, 57.8, 51.1, 51.0, 50.4, 36.0, 30.3, 28.0, 26.1, 12.9; IR (neat) 2919, 2818, 2731, 1720, 1470, 1377, 1327, 1149, 743 cm^{-1}; HRMS (CI) m/z 333.1838 [$C_{21}H_{23}N_3O$ (M + 1) requires 333.1841].

(+)-N_a-Methylvellosimine (5). The aldehyde **39** (5 mg, 0.015 mmol) was added to a suspension of NaH (60% suspension in mineral oil, 3.6 mg, 0.09 mmol) in THF (3 mL) at −78 °C. TBDMSCl (11.5 mg, 0.08 mmol) was then added, and the ice bath was removed. Stirring was continued for 45 min, and the reaction mixture was concentrated under reduced pressure to 0.5 mL. It was filtered through a plug of SiO_2 eluting with Et_2O/pentane (1:1), to give an inseparable diastereomeric mixture of **40** {HRMS (CI) m/z 448.2781 [$C_{27}H_{38}N_3OSi$ (M + 1) requires 448.2784]}. The E/Z ratio of 61:39 was determined from the ^{1}H NMR spectrum by integration of the signals for C17−H [6.34 (d, J = 12.0 Hz, 0.61 H, C17−H(E)), 6.07 (dd, J = 0.6, 5.7 Hz, 0.39 H, C17−H(Z))]. Freshly distilled BF_3·OEt_2 (4 μL, 0.030 mmol) was added to a solution of **40** (7 mg, 0.015 mmol) in degassed benzene (0.7 mL) and the reaction mixture was stirred at room temperature for 3.5 h. The volatiles were removed under reduced pressure, and MeOH (3 mL)

and aqueous KOH (0.5 M, 3 drops) were added. The solution was stirred for 24 h, the solvent was removed under reduced pressure, and CH_2Cl_2 (5 mL) was added. The mixture was dried ($MgSO_4$) and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/MeOH (9:1) to yield 1 mg (20%) of the aldehyde **39** and 2.5 mg (54%) of N_a-methylvellosimine (**5**) as a pale yellow solid. The TLC, ^{1}H and ^{13}C NMR, and MS of synthetic **5** were identical with that of an authentic sample of *ent*-**5** obtained from Prof. James M. Cook:[39] mp 236−240 °C (from $CHCl_3$); $[\alpha]^D_{20} = +91$ ($c = 0.10$, $CHCl_3$) {lit.[5] mp 255−260 °C; $[\alpha]^D_{20} = +23$ ($c = 0.01$, $CHCl_3$)}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (d, $J = 1.0$ Hz, 1 H), 7.47 (ddd, $J = 1.0$, 1.0, 7.5 Hz, 1 H), 7.30 (d, $J = 8.0$ Hz, 1 H), 7.20 (ddd, $J = 1.0$, 7.0, 8.0 Hz, 1 H), 7.09 (ddd, $J = 1.0$, 7.0, 7.5 Hz, 1 H), 5.36 (q, $J = 7.0$ Hz, 1 H), 4.27 (dd, $J = 2.5$, 10.0 Hz, 1 H), 3.67−3.60 (comp, 3 H, C5−H), 3.65 (s, 3 H), 3.19−3.21 (m, 1 H), 3.14 (dd, $J = 5.0$, 15.5 Hz, 1 H), 2.62 (dd, $J = 1.5$, 15.5 Hz, 1 H), 2.49 (d, $J = 7.5$ Hz, 1 H), 2.13 (ddd, $J = 2.0$, 9.5, 12.5 Hz, 1 H), 1.77 (ddd, $J = 2.0$, 4.0, 12.5 Hz, 1 H), 1.62 (dt, $J = 2.0$, 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 202.8, 137.4, 139.2, 134.4, 127.2, 121.1, 118.2, 119.0, 117.0, 108.8, 103.1, 54.9, 56.2, 50.6, 49.4, 32.4, 29.4, 26.6, 27.3, 12.6; IR (CH_2Cl_2) 2914, 2847, 1710, 1470, 1185, 1096, 752 cm^{-1}; HRMS (CI) *m*/*z* 307.1807 [$C_{21}H_{23}N_3O$ (M + 1) requires 307.1810].

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Supporting Information Available: Copies of ^{1}H NMR spectra of **35**, **36**, **38**, **39**, synthetic (+)-**5**, and synthetic (−)-**5** and X-ray data (CIF) for compound **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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