Applications of Vinylogous Mannich Reactions. Total Syntheses of the *Ergot* Alkaloids Rugulovasines A and B and Setoclavine

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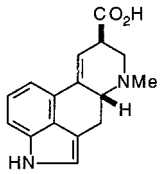
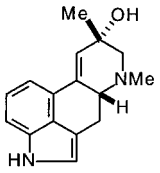
Abstract: Concise syntheses of the *Ergot* alkaloids rugulovasine A (**3a**), rugulovasine B (**3b**), and setoclavine (**2**) have been completed by strategies that feature inter- and intramolecular vinylogous Mannich reactions as the key steps. Thus, the first synthesis of **3a**,**b** commenced with the conversion of the known indole **17** into **24** via the addition of the furan **22** to the iminium ion **21**, which was generated in situ from the aldehyde **19**. Cyclization of **24** by a novel $S_{RN}1$ reaction followed by removal of the *N*-benzyl group furnished a mixture (1:2) of **3a** and **3b**. In an alternative approach to these alkaloids, the biaryl **35** was reduced with DIBAL-H to give an intermediate imine that underwent spontaneous cyclization via an intramolecular vinylogous Mannich addition to provide **36a**,**b**. *N*-Methylation of the derived benzyl carbamates **37a**,**b** followed by global deprotection gave a mixture (2:1) of rugulovasines A and B (**3a**,**b**). Setoclavine (**2**) was then prepared from the biaryl **41** using a closely related intramolecular vinylogous Mannich reaction to furnish the spirocyclic lactones **42a**,**b**. These lactones were subsequently transformed by hydride reduction and reductive methylation into the ergoline derivatives **43a**,**b**, which were in turn converted into **2** by deprotection and solvolytic 1,3-rearrangement of the allylic hydroxyl group.

Introduction

The indole alkaloids of the *Ergot* family have attracted the attention of synthetic chemists for decades.[1] Certainly the most well-known representative of this class is lysergic acid (**1**),[2,3] but other members have also played important roles on the stage of natural products chemistry. One such alkaloid is setoclavine (**2**), which is structurally related to **1**,[3,4] whereas the rugulovasines A and B (**3a**,**b**)[5,6] represent novel structural types within this family.



1



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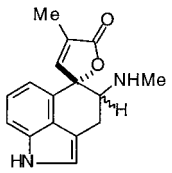
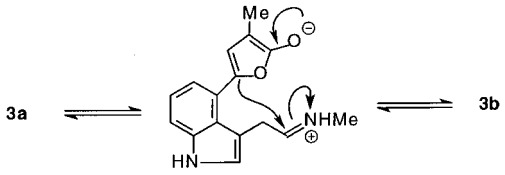


3a: β-H
3b: α-H

Most natural products are typically isolated as single enantiomers, but rugulovasines A and B were both isolated in racemic form, *and* they were observed to interconvert upon warming.[6] To account for these unusual facts, it was proposed that **3a** and **3b** underwent interconversion via the achiral intermediate **4** (Scheme 1). That this hypothesis was indeed feasible was later convincingly demonstrated by Rebek, who first prepared rugulovasine A in optically pure form and studied its equilibration to form a mixture of racemic **3a** and **3b**.[7]

Scheme 1



4

The cyclization of **4** to give either **3a** or **3b** constitutes one of the early examples of a class of carbon−carbon bond forming reactions that is generally known as the vinylogous Mannich reaction.[8] Various combinations of linear and cyclic iminium ions and enol derivatives may participate in vinylogous Mannich additions, and we have actively exploited such constructions in developing tactics and strategies for the concise syntheses of a

(1) For an excellent review of the *Ergot* alkaloids, see: Ninomiya, I.; Kiguchi, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, CA, 1990; Vol. 38, pp 1−156.

(2) For selected syntheses of lysergic acid, see: (a) Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc*. **1956**, *78*, 3087−3114. (b) Oppolzer, W.; Francotte, E.; Battig, K. *Helv. Chim. Acta* **1981**, *64*, 478−481. (c) Ninomiya, I.; Hashimoto, C.; Kiguchi, T.; Naito, T. *J. Chem. Soc., Perkin* Trans. *1* **1985**, 941−948. (d) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett*. **1988**, *29*, 3117−3120. (e) Saá, C.; Crotts, D. D.; Hsu, G.; Vollhardt, K. P. C. *Synlett* **1994**, 487−488.

(3) Rebek, J., Jr.; Tai, D. F.; Shue, Y.-K. *J. Am. Chem. Soc*. **1984**, *106*, 1813−1819.

(4) Kornfeld, E. C.; Bach, N. J. *Chem. Ind*. (*London*) **1971**, 1233−1234.

(5) Abe, M.; Ohmono, S.; Ohashi, T.; Tabuchi, T. *Agric. Biol. Chem*. **1969**, *33*, 469−471.

(6) Cole, R. J.; Kirksey, J. W.; Clardy, J.; Eickman, N.; Weinreb, S. M.; Singh, P.; Kim, D. *Tetrahedron Lett*. **1976**, 3849−3852.

(7) (a) Rebek, J.; Shue, Y.-K. *J. Am. Chem. Soc*. **1980**, *102*, 5426−5427. (b) Rebek J.; Shue, Y.-K.; Tai, D. F. *J. Org. Chem*. **1984**, *49*, 3540−3545.

(8) For reviews of the Mannich and vinylogous Mannich reactions, see: (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 1044−1070. (b) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev*. **2000**, *100*, 1929−1972. (c) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev*. **2000**, *29*, 109−118. (d) Bur, S. K.; Martin S. F. *Tetrahedron* **2001**, *57*, 3221−3242.

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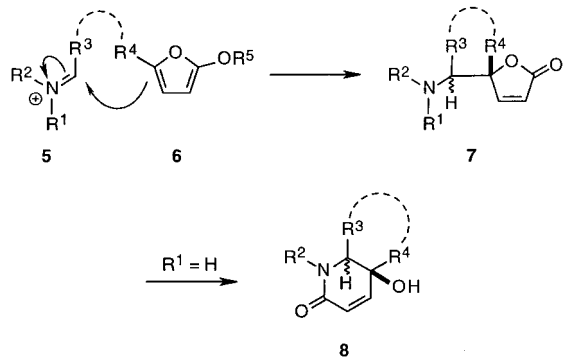
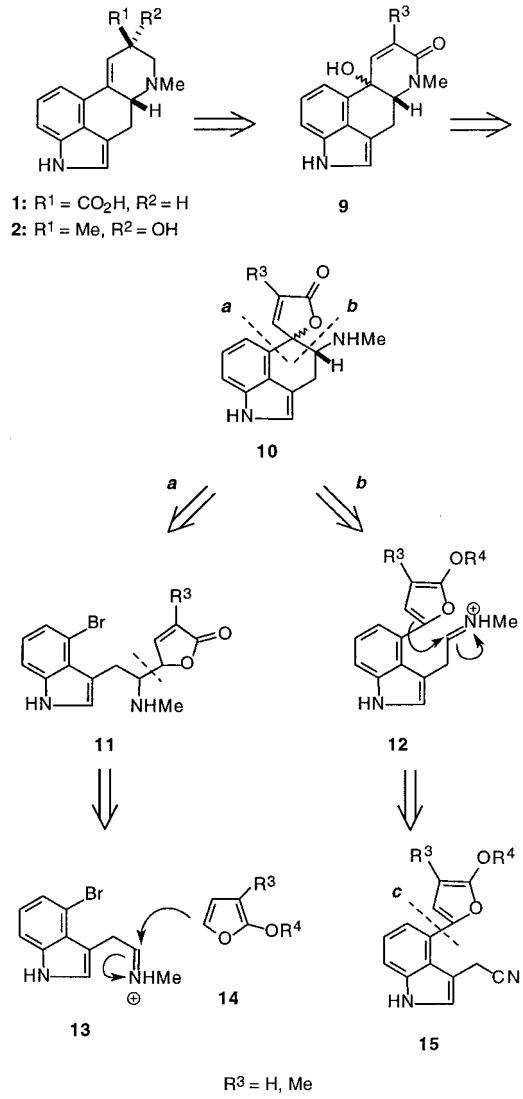
Scheme 2



Scheme 3



number of complex alkaloid natural products.[9] When 2-alkoxyfurans **6** are employed as the nucleophiles in additions to iminium ions **5**, aminoalkyl butenolides **7** are produced, and the two new stereocenters are often created with good diastereoselectivity (Scheme 2). Significantly, this type of vinylogous Mannich reaction leads directly to the molecular framework found in **3a**,**b** and other alkaloids containing derivatized butyrolactone rings as structural subunits. The transformation of the Mannich adducts **7** into hydroxy dihydropyridones **8**, or other substituted piperidines such as the one present in **4**, then requires a ring expansion that proceeds via an *O* → *N* acyl transfer. When the reacting partners in the vinylogous Mannich reaction are linked by joining R^3 and R^4, the spirobicyclic ring system **7** initially produced may be elaborated via a lactone−lactam rearrangement to give a fused nitrogen heterocycle **8**.

A combination of the efficiency and the stereoselectivity of vinylogous Mannich reactions ultimately determines their general utility in alkaloid synthesis. However, the stereochemistry of the addition is not a factor in applying this construction to the syntheses of the *Ergot* alkaloids because there is no 1,2-amino alcohol array in **1** and **2**, and *both* possible stereochemical relationships are found in the naturally occurring diastereomers **3a** and **3b**. Hence, we envisioned that a vinylogous Mannich addition might be advantageously employed as a key step in designing a novel and efficient entry to **3a**,**b** and **2** (Scheme 3).

The essence of the plan requires elaboration of the butenolide **10**, which corresponds to the rugulovasines A and B (**3a**,**b**) if R^3 = Me, into **1** and **2**. A pivotal intermediate in this sequence would likely be the lactam **9**, which could be generated from **10** by a lactone−lactam rearrangement. There are two reaction manifolds that can lead to **10**. The first of these involves cyclization of **11**, which in turn would be formed by the *inter*molecular vinylogous Mannich reaction of the iminium ion **13** and the silyloxy furan **14** (path ***a***). The second pathway features the *intra*molecular vinylogous Mannich reaction of **12** (path ***b***). A number of potential precursors of the iminium ion **12** may be formulated, but all require the intermediacy of a biaryl intermediate that is functionally related to **15**, which should be accessible via a palladium-catalyzed coupling reaction that would form bond ***c***. The reduction of this general plan to the total syntheses of rugulovasines A and B (**3a**,**b**) and setoclavine (**2**) constitutes the substance of this report.[10]

Intermolecular Vinylogous Mannich Approach to Rugulovasines A and B. The syntheses of **3a** and **3b** commenced with converting 4-bromoindole **16**[11] into the 3-indolylacetonitrile derivative **17** in 71% overall yield using a one-pot procedure that is a slight modification of known methods.[12] The indole nitrogen of **17** was then protected as a *tert*-butyl carbamate, whereupon the nitrile function was reduced using diisobutylaluminum hydride to give the aldehyde **19**, which was used without purification. If the indole N−H was not protected prior to hydride reduction, the resulting aldehyde was not particularly stable and decomposed quickly upon storage.[13] Although other carbamates could be introduced onto the indole, they were more readily cleaved in the hydride reduction step.

The stage was now set to examine the critical vinylogous Mannich reaction, but the initial experiments were somewhat

(9) For some examples, see: (a) Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161−6171. (b) Martin, S. F.; Corbett, J. W. *Synthesis* **1992**, 55−57. (c) Martin, S. F.; Clark, C. W.; Corbett, J. W. *J. Org. Chem.* **1995**, *60*, 3236−3242. (d) Martin, S. F.; Clark, C. W.; Ito, M.; Mortimore, M. *J. Am. Chem. Soc.* **1996**, *118*, 9804−9805. (e) Martin, S. F.; Bur, S. K. *Tetrahedron Lett.* **1997**, *38*, 7641−7644. (f) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990−6997. (g) Martin, S. F.; Bur, S. K. *Tetrahedron* **1999**, *55*, 8905−8914. (h) Martin, S. F.; Lopez, O. D. *Tetrahedron Lett.* **1999**, *40*, 8949−8953. (i) Martin, S. F.; Chen, K. X.; Eary, C. T. *Org. Lett.* **1999**, *1*, 79−81. (j) Bur, S. K.; Martin, S. F. *Org. Lett.* **2000**, *2*, 3445−3447.

(10) For a preliminary account of a portion of this work, see: Martin, S. F.; Liras, S. *J. Am. Chem. Soc.* **1993**, *115*, 10450−10451.

(11) 4-Bromoindole was prepared from 2-bromo-6-nitrotoluene. See: Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106−5110.

(12) (a) Somei, M.; Kizu, K.; Kunimoto, M.; Yamada, F. *Chem. Pharm. Bull.* **1985**, *33*, 3996−3708. (b) Patel, M. K.; Fox, R.; Taylor, P. D. *Tetrahedron* **1996**, *52*, 1835−1840.

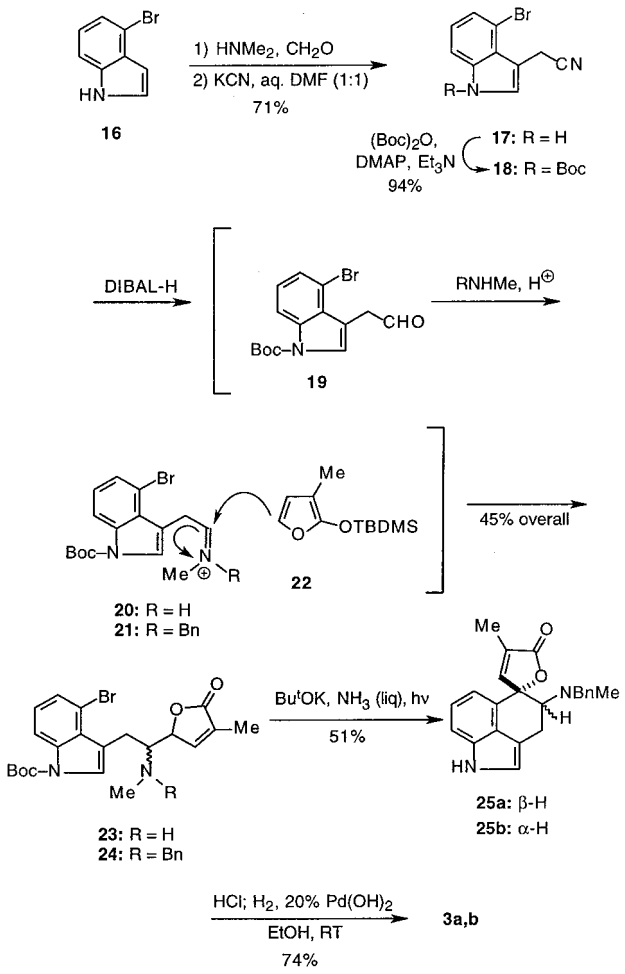
(13) For example, see: Burkard, S.; Borschberg, H.-J. *Helv. Chim. Acta* **1989**, *72*, 254−263.

discouraging. For example, when **19** was treated sequentially with methylamine and then the silyloxyfuran **22** under a variety of conditions, none of the desired adduct **23** was isolated. Aldimines derived from unhindered primary amines were known to be relatively unstable, so this result was not entirely surprising. We soon discovered that condensation of the crude aldehyde **19** with benzylmethylamine gave an intermediate enamine that underwent facile reaction with the silyloxyfuran **22** in the presence of camphorsulfonic acid to furnished a mixture (1:2) of diastereomeric adducts **24** in 45% overall yield from the nitrile **18**. Lewis acids were not found to be effective promoters of this vinylogous Mannich reaction that presumably proceeded via the iminium ion **21**.

With the aminoalkyl butenolides **24** in hand, the second key construction was at hand. The question now to be addressed was whether an intramolecular $S_{RN}1$ reaction could be used to create the hindered spirocyclic lactone moiety and to complete the construction of the rugulovasine skeleton. Such processes have enjoyed only limited application in the total synthesis of complex natural products,[14,15] and success was by no means assured. Nevertheless, we were delighted to discover that irradiation of **24** in refluxing ammonia in the presence of freshly sublimed potassium *tert*-butoxide proceeded smoothly to deliver an inseparable mixture (1:2) of *N*-benzyl rugulovasines A and B **25a**,**b** in 51% yield. The desired cyclization also proceeded fortuitously with concomitant removal of the *tert*-butyl carbamate group, thereby obviating the need for a separate deprotection step. Although we did not explore the mechanistic details to any great extent, the transformation **24** → **25a**,**b** appeared to occur by an $S_{RN}1$ mechanism, because several attempts to effect the cyclization in the absence of light under the typical reaction conditions required for aryne-type reactions (LDA, THF, −23 to 25 °C) did not provide any of the expected product.[16]

The final step of the synthesis required removal of the *N*-benzyl protecting group from **25a**,**b**, and this task proved to be more challenging than originally anticipated. Attempted debenzylation of **25a**,**b** under oxidative conditions[17] or using various chloroformates, including α-chloroethyl chloroformate and vinyl chloroformate,[18] either returned starting material or gave mixtures of products. At least part of the problem in this deprotection was attributed to the free indolic N−H in **25a**,**b** as the *N*-Boc derivative of **24** was readily debenzylated with 1-chloroethyl chloroformate in an exploratory experiment. However, reintroduction of an indolic nitrogen protecting group would have added steps to the synthesis and hence was not very appealing in the context of developing a concise approach to the target alkaloids. Eventually, we found that *N*-debenzylation of the hydrochloride salt of **25a**,**b** proceeded smoothly by hydrogenolysis using Pearlman's catalyst to give a mixture (1:2) of the rugulovasines A and B (**3a**,**b**) in 74% yield. The spectral characteristics of **3a** and **3b** were identical with those of authentic samples.[19]

Scheme 4



Intramolecular Vinylogous Mannich Approach to Rugulovasines A and B. Having demonstrated the viability of an intermolecular vinylogous Mannich reaction as a key step in the syntheses of the rugulovasines A and B, we were interested in examining the intramolecular variant that corresponded to the putative biomimetic pathway for their interconversion (Scheme 1). To establish the feasibility of inducing the key cyclization, a simple model study was first conducted. The stannyl furan **26** was prepared in 78% yield from commercially available 2-methoxyfuran. Coupling of **26** with the bromoindole **17** under Stille conditions afforded the biaryl **27**, *N*-protection of which gave **28** in 84% overall yield (Scheme 5). The original plan was to reduce the nitrile function of **28** to generate the aldehyde **29**, condensation of which with methylamine was then expected to give the imine **30** (R = Me) that would then undergo acid-catalyzed cyclization to furnish **31**. However, when **28** was treated with DIBAL-H and the reaction subjected to a standard aqueous workup, an unexpectedly facile intramolecular vinylogous aldol reaction occurred to give a mixture of the epimeric alcohols **32**; none of the expected aldehyde **29** was isolated.

The observation that rugulovasines A and B interconverted via reversible vinylogous Mannich reactions suggested that **32** might undergo a *reverse* vinylogous aldol reaction to give the aldehyde **29**. The question that naturally arose was whether the **29** thus produced might be trapped in situ with methylamine to give the imine **30** (R = Me), which could then cyclize spontaneously to furnish the desired **31**. However, reaction of **32** with methylamine under a variety of conditions afforded no detectable amounts of **31**.

(14) For a review of $S_{RN}1$ reactions, see: Norris, R. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 451−482.

(15) (a) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507−2516. (b) Goehring, R. R. *Tetrahedron Lett.* **1992**, *33*, 6045−6048.

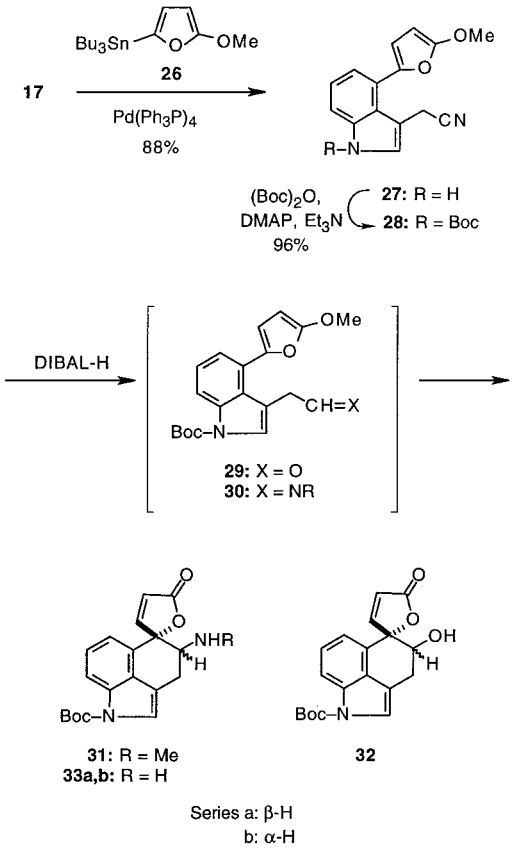
(16) Flann, C. J.; Overman, L. E.; Sarkar, A. K. *Tetrahedron Lett.* **1991**, *32*, 6993−6996.

(17) (a) Monkovic, I.; Wong, H.; Bachand, C. *Synthesis* **1985**, 770−773. (b) Gao, X.; Jones, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 1275−1278.

(18) For example, see: Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. J. *J. Org. Chem.* **1984**, *49*, 2081−2082 and references therein.

(19) We thank Professor Julius Rebek (The Scripps Research Institute) for spectra of rugulovasines A and B.

Scheme 5

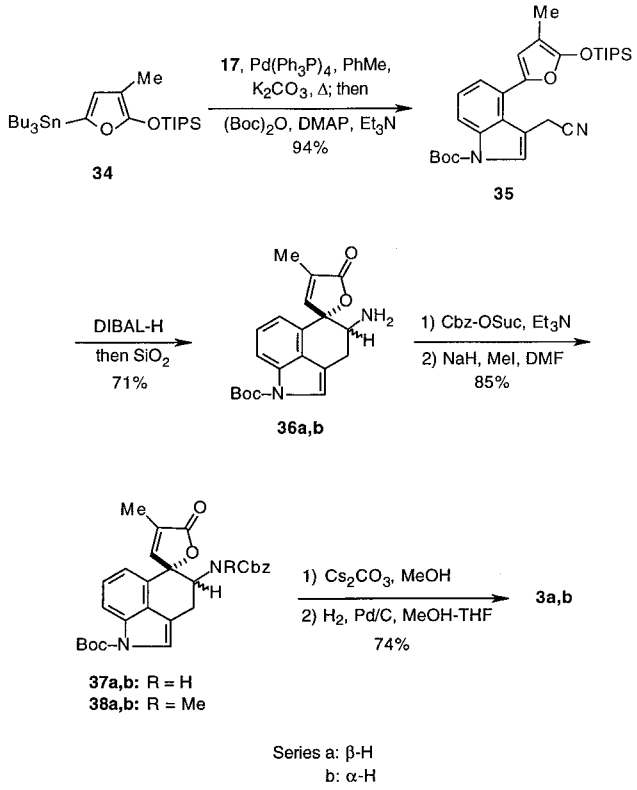


Owing to the facility with which the aldehyde **29** cyclized, it occurred to us that it might be possible to trap the intermediate imine **30** (R = H) that was first generated upon reduction of the nitrile group in **28**. After some experimentation, we found that reduction of **28** with DIBAL-H followed by the addition of *anhydrous* silica gel prior to aqueous workup furnished the vinylogous Mannich adduct **33** (R = H) as a mixture (ca. 2:1) of diastereomers in 77% yield. The established precedent for the rugulovasines to undergo reversible vinylogous Mannich reactions prompted us to expose **33** to excess methylamine in an attempt to prepare the *N*-methyl analogue **31** (R = Me). However, a number of preliminary experiments in which **33** was treated with methylamine were unavailing, and it was apparent that other tactics would ultimately have to be developed to introduce the *N*-methyl group required in the rugulovasines.

The discovery that hydride reduction of the nitrile group in **28** generated an imine that underwent spontaneous vinylogous Mannich reaction inspired a simple plan for the syntheses of the rugulovasines **3a** and **3b**. The furyl stannane **34**, which was obtained from 2-triisopropylsilyloxy-3-methylfuran[9f] by sequential metalation and stannylation with Bu_3SnCl, was coupled with **17** via a Stille reaction. It was necessary to conduct this Stille reaction in the presence of base to suppress protiodestannylation of **34**. When the Stille coupling was complete, the indole nitrogen was protected by simply adding $(Boc)_2O$, 4,4-(dimethylamino)pyridine (DMAP), and Et_3N directly to the reaction mixture to give **35** in 94% overall yield from **17**. Hydride reduction (DIBAL-H) of **35** followed by the addition of anhydrous silica gel and an aqueous workup then delivered a mixture (2:1) of diastereomeric adducts **36a**,**b** in 71% yield. Variable amounts (10−15%) of the adducts lacking the *N*-Boc group were also produced in this reaction.

Several methods for effecting the monomethylation of **36** in a single operation were explored, but the most efficient protocol

Scheme 6

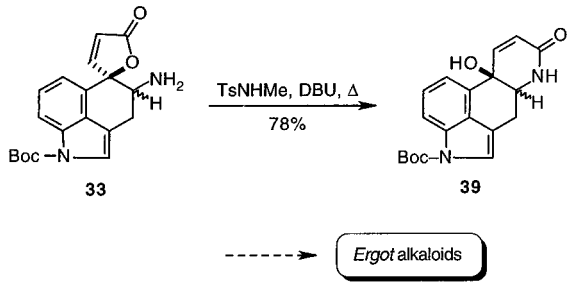


was ultimately found to be a stepwise one. Thus, reaction of **36a**,**b** with benzyl succinimidyl carbonate[20] gave a mixture of the carbamates **37a**,**b**, which were *N*-methylated under standard conditions to afford the protected rugulovasines **38a**,**b** in 85% overall yield. Global deprotection of **38a**,**b** using 30% HBr in HOAc gave **3a** and **3b** in a single operation, but the unoptimized yield was only about 50%. On the other hand, the two protecting groups could be removed sequentially to give a mixture (2:1) of **3a** and **3b** in 74% overall yield. The ordering in this deprotection sequence appeared to be critical as several attempts to remove the Cbz group first by hydrogenolysis were accompanied by variable amounts of over reduction and formation of the saturated butyrolactone. It is perhaps noteworthy that this second approach to the rugulovasines gave a mixture (2:1) of **3a** and **3b** in which **3a** was the major product, whereas the intramolecular $S_{RN}1$ reaction afforded a mixture (1:2) in which **3b** was the major product.

Synthesis of Setoclavine. The foregoing experiments clearly established the viability of both *inter*- and *intra*molecular vinylogous Mannich reactions to provide quick access to the rugulovasines A and B (**3a**,**b**). We then turned our attention to the associated question of whether it would be possible to convert the spirocyclic butyrolactone subunit found in **3a**,**b** into the fully fused tetracyclic ring system found in lysergic acid (**3**) and setoclavine (**2**) via a lactone−lactam rearrangement (cf. Scheme 1). Precedent for this key transformation may be found in a report by Rebek, who induced such an acyl transfer in a related dihydroindole system.[3] However, effecting the analogous conversion of **33**, which possesses an aromatic indole ring, into **39** proved to be more difficult than anticipated. After considerable experimentation, we discovered that heating **33** with *N*-methyl-*p*-toluenesulfonamide in the presence of DBU in a sealed tube gave the desired tetracycle **39** in 78% yield.[21] Unfortunately, despite numerous efforts, we have thus far been

(20) Paquet, A. *Can. J. Chem.* **1982**, *60*, 976−980.

Scheme 7



unable to convert compounds related to **39** efficiently into any of the naturally occurring *Ergot* alkaloids. Consequently, we elected to examine another tactic for transforming spirocyclic vinylogous Mannich adducts related to **33** into the fused ergoline ring system.

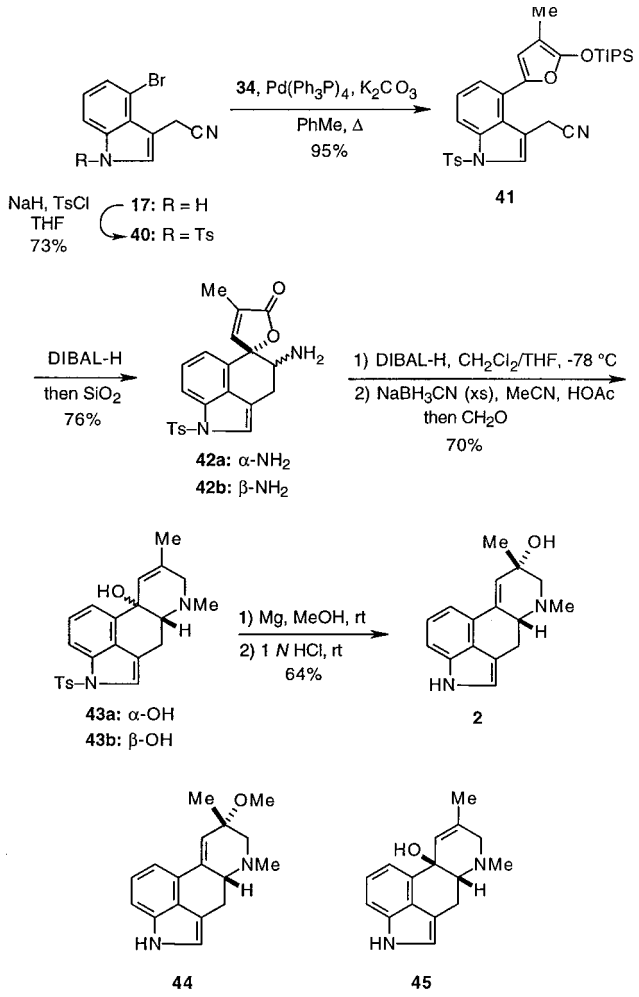
We had found that the indolic *N*-Boc protecting group was somewhat labile under the conditions required to transform **35** into **36a**,**b** via hydride reduction/vinylogous Mannich cyclization. Hence, to avoid adventitious *N*-deprotection during the synthesis of setoclavine, the bromoindole **17** was protected as its *N*-tosyl derivative **40** (73% yield). Starting **17** was invariably recovered in about 15−20% yield, but when the conditions were varied in attempts to force the reaction to completion, other side reactions intervened. The transformation of **40** into the biaryl intermediate **41** via a Stille reaction and the subsequent tandem hydride reduction/vinylogous Mannich reaction proceeded smoothly to give the spirocyclic butenolides **42a**,**b** in 76% overall yield. Reduction of **42a**,**b** with DIBAL-H provided an intermediate amino lactol that underwent facile isomerization and dehydration to generate a mixture of epimeric dihydropyridines. Although the two dihydropyridines could be separated by chromatography and characterized, they were routinely reduced with excess $NaBH_3CN$ in the presence of 38% aqueous formaldehyde to give a mixture of the diastereomeric amino alcohols **43a** and **43b** in 41% and 29% overall yields, respectively.

The *N*-tosyl protecting group was readily removed from **43a**,**b** by reduction with magnesium in MeOH. However, the diastereomeric alcohols thus produced underwent facile solvolysis and rearrangement, and setoclavine (**2**) was isolated as the major product. Two other products that were formed in this deprotection step were tentatively identified as the methyl ether **44** and the tertiary alcohol **45**. Armed with the knowledge that the acid-catalyzed rearrangements of compounds related to **44** and of **45** had been shown to give setoclavine,[3,22] we treated the crude mixture obtained upon deprotection of **43a**,**b** with aqueous acid and obtained setoclavine (**2**) in 64% overall yield; the setoclavine thus obtained gave spectral data identical with those reported.

Conclusions

Concise syntheses of the *Ergot* alkaloids rugulovasine A (**3a**), rugulovasine B (**3b**), and setoclavine (**2**) have been completed. The novel strategy that was developed for their syntheses featured inter- and intramolecular vinylogous Mannich reactions as key constructions. In the first approach to **3a** and **3b**, the intermolecular vinylogous Mannich addition of the furan **22** to the iminium ion **21** furnished **24**, thereby setting the stage for an unusual $S_{RN}1$ reaction that delivered a mixture of *N*-benzyl rugulovasines A and B; subsequent debenzylation afforded **3a** and **3b**. In the alternative approach to these alkaloids, the biaryl **35** was reduced with DIBAL-H to give an intermediate imine that spontaneously underwent an intramolecular vinylogous Mannich addition to provide a mixture of **36a**,**b** that was readily transformed into **3a** and **3b**. The related intramolecular vinylogous Mannich cyclization of **41** to give **42** was exploited as a pivotal step in the synthesis of setoclavine (**2**); the novel skeletal reorganization of **42** leading to **2** is also noteworthy. These syntheses of **2**, **3a**, and **3b** further establish the utility of vinylogous Mannich reactions for the preparation of complex alkaloid natural products, and other applications of these general processes to alkaloid synthesis are in progress, the results of which will be reported in due course.

Scheme 8



Selected Experimental Procedures

4-Bromo-3-[2-(2,5-dihydro-4-methyl-5-oxo-2-furanyl)-2-[methyl-(phenylmethyl)amino]ethyl]-1*H*-indole-1-carboxylic Acid, 1,1-Dimethylethyl Ester (24). A solution of DIBAL-H (3.2 mL, 1.0 M solution in CH_2Cl_2) was added dropwise to a solution of nitrile **18** (0.82 g, 2.45 mmol) in CH_2Cl_2 (25 mL) at −78 °C. The mixture was stirred at −78 °C for 45 min and then at room temperature for 5 h. Saturated aqueous Rochelle's salt (20 mL) was added, and the mixture was poured into saturated aqueous NH_4Cl (20 mL). After the mixture was stirred for 10 min, H_2O (20 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The

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combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give 0.75 g (91%) of crude **19** that was used in the next step without further purification.

A solution of benzylmethylamine (0.24 g, 2.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of crude **19** (0.75 g, 2.22 mmol) in CH_2Cl_2 (15 mL) at room temperature, and stirring was continued for 8 h. The solvents were removed under reduced pressure to afford the corresponding enamine (0.88 g, 1.99 mmol), which was immediately dissolved in benzene (4 mL) containing silyloxyfuran **22** (0.843 g, 3.98 mmol), and camphorsulfonic acid (0.463 g, 1.99 mmol). The resulting reaction was heated under reflux for 1 h and cooled to room temperature. EtOAc (20 mL) was added, the organic solution was washed with saturated aqueous $NaHCO_3$ (1 × 15 mL), and the aqueous layer was back-extracted with EtOAc (15 mL). The combined organic layers were washed with brine (2 × 15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography with hexanes/EtOAc (6:1) to afford 0.61 g (45% from **18**) of a diastereomeric mixture (2:1) of **24**. A small amount of the major component was separated by HPLC: ^{1}H NMR (300 MHz) δ 8.15 (d, J = 7.8 Hz, 1 H), 7.37 (s, 1 H), 7.29 (d, J = 7.8 Hz, 1 H), 7.2−7.0 (m, 7 H), 6.99 (s, 1 H), 5.27 (br s, 1 H), 3.85 (d, J = 13.9 Hz, 1 H), 3.62 (d, J = 13.9 Hz, 1 H), 3.58−3.45 (m, 1 H), 3.18−3.02 (m, 1 H), 2.37 (s, 3 H), 1.82 (d, J = 1.5 Hz, 3 H), 1.63 (s, 9 H); ^{13}C NMR (75 MHz) δ 174.6, 148.9, 148.1, 139.2, 137.1, 129.7, 128.4, 128.3, 128.1, 127.2, 126.8, 126.7, 125.0, 117.4, 114.5, 113.8, 84.1, 80.7, 64.1, 58.6, 38.1, 28.1, 22.3, 10.6; IR (CH_2Cl_2) 1754, 1753 cm^{-1}; mass spectrum (CI) m/z 541.1535 ($C_{28}H_{31}BrN_2O_4$ + H requires 541.1525), 441 (base), 230, 182.

***N*-Benzylrugulovasines A and B (25a,b).** To a solution of sublimed potassium *tert*-butoxide (84 mg, 0.75 mmol) in distilled NH_3 (24 mL) at reflux was added **24** (54 mg, 0.10 mmol). The resulting yellow-orange solution was then irradiated externally (Pyrex filter) with a Hanovia 450-W mercury lamp for 1.25 h. Solid NH_4Cl (50 mg) was then slowly added to the reaction mixture, and the ammonia was allowed to evaporate. EtOAc (25 mL) was added and the organic layer was washed with brine (2 × 5 mL). The aqueous layer was washed with EtOAc (2 × 10 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography with hexanes/EtOAc (3:1) to afford 18 mg (51%) of **25a** and **25b** as an inseparable (1:2) mixture: ^{1}H NMR (300 MHz) δ 8.00 (br s, 1 H), 7.31−7.04 (comp, 8 H), 6.97−6.37 (m, 1 H), 6.86 (d, J = 7.2 Hz, 0.66H), 6.70 (d, J = 7.2 Hz, 0.33 H), 3.85−3.59 (comp, 2 H), 3.51−3.12 (comp, 3 H), 2.40 (s, 1 H), 2.21 (s, 2 H), 2.11 (d, J = 1.3 Hz, 1 H), 1.87 (d, J = 1.3 Hz, 2 H); ^{13}C NMR (75 MHz) δ 175.1, 174.8, 151.3, 148.9, 139.8, 139.6, 134.1, 134.0, 130.3, 128.7, 128.6, 128.3, 128.2, 128.0, 126.9, 126.8, 125.9, 123.3, 122.9, 118.8, 118.5, 115.5, 114.1, 111.6, 110.8, 110.5, 88.7, 86.7, 67.5, 65.1, 60.2, 59.8, 39.8, 39.5, 29.7, 21.1, 19.1, 10.9, 10.7; IR (CH_2Cl_2) 1748, 1602 cm^{-1}; mass spectrum, m/z 358.1686 ($C_{23}H_{22}N_2O_2$ requires 358.1681), 105, 91 (base).

Rugulovasines A and B (3a,b). The hydrochloride salt of **25a,b** was prepared by adding ethanolic HCl to a solution of **25a**,**b** (20 mg, 0.056 mmol) in EtOH (0.3 mL) containing 20% $Pd(OH)_2$/C (15 mg). The resulting mixture was stirred under H_2 (1 atm) at room temperature for 9 h. The catalyst was removed by suction filtration through a pad of Celite, and the pad was washed with EtOH (2 mL). The combined filtrate and washings were concentrated under reduced pressure, and the residue was dissolved in EtOAc (10 mL). This solution was washed with saturated aqueous $NaHCO_3$ (10 mL), and the aqueous layer was back-extracted with EtOAc (2 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc to afford 11 mg (74% yield) of a mixture (1:2 by ^{1}H NMR) of rugulovasine A (**3a**) and rugulovasine B (**3b**). Pure samples of each were then obtained by repeated flash chromatography using EtOAc as the eluant.

For rugulovasine A (3a): ^{1}H NMR (300 MHz) δ 8.05 (br s, 1 H), 7.31 (d, J = 8.2 Hz, 1 H), 7.16 (d, J = 1.4 Hz, 1 H), 7.16 (t, J = 7.7 Hz, 1 H), 7.00 (br s, 1 H), 6.87 (d, J = 7.2 Hz, 1 H), 3.28 (dd, J = 14.8, 3.4 Hz, 1 H), 3.17 (dd, J = 7.5, 4.0 Hz, 1 H), 3.04 (dd, J = 15.1, 7.4 Hz, 1 H), 2.49 (s, 3 H), 2.05 (d, J = 1.4 Hz, 3 H); ^{13}C NMR (75 MHz) δ 174.4, 150.7, 134.1, 126.6, 126.5, 123.1, 119.4, 115.3, 111.4, 110.3, 88.5, 63.1, 35.1, 29.7, 25.4, 10.9.

For rugulovasine B (3b): ^{1}H NMR (300 MHz) 8.08 (br s, 1 H), 7.37 (br s, 1 H), 7.32 (d, J = 8.2 Hz, 1 H), 7.18 (t, J = 8.0 Hz, 1 H), 7.03 (br s, 1 H), 6.87 (d, J = 7.3 Hz, 1 H), 3.37−3.25 (m, 2 H), 3.05 (dd, J = 15.3, 6.4 Hz, 1 H), 2.46 (s, 3 H), 2.05 (d, J = 1.6 Hz, 3 H); ^{13}C NMR (75 MHz) δ 174.2, 150.9, 134.0, 129.4, 128.1, 123.2, 119.9, 114.9, 111.2, 109.1, 88.2, 63.6, 34.8, 29.7, 24.4, 10.8.

Tributyl(5-triisopropylsiloxy-4-methyl-2-furanyl)stannane (34). To a stirred solution of 3-methyl-2-triisopropylsilyloxyfuran[9f] (0.97 g, 3.8 mmol) and TMEDA (2.69 g, 3.5 mL, 23.1 mmol) in anhydrous hexane (40 mL) at −5 °C was added 1.1 M *sec*-BuLi in cyclohexane (3.6 mL, 3.6 mmol) over 10 min. After stirring for 6.5 h, freshly distilled Bu_3SnCl (1.29 g, 1.08 mL, 4.0 mmol) was added, and the reaction mixture was stirred for 18 h at −5 °C. The mixture was then concentrated under reduced pressure, and the residue was distilled under vacuum (240 °C Kugelrohr oven temperature, 0.2 mmHg) to afford a 2.03 g (94%) of **34** as a yellow oil: ^{1}H NMR (300 MHz) δ 6.29 (s, 1 H), 1.82 (s, 3 H), 1.60−1.48 (comp, 6 H), 1.35−1.19 (comp, 9 H), 1.09−0.85 (comp, 33 H); ^{13}C NMR (75 MHz) δ 157.4, 146.5, 126.5, 91.4, 29.0, 27.3, 17.6, 13.7, 12.4, 10.0, 8.4; IR ($CHCl_3$) 2957, 2927, 2869, 1651, 1487, 1464 cm^{-1}; mass spectrum (CI) m/z 542.2766 [$C_{26}H_{52}O_2Si^{118}Sn$ requires 542.2752], 544 (base), 542, 289, 255.

3-Cyanomethyl-1-[(4-methylphenyl)sulfonyl]-4-(4-methyl-5-triisopropylsiloxy-2-furanyl)-1*H*-indole (41). The bromide **40** (1.106 g, 2.843 mmol) was dissolved in degassed toluene (55 mL), and the furan **34** (2.007 g, 3.696 mmol), K_2CO_3 (393 mg, 2.843 mmol), and $Pd(PPh_3)_4$ (164 mg, 0.142 mmol) were added. The resulting mixture was heated under reflux for 3 h and then allowed to cool to room temperature. The solvent was removed under reduced pressure to give a residue that was purified by flash chromatography on silica gel eluting with 2:1 (v/v) hexanes/Et_2O to give nitrile **41** (1.512 g, 95%) as a pale yellow oil; ^{1}H NMR (250 MHz) δ 7.95 (d, J = 8.2 Hz, 1 H), 7.79 (d, J = 8.4 Hz, 2 H), 7.73 (s, 1 H), 7.33−7.17 (comp, 4 H), 6.16 (s, 1 H), 3.69 (d, J = 1.2 Hz, 2 H), 2.35 (s, 3 H), 1.89 (s, 3 H), 1.35−1.16 (m, 1 H), 1.06 (d, J = 6.7 Hz); ^{13}C NMR (75.5 MHz) δ 153.2, 145.3, 139.6, 135.9, 134.8, 130.0, 127.0, 125.7, 125.0, 125.3, 124.9, 124.6, 117.4, 113.7, 113.0, 112.1, 94.4, 21.5, 17.5, 16.4, 12.3, 8.6; IR ($CHCl_3$) 1600 cm^{-1}; mass spectrum (CI) m/z 563.2411 [$C_{31}H_{39}SSiN_2O_4$ (M + 1) requires 563.2400], (base), 313.

4-Amino-3,4-dihydro-4′-methyl-1-[(4-methylphenyl)sulfonyl]-spiro[benz[*cd*]indole-5(1*H*)-2′-[(5′*H*)-furan-5′-one]] (42a,b). To a cold (−78 °C) solution of the nitrile **41** (627 mg, 1.116 mmol) in CH_2Cl_2 (20 mL) was added a 1.0 M solution of DIBAL-H in CH_2Cl_2 (2.8 mL, 2.789 mmol). After the reaction was stirred at −78 °C for 45 min, the cooling bath was removed and the reaction was stirred at room temperature for 4 h. The reaction was diluted with CH_2Cl_2 (15 mL), and anhydrous (dried at 180 °C under high vacuum for 18 h) silica gel (ca. 10 g) was added in one portion under Ar at room temperature. The mixture was vigorously stirred for 5 min at room temperature, and then a saturated aqueous solution of Rochelle's salt (6 mL) was added. The mixture was stirred vigorously for 10 min, and the solids were then removed by vacuum filtration through a pad of Celite. The pad was washed successively with EtOAc (2 × 200 mL) and MeOH (50 mL). The combined filtrate and washings were dried (Na_2SO_4), and the solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with 9:1 (v/v) EtOAc/MeOH to give a mixture of **42a** and **42b** (345 mg, 76%) as a colorless oil: ^{1}H NMR (250 MHz, ∼2:1 mixture of diastereoisomers) δ 7.84 (d, J = 8.3 Hz, 0.67 H), 7.82 (d, J = 8.3 Hz, 0.33 H), 7.73 (d, J = 8.4 Hz, 0.67 H), 7.73 (d, J = 8.4 Hz, 0.67 H), 7.72 (d, J = 8.4 Hz, 1.33 H), 7.28−7.17 (comp, 4 H), 7.10 (s, 0.33 H), 7.03 (s, 0.67 H), 6.94 (d, J = 7.3 Hz, 1 H), 3.48 (dd, J = 8.9, 4.5 Hz, 0.33 H), 3.32 (dd, J = 8.5, 4.5 Hz, 0.67 H), 3.20 (dd, J = 16.5, 4.5 Hz, 0.33 H), 3.09 (dd, J = 15.6, 4.5 Hz, 0.67 H), 2.85 (dd, J = 15.6, 8.5 Hz, 0.67 H), 2.73 (dd, J = 16.5, 8.9 Hz, 0.33 H), 2.29 (s, 3 H), 1.99 (d, J = 1.2 Hz, 2 H), 1.95 (d, J = 1.4 Hz, 1 H); ^{13}C NMR (75.5 MHz, ∼2:1 mixture of diastereoisomers) δ 173.7, 149.2, 148.6, 145.0, 135.0, 133.3, 130.7, 129.9, 128.8, 128.6, 127.4, 126.8, 126.6, 125.8, 125.7, 121.1, 119.6, 118.5, 115.7, 114.2, 113.7, 87.8, 87.3, 54.8, 54.0, 28.5, 27.6,

21.4, 10.7; IR ($CHCl_3$) 1759 cm^{-1}; mass spectrum (CI) *m*/*z* 409.1227 [$C_{22}H_{21}SN_2O_4$ (M + 1) requires 409.1222], (base), 255.

8,9-Didehydro-6,8-dimethyl-1-[(4-methylphenyl)sulfonyl]ergoline-10-ol (43a,b). A 1.0 M solution of DIBAL-H in CH_2Cl_2 (420 μL, 0.420 mmol) was added dropwise to a solution of the butenolides **42a**,**b** (49 mg, 0.120 mmol) in THF (2 mL) at −78 °C. The reaction was stirred at −78 °C for 2 h, and MeOH (40 μL) was then added cautiously. The mixture was allowed to warm to room temperature, a saturated solution of aqueous NH_4Cl (4 drops) was added, and the mixture was then stirred vigorously for 30 min. The solids were removed by vacuum filtration, and the filtrate was concentrated under reduced pressure. The crude dihydropyridine thus obtained was immediately dissolved in CH_3CN (2 mL) under argon, and $NaCNBH_3$ (30 mg, 0.480 mmol) and AcOH (4 drops) were added. The reaction was stirred at room temperature for 2 h, whereupon a 38% aqueous solution of formaldehyde (6 drops) was added followed by further portions of $NaCNBH_3$ (30 mg, 0.420 mmol) and AcOH (4 drops). The reaction was stirred at room temperature for 14 h and then made basic with saturated aqueous $NaHCO_3$ (3 mL). The mixture was extracted with $CHCl_3$ (2 × 10 mL), and the combined extracts were washed with H_2O (5 mL) and saturated brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Although further purification of this residue was unnecessary for the next step, the diastereomeric alcohols could be separated and purified by flash chromatography on silica gel eluting with 11:1 (v/v) EtOAc/MeOH to give the more polar **43a** (20 mg, 41%) as pale yellow oil and its epimer **43b** (14 mg, 29%) as a pale yellow oil. For **43a:** ^{1}H NMR (500 MHz) δ 7.82 (dd, J = 8.2, 0.6 Hz, 1 H), 7.72 (d, J = 8.4 Hz, 2 H), 7.38 (d, J = 7.2 Hz, 1 H), 7.33−7.30 (m, 1 H), 7.22 (d, J = 2.0 Hz, 1 H), 7.16 (dd, J = 8.4, 0.6 Hz, 2 H), 6.34 (s, 1 H), 3.20 (d, J = 16.5 Hz, 1 H), 3.05 (dd, J = 14.7, 4.4 Hz, 1 H), 2.82−2.75 (comp, 2 H), 2.46 (dd, J = 12.0, 4.4 Hz, 1 H), 2.43 (s, 3 H), 2.31 (s, 3 H), 1.73 (s, 3 H); ^{13}C NMR (125.7 MHz) δ 144.7, 136.2, 135.5, 133.7, 132.1, 129.8, 129.1, 126.7, 125.4, 123.1, 119.9, 118.5, 117.7, 113.3, 67.0, 65.9, 61.0, 40.9, 21.5, 21.4, 20.5; IR ($CHCl_3$) 1601 cm^{-1}; mass spectrum (CI) *m*/*z* 409.1579 [$C_{23}H_{25}SN_2O_3$ (M + 1) requires 409.1586] (base), 391. For **43b**: ^{1}H NMR (500 MHz) δ 7.76 (dd, J = 8.0, 0.8 Hz, 1 H), 7.71 (d, J = 8.4 Hz, 2 H), 7.41 (d, J = 7.4 Hz, 1 H), 7.36−7.32 (m, 1 H), 7.17 (dd, J = 8.4, 0.6 Hz, 2 H), 7.14 (dd, J = 1.8 Hz, 1 H), 5.53 (s, 1 H), 3.09−3.04 (comp, 2 H), 2.93−2.88 (comp, 2 H), 2.58−2.52 (m, 1 H), 2.52 (s, 3 H), 2.31 (s, 3 H), 1.61 (s, 3 H); ^{13}C NMR (125.7 MHz) δ 144.7, 135.5, 135.5, 134.5, 133.1, 129.8, 128.0, 126.7, 126.5, 126.3, 119.9, 118.4, 117.3, 112.3, 70.1, 64.9, 52.8, 41.2, 21.5, 20.2, 14.8; IR ($CHCl_3$) 1602 cm^{-1}; mass spectrum (CI) *m*/*z* 409.1589 [$C_{23}H_{25}SN_2O_3$ (M + 1) requires 409.1586] (base), 391.

Setoclavine (2). A solution of the crude mixture of alcohols **43a**,**b** (20 mg, 0.049 mmol) in MeOH (1.5 mL) containing Mg powder (12 mg, 0.490 mmol) was stirred at room temperature for 1.5 h. The mixture was then acidified with 1 N HCl (aq) (2 mL). Saturated aqueous $NaHCO_3$ (5 mL) was then added, and the mixture was extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were washed with saturated brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with EtOAc/MeOH (5:1) to give setoclavine (**2**) (8 mg, 64%) as a white solid: mp 210−215 °C dec (lit.[23] mp 215−217 °C dec); ^{1}H NMR (500 MHz) δ 7.90 (br s, 1 H), 7.23−7.17 (comp, 3 H), 6.90 (t, J = 1.8 Hz, 1 H), 6.39 (s, 1 H), 3.53 (dd, J = 14.5, 5.7 Hz, 1 H), 3.06 (ddd, J = 11.5, 5.7 Hz, 1.8 Hz, 1 H), 3.01 (br s, 1 H), 2.80 (dd, J = 11.4, 1.3 Hz, 1 H), 2.68 (ddd, J = 14.5, 12.8, 1.8 Hz, 1 H), 2.56 (s, 3 H), 2.52 (d, J = 11.4 Hz, 1 H), 1.35 (s, 3 H); ^{13}C NMR (125.5 MHz) δ 135.9, 133.9, 127.7, 127.0, 126.6, 123.3, 118.3, 112.6, 110.8, 109.9, 66.6, 66.5, 63.3, 43.6, 27.2, 24.8; IR ($CHCl_3$) 3483 cm^{-1}; mass spectrum (CI) *m*/*z* 254.1411 [$C_{16}H_{18}N_2O$ (M) requires 254.1419], 237 (base), 154.

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Supporting Information Available: Experimental procedures and complete characterization (^{1}H and ^{13}C NMR, IR, and mass spectral data) for compounds **18**, **19**, **26**−**28**, **33a,b**, and **35**−**40** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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