Free Radical Cyclizations in Alkaloid Total Synthesis: (±)-21-Oxogelsemine and (±)-Gelsemine

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Abstract: Total syntheses of (±)-21-oxogelsemine (**3**) and (±)-gelsemine (**1**) are described. Free radical cyclizations play important roles in constructing the tricyclic core (**40** → **41**) and oxindole (**93** → **96**) substructures of the target alkaloids, and an isomerization−cyclization strategy (**101** → **102**) was used to complete construction of the gelsemine cage. Observations made along the way include intramolecular 1,4- and 1,6-hydrogen atom transfers (**64** → **65** and **40** → **47**) and a free radical cyclization-fragmentation sequence (**85** → **86** + **87**). A retroaldol−aldol strategy for adjusting oxindole stereochemistry in gelsemine-like structures is also described (**72** → **74** and **86** → **87**).

Introduction

Gelsemine (**1**) was first isolated as an amorphous base from the roots and rhizomes of *Gelsemium sempervirens* (Carolina jasmine) in 1870 by Wormley.[1,2] It was later obtained in crystalline form by Gerrard in 1883,[3] and its correct molecular formula was reported by Moore in 1910.[4] The exact nature of gelsemine, however, remained elusive until 1959 when independent reports of its structure appeared from the laboratories of Conroy and Wilson.[5,6] Structurally related alkaloids have been subsequently isolated from related plant sources (Figure 1). These include gelsevirene (**2**) and 21-oxogelsemine (**3**) from *Gelsemium sempervirens*,[7] gelsemine *N*-oxide, 19-(*S*)-hydroxydihydrogelsevirene, and 19-(*R*)-hydroxydihydrogelsevirine (**4**) from *Gelsemium elegans*,[8] and 21-oxogelsevirine, 19-(*R*)-acetoxydihydrogelsevirine (**5**), and 19-(*R*)-hydroxydihydrogelsemine (**6**) from *Gelsemium rankinii*.[7,9]

Soon after its structure was secured, reports describing synthetic approaches to gelsemine began to appear in the literature.[10−14] These studies resulted in the development of much interesting chemistry and synthetic methodology, and in 1994 two successful syntheses were finally described.[15,16] These successes were followed shortly by two other syntheses of

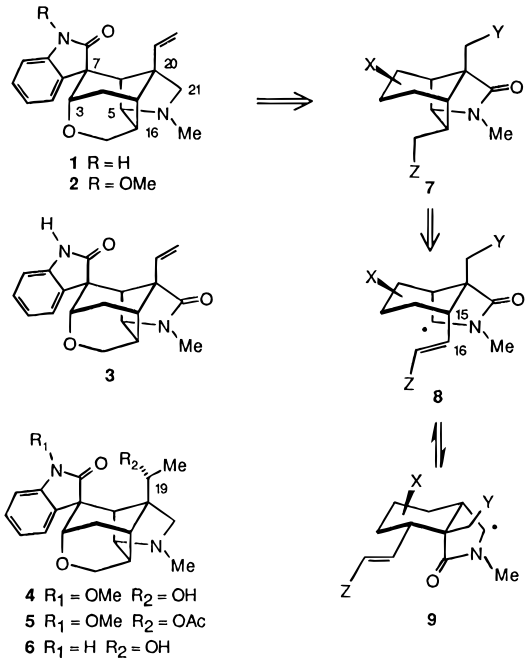

Figure 1.

[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1997.

(1) For reviews of literature related to *Gelsemium* alkaloids, see: Liu, Z.-J.; Lu, R.-R. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1988; Vol. 33, pp 83−140. Saxon, J. E. *Nat. Prod. Rep*. **1992**, 393.

(2) See: Saxton, J. E. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1965; Vol. 8, pp 93−117.

(3) Gerard, A. *Pharm. J.* **1883**, *13*, 641.

(4) Moore, C. W. *J. Chem. Soc.* **1911**, *99*, 1231.

(5) Conroy, H.; Chakrabarti, J. K. *Tetrahedron Lett.* **1959**, 6. For revisions of the NMR spectroscopic properties of gelsemine, see: Schun, Y.; Cordell, G. A. *J. Nat. Prod.* **1985**, *48*, 969.

(6) Lovell, F. M.; Pepinsky, R.; Wilson, A. J. C. *Tetrahedron Lett*. **1959**, 1.

(7) For isolation and structure of 21-oxogelsemine, see: Nikiforov, A. J.; Latzel, J.; Varmuza, K.; Wichtl, M. *Monatsh. Chem*. **1974**, *105*, 1292. For spectroscopic characterization of 21-oxogelsemine, see: Schun, Y.; Cordell, G. A.; Garland, M. *J. Nat. Prod.* **1986**, *49*, 483.

(8) Ponglux, D.; Wongseripipatana, S.; Subhadhirasakul, S.; Takayama, H.; Yokota, M.; Ogata, K.; Phisalaphong, C.; Aimi, N.; Sakai, S.-I. *Tetrahedron* **1988**, *44*, 5075.

(9) Lin, L.-Z.; Yeh, S.; Cordell, G. A.; Ni, C.-H.; Clardy, J. *Phytochemistry* **1991**, *30*, 679.

(10) Autrey, R. L., Tahk, F. C. *Tetrahedron* **1967**, *23*, 901. Autrey, R. L.; Tahk, F. C. *Tetrahedron* **1968**, *24*, 3337.

(11) Johnson, R. S.; Lovett, T. O.; Stevens, T. S. *J. Chem. Soc. (C)* **1970**, 796.

(12) Stork, G.; Krafft, M. E.; Biller, S. A. *Tetrahedron Lett.* **1987**, *28*, 1035.

(13) Fleming, I.; Loreto, M. A.; Michael, J. P.; Wallace, I. H. M. *Tetrahedron Lett.* **1982**, *23*, 2053. Fleming, I.; Loreto, M. A.; Wallace, I. H. M.; Michael, J. P. *J. Chem. Soc., Perkin Trans. 1* **1986**, 349. Clarke, C.; Fleming, I.; Fortunak, M. D.; Gallagher, P. T.; Honan, M. C.; Mann, A.; Nubling, C. O.; Raithby, P. R.; Wolff, J. J. *Tetrahedron* **1988**, *44*, 3931. Fleming, I.; Moses, R. C.; Tercel, M.; Ziv, J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 617.

(14) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem*. **1987**, *52*, 4133. Madin, A.; Overman, L. E. *Tetrahedron Lett*. **1992**, *33*, 4859. Early, W. G.; Jacobsen, E. J.; Meier, G. P.; Oh, T.; Overman, L. E. *Tetrahedron Lett*. **1988**, *29*, 3781. Earley, W. G.; Oh, T.; Overman, L. E. *Tetrahedron Lett*. **1988**, *29*, 3785. Overman, L. E.; Sharp, M. J. *J. Org. Chem*. **1992**, *57*, 1035.

(15) Sheikh, Z.; Steel, R.; Tasker, A. S.; Johnson, A. P. *J. Chem. Soc., Chem. Commun*. **1994**, 763. Dutton, J. K.; Steel, R. W.; Tasker, A. S.; Popsavin, V.; Johnson, A. P. *J. Chem. Soc., Chem. Commun.* **1994**, 765.

(16) Hiemstra, H.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem*. **1988**, *53*, 3884. Newcombe, N. J.; Ya, F.; Vijn, R. J.; Hiemstra, H.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun*. **1994**, 767.

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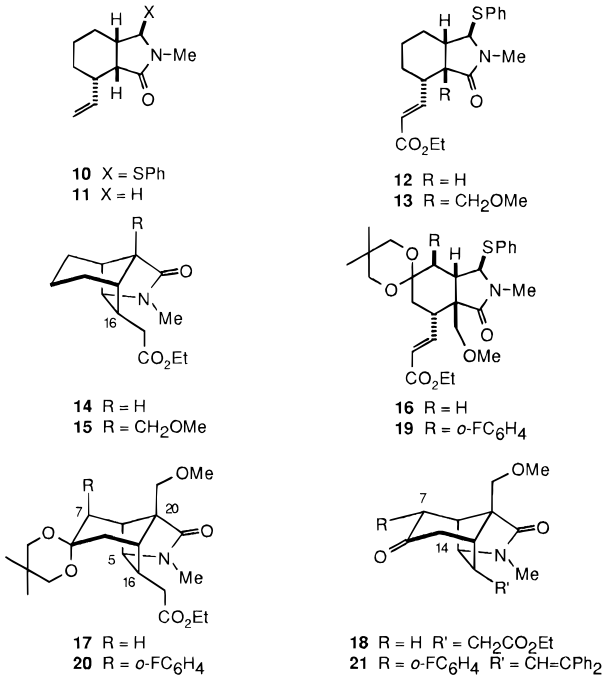


Figure 2.

gelsemine,[17,18] and it is likely that other quite different approaches will be completed before the close of this century.

Our own efforts toward gelsemine were initiated in 1984 to see if α-acylamino radical chemistry developed in our group could be used to solve what at the time was a classical unsolved problem in alkaloid synthesis.[19] Our synthetic plan was based on the belief that a tricyclic structure of type **7** could be converted into gelsemine if X, Y, and Z were designed to allow incorporation of the oxindole, the vinyl group, and the tetrahydropyran substructures of gelsemine, respectively (Figure 1). It was hoped that **7** might be prepared by 5-hexenyl radical cyclization of an α-acylamino radical of type **8**. One question associated with this plan was would the rate of cyclization of radical **8** be fast enough to compete with unproductive bimolecular processes that could occur from **9**, the expected lowest energy conformation of this free radical. Another question was would the cyclization provide the proper stereochemistry at what would become C(16) of gelsemine.

Initial Studies. A series of model studies revealed the path that was eventually followed to achieve a synthesis of gelsemine. The details of many of these studies have been described in an earlier full paper.[20] To provide continuity, however, a summary of these studies will be presented here (Figure 2). Initial work focused on the generation of **8** where X, Y, and Z were hydrogen atoms. This was accomplished by preparing sulfide **10** and treating it with tri-*n*-butyltin hydride and AIBN. Not surprisingly, this resulted in the formation of only reduction product **11** (90%), even under high dilution reaction conditions. It was hoped that rates of cyclization of more electron deficient olefins would be fast enough to compete with reduction. Thus, radical precursors **12** and **13** were prepared and subjected to typical free radical cyclization conditions. This plan was successful as cyclization products **14** and **15** were obtained in 68% and 92% yields, respectively. It is notable that these cyclizations provided the wrong stereochemistry at C(16), most likely due to allylic strain present in conformation **8** but absent in the conformation derived from a 180° rotation around the C(15)−C(16) bond.[21] This stereochemical mistake required development of a correction plan, which will be described in due course.

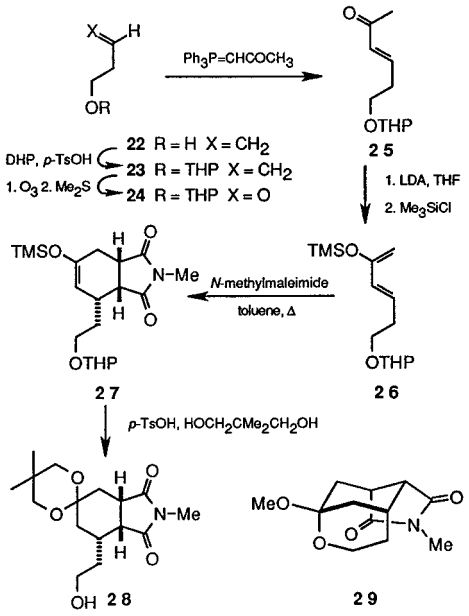
We next examined the radical derived from sulfide **16**.[22] This substrate contained a full complement of substituents needed to attempt a synthesis of gelsemine. Although we worried that the ketal might discourage cyclization for steric reasons, this was fortunately not the case as tri-*n*-butyltin hydride mediated cyclization of **16** provided **17** in 87% yield. Subsequent ketal hydrolysis afforded ketone **18** (85%).

As a final cyclization substrate, we examined sulfide **19**. We hoped that the *o*-fluorophenyl group could be used to install the oxindole portion of gelsemine using methodology developed by Fleming.[13] The stereochemistry at C(7) in **19** required that the aryl group occupy an axial site if the free radical cyclization occurred with the six-membered ring in a chair conformation. In spite of this demand, the radical derived from **19** cyclized to provide **20** in 40% yield along with 45% of the lactam derived from simple reduction of **19**. The structure of **20** was proven by X-ray crystallography.[23] The crystal structure interestingly revealed that the cyclohexane substructure of **20** adopts a boatlike conformation rather than the chairlike structure shown in Figure 2.[24] This boatlike conformation relieves steric interactions between the aryl group and the C(20)-methoxymethyl group and also the endo-oxygen of the ketal and the C(5) and C(16) hydrogens. Based on this result, we imagine that the radical derived from **19** cyclizes with the cyclohexane in a boatlike conformation. Treatment of **20** with excess phenyllithium followed by *p*-toluenesulfonic acid gave ketone **21** (74%) in which ketone hydrolysis was accompanied by epimerization at C(7). The preparation of **20** and **21** provided some insight into stereochemical aspects of the aforementioned cyclizations but did not ultimately lead to gelsemine, as several yields were too low and an inadequate supply of material prevented thorough investigation of its chemistry. Based on these problems and the serendipitous observation ketones of type **18** tend to enolize toward C(7) rather than C(14),[20] we focused on installation of the oxindole after construction of the tricyclic core of gelsemine. Preparation of a tricyclic core that was eventually used to prepare gelsemine is described below.

Preparation of Tricyclic Core Structures. Although neither were destined to be intermediates in the synthesis of gelsemine, tricyclic ketones **42** and **43** played important roles in accomplishing the synthesis. The preparation of these compounds is described in Schemes 1 and 2. The first key step in the synthesis of **42** and **43** was a Diels−Alder reaction between *N*-methylmaleimide and diene **26**. The diene was prepared on a 100-g scale from commercially available alcohol **22** in four steps (54% overall) as shown in Scheme 1 without comment.[25] Diene **26** was warmed with *N*-methymaleimide in toluene to provide cycloadduct **27**.[26] In early studies, the silyl enol ether and tetrahydropyranyl ether groups in cycloadduct **27** were hydrolyzed to give the corresponding keto alcohol, which was

(17) Kuzmich, D.; Wu, S. C.; Ha, D.-C.; Lee, C.-S.; Ramesh, S., Atarashi, S.; Choi, J.-K.; Hart, D. J. *J. Am. Chem. Soc.* **1994**, *116*, 6943.
(18) Fukuyama, T.; Liu, G. *J. Am. Chem. Soc.* **1996**, *118*, 7426.
(19) Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1982**, *104*, 1430.
(20) Choi, J.-K.; Ha, D.-C.; Hart, D. J.; Lee, C.-S.; Ramesh, S.; Wu, S. *J. Org. Chem.* **1989**, *54*, 279.
(21) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139.
(22) Experimental details for the preparation and cyclization of sulfide **19** are provided in the Supporting Information.
(23) The structures of **20**, **46**, **65a**, **70**, **74**, **90**, and **114** were determined by Dr. Judith C. Gallucci at the OSU Deparment of Chemistry Crystallography Facility. Crystallographic details for structures **46**, **114**, and two structures prepared *en route* to **20** are provided in the Supporting Information. Details for the other compounds will be reported elsewhere.[24]
(24) A comparison of solid state and solution conformational preferences of several compounds reported herein will be reported elsewhere.
(25) Although 3-buten-1-ol is commercially available, we found it convenient to prepare it using a variation of the following procedure: House, H. O.; Liang, W. C.; Weeks, P. D. *J. Org. Chem.* **1974**, *39*, 3104.

Scheme 1



then converted to ketal **28**. On a large scale, however, the hydrolysis step was accompanied by formation of significant amounts of ketal **29**. Thus, for operational reasons, it was easier to directly treat the crude cycloadduct **27** with 2 equiv of 2,2-dimethylpropan-1,3-diol and a catalytic amount of *p*-toluenesulfonic acid to provide **28** directly in 39% yield.

Conversion of **28** to **42** and **43** is described in Scheme 2. Formal dehydration of **28** following the Grieco protocol gave olefin **30** in 79% yield.[27] Reduction of the imide with sodium borohydride in methanol gave carbinol lactam **31** in 80% yield.[28] Initially, a hydroxy−ethoxy exchange in acidic ethanol was used to convert crude **31** to **32**. Ketal hydrolysis, however, caused problems when this procedure was conducted on a large scale. This problem was avoided by treating **31** with sodium hydride and iodoethane in tetrahydrofuran to afford a mixture of isomeric ethoxy lactams **32** (71%) and **33** (11%). Alkylation of the lithium enolate of **32** with either chloromethyl methyl ether or benzyl chloromethyl ether gave **34** (88%) and **35** (96%), respectively.[29] As previously reported, Johnson−Lemieux oxidation conditions were initially used to convert olefin **34** to aldehyde **36**.[30] This reaction proved to be capricious on a large scale, however, as epimerization of the aldehyde was often a problem. A workable alternative to the Johnson−Lemieux proved to be ozonolysis, followed by a reductive workup with dimethyl sulfide.[31] This provided crude **36** which was treated with ethyl (triphenylphosphoranylidene)acetate[32] to give crystalline unsaturated ester **38** in 96% overall yield. In a similar manner, ozonolysis of **35** provided **37** (76%), which was subjected to Wittig olefination to give ester **39** in 82% yield. Ethoxy−thiophenoxy exchange using thiophenol and catalytic *p*-toluenesulfonic acid in dichloromethane converted **38** and **39** into free radical precursors **16** (89%) and **40** (76%), respectively. The free radical cyclizations of **16** and **40** proceeded smoothly under standard tri-*n*-butyltin hydride-AIBN conditions to afford **17** and **41** in 87% and 64% yields, respectively. Finally, treatment of **17** and **41** with excess phenylmagnesium bromide gave tertiary alcohols that dehydrated upon treatment with *p*-toluenesulfonic acid in acetone, accompanied by ketal hydrolysis, to give tricyclic ketones **42** (54%) and **43** (87%).

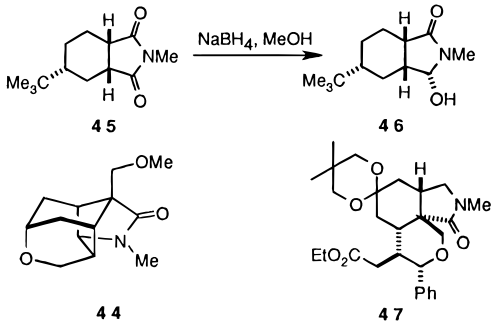


Figure 3.

At this point several tasks had to be accomplished to complete a synthesis of gelsemine. These included correction of the stereochemical mistake at C(16) and construction of the tetrahydropyran substructure, incorporation of the oxindole, and conversion of the C(20) substituent to a vinyl group. Model studies for accomplishing the first two tasks, using ketone **42** as a point of departure, have already been described (**42** → **44**).[20] Thus, reduction of the ketone using sodium borohydride provided the expected endo alcohol. Ozonolysis of the olefin provided a hydroxy aldehyde which epimerized to a tetracyclic hemiacetal upon treatment with DBU in dichloromethane. Reduction of the hemiacetal with triethylsilane−trifluoroacetic acid gave tetrahydropyran **44**. This epimerization−trapping strategy was developed fairly early in our studies, but it turned out that installation of the oxindole and applying the stereochemical correction protocol in the presence of the oxindole was quite difficult. Before continuing with the synthesis, however, several observations made during the course of preparing **42** and **43** will be described.

Some Observations. One notable step in Scheme 2 is the regioselective reduction of imide **30**. The reason for regioselectivity in this reduction is most likely due to stereoelectronic effects (Felkin−Ahn arguements) as nicely suggested by Speckamp and Hiemstra,[33] whose synthesis of gelsemine also used such a regioselective reduction. As part of our own studies designed to uncover the reasons for this selectivity, we prepared imide **45** and examined its reduction using sodium borohydride in methanol. This reduction was also highly regioselective, providing carbinol lactam **46** in 85% yield.[23,24] This result is consistent with the explanation advanced by Speckamp and Hiemstra and provides another example of stereoelectronic effects explaining regioselectivity in what to us was initially a non-obvious situation.

Another observation recorded while executing Scheme 2 was that the free radical cyclization of **41** gave compound **47** in 4−8% yields. The formation of this product can be explained by a sequence of events involving initial generation of an α-acylamino radical, 1,6-hydrogen atom transfer to provide a

(26) Although *N*-methylmaleimide is commercially available, we found it convenient to prepare for large scale work: Piutti, A.; Giustiniani, E. *Gazz. Chim. Ital.* **1896**, *26*, 431. Cava, M. P.; Deana, A. A.; Muth, K.; Mitchell, M. J. *Org. Synth.* **1961**, *41*, 93.

(27) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1975**, *30*, 3760. Sharpless, B. K.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947.

(28) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437. Chamberlin, A. R.; Chung, J. Y. L. *Tetrahedron Lett.* **1982**, *23*, 2619. Hart, D. J.; Yang, T.-K. *J. Chem. Soc., Chem. Commun.* **1983**, 135.

(29) For a preparation of benzyl chloromethyl ether, see: Connor, D. S.; Klein, G. W.; Taylor, G. N. *Org. Synth.* **1972**, *52*, 16.

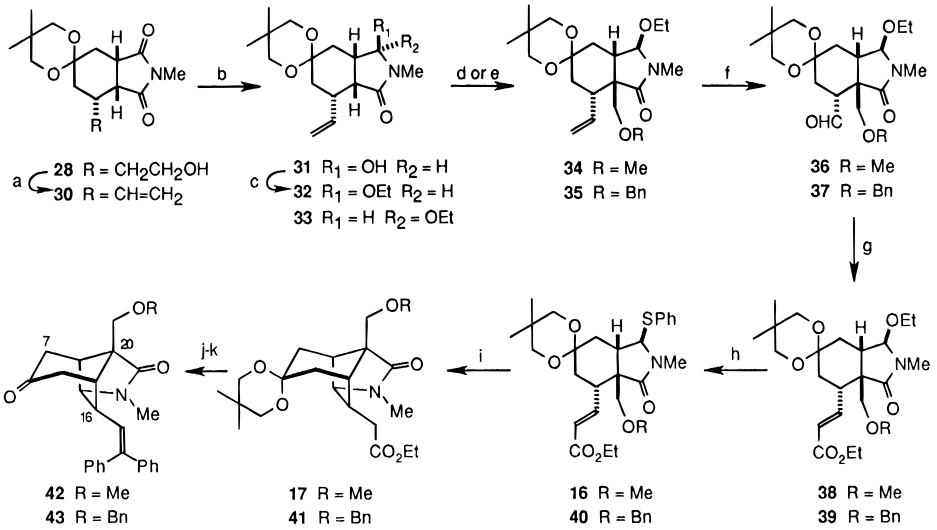
(30) Pappo, R.; Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

(31) For a convenient method for controlling selective ozonolysis of olefins see Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807.

(32) For the preparation of ethyl (triphenylphosphoranylidene)acetate, see: Denney, D. B.; Ross, S. T. *J. Org. Chem.* **1962**, *27*, 998.

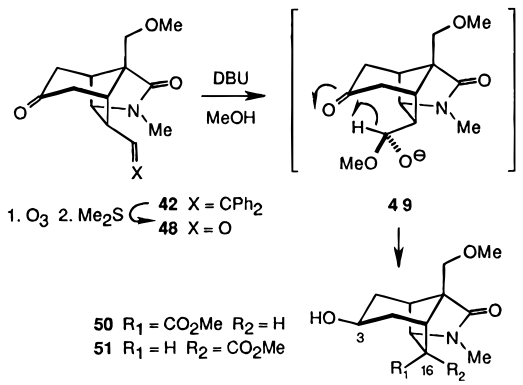
(33) Vijn, R. J.; Hiemstra, H.; Kok, J. J.; Knotter, M.; Speckamp, W. N. *Tetrahedron* **1987**, *43*, 5019.

Scheme 2[a]



[a] (a) *o*-$NO_2C_6H_4SeCN$, *n*-Bu_3P, THF; H_2O_2. (b) $NaBH_4$, MeOH, −23 °C. (c) NaH, THF, EtI. (d) LDA, THF; CH_3OCH_2Cl. (e) LDA, THF; $PhCH_2OCH_2Cl$. (f) O_3, CH_2Cl_2, MeOH; Me_2S. (g) $Ph_3P{=}CHCO_2Et$. (h) PhSH, *p*-TsOH (cat), CH_2Cl_2. (i) *n*-Bu_3SnH, AIBN (cat), PhH. (j) PhMgBr. (k) *p*-TsOH (cat), acetone, Δ.

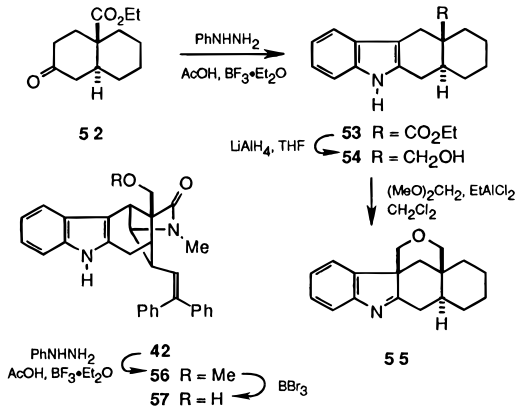
Scheme 3



benzylic radical (via a conformation of type **9**), and intramolecular addition of the benzylic radical to the unsaturated ester. It is interesting that a similar product was not observed in the cyclization of **16**, in which case a 1,6-hydrogen atom transfer would not have provided as stable a free radical.

A final interesting observation was recorded while trying to extend the epimerization−trapping procedure (**42** → **44**) to keto aldehyde **48**. For reasons that will become apparent, we hoped that treatment of **48** (prepared in 65% yield by ozonolysis of **42**) with methanol under acidic or basic conditions might lead to epimerization of the aldehyde followed by hemiacetal formation and attack at the ketone carbonyl group to form a cyclic hemiacetal at C(3). Unfortunately, treatment of **48** with acidic methanol gave only the dimethyl acetal of the aldehyde. Treatment of **48** with DBU in the presence of methanol, however, resulted in formation of a hydroxy ester in 58% yield. We initially thought this compound might have structure **50**, resulting from formation of **49** followed by an intramolecular hydride transfer (Scheme 3). This would have been fortunate, as reduction of the carbomethoxy group would have then provided a compound with a C(16)-hydroxymethyl group disposed in the manner needed to complete tetrahydropyran construction. However, NOE experiments revealed that the C(16) methyl ester had undergone a second isomerization and that the product was **51**. For example, irradiation of H(3) (δ 4.10) gave a 21% enhancement of the signal due to H(16) (δ 3.04). Obviously, adjustment of C(16) stereochemistry without a trap is not a favorable process.

Scheme 4



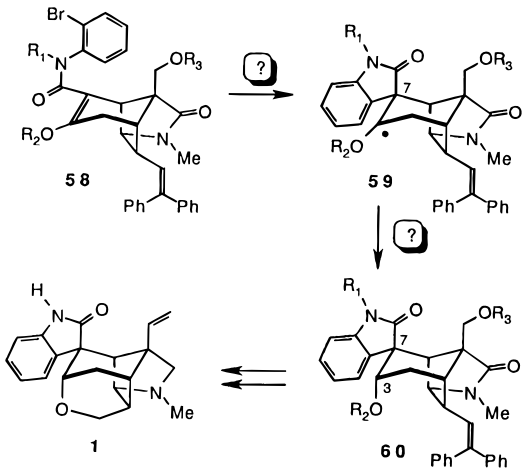
Introduction of the Oxindole: Initial Studies. As mentioned above, attempts to carry a portion of the oxindole through from the beginning of the synthesis were abandoned due to yield problems. A break came when it was observed that ketone **18** gave a good yield of the $\Delta^{3,7}$-*O*-methyl enol ether upon treatment with methanol, trimethylorthoformate, and catalytic *p*-toluenesulfonic acid. This result suggested that ketones **42** and **43** might also have a propensity for enolization toward C(7). Thus, strategies for introducing the oxindole that relied on such an enolization preference were investigated. Several unsuccessful routes were examined before achieving success. One of the more interesting dead-end routes is described in Scheme 4. We imagined that a Fischer indole synthesis would introduce a masked *o*-aminophenyl group at C(7).[35] If this could be followed by introduction of an appropriate one-carbon unit using a directed electrophilic aromatic substitution reaction, we thought the resulting indoline might be rearranged to a useful oxindole. This process was realized, in part, in a model system. For example, Fischer indole conditions converted ketone **52**[36] to indole **53** (80%). Reduction of the ester with lithium aluminum hydride gave **54** (91%) and treatment of **54** with dimethoxymethane and ethylaluminum dichloride produced

(34) We thank Dr. Jeffrey Dener and Mr. Jonathan Dawson for performing these experiments.

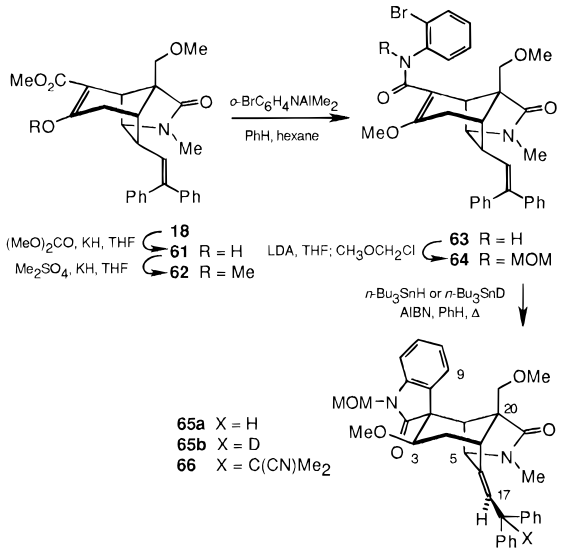
(35) Fischer, E.; Jourdan, F. *Chem. Ber.* **1883**, *16*, 2241. Sindwell, H. G.; van Orden, R. B. *Chem. Rev.* **1942**, *30*, 78.

(36) Dreiding, A.; Tomasewske, A. J. *J. Am. Chem. Soc.* **1955**, *77*, 411.

Scheme 5



Scheme 6



indoline **55** (59%). The first two steps of this process also worked well in a system relevant to gelsemine.[37] Thus, treatment of **42** with phenylhydrazine and boron trifluoride etherate in acetic acid gave the desired indole **56** (72%) and demethylation using boron tribromide gave **57** (88%). However, attempts to use the hydroxymethyl group to direct electrophilic aromatic substitutions with **56** met with failure, and this route was eventually abandoned.[22]

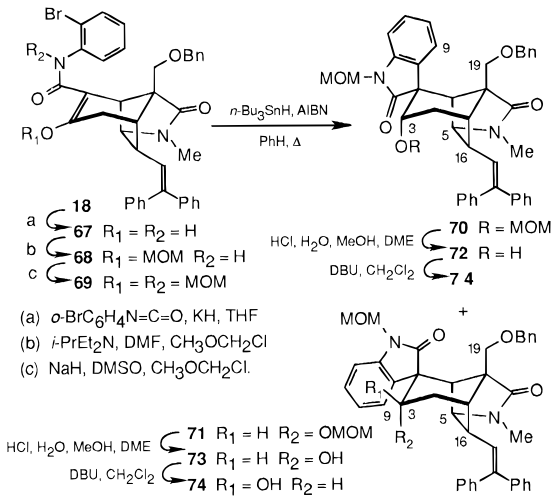
The plan that ultimately led to completion of the synthesis is shown in Scheme 5. It was imagined that free radical cyclization substrates of type **58** would be accessible from ketones **42** or **43**. We anticipated that application of a variant of an oxindole synthesis developed by Jones might then provide oxindole **60** via intermediate radical **59**.[39] It was originally thought that the success or failure of this plan would hinge upon obtaining the correct stereochemistry at C(7) in the cyclization of an aryl radical derived from **58** and at C(3) in the reduction of free radical **59**. We imagined that once a compound of type **60** was in hand, the chemistry developed to convert **42** to **44** would be used to complete the synthesis.

Aryl bromide **64** (**58** where R_1 = MOM, R_2 = R_3 = Me), the initial substrate selected for study, was prepared as outlined in Scheme 6. Treatment of **42** with potassium hydride and dimethyl carbonate gave **61** in 78% yield.[40] Conversion of **61** to vinylogous carbonate **62** was accomplished with use of potassium hydride and iodomethane or more conveniently by addition of hexamethylphosphorictriamide and dimethyl sulfate to the enolate formed in the acylation of **42**. The latter procedure gave **62** in 74% overall yield from **42**. Treatment of **62** with the amide derived from *o*-bromoaniline and trimethylaluminum,[41] followed by *N*-alkylation of the resulting amide **63** (83%) using lithium diisopropylamide and chloromethyl methyl ether, gave vinylogous urethane **64** (71%). When **64** was treated with 1.2 equiv of tri-*n*-butyltin hydride and 0.5 equiv of AIBN under high dilution conditions, oxindole **65a** was obtained in 46% yield along with two other unidentified products that contained oxindole substructures by NMR. The structure of **65a** was initially assigned on the basis of spectroscopic data. For example, the stereochemistry at C(3) was based on the appearance of H(3) as a doublet of doublets (J = 12, 6 Hz), an indication of an axial disposition for this proton. The stereochemistry of the olefin was assigned on the basis of NOE experiments that established the proximity of H(5) and H(17), and the stereochemistry at C(7) was based on NOE experiments that established the proximity of H(9) and the C(20)-methoxymethyl group. This structure was also confirmed by X-ray crystallography.[23] It is probable that **65a** was derived from cyclization of an aryl radical, followed by 1,4-hydrogen transfer to form a stabilized allylic radical, and subsequent reduction of that radical. In accord with this proposal, treatment of **64** with tri-*n*-butyltin deuteride gave only **65b** with no deuterium incorporation at C(3). Finally, one of the two unidentified products, which was clearly a 1:1 coupling product of **64** with an isobutyronitrile radical ($C_{40}H_{43}N_3O_5$ by HRMS), was tentatively assigned structure **66** (18%) based on spectroscopic data.

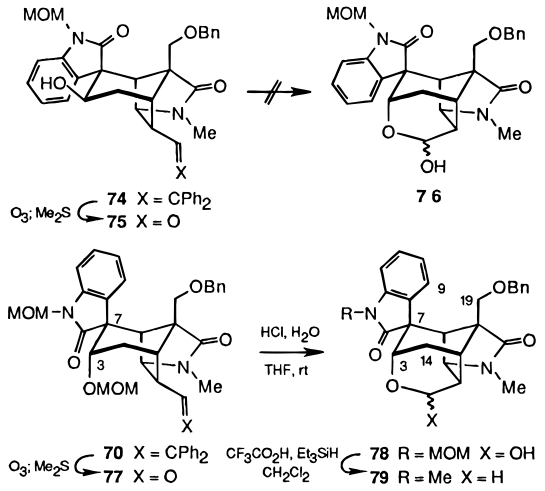
The results shown in Scheme 6 were simultaneously encouraging and discouraging. On the up side, an oxindole had been installed. On the down side, the stereochemistry at C(3) and C(7) was incorrect, and the handle for correcting the stereochemical mistake at C(16) had been destroyed. Nonetheless, it was hoped that the new stereochemical mistake at C(7) might be corrected by generating an alcohol at C(3) followed by a retroaldol−aldol condensation across the C(3)−C(7) bond. Thus, aryl bromide **69** (**58** where R_1 = R_2 = MOM, R_3 = Bn) was selected as the next substrate for study. The choice of protecting group at C(3) was based on the aforementioned need to generate an alcohol at C(3), and the change in protecting group in the C(20) substituent was based on the notion that a benzyl group would be more versatile than a methyl group. A streamlined approach to **69** is shown in Scheme 7. Acylation of **43** with *o*-bromophenylisocyanate[42] in the presence of potassium hydride gave **67** in 85% yield.[43] Proton NMR spectroscopy indicated this material existed completely as the enol tautomer in deuteriochloroform. Alkylation of **67** with chloromethyl methyl ether in the presence of Hunig's base in *N*,*N*-dimethylformamide first gave **68** (89%), which was followed by *N*-alkylation to give **69** (85%). The most interesting results with **69** were obtained when it was treated with an excess of tri-*n*-butyltin hydride and AIBN in a minimal amount of benzene. Under

(37) Hart, D. J.; Wu, S. C. *Heterocycles* **1993**, *35*, 135.
(38) Cronyn, M. W. *J. Org. Chem.* **1949**, *14*, 1013.
(39) Jones, K.; Thompson, M.; Wright, C. *J. Chem. Soc., Chem. Commun.* **1986**, *115*. Wright, C.; Shulkind, M.; Jones, K.; Thompson, M. *Tetrahedron Lett*. **1987**, *28*, 6389. Jones, K.; McCarthy, C. *Tetrahedron Lett*. **1989**, *30*, 2657.
(40) Ruest, L.; Blouin, G.; Delongchamps, P. *Synth. Commun*. **1976**, *6*, 169.
(41) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171.
(42) For a procedure for the preparation of 2-bromophenyl isocyanate using triphosgene, see: Eckert, H.; Forster, B. *Angew. Chem*. **1987**, *99*, 922.
(43) Hendi, S. B.; Hendi, M. S.; Wolfe, J. F. *Synth. Commun*. **1987**, *17*, 13. Brown, C. A. *J. Org. Chem*. **1974**, *39*, 1324.

Scheme 7



Scheme 8



these conditions, the α-alkoxy radicals derived from cyclization of an initially formed aryl radical were intercepted by the tri-*n*-butyltin hydride prior to 1,4-hydrogen atom transfer. This resulted in formation of isomeric oxindoles **70** and **71** in 28% and 9% yields, respectively. The structure of **70** was initially based on decoupling and NOE experiments and eventually confirmed by X-ray crystallography.[23] It is notable that the cyclohexane ring in **70** adopts a boatlike conformation both in the solid state and in solution.[24] The latter was evident from NOE studies that revealed the proximity of H(3) and one of the diastereotopic C(19) hydrogens. The structure of **71** was based on NMR spectroscopy and was proven by chemical correlation with **70** (*vide infra*). It is notable that H(5), H(9), and H(16) are shifted dramatically upfield in structure **71** compared to structure **70**. For example, H(9) in **71** is a doublet at 6.38 ppm, whereas there are no aromatic protons upfield of 6.88 ppm in **70**. This trend was general and proved useful in quickly determining oxindole stereochemistry for analogs of **70** and **71**.

Retroaldol−Aldol Approach to C(7) Stereochemistry. Although the yields of **70** and **71** were too low to be useful in a total synthesis, it was useful to know that reduction of the α-alkoxy radicals at C(3) gave the required stereochemistry at that center. This study also enabled examination of a retroaldol-aldol approach to adjusting the oxindole stereochemistry.[44] Thus, removal of the MOM protecting groups of **70** and **71** with aqueous hydrochloric acid in methanol−dimethoxyethane gave alcohols **72** (48%) and **73** (32%), respectively. When treated with DBU in dichloromethane at reflux for only 20 min, both **72** and **73** afforded isomeric alcohol **74** in 85% and 48% yields, respectively. The structure of **74** was consistent with spectroscopic data and was confirmed by X-ray crystallography.[23] This experiment showed that thermodynamics could be used to set the oxindole stereochemistry. It was also noted that warming **70** with hydrochloric acid in aqueous methanol at reflux for 15 h gave a mixture of **72** and **74**. Thus, it was also possible to effect the retroaldol−aldol process under acidic conditions, although the rate was slower than the base-induced isomerization.[45]

Since the C(7) stereochemical correction noted above was accomplished under the conditions used to correct the C(16) stereochemistry, it was hoped aldehyde **75** (prepared by ozonolysis of **74** in 59% yield) might isomerize to hemiacetal **76** under similar conditions. Unfortunately, treatment of **75** with DBU in dichloromethane gave only a complex mixture of products (Scheme 8). This result suggested that an equatorial C(3) hydroxyl group was not going to be useful for construction of the tetrahydropyran.

Since the retroaldol−aldol was slow in acid, it was decided to examine tetrahydropyran construction under such conditions. Ozonolysis of olefin **70** gave aldehyde **77** (65%). Treatment of **77** with hydrochloric acid accomplished hydrolysis of the methyoxymethyl ether and isomerization of the C(16) aldehyde to afford hemiacetal **78** in 54% yield. It is significant that hemiacetal formation occurred without isomerization at C(3) and C(7). The stereochemistry of the oxindole was confirmed by NOE studies. For example irradiation of H(9) showed 2%, 5%, and 9% enhancements at H(3), the axial H(14) proton, and H(19), respectively. Finally, treatment of **78** with triethylsilane and trifluoroacetic acid in dichloromethane gave tetrahydropyran **79** in 63% yield.[46] Reduction of the *N*-methoxymethyl protecting group was observed under these conditions, suggesting that the oxindole protecting group should be changed in subsequent studies or that the protecting group would have to be removed prior to hemiacetal reduction.

Observation of a Cyclization−Fragmentation. The cyclization of **69** did not supply enough **70** and **71** to make progress toward gelsemine. The major problem with the cyclization was the 1,4-hydrogen atom transfer (Scheme 6) which required that the cyclization be run at high concentrations, conditions not conducive to high yields. To deal with this problem, it was decided to postpone introduction of the diphenylethylene double bond until after the cyclization, hoping that this change would slow the rate of 1,4-hydrogen atom transfer. This plan was executed as shown in Scheme 9. Treatment of ester **41** with phenylmagnesium bromide gave carbinol **80** (87%). Alkylation of **80** using iodomethane and sodium hydride in dimethylsulfoxide afforded methyl ether **81** in quantitative yield. Ketal hydrolysis (**81** → **82**) was accomplished in 94% yield without elimination of methanol using *p*-toluenesulfonic acid in wet acetone. Ketone **82** was acylated with *o*-bromophenylisocyanate to give **83** (80%) which was converted sequentially to **84** and **85** in 84% overall yield.

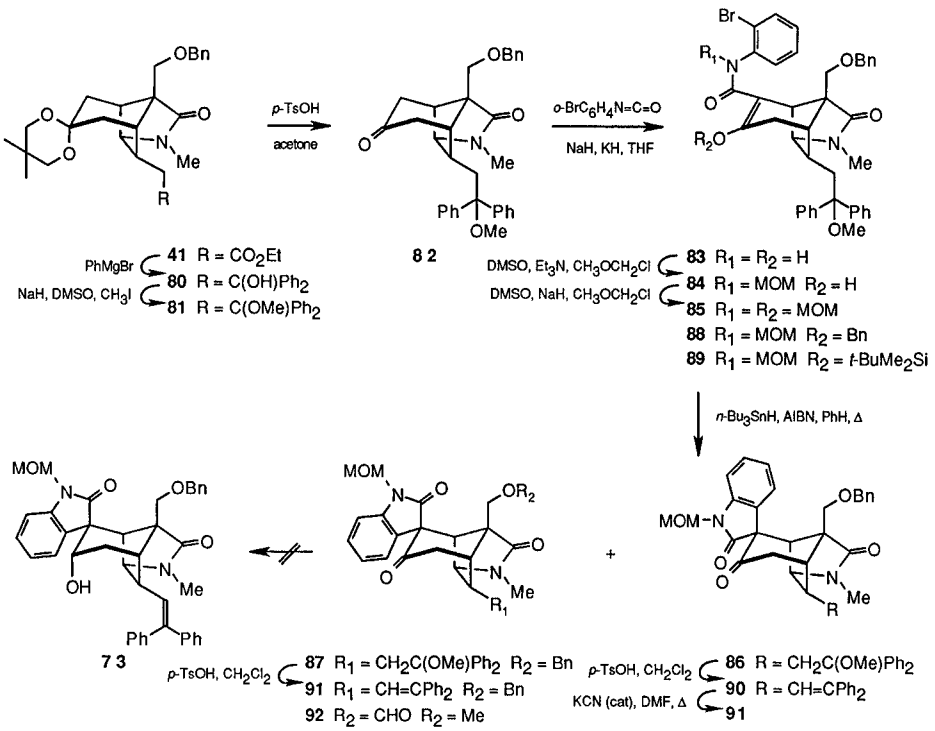
Tri-*n*-butyltin hydride mediated cyclization of **85** proceeded smoothly under high dilution conditions to afford a 55:45 mixture of oxindoles **86** and **87** in 83% combined yield. Pure samples of **86** and **87** could be obtained in diminished yield

(44) For another use of a retroaldol-aldol strategy to adjust stereochemistry, see: Hamelin, O.; Depres, J.-P.; Greene, A. E.; Tinant, B.; Declercq, J.-P. *J. Am. Chem. Soc.* **1996**, *118*, 9992.

(45) For model studies, see: Wu, S. C. Ph.D. Thesis, The Ohio State University, 1991.

(46) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633.

Scheme 9



only after a difficult separation on silica gel followed by a recrystallization. The increased yield in the cyclization was welcome, but formation of a C(3) ketone was a surprise. This product undoubtedly was the result of fragmentation of an intermediate α-alkoxy radical.[47] Thus, while the rate of 1,4-hydrogen atom transfer was slowed, another process reared its head. Several attempts to avoid the fragmentation failed. For example, benzyl ether **88** also underwent cyclization−fragmentation to provide a 1:1 mixture of **86** and **87** in 78% yield, and attempts to prepare silyl enol ether **89**, which was unlikely to undergo fragmentation, were unsuccessful.[48] It was possible, however, to apply the knowledge gained in the retroaldol−aldol studies to keto oxindoles **86** and **87**. Treatment of pure samples of **86** and **87** with *p*-toluenesulfonic acid in dichloromethane gave olefins **90** and **91** in 88% and 98% yields, respectively. The structure of **90** was established by X-ray crystallography,[23] and the structure of **91** was assigned on the basis of spectral data. Isomerization of **90** to **91** could be accomplished in 85% yield using a catalytic amount of potassium cyanide in *N*,*N*-dimethylformamide, presumably via one or the other of two retroacylation−acylation pathways. Operationally, the easiest way to prepare **90** was to convert the radical cyclization products (**86** + **87**) to a mixture of olefins (**90** + **91**) and then subject this material to the potassium cyanide mediated isomerization. In this manner, **91** could be prepared in 71% overall yield from **85**.

It was felt that if ketone **91** could be reduced to alcohol **73**, it might be possible to complete the construction of the gelsemine cage by sequential ozonolysis followed by epimerization-trapping of the resulting aldehyde. Unfortunately we were unable to accomplish the desired reduction. It was not surprising that reduction of **91** with sodium borohydride gave only equatorial alcohol **74**. It is probable that **73** was formed initially but simply isomerized to **74** under the basic reaction conditions. Attempts to reduce **91** under acidic conditions [for example, $NaBH_3CN$ at pH4 or $NaBH_4$/AcOH] or free radical conditions [for example $(TMS)_3SiH-AIBN$] failed to produce the desired products. In addition, aldehyde **92**, prepared in 67% yield by ozonolysis of the C(20)-methoxymethyl analog of **91**, did not undergo chemistry related to the conversion of aldehyde **48** to hydroxy ester **51** upon treatment with DBU in methanol. Only a complex mixture of unidentified products was obtained. Eventually this promising route was abandoned when another approach, being pursued simultaneously, proved successful.

Synthesis of the Gelsemine Cage. To overcome the problem of fragmentation of the C(3) α-alkoxy radical generated in the aryl radical cyclization, benzyl ether **88** and silyl enol ether **89** were selected for study. As mentioned above, **88** also underwent cyclization−fragmentation, and we were unable to prepare **89**. Promising results were eventually achieved using substrate **93**, which was prepared in 98% yield by treating **83** with acetic anhydride and triethylamine in the presence of 4-(dimethylamino)pyridine as shown in Scheme 10. Free radical cyclization of **93** provided three oxindoles, **94** (9%), **95** (7%), and **96** (42%).[49] The stereochemical assignments were based on treatment of pure samples of **94**−**96** with *p*-toluenesulfonic acid in dichloromethane followed by NOE studies on the resulting olefins **97** (44%), **98** (40%), and **99** (83%). Although we are still at a loss to explain why the various cyclization substrates gave different stereochemical results at the oxindole center, it was gratifying to find that **93** provided mainly the stereochemistry needed to proceed with the synthesis of gelsemine.

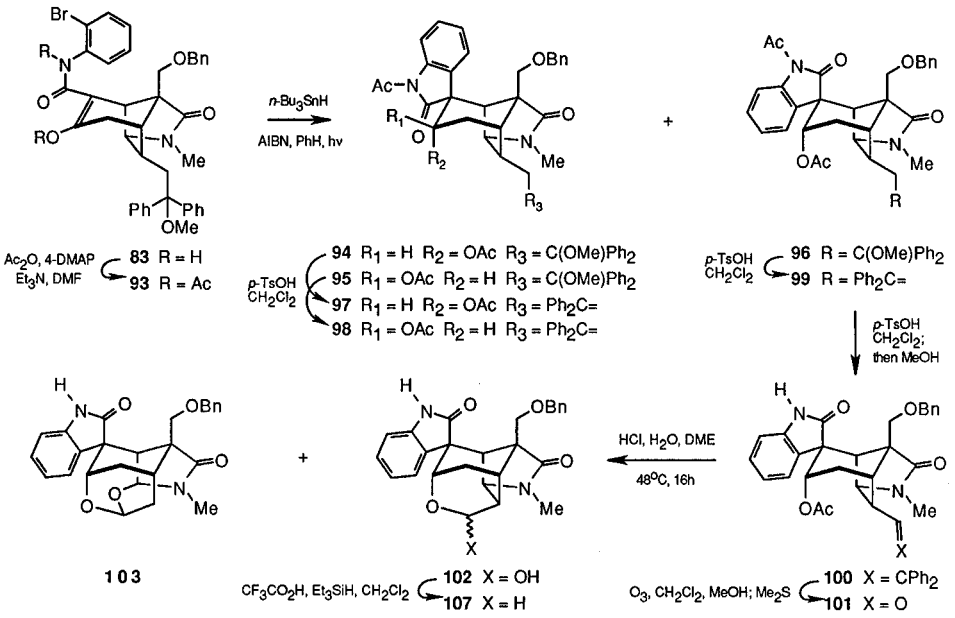
The synthesis of gelsemine was eventually accomplished from oxindole **96**. Treatment of this compound with *p*-toluenesulfonic acid in dichloromethane, followed by addition of methanol to the reaction mixture, effected sequential production of **99** and **100** in 93% overall yield. Ozonolysis of olefin **100** followed by a reductive workup gave aldehyde **101** in 65% yield, along with a compound resulting from epoxidation of **100**, as a single diastereomer, in 15% yield. Next, treatment of **101** with aqueous hydrochloric acid in dimethoxyethane at 48 °C

(47) Hart, D. J.; Kuzmich, D. *J. Chinese Chem. Soc.* **1995**, *42*, 873.

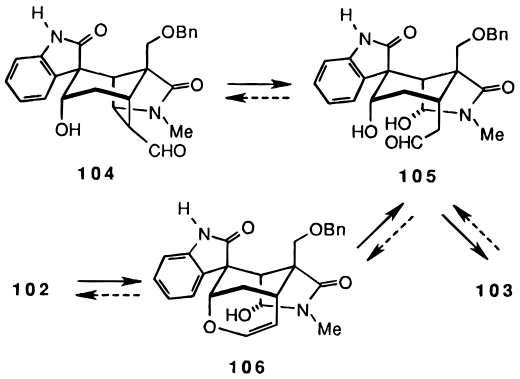
(48) The problems with silyl enol ethers were a surprise given our success with the preparation and cyclization of such compounds in a decalin model system.[45]

(49) Steglich, W.; Neises, B. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

Scheme 10



Scheme 11



for 18 h accomplished acetate hydrolysis and isomerization of the aldehyde to afford diastereomeric hemiacetals **102** (65%) and cyclic acetal **103** (14%). Initially this transformation was accomplished with tetrahydrofuran as the cosolvent. Due to the long reaction time required to hydrolyze the *O*-acetate, however, conversion of tetrahydrofuran to 4-chlorobutanol also occurred. The yield of **102** under these conditions was typically poor and may be attributed to 4-chlorobutanol reacting with either aldehyde **101** or hemiacetal **102**. Cyclic acetal **103** was an intriguing side product. Its structure was based on spectral analysis and mechanistic considerations. The mass spectrum indicated a parent ion at *m/z* 446, isomeric with hemiacetal **102**. One possible structure would be the product of acetate hydrolysis prior to formation of the hemiacetal; however, this structure was quickly ruled out since both the ^{1}H and ^{13}C NMR spectra indicated the absence of an aldehyde. The ^{1}H NMR also indicated a single isomer, and comparison of the ^{13}C NMR of **103** with hemiacetal **102** indicated a new triplet and one less doublet. These and other NMR data were consistent with proposed structure **103**. Furthermore, mechanistic considerations suggest that **103** might be formed under the reaction conditions. Construction of the C(5)−C(16) bond of gelsemine has been accomplished via acyliminium ion chemistry,[16] and thus, it seems reasonable that structure **103** could be derived from either **101** or **102** as outlined in Scheme 11. Acetate hydrolysis of **101** could be followed by a retro-Mannich reaction of the resulting alcohol **104** to give a structure of type **105**, which in turn could undergo intramolecular ketalization to afford **103**. Also possible, hemiacetal **102** could afford **106**, which could undergo enol ether hydrolysis followed by ketalization to afford **103**. Although the experiment was not performed, conversion of **102** to **103** could be confirmed by resubjecting pure **102** to the reaction conditions. It is noted that by thin-layer chromatography, it appeared that formation of cyclic acetal **103** occurred only after formation of **102**. Fortunately, the formation of **103** could be minimized with careful control of the temperature during the hydrolysis of **101**. With hemiacetal **102** in hand, treatment with triethylsilane and trifluoroacetic acid in dichloromethane afforded **107** in 83% yield.[46] A 15% NOE at H(5) upon irradiation of H(9), amongst other difference NOE experiments, clearly established that **107** was the intact gelsemine cage with the proper stereochemistry at C(7).

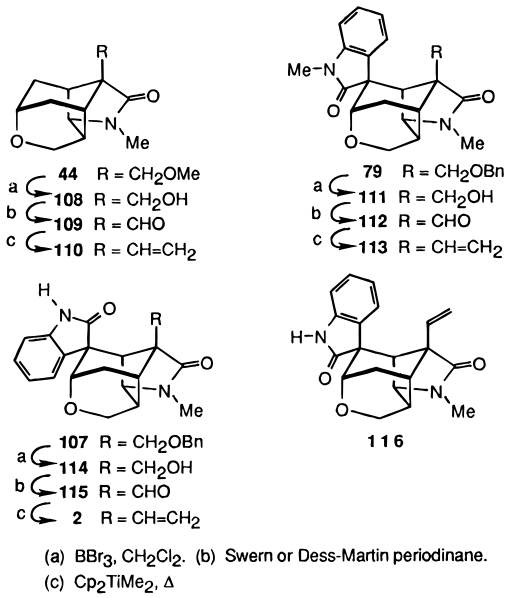
Introduction of the Vinyl Group and Completion of the Synthesis. The original plan for introduction of the C(20) vinyl group was to remove the benzyl ether protecting group, oxidize the resulting alcohol to the aldehyde, and conduct a Wittig olefination. The viability of a Wittig reaction as a final step in a synthesis of gelsemine had been demonstrated by Landeryon.[50] He had shown that protection of the oxindole portion of gelsemine as the *N*-benzyl derivative followed by oxidation of the C(20) vinyl group gave the noraldehyde of N_a-benzylgelsemine and a Wittig reaction with (methylidene)triphenylphosphorane gave N_a-benzylgelsemine in 46% yield. We first examined this approach on cage structure **44** (Scheme 12). Treatment of **44** with boron tribromide in dichloromethane gave alcohol **108** in 75% yield.[38] A Swern oxidation proceeded smoothly to afford aldehyde **109** in 92% yield.[51] Alternatively, the Dess−Martin periodinane gave aldehyde **109** in 80% yield.[52] Unfortunately, Wittig olefination of **109** was unsuccessful (*vide infra*), and, thus, other methods were explored. For example aldehyde **109** was treated with methylmagnesium bromide in diethyl ether to provide the corresponding secondary alcohol in 85% yield as a mixture of diastereomers. Dehydration of the resulting alcohol with Martin's sulfurane gave olefin **110** in quantitative yield.[53] Unfortunately, this addition−elimination sequence also failed to provide any 21-oxogelsemine when

(50) Landeryon, V. A. Ph.D. Thesis, University of Rochester, 1965; *Diss. Abstr.* **1965,** *26*, 2477.

(51) Mancuso, A. J.; Swern, E. *Synthesis* **1981**, 165.

(52) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

Scheme 12



applied to the relevant system (*vide infra*). It was suspected that either steric hindrance and/or neighboring group participation of the oxindole carbonyl group was causing the problems. Yet another olefination was examined using **109**. Treatment of **109** with bis(cyclopentadienyl)dimethyltitanium (Petasis' reagent)[54] in tetrahydrofuran at reflux gave **110** in 94% yield. At this point we proceeded cautiously and examined this olefination with a substrate derived from oxindole **79**. This substrate is sterically congested, but the oxindole is disposed such that neighboring group participation is not possible. Deprotection of the benzyl ether with boron tribromide gave alcohol **111** (72%), and Swern oxidation of the alcohol provided aldehyde **112** (86%). Olefination of **112** with dimethyltitanocene was successful as olefin **113** was obtained in 60% yield.

Application of this reaction sequence to **107** was successful. Treatment of the benzyl ether with boron tribromide gave alcohol **114** (95%) whose structure was confirmed by X-ray crystallography. Swern oxidation of **114** gave aldehyde **115** in only 50% yield, but this oxidation proceeded in 71% yield when the Dess−Martin periodinane was used. Finally treatment of **115** with Petasis' reagent in tetrahydrofuran at reflux gave (±)-21-oxogelsemine (**2**) in 87% yield. The ^{1}H and ^{13}C NMR of **2** were in agreement with reported data.[7] Furthermore a direct comparison with an authentic sample gave identical ^{1}H NMR and TLC results.[55] Since (±)-21-oxogelsemine has been converted to (±)-gelsemine (**1**) in a single step by the Johnson and Speckamp groups,[15,16] this synthesis of **2** also constitutes a synthesis of racemic gelsemine. Finally, we note that the seven-step reaction sequence for conversion of **96** to **2** was also used to prepared 7-*epi*-21-oxogelsemine (**116**) from oxindole **94**.

In summary, this route to 21-oxogelsemine (**2**) described herein requires 27 steps from 3-buten-1-ol, and the overall yield is 0.25%. These numbers compare favorably with the Johnson (27 steps from 2-phenylethanol and 0.26%) and Fukuyama (31 steps from methyl acetoacetate and 0.73%) syntheses but fall short of the Speckamp synthesis (19 steps from 3,5-hexadien-1-ol and 1.1%). Certainly more important, this research confirms that free radical cyclization strategies can be applied successfully to complex problems in alkaloid synthesis but also shows that our understanding of the stereochemical course of such reactions and competing radical reactions is not yet sufficient to preclude empirical examination of substituents in attempts to achieve a desired (or useful) reaction outcome. It is also hoped that several of the transformations uncovered herein (the conditions for direct carbamoylation of a ketone, the radical cyclization−fragmentation process, the epimerization strategies used to construct the tetrahydropyran and adjust oxindole stereochemistry) may find use elsewhere in complex molecule synthesis. Finally, we note that the chemistry of the gelsemine cage uncovered in this research suggests several shorter but high risk routes to gelsemine that might be interesting to explore.

Experimental Section

All melting points are uncorrected as are all boiling points. Proton nuclear magnetic resonance spectra are recorded in parts per million from internal chloroform, benzene, or dimethylsulfoxide on the δ scale and are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, m = multiplet), coupling constants in hertz, integration]. ^{13}C NMR data are reported as follows: chemical shift (multiplicity determined using DEPT experiments). Mass spectra were using an ionization energy of 70 eV unless stated otherwise. Solvents and reagents were dried and purified prior to use when deemed necessary; benzene, diethyl ether, THF, and toluene were distilled from sodium metal; dichloromethane was distilled from calcium hydride or passed through activity I alumina; and diisopropylamine was distilled from calcium hydride. Reactions requiring an inert atmosphere were run under nitrogen. Column chromatography was performed over EM laboratories silica gel (70−230 or 230−400 mesh). All organometallic reagents (Grignard, organic lithiums) were titrated prior to use with menthol using 1,10-phenanthroline as the indicator.[56] The order of experimental procedures follow their order of appearance in the text. For ozonolyses, the ozone was delivered using a Welsbach ozone generator.

(*E*)-6-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-3-hexene-2-one (25). Through a solution of 50 g (320 mmol) of olefin **23** in 400 mL of dichloromethane cooled in a dry ice−acetone bath was passed a stream of ozone until a pale blue color persisted. The excess ozone was purged from the mixture by passing nitrogen through the solution until it became clear. To the mixture was then added 132 g (413 mmol) of (2-oxopropylidene)triphenylphosphorane[57] in several portions. The cold bath was then removed, and the mixture was warmed to room temperature. A mild exotherm occurred at 20−25 °C, and the mixture was cooled to 15 °C. The mixture was then warmed to room temperature, stirred for 48 h, and concentrated in vacuo. The residue was diluted with ether−hexane and filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc−hexanes (15:85) and passed through 450 g of silica gel (EtOAc−hexanes, 1:9). The eluent was concentrated in vacuo, and the residue was distilled under reduced pressure (118−124 °C, 4 Torr) to afford 39 g (61%) of enone **25** as a colorless oil. Spectroscopic data for this compound have been reported elsewhere.[20]

Trimethyl[[(*E*)-1-methylene-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2-pentenyl]oxy]silane (26). To a solution of 65 mL (467 mmol) of diisopropylamine in 500 mL of THF cooled in a dry ice−acetone bath was added 200 mL (400 mmol) of 2.0 M *n*-BuLi in hexane. The mixture was stirred for 30 min and then warmed to −40 °C. After 10 min, the mixture was cooled to −78 °C, and 75 g (378 mmol) of enone **25** in 50 mL of THF was added over a 20-min period. The mixture was stirred for 20 min, and then 59 mL (467 mmol) of chlorotrimethylsilane in 30 mL of THF was added over a 20-min period. After 30 min, the cold bath was removed, and the mixture was stirred at room temperature for 4 h. The mixture was filtered through Celite, the filtercake was washed with hexane, and the filtrate was concentrated

(53) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003. Martin, J. C.; Franz, J. A. *J. Am. Chem. Soc*. **1975**, *97*, 6137.

(54) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392. Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett*. **1995**, *36*, 2393.

(55) We thank Professor G. Cordell for kindly supplying a sample of authentic 21-oxogelsemine.

(56) Watson, S. C.; Eastham, J. F. *J. Organometallic Chem.* **1967**, *9*, 165.

(57) For the preparation of (2-oxopropylidene)triphenylphosphorane, see: Ramirez, F.; Dershowitz, S. *J. Org. Chem*. **1957**, *22*, 41.

in vacuo. The residue was diluted with 500 mL of hexane and filtered, and the filtrate was concentrated in vacuo to provide 102 g (99%) of diene **26** as a yellow oil which was used without further purification. Spectroscopic data for this compound have been reported elsewhere.[20]

(±)-(8*R,9*S**,10*S**)-10-(2-Hydroxyethyl)-*N*,3,3-trimethyl-1,5-dioxaspiro[5,5]undecane-8,9-dicarboximide (28).** A mixture of 102 g (0.38 mol) of diene **26** and 50 g (0.45 mol) of *N*-methylmaleimide in 800 mL of toluene was heated at reflux for 15 h. An additional 12 g (0.108 mmol) of *N*-methylmaleimide was added, and the mixture was stirred at reflux for 1 h. The mixture was then cooled to room temperature, and 106 g (1.019 mol) of 2,2-dimethyl-1,3-propanediol and 3 g of *p*-toluenesulfonic acid monohydrate were added. The apparatus was fitted with a Dean−Stark trap and warmed under reflux with removal of water for 16 h. The mixture was cooled, concentrated in vacuo to a volume of 550 mL, and stirred over 25 g of potassium carbonate for 30 min. The mixture was passed through a 600 g pad of silica gel (EtOAc−hexanes, 25:75 → 1:1 → 75:25 → EtOAc). The eluent was concentrated in vacuo and placed on the Kugelrhor (75 °C, 0.1 Torr) to remove excess *N*-methylmaleimide and 2,2-dimethyl-1,3-propanediol to provide 46 g (39%) of imide **28** which hardened to an amber resin upon cooling. Spectroscopic data for this compound have been reported elsewhere.[20]

(±)-(8*R,9*S**,10*R**)-*N*,3,3-Trimethyl-10-vinyl-1,5-dioxaspiro[5,5]-undecane-8,9-dicarboximide (30).** To a solution of 29.9 g (93.9 mmol) of alcohol **28** and 25.5 g (112.3 mmol) of *o*-nitrophenylselenocyanate in 300 mL of THF cooled in an ice bath was added 30 mL (121.3 mmol) of tri-*n*-butylphosphine over a 5-min period. The mixture was warmed to room temperature and stirred for 2.25 h. The mixture was cooled in an ice bath, and 52 g (196 mmol) of anhydrous Na_2HPO_4 was added. After 5 min, 144 mL of 30% aqueous hydrogen peroxide was added while maintaining the temperature below 0 °C. The mixture was stirred at 40 °C for 1 h and at room temperature for 12 h. The solution was concentrated in vacuo, and the residue was partitioned between 200 mL of EtOAc and 300 mL of water. The organic layer was separated, and the aqueous phase was extracted with three 200-mL portions of EtOAc. The combined EtOAc extracts were washed with three 100-mL portions of brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was diluted with ether−hexane (1:1), filtered, and concentrated in vacuo. The residue was chromatographed over 240 g of silica gel (EtOAc−hexanes, 1:19 → 1:9 → 2:8) to afford 21.9 g (79%) of alkene **30** as a viscous red oil. Spectroscopic data for this compound have been reported elsewhere.[20]

(±)-(3′*R,3′a*S**,7′*S**,7′a*R**)-Tetrahydro-3′-hydroxy-2′,5,5-trimethyl-7′-vinylspiro[*m*-dioxane-2,5′(4′*H*)-isoindolin]-1′-one (31).** To a solution of 10.3 g (35.2 mmol) of imide **30** in 120 mL of MeOH cooled to −23 °C was added 4.0 g (105.7 mmol) of sodium borohydride over a 5-min period in several portions. The mixture was stirred at −23 °C for 30 min and then at room temperature for 2 h and then concentrated in vacuo. The residue was partitioned between 100 mL of EtOAc and 100 mL of saturated aqueous sodium bicarbonate. The basic aqueous layer was separated and extracted with five 50-mL portions of EtOAc. The combined EtOAc layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residual orange oil was chromatographed over 340 g of silica gel (ether; then EtOAc−hexane, 8:2) to provide 8.4 g (80%) of carbinol **31** as a viscous oil which solidified to an off white solid under high vacuum: mp 119−120 °C; IR (KBr) 3416, 1667 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 0.50 (s, 3H), 0.80 (s, 3H), 1.52−1.66 (m, 2H), 2.21−2.25 (m, 3H), 2.31−2.37 (m, 1H), 2.51−2.62 (m, 1H), 2.64 (s, 3H), 3.12−3.26 (m, 4H), 3.61 (broad, 1H, OH), 4.53 (m, 1H), 5.06 (m, 1H), 5.10 (s, 1H), 6.93−7.05 (m, 1H); ^{13}C NMR (75.5 MHz, C_6D_6) δ 22.1 (q), 22.2 (q), 25.6 (q), 28.5 (t), 29.6 (s), 34.8 (t), 37.8 (d), 38.3 (d), 45.6 (d), 69.5 (t), 69.6 (t), 83.3 (d), 97.6 (s), 113.5 (t), 141.26 (d), 172.7 (s); exact mass calcd for $C_{16}H_{25}NO_4$ *m/z* 295.1784, found *m/z* 295.1775. This compound decomposed when NMR data were collected in $CDCl_3$.

(±)-(3′*R,3′a*S**,7′*R**,7′a*R**)-3′-Ethoxytetrahydro-2′,5,5-trimethyl-7′-vinylspiro[*m*-dioxane-2,5′(4′*H*)-isoindolin]-1′-one (32).** To a suspension of 4.8 g (0.12 mmol) of a 60% NaH dispersion in oil (washed with three 10-mL portions of hexane) in 250 mL of THF warmed to 45 °C was added 26.9 g (91.2 mmol) of hydroxylactam **31** in several portions. After the addition, the mixture was stirred until hydrogen evolution ceased. The mixture was cooled to 30 °C, and 15 mL (0.18 mmol) of ethyl iodide was added over a 5-min period. The mixture was stirred at 30 °C for 1 h and then at 45 °C for 4 h. The mixture was then cooled to 0 °C, and the excess NaH was cautiously destroyed with EtOH. The mixture was partitioned between 500 mL of brine and 200 mL of EtOAc. The organic layer was separated and the aqueous phase was extracted with two 200-mL portions of EtOAc. The combined EtOAc layers were washed with three 200-mL portions of brine and dried ($MgSO_4$), and decolorizing carbon (Norit A) was added. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo causing a precipitate to form. Hexane was added to the precipitate, and the resulting solid was collected to afford 21 g (71%) of **32** (115−121 °C). The concentrated filtrate (6.9 g) was chromatographed over 60 g of silica gel (EtOAc−hexane, 3:7 → 1:1) and triturated with hexane to afford an additional 2.4 g (8%) of **32**. The mother liquor gave 3.4 g (11%) of additional material that was a 1:1 mixture of diastereomers **32** and **33** by ^1H NMR. Spectroscopic data for this compound have been reported elsewhere.[20]

(±)-(3′*R,3′a*S**,7′*S**,7′a*R**)-7′a-[(Benzyloxy)methyl]-3′-ethoxytetrahydro-2′,5,5-trimethyl-7′-vinylspiro[*m*-dioxane-2,5′(4′*H*)-isoindolin]-1′-one (35).** To a solution of 8.70 mL (62.1 mmol) of diisopropylamine in 50 mL of THF at −78 °C was added 20.80 mL of 2.5 M *n*-BuLi in hexane. The mixture was stirred for 30 min, and 13.5 g (41.7 mmol) of **32** in 30 mL of THF was added over a 15-min period. The mixture was stirred at −78 °C for 15 min and was then warmed to −20 °C. After 10 min, the mixture was again cooled to −78 °C, and 7.2 g (46.19 mmol) of benzyl chloromethyl ether was added. The mixture was stirred for 15 min at −78 °C, warmed to room temperature, stirred for 1 h, and partitioned between 200 mL of EtOAc and 300 mL of water. The organic layer was separated, and the aqueous phase was extracted with three 75-mL portions of EtOAc. The combined EtOAc layers were washed with four 200-mL portions of brine, dried ($MgSO_4$), treated with carbon (Norit A), filtered through Celite, and concentrated in vacuo. The residue was chromatographed over 95 g of silica gel (EtOAc−hexane, 1:4) to afford 17.8 g (96%) of **35** as a viscous oil: IR (neat) 1697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3H), 1.02 (s, 3H), 1.15 (t, J = 6.6 Hz, 3H), 1.37 (dd, J = 13.7, 13.3 Hz, 1H), 1.82 (dd, J = 15.3, 6.4 Hz, 1H), 1.98 (dd, J = 14.4, 6.2 Hz, 1H), 2.09 (dd, J = 14.1, 3.3 Hz, 1H), 2.69−2.69 (m, 2H), 2.79 (s, 3H), 3.38−3.52 (m, 6H), 3.60 (*AB*q, J = 9.0 Hz, 2H), 4.44 and 4.49 (*AB*q, J = 12.2 Hz, 2H), 4.59 (d, J = 2.4 Hz, 1H), 4.99 (dd, J = 9.0, 2.0 Hz, 1H), 5.03 (s, 1H), 6.21 (ddd, J = 16.6, 10.4, 9.5, Hz, 1H), 7.2−7.29 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.3 (q), 22.2 (q), 22.6 (q), 27.4 (q), 29.9 (s), 33.7 (t), 34.6 (t), 38.5 (d), 39.5 (d), 51.4 (s), 62.4 (t), 69.8 (t), 69.9 (t), 72.2 (t), 73.1 (t), 93.7 (d), 97.8 (s), 115.6 (t), 127.2 (d), 127.3 (d), 128.0 (d) 138.3 (d), 174.0 (s), one aromatic singlet was not resolved; exact mass calcd for $C_{26}H_{37}NO_5$ *m/z* 443.2672, found *m/z* 443.2682.

(±)-(3′*R,3′a*S**,7′*R**,7′a*S**)-7′a-[(Benzyloxy)methyl]-3′-ethoxytetrahydro-2′,5, 5-trimethyl-1′-oxospiro[*m*-dioxane-2,5′(4′*H*)-isoindoline]-7′-carboxaldehyde (37).** Through a solution of 10.0 g (22.5 mmol) of olefin **35** in 200 mL of CH_2Cl_2-MeOH (95:5) cooled to −86 °C was passed ozone gas until a pale blue color was evident, and starting material was no longer present by thin-layer chromatography (EtOAc−hexane, 3:7). Excess ozone was then purged from the mixture using a stream of nitrogen, and then 20 mL of dimethyl sulfide was added in one portion. The cold bath was then removed, and the mixture was stirred at room temperature for 10 h. The mixture was diluted with 200 mL of brine, and the organic phase was separated. The aqueous phase was extracted with two 30-mL portions of CH_2Cl_2. The combined CH_2Cl_2 layers were washed with three 50-mL portions of brine and dried ($MgSO_4$), decolorizing carbon was added, and the mixture was filtered through Celite and concentrated. The residue was triturated with ether−hexane to provide 7.8 g (78%) of aldehyde **37** which was used without further purification. An analytically pure sample was obtained from a single recrystallization from ether−hexane to afford aldehyde **37** as a crystalline white solid: mp 117−119 °C; IR (KBr) 1711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 3H), 1.06 (s, 3H), 1.16 (t, J = 7.0 Hz, 3H), 1.23 (dd, J = 14.2, 12.6 Hz, 1H), 1.36 (dd, J = 13.8, 10.1 Hz, 1H), 2.11 (ddd, J = 13.8, 6.6, 2.1 Hz, 1H), 2.60−2.68 (m, 2H), 2.84 (s, 3H), 2.88 (dd, J = 12.5, 4.2 Hz, 1H), 3.31−3.56 (m, 5H), 3.63 (d, J = 11.5 Hz, 1H), 3.81 (d, J = 9.4 Hz, 1H),

3.94 (d, J = 9.4 Hz, 1H), 4.35 (d, J = 0.7 Hz, 1H), 4.53 and 4.58 (*AB*q, J = 12.3 Hz, 2H), 7.23−7.34 (m, 5H), 10.12 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.2 (q), 22.1 (q), 22.6 (q), 26.8 (t), 28.2 (q), 29.9 (s), 35.4 (t), 39.1 (d), 46.5 (d), 51.3 (s), 63.6 (t), 69.9 (t), 70.0 (t), 72.4 (t), 73.2 (t), 95.4 (d), 96.6 (s), 127.3 (d), 127.5 (d), 128.2 (d), 137.8 (s), 174.1 (s), 202.0 (d); exact mass calcd for $C_{25}H_{35}NO_6$ *m/z* 445.2465, found *m/z* 445.2472. Anal. Calcd for $C_{25}H_{35}NO_6$: C, 67.39; H, 7.92. Found: C, 67.30; H, 7.89.

Ethyl (±)-(α*E*,3′*R,3′a*S**,7′*S**,7′*R**)-7′a-[(Benzyloxy)methyl]-3′-ethoxytetrahydro-2′,5,5-trimethyl-1′-oxospiro[*m*-dioxane-2,5′(4′*H*)-isoindoline]-7′-acrylate (39).** A mixture of 5.0 g (11.2 mmol) of **37** and 5.9 g (16.8 mmol) of (carbethoxymethylidene)triphenylphosphorane in 55 mL of CH_2Cl_2 was heated under reflux for 42 h. An additional 1.3 g (3.7 mmol) of (carbethoxymethylidene)triphenylphosphorane was then added, and the mixture was stirred under reflux for 54 h. The mixture was then concentrated in vacuo, and the residue was chromatographed over 100 g of silica (EtOAc−petroleum ether, 2:7 then, 3:7) to provide 4.2 g (73%) of ester **39** and 1.45 g of mixed fractions. The mixed fractions were chromatographed a second time to afford an additional 540 mg (9%) of **39**: IR (neat) 1698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 3H), 1.04 (s, 3H), 1.15 (t, J = 6.6 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.41 (t, J = 13.3 Hz, 1H), 1.69 (dd, J = 14.1, 7.5 Hz, 1H), 2.05 (dd, J = 14.2, 6.3 Hz, 1H), 2.16 (dd, J = 13.9, 3.1 Hz, 1H), 2.64 (m, 1H), 2.80 (s, 3H), 2.88 (m, 1H), 3.37−3.62 (m, 8H), 4.16 (dq, J = 7.2, 1.1 Hz, 2H), 4.47 (s, 2H), 4.50 (d, J = 1.5 Hz), 5.77 (d, J = 15.6 Hz, 1H), 7.21−7.33 (m, 5H), 7.38 (dd, J = 15.6, 9.5 Hz, 1H); ^{13}C NMR (62.2 MHz, $CDCl_3$) δ 14.1 (q), 15.2 (q), 22.2 (q), 22.5 (q), 27.6 (q), 29.8 (s), 33.4 (t), 37.7 (d), 38.5 (d), 49.5 (s), 51.5 (s), 59.8 (t), 62.9 (t), 69.8 (t), 69.8 (t), 71.9 (t), 73.1 (t), 94.1 (d), 97.0 (s), 122.0 (d), 127.2 (s), 127.3 (d), 128.1 (d), 138.0 (s), 148.4 (d), 166.0 (s), 173.5 (s); exact mass calcd for $C_{29}H_{41}NO_7$ *m/z* 515.2884, found *m/z* 515.2865.

Ethyl (±)-(α*E*,3′*R,3′a*S**,7′*S**,7′a*R**)-7′a-[(Benzyloxy)methyl]tetrahydro-2′,5,5-trimethyl-1′-oxo-3′-(phenylthio)spiro[*m*-dioxane-2,5′-(4′*H*)isoindoline]-7′-acrylate (40).** A mixture of 4.7 g (9.1 mmol) of ethoxylactam **39**, 1.5 g (13.7 mmol) of thiophenol, 50 mg of *p*-toluenesulfonic acid monohydrate, and 5 g of 4 Å molecular sieves in 65 mL of CH_2Cl_2 was stirred for 3 h. The mixture was diluted with 100 mL of saturated aqueous sodium bicarbonate, and the CH_2Cl_2 layer was separated. The basic aqueous phase was extracted with three 40-mL portions of CH_2Cl_2. The combined CH_2Cl_2 layers were washed with two 50-mL portions of brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed over 65 g of silica gel (EtOAc−hexane, first 2:8, then 3:7) to afford 4.1 g (76%) of **40** as a viscous oil: IR (neat) 1717, 1691 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 3H), 0.99 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.52 (dd, J = 14.2, 12.0 Hz, 1H), 1.82 (dd, J = 14.7, 5.7 Hz, 1H), 2.03 (dd, J = 14.3, 3.2 Hz, 1H), 2.34 (dd, J = 14.7, 3.6 Hz, 1H), 2.66−2.72 (m, 2H), 2.78 (d, J = 9.2 Hz, 1H), 2.89 (s, 3H), 3.37−3.48 (m, 5H), 4.13 (dq, J = 6.4 Hz, 2H), 4.25 and 4.31 (*AB*q, J = 12.1 Hz, 2H), 4.81 (d, J = 5.7 Hz, 1H), 5.70 (d, J = 15.6 Hz, 1H), 7.09 (dd, J = 15.6, 9.5 Hz, 1H,), 7.17−7.40 (m, 10H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 (q), 22.3 (q), 22.4 (q), 27.9 (q), 29.8 (s), 31.5 (t), 34.4 (t), 38.0 (d), 40.1 (d), 51.4 (s), 59.9 (t), 69.8 (t), 69.9 (t), 71.7 (t), 72.1 (d), 73.0 (t), 98.0 (s), 122.4 (d), 127.3 (d), 127.4 (d), 128.1 (d), 128.4 (d), 129.0 (d), 131.7 (s), 134.4 (d), 137.8 (s), 147.6 (d), 165.8 (s), 172.5 (s); mass spectrum *m/z* (rel intensity) 579 (M, 0.01), 472 (30), 470 (100), 379 (19), 91 (72); exact mass calcd for $C_{27}H_{36}NO_6$ (M − SC_6H_5) *m/z* 470.2381, found *m/z* 470.2515.

Ethyl (±)-(1′*R,3′a*S**,4′*R**,7′a*R**,8′*R**)-3′a-[(Benzyloxy)methyl]-tetrahydro-2′,5,5-trimethyl-3′-oxospiro[*m*-dioxane-2,6′(5′*H*)-[1,4]-methanoisoindoline]-8′-acetate (41) and Ethyl (±)-(3′*R**,4′*R**,4′a*S**,-7′a*R**,10′a*S**)-Octahydro-5,5,9′-tri methyl-10′-oxo-3′-phenylspiro-[*m*-dioxane-2,6′(7′*H*)-[1*H*]pyrano[3,4-*d*]isoindole]-4′-acetate (47).** To a solution of 21.7 g (36.8 mmol) of sulfide **40** in 900 mL of benzene heated at reflux was added a mixture of 11.6 g (40.1 mmol) of tri-*n*-butyltin hydride and 200 mg of AIBN in 110 mL of benzene over a 44-h period using a syringe pump. The mixture was cooled to room temperature and concentrated in vacuo, and the residue was diluted with one part ether and then nine parts hexane. The mixture was chilled to facilitate crystal growth, and the resulting solid was collected by filtration and washed with ether−hexane (1:1) to afford 11.3 g (65%) of **41** as a white solid: mp 108−110 °C; IR (KBr) 1726, 1687 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 3H), 1.03 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.65 (m, 1H), 1.81 (dd, J = 14.6, 2.8 Hz, 1H), 2.05 (m, 2H), 2.17 (dd, J = 16.5, 9.3 Hz, 1H), 2. 23 (dd, J = 16.5, 6.2 Hz, 1H), 2.42 (m, 1H), 2.61 (dd, J = 14.6, 3.8 Hz, 1H), 2.88 (s, 3H), 3.10 (m, 1H), 3.27 (dd, J = 11.4, 1.6 Hz, 1H), 3.40 (d, J = 11.5 Hz, 2H), 3.5 (t, J = 2.2 Hz, 1H), 3.66 (d, J = 11.5 Hz, 1H), 3.71 (d, J = 9.7 Hz, 1H), 3.90 (d, J = 9.7 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 4.58 and 4.64 (*AB*q, J = 12.4 Hz, 2H), 7.20−7.38 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0 (q), 22.1 (q), 22.6 (q), 29.6 (s), 30.3 (q), 33.4 (t), 35.3 (t), 35.9 (t), 39.1 (d), 41.1 (d), 48.6 (d), 55.4 (s), 60.2 (t), 65.0 (t), 65.6 (d), 69.4 (t), 70.4 (t), 73.4 (t), 96.3 (s), 127.1 (d), 127.4 (d), 128.0 (d), 138.5 (s), 172.2 (s), 176.0 (s); mass spectrum *m/z* (rel intensity) 231 (24), 91 (93), 57 (100); no parent peak was observed. Anal. Calcd for $C_{27}H_{37}NO_6$: C, 68.77; H, 7.91. Found: C, 68.68; H, 7.93. The filtrate was then concentrated to 100 mL, passed through a 110 g pad of silica gel (ether−hexane; 1:1) and recrystallized from ether−hexane to provide 700 mg (4%) of **47** as a white solid: mp 155−156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3H), 1.05 (s, 3H), 1.22 (m, 1H), 1.22 (t, J = 7.1 Hz, 3H), 1.35 (dd, J = 13.3, 11.7 Hz, 1H), 1.96−2.05 (m, 3H), 2.19−2.32 (m, 2H), 2.50 (broad d, J = 13.3 Hz, 1H), 2.66 (d, J = 10.0 Hz, 1H), 2.87 (s, 3H), 3.34−3.64 (m, 7H), 3.97−4.10 (m, 3H), 4.46 (d, J = 10.3 Hz, 1H), 7.23−7.34 (m, 3H), 7.48−7.51 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 (q), 22.3 (q), 22.7 (q), 29.2 (t), 29.8 (s), 30.0 (q), 33.3 (t), 34.5 (d), 37.0 (d), 37.1 (t), 39.3 (d), 47.7 (s), 51.8 (t), 60.0 (t), 69.73 (t), 69.77 (t), 72.9 (t), 84.0 (d), 96.9 (s), 127.8 (d), 128.0 (d), 128.1 (d), 140.5 (s), 171.9 (s), 174.2 (s); mass spectrum, *m/z* (rel intensity) 471 (M, 100), 425 (68), 383 (66), 317 (71), 57 (82); exact mass calcd for $C_{27}H_{37}NO_6$ *m/z* 471.2620, found *m/z* 471.2617.

(±)-(1′*R,3′a*S**,4′*R**,7′a*R**,8′*R**)-3′a-[(Benzyloxy)methyl]tetrahydro-8′-(2-hydroxy-2,2-diphenylethyl)-2′,5,5-trimethylspiro[*m*-dioxane-2,6′(5′*H*)-[1,4]methanoisoindoline]-3′-one (80).** To a solution of 4.0 g (8.5 mmol) of ester **41** in 80 mL of THF cooled to −20 °C was added a solution of PhMgBr [prepared from 8.18 g (52.1 mmol) of bromobenzene and 1.10 g (45.2 mmol) of magnesium turnings in 35 mL of anhydrous THF] over a 35-min period. The mixture was stirred at 10 °C for 5 h and at room temperature for 1 h. The mixture was then cooled to −20 °C, quenched with 150 mL of saturated ammonium chloride, and extracted with three 150-mL portions of EtOAc. The combined EtOAc layers were washed with three 250-mL portions of brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The oily residue was dissolved in 150 mL of ether, and 50 mL of hexanes was added. The mixture was allowed to stand for 18 h, and then an additional 200 mL of hexane was added. After 1 h, the resulting white solid was collected and washed with EtOAc−hexane (1:3) to provide 4.3 g (87%) of alcohol **80** as a white solid: mp 187−188 °C; IR (neat) 3399, 1685 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73 (s, 3H, CH_3), 0.99 (s, 3H), 1.55 (dd, J = 14.4, 2.7 Hz, 1H), 1.75 (broad s, 1H), 1.90−1.92 (m, 2H), 2.12 (dd, J = 14.1, 7.5 Hz, 1H), 2.20 (dd, J = 14.1, 7.5 Hz, 1H), 2.24 (s, 1H), 2.31 (broad, 1H), 2.42 (dd, J = 14.1, 4.5 Hz, 1H), 2.75 (broad, 1H), 2.93 (dd, J = 11.7, 1.8 Hz, 1H), 2.97 (s, 3H), 3.16 (dd, J = 11.4, 1.8 Hz, 1H), 3.22 (d, J = 11.6 Hz, 1H), 3.30 (d, J = 11.4, 1H), 3.38 (t, J = 2.4 Hz, 1H), 3.65 (d, J = 9.7 Hz, 1H), 3.86 (d, J = 9.7 Hz, 1H), 4.56 and 4.61 (*AB*q, J = 12.6 Hz, 2H), 7.18−7.39 (m, 15H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.1 (q), 22.6 (q), 29.4 (s), 31.1 (q), 31.5 (t), 36.5 (t), 40.4 (d), 40.8 (d), 43.6 (t), 48.6 (d), 55.6 (s), 65.4 (t), 67.8 (d), 69.4 (t), 70.5 (t), 73.4 (t), 78.0 (s), 96.4 (s), 125.9 (d), 126.0 (d), 126.6 (d), 126.7 (d), 127.1 (d), 127.3 (d), 128.01 (d), 128.05 (d), 128.1 (d), 138.7 (s), 147.1 (s), 147.9 (s), 176.5 (s); exact mass calcd for $C_{37}H_{43}NO_5$ *m/z* 581.3141, found *m/z* 581.3147. Anal. Calcd for $C_{37}H_{43}NO_5$: C, 76.39; H, 7.45. Found: C, 76.45; H, 7.49.

(±)-(1′*R,3′a*S**,4′*R**,7′a*R**,8′*R**)-3′a-[(Benzyloxy)methyl]tetrahydro-8′-(2-methoxy-2,2-diphenylethyl)-2′,5,5-trimethylspiro[*m*-dioxane-2,6′(5′*H*)-[1,4]methanoisoindoline]-3′-one (81).** To a suspension of 605 mg (15.12 mmol) of 60% NaH in mineral oil (washed with three 10-mL portions of hexane) in 65 mL of DMSO warmed to 35 °C was added 4.4 g (7.57 mmol) of alcohol **80** in several portions. The mixture was stirred for 15 min and cooled to room temperature, and 2.14 g (15.13 mmol) of iodomethane was added. The mixture was stirred for 45 min and then poured into 200 mL of ice cold saturated

aqueous ammonium chloride. The white solid was collected and washed with 1 L of water to provide 4.55 g (100%) of methyl ether **81** which was used without further purification: mp 74−79 °C; IR (KBr) 1699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.40 (m, 1H), 1.45 (dd, J = 17.1, 2.8 Hz, 1H), 1.91 (m, 2H), 2.01 (dd, J = 14.3, 3.6 Hz, 1H), 2.20 (dd, J = 14.3, 7.6 Hz, 1H), 2.29 (m, 1H), 2.44 (dd, J = 14.3, 3.6 Hz, 1H), 2.80 (m, 1H), 3.01 (s, 3H), 3.02 (s, 3H), 3.12 (dd, J = 2.8, 2.1 Hz, 1H), 3.16−3.33 (m, 3H), 3.51 (d, J = 11.5 Hz, 1H), 3.61 (d, J = 9.7 Hz, 1H), 3.83 (d, J = 9.7 Hz, 1H), 4.55 and 4.59 (*AB* q, J = 13.0 Hz, 2H), 7.15−7.35 (m, 15H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.2 (q), 22.6 (q), 29.5 (s), 31.5 (q), 31.8 (t), 36.3 (t), 37.7 (t), 39.7 (d), 40.0 (d), 48.6 (d), 50.5 (q), 55.7 (s), 65.2 (t), 67.7 (d), 69.6 (t), 70.5 (t), 73.4 (t), 82.2 (s), 96.3 (s), 126.7 (d), 126.9 (d), 127.0 (d), 127.1 (d), 127.3 (d), 127.8 (d), 127.9 (d), 128.0 (d), 138.6 (s), 144.6 (s), 145.1 (s), 176.5 (s), one aromatic doublet was not resolved; mass spectrum, *m/z* (rel intensity) 595 (M, 8), 489 (53), 474 (14), 398 (100), 197 (84), 91 (56); exact mass calcd for $C_{38}H_{45}NO_5$ *m/z* 595.3297, found *m/z* 595.3294.

(±)-(1*R,3a*S**,4*R**,7a*R**,8*R**)-3a-[(Benzyloxy)methyl]tetrahydro-8-(2-methoxy-2,2-diphenylethyl)-2-methyl-1,4-methanoisoindoline-3,6(5*H*)-dione (82).** To a solution of 4.15 g (6.97 mmol) of ketal **81** in 750 mL of acetone cooled in an ice bath was added 750 mg of *p*-toluenesulfonic acid monohydrate. The mixture was stirred for 8 h, the cold bath was then removed, and the mixture was stirred at room temperature for 16 h. The mixture was then basified with solid sodium bicarbonate, diluted with 100 mL of saturated aqueous sodium bicarbonate, and concentrated in vacuo. The residue was partitioned between 100 mL of EtOAc and 200 mL of water. The organic layer was separated, and the aqueous phase was extracted with two 100-mL portions of EtOAc. The combined organic layers were washed with three 100-mL portions of saturated aqueous sodium bicarbonate and three 100-mL portions of brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The oily residue was diluted with 125 mL of ether followed by 50 mL of hexane and cooled to 0 °C. The resulting solid was collected by filtration and washed with ether−hexane (1:1) to provide 3.35 g (94%) of ketone **82** as a white solid: mp (CH_2Cl_2−ether) 165−167 °C; IR (KBr) 1703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (broad, 1H), 1.91−2.09 (m, 3H), 2.28−2.54 (m, 5H), 2.96 (s, 3H), 3.00 (s, 3H), 3.12 (t, J = 2.0 Hz, 1H), 3.68 (d, J = 10.4 Hz, 1H), 3.92 (d, J = 10.4 Hz, 1H), 4.44 (d, J = 12.2 Hz, 1H), 4.51 (d, J = 12.2 Hz, 1H) 7.15−7.30 (m, 15H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 31.1 (q), 38.0 (t), 39.2 (t), 41.3 (d), 42.7 (t), 44.9 (d), 49.1 (d), 50.6 (q), 54.7 (s), 66.6 (t), 67.7 (d), 73.6 (t), 82.3 (s), 126.9 (d), 127.0 (d), 127.1 (d), 127.4 (d), 127.5 (d), 128.0 (d), 128.2 (d), 137.7 (s), 143.8 (s), 144.3 (s), 175.7 (s), 208.8 (s), two aromatic doublets were not resolved; exact mass calcd for $C_{33}H_{35}NO_4$ *m/z* 509.2565, found *m/z* 509.2535. Anal. Calcd for $C_{33}H_{35}NO_4$: C, 77.76; H, 6.93. Found: C, 77.69; H, 6.96.

(±)-(1*R,3a*S**,4*R**,7a*S**,8*R**)-3a-[(Benzyloxy)methyl]-2′-bromo-3a,4,5,7a-tetrahydro-6-hydroxy-8-(2-methoxy-2,2-diphenylethyl)-2-methyl-3-oxo-1,4-methanoisoindoline-7-carboxanilide (83).** To a suspension of 1.24 g (31.00 mmol) of 60% NaH in mineral oil (washed with three 10-mL portions of hexane) and 145 mg (3.62 mmol) of KH in 50 mL of THF was added 3.52 g (6.94 mmol) of ketone **82** followed by 7.2 g (36.36 mmol) of 2-bromophenylisocyanate.[42] The mixture was warmed under reflux for 5 h and then an additional 1.0 g (5.05 mmol) of 2-bromophenylisocyanate was added, and the mixture continued to reflux for 1.5 h. The mixture was cooled to −10 °C, and the excess NaH-KH was cautiously destroyed with EtOH. The mixture was stirred for 20 min and then partitioned between 250 mL of ice cold saturated aqueous ammonium chloride and 150 mL of EtOAc. The organic layer was separated, and the aqueous phase was extracted with three 80-mL portions of EtOAc. The combined organic layers were washed with three 80-mL portions of brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed over 65 g of silica gel (first CH_2Cl_2; then MeOH−CH_2Cl_2, 2:98) and then recrystallized from ether−hexane to afford, in two crops, 3.42 g (70%) of β-ketoanilide **83** as a white solid (mp 174−177 °C). The mother liquor was chromatographed over 7 g of silica gel (first CH_2Cl_2; then MeOH−CH_2Cl_2, 2:98), and the material from the column was recrystallized from ether−hexane to afford an additional 491 mg (10%) of **83** (mp 171−176 °C): IR (neat) 3409, 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (broad s, 1H), 1.77 (dd, J = 18.9, 2.3 Hz, 1H), 2.12−2.19 (m, 2H), 2.31 (dd, J = 14.2, 7.7 Hz, 1H), 2.56 (dd, J = 14.2, 3.3 Hz, 1H), 2.94 (broad s, 1H), 3.00 (s, 3H), 3.09 (s, 3H), 3.35 (d, J = 9.7 Hz, 1H), 3.52 (t, J = 1.9 Hz, 1H), 3.79 (d, J = 9.7 Hz, 1H), 4.47 (d, J = 12.6 Hz, 1H), 4.61 (d, J = 12.6 Hz, 1H), 7.01 (td, J = 7.9, 1.5 Hz, 1H), 7.17−7.37 (m, 16H), 7.55 (dd, J = 8.2, 1.5 Hz, 1H), 7.70 (s, 1H), 8.28 (dd, J = 8.2, 1.5 Hz, 1H), 13.79 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 31.5 (q), 34.6 (t), 37.4 (t), 39.4 (d), 45.1 (d), 47.9 (d), 50.6 (q), 55.9 (s), 64.1 (t), 69.6 (d), 73.3 (t), 82.1 (s), 96.9 (s), 114.4 (s), 122.1 (d), 125.4 (d), 127.02 (d), 127.06 (d), 127.1 (d), 127.3 (d), 128.0 (d), 128.1 (d), 128.3 (d), 132.2 (d), 134.8 (s), 138.1 (s), 144.1 (s), 144.4 (s), 169.3 (s), 173.3 (s), 174.8 (s), three aromatic doublets were not resolved; mass spectrum, *m/z* (rel intensity) 403 (20), 197 (100), 173 (60), 171 (62), 91 (45); exact mass calcd for $C_{40}H_{39}BrN_2O_5$ *m/z* 706.2042, found *m/z* 706.2047. An analytically pure sample was prepared by recrystallization from EtOH. Anal. Calcd for $C_{40}H_{39}BrN_2O_5$: C, 67.97; H, 5.57. Found: C, 67.70; H, 5.65.

(±)-(1*R,3a*S**,4*R**,7a*S**,8*R**)-3a-[(Benzyloxy)methyl]-2′-bromo-3a,4,5,7a-t etrahydro-8-(2-methoxy-2,2-diphenylethyl)-6-(methoxymethoxy)-2-methyl-3-oxo-1,4-methanoisoindoline-7-carboxanilide (84).** To a solution of 200 mg (0.28 mmol) of β-ketoanilide **83** in 3 mL of DMSO was added 286 mg (2.82 mmol) of triethylamine followed by 113 mg (1.41 mmol) of chloromethyl methyl ether. The mixture was stirred for 1 h, poured into 40 mL of saturated aqueous sodium bicarbonate, and extracted with three 40-mL portions of EtOAc. The combined organic layers were washed with three 40-mL portions of brine, dried ($MgSO_4$), filtered, and concentrated to provide 212 mg (100%) of β-ketoanilide **84** as a white solid which was used without further purification: mp 172−177 °C. The following data were obtained from a sample recrystallized from EtOAc−hexane: mp 191−193 °C; IR (film) 3342, 1702, 1663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (broad, 1H), 1.74 (dd, J = 18.4, 2.6 Hz, 1H), 1.99 (broad d, J = 8.4 Hz, 1H), 2.17 (dd, J = 18.4, 3.7 Hz, 1H), 2.26 (dd, J = 14.4, 8.4 Hz, 1H), 2.56 (dd, J = 14.3, 2.3 Hz, 1H), 2.98 (s, 3H), 3.12 (s, 3H), 3.27 (s, 3H), 3.32 (d, J = 9.8 Hz, 1H), 3.47 (t, J = 2.1, 1H), 3.64 (d, J = 9.8 Hz, 1H), 3.66 (t, J = 2.8 Hz, 1H), 4.44 (d, J = 12.8 Hz, 1H), 4.61 (d, J = 12.8 Hz, 1H), 4.97 (s, 2H), 6.95 (ddd, J = 9.0, 7.5, 1.6 Hz, 1H), 7.12−7.34 (m, 16H), 7.55 (dd, J = 8.0, 1.5 Hz, 1H), 8.64 (dd, J = 8.4, 1.5 Hz, 1H), 10.04 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 31.0 (t), 31.3 (q), 37.0 (t), 40.2 (d), 44.3 (d), 49.3 (d), 50.5 (q), 54.0 (s), 56.7 (q), 64.4 (t), 70.7 (d), 73.1 (t), 82.0 (s), 92.8 (t), 109.6 (s), 112.4 (s), 121.4 (d), 124.2 (d), 126.8 (d), 126.9 (d), 127.0 (d), 127.1 (d), 127.3 (d), 127.8 (d), 128.0 (d), 128.1 (d), 128.2 (d), 132.2 (d), 137.1 (s), 138.5 (s), 144.3 (s), 144.6 (s), 158.7 (s), 163.8 (s), 175.4 (s), one aromatic doublet was not resolved; mass spectrum, *m/z* (rel intensity) 752 (M, 4), 750 (M, 4), 382 (34), 197 (100), 91 (85); Anal. Calcd for $C_{42}H_{43}BrN_2O_6$: C, 67.18; H, 5.78. Found: C, 67.23; H, 5.76.

(±)-(1*R,3a*S**,4*R**,7a*S**,8*R**)-3a-[(Benzyloxy)methyl]-2′-bromo-3a,4,5,7a-tetrahydro-8-(2-methoxy-2,2-diphenylethyl)-6-(methoxymethoxy)-*N*-(methoxymethyl)-2-methyl-3-oxo-1,4-methanoisoindoline-7-carboxanilide (85).** To a solution of 212 mg (0.28 mmol) of amide **84** in 5 mL of DMSO was added 56 mg (1.39 mmol) of a 60% dispersion of NaH in mineral oil. The mixture was stirred for 5 min, and then 89 mg (1.12 mmol) of chloromethyl methyl ether was added. The mixture was stirred for 1 h, and an additional 100 mg (2.5 mmol) of 60% NaH and 183 mg (2.29 mmol) of chloromethyl methyl ether were added. The mixture was stirred for 30 min, and an additional 54 mg of chloromethyl methyl ether was added. The mixture was stirred for 1 h, then poured into 40 mL of saturated aqueous sodium bicarbonate, and extracted with three 30-mL portions of EtOAc. The combined organic layers were washed with four 40-mL portions of brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed over 12 g of silica gel (first CH_2Cl_2; then EtOAc−hexane, 3:7 → 1:1 → 6:4 → 7:3) to provide 209 mg (84%) of **85** as an oil which when concentrated from ether−hexane and afforded **85** as a white powder: IR (KBr) 1701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): At 303 K, this material gave a complicated spectrum due to the presence of geometrical isomers; mass spectrum, *m/z* (rel intensity) 796 (M, 1), 794 (M, 1), 548 (9), 197 (60), 91 (100), 45 (70); exact mass calcd for $C_{44}H_{47}BrN_2O_7$ *m/z* 796.2548 and 794.2568, found *m/z* 796.2558 and 794.2552.

(±)-(1′*R,3*S**,3′a*S**,4′*R**,7′a*S**,8′*R**)-3′a-[(Benzyloxymethyl]-3′a,7′a-dihydro-8′-(2-methoxy-2,2-diphenylethyl)-1-(methoxymethyl)-2′-methylspiro[indoline-3,7′(4′*H*)-[1,4]methanoisoindoline]-2,3′,6′-(5′*H*)-trione (86) and (±)-(1′*R**,3*R**,3′a*S**,4′*R**,7′a*S**,8′*R**)-3′a-[(Benzyloxymethyl]-3′a,7′a-dihydro-8′-(2-methoxy-2,2-diphenylethyl)-1-(methoxymethyl)-2′-methylspiro[indoline-3,7′(4′*H*)-[1,4]methanoisoindoline]-2,3′,6′(5′*H*)-trione (87). A. From MOM Ether 85.** To a solution of 185 mg (0.23 mmol) of **85** in 20 mL of benzene heated at reflux was added a mixture of 129 mg (0.44 mmol) of tri-*n*-butyltin hydride and 4 mg of AIBN in 6 mL of benzene over a 19-h period using a syringe pump. The mixture was then concentrated in vacuo. The residue was diluted with 25 mL of ether, and DBU was added dropwise until the mixture no longer became cloudy. The mixture was stirred for 18 h, then filtered through Celite, and concentrated in vacuo to near dryness. The residue was twice chromatographed over 12 g of silica gel (ether for the first column, and for the second column, CH_2Cl_2, then EtOAc−CH_2Cl_2, 5:95, then 10:90) to provide 129 mg (83%) of a 1.2:1 mixture of oxindoles **86** and **87**, respectively, by ^{1}H NMR. Typically, the mixture was used in the next step without separation, since the isomers were easier to separate at that point. Analytically pure samples of oxindoles **86** and **87** could be obtained in diminished yield, 35% and 20% respectively, after repeated chromatography (EtOAc−CH_2Cl_2) and a single recrystallization from ether−hexane. Pure oxindole **86** was a white solid: mp (ether−hexane) 191−193 °C; IR (KBr) 1707, 1611 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (broad s, 1H), 2.12 (dd, J = 19.2, 2.9 Hz, 1H), 2.25 (dd, J = 19.6, 3.0 Hz, 1H), 2.33 (dd, J = 14.0, 9.4 Hz, 1H), 2.68 (broad s, 1H), 2.74 (dd, J = 13.9, 1.0 Hz, 1H), 2.99 (broad d, J = 7.9 Hz, 1H), 3.10 (s, 3H), 3.15 (s, 3H), 3.34 (s, 3H), 3.86 (d, J = 10.4 Hz, 1H), 4.04 (broad s, 1H), 4.10 (d, J = 10.4 Hz, 1H), 4.60 (d, J = 12.0 Hz, 1H), 4.68 (d, J = 12.0 Hz, 1H), 5.08 and 5.12 (*AB*q, J = 10.9 Hz, 2H), 6.90−7.08 (m, 3H), 7.13−7.41 (m, 16H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 31.7 (q), 38.6 (t), 39.3 (d), 42.6 (t), 44.5 (d), 50.4 (q), 54.6 (d), 56.1 (q), 57.9 (s), 63.7 (s), 66.1 (d), 66.4 (t), 71.3 (t), 74.0 (t), 81.6 (s), 109.7 (d), 123.1 (d), 124.6 (d), 126.6 (d), 126.8 (d), 126.9 (d), 127.1 (d), 127.6 (d), 127.9 (d), 128.0 (d), 128.26 (d), 128.28 (d), 128.8 (d), 130.6 (s), 137.7 (s), 141.8 (s), 144.7 (s), 145.2 (s), 173.8 (s), 174.4 (s), 205.1 (s); mass spectrum, *m/z* (rel intensity) 670 (M, 18), 548 (15), 197 (17), 43 (100); exact mass calcd for $C_{42}H_{42}N_2O_6$ *m/z* 670.3042, found *m/z* 670.3050. Anal. Calcd for $C_{42}H_{42}N_2O_6$: C, 75.19; H, 6.31. Found: C, 75.26; H, 6.32. Pure oxindole **87** was also a white solid: mp (recrystallized from diethyl ether−hexane) 158−161 °C; IR (KBr) 1730, 1709 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (broad s, 1H), 2.22 (broad, 1H), 2.51−2.60 (m, 4H), 2.76 (dd, J = 18.6, 2.0 Hz, 1H), 3.03 (s, 6H), 3.14 (s, 3H), 3.38 (broad s, 1H), 4.28 and 4.34 (*AB*q, J = 9.1 Hz, 2H), 4.61 and 4.70 (*AB*q, J = 12.2 Hz, 2H), 4.94 and 5.01 (*AB* q, J = 10.9 Hz, 2H), 6.10 (d, J = 9.5 Hz, 1H), 6.86 (td, J = 7.6, 0.8 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 7.19−7.40 (m, 16H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 31.4 (q), 38.6 (t), 40.3 (d), 42.7 (t), 45.2 (d), 51.1 (q), 54.7 (d), 55.9 (q), 57.9 (s), 63.7 (s), 65.7 (t), 66.0 (d), 71.1 (t), 73.0 (t), 83.1 (s), 110.0 (d), 123.0 (d), 123.9 (d), 126.7 (d), 127.0 (d), 127.2 (d), 127.4 (d), 127.5 (d), 127.7 (s), 127.9 (d), 128.3 (d), 128.3 (d), 129.1 (d), 138.9 (s), 142.6 (s), 143.0 (s), 144.7 (s), 174.3 (s), 174.9 (s), 205.4 (s), one aromatic doublet was not resolved; mass spectrum, *m/z* (rel intensity) 670 (M, 50), 548 (61), 197 (100), 91 (80); exact mass calcd for $C_{42}H_{42}N_2O_6$ *m/z* 670.3042, found *m/z* 670.3025. Anal. Calcd for $C_{42}H_{42}N_2O_6$: C, 75.19; H, 6.31. Found: C, 74.93; H, 6.68. **B. From 88:** To a solution of 111 mg (0.13 mmol) of **88** in 7 mL of benzene heated at reflux was added a mixture of 76 mg (0.26 mmol) of tri-*n*-butyltin hydride and 3 mg of AIBN in 3 mL of benzene over a 21-h period using a syringe pump. The mixture was then concentrated in vacuo, and the residue was partitioned between 10 mL of acetonitrile and 10 mL of hexane. The acetonitrile layer was separated, washed with 12 5-mL portions of hexane, and concentrated in vacuo to provide 90 mg of a 1:1 mixture of crude oxindoles **86** and **87**, respectively, by ^{1}H NMR. The mixture of isomers was chromatographed over 3 g of silica gel (dichloromethane; then EtOAc−dichloromethane, 1:9) to provide 69 mg (78%) of a mixture of oxindoles **86** and **87**.

(±)-(1′*R,3*S**,3′a*S**,4′*R**,7′a*S**,8′*R**)-3′a-[(Benzyloxy)methyl]-8′-(2,2-diphenyl vinyl)-3′a,7′a-dihydro-1-(methoxymethyl)-2′-methylspiro[indoline-3,7′(4′*H*)-[1,4]methanoisoindoline]-2,3′,6′(5′*H*)-trione (90).** To a solution of 189 mg (0.282 mmol) of **86** in 15 mL of CH_2Cl_2 was added 100 mg of *p*-toluenesulfonic acid monohydrate. The mixture was stirred for 48 h and then passed through a 6 g pad of silica gel (EtOAc−CH_2Cl_2, 1:9). The eluent was concentrated in vacuo, and the residue was recrystallized from ether−hexane to afford 158 mg (88%) of olefin **90** as a white solid: mp 178−179 °C; IR (CCl_4) 1731, 1708 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (broad s, 1H), 2.41 (dd, J = 19.2, 2.8 Hz, 1H), 2.71 (dd, J = 19.3, 3.3 Hz, 1H), 2.81 (broad s, 1H), 3.03 (s, 3H), 3.31 (s, 3H), 3.75 (broad d, J = 9.4 Hz, 1H), 4.06 (d, J = 10.4 Hz, 1H), 4.13 (broad s, 1H), 4.32 (d, J = 10.4 Hz, 1H), 4.70 and 4.77 (*AB*q, J = 11.9 Hz, 2H), 5.06 (s, 2H), 5.86 (d, J = 9.4 Hz, 1H), 6.94−7.00 (m, 2H), 7.18−7.46 (m, 17H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 30.9 (q), 41.1 (d), 42.2 (t), 49.7 (d), 55.1 (d), 56.1 (q), 57.7 (s), 63.5 (s), 65.6 (d), 66.3 (t), 71.2 (t), 74.1 (t), 109.6 (d), 123.1 (d), 124.5 (d), 127.0 (d), 127.1 (d), 127.43 (d), 127.48 (d), 127.7 (d), 127.9 (d), 128.1 (d), 128.2 (d), 128.4 (d), 128.9 (d), 129.6 (d), 130.5 (s), 137.5 (s), 139.0 (s), 141.7 (s), 141.8 (s), 144.6 (s), 173.3 (s), 174.3 (s), 204.2 (s); mass spectrum, *m/z* (rel intensity) 638 (M, 48), 498 (83), 252 (100), 91 (92); exact mass calcd for $C_{41}H_{38}N_2O_5$ *m/z* 638.2780, found *m/z* 638.2795. Anal. Calcd for $C_{41}H_{38}N_2O_5$: C, 77.08; H, 6.00. Found: C, 77.15; H, 6.08. The structure of **90** was confirmed by X-ray crystallography.

(±)-(1′*R,3*R**,3′a*S**,4′*R**,7′a*S**,8′*R**)-3′a-[(Benzyloxy)methyl]-8′-(2,2-diphenylvinyl)-3′a,7′a-dihydro-1-(methoxymethyl)-2′-methylspiro-[indoline-3,7′(4′*H*)-[1,4]methanoisoindoline]-2,3′,6′(5′*H*)-trione (91). Method A.** To a solution of 90 mg (0.13 mmol) of **87** in 15 mL of CH_2Cl_2 was added 86 mg of *p*-toluenesulfonic acid monohydrate. The mixture was stirred for 48 h and then passed through a 6 g pad of silica gel (EtOAc−CH_2Cl_2, 15:85). The eluent was concentrated, and the residue was recrystallized from MeOH. The solid was collected by filtration and washed with ether to provide 84 mg (98%) of olefin **91** as a white solid: mp (after recrystallization from MeOH) 187−188 °C; IR (CCl_4) 1733, 1715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (broad s, 1H), 2.69 (broad s, 1H), 2.72 (dd partially obscured, J = 3.65 Hz, 1H), 2.99 (s, 3H), 3.00 (m, 2H), 3.14 (s, 3H), 3.55 (broad s, 1H), 4.41 and 4.45 (*AB*q, J = 9.1 Hz, 2H), 4.66 and 4.74 (*AB*q, J = 12.1 Hz, 2H), 4.93 and 5.02 (*AB*q, J = 11.0 Hz, 2H), 5.78 (d, J = 7.4 Hz, 1H), 5.96 (d, J = 8.7 Hz, 1H), 6.83 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H), 7.22−7.59 (m, 16H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 30.6 (q), 39.9 (d), 42.6 (t), 49.5 (d), 54.6 (d), 55.8 (q), 58.2 (s), 63.6 (s), 65.6 (t), 65.8 (d), 71.1 (t), 73.0 (t), 109.9 (d), 123.1 (d), 123.8 (d), 126.2 (d), 126.4 (d), 127.0 (d), 127.2 (d), 127.4 (s), 127.7 (d), 127.9 (d), 128.3 (d), 129.0 (d), 129.1 (d), 138.7 (s), 139.3 (s), 139.8 (s), 142.4 (s), 144.7 (s), 174.0 (s), 174.7 (s), 204.5 (s), two aromatic doublets were not resolved; mass spectrum, *m/z* 638 (M, 16), 607 (49), 91 (100); exact mass calcd for $C_{41}H_{38}N_2O_5$ *m/z* 638.2780, found *m/z* 638.2774. **Method B: Via Isomerization of Oxindole 90.** A mixture of 58 mg (0.09 mmol) of oxindole **90** and 1 mg of potassium cyanide in 5 mL of DMF was warmed to 50 °C for 68 h. The mixture was then cooled, diluted with 20 mL of saturated aqueous ammonium chloride, and extracted with three 20-mL portions of EtOAc. The combined organic layers were washed with four 30-mL portions of brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 55 mg of a 85:15 mixture of oxindoles **91** and **90**, respectively, by ^{1}H NMR. The mixture was recrystallized from MeOH to afford 49 mg (84%) of pure oxindole **91** whose ^{1}H NMR spectrum was identical to material obtained via method A.

(±)-(1*R,3a*S**,4*R**,7a*S**,8*R**)-*N*-Acetyl-3a-[(benzyloxy)methyl]-2′-bromo-3a,4,5,7a-tetrahydro-6-hydroxy-8-(2-methoxy-2,2-diphenylethyl)-2-methyl-3-oxo-1,4-methanoisoindoline-7-carboxanilide Acetate (Ester) (93).** To a solution of 2.6 g (3.67 mmol) of *β*-ketoanilide **83**, 3.7 g (36.6 mmol) of triethylamine, and 20 mg of 4-(dimethylamino)pyridine cooled to 5 °C was added a solution of 1.9 g (18.6 mmol) of acetic anhydride in 5 mL of DMF over a 2-min period. The mixture was stirred at room temperature for 30 min and then poured onto a slurry of crushed ice in 100 mL of saturated aqueous sodium bicarbonate and 300 mL of water. The white solid was collected and washed with water. The solid was dried to afford 2.8 g (98%) of **93** which was used without further purification: IR (film) 1760, 1698 cm^{-1}. The ^{1}H NMR spectrum was complex due to the presence of geometrical isomers. ^{13}C NMR (75.5 MHz, DMSO-d_6, 373 K) δ 20.7 (q), 25.0 (q), 30.9 (q), 33.2 (t), 36.8 (t), 39.3 (d), 50.3 (d), 54.9 (s), 65.2 (t), 70.8 (d), 73.1 (t), 82.1 (s), 120.6 (s), 123.5 (s), 126.6 (d), 126.7 (d),

126.9 (d), 127.0 (d), 127.2 (d), 127.34 (d), 127.36 (d), 127.8 (d), 128.0 (d), 128.1 (d), 129.0 (d), 130.8 (d), 131.0 (d), 132.6 (s), 133.5 (d), 137.6 (s), 139.1 (s), 145.0 (s), 145.2 (s), 167.5 (s), 167.6 (s), 171.5 (s), 174.1 (s), one aliphatic quartet was not resolved. During the course of acquiring ^{1}H and ^{13}C NMR data above 363 K minor peaks began to appear in the spectra due to decomposition; mass spectra, *m/z* (rel intensity) 535 (10), 533 (10), 197 (30) 91 (100). No parent ion was observed.

(±)-(1′*R,3*S**,3′a*S**,4′*R**,6′*R**,7′a*S**,8′*R**)-1-Acetyl-3′a-[(benzyloxy)methyl]-3′a, 5′,6′,7′a-tetrahydro-6′-hydroxy-8′-(2-methoxy-2,2-diphenylethyl)-2′-methylspiro[indoline-3,7′(4′*H*)-[1,4]methanoisoindoline]-2,3′-dione Acetate (Ester) (94), (±)-(1′*R**,3*S**,3′a*S**,4′*R**,6′*S**,7′a*S**,8′*R**)-1-Acetyl-3′a-[(benzyloxy)methyl]3′a,5′,6′,7′a-tetrahydro-6′-hydroxy-8′-(2-methoxy-2,2-diphenylethyl)-2′-methylspiro[indoline-3,7′(4′*H*)-[1,4]methanoisoindoline]-2,3′-dione Acetate (Ester) (95) and (±)-(1′*R**,3*R**,3′a*S**,4′*R**,6′*R**,7′a*S**,8′*R**)-1-Acetyl-3′a-[(benzyloxy)methyl]-3′a,5′,6′,7′a-tetrahydro-6′-hydroxy-8′-(2-methoxy-2,2-diphenylethyl)-2′-methylspiro[indoline-3,7′(4′*H*)-[1,4]-methanoisoindoline]-2,3′-dione Acetate (Ester) (96).** A solution of 1.5 g (1.89 mmol) of bromide **93**, 1.29 g (4.46 mmol) of tri-*n*-butyltin hydride, and 12 mg of AIBN in 500 mL of benzene cooled to 10 °C was irradiated with a mercury arc lamp for 1.5 h. An additional 541 mg (1.85 mmol) of tri-*n*-butyltin hydride was then added, and the mixture was irradiated for an additional 40 min. The mixture was then concentrated in vacuo, and the residue was partitioned between 100 mL of acetonitrile and 100 mL of hexane. The acetonitrile layer was separated, and the hexane layer was extracted with two 50-mL portions of acetonitrile. The combined acetonitrile layers were washed with eight 100-mL portions of hexane and concentrated in vacuo to provide 1.4 g of crude oxindoles which by ^{1}H NMR indicated that the mixture contained approximately 41% of oxindole **96**. The residue was chromatographed over 60 g of silica gel (CH_2Cl_2 to load the sample; then EtOAc−CH_2Cl_2, 5:95) to afford, in the following order, partially purified oxindoles **94**, **95**, and **96**. **Purification of oxindole 96:** All of the fractions containing oxindole **96** were combined and recrystallized from ether−hexane to afford 516 mg (38%) of pure oxindole **96** as a white solid: mp 132−135 °C; IR (film) 1759, 1738, 1711 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (s, 3H), 1.74 (broad s, 1H), 1.94 (broad d, J = 15.1 Hz, 1H), 2.26 (broad s, 1H), 2.45 (s, 3H), 2.56 (m, 4H), 2.92 (broad s, 1H), 2.96 (s, 3H), 3.07 (s, 3H), 3.90 (d, J = 9.2 Hz, 1H), 4.06 (d, J = 9.2 Hz, 1H), 4.59 (d, J = 12.3 Hz, 1H), 4.67 (d, J = 12.3 Hz, 1H), 5.29 (d, J = 7.9 Hz, 1H), 6.39 (d, J = 7.5 Hz, 1H), 6.92 (t, J = 7.3 Hz, 1H), 7.20−7.47 (m, 16H), 8.18 (d, J = 7.9 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.5 (q), 26.0 (q), 31.4 (q), 31.8 (t), 37.8 (t), 39.5 (d), 42.3 (d), 51.0 (q), 52.8 (d), 54.3 (s), 56.7 (s), 65.8 (d), 65.8 (t), 66.2 (d), 72.9 (t), 82.9 (s), 116.5 (d), 123.7 (d), 125.2 (d), 126.3 (s), 126.7 (d), 126.8 (d), 127.0 (d), 127.1 (d), 127.3 (d), 128.0 (d), 128.1 (d), 128.2 (d), 128.5 (d), 138.7 (s), 139.9 (s), 143.5 (s), 145.3 (s), 169.8 (s), 170.7 (s), 175.2 (s), 179.1 (s), one aromatic doublet was not resolved; mass spectrum, *m/z* (rel intensity) 712 (M, 0.4), 589 (4), 531 (8), 197 (78), 91 (100), 43 (57); exact mass calcd for $C_{44}H_{44}N_2O_7$ *m/z* 712.3148, found *m/z* 712.3115. **Purification of oxindole 95:** The filtrate from the recrystallization of oxindole **96** was combined with appropriate mixed fractions from the first column and chromatographed over 30 g of silica gel (CH_2Cl_2 to load the sample; then EtOAc−hexane, 20:80 → 30:70). Fractions containing oxindole **96** were recrystallized from ether−hexane to afford an additional 63 mg (4%) of pure oxindole **96**. The mother liquor was enriched with oxindole **95**. This material was combined with fractions containing oxindole **95** and twice recrystallized from ether−hexane to afford 99 mg (7%) of oxindole **95** as a white solid: mp 211−213 °C; IR (KBr) 1754, 1710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (broad s, 1H), 1.45 (s, 3H), 1.70 (broad dd, 2H), 2.18 (dd, J = 14.2, 8.2 Hz, 1H), 2.28 (t, J = 1.6 Hz, 1H), 2.58 (dd, J = 14.2, 2.3 Hz, 1H), 2.72 (s, 3H), 2.84 (broad, 1H), 2.99 (s, 3H), 3.14 (s, 3H), 3.66 (dd, J = 2.74, 1.8 Hz, 1H), 3.86 (d, J = 9.8 Hz, 1H), 4.02 (d, J = 9.8 Hz, 1H), 4.44 (s, 2H), 5.14 (t, J = 8.4 Hz, 1H), 6.98−7.41 (m, 18H), 8.16 (dd, J = 8.2, 0.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.9 (q), 26.7 (q), 29.7 (t), 31.8 (q), 38.0 (t), 39.3 (d), 40.1 (d), 50.3 (q), 54.2 (s), 56.7 (d), 57.0 (s), 65.8 (t), 69.7 (d), 73.1 (t), 81.7 (s), 116.1 (d), 123.3 (d), 126.6 (d), 126.77 (d), 126.79 (d), 126.8 (d), 127.08 (d), 127.10 (d), 127.16 (d), 127.3 (d), 127.7 (d), 127.80 (s), 127.88 (d), 127.9 (d), 128.0 (d), 128.1 (d), 128.2 (d), 137.9 (s), 139.6 (s), 144.6 (s), 144.8 (s), 170.5 (s), 170.9 (s), 174.8 (s), 178.4 (s), one aliphatic doublet was not resolved and three too many aromatic doublets are present; mass spectra, *m/z* (rel intensity) 712 (M, 0.6), 574 (10), 197 (100), 91 (89); exact mass calcd for $C_{44}H_{44}N_2O_7$ *m/z* 712.3148, found *m/z* 712.3131. **Purification of oxindole 94:** All of the remaining fractions and filtrates containing oxindole **94** were combined and chromatographed over 70 g of silica gel (CH_2Cl_2 to load the sample; then EtOAc−hexane, 20:80, then 25:75) to afford 127 mg (9%) of pure oxindole **94** as a white powder when concentrated from ether−hexane: mp 104−113 °C; IR (neat) 1748, 1707 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (broad d, J = 5.6 Hz, 1H), 1.56 (dd, J = 14.4, 7.4 Hz, 1H), 1.83 (s, 3H), 2.13 (m, 1H), 2.21 (dd, J = 14.1, 8.5 Hz, 1H), 2.48 (t, J = 1.7 Hz, 1H), 2.59 (dd, J = 14.3, 2.5 Hz, 1H), 2.67 (s, 3H), 2.99 (s, 3H), 3.16 (s, 3H), 3.37 (dd, J = 2.7, 1.8 Hz, 1H), 3.60 (broad d, J = 8.4 Hz, 1H), 3.82 (d, J = 10.5 Hz, 1H), 4.13 (d, J = 10.5 Hz, 1H), 4.65 and 4.72 (*AB* q, J = 11.8 Hz, 2H), 5.28 (dd, J = 9.2, 7.5 Hz, 1H), 6.98 (td, J = 7.6, 1.0 Hz, 1H), 7.15−7.40 (m, 16H), 7.50 (dd, J = 7.7, 0.8 Hz, 1H), 8.09 (dd, J = 8.1, 0.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.6 (q), 26.7 (q), 31.8 (q), 33.2 (t), 38.5 (t), 38.7 (d), 44.8 (d), 50.3 (q), 53.8 (s), 55.9 (d), 58.7 (s), 65.7 (d), 67.8 (t), 71.8 (d), 73.9 (t), 81.9 (s), 115.3 (d), 124.1 (d), 125.6 (d), 126.7 (d), 126.8 (d), 126.9 (d), 127.1 (d), 127.5 (d), 127.7 (d), 127.8 (d), 128.0 (d), 128.2 (d), 128.4 (d), 133.5 (s), 137.7 (s), 138.1 (s), 144.9 (s), 145.1 (s), 169.5 (s), 170.5 (s), 174.5 (s), 175.1 (s); mass spectrum, *m/z* (rel intensity) 712 (M, 1), 515 (13), 197 (85), 91 (100), 43 (31); exact mass calcd for $C_{44}H_{44}N_2O_7$ *m/z* 712.3148, found *m/z* 712.3167.

(±)-(1′*R,3*R**,3′a*S**,4′*R**,6′*R**,7′a*S**,8′*R**)-1-Acetyl-3′a-[(benzyloxy)methyl]-8′-(2,2-diphenylvinyl)-3′a,5′,6′,7′a-tetrahydro-6′-hydroxy-2′-methylspiro[indoline-3,7′(4′*H*)-[1,4]methanoisoindoline]-2,3′-dione Acetate (Ester) (99).** To a solution of 68 mg (0.09 mmol) of oxindole **96** in 20 mL of CH_2Cl_2 was added 20 mg of *p*-toluenesulfonic acid monohydrate. The mixture was warmed to reflux for 20 min, then cooled, and concentrated in vacuo. The residue was chromatographed over 7 g of silica gel (CH_2Cl_2 to load the sample; then EtOAc−hexane, 25:75). The material from the column was recrystallized from EtOAc−hexane to afford 54 mg (83%) of olefin **99** as a crystalline solid: mp 234−235 °C, IR (film) 1755, 1711 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 3H), 2.03 (m, partially obscured by broad s at d 2.05, 1H), 2.05 (broad s, 1H), 2.31 (broad s, 1H), 2.45 (s, 3H), 2.57 (m, 1H), 2.90 (s, 3H), 3.15 (dd, J = 2.6, 1.8 Hz, 1H), 3.36 (broad dd, J = 9.2, 2.5 Hz, 1H), 4.04 (d, J = 9.1 Hz, 1H), 4.14 (d, J = 9.1 Hz, 1H), 4.60 (d, J = 12.2 Hz, 1H), 4.68 (d, J = 12.2 Hz, 1H), 5.29 (d, J = 7.9 Hz, 1H), 5.86 (d, J = 9.3 Hz, 1H), 6.16 (dd, J = 7.6, 0.7 Hz, 1H), 6.91 (td, J = 7.6, 1.0 Hz, 1H), 7.18−7.40 (m, 13H), 7.48−7.62 (m, 3H), 8.18 (dd, J = 8.2, 0.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.5 (q), 26.0 (q), 30.6 (q), 31.8 (t), 39.3 (d), 46.6 (d), 52.7 (d), 53.8 (s), 57.2 (s), 65.5 (t), 65.7 (d), 65.7 (d), 72.9 (t), 116.5 (d), 123.8 (d), 125.2 (d), 126.4 (s), 126.5 (d), 127.1 (d), 127.38 (d), 127.40 (d), 127.6 (d), 128.0 (d), 128.2 (d), 128.6 (d), 128.8 (d), 129.6 (d), 138.6 (s), 139.7 (s), 140.1 (s), 140.2 (s), 143.9 (s), 169.4 (s), 170.6 (s), 175.1 (s), 178.8 (s), one aromatic doublet was not resolved; mass spectrum, *m/z* (rel intensity) 680 (M, 57), 193 (79), 167 (24), 91 (100), 43 (19). Anal. Calcd for $C_{43}H_{40}N_2O_6$: C, 75.85; H, 5.93. Found: C, 75.76; H, 5.95.

(±)-(1′*R,3*R**,3′a*S**,4′*R**,6′*R**,7′a*S**,8′*R**)-3′a-[(Benzyloxy)methyl]-8′-(2,2-diphenylvinyl)-3′a,5′,6′,7′a-tetrahydro-6′-hydroxy-2′-methylspiro[indoline-3,7′(4 ′*H*)-[1,4]methanoisoindoline]-2,3′-dione Acetate (Ester) (100).** To a solution of 216 mg (0.303 mmol) of oxindole **99** in 30 mL of CH_2Cl_2 was added 102 mg of *p*-toluenesulfonic acid. The reaction was monitored by thin-layer chromatography (EtOAc−hexane, 1:1), and once starting material was no longer present, 1 mL of MeOH was added to facilitate cleavage of the *N*-acetyl group. The mixture was stirred for an additional 24 h and then diluted with 50 mL of saturated aqueous sodium bicarbonate. The CH_2Cl_2 layer was separated and washed with 50 mL of saturated aqueous sodium bicarbonate and 25 mL of brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was recrystallized from EtOAc−hexane to afford 180 mg (93%) of olefin **100** as a white solid: mp 210−211 °C; IR (KBr) 1729, 1617 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 3H), 1.98 (dd, J = 15.0, 2.6 Hz, 1H), 2.10 (broad, 1H), 2.24 (broad, 1H), 2.52 (ddd, J = 15.6, 8.8, 2.7 Hz, 1H), 2.90 (s, 3H), 3.24

(dd, J = 2.8, 1.8 Hz, 1H) 3.38 (ddd, J = 9.2, 2.4, 2.4 Hz, 1H), 4.09 (d, J = 8.9 Hz, 1H), 4.18 (d, J = 9.2 Hz, 1H), 4.57 (d, J = 12.4 Hz, 1H), 4.74 (d, J = 12.3 Hz, 1H), 5.22 (d, J = 7.7 Hz, 1H), 5.89 (d, J = 9.2 Hz, 1H), 6.04 (d, J = 7.4 Hz, 1H), 6.72 (m, 2H), 7.13 (t, J = 7.8 Hz, 1H), 7.16−7.61 (m, 15H), the NH proton was not resolved; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.7 (q), 30.6 (q), 31.7 (t), 39.6 (d), 45.8 (d), 52.5 (d), 53.9 (s), 57.2 (s), 65.6 (d), 66.0 (t), 66.3 (d), 73.1 (t), 110.2 (d), 120.9 (d), 126.1 (d), 126.5 (d), 126.9 (d), 127.3 (d), 127.4 (d), 127.8 (s), 128.0 (d), 128.2 (d), 128.3 (d), 128.8 (d), 129.6 (d), 138.7 (s), 140.1 (s), 140.3 (s), 141.5 (s), 143.6 (s), 169.3 (s), 176.0 (s), 180.7 (s), two aromatic doublets were not resolved; mass spectrum, *m/z* (rel intensity) 638 (M, 14), 578 (9), 470 (16), 193 (51), 91 (100), 43 (25); Anal. Calcd for $C_{41}H_{38}N_2O_5$: C, 77.09; H, 5.99. Found: C, 77.31; H, 6.05.

(±)-(1′*R,3*R**,3′a*S**,4′*R**,6′*R**,7′a*S**,8′*S**)-3′a-[(Benzyloxy)methyl]-8′-(1,2-epoxy-2,2-diphenylethyl)-3′a,5′,6′,7′a-tetrahydro-6′-hydroxy-2′-methylspiro[indoline-3,7′(4′*H*)-[1,4]methanoisoindoline]-2,3′-dione Acetate (Ester) and (±)-(1′*R**,3*S**,3′a*R*,4′*S**,-6′*S**,7′a*R**,8′*S**)-3′a-[(Benzyloxy)methyl]-3′a,5′,6′,7′a-tetrahydro-6′-hydroxy-2′-methyl-2,3′-dioxospiro[indoline-3,7′(4′*H*]methanoisoindoline]-8′-carboxaldehyde Acetate (Ester) (101).** To a solution of 400 mg (0.626 mmol) of olefin **100** in 15 mL of CH_2Cl_2-MeOH (4:1) chilled to −78 °C was added 60 mL of a 0.094 M solution of ozone gas, prepared by passing ozone through 75 mL of CH_2Cl_2-MeOH (4:1) at a rate of 1.1 mmol/min. The addition of ozone was monitored by thin-layer chromatography (EtOAc−hexane, 1:1) and stopped once starting material was no longer evident. The mixture was then purged of ozone by passing nitrogen gas through the solution, and then 3 mL of dimethyl sulfide was added. The cold bath was removed, and the mixture was stirred at room temperature for 18 h and then concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (first CH_2Cl_2; then EtOAc−CH_2Cl_2, 1:9) to afford 62 mg (15%) of the epoxide derived from **100** as a white solid: mp 178−183 °C; IR (neat) 1726 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (s, 3H), 2.02 (dd, J = 15.7, 3.5 Hz, 1H), 2.17 (t, J = 1.5 Hz, 1H), 2.29 (broad d, J = 8.4 Hz, 1H), 2.36 (broad s, 1H), 2.55 (ddd, J = 15.7, 8.1, 2.1 Hz, 1H), 2.82 (s, 3H), 3.19 (d, J = 8.5 Hz, 1H), 3.38 (dd, J = 2.6, 2.0 Hz, 1H), 4.17 (s, 2H), 4.54 (d, J = 12.3 Hz, 1H), 4.69 (d, J = 12.3 Hz, 1H), 5.18 (d, J = 7.7 Hz, 1H), 5.59 (d, J = 7.7 Hz, 1H), 6.63−6.71 (m, 2H), 7.10 (td, J = 7.7, 0.9 Hz, 1H), 7.16−7.40 (m, 10H), 7.54−7.66 (m, 5H), 7.98 (broad s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.7 (q), 30.0 (q), 32.1 (t), 37.5 (d), 46.7 (d), 52.4 (d), 53.5 (s), 57.1 (s), 62.1 (d), 65.5 (d), 65.7 (t), 66.0 (s), 67.8 (d), 73.1 (t), 109.9 (d), 121.3 (d), 126.1 (d), 126.5 (d), 127.0 (d), 127.5 (d), 127.9 (d), 128.0 (d), 128.1 (s), 128.2 (d), 128.4 (d), 128.5 (d), 128.6 (d), 128.8 (d), 137.1 (s), 138.8 (s), 139.0 (s), 140.9 (s), 169.0 (s), 175.7 (s), 179.9 (s); mass spectrum, *m/z* (rel intensity) 654 (M, 0.1), 563 (36), 167 (73), 91 (100); exact mass calcd for $C_{41}H_{38}N_2O_6$ *m/z* 654.2729, found *m/z* 654.2768. Continued elution (EtOAc−CH_2Cl_2, 2:8 → 3:7 → 1:1 → EtOAc) gave partially purified aldehyde which was recrystallized from EtOAc−hexane to afford 186 mg (61%) of **101**. A second recrystallization from EtOAc−hexane gave 154 mg (51%) of pure **101** as a white solid: mp 235−241 °C; IR (KBr) 3426, 1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77 (s, 3H), 2.06 (dd, J = 17.5, 3.2 Hz, 1H,), 2.34 (broad s, 1H), 2.70 (m, 2H) 2.71 (s, 3H), 3.61 (broad s, 1H), 3.88 (dd, J = 2.9, 1.9 Hz, 1H), 4.21 (s, 2H), 4.57 (d, J = 12.2 Hz, 1H), 4.71 (d, J = 12.2 Hz, 1H), 5.37 (d, J = 7.7 Hz, 1H), 6.84 (d, J = 7.7 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 7.15−7.26 (m, 5H), 7.29−7.40 (m, 2H), 8.14 (broad, 1H), 9.74 (d, J = 1.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.7 (q), 30.1 (q), 31.9 (t), 32.8 (d), 52.8 (d), 53.8 (s), 57.4 (s), 58.6 (d), 63.3 (d), 65.6 (t), 65.6 (d), 73.1 (t), 110.7 (d), 121.3 (d), 125.8 (d), 127.0 (d), 127.4 (d), 127.7 (s), 128.0 (d), 129.0 (d), 138.6 (s), 141.4 (s), 169.1 (s), 175.2 (s), 180.0 (s), 200.6 (d), the overlapping doublet and triplet at 65.6 ppm was assigned from the DEPT spectrum; mass spectrum, *m/z* (rel intensity) 488 (M, 0.4), 397 (55), 91 (100), 43 (41); exact mass calcd for $C_{28}H_{28}N_2O_6$ *m/z* 488.1947, found *m/z* 488.1948.

(±)-(3*R,3′*R**,3a*S**,5*R**,7*R**,9*R**,9a*S**)-9a-[(Benzyloxy)methyl]-3,3a,7,8,9,9a-hexahydro-2-methylspiro[3,7-epoxy-5,9-methanooxocino[4,5-*c*]pyrrole-4(5*H*),3′-indoline]-1(2*H*),2′-dione (103) and (±)-(3*R**,3′*R**,4a*R**,5*S**,8*S**,8a*S**,9*S**)-5-[(Benzyloxy)methyl]-1,3,4,4a,5,7,8,8a-octahydro-1-hydroxy-7-methylspiro[3,5,8-ethanylylidene-6*H*-pyrano[3,4-*c*]pyridine-10,3′-indoline]-2′,6-dione (102).** To a solution of 62 mg (0.127 mmol) of aldehyde **101** in 2 mL of dimethoxyethane was added 7 mL of 6 N aqueous HCl. The mixture was warmed at 48 °C for 16 h, cooled to room temperature, and then made basic with sodium bicarbonate. The mixture was diluted with 20 mL of water and extracted with six 25-mL portions of EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (CH_2Cl_2; then THF−CH_2Cl_2, 2.5:97.5 → 5:95) to afford 8 mg (14%) of cyclic acetal **103** as a white solid: mp 275−310 °C (dec); IR (film) 3223, 1714 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74 (d, 1H), 1.90 (m, 1H), 2.10 (m, 2H), 2.88 (s, 3H), 3.15 (m, 2H), 3.89 (broad s, 1H), 3.97 (d, 1H), 4.46 (d, 1H), 4.49 (s, 2H), 4.96 (d, 1H), 5.45 (broad d, 1H), 6.87 (d, 1H), 7.08 (t, 1H), 7.28 (m, 6H), 7.89 (broad s, 1H), 8.32 (d, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.2 (t), 26.9 (q), 28.6 (t), 32.4 (t), 40.5 (d), 51.1 (s), 53.9 (s), 69.6 (d), 69.7 (t), 72.8 (t), 88.2 (d), 96.0 (d), 109.0 (d), 122.4 (d), 127.1 (d), 127.3 (d), 127.9 (d), 128.6 (s), 128.6 (d), 129.7 (d), 138.5 (s), 140.1 (s), 177.1 (s), 177.9 (s); mass spectrum, *m/z* (rel intensity) 446 (M, 5), 355 (100), 240 (25), 91 (92); exact mass calcd for $C_{26}H_{26}N_2O_5$ *m/z* 446.1841, found *m/z* 446.1847. Continued elution (THF−CH_2Cl_2, 7.5:92.5, then 25:75) afforded 46 mg (65%) of hemiacetal **102** as a mixture of diastereomers: IR (film) 3252 (broad), 1713 cm^{-1}; ^{13}C NMR (mixture of diastereomers, 75.5 MHz, $CDCl_3$) δ 23.1 (t), 23.2 (t), 27.4 (q), 27.5 (q), 29.3 (d), 31.1 (d), 46.7 (d), 48.0 (d), 49.7 (d), 50.0 (d), 53.2 (s), 53.5 (s), 58.6 (s), 59.0 (s), 60.9 (d), 61.9 (d), 65.9 (t), 66.1 (t), 68.3 (d), 70.8 (d), 72.6 (t), 89.7 (d), 91.2 (d), 109.3 (d), 109.7 (d), 121.7 (d), 122.0 (d), 126.8 (d), 126.9 (d), 127.2 (d), 127.8 (d), 128.2 (d), 128.4 (d), 128.6 (d), 130.3 (s), 130.4 (s), 139.0 (s), 140.1 (s), 140.4 (s), 177.6 (s), 177.7 (s), 178.5 (s), 178.7 (s), one aliphatic triplet, three aromatic doublets and one aromatic singlet were not resolved; mass spectrum, *m/z* (rel intensity) 446 (M, 1), 355 (68), 91 (100); exact mass calcd for $C_{26}H_{26}N_2O_5$ *m/z* 446.1841, found *m/z* 446.1854. The ^{1}H NMR spectrum of this material is not reported here due to its complexity.

(±)-(3*R,3′*R**,4a*R**,5*S**,8*S**,8a*S**,9*S**)-5-[Benzyloxy)methyl]-1,3,4,4a,5,7, 8,8a-octahydro-7-methylspiro[3,5,8-ethanylylidene-6*H*-pyrano[3,4-*c*]pyridine-10,3′-indoline]-2′,6-dione (107).** To a solution of 46 mg (0.103 mmol) of hemiacetal **102** in 20 mL of CH_2Cl_2 was added 0.5 mL of triethylsilane followed by 0.5 mL of trifluoroacetic acid. The mixture was stirred for 24 h at reflux, cooled to room temperature, and then diluted with 25 mL of saturated aqueous sodium bicarbonate. The CH_2Cl_2 layer was separated, and the aqueous phase was extracted with three 25-mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed over 3 g of silica gel (CH_2Cl_2; then THF-CH_2Cl_2, 15:85). The combined fractions from the column containing product were concentrated in vacuo, and the residue was recrystallized from EtOAc−hexane to provide 36 mg (83%) of tetrahydropyran **107** as a white solid: mp 187−189 °C; IR (CCl_4) 3199, 1715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (m, 3H), 2.34 (broad s, 1H), 2.76 (s, 3H), 2.81 (dd, J = 13.6, 2.9 Hz, 1H), 3.82 (d, J = 1.3 Hz, 1H), 3.89 (broad s, 1H), 3.98 (dd, J = 11.4, 0.9 Hz, 1H), 4.13 (m, 2H), 4.45 (d, J = 8.6 Hz, 1H), 4.51 and 4.56 (*AB*q, J = 11.8 Hz, 2H), 6.82 (d, J = 7.7 Hz, 1H), 7.03 (td, J = 7.6, 1.1 Hz, 1H), 7.17−7.32 (m, 6H), 7.38 (d, J = 7.6 Hz, 1H), 7.70 (broad s, 1H); ^{1}H NMR (300 MHz, C_6D_6) δ 1.42 (broad d, 1H), 1.64−1.74 (m, 2H), 2.26 (s, 3H), 2.30 (broad s, 1H), 2.70 (dd, J = 14.0, 3.2 Hz, 1H), 3.30 (d, J = 1.4 Hz, 1H), 3.34 (dd, J = 11.4, 2.0 Hz, 1H), 3.55 (dd, J = 11.4, 2.2 Hz, 1H), 3.77 (broad s, 1H), 3.38 (d, J = 8.2 Hz, 1H), 4.62 (d, J = 12.6 Hz, 1H), 4.63 (d, J = 8.1 Hz, 1H), 4.73 (d, J = 12.0 Hz, 1H), 6.30 (dd, J = 7.7, 0.8 Hz, 1H), 6.86 (td, J = 7.5, 1.2 Hz, 1H), 6.96 (td, J = 7.7, 1.3 Hz, 1H), 7.03−7.08 (m, 2H), 7.16−7.18 (m, 1H), 7.28 (ddd, J = 7.4, 1.0, 0.4 Hz, 1H), 7.41−7.44 (m, 2H), the NH was not resolved; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.2 (t), 27.5 (q), 30.9 (d), 43.0 (d), 50.0 (d), 53.7 (s), 58.6 (s), 60.6 (t), 65.8 (d), 66.0 (t), 68.7 (d), 72.7 (t), 109.4 (d), 121.7 (d), 126.8 (d), 127.0 (d), 127.6 (d), 127.8 (d), 128.2 (d), 130.7 (s), 138.9 (s), 140.4 (s), 177.4 (s), 178.6 (s); mass spectrum, *m/z* (rel intensity) 430 (M, 0.2), 339 (65), 91 (100); exact mass calcd for $C_{26}H_{26}N_2O_4$ *m/z* 430.1892, found *m/z* 430.1886.

(±)-(3*R,3′*R**,4a*R**,5*S**,8*S**,8a*S**,9*S**)-1,3,4,4a,5,7,8,8a-Octahydro-5-(hydroxymethyl)-7-methylspiro[3,5,8-ethanylylidene-6*H*-pyrano-[3,4-*c*]pyridine-10,3′-indoline]-2′6-dione (114).** To a solution of 31 mg (0.072 mmol) of benzyl ether **107** in 20 mL of CH_2Cl_2 cooled to −78 °C was added 216 μL (0.216 mmol) of 1 M boron tribromide in

CH_2Cl_2. The mixture was stirred at −78 °C for 30 min and then at −20 °C for 45 min. The mixture was quenched with 10 mL of saturated aqueous sodium bicarbonate and stirred for 3 h. The CH_2Cl_2 layer was separated, and the aqueous layer was extracted with four 25-mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The solid was triturated with two 2-mL portions of ether−hexane (1:1) to provide 23.5 mg (95%) of alcohol **114**: mp (EtOH-hexane) 303−309 °C; IR (KBr) 3464, 1725, 1696 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.90 (broad s, 1H), 1.97−2.08 (m, 2H), 2.15 (broad d, J = 7.6 Hz, 1H), 2.52 (dd, J = 3.1 Hz, second coupling constant obscured by DMSO peak, 1H), 2.64 (s, 3H), 3.65 (broad s, 1H), 3.92−4.09 (m, 5H), 4.32 (dd, J = 10.3, 4.0 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.94 (td, J = 7.6, 0.9 Hz, 1H), 7.20 (td, J = 7.6, 0.6 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 10.35 (broad, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 22.7 (t), 27.2 (q), 30.2 (d), 42.4 (d), 49.6 (d), 53.7 (s), 57.7 (t), 59.3 (s), 60.1 (t), 65.2 (d), 68.3 (d), 109.1 (d), 120.9 (d), 128.2 (d), 128.4 (d), 130.8 (s), 141.6 (s), 178.0 (s), 178.1 (s); mass spectrum, *m/z* (rel intensity) 340 (M, 24), 322 (79), 304 (24), 240 (100), 214 (57), 132 (70), 98 (77); exact mass calcd for $C_{19}H_{20}N_2O_4$ *m/z* 340.1423, found *m/z* 340.1423.

(±)-(3*R,3′*R**,4a*R**,5*S**,8*S**,8a*S**,9*S**)-4,4a,6,7,8,8a-Hexahydro-7-methyl-2′,6-dioxospiro[3,5,8-ethanylylidene-1*H*-pyrano[3,4-*c*]pyridine-10,3′-indoline]-5(3*H*)-carboxaldehyde (115).** To 23.5 mg (0.069 mmol) of alcohol **114** was added 20 mL of CH_2Cl_2−acetonitrile (1:1). The suspension was warmed with a heat gun to coax the alcohol into solution. Once dissolved, the solution was cooled to room temperature, and 77 mg (0.182 mmol) of the Dess−Martin periodinane[52] was added. The mixture was stirred at room temperature for 2 h, concentrated to 5 mL in vacuo, diluted with 15 mL of ether, filtered through Celite, and concentrated in vacuo. The residue was chromatographed over 1 g of silica gel (CH_2Cl_2; then EtOAc−CH_2Cl_2, 1:9 → 2:8 → 3:7) to provide 23 mg (98%) of aldehyde **115** which was recrystallized from EtOAc−hexane to afford 17 mg (71%) of pure aldehyde as a white solid: mp 278−280 °C; IR (KBr) 1723, 1696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.21 (ddd, J = 14.9, 5.5, 2.6 Hz, 1H), 2.28 (d, J = 8.4 Hz, 1H), 2.54 (broad s, 1H), 2.73 (dd, J = 17.9, 2.8 Hz, 1H), 2.81 (s, 3H), 2.87 (m, 1H), 3.74 (broad s, 1H), 3.99 (m, 2H), 4.15 (dd, J = 11.6, 2.2 Hz, 1H), 6.93 (d, J = 7.7 Hz, 1H), 7.09 (td, J = 7.7. 1.0 Hz, 1H), 7.30 (td, J = 7.7, 1.1 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 8.98 (s, 1H), 9.70 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.6 (t), 27.5 (q), 29.5 (d), 42.2 (d), 51.9 (d), 53.1 (s), 60.3 (t), 67.0 (d), 67.4 (s), 68.7 (d), 110.0 (d), 122.3 (d), 127.6 (d), 128.8 (d), 129.5 (s), 140.0 (s), 173.4 (s), 178.0 (s), 194.0 (d); mass spectrum, *m/z* (rel intensity) 338 (M, 13), 228 (20), 188 (40), 152 (100); exact mass calcd for $C_{19}H_{18}N_2O_4$ *m/z* 338.1266, found *m/z* 338.1270.

(±)-(3*R,3′*R**,4a*R**,5*R**,8*S**,8a*S**,9*S**)-1,3,4,4a,5,7,8,8a-Octahydro-7-methyl-5-vinylspiro[3,5,8-ethanylylidene-6*H*-pyrano[3,4-*c*]pyridine-10,3′-indoline]-2′6-dione [(±)-21-Oxogelsemine] (2).** To solution of 16.5 mg (0.048 mmol) of aldehyde **115** in 750 μL of THF was added 500 μL (0.25 mmol) of 0.5 M bis(cyclopentadienyl)-dimethyltitanium[54] in THF. The mixture was warmed under reflux for 24 h and reduced in volume to 100 μL, and an additional 1 mL (0.50 mmol) of a 0.5 M solution of bis(cyclopentadienyl)dimethyltitanium in THF was added. The mixture was stirred at reflux for an additional 24 h, then cooled to room temperature, diluted with 50 mL of ether, filtered through Celite, and concentrated in vacuo. The residue was chromatographed over 1 g of silica gel (CH_2Cl_2; then EtOAc−CH_2Cl_2, 1:9 → 2:8 → 3:7 → 4:6) to provide 14.3 mg (87%) of 21-oxogelsemine (**2**): mp 155−159 °C [lit.[2] (natural product) 148−150 °C]; IR (film) 3222, 1715, 1616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.06 (t, J = 1.3 Hz, 1H), 2.17 (ddd, J = 14.5, 5.6, 2.7 Hz, 1H), 2.22 (m, 1H), 2.49 (dd, J = 7.4, 3.0 Hz, 1H), 2.78 (s, 3H), 2.97 (dd, J = 14.5, 3.0 Hz, 1H), 3.86 (broad s, 2H), 4.00 (dd, J = 11.5, 2.0 Hz, 1H), 4.15 (dd, J = 11.5, 2.2 Hz, 1H), 5.21 (dd, J = 17.8, 1.1 Hz, 1H), 5.49 (dd, J = 11.1, 1.1 Hz, 1H), 6.06 (dd, J = 17.8, 11.1 Hz, 1H), 6.85 (dd, J = 7.7, 0.6 Hz, 1H), 7.05 (td, J = 7.6, 1.1 Hz, 1H), 7.25 (td, J = 7.8, 1.2 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.86 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.0 (t), 27.8 (q), 31.6 (d), 42.5 (d), 53.2 (s), 53.7 (d), 60.4 (s), 60.6 (t), 66.1 (d), 68.9 (d), 109.4 (d), 117.2 (t), 121.9 (d), 127.8 (d), 128.4 (d), 130.3 (s), 133.1 (d), 140.2 (d), 176.8 (s), 177.4 (s); mass spectrum, *m/z* (rel intensity) 336 (M, 100), 254 (13), 122 (69); exact mass calcd for $C_{20}H_{20}N_2O_3$ *m/z* 336.1475, found *m/z* 336.1485.

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Supporting Information Available: Experimental procedures not provided in the Experimental Section and crystallographic data for **46**, **114**, and two structures prepared *en route* to **20** (87 pages). See any current masthead page for ordering and Internet access instructions.

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