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Gelsemium Alkaloids: A Total Synthesis of $dl$-21-Oxogelsemine

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

by

Daniel Kuzmich, B. S.

The Ohio State University
1995

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CHAPTER I
GELSEMINE: BACKGROUND AND SYNTHETIC STUDIES

A. Introduction

In 1985 efforts directed toward a total synthesis of gelsemine (1) and the structurally related natural product 21-oxogelsemine (2) were initiated in our laboratories. In 1994 these efforts have culminated with a total synthesis of 21-oxogelsemine. This thesis will report in full these results. To place this work in perspective, Chapter I will present background information concerning the isolation, biological activity, structure determination and the biosynthesis of gelsemine. This information will be followed by a survey of synthetic studies directed toward key gelsemine intermediates as well as two recently reported total syntheses, with an emphasis placed on incorporation of the oxindole. Chapter 2 will present our retrosynthetic analysis and preliminary studies. Chapter 3 will discuss an improved synthesis of our key tricyclic intermediate. Chapter 4 will discuss further the problem of oxindole construction and the solution we employed. This will be followed by protocols for construction of the tetrahydropyran ring and the vinyl moiety.

B. Background

Gelsemine (1) is the principle oxindole containing alkaloid of Gelsemium sempervirens (Carolina jasmine), a common plant indigenous to the southern United States. First isolated as an amorphous base by Wormley in 1870 from the roots and rhizomes of Gelsemium sempervirens, it was later obtained in crystalline form by Gerrard in 1883. Moore was the first to obtain analytically pure gelsemine as its solvate from acetone, and he reported the correct molecular formula of gelsemine as $\text{C}_{20}\text{H}_{22}\text{N}_{2}\text{O}_{2}$. He reported its melting point (178 °C), specific rotation ($[\alpha]_D +15.9^\circ$ in chloroform), and discovered it contained a basic nitrogen ($\text{pK}_a = \ldots$).
9.37) and thus determined the specific rotation ([α]D +2.6° in water) for the hydrochloride salt.

Gelsemium alkaloids in a crude form obtained from Kou-Wen (Gelsemium elegans) have been used in traditional Chinese medicine for a long time. In the late 19th and early 20th century G. sempervirens was used in the treatment of neuralgia and migraine, but due to toxicity it is no longer used. Gelsemine is a powerful central nervous system stimulant with strychnine-like activity. The toxicity in vivo varies depending on the method of administration as well as the animal used, however, in rabbits the minimum lethal dose subcutaneous is 0.1 mg/kg.

Gelsemine has for the most part resisted extensive chemical degradation, yet in the years leading up to 1959 a number of structural features were identified. These studies confirmed the presence of a spirooxindole, a tertiary basic nitrogen containing one methyl group, a vinyl side chain in close proximity to the spirooxindole, and an unusually stable cyclic ether. The difficulty in ascertaining the correct structure of gelsemine was that these features were all contained in a compact, hexacyclic ring system of high stability.

In 1959, Conroy suggested a structure of gelsemine based on 1H NMR, biosynthetic considerations and a new chemical degradation sequence. In that same year Conroy's findings were independently confirmed by X-ray crystallography. Oxindole alkaloids structurally

![Figure 1. Oxindole Alkaloids Belonging to Gelsemium Species](image-url)
related to gelsemine continue to be isolated. These include 21-oxogelsemine (2) and gelsevirine (3) from *G. sempervirens*\(^{13}\) gelsemine *N*-oxide, 19-(S) and 19-(R)-hydroxydihydrogelsevirine (4) from *G. elegans*\(^{14}\) and 21-oxogelsevirine, 19-(R)-hydroxydihydrogelsemine (5), and 19-(R)-acetoxydihydrogelsevirine (6) from *G. rankinii*\(^{13,15}\)

Some of the chemistry of gelsemine, uncovered during determination of its structure, is shown in Scheme I. Conroy's degradative sequence gave rigorous proof of the presence of the CH\(_2\)=CH-C(C)\(_2\)-CH\(_2\)-N substructure in gelsemine, and also established that C(20) was part of a 5-membered ring.\(^7\) Lithium aluminum hydride reduction of gelsemine followed by protection of the oxindole with acetic anhydride gave \(N_a\)-acetyldeoxogelsemine. Treatment of \(N_a\)-acetyldeoxogelsemine with iodomethane gave \(N_a\)-acetyldeoxogelsemine \(N_a\)-methiodide.

**Scheme I. Conroy's Degradative Studies on Gelsemine**

![Scheme I. Conroy's Degradative Studies on Gelsemine](image)

Oxidation of the corresponding \(N_b\)-methohydroxide (7) with alkaline permanganate provided betaine 8 which underwent concerted decarboxylation-β-elimination as a dilute solution in dimethylformamide to give pentacyclic olefin 9. The \(^1\)H NMR of 9 was consistent with the presence of an exocyclic methylene. Further proof of structure 9 was obtained by
microhydrogenation with platinum in acetic acid to provide dihydro derivative 10, which by proton NMR contained an additional C-methyl group. Also, osmium tetraoxide-periodate oxidation of 9 gave amino ketone 11 with an infrared adsorption at 1748 cm\(^{-1}\), evidence for the presence of a cyclopentanone. Neutral product 12 was believed to arise via a retro-Mannich decomposition of 11.

Conroy also proposed detailed biogenetic arguments as shown in Scheme II, and suggested 13 was a likely precursor to gelsemine. This molecule bears a close structural relationship to rhyncophylline (14), and may be derived from equivalents of tryptamine and 3,4-dihydroxyphenylalanine. Oxidation of 13 would give intermediate 15 which in turn could undergo an intramolecular Michael addition to afford gelsemine substructure 16 via construction of the critical C(6)-C(20) bond. Construction of the C(5)-C(16) bond would then be achieved via an internal Mannich condensation to give 17. Finally, decarboxylation of 17 followed by adjustment of oxidation states, and ring closure, would afford gelsemine.

**Scheme II. Conroy's Proposed Biosynthesis of Gelsemine**
While Conroy's arguments were useful in the elucidation of the structure of gelsemine, Zenk and co-workers demonstrated that 13 was an unlikely precursor to gelsemine as shown in Scheme III.\textsuperscript{16} Secologanin (18) is known to be the ultimate precursor for many of the C(9)/C(10) non-tryptamine carbon skeletons common to the majority of indole alkaloids. Condensation of 18 with tryptamine (19) yields two epimers, vincoside (20) and strictosidine (21). In feeding experiments with \emph{Gelsemium sempervirens}, [6-\textsuperscript{14}C]-labeled strictosidine was incorporated into gelsemine (0.47\% incorporation). Indeed, strictosidine has been shown to be the sole biosynthetic precursor for many simple monoterpenoid indole alkaloids as well as more complex structures such as gelsemine and strychnine (22). Furthermore, while the absolute configuration of gelsemine is unknown, based on these biosynthetic considerations, and if the stereochemistry of the starred carbon in 21 is maintained throughout the biosynthesis, 1 would represent the natural enantiomer.

**Scheme III. Accepted Biosynthesis of Gelsemine**

\[ \text{CHO} \quad \overset{\star}{\text{O}} \quad \overset{\text{Glu}}{\text{O}} \quad \overset{\text{CHO}}{\text{CH}_3\text{O}_2\text{C}} \quad + \quad \overset{\text{NH}_2}{\text{H}} \quad \overset{\text{H}}{\text{6}} \quad \overset{\text{N}}{\text{H}} \quad \overset{\text{H}}{\text{N}} \quad \overset{\text{Glu}}{\text{O}} \quad \overset{\text{CH}_3\text{O}_2\text{C}}{\text{O}} \]

\[ \overset{\text{18}}{\text{19}} \quad + \quad \overset{\text{20}}{\text{21}} \]

Recently, Sakai and co-workers have proposed additional details of the biogenetic route to \emph{Gelsemium} alkaloids, and these include the conversion of 21 to gelsemine.\textsuperscript{14} They are based
on the structures of isolated compounds and include a new alkaloid, 19-(Z)-taberpsychine (23), whose biosynthesis was proposed as described in Scheme IV. If strictosidine is hydrolyzed to 24, oxidization of 24 followed by ring closure could occur to give intermediate 25, which could serve as a precursor to sarpagine type indole alkaloids including koumidine (27). Finally, ring opening (C/D) of 27, and trapping of a cation intermediate by the hydroxymethyl group would afford 23. The viability of these early steps have been demonstrated in a partial synthesis of koumine that follows this route.17

Scheme IV. Sakai’s Proposed Biosynthesis of Gelsemine

The conversion of 23 to gelsemine is shown in Scheme V. Oxidation at the β-position of indole 23 to 28, followed by rearrangement to an oxindole, would provide entry to the humantenine-type alkaloids. However, elimination of HX across carbons 6 and 7 would give indolenine 29. An ene type reaction between C(20) and C(6) would give indole 30. Finally, an oxidation and rearrangement would afford gelsemine. Further oxidation processes would give gelsevirine (3), 21-oxogelsemine (2), and 19-hydroxydihydrogelsevirine (4).
Scheme V. Sakai’s Proposed Biogenetic Synthesis of Gelsemine Continued

III. Synthetic Studies

The earliest approach reported toward a synthesis of gelsemine was described by Autrey as outlined in Scheme VI. The key steps were to involve an intermolecular Michael addition.

Scheme VI. Autrey’s Approach to Gelsemine
addition of enamine 31 to C(3) of N-benzylisatylidene-3-acetaldehyde (32) to give 33 followed by an intramolecular cyclization to afford tetracycle 34. This plan eventually proved unsuccessful due to decomposition products which could be rationalized via breakdown of adduct 35, as well as products derived from addition of the enamine to the other terminus of the olefin in 32.

Another early approach recognized that gelsemine contained a spiro[indole-3,7′[isoquinoline] skeleton. In 1970, Stevens reported the preparation of isoquinoline derivatives as shown in Scheme VII. Treatment of N-methylindol-2(3H)-one (36) with ethyl acrylate gave 37. Dieckman condensation gave 38, and further reaction with cyanoacetamide gave spiro[indoleisoquinoline]-2-one 39.

Scheme VII. Steven's Preliminary Approach to Gelsemine

Both Autry's and Steven's approach to gelsemine did not proceed past these initial stages, but are noteworthy in that both incorporate the oxindole early in the synthesis. This is in sharp contrast to subsequent workers who would reserve this task for the latter part of the synthesis. As a result, a number of elegant syntheses of caged substructures of gelsemine began to appear, and it soon became apparent that installation of the oxindole with correct stereochemistry and in high yield was not going to be an easy task.

In 1988, Stork reported a synthesis of gelsemine substructure 50 as shown in Scheme VIII. The approach features (i) a radical cyclization (40 → 41), and (ii) an internal alkylation-transannular Claisen rearrangement (48 → 50) which set the stereochemistry at the starred carbon for installation of the oxindole. The route begins with a tributylstannane-initiated radical cyclization of 40 to give bicyclic ester 41 in 95% yield. The trisubstituted ester 42 was then
prepared via a selenation-oxidation-elimination sequence in 78% yield. Reduction of 42 with diisopropylaluminum hydride gave allylic alcohol 43 in 95% yield, and esterification of 43 gave 44 in 95% yield.

Scheme VIII. Stork's Approach to Gelsemine

\[
\begin{align*}
\text{CH}_3\text{O}_2\text{C} & \quad \text{Br} \quad \text{OEt} \quad 40 \\
\text{a} & \quad \rightarrow \quad \text{CH}_3\text{O}_2\text{C} & \quad \text{Br} \quad \text{OEt} \quad 40 \\
\text{b,c} & \quad \rightarrow \quad \text{CO}_2\text{Et} & \quad \text{Et} \quad 41 (95\%) \\
\text{d} & \quad \rightarrow \quad \text{CO}_2\text{Et} & \quad \text{Et} \quad 42 (78\%) \\
\text{e} & \quad \rightarrow \quad \text{OH} & \quad \text{Et} \quad 43 (95\%) \\
\text{h} & \quad \rightarrow \quad \text{OR} & \quad \text{SiMe}_3 \quad 47 \\
\text{f} & \quad \rightarrow \quad \text{R} = \text{Et} \quad (95\%) \quad 44 \\
\text{g} & \quad \rightarrow \quad \text{R} = \text{H} \quad (75\%) \quad 45 \\
\text{g} & \quad \rightarrow \quad \text{R} = \text{COC(CH}_3)_3 \quad (85\%) \quad 46 \\
\text{i} & \quad \rightarrow \quad \text{Ph} & \quad \text{O} \quad 48 (67\%) \\
\text{j} & \quad \rightarrow \quad \text{Ph} & \quad \text{O} \quad 49 \\
\text{k} & \quad \rightarrow \quad \text{N} & \quad \text{CH}_3 \quad 1 \\
\text{l} & \quad \rightarrow \quad \text{HO} & \quad \text{O} \quad 51 \\
\end{align*}
\]

(a) n-Bu\textsubscript{3}SnH, PhH, AIBN, \Delta (b) LDA, PhSeSePh, THF (c) m-CPBA, CH\textsubscript{2}Cl\textsubscript{2}; Et\textsubscript{3}N (d) DiBAL-H, ether (e) PhCH\textsubscript{2}COOH, DCC, DMAP, CH\textsubscript{2}Cl\textsubscript{2} (f) Amberlite-H\textsuperscript{+}, THF-H\textsubscript{2}O (g) Me\textsubscript{3}CCOCl, CH\textsubscript{2}Cl\textsubscript{2}, DMAP, Et\textsubscript{3}N (h) LDA, TMSCl, THF (i) TMSOTf (j) LDA, THF, TMSCl (10 eq).
Replacement of the ethoxy group in 44 to a better leaving group was accomplished via acid hydrolysis to 45, followed by esterification with trimethylacetyl chloride to give 46. Alkylation to give lactone 48 was carried out by forming the trimethylsilyl ketene acetal of 46, followed by cyclization triggered by trimethylsilyl triflate. The Claisen rearrangement was accomplished via the silyl enol ether of lactone 48 to give 50 in 96% yield. This method would offer a rapid entry to gelsemine assuming the route can be modified such that the two amino functions required for construction of the oxindole and pyrrolidine ring could be introduced. A subsequent publication by the Stork group suggests that a rhodium-catalyzed carbon-hydrogen insertion of an α-diazoketone may be used to construct the pyrrolidine ring (50 → 51 → 52 → 1).21

In 1982, the Fleming group revealed an interest in the total synthesis of gelsemine, and reported two new stereochemically complementary oxindole syntheses as shown in Scheme IX.22 In the first route, ketone 53 was reacted with α-lithioformanilide, prepared by metal halogen exchange between n-BuLi and o-bromoformanilide. The resulting alcohol 54 was treated with

**Scheme IX. Fleming's Oxindole Syntheses**

\[ \text{53} \xrightarrow{\text{a}} \text{54} \text{ (37\%)} \xrightarrow{\text{b}} \text{55} \text{ (44\%)} \xrightarrow{\text{c}} \text{56} \text{ (94\%)} \]

\[ \text{57} \text{ (59\%)} \xrightarrow{\text{d,e}} \]

\[ \text{58} \text{ (68\%)} \text{ (30\% from 57)} \]

(a) o-bromoformanilide, n-BuLi, THF (b) NaCN, DMF (c) HCl, H₂O, Δ (d) (o-fluorobenzylidene)triphenylphosphorane (e) m-CPBA (f) AlCl₃, CH₂Cl₂ (g) CrO₃ (h) SOCl₂, NH₃ (i) NaH, diglyme
cyanide ion in dimethylformamide to give aminoindolenine 55, and exposure to aqueous acid gave oxindole 56.

In the second route, treatment of 53 with the appropriate Wittig reagent followed by oxidation with m-chloroperbenzoic acid gave olefin 57. Acid catalyzed rearrangement of 57 gave ketone 58 and desired aldehyde 59 in a 1:3 ratio, respectively. In a series of steps 59 was converted to amide 61 which cyclized upon treatment with sodium hydride in diglyme to afford oxindole 62.

Shortly after this initial report, Fleming described a synthesis of ketone 76 shown in Scheme X. The key features were (i) a Diels-Alder reaction between 1-tetrahydropyranyl-oxy-cyclohexa-1,3-diene (63) and methyl-β-nitroacrylate (64) to provide bicyclo[2.2.2]octane 65, (ii) a Lewis acid catalyzed rearrangement of 67 to bicyclo[3.2.1]octane 69, and (iii) formation of one of the quaternary center via an intramolecular reaction of an allylsilane with an acyliminium ion.

In the first key step, a Diels-Alder reaction gave 65 in modest yield due to low endo selectivity, however, considerable functionality was introduced in this single step. In a series of reactions, first the nitro group in 65 was reduced with aluminum amalgam, and the resulting amine was protected with ethyl chloroformate. Next, the ester was reduced with lithium aluminum hydride, and the resulting alcohol was acylated with acetyl chloride. Finally, the tetrahydropyranyl ether was hydrolyzed to give 66 in 81% yield. The key rearrangement (67 → 69) was accomplished by epoxidation of 66 to give 67 in 85% yield followed by treatment with magnesium bromide to afford 69, presumably proceeding through intermediate 68. Formation of the cyclic ether involved, bromination of ketone 69, followed by a protection of the alcohol as the tetrahydropyranyl ether, and then treatment of 70 with potassium carbonate in water which effectively accomplished acetate hydrolysis and displacement of the bromide. Deprotection of the tetrahydropyranyl ether in ethanolic hydrogen chloride gave diethyl ketal 71. The next phase of the synthesis involved formation of the quaternary center. Oxidation of alcohol 71 gave 72 in 94% yield. Treatment of 72 with vinylmagnesium bromide gave allylic alcohol 73, which upon reaction in an SN2' fashion with thionyl chloride gave 74 in 97%. Displacement of the allylic chloride in 74 with lithium bis(trimethylsilyl)cuprate gave allyl silane 75, which was treated with
1,3,5-trioxane in the presence of formic acid to afford 76 in 85% yield.

Scheme X. Fleming's Approach to Gelsemine

(a) Diels-Alder (b) Al/Hg, MeOH (c) EtO₂CCl (d) LiAlH₄ (e) AcCl, Et₃N (f) PyH⁺TsO⁻, EtOH (g) p-nitroperbenzoic acid (h) MgBr₂ (i) PhNMe₃Br₃ (j) DHP, H⁺ (k) K₂CO₃, H₂O (l) PyH⁺TsO⁻, EtOH (m) PCC, Al₂O₃ (n) vinylmagnesium bromide (o) SOCl₂, Et₃N, THF (p) (Me₃Si)₂CuLi, THF, HMPA (q) (CH₂O)₃, HCO₂H.

Unfortunately, with ketone 76 in hand, neither of the oxindole syntheses shown in Scheme IX was successful in providing gelsemine or its C(7) epimer. Fleming speculated that
the neighboring carbon-oxygen bond may be detrimental in some way to the carbocation chemistry in the two routes. As a means of avoiding carbocation chemistry, Fleming turned to a modified Brunner oxindole synthesis which also failed.\(^{24}\) Again, Fleming speculated that the neighboring C(3) oxygen departed as a nucleofuge from the intermediate C(7) carbanion.

With the intent of avoiding both carbocation and carbanion chemistry, Fleming reported a new oxindole synthesis shown in Scheme XI.\(^{25}\) Adamantanone (77) was condensed with nitromethane to provide \(\alpha,\beta\)-unsaturated nitro compound 78. Conjugate addition of triphenylaluminum to 78 gave nitroalkane 79. In a series of reactions 79 was dehydrated with sodium methoxide followed by treatment with acetyl chloride. Hydration of the resulting nitrile oxide gave a hydroxamic acid, which upon methylation gave 80 in 69% yield. Treatment of 80 with \(t\)-butyl hypochlorite followed by reaction with zinc acetate gave oxindole 81 in 85% yield, and reduction of the nitrogen-oxygen bond with sodium amalgam gave oxindole 82. Finally, a reaction of triphenylaluminum with 83 was performed to explore the effect of coordination of the aluminum reagent with the oxygen atom and its ability to control stereochemistry in a gelsemine.

Scheme XI. Fleming’s Alternate Oxindole Synthesis

\[77 \rightarrow 78 (91\%) \rightarrow 79 (91\%) \rightarrow 80 (33\%)\]

\[83 \rightarrow 84 (36\%) \rightarrow 82 (100\%) \rightarrow 81 (85\%)\]

(a) CH\(_3\)NO\(_2\), H\(_2\)NCH\(_2\)CH\(_2\)NH\(_2\) (b) Ph\(_3\)Al, xylene (c) NaOMe, MeOH, AcCl (d) H\(_2\)SO\(_4\), acetone (e) Mel, Na\(_2\)CO\(_3\), MeOH (f) t-BuOCl, CH\(_2\)Cl\(_2\), Zn(OAc\(_2\)) (g) Na-Hg, MeOH

with \(t\)-butyl hypochlorite followed by reaction with zinc acetate gave oxindole 81 in 85% yield, and reduction of the nitrogen-oxygen bond with sodium amalgam gave oxindole 82. Finally, a reaction of triphenylaluminum with 83 was performed to explore the effect of coordination of the aluminum reagent with the oxygen atom and its ability to control stereochemistry in a gelsemine.
Analog 84 was obtained in 36% yield. To date, application of this approach to ketone 75 has not been reported.

The Overman group is also working on a synthesis of gelsemine. Recently, as part of their ongoing studies, they disclosed a means of controlling oxindole stereochemistry by tailoring the palladium catalyst in an intramolecular Heck reaction. This required the preparation of tricyclic precursor 95 whose synthesis is shown in Scheme XII.27
The key features were (i) an anionic aza-Cope rearrangement (89 → 92) to afford isoquinoline derivative 92, and (ii) an intramolecular Mannich reaction (93 → 95) to afford tricycle 95. The synthesis begins with an aluminum trichloride catalyzed Diels-Alder between diene 85 and methyl acrylate that proceeds with high stereoselectivity (endo:exo = 8-10:1). Introduction of the terminal vinyl group was accomplished by oxidation with selenium dioxide followed by a Wittig methylenation of the resulting aldehyde to afford 87 in 62-90% yield. Curtius rearrangement of 87 gave 88 in 64% yield. Treatment of 88 with chloroacetonitrile followed by deprotection of the triisopropylsilyl group gave hydroxy cyanomethylamine 89. The [3,3]-sigmatropic rearrangement was accomplished with excess potassium hydride in tetrahydrofuran to give cis-perhydroisoquinoline 92. Treatment of 92 with bromine incorporated functionality at what would eventually become C(16) in gelsemine, and provides a potential handle for construction of the tetrahydropyran ring. Finally, a Mannich cyclization gave ketone 95.

With ketone 95 in hand, incorporation of the oxindole via the Heck reaction was explored. This approach would provide necessary functionality at C(3) for closure of the tetrahydropyran ring. Initial attempts to perform the Heck reaction (97 → 98) under standard conditions (10-20% Pd(PPh₃)₄, CH₃CN-Et₃N, Δ) proceeded in high yield, however stereoselectivity at C(4) was approximately 1.6:1. While this ratio favored the desired isomer, modified Heck conditions with a ligandless palladium(0) catalyst increased this ratio to 9:1.

Overman's improved oxindole synthesis, as well as an attempt at closing the tetrahydropyran ring, is shown in Scheme XIII. Ketone 95 was converted to the enol triflate 96 followed by carbonylation with a palladium(0) catalyst in the presence of 2-bromoaniline. Protection of the resulting anilide with 2-(trimethylsilyl)ethoxymethyl chloride gave 97 in 79% yield. Modified Heck conditions gave gelsemine intermediate 98 in 89% yield. Now, all that remains to complete a total synthesis of gelsemine is to construct the tetrahydropyran ring. Although this has yet to be accomplished, one interesting attempt is described below. Treatment of 98 with cyanide ion, surprisingly, gave aziridine 99 in 63% yield. This was converted to an aziridinium ion upon treatment with methyl triflate, and subsequent reaction with disodium tetracarbonylferrate, followed by a purge of the reaction mixture with carbon monoxide, gave cyclopentanone 100. The intent was to obtain a cyclopentanone which could be ring expanded.
via a Baeyer-Villiger oxidation, and then reduced to provide gelsemine. Unfortunately, formation of cyclopentanone 100 involves an unexpected rearrangement, and will not be amenable to this plan.

Scheme XIII. Overman's Stereoselective Oxindole Synthesis

In 1987, Speckamp and coworkers disclosed a strategy for the total synthesis of gelsemine. A total synthesis shown in Scheme XIV was reported in early 1994. The approach involved a stereospecific cyclization reaction of a triisopropylsilyl enol ether with an N-acyliminium ion intermediate which closely resembles intermediates disclosed in Conroy’s proposed biosynthesis (Scheme II). A Diels-Alder reaction between diene 101 and N-methylmaleimide (102) gave imide 103 in excellent yield as the pure endo-adduct. Elaboration of 103 to ethoxylactam 104 set up the key N-acyliminium ion cyclization. Treatment of 104 with BF₃·Et₂O gave aldehyde 106 as a separable mixture (3:1) of isomers at C(5). Reduction of aldehyde 105 with sodium borohydride gave alcohol 106 which was protected as the thexylidimethylsilyl ether.
The olefin was subjected to allylic oxidation to give enone 108.

Scheme XIV. Speckamp's Total Synthesis of Gelsemine

(a) PhMe, Δ (b) BF₃·OEt₂, CH₂Cl₂, 10 °C, 10 min (c) NaBH₄, EtOH (d) TDSCl, imidazole, DMF (e) CrO₃, 3,5-dimethylpyrazole, CH₂Cl₂, -30 °C (f) L-selectride, THF, -78 °C then Tf₂NPh, rt (g) Pd(OAc)₂, PPh₃, Et₃N, CO, 2-bromoaniline, DMF, rt, 24 h (h) NaH, SEMCl, THF, rt, 2 h (i) Pd₂(dba)₃ (dba = benzylidene acetone), Et₃N, PhMe, Δ, 4 h (j) Bu₄NF, THF, rt, 2 h (k) HgO, Tf₂O, N,N-dimethylaniline, MeNO₂, rt, 3 d (l) NaBH₄, NaOH, CH₂Cl₂, EtOH (m) Bu₄NF, THF, 4 Å sieves, Δ, 4 h (n) AlH₃, THF, -65 to 0 °C.
Initially, Speckamp explored Fleming's dianion method shown in Scheme VII to incorporate the spirooxindole from enone 108. Unfortunately, the oxindole stereochemistry obtained was incorrect. Thus, enone 108 was reduced in a 1,4-selective manner with L-selectride and subsequent \textit{in situ} trapping of the lithium enolate with \textit{N}-phenyltrifluromethanesulfonamide gave enol triflate 109 in 65\% yield. Exposure of 109 to palladium catalyzed carboxylation in the presence of 2-bromoaniline gave anilide 110 in 70\% yield and protection with 2-(trimethylsilyl)ethoxymethyl chloride gave 111. Cyclization under standard Heck conditions [\text{Pd(OAc)}_2, \text{PPh}_3, \text{Et}_3\text{N}, \text{MeCN}, \Delta, 3 \text{ days}] gave a single oxindole, however again, the observed stereochemistry was incorrect. Finally, using the modified Heck conditions disclosed by Overman, spirooxindole 112 was obtained in 60\% yield from 111 after removal of the thexyldimethylsilyl protecting group. Formation of the tetrahydropyran ring was effected with mercury(II) triflate in \textit{N,N}-dimethylaniline and reduction of the resulting organomercurial with alkaline sodium borohydride gave SEM-protected 21-oxogelsemine 113 in 48\% yield. Treatment of 113 with tetrabutylammonium fluoride gave 21-oxogelsemine (2), and reduction of 2 with alane gave gelsemine (1) in 53\% yield.

In 1994, the Johnson group reported a formal synthesis of both gelsemine and 21-oxogelsemine. Their approach involved incorporation of the oxindole portion of gelsemine from ketone 125, whose synthesis is shown in Scheme XV.\textsuperscript{30} In a key reaction, photoinduced cycloaddition of the triene 114 gave diester 115 in 53\% yield. Reduction of 115 with lithium aluminum hydride followed by treatment with silver acetate-iodine gave 116. Functional group manipulation converted the alcohol to the methyl ester. The acetate was hydrolyzed with base, and the resulting alcohol was protected as the \textit{t}-butyldimethylsilyl ether to give 117. The tetrahydrofuranyl ether of 117 was selectively cleaved with phenyltrimethylsilylselenide, and oxidative deselenylation gave olefin 118. Desilylation of 118 followed by oxidation of the resulting alcohol gave cyclobutane-\textit{ß}-ketoester 119. Cleavage of the cyclobutanone 119 was accomplished with methylamine to afford 120, as a single diastereoisomer. A reduction-oxidation sequence gave aldehyde 121 which was epimerized with methanolic potassium carbonate to allow for cyclization to hydroxy lactam 122. Dehydration of 122 gave the corresponding enamide.
Scheme XV. Johnson's Synthesis of Ketone 125

and treatment with buffered methanolic bromine gave 123. Desilylation, oxidation, and conversion of the resulting ketone to the silyl enol ether gave 124. An intramolecular Mannich
reaction with trifluoroacetic acid gave a caged intermediate resulting from formation of the C(5)-
C(6) bond, and reductive debromination of this intermediate gave ketone 125.

With ketone 125 in hand, an intermediate that closely resembles Fleming’s ketone 76, the
next task was to incorporate the oxindole as shown in Scheme XVI.\(^3\) Condensation of the
ketone 125 with lithiated 1-(methoxytrimethylsilylmethyl)benzotriazole 126 gave a mixture of (E)-
and (Z)-methoxymethylene isomers in a combined yield of 65\%, a nOe experiment indicated that
the (E)-isomer 127 was predominant. Separate irradiation of both isomers in acetonitrile gave
identical mixtures, which were combined to afford 128 and 129 (2:1 respectively) in 36\% yield. A
formal synthesis was completed by oxidation of natural gelsemine, using a three step sequence,
to 21-oxogelsemine (2) followed by conversion of 21-oxogelsemine to minor isomer 129 with
trimethyloxonium tetrafluoroborate. Acid hydrolysis of imino-ether 129 then gave 21-
oxogelsemine, and reduction of 21-oxogelsemine with diisobutylaluminum hydride gave
gelsemine (1).

**Scheme XVI. Johnson’s Formal Synthesis of Gelsemine**

(a) LDA (2 equiv.) (b) n-BuLi (2 equiv.) (c) ketone 125 (d) hv, MeCN, pyrex (e) DEAD (f) MeOH
(g) CrO\(_3\) (h) Me\(_3\)OBF\(_4\) (i) HCl, H\(_2\)O, THF (j) DIBAL-H
Gelsemine has long been one of the few remaining challenges in indole alkaloid synthesis, and finally, 35 years after its structure was reported, it has succumbed to total synthesis. The apparently impregnable nature of the molecule stems from the complexity of its bridged tetracyclic caged substructure onto which an oxindole of correct stereochemistry must be installed. The next chapter will describe our approach toward a total synthesis of gelsemine.
CHAPTER II

RETROSYNTHETIC ANALYSIS AND PREPARATION OF A KEY TRICYCLIC INTERMEDIATE

A. Introduction

This chapter is presented as a means of highlighting the accomplishments of previous group members who preceded my involvement with the gelsemine project. Their work built the foundation upon which a total synthesis of 21-oxogelsemine was eventually realized. This chapter will describe our retrosynthetic analysis, and preliminary studies which culminated in the preparation of tricyclic and tetracyclic substructures of gelsemine.

B. Retrosynthetic Analysis

Our approach to gelsemine follows the retrosynthetic analysis shown in Scheme XVII. We anticipated that gelsemine might be prepared from intermediate 130, where X, Y, and Z were suitable for the introduction of the oxindole, tetrahydrofuran, and vinyl moieties, respectively. Intermediate 130 was to come from lactam 134 via cyclization of an α-acylamino radical, which was to establish the C(5)-C(16) carbon bond of gelsemine. This approach was based on previous research from this group demonstrating that α-acylamino radical cyclizations can be used to construct C-C bonds adjacent to nitrogen.32

In depth consideration of Scheme XVII raises a number of conformational issues, as suggested by structures 131-133. Each of these will be discussed within the context of experimental observations resulting from the cyclization of various functionalized radical precursors of type 134. The syntheses of these radical precursors (135, 137, and 139) have been reported elsewhere and thus, will not be detailed here. It is noted, however, that their preparation closely parallels the synthesis of tricyclic intermediate 154, whose preparation will be discussed in detail at the end of this chapter.33
C. Preliminary Studies

Initially, Choi explored construction of the C(5)-C(16) bond of gelsemine using an α-acylamino radical cyclization that disregarded the functionality needed to construct the oxindole and tetrahydropyran moieties (equation 1). Thus, he prepared cyclization precursor 135 (134 where X = Y = Z = H). Treatment of 135 with tri-n-butyltin hydride under high dilution conditions gave only reduction product 136. This was not surprising since one would expect conformation 133 to be more stable than conformation 131 and 132. Apparently, intramolecular cyclization of the radical generated from 135 was too slow to compete with intermolecular reduction.

To deal with this problem, a strategy was adopted which not only enhanced the rate of cyclization, but also introduced functionality at C(16) that would serve as a handle for construction of the tetrahydropyran ring. Thus, Ramesh prepared cyclization precursor 137 (134 where X = Y = H and Z = CO$_2$Et). Treatment of 137 with tri-n-butyltin hydride under dilute conditions gave 138 in 68% yield along with material epimeric at C(16) in 7% yield (equation 1). While the carbethoxy group provided the rate enhancement needed to overcome bimolecular reduction, cyclization did not provide the C(16) stereochemistry needed for gelsemine. Clearly, cyclization occurred via the boat-like transition state 132, contrary to current transition state models for 5-hexenyl radical...
cyclizations which suggest that chair-like transition states are preferred, for example 131. A possible explanation for this observation is that $A^{1,3}$ strain between the $\alpha$ vinyl hydrogen of the carbethoxy group and C(3) and/or the C(2) methylene is present in 131, but absent when cyclization occurs via transition state 132. While this result was encouraging, it was clear that stereochemistry at C(16) would have to be adjusted at some point during the synthesis of gelsemine.

![Chemical structure](image)

Next, Lee prepared cyclization precursor 139 (134 where $X = H$, $Y = CH_2OCH_3$, and $Z = CO_2Et$) which extended this methodology to handle functionality suitable for incorporation of the C(20) vinyl moiety (Scheme XVII). Not surprisingly, treatment of 139 with tri-$n$-butyltin hydride and AIBN under high dilution conditions gave 140 and 141 in a 12:1 ratio, respectively (equation 2).

![Chemical structure](image)

Next, Ha developed a procedure for the synthesis of tricyclic substructure 154 as shown in Scheme XVIII which, in addition to the aforementioned functionality, carried at C(3) a handle to introduce the oxindole portion of gelsemine. The synthesis began with the preparation of diene 145.
Scheme XVIII. Ha’s Synthesis of Tricyclic Intermediate 154

(a) O₃, toluene, -78 °C; then H₂/Pd-C (b) Ph₃P=CHCOCH₃, CH₂Cl₂ (c) LDA, THF, -78 °C; then TMSCI (d) N-methylmaleimide, toluene, Δ (e) THF-H₂O-MeOH, Dowex-50 (H⁺) (f) 2,2-dimethyl-1,3-propanediol, Dowex-50 (H⁺) (g) n-Bu₃P, o-NO₂PhSeCN; then 30% H₂O₂ (h) NaBH₄, MeOH, -23 °C (i) EtOH, Dowex-50 (H⁺) (j) LDA, CH₃OCH₂Cl (k) OsO₄ (cat), NaIO₄ (l) Ph₃P=CHCO₂Et, CH₂Cl₂ (m) PhSH, Dowex-50 (H⁺) (n) n-Bu₃SnH, AIBN, PhH, Δ
Thus, protection of commercially available 3-buten-1-ol as the tetrahydropyranyl ether gave 142, and ozonolysis of the olefin followed by a reductive work-up gave aldehyde 143. A Wittig reaction of 143 with (2-oxopropylidene)triphenylphosphorane in methylene chloride gave α,β-unsaturated ketone 144, and finally, O-alkylation of the lithium enolate of 144 with trimethylsilyl chloride gave diene 145.

A Diels-Alder reaction between diene 145 and N-methylmaleimide, followed by hydrolysis of the crude cycloadduct gave keto-alcohol 146. Ketalization with 2,2-dimethyl-1,3-propanediol gave 147, and dehydration of the alcohol gave 148. Reduction of the imide with sodium borohydride followed by hydroxy-ethoxy exchange gave 149 in 82% yield. Alkylation of the lithium enolate of 149 with chloromethyl methyl ether gave the olefin 150. Johnson-Lemieux oxidation of 150, followed by Wittig olefination of the resulting aldehyde 151 with (carbethoxymethylidene)triphenylphosphorane gave α,β-unsaturated ester 152. Ethoxy-thiophenoxy exchange gave thiolactam 153, and radical cyclization under standard conditions gave, as expected, tricyclic intermediate 154 in 87% yield as a 12:1 mixture of isomers at C(16).

With gelsemine substructure 154 in hand, Ha developed a protocol for adjusting the stereochemistry at C(16), and ultimately prepared tetracyclic gelsemine substructure 159. Later, Wu developed a streamlined route to 159. Features of both syntheses are shown in Scheme XIX. The plan revolved around degradation of the C(16) acetic acid residue to the nor-aldehyde, and use of a C(3) hydroxyl group to trap the epimerizable aldehyde as a hemiacetal (157 → 158). Thus, treatment of ester 154 with excess phenylmagnesium bromide in tetrahydrofuran followed by an acidic workup gave keto olefin 155. Reduction of the ketone with sodium borohydride gave alcohol 156, and an ozonolysis followed by a reductive workup gave aldehyde 157. Treatment of 157 with DBU effectively caused epimerization of the C(16) aldehyde which was trapped by the C(3) alcohol to give hemiacetal 158, as a mixture of diastereomers. Finally, reduction of 158 with triethylsilane and trifluoroacetic acid in dichloromethane gave 159 in 84% yield.
During the course of the author's involvement with the gelsemine project, and for reasons which will become evident, an alternate method for construction of the tetrahydropyran ring was explored. Specifically, it was hoped that the chemistry depicted in Scheme XIX could be adopted to accommodate carrying a ketone at C(3). Thus, ozonolysis of 155 followed by a reductive workup gave aldehyde 160 in 65% yield. With aldehyde 160 in hand, the adjustment of C(16) stereochemistry under acidic and basic conditions in methanol was explored. For example, when treated with acid under conditions that might equilibrate the C(16) aldehyde, we hoped that an intermediate hemiacetal or hydrate might attack the C(3) carbonyl forming a cyclic hemiketal at C(3). Unfortunately, treatment of aldehyde 160 with acidic methanol gave only the corresponding dimethyl acetal. Surprisingly, treatment of aldehyde 160 with DBU in methanol did afford methyl ester 163. The formation of 163 can be rationalized via an isomerization of 160 to the aldehyde epimeric at C(16), addition of methanol to provide tetrahedral intermediate 161, followed by an
intramolecular redox reaction to afford hydroxy ester 162. We initially assumed that the stereochemistry at C(16) was as shown and imagined that this might provide an alternate path for correcting C(16) stereochemistry. However, nOe experiments indicated that C(16) methyl ester had undergone a second isomerization, that the product was in fact 163, and that again we were faced with the wrong stereochemistry at C(16). Relevant difference nOe experiments used to assign the structure of 163 are summarized in Figure 2. The stereochemistry at C(3) is based on the axial delivery of hydride via tetrahedral intermediate 161 while the stereochemistry at C(16) is assigned based on the proximity of H(3) and H(16) as well as the proximity of H(16) and H(5). Obviously, adjustment of C(16) stereochemistry without a trap is not a favorable process!

Scheme XX. Intramolecular Reduction of Ketone 155

\[ 155 \xrightarrow{O_3; Me_2S, CH_2Cl_2-MeOH;} 160 (65\%) \]

\[ 155 \xrightarrow{DBU, MeOH;} 161 \]

162 \( R_1 = CO_2Me, R_2 = H \)

163 \( R_1 = H, R_2 = CO_2Me \) (58%)
Figure 2. nOe Experiments with Alcohol 163 in Chloroform

Table 1. nOe's for Alcohol 163 in Chloroform

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<th>nOe Observed</th>
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</tr>
</tbody>
</table>

In summary, this chapter described the preparation of gellemine substructures 154 and 159 which ultimately were useful in a synthesis of 21-oxogellemine. Substructure 154 contained functionality at both C(3) and C(20), necessary for the construction of the oxindole and vinyl portions of gellemine, respectively. The synthesis of substructure 159 demonstrated that
adjustment of the C(16) stereochemistry was possible, however, whether this plan could be successfully implemented after incorporation of the oxindole remained to be seen.

Substructure 154 (Scheme XIX) was to serve as a key intermediate for incorporation of the oxindole portion of gelsemine, and while some progress had been made in this area prior to the involvement of the author, intermediates needed to continue this work were not available. Thus, the first task at hand was to prepare multi-gram quantities of 154 such that the remainder of the synthesis could be explored. The next chapter will address this problem.
CHAPTER III

AN IMPROVED SYNTHESIS OF OUR KEY TRICYCLIC INTERMEDIATE

A. Introduction

A synthesis of tricyclic intermediate 154 was described in the last chapter. Ha's skillful synthesis served as the guideline for the preparation of multigram quantities of 154, as well as a structurally related compound 170, which ultimately proved useful in the total synthesis of 21-oxogelsemine.

B. Results and Discussion

Initially, our resynthesis effort followed as closely as possible the experimental procedures developed by Ha. However, several of the procedures were not conducive to large scale synthesis. Thus, several operational changes were developed that were critical to completion of the synthesis. An improved synthesis of 154 and 170 which was the result of three individual campaigns is shown in Scheme XXI.

The synthesis begins with the preparation of diene 145. Tetrahydropyranyl ether 142 was prepared from commercially available 3-buten-1-ol as described by Ha. Next, α,β-unsaturated ketone 144 was prepared in a two step-one pot procedure which did not require isolation of volatile aldehyde 143 (Scheme XVIII). Thus, treatment of alkene 142 with ozone gas followed by (2-oxopropylidene)triphenylphosphorane afforded α,β-unsaturated ketone 144 in 61% yield. Treatment of the lithium enolate of 144 with chlorotrimethylsilane gave crude diene 145 in quantitative yield which was used in the next step without further purification. Early in the resynthesis effort, it became apparent that the Diels-Alder reaction between silyl enol ether 145 and N-methylmaleimide was going to be troublesome. While the cycloaddition appeared to proceed without incident, subsequent treatment of the crude cycloadduct with aqueous acid, to
hydrolyze of both the silyl enol ether and the tetrahydropyranyl ether, afforded keto-alcohol 146 (Scheme XVIII) in poor yield. To improve the hydrolysis step we treated the crude cycloadduct with methanol and a catalytic amount of p-toluenesulfonic acid monohydrate at room temperature to afford ketone 146 in 49% yield along with cyclic ketal 164 in 39% yield (equation 3). Formation of 164 may in part explain some of the difficulties encountered during the hydrolysis step, as well as possible side reactions that may occur during subsequent ketalization of 146.

\[
\text{TM SO.} \xrightarrow{1} \text{OTHP} \xrightarrow{1. \ N\text{-methylmaleimide}} \Phi \text{CH}_3, \Delta \xrightarrow{2. \text{MeOH}, p\text{-TsOH}, rt} 145 \quad \xrightarrow{(3)} \quad \begin{array}{c}
\text{OH} 146 (49\%) \\
\text{OH} 164 (37\%)
\end{array}
\]

Since the next step, according to Ha's procedure, was a ketalization of the resulting ketone to afford alcohol 147, we imagined that this sequence of reactions might be accomplished in one pot. Indeed, a Diels-Alder reaction between N-methylmaleimide and diene 145, followed by treatment of the crude cycloadduct with two equivalents of 2,2-dimethyl-1,3-propanediol and a catalytic amount of p-toluenesulfonic acid monohydrate, gave perhydroisoindole 147 in 39% yield from crude 145. Formal dehydration of alcohol 147 following the Grieco protocol gave olefin 148 in 79% yield. Next, reduction of the imide with sodium borohydride in methanol gave carbinol lactam 165 in 80% yield. Initially, hydroxy-ethoxy exchange in acidic ethanol was used to convert crude 165 to 149. Upon scale-up, however, ketal hydrolysis became a problem. Eventually, it was found that treatment of 165 with sodium hydride followed by ethyl iodide accomplished the same transformation to afford 149 in 82% yield as a mixture of isomers at C(3). The major isomer could be crystallized in 71% yield, however this is not necessary as the stereochemistry at C(3) is of no consequence. Next, alkylation of the lithium enolate of 149 with chloromethyl methyl ether or benzyl chloromethyl ether gave 150 and 166 in 88% and 96% yield, respectively. Initially, we prepared benzyl ether 166 believing we would have more options when it came to deprotection of the alcohol, which is required for construction of the C(20) vinyl group. While this is true, it was not necessary since we later discover that both the benzyl ether and the methyl...
Scheme XXI. Resynthesis of Gelsemine Substructures 154 and 170.

(a) O₃, CH₂Cl₂; then (Ph)₃P=CHCOCH₃ (b) LDA, TMSCI, THF (c) N-Methylmaleimide, toluene, Δ; 2,2-dimethyl-1,3-propanediol, p-TsOH (d) o-NO₂PhSeCN, n-Bu₃P; H₂O₂ (e) NaBH₄, MeOH (f) NaH, EtI, THF (g) LDA, BnOCH₂Cl or CH₃OCH₂Cl (h) O₃, MeOH; Me₂S (i) (Ph)₃P=CHCO₂Et, CH₂Cl₂ (j) PhSH, p-TsOH, CH₂Cl₂ (k) n-Bu₃SnH, AIBN, PhH, Δ
ether could be removed with BBr₃ late in the synthesis. Furthermore, the benzyl ether caused some minor problems during the synthesis, not encountered with methyl ether 150. As previously reported, Johnson-Lemieux oxidation conditions were used to convert olefin 166 to 167, however this reaction proved to be capricious, as epimerization of the aldehyde was often a problem. Furthermore, on one occasion when the Johnson-Lemieux failed, starting material was not recovered. Apparently, ethoxy-hydroxy exchange had occurred and, while this material was not fully characterized, a proton NMR indicated that the olefin was still present. The ethyl group associated with the ethoxy-lactam, however, was no longer present. As a workable alternative to the Johnson-Lemieux oxidation, ozonolysis of 166 followed by a reductive workup with dimethylsulfide gave aldehyde 167 in 43-78% yield as a crystalline solid. The variable yield may be attributed to oxidation at the benzylic position of the ether, since an ozonolysis of olefin 150 typically proceeded in high yield, and although 151 was not isolated, treatment of crude 151 with ethyl (triphenylphosphoranylidene)acetate afforded α,β-unsaturated ester 152 in 96% yield from olefin 150. Wittig olefination of aldehyde 167 gave 168 in 82% yield. Next, ethoxy-thiophenoxy exchange afforded 153 and 169 in 89% and 76% yields, respectively. Finally, free-radical cyclization of 153 and 169 gave gelsemine substructures 154 and 170 in 87% and 64% yields, respectively.

It should be noted that the radical cyclization of 153 (R = CH₃) proceeds in higher yield than 169 (R = Bn). This may be explained in part due to the formation of 173, which crystallized from the crude filtrate in 4% yield following isolation of 170. A mechanism for the formation of 173 is proposed in Scheme XXII. The structure of 173 is consistent with mass spectra data, which indicated a parent peak isomeric with 170 (M⁺ = 471), as well a ¹³C NMR spectra and ¹³C-H COSY spectra.
C. Summary

The chemistry presented in this chapter closely parallels the work of Ha and others who were involved in the early stage of the gelsemine project as described in chapter II. Several operational changes were developed during the scale-up of 154 and 170 that were critical to the completion of the synthesis of 21-oxogelsemine (2). In all, over 35 g of gelsemine substructures 154 and/or 170 were prepared in three individual campaigns. With an ample supply of these intermediates in hand, the next task was introduction of the oxindole substructure at C(4). Our plan to accomplish this task, via a free-radical cyclization, is the focus of the next chapter.
CHAPTER IV

INTRODUCTION OF THE OXINDOLE SUBSTRUCTURE OF GELSEMINE
USING A FREE RADICAL CYCLIZATION

A. Introduction

In the proceeding chapter the preparation of multigram quantities of tricyclic substructure 170 and 154 was described. The next task was to develop a protocol for installation of the oxindole portion of gelsemine with correct stereochemistry. This work was begun by my immediate predecessor, Dr. Wu. At the time of Wu's departure from the gelsemine project, preliminary results suggested that this might be accomplished via a free radical cyclization. It should be noted, Wu also explored alternative methods of oxindole construction. These involved (i) carrying an o-fluorophenyl group at C(7) that would take advantage of the chemistry used to prepare ketone 155, as well as chemistry developed by Fleming, and (ii) using ketone 155, to effect C(7) functionalization via a Fisher-indole synthesis and subsequent C(7) functionalization using intramolecular electrophilic aromatic substitutions. The first approach was abandoned due to difficulties associated with incorporation of functionality at C(7) and the overall inefficiency of throughput of material. The second approach, while successful in two model systems, failed during a critical bond construction in a gelsemine system. With the demise of these two strategies, Wu focused on incorporation of the oxindole via a free radical cyclization. Our approach involved a variant of methodology developed by Jones. Jones' method involved the cyclization of aryl radicals derived from o-bromo-N-acryloylanilides (174 → 175) as shown in equation 4.
Wu successfully demonstrated a variant of this procedure that accomplished a reductive α,α-annellation of an oxindole in both a cyclohexanone and a perhydronaphthalenone system. However, when applied to gelsemine substructure 176 stereochemical complications at C(7) and C(3) occurred. Furthermore, an unexpected 1,4-hydrogen atom transfer disturbed the C(16) functionality required for construction of the tetrahydropyran ring (176 → 179) as shown in Scheme XXIII.

Scheme XXIII. 1,4-Hydrogen Atom Abstraction

To overcome the problem of 1,4-hydrogen atom transfer, Wu increased the tri-n-butyltin hydride concentration, and reduction of the intermediate α-alkoxy radical (177) started to compete
favorably with 1,4-hydrogen atom abstraction. Indeed, the best results were obtained when the radical cyclization was conducted in neat tri-n-butyltin hydride! The two oxindoles isolated contained an axially disposed methoxy group at C(3), as well as some material with the appropriate stereochemistry at C(7). Furthermore, the functionality at C(16) remained undisturbed. Unfortunately, the major oxindole contained the wrong oxindole stereochemistry required for gelsemine. To deal with this problem, we imagined that the oxindole stereochemistry could be adjusted via a retroaldol-aldol sequence. Immediately proceeding his departure from the gelsemine project, Wu successfully demonstrated the retroaldol-aldol chemistry for a model oxindole.

At this point, the author became involved with construction of the oxindole portion of gelsemine. In the next section the preparation of a modified radical cyclization precursor of type 176 will be is described. This will be followed by a reinvestigation of this remarkable radical cyclization in neat tri-n-butyltin hydride, and finally, the consequences of adjusting oxindole stereochemistry in a gelsemine substructure via a retroaldol-aldol sequence will be described.

B. Adjustment of Oxindole Stereochemistry

The first task at hand was the preparation of radical cyclization precursor 185, as shown in Scheme XXIV. It was hoped that this precursor would allow for easy removal of the protecting group on oxygen after conducting the radical cyclization, such that a C(3) hydroxyl could be revealed to participate in retroaldol-aldol chemistry. Ketones 155 and 182 were prepared according to previously reported procedures. Thus, treatment of 154 and 172 with an excess of phenylmagnesium bromide gave tertiary alcohols 180 and 181 in 54% and 87% yields, respectively. Previously, alcohol 180 was not isolated, but treated directly with p-toluenesulfonic acid in benzene at reflux to afford keto olefin 155. Curiously, analog 181, and not keto olefin 155 or 182, was destined to become the intermediate through which the total synthesis of 21-oxogelsemine would pass. However, for this approach, treatment of 181 with p-toluenesulfonic acid in acetone gave keto olefin 182 in 82% yield. Acylation of ketone 182 using potassium hydride and o-bromophenyl isocyanate gave o-bromo-N-acryloylanilide 183 in 85% yield.46,47 A \( ^1H \) NMR of 183 in deuterated chloroform indicated that 183 existed as the enol tautomer. O-
Alkylation of 183 with chloromethyl methyl ether, in the presence of Hunig's base in dimethylformamide, gave vinylogous urethane 184 in 89% yield. Finally, N-alkylation with chloromethyl methyl ether using sodium hydride in dimethylsulfoxide gave radical cyclization precursor 185 in 85% yield. The \(^1\)H NMR spectra of 185 was complicated at room temperature due to the presence of amide geometrical isomers, however the signals did undergo coalescence upon warming the sample in dimethylsulfoxide-\(d_6\) to 373 °K.

Scheme XXIV. Preparation of Radical Cyclization Precursor 185

With potential gelsemine substructure 185 in hand, we were ready to reinvestigate the radical cyclization in neat tri-n-butyltin hydride! However, tri-n-butyltin hydride proved to be a poor solvent for 185. Thus, it was necessary to dissolve 185 in a minimal amount of benzene, with a catalytic amount of AIBN, and to add the mixture to tri-n-butyltin hydride at 80 °C in several
portions. This method afforded oxindoles 186 and 187 in 28% and 9% yields, respectively (equation 5). A $^1$H NMR of the crude reaction mixture indicated a complex mixture. Methyl singlets at $\delta$ 1.73 and $\delta$ 1.96 suggested by-products derived from 1:1 coupling of radical intermediates with an isobutyronitrile radical, consistent with observations made by Wu when he conducted the radical cyclization with 10 equivalents of tri-$n$-butyltin hydride.

The structure assignment for 186 was based on decoupling and nOe experiments, and was eventually confirmed by X-ray crystallography (Figure 6). The structure of 187 was assigned based on $^1$H NMR and by comparison to similar compounds isolated by Wu. It should be noted, the stereochemistry of the two oxindoles can quickly be assigned based on dramatic upfield chemical shifts of H(5), H(9), and H(16) (gelsemine numbering) in structure 187 compared to structure 186. For example, the oxindole proton, H(9) in 187, is a doublet at 6.38 ppm whereas there are no aromatic protons upfield of 6.88 ppm in structure 186. Furthermore, this trend appears to be general and was useful in ascertaining oxindole stereochemistry for analogues of 186 and 187.
With oxindoles 186 and 187 in hand, epimerization studies were conducted as shown in Scheme XXV. Thus, deprotection of the C(3) hydroxyl of 186 and 187 with 6N aqueous hydrochloric acid in a mixture of methanol and dimethoxyethane at 65 °C gave alcohols 188 and 189 in 48% and 32% yields, respectively. Alcohols 188 and 189 were treated with 1,8-diazabicyclo[5.4.0]undec-7-ene in dichloromethane to afford 190 in 85% yield from 188, and 190 in 48% yield from 189. In model systems Wu also noted that oxindole stereochemistry could be adjusted under acidic conditions. This may, in part, explain the low yields in the deprotection of the MOM ethers 186 and 187 under acidic conditions. Indeed, on one occasion deprotection of
186 in 6N aqueous hydrochloric acid in methanol at reflux for 15 hours gave a mixture of 188 and 190. However, this process appears to be slower than isomerization under basic conditions. The stereochemistry of 190 is consistent with model studies by Wu that suggest spirooxindoles with equatorial aryl groups are more stable than those with axial aryl groups. However, in the gelsemine system 190 was obtained as the only product of four possible isomers, whereas in the decalin model system studies by Wu, an equilibrium mixture of four possible isomers was obtained. Apparently, in the gelsemine system there is an overwhelming desire for the spirooxindole aryl group and the C(3) alcohol to be equatorial disposed. The structure of 190 was assigned based on $^1$H NMR and the aforementioned characteristic chemical shifts, and was eventually confirmed by X-ray

Scheme XXV. Adjustment of Oxindole Stereochemistry via a Retroaldol-Aldol Sequence

(a) 6N aqueous HCl-methanol-glyme, $\Delta$, 1 h (b) DBU, CH$_2$Cl$_2$
crystallography (Figure 7). It should be noted, isomerization of the oxindoles occurred under the identical conditions used to adjust the C(16) stereochemistry (Scheme XIX), as the relative rates of these two processes became an issue during construction of the tetrahydropyran substructure of gelsemine.

Figure 4 ORTEP of Oxindole 190

With 190 in hand we proceeded with exploring these issues. While we recognized that the equatorial C(3) alcohol was more stable than the axial C(3) alcohol, we hoped that the retroaldol-aldol sequence would give some of the axial disposed alcohol and only this alcohol would be trapped by the C(16) nor-aldehyde. Thus, ozonolysis of 190 gave aldehyde 191 in 59% yield. Unfortunately, treatment of 191 with DBU in dichloromethane gave only a complex mixture (equation 6).
Successful in part, epimerization studies demonstrated that it was possible to adjust oxindole stereochemistry in a gelsemine system. Unfortunately, it appeared that the resulting equatorial C(3) hydroxyl group was not useful for construction of the tetrahydropyran ring. Furthermore, the dismal yields of oxindoles 186 and 187 made it difficult to explore alternative methods of the tetrahydropyran ring construction. Eventually, the used of radical cyclization precursors of type 185 would be abandoned. Apparently, construction of the tetrahydropyran ring under basic conditions in the presence of the oxindole was not going to be an easy task. A possible solution to the problem is presented in the next section and is highlighted with the successful construction of the tetrahydropyran ring.

C. Construction of the Tetrahydropyran Ring

In the previous section we saw that isomerization of the oxindole stereochemistry was much faster in base as compared to acid. However, we did not know if the stereochemistry at C(16) could be adjusted under acidic conditions. A very encouraging result is shown in Scheme XXVI. Ozonolysis of olefin 186 followed by a reductive workup gave aldehyde 193 in 65% yield. To our delight, treatment of 193 with 6N aqueous acid accomplished hydrolysis of the methoxymethyl ether and isomerization of the C(16) nor-aldehyde to afford hemiacetal 194 in 60% yield. This is significant in that acetal formation occurred without isomerization at C(3) and C(7). Finally, treatment of 194 with triethylsilane-trifluoroacetic acid in dichloromethane gave tetrahydropyran 195 in 65% yield. It should be noted, the N-methoxymethyl protecting group was also reduced under these conditions, suggesting that the oxindole protecting groups should be changed. The structure of 195 was based on nOe experiments (Table 2).
Scheme XXVI. Construction of the Hexacyclic Cage

186 → 193 (80%)

186 → 194 (54%)

195 (63%)

(a) O₃, MeOH-CH₂Cl₂; Me₂S (b) 6N aqueous HCl, THF (c) Et₃SiH, CF₃CO₂H, CH₂Cl₂
Table 2. nOe’s for Oxindole 195 in Chloroform

<table>
<thead>
<tr>
<th>1H Irradiated</th>
<th>Chemical Shift</th>
<th>nOe Observed</th>
<th>Chemical Shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)-CH₃</td>
<td>3.20</td>
<td>H₁₂ (12%)</td>
<td>6.84</td>
</tr>
<tr>
<td>N(4)-CH₃</td>
<td>2.80</td>
<td>H₅ (7%)</td>
<td>4.77</td>
</tr>
<tr>
<td>H₃</td>
<td>3.70</td>
<td>H₉ (1%)</td>
<td>7.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H₁₄a (3%)</td>
<td>2.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H₁₄e (4%)</td>
<td>2.13</td>
</tr>
<tr>
<td>H₅</td>
<td>4.77</td>
<td>H₁₇ (3%)</td>
<td>4.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H₆ (5%)</td>
<td>2.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H₁₆ (11%)</td>
<td>2.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H₁₅ (3%)</td>
<td>2.15</td>
</tr>
<tr>
<td>H₉</td>
<td>7.37</td>
<td>H₁₀ (10%)</td>
<td>6.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H₁₉ (9%)</td>
<td>4.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H₁₄a (5%)</td>
<td>2.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H₃ (2%)</td>
<td>3.70</td>
</tr>
</tbody>
</table>

Encouraged by this result, we were confident gelsemine could be synthesized if a sufficient quantity of material with the correct stereochemistry at C(3) and C(7) was available. A plan to improve the yield of the radical cyclization, and an unexpected result are discussed in the next section.
D. A Radical Cyclization-Fragmentation-Isomerization Sequence

Our plan to improve the radical cyclization revolved around preventing the 1,4-hydrogen atom abstraction (Scheme XXI) observed by Wu. We believed this could be accomplished by delaying the introduction of the olefin in structures of type 186 and 187, since we felt it was the allylic nature of H(16) that was making it susceptible to abstraction. Toward this end, intermediates 180 and 181 could be of use. This strategy would enable us to conduct the radical cyclization under high dilution conditions used in model studies, where yields were typically high and a 1:1 ratio of oxindoles was obtained. Thus, we prepared radical cyclization precursors 205, 206 and 207 as shown in Scheme XXVII. Alkylation of carbinols 180 and 181 using methyl iodide and sodium hydride in dimethylsulfoxide afforded methyl ethers 196 and 197, respectively, in quantitative yields. We anticipated that deketalization of 196 and 197 under acidic conditions might be problematic since we hoped both compounds would eventually undergo elimination chemistry under similar conditions. However, deketalization in acetone using a catalytic amount of p-toluenesulfonic acid monohydrate afforded ketones 198 and 199, respectively, in 94% yields without competitive elimination processes. Alkylation of ketones 198 and 199 with o-bromophenylisocyanate using sodium hydride-potassium hydride in tetrahydrofuran afforded enols 200 and 201 in 74% and 80% yields, respectively. Enols 200 and 201 were O-alkylated using chloromethyl methyl ether and Hunig's base in dimethylsulfoxide to afford 202 and 203 in 91% and 100% yields, respectively. Additionally, O-alkylation of 201 was accomplished using benzyl bromide and Hunig's base in dimethylsulfoxide to afford analog 204 in 84% yield. All three compounds (202, 203, and 204) were N-alkylated using chloromethyl methyl ether and sodium hydride in dimethylsulfoxide to afford cyclization precursors 205, 206 and 207 in 78%, 84% and 89% yields, respectively.
Scheme XXVII. Preparation of Radical Cyclization Precursors 205, 206, and 207

With cyclization precursors 205, 206, 207 in hand, we explored cyclization under high dilution conditions as shown in Scheme XXVIII. To our delight, we observed a dramatic improvement in yield. However, all three substrates (205, 206, and 207) underwent an unexpected fragmentation of the incipient α-alkoxy radical to provide the corresponding β-ketoanilides. Treatment of 205 with tri-n-butyltin hydride in benzene at reflux under high dilution conditions gave crystalline oxindoles 208 and 209 in 51% and 36% yields, respectively. Similarly, treatment of 206, under identical conditions, afforded a 1:2:1 mixture, by 1H NMR, of oxindoles 210 and 211, respectively in 83% yield. Furthermore, radical cyclization of O-benzyl derivative
207 also gave a 1:1 mixture, by $^1$H NMR, of oxindoles 210 and 211, respectively, in 78% yield. Pure samples of oxindoles 210 and 211 could be obtained in diminished yield only after a difficult separation on silica gel followed by a recrystallization. Oxindole stereochemistry was assigned based on the appearance of an aromatic doublet at $\delta$ 6.08 ppm for oxindole 209, and $\delta$ 6.10 ppm for oxindole 211.

**Scheme XXVIII. Radical Cyclization-Fragmentation**

The next task was to incorporate the olefin functionality as shown in Scheme XXIX. Thus, treatment of methyl ethers 210 and 211 with p-toluenesulfonic acid monohydrate in dichloromethane at reflux gave olefins 212 and 213 in 88% and 98% yields, respectively. The structure of 212 was confirmed by X-ray crystallography (Figure 6).

Initially, we believed 213 might be useful in the synthesis of gelsemine if reduction of the C(3) carbonyl would afford an axial C(3) alcohol. Obviously, the choice of reduction conditions would be critical as the retroaldol-aldol process might follow reduction. Thus, not surprisingly, treatment of 212 with sodium borohydride in methanol gave alcohol 190 (Scheme XXV) in fair yield on a small scale. Apparently, the aforementioned concerns are real, and the propensity of C(3) hydroxy groups to participate in retroaldol-aldol chemistry must be considered whenever reduction of the C(3) carbonyl is attempted. Furthermore, subsequent oxidation of 190 using pyridinium chlorochromate offered a potential method for adjusting oxindole stereochemistry. However, upon scale up the reduction of 212 was sluggish and the yield dropped as additional
sodium borohydride was required. This two step isomerization sequence was subsequently abandoned in favor of a single step method which converted oxindole 212 to oxindole 213. Thus, treatment of oxindole 212 with potassium cyanide in dimethylformamide gave oxindole 213 in 85% yield, along with 15% of recovered starting material.

Scheme XXIX. Elimination-Isomerization of Oxindole Stereochemistry

\[
\text{210} \xrightarrow{a} \text{212 (88\%)} \xrightarrow{b} 85\%
\]

\[
\text{211} \xrightarrow{a} \text{213}
\]

(a) \(\text{p-TsOH, CH}_2\text{Cl}_2, \Delta\) (b) K\text{CN, DMF, 50 \text{\degree C}}
The radical cyclization-fragmentation-isomerization sequence presented in this section offered a useful synthesis of oxindole 213, however we have had no luck reducing the C(3) carbonyl at neutral or acidic pH, conditions that would potentially leave the oxindole and alcohol product stereochemistry undisturbed. Thus, we considered a number of alternatives that would accommodate carrying a ketone at C(3). One such approach, which involved an intramolecular reduction of the C(3) carbonyl, was presented as a model system in Chapter II (Scheme XX). Application to gelsemine substructure 209 is shown in Scheme XXX. Thus, treatment of 209 with p-toluene sulfonic acid monohydrate in dichloromethane at reflux gave olefin 214 in 98% yield. Ozonolysis of 214 followed by a reductive workup with dimethylsulfide afforded aldehyde 215 in 67% yield. We anticipated formation of structure 216 upon treatment of 215 with DBU in methanol but unfortunately, only a complex mixture of unidentified products was obtained.
Failure to reduce the C(3) carbonyl group, as well as anticipated difficulties in developing other methods of tetrahydropyran construction, forced us to consider a different approach. Thus, we focused on a means of preventing the aforementioned fragmentation processes from occurring. This approach ultimately proved successful and will be presented in the next section. However, before leaving this section we decided to see if the fragmentation shown in Scheme XXVII was general or unique to gelsemine substructures of type 204. To this end, we investigated the radical cyclization-fragmentation in a system derived from cyclohexanone as shown in Scheme XXXI. Thus, treatment of cyclohexanone (217) with o-bromophenylisocyanate and potassium hydride in glyme afforded vinylogous urethane 218 in 58% yield as a mixture of keto and enol tautomers. O-Alkylation of 218 with chloromethyl methyl ether and Hunig's base in dimethylsulfoxide gave 219 in 72% yield. This was followed by N-alkylation of 219, which proceeded in good yield using chloromethyl methyl ether and sodium hydride in dimethylsulfoxide.
to afford 220. Treatment of 218 under the same conditions afforded radical cyclization precursor 220 in 76% yield. Radical cyclization of 220 using tri-n-butyltin hydride under high dilution conditions in benzene at reflux gave only oxindoles 221 and 222 in 44% and 47% yields, respectively. Next, we conducted the cyclization in toluene at reflux and again only oxindoles 221 and 222 were present as indicated by $^1$H NMR. The structure assignment of oxindoles 221 and 222 was based on similar compounds prepared by Wu.$^{49}$ Next, we looked at the cyclization using tris(trimethylsilyl)silane in xylene at reflux, and oxindole 223 was obtained in 22% yield.$^{51}$ Apparently, the use of tris(trimethylsilyl)silane is critical since tri-n-butyltin hydride in xylene at reflux afforded only oxindoles 221 and 222, by comparison with pure samples of 221, 222 and 223 using thin-layer chromatography. To improve the fragmentation process, an attempt was made to prepare O-benzyl analogs of 219. However, treatment of 218 with both benzyl bromide

Scheme XXXI. Fragmentation Processes in Cyclohexanone System

(a) KH, $\alpha$-BrC$_6$H$_4$NCO, glyme (b) MOMCl, Hunig's base, DMF (c) NaH, MOMCl, DMF (d) n-Bu$_3$SnH, AIBN, C$_6$H$_6$, $\Delta$ (e) (TMS)$_3$SiH, AIBN, xylene, $\Delta$
or benzyl tosylate and triethylamine in dimethylsulfoxide gave only the C-alkylated product. In this regard, competitive C vs. O-alkylation processes may hamper the development of this into a useful methodology.

E. Can We Prevent the Fragmentation?

Since we were unable to construct the tetrahydropyran ring from 214 or 216, we decided to consider a different approach. Up to this point, we had demonstrated that we could overcome the problems associated with 1,4-hydrogen atom abstraction and that delaying introduction of the olefin was a sound strategy. We wondered, could we now prevent the fragmentation from occurring. To this end, we prepared radical cyclization precursor 225 and explored the radical cyclization as shown in Scheme XXXII. Treatment of 201 with acetic anhydride, triethylamine and

Scheme XXXII. Preparation of Oxindoles 226, 227, and 228

(a) Hunig's base, Ac₂O, CH₂Cl₂ (b) Ac₂O, Et₃N, DMAP, DMF (c) n-Bu₃SnH, hv
4-dimethylaminopyridine in dimethylformamide gave cyclization precursor 225 in 98% yield. Finally, free-radical cyclization of 225 using tri-n-butyltin hydride under photochemical conditions afforded, after a tedious purification process, oxindoles 226, 227, and 228 in 9%, 7%, and 42% yields, respectively. To our delight oxindole 228 was the major isomer and it contained both the desired stereochemistry at C(7) and C(3) for subsequent construction of the tetrahydropyranyl ring. The structure assignment was based on treatment of the individual isomers with p-toluenesulfonic acid monohydrate in dichloromethane to provide olefins 229, 230 and 231 in variable yield which can be attributed to cleavage of the N-acetate. Relevant nOe experiments are shown in Tables 3, 4, and 5. Note that, a large nOe between H(3) and H(a) suggests that oxindole 229 adopts a boat-like conformation.
Table 3. NOe's for Oxindole 229

<table>
<thead>
<tr>
<th>$^1$H Irradiated</th>
<th>Chemical Shift</th>
<th>nOe Observed</th>
<th>Chemical Shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>oxindole $H_{12}$</td>
<td>8.07</td>
<td>oxindole $H_{11}$ (19)</td>
<td>7.21</td>
</tr>
<tr>
<td>oxindole $H_9$</td>
<td>7.54</td>
<td>oxindole $H_{10}$ (16%)</td>
<td>6.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$H_3$ (6%)</td>
<td>5.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$H_6$ (6%)</td>
<td>2.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$H_a$ (2%)</td>
<td>4.35</td>
</tr>
<tr>
<td>$=CH$</td>
<td>5.73</td>
<td>$H_{15}$ (10%)</td>
<td>2.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCH$_3$ (7%)</td>
<td>2.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$H_{Ar}$ (19%)</td>
<td>7.25</td>
</tr>
<tr>
<td>$H_3$</td>
<td>5.38</td>
<td>oxindole $H_9$ (8%)</td>
<td>7.54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$H_a$ (10%)</td>
<td>4.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$H_{14a}$ (5%)</td>
<td>2.58</td>
</tr>
<tr>
<td>$H_{16}$</td>
<td>4.16</td>
<td>$H_5$ (12%)</td>
<td>3.48</td>
</tr>
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<td></td>
<td></td>
<td>$H_{15}$ (3%)</td>
<td>2.00</td>
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<td></td>
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<td>1.69</td>
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<td>$H_a$</td>
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<td>3.48</td>
<td>oxindole $H_9$ (6%)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>$H_{16}$ (8%)</td>
<td>4.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCH$_3$ (6%)</td>
<td>2.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$H_6$ (13%)</td>
<td>2.58</td>
</tr>
</tbody>
</table>

![Chemical structure](image1)

227 $\rightarrow$ 230 (40%)
Table 4. nOe's for Oxindole 230

<table>
<thead>
<tr>
<th>(^1\text{H} \text{ Irradiated})</th>
<th>Chemical Shift</th>
<th>nOe Observed</th>
<th>Chemical Shift</th>
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</thead>
<tbody>
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<td>H_{16}</td>
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<td>H_{5} (13%)</td>
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<tr>
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<td></td>
<td>H_{15} (5%)</td>
<td>2.00</td>
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<td></td>
<td></td>
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<td>H_{Ar} (9%)</td>
<td>7.2 (doublet)</td>
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<td>H_{16} (8%)</td>
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<td>NCH_{3} (7%)</td>
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<td>H_{a}</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>H_{14a} (10%)</td>
<td>2.08</td>
</tr>
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<td></td>
<td>H_{Ar} (23%)</td>
<td>7.2 (doublet)</td>
</tr>
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<td></td>
<td>H_{a} (27%)</td>
<td>4.22</td>
</tr>
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<td>H_{3}</td>
<td>4.87</td>
<td>H_{16} (23%)</td>
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<tr>
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<td></td>
<td>H_{14a} (5%)</td>
<td>2.24</td>
</tr>
<tr>
<td>=CH</td>
<td>5.68</td>
<td>NCH_{3} (11%)</td>
<td>2.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H_{15} (6%)</td>
<td>2.00</td>
</tr>
</tbody>
</table>

\[
\begin{align*}
\text{228} & \xrightarrow{\rho\text{-TsOH, CH}_2\text{Cl}_2} \text{231 (83%)}
\end{align*}
\]
Table 5. nOe’s for Oxindole 231

<table>
<thead>
<tr>
<th>1H Irradiated</th>
<th>Chemical Shift</th>
<th>nOe Observed</th>
<th>Chemical Shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>oxindole H_{12}</td>
<td>8.18</td>
<td>oxindole H_{11} (13%)</td>
<td>7.26 (td)</td>
</tr>
<tr>
<td>oxindole H_{9}</td>
<td>6.16</td>
<td>oxindole H_{10} (13%)</td>
<td>6.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H_{16} (15%)</td>
<td>3.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H_{5} (7%)</td>
<td>3.15</td>
</tr>
<tr>
<td>H_{16}</td>
<td>3.36</td>
<td>H_{Ar} (6%)</td>
<td>7.43 (d)</td>
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<tr>
<td></td>
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<td>oxindole H_{9} (18%)</td>
<td>6.16</td>
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<td>H_{5} (6%)</td>
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<td>H_{15} (5%)</td>
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<td></td>
<td></td>
<td>H_{14e} (2%)</td>
<td>2.03</td>
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<td>H_{5}</td>
<td>3.15</td>
<td>H_{Ar} (4%)</td>
<td>7.45 (d)</td>
</tr>
<tr>
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<td></td>
<td>oxindole H_{9} (6%)</td>
<td>6.16</td>
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<tr>
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<td></td>
<td>H_{16} (4%)</td>
<td>3.36</td>
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<tr>
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<td></td>
<td>NCH_{3} (5%)</td>
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<tr>
<td>H_{3}</td>
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<td>H_{14a} (4%)</td>
<td>2.57</td>
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<tr>
<td>H_{a}</td>
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<td>H_{a} (21%)</td>
<td>4.14</td>
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<tr>
<td></td>
<td></td>
<td>H_{14a} (6%)</td>
<td>2.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H_{6} (2%)</td>
<td>2.31</td>
</tr>
</tbody>
</table>

F. Summary

In this chapter a method for incorporation of the oxindole portion via a free-radical cyclization was described. Two methods for adjusting oxindole stereochemistry in a gelsemine system that accommodates either a C(3) alcohol or a C(3) carbonyl were presented as well as a radical cyclization-fragmentation process apparently unique to gelsemine substructure of type 205. The highlight of this chapter is, of course, the preparation of synthetically useful quantities of gelsemine substructure 228. In the next chapter a protocol for construction of the tetrahydropyranyl ring of 21-oxogeisemine is presented, and this is followed by a method for the conversion of the C(20) benzyloxymethyl group to the required C(20) vinyl group, completing the total synthesis of 21-oxogeisemine.
A. Introduction

The preceding chapter described the problems encountered with installation of the oxindole portion of gelsemine via a free radical cyclization and how these problems were overcome. This chapter will describe the final stages of a total synthesis of 21-oxogelsemine (2) and 7-epi-21-oxogelsemine (258) proceeding from oxindoles 228 and 226, respectively. Specifically, a protocol for the construction of the tetrahydropyran ring will be presented followed by a method for the conversion of the C(20) benzyloxymethyl group to the required C(20) vinyl group.

B. The Tetrahydropyran Ring. Synthesis and Discussion.

In the previous chapter, it was demonstrated that construction of the tetrahydropyran ring was possible under acidic conditions without causing epimerization at C(7) or C(3) (Scheme XXVI). Unfortunately, oxindole 186 did not have the correct stereochemistry such that the total synthesis could be achieved. With synthetically useful quantities of oxindole 228 in hand, we were prepared to attempt construction of the tetrahydropyran under acidic conditions. Thus, the first task was preparation of aldehyde 234 as shown in Scheme XXXIII. Initially, we planned to carry a protected oxindole through to the final stage of the synthesis, however the lability of the N-acetyl made this difficult. Thus, treatment of oxindole 228 with p-toluenesulfonic acid in dichloromethane was followed by the addition of methanol to facilitate cleavage of the N-acetyl group, to provide olefin 232 in 93% yield. Ozonolysis of olefin 232 followed by a reductive workup gave aldehyde 234 in 65% yield along with epoxide 233 in 15% yield. Epoxide formation is a
known side reaction of hindered olefins under ozonolysis conditions.\textsuperscript{52} The structure of epoxide 233 is based on $^1$H and $^{13}$C NMR spectra. Surprisingly, decoupling experiments indicated a dramatic upfield chemical shift for oxindole H(9) proton to $\delta$ 5.59 ppm!

Scheme XXXIII Preparation of Aldehyde 234

\begin{align*}
(a) & \quad p$-TsOH, CH$_2$Cl$_2$, $\Delta$; then MeOH, rt \\
(b) & \quad O_3, CH$_2$Cl$_2$-MeOH; then Me$_2$S
\end{align*}

Next, treatment of 234 with 6N aqueous hydrochloric acid in dimethoxyethane at 48 °C for 18 h accomplished acetate hydrolysis and isomerization of the aldehyde to afford a mixture of diastereomeric hemiacetals 236 in 65% yield along with cyclic acetal 239 in 14% yield as shown in Scheme XXXIV. Initially, this transformation was accomplished with tetrahydrofuran as the co-solvent. Due to the long reaction time required to hydrolyze the O-acetate, however, conversion of tetrahydrofuran to 4-chlorobutanol also occurred. The yield of this reaction was typically poor and this may be attributed to the 4-chlorobutanol reacting with either aldehyde 234 and/or hemiacetal 236. Cyclic acetal 239 is an intriguing side product. The structure of 239 is based on
The mass spectrum indicated a parent peak (M+=446) isomeric with hemiacetal 236. 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 proton NMR also indicated a single isomer. A comparison of the \(^{13}\)C NMR of 239 with hemiacetal 236 indicated a new triplet and one less doublet. These data are consistent with proposed structure 239. Furthermore, mechanistic considerations support this structure. Construction of the C(5)-C(16) bond of gelsemine has been accomplished via acyliminium ion chemistry. Structure 239 could be derived from either 235 and/or 236. Thus, 235 could undergo a retro-Mannich reaction to afford a structure of type 238, which in turn could undergo intramolecular ketalization to afford 239. Also possible, hemiacetal 236 could afford 237, which could undergo enol ether hydrolysis followed by ketalization to afford 239. Although the experiment was not performed, conversion of 236 to 239 could be confirmed by resubjecting pure 236 to 6\(N\) aqueous hydrochloric acid. It should be noted, as indicated by thin-layer chromatography, it appears that formation of cyclic ketal 239 occurs only after formation of 236.
Fortunately, formation of 239 can be minimized with careful control of the temperature during the hydrolysis. With hemiacetal 236 in hand, treatment with triethylsilane and trifluoroacetic acid in dichloromethane afforded 240 in 83% yield. The structure of 240 was based on a series of $^1$H NMR experiments (nOe and decoupling). Relevant nOe experiments are shown in Table 6.

**Scheme XXXIV. Preparation of Tetrahydropyran 240**

(a) 6$N$ aqueous HCl, glyme, 48 °C, 16 h  
(b) Et$_3$SiH, CF$_3$CO$_2$H, CH$_2$Cl$_2$
C. Construction of the C(20) Vinyl Group. Synthesis and Discussion.

With oxindole 240 in hand, the hexacyclic cage of gelsemine was complete and all that remained was conversion of the C(20) benzyloxymethyl group to the C(20) vinyl group. Our plan to accomplish this task involved deprotection of the benzyl ether followed by a Swern oxidation of the resulting alcohol to the corresponding aldehyde and finally, a Wittig reaction.

This approach was first explored by Lee in the model studies shown in Scheme XXXV.\textsuperscript{33} He found that treatment of 140 with boron tribromide in dichloromethane gave alcohol 241 in 98% yield. Swern oxidation of alcohol 241 then afforded aldehyde 242 in 86% yield. Finally, a Wittig reaction gave olefin 243 in 74% yield.
Furthermore, the viability of a Wittig reaction as a final step in a projected synthesis of gelsemine had been demonstrated by Landeryon.\textsuperscript{53} For example, protection of the oxindole portion of gelsemine (1) as the N\texttext{-}benzyl derivative followed by oxidation of the C(20) vinyl group gave \(\text{N}_\text{a}^\text{-}\text{benzylgelsemione-nor-aldehyde}\). A Wittig reaction of \(\text{N}_\text{a}^\text{-}\text{benzylgelsemione-nor-aldehyde}\) with triphenylmethylphosphorane gave \(\text{N}_\text{a}^\text{-}\text{benzylgelsemione}\) in 46% yield.

Although we had not anticipated problems with the final three steps of the synthesis, both the Swern oxidation and the Wittig reaction were problematic. One possible explanation is neighboring group participation by the oxindole.\textsuperscript{8} Thus, we returned to a variety of model systems to work out these final transformations. The first is shown in Scheme XXXVI. Thus, treatment of 159 with boron tribromide in dichloromethane gave alcohol 244 in 75% yield.\textsuperscript{33} A Swern oxidation proceeded smoothly to afford aldehyde 245 in 92% yield. Alternatively, the Dess-Martin periodinane gave aldehyde 245 in 80% yield.\textsuperscript{54} Unfortunately, we had no luck using a Wittig reaction for the conversion of 245 to 246. Thus, we explored other methods. Initially, a two step conversion of aldehyde 245 to olefin 246 looked promising. For example, aldehyde 245 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 the Martin sulfurane gave olefin 246 in quantitative yield.\textsuperscript{55} A one-step alternative was also developed as treatment of aldehyde with bis(cyclopentadienyl)dimethyltitanium in tetrahydrofuran at reflux gave olefin 246 in 94% yield.\textsuperscript{56} Selectivity of this reagent for the
aldehyde in the presence of the lactam is notable.$^5\text{7}$

**Scheme XXXVI. Incorporation of C(20) Vinyl Moiety**

Unfortunately, the Wittig olefination and addition-elimination procedures failed to give any 21-oxogelsemine when applied to the relevant system (vide infra). Thus, the Petasis methylenation became the focus of attention. Before applying this method to the real system, oxindole 195 was examined as a model system (Scheme XXXVII). Deprotection of benzyl ether 195 proceeded smoothly with boron tribromide in dichloromethane to afford alcohol 247 in 72% yield. Swern oxidation of alcohol 247 gave aldehyde 248 in 86% yield. Finally, treatment of 248 with dimethyltitanocene in tetrahydrofuran at reflux gave olefin 249 in 60% yield. The structure of 249 was based on $^1\text{H}$ and $^{13}\text{C}$ NMR. The stereochemistry at C(7) was based on a large nOe observed at H(9) upon irradiation of H(19) (see Appendix A).
Scheme XXXVII. Incorporation of the C(20) Vinyl Moiety on Oxindole 195

Finally, we were prepared to apply this series of reactions to the preparation of 21-oxogelsemine as shown in Scheme XXXVIII. Thus, treatment of benzyl ether 237 with boron tribromide in dichloromethane gave alcohol 250 in 95% yield. The structure of 250 was confirmed by X-ray crystallography (Figure 8). Swern oxidation of 250 gave aldehyde 251 in only 50% yield. It is suspected that neighboring participation at some stage of the oxidation is responsible for the low yield. Fortunately, oxidation of 250 with the Dess-Martin periodinane gave crystalline aldehyde 251 in 71% yield. Finally, treatment of 251 with dimethyltitanocene 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. Furthermore, a direct comparison with an authentic sample, supplied by Dr. Cordell at the University of Illinois-Chicago, gave identical $^1$H NMR and thin-layer chromatography results. The $^1$H NMR spectrum of authentic 21-oxogelsemine appears in Appendix A.
Scheme XXXVIII. Synthesis of 21-Oxogelsemine (2)

Scheme XXXVIII. Synthesis of 21-Oxogelsemine (2)

(a) BBr₃, CH₂Cl₂, -78 ºC (b) Dess-Martin periodinane, CH₂Cl₂ (c) Cp₂TiMe₂, THF, Δ

Figure 8. Ortep of Completed Hexacyclic Cage 250
A synthesis of 7-epi-21-oxogelsemine (258) was also completed as shown in Scheme XXXIX. Treatment of oxindole 226 with p-toluenesulfonic acid monohydrate in dichloromethane

Scheme XXXIX. Synthesis of 7-Epi-21-Oxogelsemine (258)

followed by the addition of methanol, to facilitate cleavage of the N-acetyl, afforded olefin 252 in 69% yield. Ozonolysis of hindered olefin 252 gave aldehyde 253 in 66% yield. Treatment of 253 with aqueous 6N hydrochloric acid in glyme at 48 °C accomplished O-acetate hydrolysis and
isomerization of the nor-aldehyde provided hemiacetal 254 in 82% yield, as a mixture of diastereomers. Reduction of 254 with triethylsilane-trifluoroacetic acid gave tetrahydropyran 255 in 73% yield. Finally, conversion of the benzyl ether into the C(20) vinyl moiety proceeded as previously described. Thus, deprotection of 255 with boron tribromide in dichloromethane afforded alcohol 256 in 88% yield and oxidation with the Dess-Martin periodinane gave aldehyde 257 in 77% yield. Treatment of 257 with dimethyltitanocene in tetrahydrofuran at reflux afforded 7-epi-21-oxogelsemine (265) in 71% yield.

D. Summary

This chapter described the completion of the total synthesis of 21-oxogelsemine (2). Specifically, a protocol for the construction of the tetrahydropyran ring and the C(20) vinyl moiety was described. Furthermore, in light of Speckamp's and Johnson's recently reported synthesis of gelsemine (1), this work also represents a formal synthesis of gelsemine (1).

In conclusion, the research presented in this thesis has resulted in the total synthesis of 21-oxogelsemine in 23 steps from diene 145. A number of structurally related analogs were also prepared. For the reader's convenience, a complete overview of the synthesis of 2 is shown in Scheme XL. The key features of the synthesis include two free radical cyclization reactions and a protocol for construction of the tetrahydropyran after installation of the oxindole structure.
Scheme XL. Total Synthesis of 21-Oxogelsemine

Overall 22-steps
0.23% yield

(a) N-Methylmaleimide, toluene, Δ; 2,2-dimethyl-1,3-propanediol, p-TsOH (b) o-NO2PhSeCN, n-Bu3P; H2O2 (c) NaBH4, MeOH (d) NaH, Et3P, THF (e) LDA, BnOCH2Cl (f) O3, MeOH; Me2S (g) (Ph)3P=CHCO2Et, CH2Cl2 (h) PhSH, p-TsOH, CH2Cl2 (i) n-Bu3SnH, AIBN, PhH, Δ (j) PhMgBr, THF (k) NaH, Me3Sn, DMF (l) acetone, p-TsOH (m) NaH/KH, o-BrC6H4NCO, THF, Δ (n) Ac2O, Et3N, DMF (o) n-Bu3SnH, hv, PhH (p) p-TsOH, CH2Cl2; MeOH (q) O3, CH2Cl2-MeOH; Me2S (r) 6 N aqueous HCl, DME, 48 °C (s) TFA, Et3SiH, CH2Cl2 (t) BBr3, CH2Cl2 (u) Dess-Martin periodinane (v) Cp2TiMe2, THF, Δ
CHAPTER VI
AN APPROACH TOWARD A TOTAL SYNTHESIS OF GELSEDINE

A. Introduction.

The highlight of the preceding chapters was the total synthesis of 21-oxogelsemine (2). Upon completion of this task, we embarked on a total synthesis of gelsedine (259). Like 21-oxogelsemine, gelsedine is an oxindole alkaloid reported to be a minor constituent of *Gelsemium sempervirens*. Gelsedine was first isolated by Schwarz and Marion in 1953 from *Gelsemium sempervirens* and, since that time, it has also been isolated from in *Gelsemium elegans*. The structure of gelsedine (259) was elucidated by Wenkert in 1962 and is based on a comparison of spectroscopic data with the related alkaloid gelsemicine (260), which has been reported to be the most toxic constituent of *Gelsemium sempervirens*. This chapter will present a brief review of efforts directed toward a total synthesis gelsedine-type alkaloids as well as a recently reported biogenetic route to these synthetically challenging targets. This will be followed by a description of our approach to gelsedine and preliminary studies directed toward its synthesis.

![Gelsedine-type Oxindole Alkaloids](image)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>259</td>
<td>R = H</td>
<td>Gelsedine</td>
</tr>
<tr>
<td>260</td>
<td>R = OMe</td>
<td>Gelsemicine</td>
</tr>
<tr>
<td>261</td>
<td>R = H, Δ^{20-Nb}</td>
<td>Gelsenicine</td>
</tr>
<tr>
<td>262</td>
<td>R = H</td>
<td>14β-Hydroxygelsedine</td>
</tr>
<tr>
<td>263</td>
<td>R = OMe</td>
<td>14β-Hydroxygelsemicine</td>
</tr>
<tr>
<td>264</td>
<td>R = H, Δ^{20-Nb}</td>
<td>Humantenidine</td>
</tr>
</tbody>
</table>

Figure 9. Gelsedine-type Oxindole Alkaloids
B. Synthetic Studies

In contrast to studies directed toward a total synthesis of gelsemine (1), gelsedine-type alkaloids have received little attention and to date, a successful total synthesis has not been reported. In 1979, Baldwin reported a synthesis of gelsedine substructure 275 as shown in Scheme XLI. The route begins with conversion of anhydride 265 to the functionally differentiated diester 266. This is followed by vicinal dihydroxylation of the olefin (266 → 268) and hydrogenolysis of the benzyl ester (267) to afford carboxylic acid 268. Lactonization of 268

Scheme XLI. Baldwin's Approach Toward Gelsedine

(a) PhCH₂OH (b) CH₂N₂ (c) m-CPBA (d) H₃O⁺ (e) H₂, Pd-C (f) Ac₂O, 90 °C (g) HSiCl₃, hv (h) K₂CO₃, MeOH (i) H₂CrO₄ (j) N₂CHCO₂C₂H₅, BF₃·OEt₂ (k) NaOH, EtOH (l) NaH, (COCl)₂, PhH (m) NH₃ (n) HOCH₂CH₂OH, p-TsOH, PhH (o) LiAlH₄, THF (p) Ac₂O, pyridine (q) H₃O⁺ (r) t-BuOCl, CCl₄, AcOH (s) hv, PhH
using acetic anhydride was accompanied with acylation of the remaining hydroxyl group to afford triester 269. Next, irradiation of lactone 269 in the presence of trichlorosilane and a catalytic amount of t-butyliperoxide afforded ether 270 in 50% yield. Hydrolysis of the acetate followed by oxidation of the resulting alcohol gave ketone 271. Conversion of 271 to acid 272 involved a ring expansion with ethyl diazoacetate in the presence of a catalytic amount of boron trifluoride etherate, and base hydrolysis of the resulting regioisomeric β-ketoesters followed by an acidic workup. Next, construction of the pyrrolidine ring was accomplished using a multi-step reaction sequence. First, 272 was converted to a mixed anhydride. Treatment of the anhydride with ammonia followed by ketalization gave amide 273. Lithium aluminum hydride reduction of amide 273 followed by acylation of the resulting amine and ketal hydrolysis gave ketone 274. Finally, N-chlorination of acetamide 274 with t-butylihochlorite gave the corresponding N-chloro amide, which upon irradiation gave pyrrolidine 275. To complete the synthesis, elaboration of the spirooxindole-hydroxamic acid group onto tricyclic intermediate 275 and introduction of the C(20) ethyl group is required. Baldwin has yet to report results regarding these issues.

In 1990, Hamer reported a short stereoselective route to the bridged tricyclic azaoxaundecane ring system of gelsedine.61 The route begins with a thermal [3+4] cycloaddition between 3,3-dimethoxycyclopropene (276) and excess 4-methyl-2H-pyran-2-one (277) to afford the oxabicyclo[3.2.2]nonadienone 278 in 78% yield. Hydrogenation of 278 with rhodium on alumina proceeded with high stereoselectivity to afford 279 in 92% yield. Surprisingly, reduction of the lactone failed to provide ether 280 using conditions employed by Baldwin (HSiCl$_3$/(t-BuO)$_2$/hv), however, reduction with lithium aluminum hydride followed by a cyclization of the resulting diol gave ether 280. Hydrolysis of the dimethyl ketal and reductive amination of the resulting ketone (281) with methylamine and sodium cyanoborohydride gave predominately amine 282. N-Chlorination with sodium hypochlorite follow by a Hofmann-Loffler-Freytag reaction gave pyrrolidine 283 in 82% yield. With the intent of incorporating the spirooxindole unit, intermediate 284 has also been prepared by dehydration of the trimethylsilyl enol ether of 281 using palladium(II) acetate/benzoquinone. Finally, Hamer anticipates that the synthesis can be modified such that C(20) ethyl group can be introduced either in the starting pyranone or by nucleophilic addition to an appropriate imine.
Scheme XLII. Hamer's Approach Toward Gelsedine

In 1990, Kende reported a total synthesis of (±)-7-epi-20-desethylgelsedine (300) as shown in Schemes XLIII and XLIV. Kende's approach differs from Baldwin's and Hamer's in that the plan requires the preparation of an all-cis trisubstituted pyrrolidine 291 early in the synthesis (Scheme XLIII). The route begins with a Michael-Dieckmann route to 3-pyrrolidinones. Thus, reaction of the methyl ester of 4-ß-butoxycrotonic acid (285) with the ethyl ester of N-carbomethoxyglycine (286) using sodium hydride in benzene at reflux gave 3-pyrrolidinone ester 287 in 42% yield. Lactonization of 287 was accomplished using trifluoroacetic acid at room temperature to afford 288 in 77% yield. A Wittig reaction of 288 with (carbo-ß-butoxymethylene)triphenylphosphorane gave olefin 289 as a mixture of geometrical isomers. Stereoselective hydrogenation of 289 over palladium on carbon gave 290 in quantitative yield. Selective reduction of lactone 290 with lithium borohydride gave diol 291 and treatment of the diol with trifluoroacetic acid in methylene chloride gave the δ-lactone 292. Finally, a Swern oxidation afforded aldehyde 293 in 86% yield.
Scheme XLIII. Kende's Synthesis of 7-Epi-20-Desethylgelsedine

With aldehyde 293 in hand, the next task was incorporation of the spirooxindole followed by cyclization to afford the pentacyclic nucleus of gelsedine. Reaction of $N$-methoxyindole (294) with di-$n$-butylboron triflate in the presence of Hunig’s base gave vinyloxyborane 295. This was allowed to react with aldehyde 293 to afford a mixture of $E$ and $Z$ olefins 296 in 42% yield. Hydrogenation of 296 over 5% palladium on carbon gave oxindole 297 as a mixture of C(7) epimers. This was of no consequence in view of subsequent enolization of the oxindole required for the cyclization step. To this end, chemoselective reduction of the lactone was accomplished using lithium tri-$n$-sec-butylborohydride in dichloromethane at 0 °C to afford 298 as a mixture of C(7) and C(3) epimers. Treatment of hemiacetal 298 with trifluoroacetic anhydride-trifluoroacetic acid (1:1) gave a single pentacyclic product 299 in 53% yield, and cleavage of the $N$-carbamate afforded 300 in 61% yield. Unfortunately, the oxindole stereochemistry did not correspond to that required for the natural product. Kende is currently exploring modifications to this route to overcome the stereochemical problems associated with proper installation of the oxindole.
Recently, Sakai has reported syntheses of gelsedine (259), gelsenicine (261) and gelselegine (312) using a biomimetic approach as shown in Schemes XLV and XLVI. The synthesis begins with the conversion of the sarpagine-type alkaloid gardnerine (301), a major constituent of *Gardneria nutans*, to (19E)-koumidine (302) via a six step sequence in 62% overall
yield. Treatment of 302 with β,β,β-trichloroethyl chloroformate in the presence of magnesium oxide gave ring opened (C/D) carbamate 303 in 94% yield. Oxidation of 303 with 2 equivalents of osmium tetroxide gave diol 304 in 28% yield along with spirooxindole 305 in 39% yield. Treatment of indole 304 with osmium tetroxide gave oxindole 304. Next, a three step sequence was used to convert 305 to humantenine-type alkaloid 306 in 75% overall yield. Finally, double bond migration was accomplished using sodium iodide and trimethylsilyl chloride in acetonitrile to afford enamine 307 in 94% yield.

Scheme XLV. Sakai’s Biomimetic Synthesis of Gelsedine and Gelselegine-Type Alkaloids

(a) AcO₂, py, rt, 8 h (b) TsCl, n-Bu₄NHSO₄, 50% KOH-benzene, rt, 3 h (c) AlCl₃, EtSH, CH₂Cl₂, -18 °C, 3 h (d) (CF₃SO₂)₂, Et₃N, CH₂Cl₂, -20 °C, 10 min (e) Pd(OAc)₂, DPPF, Et₃N, HCOOH, DMF, 60 °C, 2 h (f) LAH, THF, Δ, 6 h (g) TrocCl, MgO, aqueous THF, rt, 15 h (h) OsO₄, py, THF, -78 °C; aqueous NaHSO₃ (i) CH(OMe)₂, PPTS, THF, rt, 2 h (j) Ac₂O, Δ, 3 h (k) 5% aq. KOH, MeOH, rt, 2 h (l) TMSCl, NaI, CH₃CN, rt, 1 h

Oxidation of enamine 307 followed by treatment with sodium borohydride gave diol 308 in 97% yield as shown in Scheme XLVI. Introduction of the Nₐ-methoxyoxindole function was accomplished using a three step sequence. Thus, lactam 308 was reduced with borane
dimethylsulfide complex and the resulting amine (309) was oxidized with urea-hydrogen peroxide complex in the presence of a catalytic amount of sodium tungstate. Finally, O-methylation was accomplished with diazomethane to afford \( N_a \)-methoxyoxindole 310 in 61% overall yield. Treatment of 310 with \( N,N,N',N' \)-tetramethylazodicarboxamide and tri-\( n \)-butylphosphine in dimethylformamide gave epoxide 311 in 63% yield and deprotection of the \( N_b \)-carbamate with zinc in acetic acid gave the corresponding amine, which gradually cyclized, to afford the natural product gelselegine (312). Oxidative cleavage of the C(20)-C(21) bond of 312 with sodium periodate in aqueous methanol gave gelsenicine (261) in 64% yield. Finally, a catalytic hydrogenation of imine 261 gave gelsedine (259) in quantitative yield. This sequence of reactions with minor modifications has also been applied to gardnerine to afford gelsemicine (260). Furthermore, a total synthesis of \((+)-(19E)\)-koumidine (302) has been accomplished by

Scheme XLVI. Sakai's Synthesis of Gelsedine and Gelselegine-Type Alkaloids Continued

\[
\begin{align*}
(a) & \text{OsO}_4, \text{py}, \text{THF}, \text{rt}; \text{NaHSO}_3 \\
(b) & \text{NaBH}_4, \text{MeOH}, \text{rt}, 2 \text{ h} \\
(c) & \text{BH}_3\text{Me}_2\text{S}, \text{THF}, \Delta, 2 \text{ h} \\
(d) & \text{trimethylamine N-oxide}, \text{MeOH}, \Delta, 2 \text{ h} \\
(e) & \text{urea-H}_2\text{O}_2, \text{cat. Na}_2\text{WO}_4, \text{aqueous MeOH}, \text{rt}, 4 \text{ h} \\
(f) & \text{CH}_2\text{N}_2, \text{Et}_2\text{O} \\
(g) & \text{TMAD, } n\text{-Bu}_3\text{P, DMF, rt, 4 h} \\
(h) & \text{Zn, AcOH, rt, 4 h} \\
(i) & \text{standing for 5 d, rt} \\
(j) & \text{NaI}_2\text{O}_4, \text{aqueous MeOH, rt, 2 h} \\
(k) & \text{PtO}_2, \text{H}_2, \text{EtOH, rt, 1 h}
\end{align*}
\]
Magnus and thus, Sakai's synthesis represents a formal total synthesis of gelselegine (312), gelsenicine (261) and gelsedine (259).64

C. Retrosynthetic Analysis

We embarked on a total synthesis of gelsedine hoping to apply knowledge learned during the synthesis of gelsemine to this synthetically challenging alkaloid. Kende's synthesis suggests, just as with gelsemine, that incorporation of the oxindole with proper stereochemistry is not going to be an easy task. However, because of results obtained in the gelsemine synthesis we are aware that thermodynamics can possibly be used to correct oxindole stereochemistry. With this in mind, we imagine that an intermediate of type 313 would allow for an end-game that parallels the final steps of our gelsemine synthesis. Specifically, incorporation of the oxindole via a radical cyclization, adjustment of oxindole stereochemistry if necessary and finally, construction of the tetrahydropyran. Ketone 313 could be derived from a Dieckmann-type condensation of tetrasubstituted pyrrolidine 314. Finally, pyrrolidine 314 would be prepared from 315, to be prepared in turn from diethyl aziridine-2,3-dicarboxylate (316) and S,S'-diphenyl-1,4-dithiofumarate (317) using an azomethine ylid cycloaddition.

Scheme XLVII. Retrosynthetic Analysis
D. Preliminary Studies

The addition of azomethine ylids to various dipolarophiles constitutes a versatile route to a variety of five-membered heterocycles. Any successful implementation of this approach would require access to large quantities of precursors 316 and 317. Aziridine 316 was easily prepared in two steps from diethyl fumarate according to known procedures. However, the only reported synthesis of dithioester 317, from fumaryl chloride and the copper thiophenoxide in ethanol, proceeded in 2% yield. Previously, thioester 317 had been used in our group and an improved procedure gave 317 in 31% yield on a 2 g scale. This involved the simultaneous addition of solutions of fumaryl chloride and pyridine in ether to a chilled (-4 °C) solution of 2 eq of thiophenol in ether. Work up consisted of a cold aqueous hydrochloric acid wash followed by saturated aqueous sodium bicarbonate. Initial attempts to scale up this reaction gave diminished yields and afforded a deep red oil from which isolation of the product was very labor intensive. Eventually, the reaction was conducted in dichloromethane at room temperature in the presence of potassium carbonate and apparently, the yield is dependent upon the work up conditions. It is imperative to avoid an acidic workup. In fact, the best yield was obtained when the reaction was poured into 1N aqueous sodium hydroxide to afford crude thioester as an orange solid which after a single trituration with ether afforded 317 in 60% yield on an 80 g scale. With a convenient synthesis of dithioester 317 in hand, cycloaddition of aziridine 316 with 317 in toluene at reflux for 27 h gave pyrrolidine 315 in 52% yield as shown in Scheme XLVIII. Chromatography is avoided in that 315 crystallized from the reaction mixture upon the addition of hexane. Chemoselective reduction of the thioesters using sodium borohydride in ethanol at 0 °C, and work up with saturated aqueous ammonium chloride (5 h) gave lactone 318 in 72% yield on a 5 g scale. On one occasion the intermediate diol was isolated and, although it was not fully characterized, treatment with p-toluenesulfonic acid in dichloromethane gave lactone 318. It should be noted, that prolonged exposure to ammonium chloride during reduction-lactonization of 315 may be detrimental, since lactone 318 was obtained in 50% yield when the reaction was scaled up. Protection of alcohol 318 with t-butyldimethylsilyl chloride and imidazole in dimethylformamide gave silyl ether 319 in quantitative yield. Reduction of 319 with
diisobutylaluminum hydride in ether at -100 °C gave hemiacetal 320 in 60% yield, as a mixture of diastereomers along with 20% of recovered starting material.

With hemiacetal 320 in hand, the next task was to introduce the C(5) vinyl group, destined to become the C(20) ethyl group in gelsedine, using a Wittig reaction. Initially, this reaction was conducted with methyltriphenylphosphonium bromide and potassium t-butoxide in toluene, but alcohol 321 was obtained in only poor yield. The reaction was further complicated by transesterification due to the presence of excess potassium t-butoxide. On one occasion the only product isolated was t-butyl ester 322 in 20% yield. After numerous attempts to improve the Wittig reaction, the best conditions involved deprotonation of methyltriphenylphosphonium bromide with dimesyl potassium in dimethylsulfoxide-toluene to afford olefin 321 in 38% yield. The structure of 321 was assigned based on 1H NMR experiments (decoupling and nOe). Relevant nOe experiments are shown in Table 7.

**Scheme XLIII. Preparation of Tetrasubstituted Pyrrolidines 321 and 322**

(a) PhCH₃, Δ (b) NaBH₄, EtOH, 0 °C; aqueous NH₄Cl (c) TBDMSCl, imidazole, DMF (d) DIBAL-H, Et₂O, -100 °C (e) (Ph)₃PCH₃Br, t-BuOK, PhCH₃ (f) (Ph)₃PCH₃Br, KH, DMSO, PhCH₃
Table 7. nOe’s for Pyrrolidine 321 in Chloroform

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<td></td>
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With tetrasubstituted pyrroldines 321 and 322 in hand, the next task was elaboration of the C(2) ester and C(4) hydroxymethyl groups to provide condensation precursor 330. This was accomplished as shown in Scheme XLIX. Thus, conversion of alcohols 321 and 322 to methanesulfonates 323 and 324 proceeded in 88% and 98% yields, respectively. Displacement of the mesylates using potassium cyanide afforded nitriles 325 and 326 in 79% and 78% yields, respectively. The C(2) ester was homologated by two carbons as follows. We were unable to reduce the t-butyl ester 326 under mild conditions, however ethyl ester 325 was reduced with
Scheme XLIX. Preparation of Condensation Precursor 330

(a) MsCl, Et₃N, CH₂Cl₂ (b) KCN, DMF, 80 °C (c) NaBH₄ (excess), MeOH (d) Dess-Martin, CH₂Cl₂, pyridine (e) (Ph)₃P=CHCN, CH₂Cl₂ (f) H₂, Pd/C, EtOH

sodium borohydride in methanol or with lithium borohydride in ether to afford alcohol 327 in 50-60% yield. Oxidation of 327 with the Dess-Martin periodinane, buffered with pyridine, gave aldehyde 328 in 87% yield. A Wittig reaction with cyanomethylidene phosphorane in dichloromethane gave α,β-unsaturated nitrile 329 in 97% yield. The structure of 329 was confirmed by a series of NOe experiments (Table 8). Finally, hydrogenation of 329 over palladium on carbon in ethanol gave dinitrile 330 in 65% yield.
With cyclization precursor 330 in hand, we had hoped that treatment with based would afford a mixture of enaminonitriles. Obtaining a mixture would be of no consequence since hydrolysis and decarboxylation would afford only tricyclic ketone 313. However, nOe experiments with pyrrolidine 321 and 229 suggest that substituents at C(2), C(3), and C(5) occupy pseudo-equatorial positions on the pyrrolidine ring. Of course cyclization cannot occur from this conformation. Thus, not surprisingly, treatment of 330 with potassium $t$-butoxide in toluene at 85 °C did not afford enaminonitrile 331 or 332. While starting material was gone and chromatography afforded a homogeneous product, spectral data were inclusive. In the $^{13}$C NMR all peaks were doubled which indicated the presence of a mixture of isomers or a dimer. In the proton NMR a number of peaks were doubled, however, the integration was not 1:1. Thus, dimers can be ruled out. A pair of singlets at δ 119.6, 120.3 and 174.6, 175.1 ppm in the $^{13}$C NMR, suggest an enaminonitrile, however, the presence of an additional triplet in the product compared to the starting material does not support structures 331 and 332. An additional triplet may be explained by the presence of potassium metal in the potassium $t$-butoxide which could have caused reduction of one the nitrile groups. The mass spectrum indicates a parent ion at m/z 456 which is not consistent with a dimeric structure, but does not rule this possibility out. Obviously, this cyclization requires further consideration. Perhaps, an alternate approach which incorporates the oxindole via a Wittig type reaction with aldehyde 328 followed by reduction of the C(4) nitrile to an aldehyde would allow closure of the ring via an aldol condensation. These are conditions we are already familiar with from the gelsemine system. Finally, another approach might involve removal of the $N$-benzyl and the $t$-butyldimethylsilyl groups (333 → 334), followed by tying back the unprotected amine and alcohol groups (334 → 335). This would force the C(2)
and C(4) substituents of the pyrrolidine ring in close proximity to each other, a process that should favor subsequent cyclizations.

![Chemical Structure](image)

**Figure 11. nOe Experiments with Pyrrolidine 329 in Chloroform**

**Table 8. nOe’s for Pyrrolidine 329 in Chloroform**

<table>
<thead>
<tr>
<th>1H Irradiated</th>
<th>Chemical Shift</th>
<th>nOe Observed</th>
<th>Chemical Shift</th>
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In summary, an azomethine ylid approach to tetrasubstituted pyrrolidine 330 has been described from readily available starting materials. The route introduces a high degree of
functionality early in the synthesis, and differs from recently reported synthesis in that the C(20) ethyl group of gelsedine is introduced early in the synthesis. While the tricyclic substructure of gelsedine was not obtained, the route offers considerable flexibility and will clearly be the subject of future research.
EXPERIMENTAL

All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected as are all boiling points. Proton nuclear magnetic resonance spectra were recorded on Bruker AC-200, Bruker AM-250, Bruker WM -300, Bruker AC-300, or Bruker AM-500 spectrometers and recorded in parts per million from internal chloroform, benzene, or dimethylsulfoxide on the δ scale. The 1H NMR spectra are reported as follow: chemical shift [multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz, integration, interpretation]. For all structures containing the tricyclic substructure of gelsemine, assignments are made using the gelsemine numbering system. For all 1H NMR marked with an asterisk (*), assignments are supported by decoupling and/or nOe experiments. 13C NMR data were obtained with Bruker AC-200, Bruker AM-250, Bruker AC-300, or Bruker AM-500 spectrometers. Infrared spectra were taken with Perkin-Elmer 1600 instruments. Mass spectra were obtained on Kratos MS-30 or Katos VG70-250s instruments at an ionization energy of 70 eV. Compounds for which an exact mass is reported exhibited no significant peaks at m/e greater than that of the parent. Combustion analyses were performed by Atlantic MicroLaboratories, Inc., Norcross, Georgia.

Solvents and reagents were dried and purified prior to use when deemed necessary; benzene, diethyl ether, tetrahydrofuran, 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. Analytical thin-layer chromatography was conducted using EM Laboratories 0.25 mm thick precoated silica gel 60F-254 plates. Column chromatography was preformed 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.\textsuperscript{74} The order of experimental procedures follow their order of appearance in the text. For all ozonolyses, ozone gas was delivered using a Welsbach ozone generator.

\[
\begin{align*}
\text{OCH}_3 & \quad \text{O} \\
\text{NMe} & \quad \text{O} \\
\text{H}
\end{align*}
\]

\textbf{160}

\((\pm)-(1R^*,3aR^*,4S^*,7aS^*,8S^*)\)-Hexahydro-3a-(methoxymethyl)-2-methyl-3,6-dioxo-1,4-

methanoisoleidolline-8-carboxaldehyde (160). Through a solution of 143 mg (0.355 mmol) of

alkene 159 in 15 mL of dichloromethane-methanol (4:1) cooled to $-78^\circ C$ was passed ozone gas

until a pale blue color persisted. The mixture was stirred for 5 min and then the excess ozone

was purged from the mixture by passing nitrogen gas through the mixture until it was clear, and

then 1 mL of dimethylsulfide was added and cold bath was removed. The mixture was stirred at

room temperature for 18 h and concentrated in vacuo. The residue was chromatographed over

10 g of silica gel (first dichloromethane; then ethyl acetate-dichloromethane, 1:9, then 1:1; finally

ethyl acetate) to provide 58 mg (65\%) of aldehyde 160 as a clear oil: IR (neat) 1693 cm$^{-1}$; $^1$H

NMR (300 MHz, CDCl$_3$) $\delta$ 2.26 (dd, $J = 21.7, 2.8$ Hz, 1 H), 2.42 (dd, $J = 19.0, 3.5$ Hz, 1 H), 2.64

(m, 2 H), 2.71 (s, 3 H, NCH$_3$), 2.75 (m, 2 H), 2.79 (br s, 1 H), 3.30 (s, 3 H, OCH$_3$), 3.77 (d, $J =

10.4$ Hz, 1 H, CH$_2$OMe), 3.92 (d, $J = 10.4$ Hz, 1 H, CH$_2$OMe), 4.02 (dd, $J = 2.4, 1.9$ Hz, 1 H, CH$_2$N)

9.73 (s, 1 H, CHO); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 29.7 (q), 34.1 (d), 39.2 (t), 42.8 (t), 49.3

d, 54.9 (s), 59.4 (q), 62.3 (d), 64.9 (d), 69.1 (t), 174.8 (s), 198.8 (d), 207.1 (s); mass spectrum,

$m/z$ (relative intensity) 251 (M$^+$, 10), 223 (40), 122 (100); exact mass calcd. for C$_{13}$H$_{17}$NO$_4$ $m/z$

251.1158, found $m/z$ 251.1119.
Methyl (±)-(1R*,3aR*,4S*,6R*,7aS*,8S*)-hexahydro-6-hydroxy-3a-(methoxymethyl)-2-methyl-3-oxo-1,4-methanolsindoline-8-carboxylate (162). To a solution of 15 mg (0.059 mmol) aldehyde 160 in 1 mL of methanol was added 1 drop of DBU. The mixture was stirred at room temperature for 72 h, concentrated in vacuo and chromatographed over 1 g of silica gel (dichloromethane; then tetrahydrofuran-dichloromethane, 10:90, then 15:85) to provide 10 mg (58%) of ester 162 as a white solid: mp (ethyl acetate-hexane) 165-166 °C; IR (KBr) 3473, 1739, 1686 cm⁻¹; ¹H NMR* (300 MHz, CDCl₃) δ 1.63-1.73 (m, 2 H, C₇aH and C₁₄aH), 1.84 (br, 1 H, OH), 2.08 (ddd, J = 15.2, 7.8, 2.5 Hz, 1 H, C₇eH), 2.17 (ddd, J = 13.5, 7.4, 4.5 Hz, 1 H, C₁₄eH), 2.34 (m, 1 H, C₇H), 2.59 (m, 1 H, C₁₅H), 2.70 (s, 3 H, NCH₃), 3.04 (dd, J = 3.1, 2.1 Hz, 1 H, HCCO₂Me), 3.41 (s, 3 H, CH₂OCH₃), 3.66 (s, 3 H, CO₂CH₃), 3.78 (d, J = 9.8 Hz, 1 H, CH₂OMe), 3.98 (dd, J = 3.3, 1.8 Hz, 1 H, CHN), 3.94 (d, J = 9.9 Hz, 1 H, CH₂OMe), 4.10 (quintet, J = 7.8 Hz, 1 H, HCOH); ¹³C NMR (75.5 MHz, CDCl₃) δ 29.1 (q), 31.4 (t), 33.7 (t), 36.4 (d), 50.6 (d), 50.8 (d), 51.8 (q), 56.4 (s), 59.5 (q), 63.2 (d), 65.7 (d), 67.5 (l), 171.3 (s), 175.7 (s); mass spectrum, m/z (relative intensity) 283 (M⁺, 17), 123 (100), 45 (38); exact mass calcd. for C₁₄H₂₁NO₅ m/z 283.1420, found m/z 283.1422.

(E)-6-[(Tetrahydro-2H-pyran-2-yl)oxy]-3-hexene-2-one (144). Through a solution of 50 g (320 mmol) of olefin 142 in 400 mL of dichloromethane cooled in a dry ice-acetone bath was
passed ozone gas until a pale blue color persisted. The excess ozone was then 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-oxopropylidenetriphenyl)phosphorane 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, filtered, and the mother liquor was concentrated in vacuo. The residue was dissolved in ethyl acetate-hexanes (15:85) and passed through a 450 g pad of silica gel (ethyl acetate-hexanes, 1:9). The eluent was concentrated in vacuo and distilled under reduced pressure (118-124 °C, 4 mmHg) to afford 39 g (61%) of enone 144 as a colorless oil. A 1H NMR spectrum of 144 was consistent with previously reported data and appears in Appendix A. Minor impurities are attributed to aldehyde 143 which co-distilled with the product.

\[
\text{Me}_3\text{SiO} \quad \text{OTHP}
\]

145

Trimethyl[(E)-1-methylene-5-[(tetrahydro-2H-pyran-2-yl)oxy]-2-pentenyl]oxy]silane (145). To a solution of 65 mL (467 mmol) of diisopropylamine in 500 mL of tetrahydrofuran cooled in a dry ice-acetone bath was added 200 mL (400 mmol) of 2.0 M n-butyllithium 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 144 in 50 mL of tetrahydrofuran was added over a 20-min period. The mixture was stirred for 20 min, and then 59 mL (467 mmol) of trimethylsilyl chloride in 30 mL of tetrahydrofuran 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 filter cake was washed with hexane and the mother liquor was concentrated in vacuo. The residue was diluted with 500 mL of hexane, filtered, and the filtrate was concentrated in vacuo to provide 102 g (99%) of diene 145 as a yellow oil which was used without further
A 1H NMR spectrum was identical to that previously reported for 145 and appears in Appendix A.

(±)-(1R*,2S*,3S*)-3-(2-Hydroxyethyl)-N-methyl-5-oxo-1,2-cyclohexanedicarboximide (146) and (±)-(1R*,5S*,6S*,7R*)-1-Methoxy-N-methyl-2-oxabicyclo[3.3.1]nonane-6,7-dicarboximide (164). A mixture of 7.5 g (27.7 mmol) of diene 145 and 3.1 g (27.7 mmol) of N-methylmaleimide in 80 mL of toluene was heated at reflux for 4 h. The mixture was then cooled and concentrated in vacuo to afford 10.5 g of crude cycloadduct. A 1H NMR appears in Appendix A. The residue was dissolved in 100 mL of methanol and 250 mg of p-toluenesulfonic acid monohydrate was added. The mixture was stirred at room temperature for 2 h, and filtered to remove a small amount of white precipitate. The filtrate was then concentrated in vacuo and the resulting residue chromatographed over silica gel (ethyl acetate) to provide crude 164 which was triturated with ether to afford 2.5 g (37%) of 164 as a solid. An analytically pure sample was recrystallized from ethyl acetate-hexane to afford 164 as a crystalline white solid: mp 134-136 °C; IR (KBr) 1770, 1702 cm⁻¹; 1H NMR (200 MHz, CDCl₃) δ 1.30-1.42 (m, 1 H), 1.55-1.77 (m, 3 H), 1.91 (ddd, J = 13.3, 2.8, 2.8 Hz, 1 H), 2.75-2.95 (m, 2 H), 2.98 (s, 3 H, NCH₃), 3.04-3.15 (m, 2 H), 3.31 (s, 3 H, OCH₃), 3.39-3.44 (m, 1 H, CH₂O), 3.57-3.70 (m, 1 H, CH₂O); 13C NMR (250 MHz, CDCl₃) δ 24.1 (q), 26.1 (q), 28.3 (d), 29.9 (t), 32.6 (t), 38.3 (d), 43.1 (d), 47.9 (q), 58.6 (t), 96.9 (s), 178.1 (s), 179.1 (s); mass spectrum, m/z (relative intensity) 239 (M⁺, 0.09), 208 (2), 113 (100); exact mass calcd. for C₁₂H₁₇NO₄ m/z 239.1158, found m/z 239.1152.

Anal. calcd. for C₁₂H₁₇NO₄: C, 60.24; H, 7.16. Found: C, 60.41; H, 7.22.

Continued elution (methanol-dichloromethane, 1:9) afforded 3.1 g (49%) of keto alcohol 146 as a
viscous oil. A $^1$H NMR spectrum was identical to that previously reported for 146 as shown in Appendix A.

($\pm$)-(8$R^*$,9$S^*$,10$S^*$)-10-(2-Hydroxyethyl)-N,3,3-trimethyl-1,5-dioxaspiro[5,5]undecane-8,9-dicarboximide (147). A mixture of 102 g (0.38 mol) diene 145 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 then added and the mixture was stirred at reflux for 1 h. The mixture was then cooled, and 106 g (1.019 mol) of 2,2-dimethyl-1,3-propanediol and 3 g of p-toluenesulfonic acid monohydrate was added. The condenser was fitted with a Dean-Stark trap for continuous removal of water, and the mixture was heated at reflux for 16 h. The mixture was cooled, concentrated in vacuo to 550 mL, and was stirred over 25 g of potassium carbonate for 30 min. The mixture was passed through a 600 g pad of silica gel (ethyl acetate-hexanes, 25:75, then 1:1, then 75:25; then ethyl acetate). The eluent from the pad was concentrated in vacuo and placed on the Kugelrohr (75 °C, 0.1 mmHg) to remove excess N-methylmaleimide and 2,2-dimethyl-1,3-propanediol to provide 46 g (39%) of imide 147 which hardened to an amber resin upon cooling. A $^1$H NMR was identical to that previously reported for 147 and appears in Appendix A.
(±)-(8R*,9S*,10R*)-N,3,3-Trimethyl-10-vinyl-1,5-dioxaspiro[5,5]undecane-8,9-dicarboximide (148). To a solution of 29.9 g (93.9 mmol) of alcohol 147 and 25.5 g (112.3 mmol) of o-nitrophenylselenocyanate\(^\text{\textsuperscript{38}}\) in 300 mL of tetrahydrofuran 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 then cooled in an ice bath; and 52 g (196 mmol) of anhydrous disodium hydrogen phosphate 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 tetrahydrofuran was then concentrated and the residue was partitioned between 200 mL of ethyl acetate and 300 mL of water. The organic layer was separated and the aqueous phase was extracted with three 200-mL portions of ethyl acetate. The combined ethyl acetate layers 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 (ethyl acetate-hexanes, 1:19, then 1:9, then 2:8) to afford 21.9 g (79%) of alkene 148 as a viscous red oil.
(±)-(3'R,3'aS',7'S,7'aR')-Tetrahydro-3'-hydroxy-2',5,5-trimethyl-7'-vinylspiro[m-
dioxane-2,5'(4'R)-isolinol]-1'-one (165). To a solution of 10.3 g (35.2 mmol) of imide 148 in
120 mL of methanol 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 concentrated in vacuo. The residue was partitioned between 100 mL of
ethyl acetate and 100 mL of saturated aqueous sodium bicarbonate. The basic aqueous layer
was separated and extracted with five 50-mL portions of ethyl acetate. The combined ethyl
acetate layers were dried (MgSO₄), filtered, and concentrated in vacuo. The orange oil was
chromatographed over 340 g of silica gel (ether; then ethyl acetate-hexane, 8:2) to provide 8.4 g
(80%) of carbinol 164 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, C₆D₆) δ 0.50 (s, 3 H, CH₃), 0.80
(s, 3 H, CH₃), 1.52-1.66 (m, 2 H), 2.21-2.25 (m, 3 H), 2.31-2.37 (m, 1 H), 2.51-2.62 (m, 1 H), 2.64
(s, 3 H, NCH₃), 3.12-3.26 (m, 4 H, OCH₂ manifold), 3.61 (br, 1 H, OH), 4.53 (m, 1 H, =CH₂), 5.06
(m, 1 H, =CH₂), 5.10 (s, 1 H, HCOH), 6.93-7.05 (m, 1 H, =CH): ¹³C NMR (75.5 MHz, C₆D₆) 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); mass spectrum, m/z (relative intensity) 295
(M⁺,21), 277 (27), 128 (100); exact mass calcd. for C₁₆H₂₅NO₄ m/z 295.1784, found m/z
295.1775. This compound decomposed when the NMR data was obtained in CDCl₃.
(±)-(3'R,3'aS,7'R,7'aR)-3'-Ethoxytetrahydro-2',5,5-trimethyl-7'-vinylspiro[mdioxane-2,5'(4'H)-isindoline]-1'-one (149). To a suspension of 4.8 g (0.12 mmol) of 60% sodium hydride, washed with three 10-mL portions of hexane, in 250 mL of tetrahydrofuran warmed to 45 °C was added 26.9 g (91.2 mmol) of hydroxylactam 165 in several portions. After the addition, the mixture was stirred until hydrogen evolution ceased. The mixture was then 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 sodium hydride was cautiously destroyed with ethanol. The mixture was partitioned between 500 mL of brine and 200 mL of ethyl acetate. The organic layer was separated and the aqueous phase was extracted with two 200-mL portions of ethyl acetate. The combined ethyl acetate layers were washed with three 200-mL portions of brine, dried (MgSO₄), decolorizing carbon (Norit A) was added, and the mixture was filtered through Celite and 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 149 (115-121 °C). The filtrate (6.9 g) was chromatographed over 60 g of silica gel (ethyl acetate-hexane, 3:7 then 1:1) and triturated with hexane. The resulting solid was collected by filtration to afford an additional 2.4 g (8%) of 149. The filtrate, 3.4 g (11%), was determined to be a 1:1 mixture of diastereomers at C(3) by ¹H NMR. The ¹H spectrum of 149 was identical to that reported elsewhere, and appears in Appendix A.
(±)-(3'R,3'aS',7'S',7'aR')-3'-Ethoxytetrahydro-7'a-(methoxymethyl)-2',5,5-trimethyl-7'-vinylspiro[m-dioxane-2,5' (4'H)-isodolin]-1'-one (150). To a solution of 18 mL of diisopropylamine in 100 mL of tetrahydrofuran cooled in a dry ice-acetone bath was added 66 mL (105 mmol) of 1.6 M n-butyllithium in hexane while maintaining the temperature below -60 °C. The mixture was stirred at -78 °C for 15 min, then at -40 °C for 15 min, and then cooled to -78 °C. To the mixture was added 23.8 g (72.4 mmol) of lactam 149 [single diastereomer at C(3)] in several portions, followed by 3.4 g (10.4 mmol) of lactam 149 [1:1 mixture of diastereomers at C(3)] in 25 mL of tetrahydrofuran. The mixture was stirred at -78 °C for 10 min, at -20 °C for 5 min, and then was cooled to -78 °C and 10.6 g (135 mmol) of chloromethyl methyl ether was added in one portion. The mixture stirred at room temperature for 2 h, and was then concentrated in vacuo to approximately 100 mL. To the resulting residue was added 100 mL of saturated aqueous sodium bicarbonate and 100 mL of ethyl acetate. The organic layer was separated and the aqueous phase was extracted with three 50-mL portions of ethyl acetate. The combined ethyl acetate layers were washed with three 100-mL portions of brine, dried (MgSO4), decolorizing carbon (Norit A) was added, and the mixture was filtered through Celite and concentrated in vacuo. The crude residue was chromatographed over 300 g of silica gel (ethyl acetate-hexane; 1:9, then 15:85, then 20:80, then 25:75) to provide 26.7 g (88%) of 150 whose 1H NMR spectrum was consistent with previously reported data.
(±)-(3'R*,3'aS*,7'S*,7'aR*)-7'-a-[(Benzyloxy)methyl]-3'-ethoxytetrahydro-2',5,5-trimethyl-7'-vinylspiro[m-dioxane-2,5'(4'H)-isindolin]-1'-one (166). To a solution of 8.70 mL (62.1 mmol) of diisopropylamine in 50 mL of tetrahydrofuran at -78 °C was added 20.80 mL of 2.5 M n-butyllithium in hexane. The mixture was stirred for 30 min, and 13.5 g (41.7 mmol) of 149 in 30 mL of tetrahydrofuran 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 ethyl acetate and 300 mL of water. The organic layer was separated and the aqueous phase was extracted with three 75-mL portions of ethyl acetate. The combined ethyl acetate layers were washed with four 200-mL portions of brine, dried (MgSO₄), treated with carbon (Norit A), filtered through Celite and concentrated in vacuo. The residue was chromatographed over 95 g of silica gel (ethyl acetate-hexane, 1:4) to afford 17.8 g (96%) of 166 as a viscous oil: IR (neat) 1697 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.85 (s, 3 H, CH₃), 1.02 (s, 3 H, CH₃), 1.15 (t, J = 6.6 Hz, 3 H, CH₃), 1.37 (dd, J = 13.7, 13.3 Hz, 1 H, C₆H), 1.82 (dd, J = 15.3, 6.4 Hz, 1 H, C₄H), 1.98 (dd, J = 14.4, 6.2 Hz, 1 H, C₄H), 2.09 (dd, J = 14.1, 3.3 Hz, 1 H, C₆H), 2.69-2.69 (m, 2 H, C₃aH and C₇H), 2.79 (s, 3 H, NCH₃), 3.38-3.52 (m, 6 H, OCH₂Me and OCH₂), 3.60 (ABq, J = 9.0 Hz, 2 H, CH₂OBn), 4.44 and 4.49 (ABq, J = 12.2 Hz, 2H, OCH₂Ph), 4.59 (d, 2.4 Hz, CH₃OEt), 4.99 (dd, J = 9.0, 2.0 Hz, 1 H, C=CH₂), 5.03 (s, 1 H, C=CH₂), 6.21 (ddd, J = 16.6, 10.4, 9.5, Hz, 1 H, CHCH=CH₂), 7.2-7.29 (m, 5 H, ArH); ¹³C NMR (75.5 MHz, CDCl₃) 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; mass spectrum, m/z (relative intensity) 398 (3), 356 (6), 276
(±)-(3'R*,3'aS*,7'R*,7'aS*)-7'a-[(Benzyloxy)methyl]-3'-ethoxytetrahydro-2',5,5-trimethyl-1'-oxospiro[m-dioxane-2,5' (4'H)-Isoindoline]-7'-carboxaldehyde (167). Through a solution of 10.0 g (22.5 mmol) of olefin 166 in 200 mL of dichloromethane-methanol (95:5) cooled to -86 ºC was passed ozone gas until a pale blue color was evident and starting material was no longer present by thin-layer chromatography (ethyl acetate-hexane, 3:7). Excess ozone was then purged from the mixture using a stream of nitrogen, and then 20 mL of dimethylsulfide 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 dichloromethane. The combined dichloromethane layers were washed with three 50 mL portions of brine, dried (MgSO4), 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 which was used without further purification. An analytically pure sample was obtained from a single recrystallization from ether-hexane to afford aldehyde 167 as a crystalline white solid: mp 117-119 ºC; IR (KBr) 1711 cm⁻¹; ¹H NMR* (300 MHz, CDCl₃) δ 0.83 (s, 3 H, CH₃), 1.06 (s, 3 H, CH₃), 1.16 (t, J = 7.0 Hz, 3 H, CH₃), 1.23 (dd, J = 14.2, 12.6 Hz, 1 H, C₄H), 1.36 (dd, J = 13.8, 10.1 Hz, 1 H, C₆H), 2.11 (dd, J = 13.8, 6.6, 2.1 Hz, 1 H, C₄H), 2.60-2.68 (m, 2 H, C₇H and C₃H), 2.84 (s, 3 H, NCH₃), 2.88 (dd, J = 12.5, 4.2 Hz, 1 H, C₆H), 3.31-3.56 (m, 3 H, OCH₂; and 2 H, OCH₂Me), 3.63 (d, J = 11.5 Hz, 1 H, OCH₂), 3.81 (d, J = 9.4 Hz, 1 H, CH₂OBn), 3.94 (d, J = 9.4 Hz, 1 H, CH₂OBn), 4.35 (d, J = 0.7 Hz, 1 H, C(OEt)), 4.53 and 4.58 (ABq, J = 12.3 Hz, 2 H,
OCH$_2$Ph), 7.23-7.34 (m, 5 H, ArH), 10.12 (s, 1 H, CHO); $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 15.2 (q), 22.1 (q), 22.6 (q), 26.8 (l), 28.2 (q), 29.9 (s), 35.4 (t), 39.1 (d), 46.5 (d), 51.3 (s), 63.6 (l), 69.9 (l), 70.0 (l), 72.4 (l), 73.2 (l), 95.4 (d), 96.6 (s), 127.3 (d), 127.5 (d), 128.2 (d), 137.8 (s), 174.1 (s), 202.0 (d); mass spectrum m/z (relative intensity) 445 (M+, 3), 427 (13), 324 (26), 311 (68), 296 (88), 91 (100); 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 (±)-(αE,3'R*,3'aS*,7'S*,7'R*)-3'-ethoxytetrahydro-7'a-(methoxymethyl)-2',5,5-trimethyl-1'-oxospiro[m-dioxane-2,5'(4'H)-isoxindoline]-7'-acrylate (152). Through a solution of 13.0 g (35.4 mmol) of olefin 150 in 250 mL of methanol cooled to -78 °C was passed ozone gas until a pale blue color persisted. The excess ozone was then purged from the mixture using a stream of nitrogen, and then 10 mL of dimethylsulfide was added in one portion. The cold bath was then removed, and the mixture was stirred at room temperature for 2.5 h. The mixture was concentrated in vacuo, and the residue was diluted with 100 mL of dichloromethane and 37 g (105 mmol) of (carbethoxymethylidene)triphenylphosphorane was added. The mixture was stirred at reflux for 48 h, and then concentrated in vacuo. The oily residue was diluted with 300 mL of ether followed by 200 mL of hexane. The resulting Wittig by-products that crystallized/precipitated were removed by filtration. The mother liquor was combined with an identical run of 10 g of 150, and passed through a 163 g pad of silica gel (tetrahydrofuran-hexane, 20:80, then 30:70) to provide 25.1 g (92%) of ester 152 as an oil. An additional 1.2 g (4.7%) of 152 was trapped on the Wittig by-products and was liberated by re-dissolving the Wittig by-products, slowly recrystallizing from ether-hexane, and removing the by-products by filtration.
The mother liquor was then passed through a 12 g pad of silica gel (tetrahydrofuran-hexane, 30:70) as above. Spectral data for this material was identical to that reported elsewhere. A $^1$H NMR spectrum is included in Appendix A.

**Ethyl** $^\pm$-$\alpha$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'$)-isoindoline]-7'$-acrylate (168). A mixture of 5.0 g (11.2 mmol) of 167 and 5.9 g (16.8 mmol) of (carbethoxymethylidene)triphenylphosphorane in 55 mL of dichloromethane 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 (ethyl acetate-petroleum ether, 2:7 then, 3:7) to provide 4.2 g (73%) of ester 168 and 1.45 g of mixed fractions. The mixed fractions were chromatographed a second time to afford an additional 540 mg (9%) of 168: IR (neat) 1698 cm$^{-1}$; $^1$H NMR* (300 MHz, CDCl$_3$) $\delta$ 0.84 (s, 3 H, CH$_3$), 1.04 (s, 3 H, CH$_3$), 1.15 (t, $J$ = 6.6 Hz, 3 H, CH$_3$), 1.27 (t, $J$ = 7.1 Hz, 3 H, CH$_3$), 1.41 (t, $J$ = 13.3 Hz, 1 H, C$_{6}$H), 1.69 (dd, $J$ = 14.1, 7.5 Hz, 1 H, C$_{4}$H), 2.05 (dd, $J$ = 14.2, 6.3 Hz, 1 H, C$_{4}$H), 2.16 (dd, $J$ = 13.9, 3.1 Hz, 1 H, C$_{6}$H), 2.64 (m, 1 H, C$_{3}$aH), 2.80 (s, 3 H, NCH$_3$), 2.88 (m, 1 H, C$_{7}$aH), 3.37-3.62 (m, 8 H, OCH$_2$), 4.16 (dq, $J$ = 7.2, 1.1 Hz, 2 H, CO$_2$CH$_2$CH$_3$), 4.47 (s, 2 H, OCH$_2$Ph), 4.50 (d, $J$ = 1.5 Hz, 1 H, C$_{3}$H), 5.77 (d, $J$ = 15.6 Hz, 1 H, =CHCO$_2$Et), 7.21-7.33 (m, 5 H, ArH), 7.38 (dd, $J$ = 15.6, 9.5 Hz, 1 H, =CH); $^{13}$C NMR (62.2 MHz, CDCl$_3$) $\delta$ 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); mass spectrum m/z (relative
intensity) 515 (M⁺, 4), 486 (14), 470 (21), 424 (68), 239 (31), 91 (100); exact mass calcd. for
C₂₉H₄₁NO₇ m/z 515.2884, found m/z 515.2865.

Ethyl (±)-(α,E,3'R⁺,3'aS⁺,7'S⁺,7'aR⁺)-tetrahydro-7'a-(methoxymethyl)-2',5,5-trimethyl-
1'-oxo-3'-[phenylthio]spiro[dioxane-2,5'(4'H)isoindoline]-7'-acrylate (153). A mixture of
26.1 g (59.5 mmol) of ethoxylactam 152, 13.9 g (13.7 mmol) of thiophenol, 600 mg of p-
toluenesulfonic acid monohydrate, and 20 g of 4 Å molecular sieves in 500 mL of
dichloromethane was stirred for 9 h. The mixture was then filtered through Celite, diluted with
300 mL of saturated aqueous sodium bicarbonate and the dichloromethane layer was separated.
The aqueous phase was extracted with three 50-mL portions of dichloromethane. The combined
dichloromethane layers were dried (MgSO₄), filtered and concentrated in vacuo. The residue
was passed through a 25 g pad of silica gel (ethyl acetate-hexane, 20:80, then 30:70) to afford 27
g (89%) of 153 as a viscous oil. An ¹H NMR spectrum of 153 appears in Appendix A and it is
consistent with previously reported spectra.
Ethyl (±)-(αE,3'R',3'aS',7'S',7'aR')-7'a-[(benzyloxy)methyl]tetrahydro-2',5,5-tri-
methyl-1'-oxo-3'-{phenylthio}spiro[m-dioxane-2,5'(4'H)isoindoline]-7'-acrylate (169). A
mixture of 4.7 g (9.1 mmol) of ethoxylactam 168, 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 dichloromethane
was stirred for 3 h. The mixture was diluted with 100 mL of saturated aqueous sodium
bicarbonate and the methylene chloride layer was separated. The basic aqueous phase was
extracted with three 40-mL portions of dichloromethane. The combined dichloromethane layers
were washed with two 50-mL portions of brine, dried (MgSO₄), filtered and concentrated in vacuo.
The residue was chromatographed over 65 g of silica gel (ethyl acetate-hexane, first 2:8, then
3:7) to afford 4.1 g (76%) of 169 as a viscous oil: IR (neat) 1717, 1691 cm⁻¹; ¹H NMR* (300 MHz,
CDCl₃) δ 0.87 (s, 3 H, CH₃), 0.99 (s, 3 H, CH₃), 1.25 (t, J = 7.1 Hz, 3 H, CH₃), 1.52 (dd, J = 14.2,
12.0 Hz, 1 H, C₆-H), 1.82 (dd, J = 14.7, 5.7 Hz, 1 H, C₄-H), 2.03 (dd, J = 14.3, 3.2 Hz, 1 H, C₆-H),
2.34 (dd, J = 14.7, 3.6 Hz, 1 H, C₄-H), 2.66-2.72 (m, 2 H, C₇-H and C₃-H), 2.78 (d, J = 9.2 Hz, 1
H, OCH₂), 2.89 (s, 3 H, NCH₃), 3.37-3.48 (m, 5 H, OCH₂), 4.13 (dq, J = 6.4 Hz, 2 H, CO₂CH₂Me),
4.25 and 4.31 (ABq, J = 12.1 Hz, 2 H, OCH₂Ph), 4.81 (d, J = 5.7 Hz, 1 H, C₃-H), 5.70 (d, J = 15.6
Hz, 1 H, =CH), 7.09 (dd, J = 15.6, 9.5 Hz, 1 H, =CHCO₂Et), 7.17-7.40 (m, 10 H, ArH); ¹³C NMR
(75.5 MHz, CDCl₃) 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 (relative intensity) 579 (M⁺, 0.01), 472 (30), 470 (100), 379 (19), 91
(72); exact mass calcd. for C₂₇H₉₆NO₆ (M⁺-SC₆H₅) m/z 470.2381, found m/z 470.2515.
Ethyl (±)-(1'R,3'S,4'R,7'aR',8'R')-tetrahydro-3'S-(methoxymethyl)-2',5,5-trimethyl-3'-oxospiro[m-dioxane-2,6'(5'H)-[1,4]methanoloisindoline]-8'-acetate (154). To a solution of 15.5 g (30.2 mmol) of 153 in 750 mL of benzene heated at reflux was added a mixture of 10.1 g (34.5 mmol) of tri-n-butyltin hydride and 200 mg of AIBN in 123 mL of benzene over a 105-h period using a syringe pump. The mixture was cooled and concentrated in vacuo, and the residue was partitioned between 100 mL of acetonitrile and 200 mL of hexane. The acetonitrile layer was separated and the hexane layer was extracted with three 100-mL portions of acetonitrile. The combined acetonitrile layers were washed with two 50-mL portions of hexane and concentrated in vacuo to afford 12.2 g of a thick oil. The crude oil was chromatographed over 80 g of silica gel (dichloromethane; then ethyl acetate-dichloromethane, 10:90, then 20:80) to afford 10.2 g (87%) of 154 as a viscous oil. An 1H NMR spectrum of 154 appears in Appendix A and it is consistent with previously reported spectral data.

Ethyl (±)-(1'R,3'S,4'R,7'aR',8'R')-3'a-[(benzyloxy)methyl]tetrahydro-2',5,5-trimethyl-3'-oxospiro[m-dioxane-2,6'(5'H)-[1,4]methanoloisindoline]-8'-acetate (170) and Ethyl
(±)-(3'R,4'R,4'aS,7'aR,10'aS')-octahydro-5,5,9'-trimethyl-10'-oxo-3'-phenylspiro[m-dioxane-2,6'(7'H)-[1H]pyrano[3,4-d]isoxindole]-4'-acetate (173). To a solution of 21.70 g (36.8 mmol) of 169 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 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 solid was collected by filtration and washed with ether-hexane (1:1) to afford 11.3 g (65%) of 170 as a white solid: mp 108-110 °C; IR (KBr) 1726, 1687 cm⁻¹; ¹H NMR* (300 MHz, CDCl₃) δ 0.83 (s, 3 H, CH₃), 1.03 (s, 3 H, CH₃), 1.24 (t, J = 7.1 Hz, 3 H, CH₃), 1.65 (m, 1 H), 1.81 (dd, J = 14.6, 2.8 Hz, 1 H), 2.05 (m, 2 H), 2.17 (dd, J = 16.5, 9.3 Hz, 1 H, CH₂CO₂Et), 2.23 (dd, J = 16.5, 6.2 Hz, 1 H, CH₂CO₂Et), 2.42 (m, 1 H), 2.61 (dd, J = 14.6, 3.8 Hz, 1 H), 2.88 (s, 3 H, NCH₃), 3.10 (m, 1 H, C₈H), 3.27 (dd, J = 11.4, 1.6 Hz, 1 H ketal CH₂O), 3.40 (d, J = 11.5 Hz, 2 H, ketal CH₂O), 3.5 (t, J = 2.2 Hz, 1 H, CHN), 3.66 (d, J = 11.5 Hz, 1 H, ketal CH₂O), 3.71 (d, J = 9.7 Hz, 1 H, CH₂OBn), 3.90 (d, J = 9.7 Hz, 1 H, CH₂OBn), 4.11 (q, J = 7.1 Hz, 2 H, CO₂CH₂Me), 4.58 and 4.64 (ABq, J = 12.4 Hz, 2 H, OCH₂Ph), 7.20-7.38 (m, 5 H, ArH); ¹³C NMR (75.5 MHz, CDCl₃) δ 14.1 (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 (relative intensity) 231 (24), 91 (93), 57 (100); no parent peak was observed.

Anal calcd. for C₂₇H₃₇NO₆: 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 173 as a white solid: mp 155-156 °C; ¹H NMR* (300 MHz, CDCl₃) δ 0.85 (s, 3 H, CH₃), 1.05 (s, 3 H, CH₃), 1.22 (m, 1 H, obscured by overlapping triplet), 1.22 (t, J = 7.1 Hz, 3 H, CO₂CH₂CH₃), 1.35 (dd, J = 13.3, 11.7 Hz, 1 H), 1.96-2.05 (m, 3 H), 2.19-2.32 (m, 2 H), 2.50 (br d, J = 13.3 Hz, 1 H), 2.66 (d, J = 10.0 Hz, 1 H, CH₂N), 2.87 (s, 3 H, NCH₃), 3.34-3.64 (m, 7 H, five OCH₂ manifold and one CH₂N), 3.97-4.10 (m, 3 H, ester OCH₂ and one OCH₂), 4.46 (d, J = 10.3 Hz, 1 H, CHPPh), 7.23-7.34 (m, 3 H, ArH), 7.48-7.51 (m, 2 H, ArH); ¹³C NMR (75.5 MHz, CDCl₃) 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
(±)-(1'R*,3'aS*,4'R*,7'aR*,8'R*)-Tetrahydro-8'-(2-hydroxy-2,2-diphenylethyl)-3'a-(methoxymethyl)-2',5,5-trimethylspiro[m-dioxane-2,6'-(5'H)-[1,4]methanoisoldoline]-3'-one (180). To a solution of 6.75 g (17.09 mmol) of ester 154 in 100 mL of tetrahydrofuran cooled to -20 °C was added 65 mL (104 mmol) of 1.6 M phenylmagnesium bromide in tetrahydrofuran over a 10-min period. The cold bath was then removed and the mixture was stirred at room temperature for 1.5 h. The mixture was then cooled to -20 °C, quenched with 250 mL of saturated aqueous ammonium chloride and extracted with three 100-mL portions of ethyl acetate. The combined ethyl acetate layers were washed with three 80-mL portions of brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was diluted with first ether and then hexane and was then allowed to stand for three days. The solid was collected by filtration and was washed with hexane to provide 4.7 g (54%) of alcohol 180 as a white solid: mp 111-113 °C; IR (KBr) 3397, 1684 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.74 (s, 3 H, CH₃), 1.01 (s, 3 H, CH₃), 1.56 (dd, J = 14.5, 2.8 Hz, 1 H), 1.74 (br s, 1 H), 1.93 (m, 2 H), 2.10 (dd, J = 14.1, 7.5 Hz, 1 H), 2.16 (s, 1 H), 2.24 (m, 2 H), 2.42 (dd, J = 14.1, 4.4 Hz, 1 H), 2.76 (m, 1 H, C₁₅H₁), 2.91 (dd, J = 11.7, 2.1 Hz, 1 H, ketal CH₂O), 2.97 (s, 3 H, NCH₃), 3.23 (m, 2 H, ketal CH₂O), 3.38 (s, 3 H, OCH₃), 3.36-3.40 (m, 2 H, CHN and one ketal CH₂O), 3.55 (d, J = 9.6 Hz, 1 H, CH₂OMe), 3.78 (d, J = 9.6 Hz, 1 H, CH₂OMe), 7.18-7.38 (m, 10 H, ArH); ¹³C NMR (75.5 MHz, CDCl₃) δ 22.0 (q), 22.6 (q), 29.4 (s), 31.0 (q), 31.1 (t), 36.6 (t), 40.3 (d), 40.6 (d), 43.7 (t), 48.4 (d), 55.5 (s), 59.5 (q),
67.72 (t), 67.72 (d.), 69.3 (t), 70.6 (t), 77.9 (s), 125.8 (d), 125.9 (d), 126.5 (d), 126.7 (d), 127.9 (d), 146.9 (s), 147.9 (s), 176.4 (s), the overlapping triplet and doublet at 67.72 ppm were resolved in the DEPT spectrum, one aromatic doublet was not resolved; mass spectrum, m/z (relative intensity) 505 (M+, 13), 351 (28), 322 (100); exact mass calcd. for C_{31}H_{39}NO_{5} m/z 505.2829, found m/z 505.2835.

The filtrate was chromatographed over 70 g of silica gel (first dichloromethane; then methanol-dichloromethane, 2:98, then 4:96) to provide 2.25 g of 180 which was recrystallized from ether-hexane to afford an additional 1.5 g (17%) of 180.

\[
\begin{align*}
&\text{OBn} \\
&\text{O} \\
&\text{NMe} \\
&\text{Ph} \\
&\text{OH}
\end{align*}
\]

\text{181}

(±)-(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]methanolisoindoline]-3'-one (181). To a solution of 4.0 g (8.5 mmol) of ester 170 in 80 mL of tetrahydrofuran cooled to -20 °C was added a solution of phenylmagnesium bromide [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 tetrahydrofuran] 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 ethyl acetate. The combined ethyl acetate 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 then 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 ethyl acetate-hexane (1:3) to provide 4.3 g (87%) of alcohol 181 as a white solid: mp 187-188 °C; IR
(neat) 3399, 1685 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.73 (s, 3 H, CH\(_3\)), 0.99 (s, 3 H, CH\(_3\)), 1.55 (dd, \(J = 14.4\), 2.7 Hz, 1 H), 1.75 (br s, 1 H), 1.90-1.92 (m, 2 H), 2.12 (dd, \(J = 14.1\), 7.5 Hz, 1 H, C\(_6\)H\(_2\)(OH)Ph\(_2\)), 2.20 (dd, \(J = 14.1\), 7.5 Hz, 1 H), 2.24 (s, 1 H), 2.31 (br, 1 H), 2.42 (dd, \(J = 14.1\), 4.5 Hz, 1 H), 2.75 (br, 1 H, C\(_6\)H), 2.93 (dd, \(J = 11.7\), 1.8 Hz, 1 H, ketal CH\(_2\)O)), 2.97 (s, 3 H, NCH\(_3\)), 3.16 (dd, \(J = 11.4\), 1.8 Hz, 1 H, ketal CH\(_2\)O), 3.22 (d, \(J = 11.6\) Hz, 1 H, ketal CH\(_2\)O), 3.30 (d, \(J = 11.4\), 1 H, ketal CH\(_2\)O), 3.38 (t, \(J = 2.4\) Hz, 1 H, CHN), 3.65 (d, \(J = 9.7\) Hz, 1H, CH\(_2\)OBn), 3.86 (d, \(J = 9.7\) Hz, 1 H, CH\(_2\)OBn), 4.56 and 4.61 (ABq, \(J = 12.6\) Hz, 2 H, OCH\(_2\)Ph), 7.18-7.39 (m, 15 H, ArH); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 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); mass spectrum, \(m/z\) (relative intensity) 581 (M\(^+\), 0.2), 442 (3), 398 (7), 91 (100); exact mass calcd. for C\(_{37}\)H\(_{43}\)N\(_5\)O\(_5\) \(m/z\) 581.3141, found \(m/z\) 581.3147.

Anal. calcd. for C\(_{37}\)H\(_{43}\)N\(_5\)O\(_5\): C, 76.39; H, 7.45. Found: C, 76.45; H, 7.49.

(±)-(1\(R^1\),3a\(S^*\),4\(R^1\),7a\(R^1\),8\(R^1\))-3a-[(Benzyloxy)methyl]-8-(2,2-diphenylvinyl)tetrahydro-2-methyl-1,4-methanoloisoindoline-3,6(5H)-dione (182). A mixture of 1.45 g (2.5 mmol) of 181 and 300 mg p-toluenesulfonic acid monohydrate in 50 mL of acetone was warmed under reflux for 20 h. The mixture was then concentrated in vacuo, and the residue was chromatographed over 50 g of flash silica gel (ethyl acetate-hexane, 35:65) to provide 1.1 g of crude olefin 182 which was recrystallized from ether-hexane to afford 976 mg (82%) of pure 182 as a white solid: mp 99-101 °C, IR (film) 1704 cm\(^{-1}\), \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.00-2.10 (m, 2 H), 2.30 (dd, \(J =\)
18.5, 3.0 Hz, 1 H), 2.47 (dd, J = 19.5, 6.9 Hz, 1 H), 2.56-2.66 (m, 3 H), 3.01 (s, 3 H, CH$_3$), 3.44 (t, J = 2.2 Hz, 1 H, CHN), 3.83 (d, J = 10.4 Hz, 1 H, CH$_2$OBn), 4.04 (d, J = 10.4 Hz, 1 H, CH$_2$OBn), 4.51 (d, J = 12.2 Hz, 1 H, OCH$_2$Ph), 4.57 (d, J = 12.2 Hz, 1 H, OCH$_2$Ph), 5.82 (d, J = 9.5 Hz, 1 H, =CH), 7.11-7.41 (m, 15 H, ArH); $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 30.4 (q), 39.0 (t), 41.5 (d), 42.4 (t), 48.9 (d), 50.0 (d), 55.0 (s), 66.7 (t), 67.9 (d), 73.7 (t), 126.5 (d), 126.8 (d), 127.54 (d), 127.58 (d), 127.65 (d), 127.69 (d), 128.2 (d), 128.3 (d), 128.5 (d), 129.1 (d), 137.6 (s), 139.1 (s), 140.9 (s), 144.3 (s), 175.5 (s), 207.7 (s); mass spectrum, m/z (relative intensity) 371 (10), 193 (100), 122 (66), 91 (69); no parent peak was present.

(±)-(1$^{R^*}$,3a$^{S^*}$,4$^{R^*}$,7a$^{S^*}$,8$^{R^*}$)-3a-[((Benzyloxy)methyl]-2'-bromo-3a,4,5,7a-tetrahydro-6-hydroxy-8-(2,2-diphenylvinyl)-2-methyl-3-oxo-1,4-methanoisoindoline-7-carboxanilide (183). A mixture of 4.0 g (8.38 mmol) of ketone 182, 7.1 g (35.8 mmol) of 2-bromophenylisocyanate, and 1.4 g (35.6 mmol) of hexane-washed potassium hydride in 200 mL of tetrahydrofuran was heated at reflux for 4.5 h. The mixture was cooled to 0 °C, and the excess potassium hydride cautiously destroyed with sec-butyl alcohol. The mixture was neutralized with 250 mL of saturated aqueous ammonium chloride, and extracted with four 100-mL portions of ethyl acetate. The combined ethyl acetate layers were washed with 100 mL of saturated aqueous ammonium chloride, three 100-mL portions of brine, dried (MgSO$_4$), treated with decolorizing carbon (Norit A), filtered through Celite and concentrated in vacuo. The residue was triturated with 100 mL of ether and the solid was collected by filtration to provide 5 g of anilide 183. The filtrate was chromatographed over 50 g of silica gel (methylene chloride; then...
ethyl acetate-hexane, 3:7) to provide an additional 400 mg of 183. The combined 5.4 g was triturated with ethanol, chilled to -78 °C and collected by filtration to provide 4.85 g (85%) of anilide 183 as an off white solid: mp 198-204 °C; IR (film) 3283, 1687, 1626, cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.02 (br s, 1 H), 2.12 (dd, J = 18.8, 2.4 Hz, 1 H, C₁₄H), 2.52 (dd, J = 18.8, 3.6 Hz, 1 H, C₁₄H), 2.82 (br d, J = 9.8 Hz, 1 H, =CHCH), 2.68 (br s, 1 H), 3.09 (s, 3 H, NCH₃), 3.51 (d, J = 9.7 Hz, 1 H, CH₂OBn), 3.74 (br s, 1 H, CHN), 3.94 (d, J = 9.7 Hz, 1 H, CH₂OBn), 4.53 (d, J = 12.5 Hz, 1 H, OCH₂Ph), 4.66 (d, J = 12.5 Hz, 1 H, OCH₂Ph), 5.82 (d, J = 9.8 Hz, 1 H, =CH), 6.99-7.42 (m, 17 H, ArH), 7.56 (dd, J = 8.0, 1.3 Hz, 1 H, ArH), 7.69 (s, 1 H, NH), 8.23 (dd, J = 8.2, 1.5 Hz, 1 H, ArH), 13.75 (s, 1 H, OH); ¹³C NMR (75.5 MHz, CDCl₃) δ 30.8 (q), 34.4 (t), 40.0 (d), 47.9 (d), 50.2 (d), 56.1 (s), 64.0 (t), 69.4 (d), 73.4 (t), 96.6 (s), 114.5 (s), 122.5 (d), 125.6 (d), 126.5 (d), 126.9 (d), 127.4 (d), 127.5 (d), 127.7 (d), 128.2 (d), 128.4 (d), 128.6 (d), 129.2 (d), 132.2 (d), 134.7 (s), 138.1 (s), 139.2 (s), 141.2 (s), 144.1 (s), 169.2 (s), 172.7 (s), 174.8 (s), two aromatic doublets were not resolved; mass spectrum (FAB), m/z (relative intensity) 677.3 (M⁺ +1, 46), 675.3 (M⁺ +1, 45), 504 (48), 204 (38), 154 (70), 136 (100); mass spectrum (El), m/z (relative intensity) 477 (5), 371 (22), 193 (89), 122 (81), 91 (100). No parent peak was observed in the El spectrum.


(±)-(1R,3aS*,4R*,7aS*,8R*)-3a-[(Benzyloxy)methyl]-2'-bromo-3a,4,5,7a-tetrahydro-8-(2,2-diphenylvinyl)-6-(methoxymethoxy)-2-methyl-3-oxo-1,4-methanoloisoIndoline-7-carboxanilide (184). To a solution of 4.5 g (6.6 mmol) of enol 182 in 100 mL of anhydrous
dimethylformamide was added 2.09 g (16.2 mmol) of diisopropylethylamine followed by 1.06 g (12.5 mmol) of chloromethyl methyl ether. After 30 min, the mixture was poured onto a slurry of crushed ice in 300 mL of saturated aqueous sodium bicarbonate. The solid was collected by filtration and washed with water. The still moist filter cake was dissolved in 300 mL of dichloromethane, dried (MgSO₄), filtered and concentrated in vacuo. The residue was triturated with ether-hexane, and the solid was collected by filtration to afford 4.3 g (89%) of 184 as a tan solid: mp 183-184 °C; IR (KBr), 1702, 1654 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.12 (br s, 1 H), 2.36 (dd, J = 18.1, 2.6 Hz, 1 H, C₁₄ H), 2.63 (dd, J = 18.2, 3.5 Hz, 1 H, C₁₄ H), 2.72 (br d, J = 10.1 Hz, 1 H, =CHCH), 3.05 (s, 3 H, NCH₃), 3.17 (s, 3 H, OCH₃), 3.53 (br s, 1 H), 3.55 (d, J = 9.9 Hz, 1 H, CH₂OBn), 3.75 (br s, 1 H, CHN), 3.78 (d, J = 9.9 Hz, 1 H, CH₂OBn), 4.55 (d, J = 12.6 Hz, 1 H, OCH₂Ph), 4.65 (d, J = 12.6 Hz, 1 H, OCH₂Ph), 4.91 (d, J = 7.0 Hz, 1 H, OCH₂O), 5.04 (d, J = 7.0 Hz, 1 H, OCH₂O), 5.83 (d, J = 10.1 Hz, 1 H, =CH), 6.94 (td, J = 7.5, 1.5 Hz, 1 H, ArH), 7.13-7.38 (m, 16 H, ArH), 7.54 (dd, J = 8.0, 1.4 Hz, 1 H, ArH), 8.61 (dd, J = 8.4, 1.5 Hz, 1 H, ArH), 9.95 (br s, 1 H, NH); ¹³C NMR (75.5 MHz, CDCl₃) δ 30.5 (q), 31.2 (t), 40.7 (d), 49.5 (d), 49.7 (d), 54.2 (s), 56.7 (q), 64.5 (t), 70.5 (d), 73.3 (t), 92.9 (t), 109.9 (s), 112.4 (s), 121.4 (d), 124.3 (d), 126.8 (d), 127.1 (d), 127.2 (d), 127.3 (d), 127.4 (d), 128.1 (d), 128.2 (d), 128.4 (d), 129.4 (d), 132.2 (d), 137.0 (s), 138.4 (s), 139.6 (s), 141.2 (s), 143.5 (s), 158.0 (s), 163.6 (s), 175.3 (s), one aromatic doublet was not resolved; mass spectrum, (FAB) m/z (relative intensity) 721 (M⁺ +1, 49), 719 (M⁺ +1, 47), 426 (39), 154 (85), 136 (100); exact mass (El) calcd. for C₄₁H₉₉BrN₂O₅ m/z 720.2023 and 718.2043, found m/z 720.2020 and 718.2053.

Anal. calcd. for C₄₁H₉₉BrN₂O₅: C, 68.42; H, 5.46. Found: C, 68.35; H, 5.43.
(±)-(1R*,3aS*,4R*,7aS*,8R*)-3a-[(Benzyloxy)methyl]-2'-bromo-3a,4,5,7a-tetrahydro-8-(2,2-diphenylvinyl)-6-(methoxymethoxy)-N-(methoxymethyl)-2-methyl-3-oxo-1,4-methanolsindoline-7-carboxanilide (185). To a suspension of 62 mg (1.55 mmol) of 60% sodium hydride washed with three 2-mL portions of hexane in 5 mL of dimethylsulfoxide was added 465 mg (0.69 mmol) of 184 in several portions. The mixture was warmed to 45 °C for 15 min, cooled to room temperature and then 151 mg (1.89 mmol) of chloromethyl methyl ether was added. The mixture stirred for 30 min, and then 22 mg (0.55 mmol) of 60% sodium hydride in mineral oil was added followed by 54 mg (0.66 mmol) of chloromethyl methyl ether, and the mixture was stirred for 30 min. The mixture was then poured into 150 mL of ice cold saturated aqueous sodium bicarbonate. The resulting solid was collected by filtration and washed with water. The still moist filter cake was dissolved in 70 mL of dichloromethane, dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (first dichloromethane-hexane, 1:1; then dichloromethane; then ethyl acetate-dichloromethane, 2:98, then, 5:95, then 10:90; and finally ethyl acetate-hexane, 1:1) to provide 450 mg (85%) of 185 as a mixture of geometric isomers: IR (film) 1703, 1659 cm⁻¹; ¹³C NMR (75.5 MHz, DMSO-d₆, 373 °K) δ 29.4 (t), 29.5 (q), 40.3 (d), 48.5 (d), 50.3 (d), 53.8 (s), 55.0 (q), 55.4 (q), 64.6 (t), 69.5 (d), 72.5 (t), 88.4 (t), 92.4 (t), 110.1 (s), 121.8 (s), 125.9 (d), 126.4 (d), 126.48 (d), 126.5 (d), 126.6 (d), 127.19 (d), 127.21 (d), 127.3 (d), 127.5 (d), 127.8 (d), 128.5 (d), 128.6 (d), 130.9 (d), 132.2 (d), 138.1 (s), 138.8 (s), 139.1 (s), 141.0 (s), 142.3 (s), 150.0 (s), 167.7 (s), 173.7 (s); mass spectrum, m/z (relative intensity) 764 (M⁺, 66), 762 (M⁺, 67), 547 (35), 395 (58), 204 (58), 191 (57), 91 (100), 45 (49); exact mass calcd. for C₄₃H₄₃BrN₂O₆ m/z 764.2285 and 762.2305, found m/z
764.2318 and 762.2286. The \(^1\)H NMR of this material was not interpreted due to complexity associated with geometrical isomers. This spectrum is, however, included in Appendix A.

\[
\begin{align*}
\text{MOM-N} & \quad \text{O} \\
\text{MOM-} & \quad \text{Obn} \\
\text{Ph Ph} & \quad \text{NCH}_3 \\
\end{align*}
\]

\(\pm\)-(1'R\(^+\),3S\(^+\),3a'S\(^+\),4'R\(^+\),6'R\(^+\),7'aS\(^+\),8'R\(^+\))-3'a-[(Benzyloxy)methyl]-8'-(2,2-diphenylviny)-3'a,5',6',7'a-tetrahydro-6'-(methoxymethoxy)-1-(methoxymethyl)-2'-methylispiro[indoline-3,7'(4'H)-[1,4]methanoisoindoline]-2,3'-dione (186) and \((\pm)-(1'R\(^+\),3R\(^+\),3a'S\(^+\),4'R\(^+\),6'R\(^+\),7'aS\(^+\),8'R\(^+\))-3'a-[(Benzyloxy)methyl]-8'-(2,2-diphenylviny)-3'a,5',6',7'a-tetrahydro-6'-(methoxymethoxy)-1-(methoxymethyl)-2'-methylispiro[indoline-3,7'(4'H)-[1,4]methanoisoindoline]-2,3'-dione (187). To 3 mL of tri-n-butyltin hydride warmed to 80 °C was added 440 mg (0.578 mmol) of 185 and 20 mg of AlBN in 5 mL of benzene over a 5-min period. The mixture was stirred for 30 min, and was then concentrated and partitioned between 20 mL of hexane and 45 mL of acetonitrile. The acetonitrile layer was separated, washed with seven 20-mL portions of hexane, and concentrated to provide 410 mg of a viscous oil. A \(^1\)H NMR indicated a complex mixture containing some tin impurities. The residue was dissolved in 2 mL of dichloromethane, 1 drop of DBU was added, and the mixture was chromatographed over 5 g of silica gel (first dichloromethane; then ethyl acetate-dichloromethane, 2:98) to provide a clear oil which was diluted with hot acetonitrile to afford 112 mg (28%) of oxindole 186 as a white crystalline solid: 124-125 °C; IR (KBr) 1724, 1698 cm\(^{-1}\); \(^1\)H NMR* (300 MHz, CDCl\(_3\)) \(\delta\) 1.77 (dd, \(J = 13.9, 8.7\) Hz, 1 H, C\(_{14}\)H), 1.96 (dt, \(J = 6.9, 1.5\) Hz, 1 H, C\(_{16}\)H), 2.46 (ddd, \(J = 13.8, 9.1, 7.6\) Hz, 1 H, C\(_{14}\)H), 2.57 (br s, 1 H, C\(_6\)H), 2.72 (s, 3 H, NCH\(_3\)), 2.88 (s, 3 H, OCH\(_3\)), 3.26 (s, 3 H, OCH\(_3\)), 3.44 (dd, \(J = 3.0, 1.8\) Hz, 1 H, CHN), 3.96 (d, \(J = 9.9\) Hz, 1 H, C\(_{15}\)H), 4.44 (t, \(J = 7.2\) Hz, 1 H, C\(_{14}\)H), 4.72 (s, 1 H, OCH\(_3\))
Hz, 1 H, CH$_2$OBn or NCH$_2$O), 3.97 (d, $J = 7.1$ Hz, 1 H, CH$_2$OBn or NCH$_2$O), 4.27 (d, $J = 6.9$ Hz, 1 H, CH$_2$OBn or NCH$_2$O), 4.32 (d, $J = 10.4$ Hz, 1 H, CH$_2$OBn or NCH$_2$O), 4.39 (t, $J = 9.0$ Hz, 1 H, C$_3$H), 4.46 (ddd, $J = 9.0$, 3.0, 1.5 Hz, 1 H, C$_{16}$H), 4.73 (d, $J = 11.8$ Hz, 1 H, OCH$_2$Ph), 4.79 (d, $J = 11.8$ Hz, 1 H, OCH$_2$Ph), 5.02 (s, 2 H, OCH$_2$O), 5.70 (d, $J = 9.0$ Hz, 1 H, =CH), 6.83-6.90 (m, 2 H, ArH), 7.13-7.44 (m, 16 H, ArH), 7.53 (d, $J = 7.26$ Hz, 1 H, ArH); $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 30.9 (q), 33.4 (t), 40.8 (d), 51.0 (d), 54.70 (q), 54.79 (s), 55.9 (q), 56.1 (d), 65.6 (s), 68.2 (t), 71.0 (t), 73.2 (d), 74.0 (t), 94.7 (t), 108.1 (d), 123.1 (d), 124.3 (d), 127.0 (d), 127.14 (d), 127.18 (d), 127.4 (d), 127.8 (d), 128.01 (d), 128.04 (d), 129.5 (d), 129.8 (d), 135.3 (s), 137.9 (s), 139.5 (s), 140.8 (s), 142.1 (s), 143.6 (s), 174.7 (s), 175.0 (s); mass spectrum, m/z (relative intensity) 684 (M+, 47) 436 (17), 336 (28), 91 (100); exact mass calcd. for C$_{43}$H$_{44}$N$_2$O$_6$ m/z 684.3199, found m/z 684.3217. The structure of 186 was confirmed by X-ray crystallography.

Continued elution (ethyl acetate-dichloromethane, 5:95, then 10:90, then 15:85) afforded 65 mg of partially purified oxindole 187. A second chromatography over 4 g of silica gel (first dichloromethane; then ethyl acetate-dichloromethane, 2:98, then 4:96, then 6:94, then 8:92, then 10:90) afforded 37 mg (9%) of oxindole 187 as a clear oil: IR (neat) 1715 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 2.01 (m, 2 H), 2.18 (br s, 1 H), 2.50 (dd, $J = 12.6$, 6.9 Hz, 1 H, C$_{14}$H), 2.90 (s, 3 H, NCH$_3$ or OCH$_3$), 2.91 (s, 3 H, NCH$_3$ or OCH$_3$), 3.12 (s, 3 H, OCH$_3$), 3.33 (dd, $J = 2.9$, 1.6 Hz, 1 H, C$_5$H), 3.68 (d, $J = 7.0$ Hz, 1 H, CH$_2$OBn), 3.97-4.03 (m, 2 H, C$_3$H and C$_{16}$H), 4.02 (d, $J = 7.0$ Hz, 1 H, CH$_2$OBn), 4.16 (d, $J = 8.8$ Hz, 1 H, NCH$_2$O), 4.25 (d, $J = 8.8$ Hz, 1 H, NCH$_2$O), 4.57 (d, $J = 12.3$ Hz, 1 H, OCH$_2$Ph), 4.64 (s, 1 H, OCH$_2$Ph), 4.91 (d, $J = 10.9$ Hz, 1 H, OCH$_2$O), 5.04 (d, $J = 10.9$ Hz, 1 H, OCH$_2$O), 5.88 (d, $J = 9.2$ Hz, 1 H, =CH), 6.38 (d, $J = 7.3$ Hz, 1 H, oxindole C$_9$H), 6.88 (td, $J = 7.6$, 0.8 Hz, 1 H, ArH), 6.94 (d, $J = 7.5$ Hz, 1 H, ArH), 7.12-7.57 (m, 16 H, ArH); $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 30.6 (q), 32.3 (t), 39.5 (d), 45.0 (d), 53.3 (d), 54.2 (s), 55.2 (q), 55.8 (q), 57.7 (s), 65.7 (d), 66.0 (t), 69.8 (d), 71.0 (t), 72.6 (t), 95.3 (t), 109.2 (d), 122.0 (d), 126.5 (d), 126.8 (d), 127.09 (d), 127.14 (d), 127.3 (d), 127.7 (d), 127.9 (d), 128.1 (d), 128.20 (d), 128.26 (d), 128.5 (d), 129.6 (d), 139.1 (s), 140.1 (s), 140.4 (s), 141.3 (s), 143.5 (s), 176.0 (s), 179.3 (s), one aromatic doublet was not resolved; mass spectrum, m/z (relative intensity) 684 (M+, 25), 283 (39), 252 (47), 91 (100), 45 (85); exact mass calcd. for C$_{43}$H$_{44}$N$_2$O$_6$ m/z 684.3199, found m/z 684.3217.
(±)-(1'R*,3'S*,3a'S*,4'R*,6'R*,7'aS*,8'R*)-3'a-[(Benzyloxy)methyl]-8'-(2,2-diphenylvinyl)-3'a,5',6',7'a-tetrahydro-6'-hydroxy-1-(methoxymethyl)-2'-methylspiro[indoline-3,7'(4'H)[1,4]methanoisoindoline]-2,3'-dione (188). To a solution of 80 mg (0.116 mmol) of oxindole 186 in 18 mL of methanol-glyme (1:1) was added 1 mL of 6N aqueous hydrochloric acid. The mixture was warmed at 60 °C for 5 h, cooled to room temperature, diluted with 40 mL of saturated aqueous sodium bicarbonate, and extracted with three 20-mL portions of ethyl acetate. The combined organic layers were washed with three 20-mL portions of brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was recrystallized from ether-hexane to provide 38 mg (48%) of alcohol 188 as a white solid: mp 178-186 °C; IR (neat) 3380, 1723, 1709, 1691 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.64 (m, 2 H), 1.93 (br d, J = 5.7 Hz, 1 H), 2.45-2.53 (m, 1 H), 2.50 (br s, 1 H), 2.90 (s, 3 H, NCH₃), 3.26 (s, 3 H, OCH₃), 3.44 (dd, J = 3.0, 1.8 Hz, 1 H, CHN), 3.89 (d, J = 10.3 Hz, 1 H, CH₂OBn), 4.25 (d, J = 10.3 Hz, 1 H, CH₂OBn), 4.25 (d, coupling obscured by overlapping doublet, 1 H, C₁₆H₂), 4.36 (br, 1 H, C₃H), 4.68 and 4.77 (ABq, J = 11.9 Hz, 2 H, OCH₂O), 5.73 (d, J = 9.4 Hz, 1 H, =CH), 6.88-6.94 (m, 2 H, ArH), 7.16-7.47 (m, 17 H, ArH); ¹³C NMR (75.5 MHz, CDCl₃) δ 30.8 (q), 36.6 (t), 40.8 (d), 50.4 (d), 56.12 (d), 56.18 (q), 56.26 (s), 58.8 (s), 65.6 (d), 67.8 (l), 68.7 (d), 71.1 (l), 74.1 (l), 108.7 (d), 123.4 (d), 124.2 (d), 127.08 (d), 127.14 (d), 127.19 (d), 127.5 (d), 127.80 (d), 127.88 (d), 128.0 (d), 128.2 (d), 128.8 (d), 129.8 (d), 135.1 (s), 137.8 (s), 139.6 (s), 140.6 (s), 141.8 (s), 143.7 (s), 175.0 (s), 175.6 (s), one aromatic doublet was not resolved; mass spectra, m/z (relative intensity) 640 (M⁺, 100), 532 (37), 252 (71), 91 (33); exact mass calcd. for C₄₁H₄₀N₂O₅ m/z 640.2939, found m/z 640.2911.
(±)-(1'R*,3R*,3a'S*,4'R*,6'R*,7'aS*,8'R*)-3'a-[(Benzyloxy)methyl]-8'-(2,2-diphenylvinyl)-3'a,5',6',7'a-tetrahydro-6'-hydroxy-1-(methoxymethyl)-2'-methylisoprop[1,4]methanoisoindoline]-2,3'-dione (189). To a solution of 80 mg (0.116 mmol) of oxindole 187 in 9 mL of glyme was added 1 mL of 6N aqueous hydrochloric acid. The mixture was warmed at 60 °C for 5 h, cooled to room temperature, diluted with 40 mL of saturated aqueous sodium bicarbonate, and extracted with three 10-mL portions of ethyl acetate. The combined organic layers were washed with three 10-mL portions of brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (ethyl acetate-hexane, 1:9, then 2:8, then 3:7). The material from the column was recrystallized from ether-hexane to afford 24 mg (32%) of alcohol 189 as a white solid: mp 188-194 °C; ¹H NMR (300 MHz, CDCl₃) δ 2.02 (dd, J = 4.4 Hz, large coupling obscured by peak at 2.02-2.06 ppm, 1 H), 2.02-2.06 (br s, 1 H), 2.18 (br s, 1 H), 2.47-2.54 (m, 1 H, C₁₄H), 2.91 (s, 3 H, NCH₃), 3.12 (s, 3 H, OCH₃), 3.26 (dd, J = 3.1, 1.8 Hz, 1 H, CHN), 3.98 (dd, J = 8.6, 3.0, 1.5 Hz, 1 H, C₁₆H), 4.13 (m, 1 H), 4.15 (d, J = 8.7 Hz, 1 H, CH₂OBn), 4.22 (d, J = 8.8 Hz, 1 H, CH₂OBn), 4.56 (m, 1 H), 4.57 (d, J = 12.0 Hz, 1 H, OCH₂Ph), 4.64 (d, J = 12.3 Hz, 1 H, OCH₂Ph), 4.88 (d, J = 10.9 Hz, 1 H, NCH₂O), 5.03 (d, J = 10.9 Hz, 1 H, NCH₂O), 5.87 (d, J = 8.9 Hz, 1 H, =CH), 6.21 (dd, J = 7.0, 0.5 Hz, 1 H, oxindole C₉H), 6.86 (td, J = 7.5, 0.9 Hz, 1 H, ArH), 6.96 (d, J = 7.3 Hz, 1 H, ArH), 7.21-7.59 (m, 16 H, ArH); ¹³C NMR (75.5 MHz, CDCl₃) δ 30.6 (q), 33.5 (t), 39.6 (d), 45.1 (d), 53.2 (d), 55.2 (s), 56.0 (q), 57.8 (s), 64.7 (d), 65.5 (d), 66.0 (t), 71.1 (t), 72.8 (t), 109.6 (d), 122.2 (d), 126.4 (d), 126.80 (d), 126.83 (d), 127.1 (d), 127.2 (d), 127.3 (d), 127.9 (d), 128.2 (d), 128.4 (d), 128.61 (d), 128.64 (d), 129.6 (d), 139.1 (s), 140.0 (s), 140.4 (s), 142.0 (s), 143.6 (s), 175.9 (s), 179.3 (s), one aromatic singlet was not resolved; mass spectra, m/z (relative
(±)-(1'R*,3R*,3a'S*,4'R*,6'S*,7'aS*,8'R*)-3'a-[(Benzylxoy)methyl]-8'-((2,2-diphenylvinyl)-3'a,5',6',7'a-tetrahydro-6'-hydroxy-1-(methoxymethyl)-2'-methylspiro[indoline-3,7'(4'H)-[1,4]methanoisoindoline]-2,3'-dione (190). From oxindole 188. To a solution of 65 mg (0.258 mmol) of 188 in 10 mL of dichloromethane was added 2 drops of DBU. The mixture was warmed at reflux for 20 min, concentrated and passed through a pad of 2 g of silica gel (ethyl acetate-dichloromethane, 10:90). The residue was recrystallized from acetonitrile to afford 55 mg (85%) of oxindole 190 as a white solid: mp 222-224 °C; IR (KBr) 3372, 1730, 1677 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.96 (d, J = 11.0 Hz, 1 H), 2.02 (m, 2 H), 2.29-2.36 (m, 2 H), 2.89 (s, 3 H, NCH₃), 3.10 (s, 3 H, OCH₃), 3.23 (br d, J = 8.7 Hz, 1 H, C₁₆H), 3.41 (dd, J = 3.0, 1.7 Hz, 1 H, C₅H), (br dd, J = 18.5, 8.4 Hz, 1 H, C₃H), 4.21 (d, J = 8.6 Hz, 1 H, CH₂OBn), 4.43 (d, J = 8.6 Hz, 1 H, CH₂OPh), 4.58 and 4.64 (ABq, J = 12.2 Hz, 2 H, NCH₂O), 4.91 (d, J = 10.9 Hz, 1 H, OCH₂Ph), 5.02 (d, J = 10.9 Hz, 1 H, OCH₂Bn), 5.82 (d, J = 8.7 Hz, 1 H, =CH), 6.17 (d, J = 7.2 Hz, 1 H, oxindole C₃H), 6.93-6.99 (m, 2 H, ArH), 7.09-7.39 (m, 13 H, ArH), 7.47-7.62 (m, 3 H, ArH); ¹³C NMR (62.9 MHz, CDCl₃) δ 30.7 (q), 33.1 (t), 40.7 (d), 45.8 (d), 55.5 (s), 55.6 (d), 55.8 (q), 58.1 (s), 65.7 (d), 66.0 (t), 68.9 (d), 70.9 (t), 72.9 (t), 109.7 (d), 122.8 (d), 122.9 (d), 126.5 (d), 126.9 (d), 127.2 (d), 127.6 (d), 127.7 (d), 127.9 (d), 128.3 (d), 128.5 (d), 129.0 (d), 129.2 (d), 131.1 (s), 139.1 (s), 140.02 (s), 140.07 (s), 141.6 (s), 144.2 (s), 175.5 (s), 177.2 (s), one aromatic doublet was not resolved; mass spectrum, m/z (relative intensity) 640
(M⁺, 19), 532 (9), 252 (52), 91 (100), 45 (33); exact mass calcd. for C₄₁H₄₀N₂O₅ m/z 640.2939, found m/z 640.2939. The structure of 190 was confirmed by X-ray crystallography.

From oxindole 189: To a solution of 21 mg (0.037 mmol) of 189 in 5 mL of dichloromethane was added 1 drop of DBU. The mixture was stirred at room temperature for 30 min and then concentrated. The residue was recrystallized from acetonitrile to afford 10 mg (47%) of 190 as a white solid: mp 217-219 °C. The ¹H NMR of this material was identical to material obtained in a similar fashion from oxindole 188.

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\text{MOM} \quad \text{OBn} \\
\text{NMe} \\
\text{191}
\]

\[\text{MOM} \quad \text{OBn} \quad \text{NMe} \]

(±)-(1'R⁺,3'R⁺,3'aR⁺,4'S⁻,6'R⁺,7'aR⁺,8'S⁺)-3'a·[(Benzyloxy)methyl]-3'a,5',6',7'a-tetrahydro-6'-hydroxy-1-(methoxymethyl)-2'-methyl-2,3'-dioxospiro[indenone-3,7'(4'H)-[1,4]methanoisoindoline]-8'-carboxaldehyde (191). To a mixture of 45 mg (0.07 mmol) of olefin 190 in 15 mL of dichloromethane-methanol (4:1) was added a few mg of Sudan III indicator. The resulting red solution was cooled to -78 °C, and then ozone gas was passed through the solution until the red color faded. To the mixture was added 1 mL of dimethylsulfide and stirring was continued at room temperature for 18 h. The mixture was then concentrated in vacuo and the residue was chromatographed over 2 g of silica gel (dichloromethane; then ethyl acetate-dichloromethane, 10:90, then 20:80, then 30:70, then 1:1) to afford 21 mg (59%) of aldehyde 215 as a foam: IR 3421 (broad), 1724 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.25 (br s, 1 H), 2.22-2.40 (m, 2 H), 2.47 (t, J = 1.6 Hz, 1 H), 2.69 (br, 1 H, OH), 2.71 (s, 3 H, NCH₃), 3.11 (s, 3 H, OCH₃), 3.29 (t, J = 1.4 Hz, 1 H), 4.09 (dd, J = 3.2, 1.6 Hz, 1 H, CHN), 4.20 (d, J = 8.6 Hz, 1 H, CH₂OBn), 4.41 (dd, J = 10.4 Hz, 1 H, C₃H), 4.51 (d, J = 8.6 Hz, 1 H, CH₂OBn), 4.58 and 4.62 (ABq, J = 12.2 Hz, 2 H, OCH₂Ph), 4.94 (d, J = 11.0 Hz, 1 H, NCH₂O), 5.05 (d, J = 11.0 Hz, 1 H,
NCH$_2$O), 7.02 (d, $J$ = 7.7 Hz, 1 H, ArH), 7.14-7.36 (m, 8 H, ArH), 9.60 (d, $J$ = 1.8 Hz, 1 H, CHO); $^{13}$C NMR (75.5 MHz, CDC$_3$) δ 30.2 (q), 32.7 (t), 34.3 (d), 55.4 (s), 55.9 (q), 56.2 (d), 58.3 (d), 62.9 (d), 65.6 (t), 68.2 (d), 71.0 (t), 72.8 (t), 110.1 (d), 122.7 (d), 123.0 (d), 127.0 (d), 127.1 (d), 127.9 (d), 129.0 (d), 130.0 (s), 138.8 (s), 141.8 (s), 174.7 (s), 176.6 (s), 199.8 (s), one aliphatic singlet was not resolved; mass spectrum m/z (relative intensity) 490 (24), 458 (10), 367 (37), 91 (100), 45 (34); exact mass calcd. for C$_{28}$H$_{30}$N$_2$O$_6$ m/z 490.2105, found m/z 490.2096.

$^{193}$

($\pm$)-(1$^R$$^*$,3$S$$^*$,3'a$R$$^*$,4$'$S$$^*$,6$'$S$$^*$,7'a$R$$^*$,8'S$^*$)-3'a-[(Benzyloxy)methyl]-3'a,5',6',7'a-tetrahydro-6'--(methoxymethoxy)-1-(methoxymethyl)-2'-methyl-2,3'-dioxospiro[indoline-3,7'(4'H)-[1,4]methanoiso!ndoline]-8'-carboxaldehyde (193). Through a solution of 135 mg (0.19 mmol) of olefin 186 in 16 mL of methanol-dichloromethane (15:1) cooled to -78 °C was passed ozone gas until a pale blue color persisted. The mixture was stirred for 5 min, and then the excess ozone was purge from the mixture by passing nitrogen gas through the solution until it was clear. To the mixture was then added with 1 mL of dimethylsulfide. The cold bath was removed and the mixture was stirred at room temperature for 18 h, and then concentrated in vacuo. The residue was chromatographed over 4 g of silica gel (dichloromethane; then ethyl acetate-dichloromethane, 5:95, then 10:90, then 15:85, then 25:75, then 1:1) to provide 81 mg (80%) of material which was recrystallized for ethyl acetate-hexane to afford 69 mg (69%) of aldehyde 193 as a white solid: mp 147-149 °C; IR (film) 1716 cm$^{-1}$; $^1$H NMR (300 MHz, CDC$_3$) δ 1.92 (dd, $J$ = 13.6, 8.1 Hz, 1 H), 2.58-2.63 (m, 3 H), 2.70 (s, 3 H, OCH$_3$ or NCH$_3$), 2.74 (s, 3 H, OCH$_3$ or NCH$_3$), 3.32 (s, 3 H, OCH$_3$), 4.01 (m, 3 H), 4.35 (m, 3 H), 4.47 (t, $J$ = 8.7 Hz, 1 H, C$_3$H)$_{2}$,
4.74 (m, 2 H, OCH$_2$Ph), 5.02 (d, $J = 10.9$ Hz, 1 H, OCH$_2$O), 5.17 (d, $J = 10.9$ Hz, 1 H, OCH$_2$O), 6.91 (m, 2 H, ArH), 7.16 (m, 6 H, ArH), 7.54 (d, $J = 7.5$ Hz, 1 H, ArH), 9.85 (s, 1 H, HC=O); $^{13}$C NMR (75.5 MHz, CDCl$_3$) 30.2 (q), 32.0 (d), 33.8 (t), 54.7 (q), 55.0 (s), 55.5 (d), 56.0 (q), 59.0 (s), 62.6 (d), 65.1 (d), 67.7 (t), 71.1 (t), 72.8 (d), 74.1 (t), 94.7 (t), 108.6 (d), 123.6 (d), 124.3 (d), 127.5 (d), 127.0 (d), 128.20 (d), 128.29 (d), 135.0 (s), 137.7 (s), 140.5 (s), 174.2 (s), 175.7 (s), 199.6 (d); mass spectrum, $m/z$ (relative intensity) 534 (M$^+$, 94), 458 (34), 317 (55), 91 (100); exact mass calcd. for C$_{30}$H$_{34}$N$_2$O$_7$ $m/z$ 534.2365, found $m/z$ 534.2376.

$^{194}$

(±)-(3'R*,3'S*,4aR*,5S*,8aS*,9S*)-5-([Benzyloxy)methyl]-1,3,4,4a,5,7,8,8a-octahydro-1-hydroxy-1'-(methoxymethyl)-7-methylspiropyran[3,4-c]pyridine-10,3'-indoline)-2',6-dione (194). To a solution of 80 mg (0.149 mmol) of aldehyde 193 in 8 mL of tetrahydrofuran was added 2 mL of 6N aqueous hydrochloric acid. The mixture was stirred at room temperature for 18 h, and was then made basic with sodium bicarbonate and concentrated in vacuo. The residue was diluted with 10 mL of water and extracted with three 10-mL portions of ethyl acetate. The combined organic layers were washed with three 10-mL portions of ethyl acetate. The combined organic layers were washed with three 10-mL portions of brine, dried (MgSO$_4$), filtered and concentrated in vacuo. The residue was recrystallized from ethyl acetate-hexane to provide 40 mg (54%) of hemiacetal 194 as a single diastereomer: mp (ethyl acetate-hexane) 198-199 ºC; IR (KBr) 3482, 1708 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 1.89 (br s, 1 H), 2.31 (m, 3 H), 2.74-2.83 (m, 1 H), 2.78 (s, 3 H, NCH$_3$), 3.31 (s, 3 H, OCH$_3$), 3.66 (br s, 1 H), 3.74 (br s, 1 H), 4.10 (d, $J = 10.0$ Hz, 1 H, CH$_2$OBn), 4.29 (d, $J = 10.1$ Hz, 1 H, CH$_2$OBn), 4.44 and 4.50 (ABq, $J = 11.8$ Hz, 2 H, OCH$_2$Ph), 4.65 (s, 1 H), 5.07 and 5.15 (ABq, $J = 10.7$ Hz, 2 H, NCH$_2$O), 5.61 (s, 1 H, (HO)CHO), 6.96-7.40 (m, 9 H, ArH):
$^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 24.5 (t), 27.5 (q), 29.1 (d), 46.7 (d), 49.9 (d), 53.8 (s), 56.2 (q), 58.3 (s), 60.5 (d), 66.2 (t), 70.0 (d), 71.2 (t), 73.4 (t), 91.4 (d), 109.5 (d), 122.5 (d), 125.0 (d), 127.3 (d), 127.6 (d), 127.9 (d), 128.5 (d), 128.9 (s), 137.8 (s), 141.1 (s), 176.2 (s), 176.9 (s); mass spectrum, m/z (relative intensity) 490 (M$^+$, 51), 384 (40), 91 (100); exact mass calcd. for C$_{28}$H$_{30}$N$_2$O$_6$ m/z 490.2103, found m/z 490.2084. The mother liquor was chromatographed over 1 g of silica gel (first dichloromethane, then ethyl acetate-dichloromethane 10:90, then 20:80, then 30:70, then 40:60) to provide an additional 15 mg (20%) of hemiacetal 194.

(±)-(3R*,3'S*,4aR*,5S*,8S*,8aS*)-5-[(Benzyloxy)methyl]-1,3,4,4a,5,7,8,8a-octahydro-1',7-dimethylspiro[3,5,8-ethanyllidene-6H-pyrano[3,4-c]pyridine-10,3'-indoline]-2',6-dione (195). To a solution of 40 mg (0.082 mmol) of hemiacetal 194 and 1 mL of triethylsilane in 1 mL of dichloromethane was added 1 mL of trifluoroacetic acid. The mixture was stirred at room temperature for 18 h, made basic with sodium bicarbonate, diluted with 10 mL of water, and extracted with three 10-mL portions of ethyl acetate. The combined organic layers were washed with three 10-mL portions of ethyl acetate, The combined organic layers were washed with three 10-mL portions of ethyl acetate, then methanol-dichloromethane, 2:98. Appropriate combined fractions from the column were recrystallized from ethyl acetate-hexane to provide 23 mg (63%) of 195 as a white solid: mp 192-193 °C; IR (KBr) 1715, 1684 cm$^{-1}$; $^1$H NMR$^*$ (300 MHz, CDCl$_3$) $\delta$ 2.13 (m, 3 H, C$_{14}$H, C$_{15}$H, and C$_{16}$H), 2.29 (br s, 1 H, C$_6$H), 2.38 (dd, $J$ = 13.9, 3.4 Hz, 1 H, C$_{14}$H), 2.80 (s, 3 H, NCH$_3$), 3.20 (s, 3 H, oxindole NCH$_3$), 3.70 (br s, 1 H, C$_3$H), 4.04 and 4.12 (qd, $J$ = 11.0, 2.6 Hz, 2 H, C$_{17}$H), 4.09 (d, $J$ = 10.0 Hz, 1 H, CH$_2$OBn), 4.28 (d, $J$ = 10.1 Hz, 1 H, CH$_2$OBn), 4.47 (ABq, $J$ = 11.8 Hz, 2 H, OCH$_2$Ph), 4.77 (d, $J$ = 1.6 Hz, 1
H, C$_6$H$_5$), 6.84 (d, $J = 7.8$ Hz, 1 H, oxindole ArH), 6.95 (td, $J = 7.7$, 1.0 Hz, 1 H, oxindole ArH), 7.05-7.08 (m, 2 H, ArH), 7.21-7.30 (m, 4 H, ArH), 7.37 (d, $J = 7.6$ Hz, 1 H, oxindole ArH); $^{13}$C
NMR (75.5 MHz, CDCl$_3$) d 24.8 (t), 26.1 (q), 27.5 (q), 30.7 (d), 42.6 (d), 49.6 (d), 54.1 (s), 58.2 (s), 61.1 (t), 64.1 (d), 66.4 (t), 70.8 (d), 73.4 (t), 108.0 (d), 121.8 (d), 124.8 (d), 127.2 (d), 127.6 (d), 127.9 (d), 128.2 (d), 129.7 (s), 138.0 (s), 143.0 (s), 175.6 (s), 176.8 (s); mass spectra, m/z
(relative intensity) 444 (M$^+$, 45), 353 (35), 91 (100); exact mass calcd for C$_{27}$H$_{28}$N$_2$O$_4$ m/z 444.2048, found m/z 444.2042.

![Structural formula](image)

(±)-(1'R$^*$,3'aS$^*$,4'R$^*$,7'aR$^*$,8'R$^*$)-Tetrahydro-8'-
(2-methoxy-2,2-diphenylethyl)-3'a-
(methoxymethyl)-2',5,5-trimethylspirom-
[dioxane-2,6'(5'H)-[1,4]methanoisoindoline]-3'-one
(196). To a suspension of 633 mg (15.84 mmol) of 60% sodium hydride in mineral oil (washed
with three 5-mL portions of hexane) in 30 mL of dimethylsulfoxide warmed to 45 °C was added
4.4 g (8.71 mmol) of alcohol 180 in several portions. The mixture was stirred for 15 min, cooled
to 35 °C, and 6.84 g (48.18 mmol) of iodomethane was added. The mixture was stirred for 5 h,
and was then partitioned between 100 mL of saturated aqueous ammonium chloride and 100 mL
of ethyl acetate. The organic layer was separated and the aqueous phase was extracted with two
50-mL portions of ethyl acetate. The combined organic layers were washed with five 50-mL
portions of brine, dried (MgSO$_4$), filtered and concentrated in vacuo to provide 4.12 g (100%) of
methyl ether 196 which was used without further purification: mp 145-148 °C; IR (KBr) 1702 cm$^{-1}$
; $^1$H NMR (300 MHz, CDCl$_3$) δ 0.80 (s, 3 H, CH$_3$), 1.06 (s, 3 H, CH$_3$), 1.38 (br s, 1 H), 1.46 (dd,
$J = 14.4$, 2.7 Hz, 1 H), 1.94 (m, 2 H), 2.04 (dd, $J = 14.4$, 3.7 Hz, 1 H), 2.19 (dd, $J = 14.4$, 6.6 Hz, 1
H), 2.25 (br, 1 H), 2.43 (dd, $J = 14.4$, 3.6 Hz, 1 H), 2.80 (m, 1 H), 2.99 (s, 3 H, OCH$_3$ or NCH$_3$),
3.00 (s, 3 H, OCH3 or NCH3), 3.10 (br s, 1 H, CHN), 3.22-3.27 (m, 2 H, OCH2 manifold), 3.35 (s, 3 H, OCH3), 3.36 (br s, 1 H), 3.48-3.53 (m, 2 H, OCH2 manifold), 3.74 (d, J = 9.6 Hz, 1 H, OCH2 manifold), 7.15-7.34 (m, 10 H, ArH); 13C NMR (75.4 MHz, CDCl3) δ 22.1 (q), 22.6 (q), 29.5 (s), 31.4 (q), 31.6 (t), 36.4 (l), 37.6 (l), 39.7 (d), 40.0 (d), 48.4 (d), 50.4 (q), 55.6 (s), 59.5 (q), 67.6 (l), 67.6 (d), 69.5 (l), 70.5 (l), 82.2 (s), 96.3 (s), 126.74 (d), 126.77 (d), 126.8 (d), 126.9 (d), 127.7 (d), 127.9 (d), 144.6 (s), 145.0 (s), 176.3 (s), the overlapping triplet and doublet at 67.69 ppm were resolved in the DEPT spectrum; mass spectrum, m/z (relative intensity) 519 (M+, 9), 365 (19), 322 (100), 197 (68); exact mass calcld. for C32H41N05 m/z 519.2986, found m/z 519.2981.

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{\text{OBn}} \quad \text{NMe} \\
\text{OMe}
\]

\((\pm)-(1'R',3'aS',4'R',7'aR',8'R')-3'a-[(\text{Benzyloxy})\text{methyl}]{\text{tetrahydro-8'}-\text{(2-methoxy-2,2-diphenylethyl)-2',5,5-trimethylspiro[6-dioxane-2,6'(5'H)\text{-}[1,4]methanoisindoline]-3'}-\text{one}}\) (197). To a suspension of 605 mg (15.12 mmol) of 60% sodium hydride in mineral oil (washed with three 10-mL portions of hexane) in 65 mL of dimethylsulfoxide warmed to 35 °C was added 4.4 g (7.57 mmol) of alcohol 181 in several portions. The mixture was stirred for 15 min, 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 by filtration and washed with 1 L of water to provide 4.55 g (100%) of methyl ether 181 which was used without further purification: mp 74-79 °C; IR (KBr) 1699 cm\(^{-1}\); 1H NMR (300 MHz, CDCl3) δ 0.80 (s, 3 H, CH3), 10.5 (s, 3 H, CH3), 1.40 (m, 1 H), 1.45 (dd, J = 17.1, 2.8 Hz, 1 H), 1.91 (m, 2 H), 2.01 (dd, J = 14.3, 3.6 Hz, 1 H), 2.20 (dd, J = 14.3, 7.6 Hz, 1 H), 2.29 (m, 1 H), 2.44 (dd, J = 14.3, 3.6 Hz, 1 H), 2.80 (m, 1 H), 3.01 (s, 3 H, CH3), 3.02 (s, 3 H, CH3), 3.12 (dd, J = 2.8, 2.1 Hz, 1 H, CHN), 3.16-3.33 (m, 3 H, OCH2 manifold), 3.51
(d, $J = 11.5$ Hz, 1 H, OCH$_2$ manifold), 3.61 (d, $J = 9.7$ Hz, 1 H, CH$_2$OBn), 3.83 (d, $J = 9.7$ Hz, 1 H, CH$_2$OBn), 4.55 and 4.59 (ABq, $J = 13.0$ Hz, 2 H, OCH$_2$Ph), 7.15-7.35 (m, 15 H, ArH); $^{13}$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 (l), 67.7 (d), 69.6 (l), 70.5 (l), 73.4 (l), 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), 144.4 (s), 145.1 (s), 176.5 (s), one aromatic doublet was not resolved; mass spectrum, $m/z$ (relative 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$^R$,3$^a$S*,4$^R$,7a$^R$,8$^R$*)-Tetrahydro-8-(2-hydroxy-2,2-diphenylethyl)-2-methyl-1,4-methanoloisoindoline-3,6(5H)-dione (198). To a solution of 3.0 g (5.78 mmol) of ketal 196 in 500 mL of acetone was added 1 mL of water followed by 500 mg of p-toluenesulfonic acid monohydrate. The mixture was stirred at room temperature for 4.5 h, was made basic with solid sodium bicarbonate, and then diluted with 50 mL of water. The mixture was concentrated in vacuo, and the residue partitioned between 200 mL of ethyl acetate and 200 mL of water. The organic layer was separated and the aqueous phase extracted with two 100-mL portion of ethyl acetate. The combined organic layers were washed with three 100-mL portions of brine, dried (MgSO$_4$), filtered and concentrated in vacuo. The residue was diluted with first ether and then hexane. The mixture was concentrated until crystals began to form and was then cooled in an ice bath. The resulting solid was collected by filtration and washed with hexane to provide 2.37 g (94%) of ketone 198 as a white solid: mp 129-132 °C; IR (KBr) 1698 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 1.60 (br, 1 H), 1.92 (m, 1 H), 1.99-2.12 (m, 2 H), 2.28-2.53 (m, 5 H), 2.97 (s, 3 H, OCH$_3$)
or NCH₃), 3.00 (s, 3 H, OCH₃ or NCH₃), 3.11 (dd, J = 2.6, 1.8 Hz, 1 H, CHN), 3.28 (s, 3 H, OCH₃), 3.58 (d, J = 10.3 Hz, 1 H, OCH₂Ph), 3.84 (d, J = 10.3 Hz, 1 H, OCH₂Ph), 7.11-7.31 (m, 10 H, ArH); ¹³C NMR (75.4 MHz, CDCl₃) δ 31.1 (q), 38.0 (l), 39.1 (l), 41.1 (d), 42.6 (l), 44.8 (d), 48.9 (d), 50.6 (q), 54.6 (s), 59.2 (q), 67.6 (d), 69.2 (l), 82.2 (s), 126.8 (d), 127.02 (d), 127.09 (d), 128.0 (d), 143.7 (s), 144.3 (s), 175.6 (s), 208.8 (s), two aromatic doublets were not resolved; mass spectrum, m/z (relative intensity) 433 (M⁺, 1), 236 (8), 197 (100); exact mass calcd. for C₂₇H₃₁NO₄ m/z 433.2254, found m/z 433.2253.

(±)-(1R,3aS,4R,7aR,8R)-3a-[(Benzyloxy)methyl]tetrahydro-8-(2-methoxy-2,2-diphenylethyl)-2-methyl-1,4-methanolsoindoline-3,6(5H)-dione (199). To a solution of 4.15 g (6.97 mmol) of ketal 197 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 made basic 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 ethyl acetate and 200 mL of water. The organic layer was separated and the aqueous phase extracted with two 100-mL portion of ethyl acetate. The combined organic layers were washed with three 100-mL portions of saturated aqueous sodium bicarbonate, three 100-mL portions of brine, dried (MgSO₄), 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 solid was collected by filtration and washed with ether-hexane (1:1) to provide 3.35 g (94%) of ketone 199 as a white solid: mp (dichloromethane-ether) 165-167 °C; IR (KBr) 1703 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.45 (br,
1 H), 1.91-2.09 (m, 3 H), 2.28-2.54 (m, 5 H), 2.96 (s, 3 H, CH₃), 3.00 (s, 3 H, CH₃), 3.12 (t, J = 2.0 Hz, 1 H, CH₂N), 3.68 (d, J = 10.4 Hz, 1 H, CH₂OBn), 3.92 (d, J = 10.4 Hz, 1 H, CH₂OBn), 4.44 (d, J = 12.2 Hz, 1 H, OCH₂Ph), 4.51 (d, J = 12.2 Hz, 1 H, OCH₂Ph) 7.15-7.30 (m, 15 H, ArH); ¹³C NMR (75.5 MHz, CDCl₃) 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; mass spectrum, m/z (relative intensity) 509 (M⁺, 0.3), 403 (33), 197 (100), 91 (60); exact mass calcd. for C₃₃H₃₅NO₄ m/z 509.2565, found m/z 509.2535.

Anal. calcd. for C₃₃H₃₅NO₄: C, 77.76; H, 6.93. Found: C, 77.69; H, 6.96.

(±)-(1'R,3aS*,4'R,7aS*,8'R)-2'-bromo-3a,4,5,7a-tetrahydro-6-hydroxy-8-(2-methoxy-2,2-diphenylethyl)-3a-(methoxy methyl)-2-methyl-3-oxo-1,4-methanoisindoline-7-carboxanilide (200). To a suspension of 928 mg (23.2 mmol) of 60% sodium hydride in mineral oil (washed with three 10-mL portions of hexane) and 127 mg (3.17 mmol) of potassium hydride in 50 mL of tetrahydrofuran was added 2.1 g (4.86 mmol) of ketone 198 followed by 4.07 g (20.55 mmol) of 2-bromophenylisocyanate. The mixture was warmed at reflux of 2 h and then an additional 1.4 g (7.07 mmol) of 2-bromophenylisocyanate was added and the mixture continued to reflux for 12 h. The mixture was cooled to 0 °C and the excess sodium hydride-potassium hydride cautiously destroyed with ethanol. The mixture was partitioned between 200 mL of ice cold saturated aqueous ammonium chloride and 100 mL of ethyl acetate. The organic layer was
separated and the aqueous phase extracted with three 80-mL portions of ethyl acetate. The combined organic layers were washed with three 80-mL portions of brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed over 65 g of silica gel (first dichloromethane; then ethyl acetate-dichloromethane, 10:90, then 20:80, then 30:70) to provide material which was recrystallized from ether-hexane to afford 2.25 g (74%) of anilide 200 as a white solid: mp 122-129 °C; IR (KBr) 3409, 1705 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.42 (br s, 1 H, C₁₅H), 1.79 (dd, J = 18.9, 2.40 Hz, 1 H, C₁₄H), 2.16 (m, 1 H, C₁₆H), 2.21 (dd, J = 19.0, 3.5 Hz, 1 H, C₁₄H), 2.30 (dd, J = 14.2, 7.7 Hz, 1 H, CH₂C(OMe)Ph₂), 2.54 (d, J = 14.2, 3.2 Hz, 1 H, CH₂C(OMe)Ph₂), 2.23 (br s, 1 H, C₆H), 3.00 (s, 3 H, CH₃), 3.07 (s, 3 H, CH₃), 3.29 (d, J = 9.6 Hz, 1 H, CH₂OMe), 3.33 (s, 3 H, OCH₃), 3.50 (t, J = 2.2 Hz, 1 H, CHN), 3.69 (d, J = 9.6 Hz, 1 H, CH₂OMe) 7.00 (td, J = 7.5, 1.5 Hz, 1 H, ArH), 7.18-7.36 (m, 11 H, ArH), 7.55 (dd, J = 8.0, 1.4 Hz, 1 H, ArH), 7.70 (s, 1 H, NH), 8.29 (dd, J = 8.3, 1.5 Hz, 1 H, ArH), 13.83 (s, 1 H, OH); ¹³C NMR (75.5 MHz, CDCl₃) δ 31.4 (q), 34.5 (t), 37.2 (t), 39.3 (d), 44.9 (d), 47.7 (d), 50.6 (q), 55.7 (s), 59.6 (q), 66.9 (t), 69.5 (d), 82.0 (s), 97.0 (s), 114.3 (s), 122.2 (d), 125.4 (d), 126.9 (d), 127.0 (d), 127.1 (d), 128.0 (d), 128.1 (d), 128.3 (d), 132.1 (d), 134.7 (s), 144.1 (s), 144.4 (s), 169.2 (s), 173.0 (s), 174.7 (s), one aromatic doublet was not resolved; mass spectrum, m/z (relative intensity) 197 (100); exact mass calcd. for C₃₄H₃₅BrNO₅ m/z 630.1729 and 632.1709, found m/z 630.1721 and 632.1746.
(±)-(1R*,3aS*,4R*,7aS*,8R*)-3a-[(Benzyloxy)methyl]-2'-bromo-3a,4,5,7a-tetrahydro-6-hydroxy-8-(2-methoxy-2,2-diphenylethyl)-2-methyl-3-oxo-1,4-methanolidinoline-7-carboxanilide (201). To a suspension of 1.24 g (31.00 mmol) of 60% sodium hydride in mineral oil (washed with three 10-mL portions of hexane) and 145 mg (3.62 mmol) of potassium hydride in 50 mL of tetrahydrofuran was added 3.52 g (6.94 mmol) of ketone 199 followed by 7.2 g (36.36 mmol) of 2-bromophenylisocyanate. 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 sodium hydride-potassium hydride cautiously destroyed with ethanol. The mixture was stirred for 20 min, and then partitioned between 250 mL of ice cold saturated aqueous ammonium chloride and 150 mL of ethyl acetate. The organic layer was separated and the aqueous phase extracted with three 80-mL portions of ethyl acetate. The combined organic layers were washed with three 80-mL portions of brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed over 65 g of silica gel (first dichloromethane; then methanol-dichloromethane, 2:98) and then recrystallized from ether-hexane to afford, in two crops, 3.42 g (70%) of β-ketoanilide 201 as a white solid: mp 174-177 °C; IR (neat) 3409, 1697 cm⁻¹; ¹H NMR (CDCl₃) δ 1.43 (br s, 1 H, C₁₅H), 1.77 (dd, J = 18.9, 2.3 Hz, 1 H, C₁₄H), 2.12-2.19 (m, 2 H, C₁₆H and C₁₄H), 2.31 (dd, J = 14.2, 7.7 Hz, 1 H, CH₂C(OMe)Ph), 2.56 (dd, J = 14.2, 3.3 Hz, 1 H, CH₂C(OMe)Ph), 2.94 (br s, 1 H, C₆H), 3.00 (s, 3 H, CH₃), 3.09 (s, 3 H, CH₃), 3.35 (d, J = 9.7 Hz, 1 H, CH₂OBn), 3.52 (t, J = 1.9 Hz, 1 H, CHN), 3.79 (d, J = 9.7 Hz, 1 H, CH₂OBn), 4.47 (d, J =
12.6 Hz, 1 H, OCH₂Ph), 4.61 (d, J = 12.6 Hz, 1 H, OCH₂Ph), 7.01 (td, J = 7.9, 1.5 Hz, 1 H, ArH), 7.17-7.37 (m, 16 H, ArH), 7.55 (dd, J = 8.2, 1.5 Hz, 1 H, ArH), 7.70 (s, 1 H, NH), 8.28 (dd, J = 8.2, 1.5 Hz, 1 H, ArH), 13.79 (s, 1 H, OH); ¹³C NMR (300 MHz, CDCl₃) 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 (relative intensity) 403 (20), 197 (100), 173 (60), 171 (62), 91 (45); exact mass calcd. for C₄₀H₃₉BrN₂O₅ m/z 706.2042, found m/z 706.2047.


The filtrate was chromatographed over 7 g of silica gel (first dichloromethane; then methanol-dichloromethane, 2:98) and the material from the column was recrystallized from ether-hexane to afford an additional 491 mg (10%) of 201: mp 171-176°C.
and was then poured into 100 mL of ice cold saturated sodium bicarbonate. The resulting white solid was collected by filtration, and the filter cake was washed with 300 mL of water. The solid was then dissolved in 100 mL of dichloromethane, dried (MgSO₄), treated with decolorizing carbon (Norit A), filtered through Celite, and concentrated to provide 778 mg (91%) of 202 as a glassy solid: mp 181-185 °C; IR (film) 3330, 1694 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.51 (br s, 1 H, C₁₅H), 1.84 (dd, J = 18.4, 2.5 Hz, 1 H, C₁₄H), 2.02 (m, 1 H, C₁₆H), 2.25 (dd, J = 14.3, 8.3 Hz, 1 H, CH₂C(OMe)Ph₂), 2.33 (dd, J = 19.4, 3.6 Hz, 1 H, C₁₄H), 2.55 (dd, J = 14.3, 2.2 Hz, 1 H, CH₂C(OMe)Ph₂), 2.98 (s, 3 H, CH₃), 3.09 (s, 3 H, CH₃), 3.11 (s, 3 H, OCH₃), 3.37 (m, 2 H, one CH₂OMe and C₆H), 3.48 (s, 3 H, OCH₃), 3.55 (d, J = 9.9 Hz, 1 H, CH₂OMe), 3.63 (t, J = 2.2 Hz, 1 H, CHN), 5.07 (d, J = 6.9 Hz, 1 H, OCH₂O), 5.13 (d, J = 6.9 Hz, 1 H, OCH₂O), 6.92 (td, J = 7.6, 1.5 Hz, 1 H, ArH), 7.17-7.33 (m, 11 H, ArH), 7.53 (dd, J = 8.0, 1.4 Hz, 1 H, ArH), 8.60 (dd, J = 8.0, 1.5 Hz, 1 H, ArH), 10.11 (s, 1 H, NH); ¹³C NMR (75.5 MHz, CDCl₃) δ 30.9 (t), 31.3 (q), 36.9 (t), 40.0 (d), 44.1 (d), 49.1 (d), 50.4 (q), 53.9 (s), 56.9 (q), 59.6 (q), 67.5 (t), 70.6 (d), 82.0 (s), 92.8 (t), 109.7 (s), 112.3 (s), 121.3 (d), 124.2 (d), 126.8 (d), 126.9 (d), 127.0 (d), 127.8 (d), 128.0 (d), 128.1 (d), 132.1 (d), 137.0 (s), 144.3 (s), 144.5 (s), 158.7 (s), 163.7 (s), 175.3 (s), one aromatic doublet was not resolved; mass spectrum, m/z (relative intensity) 676 (M⁺, 3), 674 (M⁺, 3), 197 (51), 45 (100); exact mass calcd. for C₃₆H₃₉BrN₂O₆ m/z 676.1972 and 674.1992, found m/z 676.1972 and 764.1993.
(±)-(1'R,3aS*,4'R,7aS*,8'R*)-3a-[(Benzyloxy)methyl]-2'-bromo-3a,4,5,7a-tetrahydro-8-
(2-methoxy-2,2-diphenylethyl)-6-[(methoxymethoxy)-2-methyl-3-oxo-1,4-
methanoisoindoline-7-carboxanilide (203). To a solution of 200 mg (0.28 mmol) of β-
ketoanilide 201 in 3 mL of dimethylsulfoxide 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,
and was then poured into 40 mL of saturated aqueous sodium bicarbonate, and extracted with
three 40-mL portions of ethyl acetate. The combined organic layers were washed with three 40-
ml portions of brine, dried (MgSO4), filtered and concentrated to provide 212 mg (100%) of β-
ketoanilide 203 as a white solid which was used without further purification: mp 172-177 °C. The
following data were obtained from a sample recrystallized from ethyl acetate-hexane: mp 191-
193 °C; IR (film) 3342, 1702, 1663 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.46 (br, 1 H, C₁₅H), 1.74
(dd, J = 18.4, 2.6 Hz, 1 H, C₁₄H), 1.99 (br d, J = 8.4 Hz, 1 H, C₁₆H), 2.17 (dd, J = 18.4, 3.7 Hz, 1
H, C₁₄H), 2.26 (dd, J = 14.4, 8.4 Hz, 1 H, CH₂C(OMe)Ph₂), 2.56 (dd, J = 14.3, 2.3 Hz, 1 H,
CH₂C(OMe)Ph₂), 2.98 (s, 3 H, NCH₃), 3.12 (s, 3 H, OCH₃), 3.27 (s, 3 H, OCH₃), 3.32 (d, J = 9.8
Hz, 1 H, CH₂OBn), 3.47 (t, J = 2.1, 1 H, C₆H), 3.64 (d, J = 9.8 Hz, 1 H, CH₂OBn), 3.66 (t, J = 2.8
Hz, 1 H, CH₂OBN), 4.44 (d, J = 12.8 Hz, 1 H, OCH₂Ph), 4.61 (d, J = 12.8 Hz, 1 H, OCH₂Ph), 4.97 (s,
2 H, OCH₂O), 6.95 (ddd, J = 9.0, 7.5, 1.6 Hz, 1 H, ArH), 7.12-7.34 (m, 16 H, ArH), 7.55 (dd, J =
8.0, 1.5 Hz, 1 H, ArH), 8.64 (dd, J = 8.4, 1.5 Hz, 1 H, ArH), 10.04 (s, 1 H, NH); ¹³C NMR (75.5
MHz, CDCl₃) 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),
131

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 (relative intensity) 752 (M+, 4), 750 (M+, 4), 382 (34), 197
(100), 91 (85); exact mass calcd. for C_{42}H_{43}BrN_{2}O_{6} m/z 752.2286 and 750.2306, found m/z
752.2307 and 750.2289.

Anal. calcd. for C_{42}H_{43}BrN_{2}O_{6}: C, 67.18; H, 5.78. Found: C, 67.23; H, 5.76.

\[ \text{OBn} \]
\[ \text{Me} \]
\[ \text{OMe} \]
\[ \text{NMe} \]
\[ \text{Ph} \]
\[ \text{Ph} \]

(±)-(1R,3aS,4R*,7aS*,8R*)-6-(Benzyloxy)-3a-[(benzyloxy)methyl]-2'-bromo-
3a,4,5,7a-tetrahydro-8-(2-methoxy-2,2-diphenylethyl)-2-methyl-3-oxo-1,4-
methanolsoindoline-7-carboxanilide (204). To a solution of 200 mg (0.28 mmol) of β-
ketoanilide 201 in 3 mL of dimethylsulfoxide was added 286 mg (2.83 mmol) of triethylamine
followed by 181 mg (1.42 mmol) of benzyl bromide. The mixture was warmed to 40 °C for 5.5 h,
and then an additional 290 mg (2.87 mmol) of triethylamine and 183 mg (1.43 mmol) of benzyl
bromide was added. The mixture was stirred for 1 h, and was poured into 50 mL of saturated
aqueous sodium bicarbonate, and extracted with three 30-mL portions of ethyl acetate. The
combined organic layers were washed with three 40-mL portions of brine, dried (MgSO_{4}), filtered
and concentrated in vacuo. The residue was chromatographed over 12 g of silica gel
dichloromethane; then ethyl acetate-dichloromethane, 5:95, then 10:90, then 30:70) to provide
190 mg (84%) of 204: mp (ethyl acetate-hexane) 185-186 °C; IR (KBr) 3328, 1699 cm^{-1}; \textsuperscript{1}H
NMR (300 MHz, CDCl_{3}) \delta 1.37 (br, 1 H, C_{15}H), 1.57 (dd, J = 18.2, 2.4 Hz, 1 H, C_{14}H), 1.97-2.02 (m, 2
H, C_{14}H and C_{16}H), 2.21 (dd, J = 14.3, 8.5 Hz, 1 H, CH\_2C(OMe)Ph\_2), 2.57 (dd, J = 14.3, 1.9 Hz, 1 H, CH\_2C(OMe)Ph\_2), 2.96 (s, 3 H, NCH\_3), 3.10 (s, 3 H, OCH\_3), 3.26 (d, J = 9.9 Hz, 1 H, CH\_2OBn), 3.41 (d, J = 9.8 Hz, 1 H, CH\_2OBn), 3.42 (br, 1 H, C\_6H), 3.68 (t, J = 2.2 Hz, 1 H, CH\_N), 4.38 (ABq, 2 H, OCH\_2Ph), 4.87 and 5.05 (ABq, J = 13.2 Hz, 2 H, OCH\_2Ph), 6.91 (td, J = 7.8, 1.5 Hz, 1 H, ArH), 7.15-7.37 (m, 21 H, ArH), 7.49 (dd, J = 7.9, 1.4 Hz, 1 H, ArH), 8.58 (dd, J = 8.3, 1.5 Hz, 1 H, ArH), 10.04 (s, 1 H, NH); 13C NMR (300 MHz, CDCl\_3) δ 31.3 (q), 31.6 (t), 36.8 (t), 40.2 (d), 43.8 (d), 49.5 (d), 50.3 (q), 53.8 (s), 64.5 (t), 69.9 (t), 70.9 (d), 73.0 (t), 81.8 (s), 108.3 (s), 112.7 (d), 121.7 (s), 124.2 (d), 126.69 (d), 126.74 (d), 126.8 (d), 126.9 (d), 127.1 (d), 127.2 (d), 127.8 (d), 128.0 (d), 128.1 (d), 128.5 (d), 128.9 (d), 132.2 (d), 135.9 (s), 137.1 (s), 138.5 (s), 144.2 (s), 144.9 (s), 160.3 (s), 164.0 (s), 175.4 (s), two aromatic doublets were not resolved; mass spectrum, m/z (relative intensity) 798 (M\^+, 0.2), 796 (M\^+, 0.2), 197 (85), 91 (100); exact mass calcld. for C\_{47}H\_{45}BrN\_2O\_5 m/z 798.2493 and 796.2513, found m/z 798.2490 and 796.2534.

Anal. calcld. for C\_{47}H\_{45}BrN\_2O\_5: C, 70.76; H, 5.64. Found: C, 70.30; H, 5.72.

(\pm)-(1\_R^*,3aS^*,4R^*,7aS^*,8R^*)-2'-bromo-3a,4,5,7a-tetrahydro-8-(2-methoxy-2,2-diphenylethyl)-6-(methoxymethoxy)-3a-(methyloxymethyl)-N-(methyloxymethyl)-2-methyl-3-oxo-1,4-methanolsoIndollne-7-carboxanillide (205). To a solution of 600 mg (0.88 mmol) of amide 202 in 15 mL of dimethylsulfoxide was added 177 mg (4.42 mmol) of a 60% dispersion of sodium hydride in mineral oil. The mixture was stirred for 30 min, and then 332 mg (4.14 mmol) of chloromethyl methyl ether was added. The mixture was stirred for 2.5 h, and an additional 35.5
mg (0.88 mmol) of 60% sodium hydride and 70.3 mg (0.88 mmol) of chloromethyl methyl ether was added. The mixture was stirred for 2 h, and was then poured into 50 mL of saturated aqueous sodium bicarbonate and extracted with three 30-mL portions of ethyl acetate. The combined organic layers were washed with five 50-mL portions of brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (first dichloromethane; then ethyl acetate-hexane, 1:1) to provide 46 mg (8%) of starting material and 120 mg of mixed material containing starting material and 205. Continued elution afforded 500 mg (78%) of pure 205 as a mixture of geometric isomers: IR (KBr) 1701 cm⁻¹; H NMR (300 MHz, CDCl₃) At 303 °K, this material gave a complicated spectrum due to the presence of geometrical isomers; mass spectrum, m/z (relative intensity) 720 (M⁺, 1), 718 (M⁺, 1), 594 (8), 197 (50), 45 (100); exact mass calcd. for C₃₈H₄₃BrN₂O₇ m/z 720.2234 and 718.2254, found m/z 720.2237 and 718.2256. Recovered starting material and mixed fractions were resubjected to the above conditions to provide an additional 100 mg (15%) of 205.

![Structural formula of 206](image)

(±)-(1R*,3aS*,4R*,7aS*,8R*)-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 (206). To a solution of 212 mg (0.28 mmol) of amide 203 in 5 mL of dimethylsulfoxide was added 56 mg (1.39 mmol) of a 60% dispersion of sodium hydride 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% sodium hydride and 183 mg (2.29 mmol) of chloromethyl methyl ether was 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, and was then poured into 40 mL of saturated aqueous sodium bicarbonate, and extracted with three 30-mL portions of ethyl acetate. The combined organic layers were washed with four 40-mL portions of brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed over 12 g of silica gel (first dichloromethane; then ethyl acetate-hexane, 3:7, then 1:1, then 6:4, then 7:3) to provide 209 mg (84%) of 206 as an oil which when concentrated from ether-hexane afforded 206 as a white powder: IR (KBr) 1701 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) At 303 °K, this material gave a complicated spectrum due to the presence of geometrical isomers; mass spectrum, m/z (relative intensity) 796 (M⁺, 0.9), 794 (M⁺, 0.9), 548 (9), 197 (60), 91 (100), 45 (70); exact mass calcd. for C₄₄H₄₇BrN₂O₇ m/z 796.2548 and 794.2568, found m/z 796.2558 and 794.2552.

![Structure of 207](image)

(±)-(1R,3aS*,4R*,7aS*,8R*)-6-(Benzyloxy)-3a-[(benzyloxy)methyl]-2'-bromo-3a,4,5,7a-tetrahydro-8-(2-methoxy-2,2-diphenylethyl)-N-(methoxymethyl)-2-methyl-3-oxo-1,4-methanoisoldoline-7-carboxanilide (207). To a solution of 130 mg (0.16 mmol) of amide 204 in 2 mL of dimethysulfoxide was added 32 mg (0.8 mmol) of a 60% dispersion of sodium hydride in mineral oil. The mixture was stirred for 10 min, and then 54 mg (0.67 mmol) of chloromethyl methyl ether was added. The mixture was stirred for 1 h, and an additional 15 mg
(0.37 mmol) of 60% sodium hydride and 27 mg (0.33 mmol) of chloromethyl methyl ether was added. The mixture was stirred for 30 min, diluted with 20 mL of saturated aqueous sodium bicarbonate and extracted with three 10-mL portions of ethyl acetate. The combined organic layers were washed with four 10-mL portions of brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed over 6 g of silica gel (first dichloromethane; then ethyl acetate-hexane, then 1:1, then 6:4, then 7.5:2.5) to provide 123 mg (89%) of 207 as a white powder: IR (KBr) 1701 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) At 303 °K, this material gave a complicated spectrum due to the presence of geometrical isomers; mass spectrum, m/z (relative intensity) 842 (M⁺, 0.4) 840 (M⁺, 0.4) 670 (6), 548 (10), 197 (42), 91 (100); exact mass calcd. for C₄₈H₄₉BrN₂O₆ m/z 842.2755 and 840.2774, found m/z 842.2759 and 840.2759.

(±)-(1'R*,3'S*,3'aS*,4'R*,7'aS*,8'R*)-3'a,7'a-Dihydro-8'-{(2-methoxy-2,2-diphenylethyl)-1-(methoxymethyl)-3'a-(methyloxymethyl)-2'-methylispiro[indoline-3,7' (4'H)-[1,4]methanoisoindoline]-2,3',6'(5'H)-trione (208) and (±)-(1'R*,3'R*,3'aS*,4'R*,7'aS*,8'R*)-3'a,7'a-Dihydro-8'-{(2-methoxy-2,2-diphenylethyl)-1-(methoxymethyl)-3'a-(methyloxymethyl)-2'-methylispiro[indoline-3,7' (4'H)-[1,4]methanoisoindoline]-2,3',6'(5'H)-trione (209). To a solution of 600 mg (0.83 mmol) of 205 in 95 mL of benzene heated at reflux was added a mixture of 432 mg (1.48 mmol) of tri-n-butyltin hydride and 13 mg of AIBN in 20 mL of benzene over a 24-h period using a syringe pump. The mixture was concentrated in vacuo, and the residue was partitioned between 50 mL of acetonitrile and 50 mL of hexane. The
acetonitrile layer was separated and the hexane layer was extracted with 50 mL of acetonitrile. The combined acetonitrile layers were washed with twelve 25-mL portions of hexane, and concentrated in vacuo to provide 474 mg of a 1.7:1 mixture of crude 208 and 209, respectively, by $^1$H NMR. The residue was chromatographed over 12 g of silica gel (first dichloromethane; then ethyl acetate-dichloromethane, 5:95) to provide 252 mg (51%) of oxindole 208 as a white solid: mp (ethyl acetate-hexane) 215-217 °C; IR (KBr) 1702, 1610 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.33 (br s, 1 H, C$_{15}$H), 2.15 (dd, $J$ = 19.2, 3.0 Hz, 1 H, C$_{14}$H), 2.26-2.36 (m, 2 H, C$_{14}$H and CH$_2$CPh$_2$), 2.61 (br s, 1 H, C$_6$H), 2.72 (dd, $J$ = 14.1, 1.8 Hz, 1 H, CH$_2$CPh$_2$), 3.00 (br d, $J$ = 9.4 Hz, 1 H, C$_{15}$H), 3.08 (s, 3 H, NCH$_3$ or OCH$_3$), 3.14 (s, 3 H, NCH$_3$ or OCH$_3$), 3.34 (s, 3 H, OCH$_3$), 3.40 (s, 3 H, OCH$_3$), 3.76 (d, $J$ = 10.2 Hz, 1 H, CH$_2$OMe), 3.99 (m, 2 H, CHN and CH$_2$OMe), 5.07 and 5.12 (ABq, $J$ = 10.8 Hz, 2 H, NCH$_2$O), 6.98-7.05 (m, 3 H, ArH), 7.13-7.41 (m, 11 H, ArH); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 31.6 (q), 38.5 (t), 39.1 (d), 42.5 (t), 44.4 (d), 50.3 (q), 54.5 (d), 56.0 (q), 57.5 (s), 58.9 (q), 63.6 (s), 66.0 (d), 68.4 (t), 71.2 (t), 81.5 (s), 109.7 (d), 123.0 (d), 124.2 (d), 126.5 (d), 126.7 (d), 126.8 (d), 127.0 (d), 127.9 (d), 128.1 (d), 128.8 (d), 130.5 (s), 141.7 (s), 144.6 (s), 145.1 (s), 173.7 (s), 174.3 (s), 205.1 (s); mass spectrum, m/z (relative intensity) 594 (M$^+$, 83), 562 (26), 197 (89), 45 (100); exact mass calcd. for C$_{36}$H$_{36}$N$_2$O$_6$ m/z 594.2731, found m/z 594.2723.

Continued elution (ethyl acetate-dichloromethane, 10:90, then 15:85, then 25:75, then 33:67, then 1:1) afforded 180 mg (36%) of oxindole 209 as a white solid: mp (ethyl acetate-hexane) 220-222 °C; IR (KBr) 1731, 1707 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.98 (br, 1 H), 2.20 (br, 1 H), 2.52-2.59 (m, 4 H), 2.76 (br d, $J$ = 16.7 Hz, 1 H), 3.01 (s, 3 H, OCH$_3$ or NCH$_3$), 3.03 (s, 3 H, OCH$_3$ or NCH$_3$), 3.24 (s, 3 H, OCH$_3$), 3.36 (br s, 1 H, CHN), 3.41 (s, 3 H, OCH$_3$), 4.14 (d, $J$ = 9.1 Hz, 1 H, CH$_2$OMe), 4.23 (d, $J$ = 9.1 Hz, 1 H, CH$_2$OMe), 4.97 (d, $J$ = 11.0 Hz, 1 H, NCH$_2$O), 5.04 (d, $J$ = 11.0 Hz, 1 H, NCH$_2$O), 6.08 (d, $J$ = 7.4 Hz, 1 H, oxindole ArH), 6.66 (td, $J$ = 7.6, 0.9 Hz, 1 H, ArH), 6.97 (d, $J$ = 7.4 Hz, 1 H, ArH), 7.23-7.37 (m, 11 H, ArH); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 31.4 (q), 38.6 (t), 40.3 (d), 42.7 (t), 45.2 (d), 51.1 (q), 54.8 (d), 55.8 (q), 57.7 (s), 58.9 (q), 63.7 (s), 66.0 (d), 67.7 (t), 71.1 (t), 83.1 (s), 109.9 (d), 123.0 (d), 123.9 (d), 126.7 (d), 127.0 (d), 127.3 (d), 127.5 (d), 127.7 (s), 128.2 (d), 128.3 (d), 129.1 (d), 142.5 (s), 143.0 (s), 144.7 (s), 174.3 (s), 174.9 (s), 205.2 (s); mass spectrum, m/z (relative intensity) 594 (M$^+$, 94), 562 (28), 393
(±)-(1'R',3'S*,3'aS*,4'R',7'aS*,8'R')-3'a-[(Benzylloxymethyl)-3'a,7'a-dihydro-8'-(2-methoxy-2,2-diphenylethyl)-1-(methoxymethyl)-2'-methylspiro[indoline-3,7'(4'H)-[1,4]methanolsoindoline]-2,3',6'(5'H)-trione (210) and (±)-(1'R',3'R*,3'aS*,4'R',7'aS*,8'R')-3'a-[(Benzylloxymethyl)-3'a,7'a-dihydro-8'- (2-methoxy-2,2-diphenylethyl)-1-(methoxymethyl)-2'-methylspiro[indoline-3,7'(4'H)-[1,4]methanolsoindoline]-2,3',6'(5'H)-trione (211). A. From MOM Ether 206. To a solution of 185 mg (0.23 mmol) of 206 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, and was 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, dichloromethane, then ethyl acetate-dichloromethane, 5:95, then 10:90) to provide 129 mg (83%) of a 1.2:1 mixture of oxindoles 210 and 211, respectively, by 1H 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 210 and 211 could be obtained in diminished yield, 35% and 20% respectively, after repeated chromatography (ethyl acetate-dichloromethane) and a single recrystallization from ether-hexane. Pure oxindole 210 was a white solid: mp (ether-hexane) 191-193 °C; IR (KBr) 1707, 1611 cm⁻¹; 1H NMR (300 MHz, CDCl₃) δ 1.33 (br s, 1 H),
2.12 (dd, \( J = 19.2, 2.9 \) Hz, 1 H, C\(_{14}\)H), 2.25 (dd, \( J = 19.6, 3.0 \) Hz, 1 H, C\(_{14}\)H), 2.33 (dd, \( J = 14.0, 9.4 \) Hz, 1 H, CH\(_2\)Ph), 2.68 (br s, 1 H), 2.74 (dd, \( J = 13.9, 1.0 \) Hz, 1 H, CH\(_2\)Ph), 2.99 (br d, \( J = 7.9 \) Hz, 1 H, C\(_{16}\)H), 3.10 (s, 3 H, NCH\(_3\)), 3.15 (s, 3 H, OCH\(_3\)), 3.34 (s, 3H, OCH\(_3\)), 3.86 (d, \( J = 10.4 \) Hz, 1 H, CH\(_2\)OBn), 4.04 (br s, 1 H, CHN), 4.10 (d, \( J = 10.4 \) Hz, 1 H, CH\(_2\)OBn), 4.60 (d, \( J = 12.0 \) Hz, 1 H, OCH\(_2\)Ph), 4.68 (d, \( J = 12.0 \) Hz, 1 H, CH\(_2\)OPh), 5.08 and 5.12 (ABq, \( J = 10.9 \) Hz, 2 H, NCH\(_2\)O), 6.90-7.08 (m, 3 H, ArH), 7.13-7.41 (16 H, ArH); \(^{13}\)C NMR (62.9 MHz, CDCl\(_3\)) \( \delta \) 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, \( m/z \) (relative intensity) 670 (M\(^+\), 18), 548 (15), 197 (17), 43 (100); exact mass calcd. for C\(_{42}\)H\(_{42}\)N\(_2\)O\(_6\) \( m/z \) 670.3042, found \( m/z \) 670.3050.

Anal. calcd. for C\(_{42}\)H\(_{42}\)N\(_2\)O\(_6\): C, 75.19; H, 6.31. Found: C, 75.26; H, 6.32.

Pure oxindole 211 was also a white solid: mp (ether-hexane) 158-161 °C; IR (KBr) 1730, 1709 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 1.99 (br s, 1 H), 2.22 (br, 1 H), 2.51-2.60 (m, 4 H), 2.76 (dd, \( J = 18.6, 2.0 \) Hz, 1 H, C\(_{14}\)H), 3.03 (s, 6 H, NCH\(_3\) and OCH\(_3\)), 3.14 (s, 3 H, OCH\(_3\)), 3.38 (br s, 1 H, CHN), 4.28 and 4.34 (ABq, \( J = 9.1 \) Hz, 2 H, CH\(_2\)OBn), 4.61 and 4.70 (ABq, \( J = 12.2 \) Hz, 2 H, OCH\(_2\)Ph), 4.94 and 5.01 (ABq, \( J = 10.9 \) Hz, 2 H, NCH\(_2\)O), 6.10 (d, \( J = 9.5 \) Hz, 1 H, oxindole ArH), 6.86 (td, \( J = 7.6, 0.8 \) Hz, 1 H, ArH), 6.97 (d, \( J = 7.6 \) Hz, 1 H, ArH), 7.19-7.40 (m, 16 H, ArH); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 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, \( m/z \) (relative intensity) 670 (M\(^+\), 50), 548 (61), 197 (100), 91 (80); exact mass calcd. for C\(_{42}\)H\(_{42}\)N\(_2\)O\(_6\) \( m/z \) 670.3042, found \( m/z \) 670.3025.

Anal. calcd. for C\(_{42}\)H\(_{42}\)N\(_2\)O\(_6\): C, 75.19; H, 6.31. Found: C, 74.93; H, 6.68.

B. From \( \beta \)-Benzyl Protected \( \beta \)-Ketoanilide 207: To a solution of 111 mg (0.13 mmol) of 207 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 twelve 5-mL portions of hexane, and concentrated in vacuo to provide 90 mg of a 1:1 mixture of crude oxindoles 210 and 211, respectively, by $^1$H NMR. The mixture of isomers was chromatographed over 3 g of silica gel (dichloromethane; then ethyl acetate-dichloromethane, 1:9) to provide 69 mg (78%) of oxindoles 210 and 211.

![Chemical structure of oxindole 212](attachment:image.png)

(±)-(1$^R$,3$^S$,3$^a$S,4$^R$,7$^a$S,8$^R$)-3$^a$-[(Benzyloxy)methyl]-8$^c$-(2,2-diphenylvinyl)-3$^a$,7$^a$-dihydro-1-(methoxymethyl)-2$^c$-methylspiro[indoline-3,7$^c$(4$^c$H)$^c$-1,4)methanoisoindoline]-2,3$^c$,6$^c$(5$^c$H)-trione (212). To a solution of 189 mg (0.282 mmol) of 210 in 15 mL of dichloromethane was added 100 mg of p-toluenesulfonic acid monohydrate. The mixture was stirred for 48 h, and was then passed through a 6 g pad of silica gel (ethyl acetate-dichloromethane, 1:9). The eluent was concentrated in vacuo and the residue was recrystallized from ether-hexane to afford 158 mg (88%) of olefin 212 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 (br s, 1 H), 2.41 (dd, $J = 19.2, 2.8$ Hz, 1 H, C$_{14}$H), 2.71 (dd, $J = 19.3, 3.3$ Hz, 1 H, C$_{14}$H), 2.81 (br s, 1 H), 3.03 (s, 3 H, NCH$_3$), 3.31 (s, 3 H, OCH$_3$), 3.75 (br d, $J = 9.4$ Hz, 1 H, C$_{16}$H), 4.06 (d, $J = 10.4$ Hz, 1 H, CH$_2$OBn), 4.13 (br s, 1 H, CHN), 4.32 (d, $J = 10.4$ Hz, 1 H, CH$_2$OBn), 4.70 and 4.77 (ABq, $J = 11.9$ Hz, 2 H, OCH$_2$Ph), 5.06 (s, 2 H, NCH$_2$O), 5.86 (d, $J = 9.4$ Hz, 1 H, =CH), 6.94-7.00 (m, 2 H, ArH), 7.18-7.46 (m, 17 H, ArH); $^{13}$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 (l), 71.2 (l), 74.1 (l), 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 (relative intensity) 638 (M+, 48), 498 (83), 252 (100), 91 (92); exact mass calc. for C_{41}H_{38}N_{2}O_{5} m/z 638.2780, found m/z 638.2795. The structure of 212 was confirmed by X-ray crystallography.

Anal. calc. for C_{41}H_{38}N_{2}O_{5}: C, 77.08; H, 6.00. Found: C, 77.15; H, 6.08.

![Diagram of 213](image-url)

(±)-(1'\textsuperscript{R},3'\textsuperscript{R},3'a\textsuperscript{S},4'\textsuperscript{R},7'a\textsuperscript{S},8'\textsuperscript{R})-3'a-[(Benzyloxy)methyl]-8'-(2,2-diphenylvinyl)-3'a,7'a-dihydro-1-(methoxymethyl)-2'-methylspiro[indoline-3,7'\textsuperscript{(4'H)}]-[1,4]methanoisooindoline]-2,3',6'(5'H)-trione (213). Method A: To a solution of 90 mg (0.13 mmol) of 211 in 15 mL of dichloromethane was added 86 mg of p-toluenesulfonic acid monohydrate. The mixture was stirred for 48 h, and was then passed through a 6 g pad of silica gel (ethyl acetate-dichloromethane, 15:85). The eluent was concentrated and the residue was recrystallized from methanol. The solid was collected by filtration, and washed with ether to provide 84 mg (98%) of olefin 211 as a white solid: mp (methanol) 187-188 °C; IR (CCl\textsubscript{4}) 1733, 1715 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \textsuperscript{\delta} 2.35 (br s, 1 H), 2.69 (br s, 1 H), 2.72 (dd partially obscured, J = 3.65, 1 H), 2.99 (s, 3 H, NCH\textsubscript{3}), 3.00 (m, 2 H), 3.14 (s, 3 H, OCH\textsubscript{3}), 3.55 (br s, 1 H, CHN), 4.41 and 4.45 (ABq, J = 9.1 Hz, 2 H, CH\textsubscript{2}OBn), 4.66 and 4.74 (ABq, J = 12.1 Hz, 2 H, OCH\textsubscript{2}Ph), 4.93 and 5.02 (ABq, J = 11.0 Hz, 2 H, NCH\textsubscript{2}O), 5.78 (d, J = 7.4 Hz, 1 H, =CH or oxindole C\textsubscript{9}H), 5.96 (d, J = 8.7 Hz, 1 H, =CH or oxindole C\textsubscript{9}H), 6.83 (l, J = 7.5 Hz, 1 H, ArH), 6.97 (d, J = 7.8 Hz, 1 H, ArH), 7.22-7.59 (m, 16 H, ArH); \textsuperscript{13}C NMR (75.5 MHz, CDCl\textsubscript{3}) \textsuperscript{\delta} 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 (d), 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), 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\(_{2}\)O\(_{5}\) \( m/z \) 638.2780, found \( m/z \) 638.2774.

Method B: Via Isomerization of Oxindole 212. A mixture of 58 mg (0.09 mmol) of oxindole 212 and 1 mg of potassium cyanide in 5 mL of dimethylformamide 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 ethyl acetate. 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 213 and 212, respectively, by \( ^1\)H NMR. The mixture was recrystallized from methanol to afford 49 mg (84%) of pure oxindole 213 whose \( ^1\)H NMR spectrum was identical to material obtained via method A.

![Chemical Structure](image)

\( \text{214} \)

\((\pm)-1'\ R,3R,3'aS',4'R,7'aS',8'R')-8'(2,2'-Diphenylvinyl)-3'a,4',5',7'a\text{-tetrahydro-1,3'-bls(methoxymethyl)-2'-methylspiro[indoline-3,7'\(6'H\rbrack\text{[1,4]methanoisindoline}-2,3'-6'-trione (214). To a solution of 135 mg (0.22 mmol) of 209 in 15 mL of dichloromethane was added 70 mg of \( p\)-toluenesulfonic acid monohydrate. The mixture was warmed to reflux for 45 min, cooled and diluted with saturated aqueous sodium bicarbonate. The dichloromethane layer was separated and the aqueous phase was extracted with three 25-mL portions of dichloromethane. The combined dichloromethane layers were dried (K\(_2\)CO\(_3\)), filtered and concentrated to afford 126 mg (98%) of oxindole 214 as a white solid: mp 230-232 °C; IR (KBr)
1708 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.32 (br s, 1 H, C\(_{15}\)H), 2.60 (t, \(J = 1.9\) Hz, 1 H, C\(_6\)H), 2.70 (dd, \(J = 18.4, 3.7\) Hz, 1 H, C\(_{14}\)H), 2.96 (s, 3 H, NCH\(_3\)), 3.00 (m, 2 H, C\(_{16}\)H and C\(_{14}\)H), 3.24 (s, 3 H, OCH\(_3\)), 3.44 (s, 3 H, OCH\(_3\)), 3.51 (t, \(J = 1.9\) Hz, 1 H, C\(_6\)H), 4.23 (d, \(J = 9.0\) Hz, 1 H, CH\(_2\)OMe), 4.33 (d, \(J = 9.0\) Hz, 1 H, CH\(_2\)OMe), 4.97 (d, \(J = 11.0\) Hz, 1 H, NCH\(_2\)O), 5.05 (d, \(J = 11.0\) Hz, 1 H, NCH\(_2\)O), 5.75 (d, \(J = 7.4\) Hz, 1 H, oxindole C\(_9\)H or =CH), 5.93 (d, \(J = 8.8\) Hz, 1 H, =CH or oxindole C\(_9\)H), 6.81 (td, \(J = 7.6, 0.8\) Hz, 1 H, ArH), 6.96 (d, \(J = 7.6\) Hz, 1 H, oxindole ArH), 7.20-7.30 (m, 8 H, ArH), 7.45-7.58 (m, 3 H, ArH); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 30.6 (q), 39.9 (d), 42.6 (t), 49.5 (d), 54.7 (d), 55.8 (q), 58.1 (s), 58.9 (q), 63.6 (s), 65.8 (d), 67.6 (t), 71.1 (t), 109.9 (d), 123.1 (d), 123.9 (d), 126.2 (d), 126.4 (d), 127.4 (s), 127.8 (d), 128.3 (d), 129.0 (d), 129.1 (d), 139.4 (s), 139.8 (s), 142.4 (s), 144.7 (s), 174.1 (s), 174.7 (s), 204.5 (s), two aromatic doublets were not resolved; mass spectrum, \(m/z\) (relative intensity) 562 (M\(^+\), 29), 498 (65), 282 (55), 252 (100), 45 (93); exact mass calcd. for C\(_{35}\)H\(_{34}\)N\(_2\)O\(_5\) \(m/z\) 562.2469, found \(m/z\) 562.2454.

![MOM OCH.](image)

(\(\pm\)\)-(1'R\(^*\),3'S\(^*\),3'aR\(^*\),4'S\(^*\),7'aR\(^*\),8'S\(^*\))-3'a,5',6',7'a-Tetrahydro-1,3'a-bis(methoxymethyl)-2'-methyl-2,3',6'-trioxospiro[indoline-3,7' (4'H)-[1,4]methanolsoindoline]-8'-carboxaldehyde (215). To a mixture of 125 mg (0.22 mmol) of olefin 214 in 25 mL of dichloromethane-methanol (4:1) was added a few mg of Sudan III indicator.\(^\text{41}\) The resulting red solution was cooled to -78 °C, and then ozone gas was passed through the solution until the red color faded. To the mixture was added 2 mL of dimethylsulfide and stirring was continued at room temperature for 18 h. The mixture was then concentrated in vacuo and the residue was chromatographed over 4 g of silica gel (dichloromethane; then ethyl acetate-dichloromethane, 10:90, then 20:80, then 30:70, then 1:1) to afford 62 mg (67%) of
aldehyde 215 as a off white solid: mp 242-244 °C (dec); IR (KBr) 1728, 1708 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.74 (m, 1 H, partially obscured by singlet at δ 2.75), 2.75 (s, 3 H, NCH₃), 2.76 (dd, J = 3.9 Hz, second coupling constant was obscured by the singlet at δ 2.75, 1 H, C₁₄H), 2.97 (br m, 1 H), 3.08 (br s, 1 H), 3.17 (dd, J = 18.2, 2.4 Hz, 1 H, C₁₄H), 3.28 (s, 3 H, OCH₃), 3.43 (s, 3 H, OCH₃), 4.21 (dd, J = 2.8, 1.8 Hz, 1 H, C₅H), 4.26 (d, J = 9.0 Hz, 1 H, CH₂OMe), 4.39 (d, J = 9.0 Hz, 1 H, CH₂OMe), 5.01 (d, J = 11.1 Hz, 1 H, NCH₂O), 5.11 (d, J = 11.1 Hz, 1 H, NCH₂O), 7.06-7.18 (m, 3 H, ArH), 7.38 (td, J = 7.6, 1.4 Hz, 1 H, ArH), 9.77 (d, J = 1.0 Hz, 1 H, CHO); ¹³C NMR (75.5 MHz, CDCl₃) δ 30.2 (q), 33.4 (d), 43.0 (t), 55.6 (d), 56.0 (q), 58.3 (s), 59.0 (q), 61.6 (d), 63.3 (d), 63.9 (s), 67.4 (t), 71.4 (t), 110.5 (d), 123.5 (d), 124.1 (d), 127.2 (s), 129.9 (d), 142.6 (s), 173.5 (s), 174.1 (s), 198.5 (d), 204.0 (s); mass spectrum, m/z (relative intensity) 412 (M⁺, 66), 380 (24), 45 (100); exact mass calcd. for C₂₂H₂₄N₂O₆ m/z 412.1635, found m/z 412.1635.

2'-Bromo-2-hydroxy-1-cyclohexene-1-carboxanilide (218). To a suspension of 147 mg (3.67 mmol) of potassium hydride in 5 mL of dimethoxymethane warmed to 70 °C was added a solution of 300 mg (3.06 mmol) of cyclohexanone (217) in 5 mL of dimethoxyethane over a 30-min period. The mixture was stirred for 30 min, cooled to 0 °C and then a solution of 610 mg (3.08 mmol) of 2-bromophenylisocyanate in 5 mL of dimethoxyethane was added over a 5-min period. The mixture was stirred at room temperature for 18 h, and was then cautiously quenched with methanol and stirred for 5 min. The resulting residue was partitioned between 30 mL of ether-hexane (1:1) and 15 mL of 2N aqueous sodium hydroxide. The basic aqueous layers was separated and the organic phase was extracted with four 10-mL portions of 2N aqueous sodium hydroxide. The combined basic aqueous layers were washed with three 20-mL portions of ether-hexane (1:1), neutralized with ammonium chloride and extracted with three 30-mL portions of
ethyl acetate. The combined ethyl acetate layers were washed with three 20-mL portions of saturated aqueous sodium bicarbonate, two 20-mL portions of brine, dried (MgSO₄), filtered and concentrated in vacuo to provide 526 mg (58%) of 218 as a mixture of keto and enol tautomers. The following data was obtained from a sample that was recrystallized from ethyl acetate-hexane: mp 100-101 °C, IR (KBr) 3393, 1634 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) indicated a 1:1 mixture of enol and keto tautomers and was not interpreted due to its complexity, however it does appear in Appendix A; ¹³C NMR (mixture of enol and keto tautomers, 75.5 MHz, CDCl₃) δ 21.6 (t), 22.4 (t), 22.6 (t), 24.3 (t), 27.2 (t), 29.4 (t), 31.7 (t), 42.1 (t), 56.0 (d), 97.5 (s), 113.8 (s), 113.9 (s), 121.9 (d), 122.4 (d), 124.9 (d), 125.1 (d), 127.9 (d), 128.2 (d), 132.0 (d), 132.3 (d), 135.3 (s), 135.8 (s), 167.1 (s), 170.6 (s), 172.6 (s), 210.3 (s); mass spectrum, m/z (relative intensity) 297 (M⁺, 16), 295 (M⁺, 17), 216 (28), 172 (94), 170 (100), 125 (19); exact mass calcd. for C₁₃H₁₄BrNO₂ m/z 297.0188 and 295.0208, found m/z 297.0189 and 295.0199.

2'-Bromo-2-(methoxymethoxy)-1-cyclohexene-1-carboxanilide (219). To a mixture of 225 mg (0.76 mmol) of 218 in 2 mL of dimethylsulfoxide was added 383 mg (3.79 mmol) of triethylamine followed by 297 mg (3.80 mmol) of chloromethyl methyl ether. The mixture was stirred for 45 min, diluted with 20 mL of saturated aqueous sodium bicarbonate and extracted with three 15-mL portions of ethyl acetate. The combined organic layers were washed with four 10-mL portions of brine, dried (MgSO₄), filtered and concentrated. The residue was chromatographed over 9 g of silica gel (ethyl acetate-hexane, 5:95) to afford 185 mg (72%) of 219 as an oil which partially solidified to a sticky solid under house vacuum: IR (neat) 3316 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.60-1.77 (m, 4 H), 2.47 (m, 4 H), 3.47 (s, 3 H, OCH₃), 5.22 (s, 2 H, OCH₂Me), 6.91 (ddd, J = 9.0, 7.4, 1.6 Hz, 1 H, ArH), 7.28 (td, J = 8.4, 1.1 Hz, 1 H, ArH), 7.52 (dd,
\[ J = 7.9, 1.5 \text{ Hz}, 1 \text{ H, ArH}, 8.62 \text{ (dd, } J = 8.4, 1.5 \text{ Hz}, 1 \text{ H, ArH}, 10.26 \text{ (br, 1 H, NH)}; \]

\[ ^{13}\text{C NMR (75.5 MHz, CDCl}_3 \text{) } \delta 21.9 \text{ (t), 22.4 (t), 24.7 (t), 25.5 (t), 56.9 (q), 92.3 (t), 112.5 (s), 112.71 (s), 121.6 (d), 123.9 (d), 128.1 (d), 132.0 (d), 137.4 (s), 157.1 (s), 165.2 (s); mass spectrum, } m/z \text{ (relative intensity) 341 (M}^+, 15), 339 (M}^+, 14), 228 (100), 45 (32); \text{ exact mass calcd. for } C_{15}H_{18}BrNO_3 m/z 341.0450 \text{ and 339.0470, found } m/z 341.0437 \text{ and 339.0482.} \]

(220). To a mixture of 60 mg (0.17 mmol) of 219 in 2 mL of dimethylsulfoxide was added 60 mg (1.5 mmol) of 60% sodium hydride in mineral oil. The mixture was stirred for 10 min and then 106 mg (1.35 mmol) of chloromethyl methyl ether was added. The mixture was stirred for 6 h, diluted with 25 mL of saturated aqueous ammonium chloride and extracted with three 15-mL portions of ethyl acetate. The combined organic layers were washed with three 25-mL portions of brine, dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The residue was chromatographed over 800 mg of silica gel (ethyl acetate-hexane, 5:95, then 10:90, then 25:75) to provide 51 mg (76%) of 220 as an oil: IR (neat) 2936, 1661 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.15-1.23 (m, 2 H), 1.33-1.39 (m, 1 H), 1.49-1.55 (m, 1 H), 1.65-2.31 (m, 4 H), 3.43 (s, 3 H, OCH$_3$), 3.46 (s, 3 H, OCH$_3$), 4.53 (d, $J = 10.4$ Hz, 1 H, OCH$_2$O), 4.80 (d, $J = 6.6$ Hz, 1 H, NCH$_2$O), 4.90 (d, $J = 6.6$ Hz, 1 H, NCH$_2$O), 5.69 (d, $J = 10.4$ Hz, 1 H, OCH$_2$O), 7.16 (td, $J = 7.7$, 1.8 Hz, 1 H, ArH), 7.26 (td, $J = 7.7$, 1.6 Hz, 1 H, ArH), 7.45 (dd, $J = 7.8$, 1.7 Hz, 1 H, ArH), 7.58 (dd, $J = 7.8$, 1.5 Hz, 1 H, ArH), minor impurities may be attributed to geometrical isomerization; $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 21.4 (t), 22.1 (t), 24.5 (t), 25.1 (t), 56.2 (q), 56.5 (q), 77.03 (t), 93.2 (t), 115.5 (s), 122.5 (s), 127.2 (d), 129.3 (d), 131.7 (d), 132.8 (d), 139.7 (s), 148.7 (s), 171.8 (s); mass spectrum, $m/z$ (relative intensity) 386 (M$^+$, 0.06), 384 (M$^+$, 0.07), 228 (55), 185 (44), 183 (46), 45 (100); exact mass
calcd. for C\textsubscript{17}H\textsubscript{22}BrNO\textsubscript{4}+H m/z 386.0790 and 384.0810, found m/z 386.0766 and 384.0772.

\[(\pm)-(1R^*,2R^*)-2-(\text{Methoxymethoxy})-1'-\text{(methoxymethyl)}\text{spiro[}\text{cyclohexane-1,3'-indolin]}-2'-\text{one}\ (221) \text{ and } (\pm)-(1R^*,2S^*)-2-(\text{Methoxymethoxy})-1'-\text{(methoxymethyl)}\text{spiro[}\text{cyclohexane-1,3'-indolin]}-2'-\text{one}\ (222).\]

To a solution of 26 mg (0.068 mmol) of 220 in 2 mL of benzene warmed at reflux was added a solution of 38 mg (0.133 mmol) of tri-n-butyltin hydride and 2 mg of AIBN in 2 mL of benzene over a 14-h period via a syringe pump. The mixture was concentrated in vacuo, and then diluted with 15 mL of hexane and 5 mL of acetonitrile. The acetonitrile layer was separated and the hexane layer was extracted with two 5-mL portions of acetonitrile. The acetonitrile layer was washed with 2 mL of hexane and concentrated in vacuo. The residue was diluted with ethyl acetate-hexane (2:98), a drop of DBU was added, and the solution was chromatographed over 2 g of silica gel (ethyl acetate-hexane, 2:98, then 4:96, then 6:94) to afford 9 mg (44%) of oxindole 221 as a clear oil: IR (neat) 1716 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \delta 1.43 (m, 1 H), 1.55 (m, 1 H), 1.80 (m, 2 H), 1.95 (m, 2 H), 2.15 (m, 1 H), 2.32 (m, 1 H), 2.73 (s, 3 H, CH\textsubscript{3}), 3.30 (s, 3 H, CH\textsubscript{3}), 3.89 (dd, J = 11.7, 4.5 Hz, 1 H, CHOMOM), 4.10 (d, J = 7.1 Hz, 1 H, NCH\textsubscript{2}O), 4.44 (d, J = 7.1 Hz, 1 H, NCH\textsubscript{2}O), 5.09 (d, J = 10.9 Hz, 1 H, OCH\textsubscript{2}O), 5.18 (d, J = 10.9 Hz, 1 H, OCH\textsubscript{2}O), 6.97 (dd, J = 7.3, 2.0 Hz, 1 H, ArH), 7.08 (td, J = 7.5, 1.0 Hz, 1 H, ArH), 7.23 (m, 2 H, ArH); \textsuperscript{13}C NMR (75.5 MHz, CDCl\textsubscript{3}) \delta 19.8 (t), 24.3 (t), 26.4 (t), 34.3 (t), 52.0 (s), 54.7 (q), 55.6 (q), 70.6 (t), 79.0 (d), 94.2 (t), 108.7 (d), 121.9 (d), 122.5 (d), 127.6 (d), 133.1 (s), 141.9 (s), 178.4 (s); mass spectrum, m/z (relative intensity) 305 (M\textsuperscript{+}, 12), 229 (100), 201 (34), 158 (31), 45 (5); exact mass calcd. for C\textsubscript{17}H\textsubscript{23}NO\textsubscript{4} m/z 305.1627, found m/z 305.1632.
Continued elution afforded 9.7 mg (47%) of oxindole 222 as clear oil: \( \text{IR (neat) } 1722 \text{ cm}^{-1}; \text{H NMR (300 MHz, CDCl}_3 \text{) } \delta 1.56-2.02 \text{ (m, 7 H), 2.16 \text{ (m, 1 H), 3.17 \text{ (s, 3 H, CH}_3\text{), 3.29 \text{ (s, 3 H, CH}_3\text{), 4.06 \text{ (dd, } J = 11.5, 4.7 \text{ Hz, 1 H, CH}_3\text{O MOM), 4.45 \text{ (d, } J = 6.8 \text{ Hz, 1 H, NCH}_2\text{O), 4.51 \text{ (d, } J = 6.8 \text{ Hz, 1 H, NCH}_2\text{O), 5.13 and 5.18 \text{ (ABq, } J = 10.9 \text{ Hz, 2 H, OCH}_2\text{O), 7.09 \text{ (m, 2 H, ArH), 7.31 \text{ (td, } J = 7.7, 1.2 \text{ Hz, 1 H, ArH), 7.59 \text{ (d, } J = 7.5 \text{ Hz, 1 H, ArH); }^{13}\text{C NMR (75.5 MHz, CDCl}_3 \text{) } \delta 20.2 \text{ (t), 23.7 \text{ (t), 27.4 \text{ (t), 33.7 \text{ (t), 53.9 \text{ (s), 55.2 \text{ (q), 55.7 \text{ (q), 71.1 \text{ (t), 78.5 \text{ (d), 95.1 \text{ (t), 109.3 \text{ (d), 122.2 \text{ (d), 125.4 \text{ (d), 127.7 \text{ (d), 130.8 \text{ (s), 142.0 \text{ (s), 180.0 \text{ (s); mass spectrum, } m/z \text{ (relative intensity) 305 (M}^+\text{, 8), 229 (100), 201 (45), 158 (43), 45 (23); exact mass calcd. for C}_{17}\text{H}_{23}\text{N}_4\text{O}_4 \text{ m/z } 305.1627, found } m/z 305.1627.}

(\pm)-1'-\text{(Methoxymethyl)spiro[cyclohexane-1,3'-indoline]-2,2'-dione (223). To a solution of 120 mg (0.312 mmol) of 220 in 5 mL of xylene warmed at reflux was added a solution of 121 mg (0.487 mmol) of tristrimethylsilylsilane and 6 mg of AIBN in 5 mL of xylene over a 20-h period via a syringe pump. The mixture was then concentrated in vacuo, and partitioned between 5 mL of hexane and 5 mL of acetonitrile. The acetonitrile layer was separated and the hexane layer was extracted with 5 mL of acetonitrile. The combined acetonitrile layers were concentrated in vacuo, and the residue was chromatographed over 4 g of silica gel (ethyl acetate-hexane, 2:98, then 4:96, then 5:95, then 20:80) to afford 14 mg (5%) of 221 followed by 18 mg (22%) of ketone 223 as a clear oil: IR (neat) 1737, 1704 \text{ cm}^{-1}; \text{H NMR (300 MHz, CDCl}_3 \text{) } \delta 1.5-2.21 \text{ (m, 4H), 2.25-2.40 \text{ (m, 2 H), 2.57-2.66 \text{ (m, 1 H), 2.95-3.03 \text{ (m, 1 H), 3.31 \text{ (s, 3 H, OCH}_3\text{), 5.11 \text{ (s, 2 H, NCH}_2\text{O), 7.03 \text{ (dd, } J = 7.8, 0.4 \text{ Hz, 1 H, ArH), 7.12 \text{ (td, } J = 7.5, 1.0 \text{ Hz, 1 H, ArH), 7.25-7.36 \text{ (m, 2 H, ArH); }^{13}\text{C NMR (75.5 MHz, CDCl}_3 \text{) } \delta 20.2 \text{ (t), 26.5 \text{ (t), 37.1 \text{ (t), 39.4 \text{ (t), 56.0 \text{ (q), 63.7 \text{ (s), 71.3 \text{ (t), 109.7 \text{ (d), 123.0 \text{ (d), 124.4 \text{ (d), 128.6 \text{ (d), 128.9 \text{ (s), 141.4 \text{ (s), 174.9 \text{ (s),}}}

\begin{center}
\includegraphics[width=0.5\textwidth]{223.png}
\end{center}
204.5 (s); mass spectrum, $m/z$ (relative intensity) 259 (M+, 36), 228 (14), 199 (28), 171 (100), 130 (30), 45 (94); exact mass calcd. for C$_{15}$H$_{17}$NO$_3$ 259.1209, found $m/z$ 259.1233. Continued elution afforded 29 mg (36%) of 222.

![Chemical Structure of 224](image)

$(\pm$)-(1$R^*$,3$'aS^*$,4$R^*$,7$aS^*$,8$R^*$)-3a-[(Benzylxoy)methyl]-2'-bromo-3a,4,5,7a-tetrahydro-6-hydroxy-8-(2-methoxy-2,2-diphenylethyl)-2-methyl-3-oxo-1,4-methanoisindoline-7-carboxanilide acetate (ester) (224). To a solution of 250 mg (0.35 mmol) of 201 in 25 mL of dichloromethane was added 228 mg (1.76 mmol) of diisopropylethylamine followed by 54 mg (0.52 mmol) of acetic anhydride. The mixture was stirred for 1 h, and then an additional 684 mg (5.30 mmol) of diisopropylethylamine and 306 mg (3.00 mmol) of acetic anhydride was added. The mixture was stirred for 2 h, and was then diluted with 50 mL of brine and the dichloromethane layer was separated. The aqueous phase was extracted with two 20-mL portions of dichloromethane and the combined organic layers were washed with three 50-mL portions of brine, dried (MgSO$_4$), filtered and concentrated in vacuo. The residue was triturated with ether-hexane and the solid was collected by filtration and washed with cold hexane to afford 264 mg (100%) of 224 as a white solid: mp 99-105 °C; IR (neat) 3387, 1775, 1698 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.42-1.55 (m, 2 H), 1.79 (dd, $J = 18.5$, 2.5 Hz, 1 H), 2.23 (s, 3 H, CH$_3$CO$_2$), 2.26-2.38 (m, 2 H), 2.55 (dd, $J = 13.7$, 2.4 Hz, 1 H), 3.02 (s, 3 H, NCH$_3$ or OCH$_3$), 3.07 (s, 3 H, NCH$_3$ or OCH$_3$), 3.23 (t, $J = 1.9$ Hz, 1 H), 3.51 (d, $J = 9.9$ Hz, 1 H, CH$_2$OBn), 3.65 (t, $J = 2.3$ Hz, 1 H), 3.77 (d, $J = 9.9$ Hz, 1 H, CH$_2$OBn), 4.52 and 4.59 (ABq, $J = 12.5$ Hz, 2 H, OCH$_2$Ph), 6.98 (td,
$J = 7.7, 1.5 \text{ Hz}, 1 \text{ H, ArH}$, 7.14-7.34 (m, 16 H, ArH), 7.54 (dd, $J = 8.0, 1.4 \text{ Hz}, 1 \text{ H, ArH}$), 8.38 (s, 1 H, NH), 8.42 (dd, $J = 8.3, 1.4 \text{ Hz}, 1 \text{ H, ArH}$); $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 21.3 (q), 31.4 (q), 33.6 (t), 37.3 (t), 39.9 (d), 44.0 (d), 50.0 (d), 50.5 (q), 54.7 (s), 64.6 (t), 70.9 (d), 73.4 (t), 82.0 (s), 112.2 (s), 120.2 (s), 121.7 (d), 125.1 (d), 126.8 (d), 127.0 (d), 127.1 (d), 127.3 (d), 127.8 (d), 128.05 (d), 128.08 (d), 128.3 (d), 132.2 (d), 135.7 (s), 138.4 (s), 144.46 (s), 144.52 (s), 152.2 (s), 162.7 (s), 167.4 (s), 174.9 (s), two aromatic doublets were not resolved; mass spectrum, $m/z$ (relative intensity) 403 (33), 388 (25), 197 (100), 173 (78), 171 (74), 134 (63), 105 (20), 91 (46), 43 (29). No parent ion was observed.

(±)-(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-methanoloisoindoline-7-carboxanilide acetate (ester) (225). From 201. To a solution of 2.6 g (3.67 mmol) of β-ketoanilide 201, 3.7 g (36.6 mmol) of triethylamine and 20 mg of 4-dimethylaminopyridine cooled to 5 °C was added a solution of 1.9 g (18.6 mmol) of acetic anhydride in 5 mL of dimethylformamide over a 2-min period. The mixture was stirred at room temperature for 30 min, and was 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 by filtration and washed with water. The solid was dried by pulling house vacuum through the filter cake to afford 2.8 g (98%) of 225 which was used without further purification: IR (film) 1760, 1698 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): The $^1$H NMR spectrum was complex due to the presence of
geometrical isomers. Proton NMR spectra at 303 °K and 363 °K appear in Appendix A; 13C NMR
(75.5 MHz, DMSO-d6, 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), 127.6 (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 to course of acquiring 1H and 13C
NMR data above 363 °K minor peaks began to appear in the spectra due to decomposition; mass
spectra, m/z (relative intensity) 535 (10), 533 (10), 197 (30) 91 (100). No parent ion was
observed.

\[ \begin{align*}
\text{OBn} & \quad \text{Ac} - \text{N} \\
\text{--} & \\
\text{NMe} & \quad \text{AcO} \\
\text{Ph} & \quad \text{Ph} \\
\text{OBn} & \quad \text{Ac} - \text{N}, \quad \text{AcO}, \quad \text{NMe} \\
\text{Ph} & \quad \text{Ph} \\
\text{OMe} & \quad \text{OMe} \\
\end{align*} \]

(±)-(1'\text{R'},3'S',3'aS',4'R',6'R',7'aS',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) (226) and (±)-(1'\text{R'},3'S',3'aS',4'R',6'S',7'aS',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) (227) and (±)-(1'\text{R'},3'R',3'aS',4'R',6'R',7'aS',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) (228). A solution of 1.5 g (1.89 mmol) of
bromide 225, 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 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 228. The crude residue was chromatographed over 60 g of silica gel (dichloromethane to load the sample; then ethyl acetate-dichloromethane, 5:95) to afforded, in the following order, partially purified oxindoles 226, 227, 228.

**Purification of oxindole 228:** All of the fractions containing oxindole 228 were combined and recrystallized from ether-hexane to afford 516 mg (38%) of pure oxindole 228 as a white solid: mp 132-135 °C; IR (film) 1759, 1738, 1711 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.68 (s, 3 H, CH$_3$CO$_2$), 1.74 (br s, 1 H, C$_{15}$H), 1.94 (br d, $J$ = 15.1 Hz, 1 H), 2.26 (br s, 1 H, C$_6$H)), 2.56 (m, 4 H), 2.45 (s, 3 H, NCOCH$_3$), 2.92 (br s, 1 H, CHN), 2.96 (s, 3 H, NCH$_3$), 3.07 (s, 3 H, OCH$_3$), 3.90 (d, $J$ = 9.2 Hz, 1 H, CH$_2$OBn), 4.06 (d, $J$ = 9.2 Hz, 1 H, CH$_2$OBn), 4.59 (d, $J$ = 12.3 Hz, 1 H, OCH$_2$Ph), 4.67 (d, $J$ = 12.3 Hz, 1 H, OCH$_2$Ph), 5.29 (d, $J$ = 7.9 Hz, 1 H, C$_3$H), 6.39 (d, $J$ = 7.5 Hz, 1 H, oxindole C$_9$H), 6.92 (t, $J$ = 7.3 Hz, 1 H, oxindole ArH), 7.20-7.47 (m, 16 H, ArH), 8.18 (d, $J$ = 7.9 Hz, 1 H, oxindole C$_{12}$H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 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 (relative intensity) 712 (M$^+$, 0.4), 589 (4), 531 (8), 197 (78), 91 (100), 43 (57); exact mass calcd. for C$_{44}$H$_{44}$N$_2$O$_7$ m/z 712.3148, found m/z 712.3115.

**Purification of oxindole 227:** The filtrate from the recrystallization of oxindole 228 was combined with mixed fractions from the first column and chromatographed over 30 g of silica gel (dichloromethane to load the sample; then ethyl acetate-hexane, 20:80, then 30:70). Fractions containing oxindole 228 were recrystallized from ether-hexane to afford and additional 63 mg (4%) of pure oxindole 228. The filtrate from oxindole 228 was enriched with oxindole 227. This
material was combined with fractions containing oxindole 227 and twice recrystallized from ether-hexane to afford 99 mg (7%) of oxindole 227 as a white solid: mp 211-213 °C; IR (KBr) 1754, 1710 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, assignments based on decoupling experiments) δ 1.28 (br s, 1 H, C₁₅H), 1.45 (s, 3 H, CH₃CO₂), 1.70 (br dd, 2 H, C₁₄α and C₁₄β), 2.18 (dd, J = 14.2, 8.2 Hz, 1 H, CH₂C(Ph)₂OMe), 2.28 (t, J = 1.6 Hz, 1 H, C₆H), 2.58 (dd, J = 14.2, 2.3 Hz, 1 H, CH₂C(Ph)₂OMe), 2.72 (s, 3 H, NCOCH₃), 2.84 (br, 1 H, C₁₆H), 2.99 (s, 3 H, NCH₃), 3.14 (s, 3 H, OCH₃), 3.66 (dd, J = 2.74, 1.8 Hz, 1 H, C₃H), 3.86 (d, J = 9.8 Hz, 1 H, CH₂OBn), 4.02 (d, J = 9.8 Hz, 1 H, CH₂OBn), 4.44 (s, 2 H, OCH₂Ph), 5.14 (t, J = 8.4 Hz, 1 H, C₃H), 6.98-7.41 (m, 18 H, ArH), 8.16 (dd, J = 8.2, 0.6 Hz, 1 H, ArH); ¹³C NMR (75.5 MHz, CDCl₃) 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), 65.8 (t), 69.7 (d), 73.1 (t), 81.7 (s), 116.1 (d), 123.3 (d), 126.6 (d), 126.77 (d), 126.8 (d), 127.08 (d), 127.10 (d), 127.16 (d), 127.3 (d), 127.7 (d), 127.8 (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 (relative intensity) 712 (M⁺, 0.6), 574 (10), 197 (100), 91 (89); exact mass calcd. for C₄₄H₄₄N₂O₇ m/z 712.3148, found m/z 712.3131.

Purification of oxindole 227: All of the remaining fractions and filtrates containing oxindole 227 were combined and chromatographed over 70 g of silica gel (dichloromethane to load the sample; then ethyl acetate-hexane, 20:80, then 25:75) to afford 127 mg (9%) of pure oxindole 227 as a white powder when concentrated from ether-hexane: mp 104-113 °C; IR (neat) 1748, 1707 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.21 (br d, J = 5.6 Hz, 1 H, C₁₅H), 1.56 (dd, J = 14.4, 7.4 Hz, 1 H), 1.83 (s, 3 H, CH₃CO₂), 2.13 (m, 1 H), 2.21 (dd, J = 14.1, 8.5 Hz, 1 H), 2.48 (t, J = 1.7 Hz, 1 H, C₆H), 2.59 (dd, J = 14.3, 2.5 Hz, 1 H), 2.67 (s, 3 H, NCOCH₃), 2.99 (s, 3 H, NCH₃), 3.16 (s, 3 H, OCH₃), 3.37 (dd, J = 2.7, 1.8 Hz, 1 H, CHN), 3.60 (br d, J = 8.4 Hz, 1 H, C₁₆H), 3.82 (d, J = 10.5 Hz, 1 H, CH₂OBn), 4.13 (d, J = 10.5 Hz, 1 H, CH₂OBn), 4.65 and 4.72 (ABq, J = 11.8 Hz, 2 H, OCH₂Ph), 5.28 (dd, J = 9.2, 7.5 Hz, 1 H, C₃H), 6.98 (td, J = 7.6, 1.0 Hz, 1 H, oxindole ArH), 7.15-7.40 (m, 16 H, ArH), 7.50 (dd, J = 7.7, 0.8 Hz, 1 H, oxindole ArH), 8.09 (dd, J = 8.1, 0.6 Hz, 1 H, oxindole ArH); ¹³C NMR (75.5 MHz, CDCl₃) 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), 56.7 (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 (relative intensity) 712 (M⁺, 1), 515 (13), 197 (85), 91 (100), 43 (31); exact mass calcd. for C₄₄H₄₄N₂O₇ m/z 712.3148, found m/z 712.3167.

(±)-(1'R,3'S,3'aR,4'R,6'R,7'aS,8'R)-1-Acetyl-3'a-[(benzyloxy)methyl]-8'-[2,2-diphenylyvinyl]-3'a,5',6',7'a-tetrahydro-6'-hydroxy-2'-methylspiro[indoline-3,7'(4'H)-[1,4]methanoisolinodoline]-2,3'-dione acetate (ester) (229). To a solution of 87 mg (0.12 mmol) of oxindole 226 in 25 mL of dichloromethane was added 55 mg of p-toluenesulfonic acid monohydrate. The mixture was warmed to reflux for 5 min, and then cooled and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (dichloromethane to load the sample; then ethyl acetate-hexane, 5:95) to afford 37 mg (44%) of olefin 229 as a white solid: mp 94-105 °C; IR (film) 1748, 1712 cm⁻¹; 1H (300 MHz, CDCl₃) δ 1.69 (m, 1 H, C₁₄aH), 1.70 (s, 3 H, CH₃CO₂), 2.00 (br d, J = 5.9 Hz, 1 H, C₁₅H), 2.54 (s, 3 H, NCOCH₃), 2.58 (t, J = 1.8 Hz, 1 H, C₆H), 2.58 (m, 1 H, C₁₄aH), 2.92 (s, 3 H, NCH₃), 3.48 (dd, J = 3.1, 1.8 Hz, 1 H, C₅H), 4.01 (d, J = 10.5 Hz, 1 H, CH₂OBn), 4.16 (ddd, J = 9.2, 3.0, 1.7 Hz, 1 H, C₁₆H), 4.35 (d, J = 10.5 Hz, 1 H, CH₂OBn), 4.72 and 4.78 (ABq, J = 11.8 Hz, 2 H, OCH₂Ph), 5.38 (dd, J = 9.1, 7.8 Hz, 1 H, C₃H), 5.73 (d, J = 9.3 Hz, 1 H, -CH), 6.99 (td, J = 7.6, 1.0 Hz, 1 H, oxindole H₁₀), 7.19-7.47 (m, 16 H, ArH), 7.54 (dd, J = 7.7, 1.0 Hz, 1 H, oxindole H₉), 8.07 (dd, J = 8.2, 0.7 Hz, 1 H, oxindole H₁₂); 13C NMR (75.5 MHz, CDCl₃) δ 20.5 (q), 26.6 (q), 30.9 (q), 32.7 (t), 40.1 (d), 50.3 (d), 53.5 (s),
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56.2 (d), 59.1 (s), 65.5 (d), 67.8 (l), 71.4 (d), 74.0 (t), 115.3 (d), 124.0 (d), 125.7 (d), 126.9 (d), 127.1 (d), 127.2 (d), 127.3 (d), 127.5 (d), 127.8 (d), 128.1 (d), 128.2 (d), 128.3 (d), 128.5 (d), 129.7 (d), 133.2 (s), 138.2 (s), 139.7 (s), 141.3 (s), 143.9 (s), 169.5 (s), 170.5 (s), 174.5 (s), 174.7 (s); mass spectrum, m/z (relative intensity) 680 (M+, 18), 193 (16), 91 (100), 43 (33); exact mass calcd. for C₄₃H₄⁰N₂O₆ m/z 680.2886, found m/z 680.2881.

(±)-(1'R,3'S,3'aR*,4'R*,6'S*,7'aS*,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]methanoiso!ndoline]-2,3'-dione acetate (ester) (230). To a solution of 69 mg (0.09 mmol) of oxindole 227 in 20 mL of dichloromethane was added 42 mg of p-toluenesulfonic acid monohydrate. The mixture was warmed to reflux for 5 min, and then cooled and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (dichloromethane to load the sample; then ethyl acetate-hexane, 2:98) to afford 26 mg (40%) of olefin 230 as a clear oil: IR (neat) 1756, 1711 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.43 (s, 3 H, CH₃CO₂), 2.00 (br s, 1 H, C₁₅H), 2.08 (dd, J = 11.8, 1.5 Hz, 1 H, C₁₄aH), 2.24 (ddd, J = 13.8, 8.5, 4.5 Hz, 1 H, C₁₄bH), 2.40 (br s, 1 H, C₆H), 2.71 (s, 3 H, NCOCH₃), 3.02 (br s, 1 H, NCH₃), 3.50 (br d, J = 9.6 Hz, 1 H, C₁₆H), 3.73 (dd, J = 2.8, 1.9 Hz, 1 H, C₅H), 4.02 (d, J = 9.8 Hz, 1 H, CH₂OBn), 4.22 (d, J = 9.8 Hz, 1 H, CH₂OBn), 4.50 and 4.55 (ABq, J = 12.1 Hz, 2 H, OCH₂Ph), 4.87 (t, J = 9.6 Hz, 1 H, C₃H), 5.68 (d, J = 9.4 Hz, 1 H, CH₂OBn), 6.04 (td, J = 7.6, 0.8 Hz, 1 H, ArH), 7.04-7.12 (m, 2 H, ArH), 7.15-7.50 (m, 15 H, ArH), 8.18 (d, J = 8.2 Hz, 1 H, ArH); ¹³C NMR (75.5 MHz, CDCl₃) δ 19.8 (q), 26.6 (q), 29.8 (l), 30.8 (q), 40.3 (d), 45.7 (d), 54.0 (s), 56.7 (d), 57.1 (s), 65.64 (d), 65.69 (l), 69.4 (d), 73.2
(±)-(1'R,3'R,3'aS*,4'R,6'R,7'aS*,8'R*)-1-Acetyl-3'a-[(benzyloxymethyl)-8'-(2,2-diphenylvinyl)-3'a,5',6',7'a-tetrahydro-6'-hydroxy-2'-methylspiro[indoline-3,7'-(4'H)-[1,4]methanolsolindoline]-2,3'-dione acetate (ester) (231). To a solution of 68 mg (0.09 mmol) of oxindole 228 in 20 mL of dichloromethane was added 20 mg of p-toluenesulfonic acid monohydrate. The mixture was warmed to reflux for 20 min, and then cooled and concentrated in vacuo. The residue was chromatographed over 7 g of silica gel (dichloromethane to load the sample; then ethyl acetate-hexane, 25:75). The material from the column was recrystallized from ethyl acetate-hexane to afford 54 mg (83%) of olefin 231 as a crystalline solid: mp 234-235 °C, IR (film) 1755, 1711 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, assignments based on nOe’s) δ 1.51 (s, 3 H, CH₃CO₂), 2.03 (m, 1 H, C₁₄H), 2.31 (br s, 1 H, C₆H), 2.45 (s, 3 H, NCOCH₃), 2.57 (m, 1 H, C₁₄aH), 2.90 (s, 3 H, NCH₃), 3.15 (dd, J = 2.6, 1.8 Hz, 1 H, C₅H), 3.36 (br dd, J = 9.2, 2.5 Hz, 1 H, C₁₆H), 4.04 (d, J = 9.1 Hz, 1 H, CH₂OBn), 4.14 (d, J = 9.1 Hz, 1 H, CH₂OBn), 4.60 (d, J = 12.2 Hz, 1 H, OCH₂Ph), 4.68 (d, J = 12.2 Hz, 1 H, OCH₂Ph), 5.29 (d, J = 7.9 Hz, 1 H, C₃H), 5.86 (d, J = 9.3 Hz, 1 H, =CH), 6.16 (dd, J = 7.6, 0.7 Hz, 1 H, oxindole H₉), 6.91 (td, J = 7.6, 1.0 Hz, 1 H, oxindole H₁₀), 7.18-7.40 (m, 13 H, ArH), 7.48-7.62 (m, 3 H, ArH), 8.18 (dd, J = 8.2, 0.7 Hz, 1 H, oxindole H₁₂); ¹³C NMR (75.5
MHz, CDCl₃) 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), 127.36 (d), 127.40 (d), 127.6 (d), 128.0 (d), 128.2 (d), 128.6 (d), 128.8 (d), 129.6 (d), 130.5 (s), 130.6 (q), 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 (relative intensity) 680 (M+, 57), 193 (79), 167 (24), 91 (100), 43 (19); exact mass calcd. for C₄₃H₄₀N₂O₆ m/z 680.2886, found m/z 680.2887.

Anal. calcd. for C₄₃H₄₀N₂O₆: C, 75.85; H, 5.93. Found: C, 75.76; H, 5.95.

(±)-(1'R*,3'R*,3'aS*,4'R*,6'R*,7'aS*,8'R*)-3'a-[(Benzyloxy)methyl]-8'-{(2,2-diphenylvinyl)-3'a,5',6',7'a-tetrahydro-6'-hydroxy-2'-methyl]spiro[indoline-3,7'(4'H)-[1,4]methanoisoindoline]-2,3'-dione acetate (ester) (232). To a solution of 216 mg (0.303 mmol) of oxindole 228 in 30 mL of dichloromethane was added 102 mg of p-toluenesulfonic acid. The reaction was monitored by thin-layer chromatography (ethyl acetate-hexane, 1:1) and once starting material was no longer present, 1 mL of methanol was added to facilitate cleavage of the N-acetyl group. The mixture was stirred for an additional 24 h and was then diluted with 50 mL of saturated aqueous sodium bicarbonate. The dichloromethane layer was separated and washed with 50 mL of saturated aqueous sodium bicarbonate, 25 mL of brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was recrystallized from ethyl acetate-hexane to afford 180 mg (93%) of olefin 232 as a white solid: mp 210-211 °C; IR (KBr) 1729, 1617 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.47 (s, 3 H, CH₃CO₂), 1.98 (dd, J = 15.0, 2.6 Hz, 1 H, C₁₄H), 2.10 (br, 1 H, C₁₅H), 2.24 (br, 1 H, C₆H), 2.52 (ddd, J = 15.6, 8.8, 2.7 Hz, 1 H, C₁₄H), 2.90 (s, 3 H, NCH₃), 3.24 (dd, J = 2.8, 1.8 Hz, 1 H, CHN) 3.38 (ddd, J = 9.2, 2.4, 2.4 Hz, 1 H, C₁₅H), 4.09 (d, J = 8.9 Hz, 1
(±)-(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'-methylspirol[indoline-3,7'(4'H)-[1,4]methanoloisindoline]-2,3'-dione acetate (ester) (233) 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'-dioxospirol[indoline-3,7'(4'H)methanoloisindoline]-8'-carboxaldehyde acetate (ester) (234). To a solution of 400 mg (0.626 mmol) of olefin 232 in 15 mL of dichloromethane-methanol (4:1) chilled to -78 °C was added 60 mL of a 0.094 M solution of ozone gas, prepared by passing ozone gas through 75 mL of dichloromethane-methanol (4:1) at a rate of 1.1 mmol/min. The addition of ozone was monitored by thin-layer chromatography (ethyl acetate-hexane, 1:1) and was 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, the mixture was stirred at room temperature for 18 h, and was then concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (first dichloromethane; then ethyl acetate-dichloromethane, 1:9) to afford 62 mg (15%) of epoxide 233 as a white solid: mp 178-183 °C; IR (neat) 1726 cm⁻¹; ¹H NMR* (300 MHz, CDCl₃) δ 1.52 (s, 3 H, CH₃C₂), 2.02 (dd, J = 15.7, 3.5 Hz, 1 H, C₁₄H), 2.17 (t, J = 1.5 Hz, 1 H, C₆H), 2.29 (br d, J = 8.4 Hz, 1 H, C₁₆H), 2.36 (br s, 1 H, C₁₅H), 2.55 (ddd, J = 15.7, 8.1, 2.1 Hz, 1 H, C₁₄H), 2.82 (s, 3 H, NCH₃), 3.19 (d, J = 8.5 Hz, 1 H, epoxide CH), 3.38 (dd, J = 2.6, 2.0 Hz, 1 H, C₅H), 4.17 (s, 2 H, CH₂OBn), 4.54 (d, J = 12.3 Hz, 1 H, OCH₂Ph), 4.69 (d, J = 12.3 Hz, 1 H, CH₂OPh), 5.18 (d, J = 7.7 Hz, 1 H, C₃H), 5.59 (d, J = 7.7 Hz, 1 H, oxindole C₉H), 6.63-6.71 (m, 2 H, ArH), 7.10 (td, J = 7.7, 0.9 Hz, 1 H, ArH), 7.16-7.40 (m, 10 H, ArH), 7.54-7.66 (m, 5 H, ArH), 7.98 (br s, 1 H, NH); ¹³C NMR (75.5 MHz, CDCl₃) 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 (l), 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 (relative intensity) 654 (M⁺, 0.1), 563 (36), 167 (73), 91 (100); exact mass calc'd. for C₃₅H₄₈N₂O₆ m/z 654.2729, found m/z 654.2768.

Continued elution (ethyl acetate-dichloromethane, 2:8, then 3:7, then 1:1; and finally ethyl acetate) gave partially purified aldehyde which was recrystallized from ethyl acetate-hexane to afford 186 mg (61%) of 234. A second recrystallization from ethyl acetate-hexane gave 154 mg (51%) of pure 234 as a white solid: mp 235-241 °C; IR (KBr) 3426, 1720 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.77 (s, 3 H, CH₃CO₂), 2.06 (dd, J = 17.5, 3.2 Hz, 1 H, C₁₄H), 2.34 (br s, 1 H, C₁₅H or C₆H), 2.70 (m, 2 H, C₁₄H and C₆H or C₁₅H) 2.71 (s, 3 H, NCH₃), 3.61 (br s, 1 H, C₁₆H), 3.88 (dd, J = 2.9, 1.9 Hz, 1 H, CHN), 4.21 (s, 2 H, CH₂OBn), 4.57 (d, J = 12.2 Hz, 1 H, OCH₂Ph), 4.71 (d, J = 12.2 Hz, 1 H, OCH₂Ph), 5.37 (d, J = 7.7 Hz, 1 H, C₃H), 6.84 (d, J = 7.7 Hz, 1 H, ArH), 7.01 (t, J = 7.5 Hz, 1 H, ArH), 7.15-7.26 (m, 5 H, ArH), 7.29-7.40 (m, 2 H, ArH), 8.14 (br, 1 H, NH), 9.74 (d, J = 1.6 Hz, 1 H, CHO); ¹³C NMR (75.5 MHz, CDCl₃) δ 20.7 (q), 30.1 (q), 31.9 (l), 32.8 (d), 52.8 (d), 53.8 (s), 57.4 (s), 58.6 (d), 63.3 (d), 65.6 (l), 65.6 (d), 73.1 (l), 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 (relative intensity) 488 (M+, 0.4), 397 (55), 91 (100), 43 (41); exact mass calcd. for C_{28}H_{28}N_{2}O_{6} m/z 488.1947, found m/z 488.1948.

(±)-(3R*,3'R*,3aS*,5R*,7R*,9R*,9aS*)-9a-[(Benzyloxy)methyl]-3,3a,7,8,9,9a-hexamethyldro-2-methylspiro[3,7-epoxy-5,9-methanooxocino[4,5-c]pyrrole-4(5H),3'-Indoline]-1(2H),2'-dione (239) and (±)-(3R*,3'R*,4aR*,5S*,8S*,8aS*,9S*)-5-[(Benzyloxy)methyl]-1,3,4,4a,5,7,8,8a-octahydro-1-hydroxy-7-methylspiro[3,5,8-ethanylylidene-6H-pyrano[3,4-c]pyrldine-10,3'-Indoline]-2',6-dione (236). To a solution of 62 mg (0.127 mmol) of aldehyde 234 in 2 mL of dimethoxyethane was added 7 mL of 6N aqueous hydrochloric acid. The mixture was warmed at 48 °C for 16 h, cooled to room temperature and was then made basic with sodium bicarbonate. The mixture was diluted with 20 mL of water and was extracted with six 25-mL portions of ethyl acetate. The combined organic layers were dried (MgSO_{4}), filtered and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (dichloromethane; then tetrahydrofuran-dichloromethane, 2.5:97.5, then 5:95) to afford 8 mg (14%) of cyclic acetal 239 as a white solid: mp 275-310 °C (dec); IR (film) 3223, 1714 cm^{-1}; ^1H NMR (300 MHz, CDCl_{3}) δ 1.74 (d, 1 H), 1.90 (m, 1 H), 2.10 (m, 2 H), 2.88 (s, 3 H, NCH_{3}), 3.15 (m, 2 H), 3.89 (br s, 1 H, C_{3}H), 3.97 (d, 1 H, CH_{2}OBn), 4.46 (d, 1 H, CH_{2}OBn), 4.49 (s, 2 H, OCH_{2}Ph), 4.96 (d, 1 H, OCHN), 5.45 (br d, 1 H, OCHO), 6.87 (d, 1 H, ArH), 7.08 (t, 1 H, ArH), 7.28 (m, 6 H, ArH), 7.89 (br s, 1 H, NH), 8.32 (d, 1 H, ArH); ^13C NMR (75.5 MHz, CDCl_{3}) δ 25.2 (l), 26.9 (q), 28.6 (l), 32.4 (l), 40.5 (d), 51.1 (s), 53.9 (s), 69.6 (d), 69.7 (l), 72.8 (l), 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 (relative intensity) 446 (M+, 5), 355 (100), 240 (25), 91 (92); exact mass calcd. for C\textsubscript{26}H\textsubscript{26}N\textsubscript{2}O\textsubscript{5} m/z 446.1841, found m/z 446.1847.

Continued elution (tetrahydrofuran-dichloromethane, 7.5:92.5, then 25:75) afforded 46 mg (65%) of hemiacetal 236 as a mixture of diastereomers: IR (film) 3252 (broad), 1713 cm\textsuperscript{-1}; \textsuperscript{13}C NMR (mixture of diastereomers, 75.5 MHz, CDCl\textsubscript{3}) \(\delta\) 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 (l), 66.1 (l), 68.3 (d), 70.8 (d), 72.6 (l), 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 (relative intensity) 446 (M+, 1), 355 (68), 91 (100); exact mass calcd. for C\textsubscript{26}H\textsubscript{26}N\textsubscript{2}O\textsubscript{5} m/z 446.1841, found m/z 446.1854. The \textsuperscript{1}H NMR spectrum of this material is not reported here due to its complexity, but appears in Appendix A.

\[\text{(±)-(3R*,3'R*,4aR*,5S*,8S*,8aS*,9S*)-5-[Benzyloxy)methyl]-1,3,4,4a,5,7,8,8a-octahydro-7-methylspiro[3,5,8-ethanlylidene-6H-pyrano[3,4-c]pyridine-10,3'-indoline]-2',6-dione (240).}\]

To a solution of 46 mg (0.103 mmol) of hemiacetal 236 in 20 mL of dichloromethane was added 500 \(\mu\)L of triethylsilane followed by 500 \(\mu\)L 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 dichloromethane layer was separated and the aqueous phase extracted with three 25-mL portions of dichloromethane. The combined organic layers were dried (MgSO\textsubscript{4}), filtered, and concentrated in vacuo. The residue was chromatographed over 3g of silica gel (dichloromethane; then tetrahydrofuran-dichloromethane,
The combined fractions from the column containing product were concentrated in vacuo and the residue was recrystallized from ethyl acetate-hexane to provide 36 mg (83%) of tetrahydropyran 240 as a white solid: mp 187-189 °C; IR (thin film CCl₄) 3199, 1715 cm⁻¹; ¹H NMR* (300 MHz, CDCl₃) δ 2.16 (m, 3 H, C₁₆H and C₁₅H and C₁₄H), 2.34 (br s, 1 H, C₆H), 2.76 (s, 3 H, NCH₃), 2.81 (dd, J = 13.6, 2.9 Hz, 1 H, C₁₄H), 3.82 (d, J = 1.3 Hz, 1 H, C₅H), 3.89 (br s, 1 H, C₃H), 3.98 (dd, J = 11.4, 0.9 Hz, 1 H, C₁₇H), 4.13 (m, 2 H, C₁₇H and CH₂OBn), 4.45 (d, J = 8.6 Hz, 1 H, CH₂OBn), 4.51 and 4.56 (ABq, J = 11.8 Hz, 2 H, OCH₂Ph), 6.82 (d, J = 7.7 Hz, 1 H, oxindole C₁₂H), 7.03 (td, J = 7.6, 1.1 Hz, 1 H, oxindole C₁₁H), 7.17-7.32 (m, 6 H, oxindole C₁₀H and ArH), 7.38 (d, J = 7.6 Hz, 1 H, oxindole C₆H), 7.70 (br s, 1 H, NH); ¹H NMR (300 MHz, C₆D₆) δ 1.42 (br d, 1 H, C₁₆H), 1.64-1.74 (m, 2 H, C₁₅H and C₁₄H), 2.26 (s, 3 H, NCH₃), 2.30 (br s, 1 H, C₆H), 2.70 (dd, J = 14.0, 3.2 Hz, 1 H, C₁₄H), 3.30 (d, J = 1.4 Hz, 1 H, C₅H), 3.34 (dd, J = 11.4, 2.0 Hz, 1 H, C₁₇H), 3.55 (dd, J = 11.4, 2.2 Hz, 1 H, C₁₇H), 3.77 (br s, 1 H, C₃H), 3.38 (d, J = 8.2 Hz, 1 H, CH₂OBn), 4.62 (d, J = 12.6 Hz, 1 H, OCH₂Ph), 4.63 (d, J = 8.1 Hz, 1 H, CH₂OBn), 4.73 (d, J = 12.0 Hz, 1 H, OCH₂Ph), 6.30 (dd, J = 7.7, 0.8 Hz, 1 H, oxindole C₁₂H), 6.86 (td, J = 7.5, 1.2 Hz, 1 H, oxindole ArH), 6.96 (td, J = 7.7, 1.3 Hz, 1 H, oxindole ArH), 7.03-7.08 (m, 2 H, ArH), 7.16-7.18 (m, 1 H, ArH), 7.28 (ddd, J = 7.4, 1.0, 0.4 Hz, 1 H, oxindole C₉H), 7.41-7.44 (m, 2 H, ArH), the NH proton was not resolved; ¹³C NMR (75.5 MHz, CDCl₃) 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 (relative intensity) 430 (M⁺, 0.2), 339 (65), 91 (100); exact mass calcd. for C₂₆H₂₆N₂O₄ m/z 430.1892, found m/z 430.1886.
(±)-(3R*,4aR*,5S*,8S*,8aS*,9S*)-Octahydro-5-(hydroxymethyl)-7-methyl-3,5,8-ethanyllylidene-6H-pyrano[3,4-c]-pyridin-6-one (244) To a stirred solution of 610 mg (2.57 mmol) of 159 in 20 mL of dichloromethane cooled to -78 °C (dry ice-acetone bath) was added 4 mL (4.0 mmol) of 1.0 M boron tribromide in dichloromethane. After 1 h, an additional 2 mL (2.0 mmol) of boron tribromide was added, and the mixture continued to stir for an additional 1 h. The cold bath was then removed and the mixture was stirred at room temperature for 15 min. The mixture was cooled to -78 °C, quenched with 2 mL of methanol, and diluted with 30 mL of saturated aqueous sodium bicarbonate. The dichloromethane layer was separated and the basic aqueous layer was extracted with three 20-mL portions of dichloromethane. The combined organic extracts were dried (MgSO₄), treated with carbon (Norit A), filtered through Celite and concentrated in vacuo. To the oily residue, which began to crystallize, was added 10 mL of ethyl acetate followed by 30 mL of hexane. The mixture sat for 18 h to provide 308 mg of solid in two crops. Additional product was obtained from the basic aqueous washings. The aqueous phase was concentrated in vacuo, suspended in a mixture of methanol-dichloromethane, stirred for several hours, filtered and concentrated in vacuo. The residue was passed through a small pad of silica gel eluting with first dichloromethane followed by 2% methanol in dichloromethane to afford an additional 175 mg of solid which was combined with the 308 mg and recrystallized from dichloromethane-hexane to afford 429 mg (75%) of alcohol 244 as a white solid: mp 143.2-143.8 °C; IR (KBr) 3401 (broad), 1675 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.69 (br, 2 H, C₇H), 1.81 (dd, J = 14.8, 3.0 Hz, 1 H, C₁₄H), 2.06-2.14 (m, 3 H, C₆H, C₁₄H, and C₁₆H), 2.27 (br, 1 H, C₁₅H), 2.78 (s, 3 H, NCH₃), 3.42 (t, J = 6.6 Hz, 1 H, OH), 3.63 (d, J = 1.6 Hz, 1 H, CHN), 3.78 (dd, J = 11.4, 2.0 Hz, 1 H, C₁₇H), 3.94-3.99 (m, 4 H, CH₂OH, CHOC₂H₂): ¹³C NMR (75.5 MHz, CDCl₃) δ 23.6 (t), 27.0 (q), 30.5 (t), 31.1 (d), 42.9 (d), 44.8 (d), 57.2 (s), 58.2 (t), 60.6 (t), 66.0 (d), 68.9 (d), 179.3
(±)-(3R*,4aR*,5S*,8S*,8aS*,9S*)-Hexahydro-7-methyl-6-oxo-3,5,8-ethanylidene-1H-pyano[3,4-c]-pyridine-5(3H)-carboxaldehyde (245). Method A: To a solution of 0.907 mL (10.39 mmol) of oxalyl chloride in 10 mL of dichloromethane cooled to -78 °C was added 1.47 mL (20.79 mmol) of dimethyl sulfoxide in 10 mL of dichloromethane over a 10-min period. The solution was stirred for 30 min, and 464 mg (2.08 mmol) of alcohol 244 in 10 mL of dichloromethane was added over a 10-min period. The solution was stirred at -78 °C for 1 h, and then 1 mL of triethylamine was added. The cold bath was removed, the mixture was stirred at room temperature for 18 h, and diluted with 25 mL of saturated aqueous sodium bicarbonate. The organic phase was separated, and the basic aqueous layer was extracted with two 25-mL portions of dichloromethane. The combined organic extracts were washed with three 25-mL portions of brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (ether followed by tetrahydrofuran) to provide 426 mg (92%) of aldehyde 245 as an off white solid. An analytically pure sample was obtained by triturating the solid with ether followed by a recrystallization from ethyl acetate-hexane: mp 100-105 °C; IR (film) 1721, 1682 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.76 (dd, J = 14.9, 2.8 Hz, 1 H, C₇H), 1.79 (dd, J = 14.8, 2.9 Hz, 1 H, C₇H), 2.07 (ddd, J = 15.1, 3.4, 3.4 Hz, 1 H, C₁₄H), 2.12-2.21 (m, 2 H, C₁₄H and C₁₆H), 2.54 (br, 1 H, C₆H), 2.64 (br, 1 H, C₁₅H), 2.80 (s, 3 H, NCH₃), 3.65 (d, J = 1.5 Hz, 1 H, C₈H), 3.81 (dd, J = 11.5, 2.0 Hz, 1 H, C₁₇H), 3.95 (br, 1 H, C₃H), 3.99 (dd, J = 11.5, 2.2 Hz, 1 H, C₁₇H), 10.12 (s, 1 H, CHO); ¹³C NMR (75.5 MHz, CDCl₃) δ 24.6 (t), 27.2 (q),
mass spectrum, \( m/z \) (relative intensity) 221 (M\(^+\), 3), 193 (100), 138 (44); exact mass calcd. for 
\[ \text{C}_{12}\text{H}_{15}\text{NO}_3 \]  \( m/z \) 221.1051, found \( m/z \) 221.1049.

Anal. calcd. for \( \text{C}_{12}\text{H}_{15}\text{NO}_3 \): C, 65.13; H, 6.84. Found: C, 65.04; H, 6.88.

**Method B:** To a solution of 4.8 mg (0.0215 mmol) of alcohol 244 in 1 mL of dichloromethane was added 12.6 mg (0.0297 mmol) of the Dess-Martin periodinane in one portion.\(^{54}\) The mixture was stirred at room temperature for 30 min, diluted with 5 mL of ether, filtered and concentrated in vacuo. The residue was chromatographed over 750 mg of silica gel (first dichloromethane; then ethyl acetate-dichloromethane, 1:9, 2:8, 3:7) to provide 3.8 mg (80%) of aldehyde 245, whose \(^1\)H NMR was identical to material obtained via method A.

\[
(\pm)-(3R^*,4aR^*,5R^*,8S^*,8aS^*,9S^*)-(\pm)-\text{Octahydro-7-methyl-5-vinyl-3,5,8-ethanylidene-6H-pyrano[3,4-c]pyridin-6-one (246)}
\]

**Method A:** To a solution of 32 mg (0.143 mmol) of aldehyde 245 in 2 mL of tetrahydrofuran, cooled to -78 °C was added 75 µL (225 mmol) of 3 M methylmagnesium bromide in diethyl ether. The cold bath was removed, and the mixture was stirred at room temperature for 20 min, cooled to -78 °C, quenched with 4 mL of saturated aqueous ammonium chloride, and extracted with three 10-mL portions of ethyl acetate followed by three 10-mL portions of dichloromethane. The combined organic extracts were dried (MgSO\(_4\)), filtered and concentrated in vacuo to provide 29.1 mg (85%) of alcohol 246a as a white solid. A \(^1\)H NMR indicated the alcohol was a mixture of diastereomers, and is not reported here, but does appear in Appendix A. This material was used without further characterization.

To a solution of 14 mg (0.0585 mmol) of the alcohol in 2 mL of dichloromethane was
added 85 mg (0.117 mmol) of Martin's sulfurane \text{bis}[\alpha,\alpha\text{-bis(trifluoromethyl)benzene-}
methanolato]\text{diphenylsulfur}. The mixture was stirred for 20 min and then chromatographed
over 1 g of silica gel (first dichloromethane; then methanol-dichloromethane, 2:98). A second
chromatography over 1 g of silica gel (dichloromethane to load the sample; then ethyl acetate-
hexane, 3:7, then 1:1; then methanol-dichloromethane, 2:98) gave 13.2 mg (100%) of olefin 246,
which solidified upon standing: mp 102-107 °C; IR (KBr) 1717, 1682 cm⁻¹; \textsup{1}H NMR (300 MHz,
\text{CDCl}_3) \delta 1.67-1.89 (m, 3 H), 2.02-2.19 (m, 3 H), 2.28 (br, 1 H), 2.77 (s, 3 H, NCH₃), 3.62 (br s, 1
H, CH(N)), 3.78 (dd, J = 11.3, 1.9 Hz, 1 H, CH₂O), 3.91 (br s, 1 H, OCH), 3.96 (dd, J = 11.3, 2.1
Hz, 1 H, CH₂O), 5.29 (dd, J = 17.8, 1.4 Hz, 1 H, C=CH₂), 5.50 (dd, J = 11.1, 1.4 Hz, 1 H, C=CH₂),
5.99 (dd, J = 17.8, 11.1 Hz, 1 H, =CH); \textsup{13}C NMR (75.5 MHz, \text{CDCl}_3) \delta 24.6 (t), 27.5 (q), 30.8 (t),
34.1 (d), 42.8 (d), 45.80 (d), 59.7 (s), 60.7 (t), 66.4 (d), 68.5 (d), 120.1 (t), 132.2 (d), 177.7 (s);
mass spectrum, m/z (relative intensity) 219 (M⁺, 74), 137 (100); exact mass calcd. for C₁₃H₁₇NO₂
m/z 219.1259, found m/z 219.1260.

**Method B:** To a solution of 50 mg (0.226 mmol) of aldehyde 245 in 1.8 mL of
tetrahydrofuran was added 1.8 mL (0.90 mmol) of 0.5 M bis(cyclopentadienyl)dimethyltitanium in
tetrahydrofuran. The mixture was warmed at reflux for 24 h, cooled and concentrated by sitting
open to the air for 18 h. The solid residue was suspended in a mixture of dichloromethane-
tetrahydrofuran, and stirred for several hours. The mixture was filtered through Celite, and the
filtrate was concentrated in vacuo. The residue was chromatographed over 6 g of silica gel (first
dichloromethane, then ethyl acetate) to provide 46.6 mg (94%) of olefin 246, whose \textsup{1}H NMR was
identical to olefin obtained via method A.
(±)-(3R*,3'S*,4aR*,5S*,8S*,8aS*,9S*)-1,3,4,4a,5,7,8,8a-Octahydro-5-(hydroxymethyl)-1',7-dimethylspiro[3,5,8-ethanylidene-6H-pyran[3,4-c]pyridine-10,3'-indoline]-2',6-dione (247). To a solution of 25 mg (0.0563 mmol) of benzyl ether 195 in 20 mL of dichloromethane cooled to -78 °C was added 120 μL (0.12 mmol) of 1 M boron tribromide in dichloromethane. The mixture was stirred at -78 °C for 30 min, and then at room temperature for 2 h. The mixture was again cooled to -50 °C and 100 μL (0.10 mmol) of 1 M boron tribromide was added. The cold bath was removed, and after 30 min at room temperature the mixture was cooled to -20 °C, quenched with 1 mL of methanol, and concentrated in vacuo. The residue was chromatographed over 1 g of silica gel (ethyl acetate), and then partitioned between 5 mL of ethyl acetate and 5 mL of saturated aqueous sodium bicarbonate. The basic aqueous phase was separated and further extracted with two 5-mL portions of ethyl acetate. The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo. The residue was again chromatographed over 2 g of silica gel (first dichloromethane; then ethyl acetate-dichloromethane, 25:75, then 1:1) to provide 14.4 mg (72%) of alcohol 247 as a solid: mp 241-247 °C (dec); IR (KBr) 3455, 1708, 1610 cm⁻¹; ¹H NMR* (300 MHz, CDCl₃) δ 2.07 (br s, 1 H, C₆H), 2.16 (br d, J = 7.8 Hz, 1 H, C₁₆H), 2.29 (ddd, J = 15.1, 5.4, 2.5 Hz, 1 H, C₁₄H), 2.35 (dd, J = 14.8, 3.0 Hz, 1 H, C₁₄H), 2.54 (dd, J = 7.2, 5.7 Hz, 1 H, C₁₂H), 2.81 (s, 3 H, NCH₃), 3.19 (s, 3 H, NCH₃), 3.77 (br s, 1 H, C₃H), 3.89 (bs, 1 H, OH), 4.06-4.17 (m, 3 H, C₁₁H and C₁₉H), 4.48 (d, J = 12.0 Hz, 1 H, C₁₉H), 4.76 (d, J = 1.7 Hz, 1 H, C₁₂H), 6.84 (dd, J = 7.8, 0.8 Hz, 1 H, ArH), 7.06 (td, J = 7.7, 1.1 Hz, 1 H, ArH), 7.31 (td, J = 7.7, 1.1 Hz, 1 H, ArH), 7.43 (d, J = 7.6 Hz, 1 H, ArH); ¹³C NMR (75.5 MHz, CDCl₃) δ 24.3 (t), 26.2 (q), 27.2 (q), 29.5 (d), 42.3 (d), 51.3 (d), 54.0 (s), 58.3 (s), 60.1 (t), 61.1 (t), 64.7 (d), 70.4 (d), 108.3 (d), 122.2 (d), 124.3 (d), 128.6 (d), 129.4 (s), 143.2 (s), 175.3 (s), 178.6 (s); mass
spectrum, m/z (relative intensity) 354 (100), 336 (55), 254 (60), 228 (51); exact mass calcd. for C_{20}H_{22}N_{2}O_{4} m/z 354.1579, found m/z 354.1574.

![Chemical structure]

(±)-(3R*,3'S*,4aR*,5S*,8S*,8aS*,9S*)-4,4a,6,7,8,8a-Hexahydro-1',7-dimethyl-2',6-dioxospiro[3,5,8-ethanoylidene-1H-pyran-3,4-c]pyridine-10,3'-indoline]-5(3H)-carboxaldehyde (248). To a solution of 43 μL (0.492 mmol) of oxalyl chloride in 1 mL of dichloromethane cooled to -78 °C was added 70 μL (0.985 mmol) of dimethyl sulfoxide in several portions. The mixture was stirred for 45 min, and 14 mg (0.0395 mmol) of alcohol 247 in 2 mL of dichloromethane was added. The mixture continued to stir at -78 °C for 45 min, and then 100 μL of triethylamine was added. The cold bath was removed, and the mixture was stirred at room temperature of 18 h, diluted with 5 mL of saturated aqueous sodium bicarbonate, and extracted with four 5-mL portions of dichloromethane. The combined organic extracts were washed with four 5-mL portions of brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed over 1 g of silica gel (first dichloromethane; then tetrahydrofuran-dichloromethane, 1:9) to provide 11.9 mg (86%) of aldehyde 248 as an oil, which crystallized upon standing: mp (dichloromethane-hexane) 290-292 °C (dec); IR (neat) 1774, 1704, 1654 cm⁻¹; ¹H NMR* (300 MHz, CDCl₃) δ 2.23 (br d, J = 8.1 Hz, 1 H, C_{16}H), 2.31 (ddd, J = 15.3, 5.3, 2.6 Hz, 1 H, C_{14a}H), 2.42 (dd, J = 15.1, 2.8 Hz, 1 H, C_{14a}H), 2.74 (br s, 1 H, C_{6}H), 2.82 (s, 3 H, NCH₃), 2.88 (dd, J = 8.0, 5.9 Hz, 1 H, C_{15}H), 3.22 (s, 3 H, NCH₃), 3.65 (br s, 1 H, C_{3}H), 4.09 (br s, 2 H, C_{17}H), 4.79 (d, J = 1.6 Hz, 1 H, C_{5}H), 6.87 (d, J = 7.8 Hz, 1 H, ArH), 6.96-7.05 (m, 2 H, ArH), 7.31 (td, J = 7.1, 1.8 Hz, 1 H, ArH), 9.85 (s, 1 H, CHO); ¹³C NMR (75.5 MHz, CDCl₃) δ 24.6 (t), 26.2 (q), 27.4 (q), 29.1 (d), 42.0 (d), 52.2 (d), 53.2 (s), 60.6 (t), 65.7 (d), 68.9 (s), 70.2 (d),
108.5 (d), 122.7 (d), 124.4 (d), 128.8 (d), 129.0 (s), 143.0 (s), 172.7 (s), 174.7 (s), 199.5 (d); mass spectrum, \( m/z \) (relative intensity) 352 (M\(^+\), 22), 324 (6), 202 (62) 152 (100); exact mass calcd. for \( C_{20}H_{20}N_2O_4 \) \( m/z \) 352.1422, found \( m/z \) 352.1427.

\[ \begin{align*}
\text{Me} & \text{N} \\
& \text{O} \\
& \text{N} \\
& \text{O} \\
& \text{O} \\
\text{C} & \text{H} \\
& \text{CH}_3
\end{align*} \]

\((-\cdot 3R^*, 3S^*, 4aR^*, 5R^*, 8S^*, 8aS^*, 9S^*)-1, 3, 4, 4a, 5, 7, 8, 8a-\text{Octahydropyridine-1', 7-dione}} (249).

To a solution of 10.8 mg (0.0306 mmol) of aldehyde 248 in 2.5 mL of tetrahydrofuran was added 110 \( \mu \)L (0.055 mmol) of 0.5 M dimethyltitanocene\(^\text{56} \) in tetrahydrofuran. The mixture was warmed at reflux for 4 h, and concentrated in vacuo. A \( ^1H \) NMR indicated two sets of NCH\(_3\)'s in a ratio of 2:1. The material was then concentrated, dissolved in 5 mL of tetrahydrofuran and 400 \( \mu \)L (0.220 mmol) of 0.5 M dimethyltitanocene in tetrahydrofuran was added. The mixture was warmed at reflux for 12 h, cooled and concentrated in vacuo. The residue was chromatographed over 1 g of silica gel (dichloromethane; then ethyl acetate-dichloromethane, 3:7). The material from the column was triturated with three 1-mL portions of ether to afford 6.5 mg (60%) of olefin 249: mp 249-252 °C (dec); IR (KBr) 1707, 1610 cm\(^{-1} \); \(^1H\) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 2.17 (br s, 1 H, C\(_{16}\)H), 2.22 (dd, \( J = 8.9, 2.4 \) Hz, 1 H, C\(_{14}\)H), 2.23 (br, 1 H, C\(_2\)H), 2.56 (dd, \( J = 14.2, 3.1 \) Hz, C\(_{14}\)H), 2.59 (b, 1 H, C\(_{12}\)H), 2.81 (s, 3H, CH\(_3\)), 3.21 (s, 3 H, CH\(_3\)), 3.63 (br s, 1 H, C\(_3\)H), 4.10 (ab qd, \( J = 11.0, 1.9 \) Hz, 2 H, C\(_{17}\)H), 4.77 (d, \( J = 1.6 \) Hz, 1 H, C\(_5\)H), 5.37 (dd, \( J = 17.9, 1.5 \) Hz, 1 H, C\(_{15}\)H), 5.71 (dd, \( J = 11.0, 0.8 \) Hz, 1 H, C=CH\(_2\)), 6.00 (dd, \( J = 17.9, 11.0 \) Hz, 1 H, =CH), 6.83 (dd, \( J = 7.8, 0.6 \) Hz, 1 H, ArH), 7.00 (td, \( J = 7.6, 1.1 \) Hz, 1 H, ArH), 7.29 (td, \( J = 7.7, 1.1 \) Hz, 1 H, ArH), 7.70 (dd, \( J = 7.6, 0.6 \) Hz, 1 H, ArH); \(^{13}C\) NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 24.0 (t), 26.1 (q), 27.7 (q), 30.4 (d), 42.1 (d), 52.7 (d), 53.9 (s), 61.1 (t), 61.2 (s), 64.7 (d), 71.0 (d), 107.9 (d), 119.8 (t),
121.7 (d), 126.7 (d), 128.37 (d), 129.3 (s), 134.9 (d), 143.0 (s), 175.4 (s), 176.1 (s); mass spectrum, \textit{m/z} (relative intensity) 350 (M\(^+\), 100), 268 (17), 122 (42); exact mass calcd. for C\(_{21}\)H\(_{22}\)N\(_2\)O\(_3\) \textit{m/z} 350.1630, found \textit{m/z} 350.1638.

![Chemical structure of compound 250](image)

\((\pm)-(3R',3'R',4aR',5S',8S',8aS',9S')-1,3,4,4a,5,7,8,8a-Octahydro-5-(hydroxymethyl)-7-methylspiro[3,5,8-ethanylylidene-6H-pyrano[3,4-c]pyridine-10,3'-indoline]-2'-6-dione (250).

To a solution of 31 mg (0.072 mmol) of benzyl ether 237 in 20 mL of dichloromethane cooled to -78 °C was added 216 \(\mu\)L (0.216 mmol) of 1 M boron tribromide in dichloromethane. 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 dichloromethane layer was separated and the aqueous layer extracted with four 25-mL portions of dichloromethane. 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 250: mp (ethanol-hexane) 303-309 °C; IR (KBr) 3464, 1725, 1696 cm\(^{-1}\); \(^1\)H NMR (300 MHz, DMSO-d\(_6\)) \(\delta\) 1.90 (br s, 1 H), 1.97-2.08 (m, 2 H, C\(_{14}\)H), 2.15 (br d, \(J = 7.6\) Hz, 1 H), 2.52 (dd, \(J = 3.1\) Hz, second coupling constant obscured by DMSO peak, 1 H), 2.64 (s, 3 H, NCH\(_3\)), 3.65 (br s, 1 H, C\(_3\)H), 3.92-4.09 (m, 5 H), 4.32 (dd, \(J = 10.3, 4.0\) Hz, 1 H, C\(_{17}\)H), 6.80 (d, \(J = 7.6\) Hz, 1 H, ArH), 6.94 (td, \(J = 7.6, 0.9\) Hz, 1 H, ArH), 7.20 (td, \(J = 7.6, 0.6\) Hz, 1 H, ArH), 7.38 (d, \(J = 7.5\) Hz, 1 H, ArH), 10.35 (br, 1 H, NH); \(^{13}\)C NMR (75.5 MHz, DMSO-d\(_6\)) \(\delta\) 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, \textit{m/z} (relative 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\(_2\)O\(_4\) \textit{m/z} 340.1423, found \textit{m/z} 340.1423.
(±)-(3R*,3'R*,4aR*,5S*,8S*,8aS*,9S*)-4,4a,6,7,8,8a-Hexahydro-7-methyl-2',6-dioxospiro[3,5,8-ethanylylde-1H-pyran-3,4-c]pyridine-10,3'-indoline]-5(3H)-carboxaldehyde (251). To 23.5 mg (0.069 mmol) of alcohol 250 was added 20 mL of dichloromethane-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 periodinane54 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 (dichloromethane; then ethyl acetate-dichloromethane, 1:9, then 2:8, then 3:7) to provide 23 mg (98%) of aldehyde 251 which was recrystallized from ethyl acetate-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, CDCl₃) δ 2.21 (ddd, J = 14.9, 5.5, 2.6 Hz, 1 H, C₁₄ᵉH), 2.28 (d, J = 8.4 Hz, 1 H, C₁₆H), 2.54 (br s, 1 H, C₆H), 2.73 (dd, J = 17.9, 2.8 Hz, 1 H, C₁₄ᵃH), 2.81 (s, 3 H, NCH₃), 2.87 (m, 1 H, C₁₅H), 3.74 (br s, 1 H,C₃H), 3.99 (m, 2 H, C₁₇H and CHN), 4.15 (dd, J = 11.6, 2.2 Hz, 1 H, C₁₇H), 6.93 (d, J = 7.7 Hz, 1 H, ArH), 7.09 (td, J = 7.7. 1.0 Hz, 1 H, ArH), 7.30 (td, J = 7.7, 1.1 Hz, 1 H, ArH), 7.38 (d, J = 7.6 Hz, 1 H, ArH), 8.98 (s, 1 H, NH), 9.70 (s, 1 H, CHO); ¹³C NMR (75.5 MHz, CDCl₃) 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 (relative intensity) 338 (M⁺, 13), 228 (20), 188 (40), 152 (100); exact mass calcd. for C₁₉H₁₈N₂O₄ 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-ethanoyllylidene-6H-pyrano[3,4-c]pyridine-10,3'-indoline]-2'-6-dione (2). (±)-21-Oxogelsemine (2). To solution of 16.5 mg (0.048 mmol) of aldehyde 251 in 750 µL of tetrahydrofuran was added 500 µL (0.25 mmol) of 0.5 M bis(cyclopentadienyl)dimethyltitanium in tetrahydrofuran. The mixture was warmed under reflux for 24 h, 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 tetrahydrofuran was added. The mixture was stirred at reflux for an additional 24 h and was 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 (dichloromethane; then ethyl acetate-dichloromethane, 1:9, then 2:8, then 3:7, then 4:6) to provide 14.3 mg (87%) of 21-oxogelsemine (2): mp 155-159 °C [lit² (natural product) 148-150 °C]; IR (film) 3222, 1715, 1616 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.06 (t, J = 1.3 Hz, 1 H, C₆H), 2.17 (ddd, J = 14.5, 5.6, 2.7 Hz, 1 H, C₁₄₆H), 2.22 (m, 1 H, C₁₆H), 2.49 (dd, J = 7.4, 3.0 Hz, 1 H, C₁₈H), 2.78 (s, 3 H, NCH₃), 2.97 (dd, J = 14.5, 3.0 Hz, 1 H, C₁₄₆H), 3.68 (br s, 2 H, C₃H and C₅H), 4.00 (dd, J = 11.5, 2.0 Hz, 1 H, C₁₇H), 4.15 (dd, J = 11.5, 2.2 Hz, 1 H, C₁₁H), 5.21 (dd, J = 17.8, 1.1 Hz, 1 H, =CH₂), 5.49 (dd, J = 11.1, 1.1 Hz, 1 H, =CH₂), 6.06 (dd, J = 17.8, 11.1 Hz, 1 H, =CH), 6.85 (dd, J = 7.7, 0.6 Hz, 1 H, ArH), 7.05 (td, J = 7.6, 1.1 Hz, 1 H, ArH), 7.25 (td, J = 7.8, 1.2 Hz, 1 H, ArH), 7.39 (d, J = 7.6 Hz, 1 H, ArH), 7.86 (s, 1 H, NH); ¹³C NMR (75.5 MHz, CDCl₃) 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 (l), 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 (relative intensity) 336 (M⁺, 100), 254 (13), 122 (69); exact mass calcd. for C₂₀H₂₀N₂O₃ m/z 336.1475, found m/z 336.1485
(±)-(1'R*,3S*,3'aS*,4'R*,6'R*,7'aS*,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) (252). To a mixture of 127 mg (0.178 mmol) of oxindole 226 in 25 mL of dichloromethane was added 3 g (0.194 mmol) of p-toluenesulfonic acid monohydrate. The mixture was warmed under reflux for 3 h, cooled to room temperature and 1 mL of methanol to facilitate hydrolysis of the N-acetate. The mixture was stirred for an additional 24 h and diluted with 20 mL of saturated aqueous sodium bicarbonate. The dichloromethane layer was separated, and the aqueous layer was extracted with three 25-mL portions of dichloromethane. The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed over 6 g of silica gel (dichloromethane to load the sample; then ethyl acetate-hexane, 25:75, then 30:70), and then recrystallized from ethyl acetate-hexane to provide 78 mg (69%) of olefin 252 as a white solid: mp 211-213 °C; IR (KBr) 3399, 3027, 2924, 1726, 1618 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.64 (s, 3 H, CH₃CO₂), 1.70 (m, 1 H), 1.96 (m, 1 H), 2.35 (br s, 1 H), 2.58 (m, 1 H), 2.94 (s, 3 H, NCH₃), 3.68 (dd, J = 3.1, 1.8 Hz, 1 H, CHN), 4.00 (d, J = 10.3, 1 H, CH₂OBn), 4.20 (ddd, J = 9.7, 3.0, 1.7 Hz, 1 H, CHCH=CPh₂), 4.31 (d, J = 10.4 Hz, 1 H, CH₂OBn), 4.70 and 4.75 (ABq, J = 11.9 Hz, 2 H, OCH₂Ph), 5.32 (dd, J = 9.1, 6.6 Hz, 1 H, OCH), 5.71 (d, J = 9.8 Hz, 1 H, =CH), 6.67 (dd, J = 7.6, 0.4 Hz, 1 H, oxindole ArH), 6.84 (td, J = 7.6, 1.0 Hz, 1 H, oxindole ArH), 7.11 (td, J = 7.7, 1.0 Hz, 1 H, oxindole ArH), 7.16-7.47 (m, 16 H, ArH); ¹³C NMR (75.5 MHz, CDCl₃) δ 20.65 (q), 31.00 (q), 32.51 (t), 40.38 (d), 49.53 (d), 53.45 (s), 55.49 (d), 58.69 (s), 65.59 (d), 67.60
(±)-(1'R*,3'R*,3'aR,4'S*,6'S*,7'aR*,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)-methanoisindoline]-8'-carboxaldehyde acetate (ester) (253). To a solution of 233 mg (0.365 mmol) of olefin 252 in 40 mL of dichloromethane and 10 mL of methanol was added 1 mL of a 0.1% solution of Sudan III in dichloromethane. The mixture was cooled to -78 °C and ozone gas was passed through the red solution until it became clear. To the mixture was added 2 mL of dimethylsulfide and the cold bath was removed. The mixture was stirred at room temperature for 18 h, concentrated in vacuo, and the residue twice chromatographed over 6 g of silica gel (dichloromethane; then ethyl acetate-dichloromethane, 2:8, then 3:7, then 1:1, then ethyl acetate) to provide material which was recrystallized from ethyl acetate-hexane to afford 118 mg (66%) of aldehyde 253 as a white solid: mp 148-159 °C; IR (KBr) 1718 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.81 (s, 3 H, CH₃CO₂), 1.83 (m, 1 H), 2.65 (s, 1 H), 2.74 (s, 3 H, NCH₃), 2.76 (m, 2 H), 4.07 (d, J = 10.4 Hz, 1 H, CH₂OBn), 4.13 (dd, J = 3.0, 1.9 Hz, 1 H, C₁₆H), 4.36 (d, J = 10.4 Hz, 1 H, CH₂OBn), 4.64 (br s, 1 H, CHN), 4.71 and 4.77 (ABq, J = 11.6 Hz, 2 H, OCH₂Ph), 5.53 (br t, J = 8.9 Hz, 1 H, C₃H), 6.78 (d, J = 7.7 Hz, 1 H, ArH), 6.85 (td, J = 7.6, 0.8 Hz, 1 H, ArH), 7.14 (td, J = 7.7, 1.0 Hz, 1 H, ArH),
7.24-7.40 (m, 5 H, ArH), 7.45 (d, J = 7.5 Hz, 1 H, ArH), 8.15 (br s, 1 H, NH), 9.86 (s, 1 H, CHO);

$^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 20.6 (q), 30.3 (q), 31.9 (d), 33.0 (t), 53.6 (s), 55.5 (d), 58.9 (s),
62.6 (d), 64.4 (d), 67.5 (l), 70.0 (d), 74.0 (l), 109.0 (d), 123.1 (d), 124.6 (d), 127.5 (d), 127.8 (d),
128.2 (d), 128.4 (d), 134.7 (s), 137.6 (s), 139.3 (s), 169.7 (s), 174.4 (s), 176.4 (s), 199.7 (s); mass
spectrum, $m/z$ (relative intensity) 488 (M$^+$, 1), 382 (17), 323 (35), 91 (100); exact mass calcd. for
C$_{28}$H$_{28}$N$_2$O$_6$ $m/z$ 488.1947, found $m/z$ 488.1951.

![Image of structure 254]

(±)-(3$^R$,3$'$$^S$,4$a$$^R$,5$S$, 8$S$, 8a$^S$, 9$S$)-5-[(Benzyloxy)methyl]-1,3,4,4a,5,7,8,8a-
octahydro-1-hydroxy-7-methylspiro[3,5,8-ethanylylidene-6H-pyran[3,4-c]pyridine-10,3'-
Indoline]-2',6-dione (254). To a solution of 103 mg (0.221 mmol) of aldehyde 253 in 4 mL of
dimethoxyethane was added 7 mL of 6 N aqueous hydrochloric acid. The mixture was warmed to
48 °C, and stirred for 5 h. The resulting solution was made basic with 25 mL of saturated aqueous sodium bicarbonate, and extracted with four 25-mL portions of ethyl acetate. The
combined organic layers were dried (MgSO$_4$), filtered and concentrated in vacuo. The residue
was chromatographed over 6 g of silica gel (first ethyl acetate; then tetrahydrofuran-ethyl acetate,
3:7, then 1:1) to provide 77 mg (82%) of hemiacetal 254 as a mixture of diastereomers: mp 150-
185 °C; IR (KBr) 3261, 1734, 1686, cm$^{-1}$; $^{13}$C NMR (major diastereomer, 75.5 MHz, DMSO-d$_6$) $\delta$
24.5 (l), 27.5 (q), 29.3 (d), 47.2 (d), 49.7 (d), 53.4 (s), 58.0 (s), 60.2 (d), 66.4 (l), 69.6 (d), 72.5 (l),
90.5 (d), 109.4 (d), 121.1 (d), 125.6 (d), 127.4 (d), 127.6 (d), 128.1 (d), 128.3 (d), 130.4 (s), 138.4
(s), 141.6 (s), 176.8 (s), 177.0 (s); mass spectrum, $m/z$ (relative intensity) 446 (M$^+$, 20), 340 (13),
239 (32), 91 (100); exact mass calcd. for C$_{28}$H$_{28}$N$_2$O$_6$ $m/z$ 446.5018, found $m/z$ 446.1839. The
1H NMR spectrum of this material is not reported here due to its complexity, but appears in Appendix A.

(±)-(3'R,3'S',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-6H-pyran-3,4-c]pyridine-10,3'-indolone]-2',6-dione (255). To a solution of 76 mg (0.169 mmol) of hemiacetal 254 and 1 mL of triethylsilane in 40 mL of dichloromethane was added 1 mL of trifluoroacetic acid. The mixture was stirred at room temperature for 5 h, made basic with solid sodium bicarbonate, and diluted with 50 mL of water. The dichloromethane layer was separated and the basic aqueous phase was extracted with two 25-mL portions of dichloromethane. The combined organic extracts were dried (MgSO4), filtered, and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (first dichloromethane; then tetrahydrofuran-dichloromethane, 5:95) to provide 53 mg (73%) of ether 255: mp (ethyl acetate-hexane) 224-226 °C; IR (KBr) 3245, 1716, 1617 cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 2.12-2.25 (m, 3 H), 2.36 (m, 2 H), 2.80 (s, 3 H, NCH3), 3.77 (br s, 1 H, CH2OBn), 4.01-4.12 (m, 3 H, both C17H and one CH2OBn), 4.28 (d, J = 10.1 Hz, 1 H, CH2OBn), 4.45 and 4.45 (abq, J = 11.7 Hz, 2 H, OCH2Ph), 4.73 (d, J = 1.2 Hz, 1 H, C3H), 6.90 (m, 2 H, ArH), 7.05 (m, 2 H, ArH), 7.16-7.35 (m, 5 H, ArH), 8.24 (br s, 1 H, NH); 13C NMR (75.5 MHz, CDCl3) δ 24.8 (t), 27.6 (q), 30.6 (d), 42.6 (d), 49.4 (d), 54.5 (s), 58.2 (s), 61.0 (t), 64.0 (d), 66.4 (t), 70.7 (d), 73.3 (t), 109.8 (d), 121.6 (d), 125.0 (d), 127.2 (d), 127.6 (d), 127.9 (d), 128.2 (d), 130.2 (s), 138.0 (s), 140.5 (s), 177.0 (s), 177.8 (s); mass spectrum (relative intensity) m/z 430 (M+), 324 (26), 91 (100); exact mass calcd. for C26H26N2O4 m/z 430.5024, found m/z 430.1898.
(±)-(3S,3'S,4aR,5S,8S,8aS,9S)-1,3,4,4a,5,7,8,8a-Octahydro-5-(hydroxymethyl)-7-methylspiro[3,5,8-ethanoylidene-6H-pyrano[3,4-c]pyridine-10,3'-indoline]-2'-6-dione (256).

To a solution of 46 mg (0.107 mmol) of benzyl ether 255 in 15 mL of dichloromethane cooled to -78 °C was added 320 μL (0.320 mmol) of 1 M boron tribromide in dichloromethane. The mixture was stirred at -78 °C for 30 min, and then warmed to -20 °C over 30 min. After 30 min at -20 °C, the mixture was quenched with 10 mL of saturated aqueous sodium bicarbonate and stirred for 1 h. The dichloromethane layer was separated and the aqueous layer further extracted with two 30-mL portions of ethyl acetate. The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The residue was triturated with three 3-mL portions of hexane to provide 32 mg (88%) of alcohol 256 as a white solid: mp >310 °C; IR (KBr) 3503, 3257, 1715, 1689 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 2.04 (m, 3 H), 3.34 (dd, J = 14.6, 3.1 Hz, 1 H, C₁₄H), 2.68 (s, 3 H, NCH₃), 3.46 (s, 1 H), 3.86 (br, 2 H, CH₂OH), 4.11 (qd, J = 11.4, 4.7 Hz, 2 H, C₇H), 4.34 (br s, 1 H, C₃H or C₅H), 4.65 (br s, 1 H, C₉H or C₅H), 6.79 (d, J = 7.6 Hz, 1 H, ArH), 6.89 (t, J = 7.5 Hz, 1 H, ArH), 7.15 (t, J = 7.5 Hz, 1 H, ArH), 7.53 (d, J = 7.6 Hz, 1 H, ArH), 10.39 (s, 1 H, NH), the OH proton was not resolved; ¹³C NMR (75.5 MHz, DMSO-d₆) δ 24.1 (t), 27.3 (q), 30.3 (d), 42.0 (d), 48.7 (d), 54.3 (s), 57.6 (t), 59.0 (s), 60.8 (t), 63.6 (d), 71.0 (d), 109.1 (d), 121.1 (d), 125.8 (d), 128.0 (d), 130.6 (s), 141.6 (s), 176.9 (s), 177.5 (s); mass spectrum, m/z (relative intensity) 340 (M⁺, 100), 322 (41), 240 (59); exact mass calcd. for C₁₉H₂₀N₂O₄ m/z 340.1422, found m/z 340.1425.
(±)-(3R*,3'S*,4aR*,5'S*,8'S*,8aS*,9S*)-4,4a,6,7,8,8a-Hexahydro-7-methyl-2',6-dioxospiro[3,5,8-ethanoyliden-1H-pyran[3,4-c]pyridine-10,3'-indoline]-5(3H)-carboxaldehyde (257). To a solution of 30 mg (0.088 mmol) of alcohol 256 in 20 mL of tetrahydrofuran-acetonitrile (1:1) was added 93 mg (0.219 mmol) of the Dess-Martin periodinane. The mixture stirred for 2 h, and an additional 95 mg (0.224 mmol) of periodinane and 5 mL of dichloromethane was added. Stirring continued for an additional 18 h and the mixture was then concentrated in vacuo. The residue was diluted with ether and filtered through Celite. The filtrate was washed with two 10-mL portions of saturated aqueous sodium bicarbonate. The combined basic aqueous layers were extracted with three 10-mL portions of ethyl acetate. The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The residue was dissolved in hot ethyl acetate-dichloromethane and hexane was added to provide 23 mg (77%) of crystalline aldehyde 257 as a white solid: mp >315 °C (dec); IR (KBr) 3265, 1727 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.24 (br d, J = 8.3, 1 H, C₁₆H), 2.32 (ddd, J = 15.2, 5.3, 2.6 Hz, 1 H, C₁₄H), 2.43 (dd, J = 2.9 Hz, 1 H, C₁₄H), 2.82 (br s, 1 H, C₆H), 2.83 (s, 3 H, NCH₃), 2.89 (br t, 1 H, C₁₅H), 3.74 (br t, J = 2.6 Hz, 1 H, C₃H), 4.08 (br s, 2 H, C₁₇H), 4.76 (d, J = 1.7 Hz, 1 H, C₅H), 6.91 (d, J = 7.6 Hz, 1 H, ArH), 6.95-7.02 (m, 2 H, ArH), 7.21-7.27 (m, 1 H, ArH), 8.07 (br s, 1 H, NH), 9.87 (s, 1 H, CHO); ¹³C NMR (75.5 MHz, DMSO-d₆) δ 24.3 (t), 27.3 (q), 28.8 (d), 41.5 (d), 51.0 (d), 53.3 (s), 60.3 (t), 65.2 (d), 68.8 (q), 70.0 (d), 109.9 (d), 121.3 (d), 124.3 (d), 128.6 (d), 130.2 (s), 141.9 (s), 172.8 (s), 175.9 (s), 201.8 (d); mass spectrum, m/z (relative intensity) 338 (M⁺, 16), 228 (22), 188 (35), 152 (100), 42 (46); exact mass calcd. for C₁₉H₁₈N₂O₄ m/z 338.1266, found m/z 338.1262.
(±)-(3R*,3S*,4aR*,5R*,8S*,8aS*,9S*)-1,3,4,4a,5,7,8,8a-Octahydro-7-methyl-5-vinylspiro[3,5,8-ethanlylyldene-6H-pyrano[3,4-c]pyridine-10,3'-Indoline]-2'6-dlone (258).

(±)-21-Oxo-(7R)-gelsemine (258). A mixture of 19 mg (0.056 mmol) of aldehyde 257 and 1 mL (0.50 mmol) of 0.5 M bis(cyclopentadienyl)dimethyltitanium in tetrahydrofuran was warmed under reflux for 40 h. The mixture was cooled to room temperature, 1.5 mL of tetrahydrofuran was added and the mixture allowed to stand for 18 h. The titanium impurities that precipitated were removed by filtration through Celite and washed with dichloromethane. The filtrate was concentrated in vacuo and the residue chromatographed over 1 g of flash silica gel (first dichloromethane; then ethyl acetate-dichloromethane, 1:9, then 25:75, then 1:1, then 75:25) to provide 13.5 mg (71%) of 7-epi-21-oxogelsemine (258) as a off white solid: mp 305-306 °C (dec); IR (KBr) 3236, 1719, 1686 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.21 (m, 3 H, C₆H, C₁₄H, C₁₆H), 2.54 (dd, J = 14.1, 2.4 Hz, 1 H, C₁₄H), 2.60 (br t, partially obscured by dd at δ 2.54, J = 7.4 Hz, 1 H, C₁₅H), 2.81 (s, 3 H, NCH₃), 3.69 (br t, J = 2.6 Hz, 1 H, C₃H), 4.08 (br s, 2 H, C₁₇H), 4.73 (d, J = 1.6 Hz, 1 H, C₁₅H), 5.37 (dd, J = 17.9, 1.1 Hz, 1 H, C₁₈H), 5.70 (dd, J = 11.0, 1.0 Hz, 1 H, C₁₉H), 6.01 (dd, J = 17.9, 11.0 Hz, 1 H, C₁₉H), 6.87, J = 7.7, 0.7 Hz, 1 H, ArH), 6.96 (dt, J = 7.7, 1.1 Hz, 1 H, ArH), 7.21 (dt, J = 7.7, 1.1 Hz, 1 H, ArH), 7.66 (dd, J = 7.7, 0.3 Hz, 1 H, ArH), 8.20 (br s, 1 H, NH); ¹³C NMR (75.5 MHz, CDCl₃) δ 23.9 (t), 27.8 (q), 30.3 (d), 42.1 (d), 52.6 (d), 54.3 (s), 61.0 (t), 61.2 (s), 64.6 (d), 70.9 (d), 109.5 (d), 119.9 (t), 121.5 (d), 127.0 (d), 128.3 (d), 129.8 (s), 134.8 (d), 140.2 (s), 176.2 (s), 177.1 (s); mass spectrum, m/z (relative intensity) 338 (M⁺, 100), 254 (13), 122 (62); exact mass calcd. for C₂₀H₂₀N₂O₃ m/z 336.1475, found m/z 336.1478.
Diethyl N-benzylaziridine-2,3-dicarboxylate (316). To a solution of 27.6 g (160.5 mmol) of diethylfumarate in 100 mL of dichloromethane was added 0.5 mL of 49% aqueous hydrobromic acid followed by 25.5 g (160.0 mmol) of bromine. The mixture was stirred for 5 d, and then washed with 100 mL of saturated aqueous sodium sulfite and 100 mL of saturated aqueous sodium bicarbonate. The combined aqueous layers were extracted with two 25-mL portions of dichloromethane. The combined dichloromethane layers were washed with two 100-mL portions of brine, dried (MgSO₄), filtered and concentrated to afford 48.8 g (90%) of diethyl (meso)-dibromosuccinate 316a which was used without further purification. The ¹H NMR spectrum of this material is not reported here, but does appears in Appendix A.

To a solution of 20 g (59.2 mmol) of diethyl (meso)-dibromosuccinate in 300 mL of 95% ethanol was added 20 g (183.3 mmol) of benzylamine. The mixture was stirred for 3 d, and concentrated in vacuo. The residue was diluted with ether and the insoluble salts were removed by filtration, and washed with ether. The mother liquor was concentrated and the oily residue was chromatographed over 150 g of silica gel (ethyl acetate-hexane, 2.5:97.5, then, 5:95, then 10:90, then 15:85) to provide 10.2 g of partially purified aziridine 316. A second chromatography over 75 g of silica gel (ethyl acetate-hexane, 2.5:97.5, then 5:95, then 8:92, then 10:90) gave 8.0 g (48%) of pure aziridine 316 as a yellow oil. The ¹H NMR spectrum of this material is not reported here, but does appears in Appendix A.
S,S'-Diphenyl-1,4-Dithiofumarate (317). To solution of 79 g (0.52 mol) of fumaryl chloride in 900 mL of dichloromethane was added 142 g (1.04 mol) of potassium carbonate followed by 102 g (0.93 mol) of thiophenol in 900 mL of dichloromethane over a 7-h period. The mixture was then poured into an ice cold (crushed ice) solution of 60 g of sodium hydroxide in 1.5 L of water over a 1.2-h period, while maintaining the temperature below 10 °C. The dichloromethane layer was separated and the aqueous layer was extracted with three 200-mL portions of dichloromethane. The combined organic layers were washed with three 1-L portions of brine, dried (MgSO$_4$), decolorizing carbon (Norit A) was added, and the mixture was filtered through Celite and concentrated. The residual red solid was triturated with ether, chilled to -20 °C, collected by filtration and washed with ether-hexane (1:1) to provide 83 g (60%) of dithioester 317 as a yellow solid. This material was used without further purification: mp 133-135 °C (lit 125-129 °C). The product can be recrystallized from hot ethyl acetate-hexane if desired (mp 135-136 °C). A $^1$H NMR spectrum of 317 is not reported here, but does appear in Appendix A.

Diethyl (±)-(2$R^*$,3$R^*$,4$R^*$,5$S^*$)-1-benzyl-3,4-bis[(phenylthio)carbonyl]-2,5-pyrroolidinedicarboxylate (315). To a solution of 15.0 g (53.0 mmol) of diethyl-N-benzyl-aziridine-2,3-dicarboxylate 316 in 130 mL of toluene was added 16.7 g (55.7 mmol) of S,S'-diphenyl 1,4-dithiofumarate 317. The mixture was warmed under reflux for 27 h, cooled to room temperature,
and concentrated in vacuo. The residue was diluted with 250 mL of ether followed by 375 mL of hexane. The mixture was allowed to stand at room temperature of 72 h, and the resulting solid was collected by filtration and washed with ether-hexane (1:1) to provide 16.2 g (52%) of pyrrolidine 315 as an off white solid: mp 94-96 °C; IR (neat) 1731 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.21 (t, J = 7.1 Hz, 3 H, CH₃), 1.30 (t, J = 7.2 Hz, 3 H, CH₃), 3.88-4.25 (m, 9 H), 4.40 (dd, J = 9.4, 7.4 Hz, 1 H, CHCO₂SPh), 7.24-7.36 (m, 5 H, ArH), 7.38 (s, 5 H, ArH), 7.42 (s, 5 H, ArH); ¹³C NMR (75.5 MHz, CDCl₃) δ 13.9 (q), 14.1 (q), 56.2 (d), 56.6 (d), 56.9 (l), 61.0 (l), 61.2 (l), 66.5 (d), 67.6 (d), 126.6 (s), 126.9 (s), 127.4 (d), 128.2 (d), 128.9 (d), 129.1 (d), 129.56 (d), 129.57 (d), 134.2 (d), 134.3 (d), 136.9 (s), 169.7 (s), 170.6 (s), 192.7 (s), 196.5 (s), one aromatic doublet was not resolved; mass spectrum, m/z (relative intensity) 577 (M⁺, 1), 506 (7), 504 (51), 110 (22), 109 (18), 91 (100); exact mass calcd. for C₃₁H₃₁N₆O₆S₂ m/z 577.1594, found m/z 577.1605.

Anal. calcd. for C₃₁H₃₁N₆O₆S₂: C, 64.45; H, 5.41. Found: C, 64.39; H, 5.44.

Ethyl (±)-(2'R,3'R,3a'R,6a'S')-1-benzylhexahydro-3-(hydroxymethyl)-6-oxo-1H-furo-[3,4-b]pyrrole-2-carboxylate (318). To a suspension of 5.4 g (9.26 mmol) of dithioester 315 in 150 mL of tetrahydrofuran-ethanol (2:1) chilled to -5 °C was added 1.33 g (35.1 mmol) of sodium borohydride in several portions over a 2-h period. The mixture was stirred for 15 min, and then 27 g of ammonium chloride was added followed by 75 mL of water in several portions. The mixture was stirred for 5 h, and was then concentrated to near dryness in vacuo. The residue was partitioned between 200 mL of water and 75 mL of ethyl acetate. The organic layer was separated and the aqueous phase was extracted with two 50-mL portions of ethyl acetate. The
combined organic layers were washed with three 100-mL portions of brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (ethyl acetate-dichloromethane, 10:90, then 20:80, then 30:70, and finally 50:50) to provide 2.1 g (72%) of lactone 318 as a clear oil: IR (neat) 3454 (broad), 1763, 1726 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.21 (t, J = 7.1 Hz, 3 H, CH₃), 1.91 (br, 1 H, OH), 2.42-2.49 (m, 1 H, C₂H), 2.93-3.02 (m, 1 H, C₃H), 3.48 (d, J = 5.6 Hz, 1 H, C₂H), 3.63 (qd, J = 10.6, 6.0 Hz, 2 H, CH₂OH), 3.61 (d, J = 8.6 Hz, 1 H, C₆aH), 4.04 (q, J = 7.2 Hz, 2 H, CO₂CH₂Me), 4.13 (s, 2 H, NCH₂Ph), 4.25 (dd, J = 9.3, 5.3 Hz, 1 H, C₄H), 4.45 (t, J = 9.1 Hz, 1 H, C₄H), 7.23-7.34 (m, 5 H, ArH); ¹³C NMR (75.5 MHz, CDCl₃) δ 13.9 (q), 41.5 (d), 50.5 (d), 54.1 (t), 61.1 (t), 62.7 (d), 63.8 (t), 67.7 (d), 71.5 (t), 127.4 (d), 128.2 (d), 129.5 (d), 135.9 (s), 172.3 (s), 175.0 (s); mass spectrum, m/z (relative intensity) 319 (M⁺, 1), 246 (77), 91 (100), 69 (32); exact mass calcd. for C₁₇H₂₁NO₅ m/z 319.1420, found m/z 319.1422.

![319](image)

Ethyl (±)-(2R*,3R*,3aR*,6aS*)-1-benzyl-3-[(tert-butyldimethylsiloxy)methyl]hexahydro-6-oxo-1H-furo[3,4-b]pyrrole-2-carboxylate (319). To solution of 4.6 g (14.42 mmol) of alcohol 318 and 1.23 g (18.08 mmol) of imidazole in 50 mL of N,N-dimethylformamide was added 2.65 g (17.66 mmol) of t-butyldimethylsilyl chloride. The mixture was stirred at room temperature for 4.5 h, and then an additional 416 mg (6.1 mmol) of imidazole and 870 mg (5.8 mmol) of t-butyldimethylsilyl chloride was added. The mixture was stirred for 18 h, and was then partitioned between 250 mL of saturated aqueous sodium bicarbonate and 50 mL of ethyl acetate. The organic layer was separated and the aqueous phase was extracted with three 75-mL portions of ethyl acetate. The combined organic layers were washed with six 75-mL portions of brine, dried
(MgSO₄), filtered and concentrated in vacuo to provide 7.4 g of crude silyl ether 319 which was chromatographed over 50 g of silica gel (first hexane; then ethyl acetate-hexane, 5:95, 10:90, 15:85) to provide 6.2 g (100%) of pure silyl ether 319 as a viscous oil: IR (neat) 1770, 1743 cm⁻¹; ¹H NMR* (300 MHz, CDCl₃) δ 0.00 (s, 6 H, SiCH₃), 0.82 (s, 9 H, CCH₃), 1.17 (t, J = 7.1 Hz, 3 H, CH₃), 2.37 (m, 1 H, C₃H), 2.90 (m, 1 H, C₃₆H), 3.43 (d, J = 6.3 Hz, 1 H, C₂H), 3.49 (dd, J = 10.0, 5.7 Hz, 1 H, CH₂OSi), 3.59 (m, 1 H, CH₂OSi), 3.59 (d, J = 10.0 Hz, 1 H, C₆₆H), 3.98 (q, J = 7.1 Hz, 2 H, CO₂CH₂Me), 4.01 (d, J = 14.0 Hz, 1 H, NCH₂Ph), 4.12 (d, J = 14.1 Hz, 1 H, NCH₂Ph), 4.29 (dd, J = 9.0, 6.1 Hz, 1 H, C₄H), 4.41 (t, J = 8.8 Hz, 1 H, C₄H), 7.20-7.30 (m, 5 H, ArH); ¹³C NMR (75.5 MHz, CDCl₃) δ -5.6 (q), 13.9 (q), 17.9 (s), 25.6 (q), 42.0 (d), 50.5 (d), 54.5 (t), 60.7 (t), 63.1 (d), 63.3 (t), 67.5 (d), 71.6 (t), 127.3 (d), 128.06 (d), 129.7 (d), 135.7 (s), 172.4 (s), 175.1 (s); mass spectrum, m/z (relative intensity) 433 (M⁺, 3), 360 (85), 91 (100); exact mass calcd. for C₂₃H₃₅NO₅Si m/z 433.2285, found m/z 433.2276.

**Ethyl (±)-(2R,3R,3aR,6aS*)-1-benzyl-3-[(tert-butyldimethylsiloxy)methyl]hexahydro-6-hydroxy-1H-furo[3,4-b]pyrrole-2-carboxylate (320).** To a solution of 6.5 g (15.01 mmol) of lactone 319 in 250 mL of ether cooled to -100 °C was added 19.7 mL (19.70 mmol) of 1 M diisobutylaluminum hydride in hexane over a 45-min period. The mixture was stirred for 25 min, and was then quenched with 30 mL of absolute ethanol. The cold bath was removed, the mixture was warmed to room temperature, and then concentrated. The residue was dissolved in ether and passed through a pad of 34 g of silica gel (ether). The ether was concentrated in vacuo and the residue chromatographed over 145 g of silica gel (hexane-dichloromethane-ethyl acetate, first 60:39:1, then 60:38:2; then ethyl acetate-hexane, 30:70) to provide 1.27 g (20%) of
recovered lactone 319. Continued elution afforded 3.9 g (60%) of hemiacetal 320 as a mixture of diastereomers: IR (neat) 3408 (broad), 1731 cm\(^{-1}\); \(^1\)H NMR (major diastereomer, 300 MHz, CDCl\(_3\)) \(\delta\) 0.03 (s, 3 H, SiCH\(_3\)), 0.04 (s, 3 H, SiCH\(_3\)), 0.88 (s, 9 H, Si(CH\(_3\))\(_3\)), 1.20 (t, \(J = 7.1\) Hz, 3 H, CO\(_2\)CH\(_2\)CH\(_3\)), 2.27 (m, 1 H), 2.81 (m, 1 H), 3.54-3.66 (m, 4 H), 3.70-3.85 (m, 4 H), 4.03 (q, \(J = 7.1\) Hz, 2 H, CO\(_2\)CH\(_2\)Me), 4.80 (br d, 1 H, C\(_6\)H), 5.72 (br, 1 H, OH), 7.23-7.37 (m, 5 H, ArH), [peaks at \(\delta\) 0.86 (s, CCH\(_3\)), 1.24 (t, \(J = 7.1\) Hz, CO\(_2\)CH\(_2\)CH\(_3\)), 4.86 (br d, C\(_6\)H), are attributed to the minor diastereomer]; \(^13\)C NMR (major diastereomer, 75.5 MHz, CDCl\(_3\)) \(\delta\) -5.66 (q), -5.61 (q), 14.0 (q), 18.1 (s), 25.7 (q), 44.4 (d), 50.9 (d), 58.7 (t), 60.9 (t), 62.2 (t), 68.4 (t), 70.7 (d), 71.0 (d), 95.6 (d), 127.7 (d), 128.3 (d), 129.5 (d), 136.4 (s), 173.0 (s); mass spectrum, \(m/z\) (relative intensity) 435 (M\(^+\), 2), 362 (73), 316 (15), 244 (13), 91 (100); exact mass calcd. for C\(_{23}\)H\(_{37}\)NO\(_5\)Si \(m/z\) 435.2442, found \(m/z\) 435.2435.

\[ HO \quad OTBDM S \]

\[ \text{5} \quad \text{N} \quad \text{2} \quad \text{CO}_2\text{Et} \]

Bn

321

Ethyl (±)-(2\(R^*\),3\(R^*\),4\(R^*\),5\(R^*\))-1-benzyl-3-[(tert-butyldimethylsiloxy)methyl]-4-(hydroxymethyl)-5-vinyl-2-pyrrolidinecarboxylate (321). To a suspension of 591 mg (14.77 mmol) potassium hydride in 20 mL of toluene was added 5 mL of dimethylsulfoxide. The mixture was stirred for 15 min, until hydrogen evolution ceased and then 6.6 g (18.48 mmol) of methyltriphenylphosphonium bromide was added in several portions. The yellow solution was stirred for 15 min, cooled to 10 °C, and then 1.6 g (3.67 mmol) of hemiacetal 320 in 8 mL of toluene was added. The reaction was closely monitored by tlc (30% ethyl acetate-hexane), and after 45 min the mixture was poured into 1N aqueous hydrochloric acid. The mixture was then made basic with saturated aqueous sodium bicarbonate, and extracted with three 25-mL portions of ethyl acetate. The combined organic layers were washed with three 40-mL portions of brine,
dried (MgSO₄), filtered and concentrated in vacuo. The residue was diluted with ether-hexane.

The Wittig by-products that precipitated/crystallized were removed by filtration. The filtrate was concentrated in vacuo and the residue was passed through a 8 g pad of silica gel (ethyl acetate-hexane, 3:7). This material (976 mg) was then combined with similar runs of 120 mg and 113 mg which gave 58 mg and 41 mg of crude product, respectively, for further purification. Chromatography over 13 g of silica gel (dichloromethane-hexane, 1:1; then dichloromethane; then ethyl acetate-dichloromethane, 2:98, 10:90) gave 593 mg (37%) of olefin 321 as a clear oil:

IR (neat) 3432 (br), 1744 cm⁻¹; ¹H NMR* (300 MHz, CDCl₃) δ -0.01 (s, 3 H, SiCH₃), 0.01 (s, 3 H, SiCH₃), 0.84 (s, 9 H, Si(CH₃)₃), 1.17 (t, J = 7.1 Hz, 3 H, CO₂CH₂CH₃), 2.09 (m, 1 H, C₄H), 2.34 (m, 1 H, C₃H), 3.05 (d, J = 7.2 Hz, 1 H, C₂H) 3.37 (t, J = 7.4 Hz, 1 H, C₃H), 3.55 (m, 3 H, one CH₂OH, one CH₂OSi and OH), 3.59 (d, J = 12.3 Hz, 1 H, NCH₂Ph), 3.67 (dd, J = 10.0, 4.4 Hz, 1 H, CH₂OSi), 3.78 (dd, J = 10.7, 4.4 Hz, 1 H, CH₂OH), 3.87 (d, J = 13.9 Hz, 1 H, NCH₂Ph), 3.97 (qd, J = 7.1, 1.4 Hz, 2 H, CO₂CH₂Me), 5.30 (m, 2 H, =CH₂), 5.95 (m, 1 H, =CH), 7.16-7.29 (m, 5 H, ArH); ¹³C NMR (75.5 MHz, CDCl₃) δ -5.6 (q), 13.9 (q), 18.0 (s), 25.6 (q), 47.1 (d), 48.3 (d), 55.3 (t), 60.6 (t), 63.5 (t), 64.1 (t), 66.3 (d), 68.8 (d), 119.2 (t), 127.1 (d), 127.8 (d), 129.8 (d), 135.7 (s), 136.8 (d), 173.0 (s); mass spectrum, m/z (relative intensity) 433 (M⁺, 2), 376 (8), 360 (89), 91 (100); exact mass calcd. for C₂₄H₃₉N⁰₄Si m/z 433.2649, found m/z 433.2646.

![Chemical Structure](image)

**322**

tert-Butyl (±)-(2R*,3 R*,4R*,5R*)-1-benzyl-3-[(tert-butylidimethylsiloxy)methyl]-4-(hydroxymethyl)-5-vinyl-2-pyrrolidinecarboxylate (322). To a suspension of 2.0 g (21.4 mmol) of potassium t-butoxide, prepared from 835 mg (21.4 mmol) of potassium metal and freshly distilled t-buty1 alcohol, in 10 mL of toluene was added 8.2 g (22.9 mmol) of
methyltriphenylphosphonium bromide in several portions. The mixture was stirred at room
temperature for 15 min and then 1.2 g (2.7 mmol) of hemiacetal 320 in 5 mL of toluene was
added. The mixture was warmed to 45 °C for 20 min, poured into cold 1 N aqueous hydrochloric
acid, neutralized with solid sodium bicarbonate and extracted with three 30-mL portions of ethyl
acetate. The combined organic layers were washed with three 30-mL portions of brine, dried
(MgSO₄), filtered and concentrated. The residue was diluted with ether-hexane and the Wittig by-
products that crystallized were removed by filtration. The mother liquor was passed through a 10
g pad of silica gel (ethyl acetate-hexane, 3:7) to provide 259 mg (20%) of olefin 322 as a clear oil:
IR (neat) 3400 (broad) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.00 (s, 3 H, SiCH₃), 0.01 (s, 3 H,
SiCH₃), 0.84 (s, 9 H, SiC(CH₃)₃), 1.37 (s, 9 H, CO₂C(CH₃)₃), 2.08 (m, 1 H, C₄H), 2.29 (s, 1 H,
C₃H), 2.94 (d, J = 7.5 Hz, 1 H, C₂H), 3.35 (dd, J = 8.3, 7.1 Hz, 1 H, C₅H), 3.32-3.85 (m, 6 H,
CH₂O manifold and NCH₂Ph), 5.25 (m, 1 H, =CH₂), 5.30 (m, 1 H, =CH₂), 5.94 (m, 1 H, =CH),
7.19-7.29 (m, 5 H, ArH), the OH proton was not resolved; ¹³C NMR (75.5 MHz, CDCl₃) δ -5.6 (q,
18.0 (s), 25.7 (q), 27.7 (q), 47.1 (d), 48.5 (d), 55.0 (t), 63.5 (t), 64.2 (t), 66.5 (d), 68.6 (d), 80.8 (s),
118.8 (t), 127.0 (s), 129.8 (d), 135.9 (s), 137.1 (d), 172.2 (s); mass spectrum, m/z
(relative intensity) 461 (M⁺, 0.2), 360 (100), 91 (54); exact mass calc. for C₂₆H₄₃N₀₄Si m/z
461.2963, found m/z 461.2973.

![Diagram](323.png)

Ethyl (±)-(2R*,3R*,4R*,5R*)-1-benzyl-3-[(tert-butyldimethylsiloxy)methyl]-4-(hydroxy-
methyl)-5-vinyl-2-pyrrolidinecarboxylate, methanesulfonate (ester) (323). To a solution of
585 mg (1.34 mmol) of alcohol 321 in 15 mL of dichloromethane cooled to 5 °C was added 334
mg (2.92 mmol) of methanesulfonyl chloride followed by 314 mg (3.10 mmol) of triethylamine.
The mixture was stirred of 20 min, and then 35 mL of saturated aqueous sodium bicarbonate was added and the organic phase was separated. The aqueous layer was extracted with two 25-mL portions of dichloromethane. The combined organic layers were washed with 50 mL of brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (first dichloromethane-hexane, 1:1; then dichloromethane; then ethyl acetate-dichloromethane, 3:97). A second chromatography over 10 g of silica gel (hexane; then ethyl acetate-hexane, 2:98, 3:97, 5:95, 8:92, 10:90, 20:80) gave 610 mg (88%) of mesylate 323 as a clear oil: IR (neat) 1738 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.00 (s, 3 H, SiCH₃), 0.01 (s, 3 H, SiCH₃), 0.84 (s, 9 H, CCH₃), 1.11 (t, J = 7.1 Hz, 3 H, CO₂CH₂CH₃), 2.27 (m, 1 H, C₄H), 2.40 (m, 1 H, C₅H), 2.97 (s, 3 H, SO₂CH₃), 3.20 (d, J = 6.3 Hz, 1 H, C₂H), 3.45 (t, J = 7.7 Hz, 1 H, C₆H), 3.58 (m, 3 H), 3.81-3.93 (m, 3 H), 4.31-4.41 (m, 2 H), 5.28 (dd, J = 10.2, 1.3 Hz, 1 H, =CH₂), 5.35 (d, J = 17.2, 1.0 Hz, 1 H, C=CH₂), 5.77 (m, 1 H, =CH), 7.16-7.28 (m, 5 H, ArH); ¹³C NMR (75.5 MHz, CDCl₃) δ -5.6 (q), 13.8 (q), 18.0 (s), 25.7 (q), 36.9 (q), 44.0 (d), 47.1 (d), 55.6 (t), 60.4 (t), 63.6 (t), 66.7 (d), 67.8 (d), 70.5 (t), 119.2 (t), 126.9 (d), 127.8 (d), 129.4 (d), 136.0 (d), 136.6 (s), 173.5 (s); mass spectrum, m/z (relative intensity) 511 (M⁺, 2), 438 (100), 324 (7), 153 (24), 91 (91), 73 (12), exact mass calcd. for C₂₅H₄₁N O₆SSi m/z 511.2425, found m/z 511.2422.

**tert-Butyl (±)-(2R,3 R',4'R',5'R')-1-benzyl-3-[(tert-butylidimethylsiloxy)methyl]-4-(hydroxymethyl)-5-vinyl-2-pyrrolidinecarboxylate, methanesulfonate (ester) (324).** To a solution of 255 mg (0.55 mmol) of alcohol 322 in 10 mL of dichloromethane cooled to 10 °C was added 125 mg (1.09 mmol) of methanesulfonyl chloride followed by 116 mg (1.14 mmol) of triethylamine. The mixture was stirred for 15 min, diluted with 35 mL of saturated aqueous
sodium bicarbonate and the organic layer was separated. The aqueous phase was extracted with 10 mL of dichloromethane. The combined organic layers were washed with two 20-mL portions of brine, dried (MgSO₄), filtered and concentrated in vacuo to afford 293 mg (98%) of mesylate 324 as a clear oil which was used without further purification: IR (neat) 1737 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.00 (s, 3 H, SiCH₃), 0.01 (s, 3 H, SiCH₃), 0.85 (s, 9 H, Si(CH₃)₃), 1.33 (s, 9 H, CO₂CCH₃), 2.20 (m, 1 H, C₄H), 2.43 (m, 1 H, C₃H), 2.97 (s, 3 H, SO₂CH₃), 3.12 (d, J = 5.5 Hz, 1 H, C₂H), 3.45 (t, J = 7.6 Hz, 1 H, C₅H), 3.60 (m, 3 H), 3.87 (d, J = 13.4 Hz, 1 H), 4.36 (br ABq, 2 H), 5.27 (d, J = 10.3 Hz, 1 H, =CH₂), 5.35 (d, J = 17.1 Hz, 1 H, =CH₂), 5.76 (m, 1 H, =CH), 7.18-7.29 (m, 5 H, ArH); ¹³C NMR (75.5 MHz, CDCl₃) δ -5.7 (q), 17.9 (s), 25.6 (q), 27.6 (q), 36.8 (q), 44.0 (d), 47.0 (d), 55.1 (t), 63.5 (t), 66.5 (d), 67.4 (d), 70.3 (t), 80.4 (s), 118.9 (t), 126.8 (d), 127.8 (d), 129.5 (d), 136.0 (d), 136.5 (s), 172.6 (s); mass spectrum, m/z (relative intensity) 539 (M⁺, 0.2), 438 (100), 324 (24), 91 (86); exact mass calcd. for C₂₇H₄₅N₅O₆SSi m/z 5329.2738, found m/z 539.2731.

![325](image)

**Ethyl (±)-(2R*,3R*,4R*,5R*)-1-benzyl-3-[(tert-butyldimethylsiloxy)methyl]-4-(cyano-methyl)-5-vinyl-2-pyrrolidinecarboxylate (325).** To a solution of 600 mg (1.17 mmol) of mesylate 323 in 10 mL of dimethylformamide was added 780 mg (12.0 mmol) of potassium cyanide. The mixture was warmed to 80 °C, stirred for 16 h, and an additional 390 mg (6.0 mmol) of potassium cyanide was then added. The mixture was stirred for 6 h, and was then cooled to room temperature, and partitioned between 25 mL of saturated aqueous sodium bicarbonate and 25 mL of ethyl acetate. The organic layer was separated and the aqueous phase was extracted with three 20-mL portions of ethyl acetate. The combined organic layers were washed with five
25-mL portions of brine, dried (MgSO₄), filtered and concentrated in vacuo. The crude residue was chromatographed over 6 g of silica gel (first hexane; then ethyl acetate-hexane, 3:97, then 5:95) to provide 410 mg (79%) of nitrile 325 as a clear oil: IR (neat) 2247, 1740 cm⁻¹; ¹H NMR (300 MHz, C₆D₆) δ -0.4 (s, 3 H, SiCH₃), -0.3 (s, 3 H, SiCH₃), 0.82 (t, J = 7.1 Hz, 3 H, CO₂CH₂CH₃), 0.87 (s, 9 H, C(CH₃)₃), 1.93 (dd, J = 15.8, 5.4 Hz, 1 H, CH₂CN), 2.02 (m, 1 H, C₄H), 2.32 (m, 1 H, C₃H), 2.33 (dd, J = 15.9, 9.4 Hz, 1 H, CH₂CN), 3.21 (m, 2 H), 3.44 (m, 3 H), 3.71 (qd, J = 7.1, 2.0 Hz, 2 H, CO₂CH₂CH₃), 3.81 (d, J = 13.9 Hz, 1 H, OCH₂), 4.96 (dd, J = 9.9, 1.8 Hz, 1 H, =CH₂), 5.07 (dd, J = 16.1, 0.7 Hz, 1 H, =CH₂), 5.40 (dd, J = 18.2, 10.1, 8.14 Hz, 1 H, =CH), 7.00-7.24 (m, 5 H, ArH); ¹³C NMR (75.5 MHz, C₆D₆) δ -5.4 (q), 14.0 (q), 18.3 (s), 18.9 (t), 26.0 (q), 41.9 (d), 50.1 (d), 56.0 (l), 60.4 (l), 63.9 (l), 67.2 (d), 68.6 (d), 119.1 (s), 119.3 (l), 127.2 (d), 128.1 (d), 129.7 (d), 136.5 (d), 137.6 (s), 173.0 (s); mass spectrum, m/z (relative intensity) 442 (M⁺, 2), 369 (97), 237 (5), 91 (100), 73 (23); exact mass calcd. for C₂₅H₃₈N₂O₃Si m/z 442.2653, found m/z 442.2655.

![Structure of 326](image)

**tert-Butyl (±)-(2'R,3'R,4'R,5'R)-1-benzyl-3-[(tert-butyldimethylsiloxy)methyl]-4-(cyanomethyl)-5-vinyl-2-pyrrolidinecarboxylate (326).** To a solution of 290 mg (0.54 mmol) of mesylate 324 in 25 mL of dimethylformamide was added 450 mg (6.92 mmol) of potassium cyanide. The mixture was warmed to 90 °C, stirred for 12 h, poured into 25 mL of saturated aqueous sodium bicarbonate and extracted with three 15-mL portions of ethyl acetate. The combined organic layers were washed with five 20-mL portions of brine, dried (MgSO₄), filtered and concentrated in vacuo to provide 248 mg (98%) of crude 326 which was chromatographed over 5 g of silica gel (first hexane; then ethyl acetate-hexane, 3:97, then 5:95) to provide 198 mg
(78%) of pure nitrile 326 as a clear oil: IR (neat) 2248, 1737 cm\(^{-1}\); \(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)) \(\delta\) -0.02 (s, 3 H, SiCH\(_3\)), 0.00 (s, 3 H, SiCH\(_3\)), 0.89 (s, 9 H, SiC(CH\(_3\))\(_3\)), 1.23 (s, 9 H, CO\(_2\)C(CH\(_3\))\(_3\)), 1.93 (dd, \(J = 16.3, 5.4\) Hz, 1 H, CH\(_2\)CN), 2.08 (m, 1 H, C\(_4\)H), 2.33 (m, 1 H, C\(_3\)H), 2.41 (dd, \(J = 16.3, 10.0\) Hz, 1 H, CH\(_2\)CN), 3.14 (d, \(J = 5.6\) Hz, 1 H, C\(_2\)H), 3.25 (t, \(J = 7.7\) Hz, 1 H, C\(_3\)H), 3.46 (qd, \(J = 10.2, 5.7\) Hz, 2 H, CH\(_2\)OSi), 3.51 (d, \(J = 14.6\) Hz, 1 H, NCH\(_2\)Ph), 3.82 (d, \(J = 14.0\) Hz, 1 H, NCH\(_2\)Ph), 4.95 (d, \(J = 10.1\) Hz, 1 H, =CH\(_2\)), 5.07 (d, \(J = 17.2\) Hz, 1 H, =CH\(_2\)), 5.40 (ddd, \(J = 17.2, 10.1, 8.1\) Hz, 1 H, =CH), 7.02-7.27 (m, 5 H, ArH); \(^1\)C NMR (75.5 MHz, C\(_6\)D\(_6\)) \(\delta\) -5.4 (q), -5.3 (q), 18.3 (s), 18.8 (t), 26.0 (q), 27.8 (q), 42.0 (d), 50.1 (d), 55.9 (t), 64.0 (t), 67.5 (d), 68.5 (d), 80.2 (s), 119.1 (s), 119.1 (s), 127.2 (d), 128.2 (d), 129.8 (d), 136.6 (d), 137.7 (s), 172.4 (s); mass spectrum, \(m/z\) (relative intensity) 470 (M\(^+\), 0.2), 369 (100), 91 (83); exact mass calcd. for C\(_{27}\)H\(_{42}\)N\(_2\)O\(_3\)Si \(m/z\) 470.2966, found \(m/z\) 470.2977.

\[
\begin{align*}
\text{CN} & \quad \text{OTBDMS} \\
\begin{array}{c}
\text{N} \\
\text{OH}
\end{array} & \quad \begin{array}{c}
\text{Bn}
\end{array}
\end{align*}
\]

(\(\pm\)\-(2\(R\),3\(R\),4\(R\),5\(R\))-1-Benzyl-4-[(\(tert\)-butyldimethylsiloxy)methyl]-5-(hydroxymethyl)-2-vinyl-3-pyrrolidineacetonitrile (327)). To a solution of 354 mg (0.80 mmol) of ester 325 in 10 mL of methanol was added 400 mg (10.2 mmol) of sodium borohydride in several portions. The mixture was stirred for 30 min, an additional 400 mg (10.2 mmol) of sodium borohydride was added and the mixture stirred for 18 h. An additional two 400 mg (10.2 mmol) portions of sodium borohydride were added over 6 h. The mixture was then added to ice cold 1 \(N\) aqueous hydrochloric acid, neutralized with saturated aqueous sodium bicarbonate and extracted with four 25-mL portion of ethyl acetate. The combined organic layers were washed with 25 mL of saturated aqueous sodium bicarbonate, three 25-mL portion of brine, dried (MgSO\(_4\)), filtered and concentrated in vacuo to provide 290 mg of crude alcohol 327 which was
chromatographed over 4 g of silica gel (ethyl acetate-hexane; first 5:95, then 8:92, then 10:90, then 20:80) to provide 193 mg (60%) of pure alcohol 327 as a viscous oil: IR (neat) 3319 cm⁻¹;¹H NMR (300 MHz, C₆D₆) δ -0.04 (s, 3 H, SiCH₃), -0.02 (s, 3 H, SiCH₃), 0.88 (s, 9 H, SiC(CH₃)₃), 1.80-2.02 (m, 4 H), 2.05 (m, 1 H), 2.43 (m, 1 H), 3.13 (m, 1 H), 3.24-3.39 (m, 5 H), 3.59 (d, J = 14.3 Hz, 1 H), 4.90-4.00 (m, 2 H, =CH₂), 5.25-5.37 (m, 1 H, =CH), 7.02-7.21 (m, 5 H); ¹³C NMR (75.5 MHz, C₆D₆) δ -5.4 (q), 18.3 (s), 19.1 (l), 26.0 (q), 41.1 (d), 48.1 (d), 55.6 (l), 61.4 (l), 64.4 (l), 67.9 (d), 69.3 (d), 119.0 (l), 119.3 (s), 127.4 (d), 128.5 (d), 129.1 (d), 137.1 (d), 138.6 (s), a peak at 99.9 (l) ppm is an instrument artifact; mass spectrum, m/z (relative intensity) 385 (3), 369 (100), 343 (19), 91 (72), 73 (15), no parent peak present.

CN OTBDMS

328

(±)-(2R⁰,3R⁰,4R⁰,5R⁰)-1-Benzyl-4-[( tert-butyldimethylsiloxy)methyl]-5-formyl-2-vinyl-3-pyrrolidineacetonitrile (328). To a solution of 190 mg (0.475 mmol) of alcohol 327 and 500 µL of pyridine in 35 mL of dichloromethane was added 834 mg (1.97 mmol) of the Dess-Martin periodinane.⁵⁴ The mixture was stirred for 30 min, and then 30 mL of saturated aqueous sodium bicarbonate was added. The dichloromethane layer was separated, and the aqueous layer extracted with three 20-mL portions of dichloromethane. The combined organic extracts were washed with 30 mL of brine, dried (MgSO₄), filtered through Celite and concentrated in vacuo. The residue was triturated with 4% ethyl acetate in hexane and the mother liquor was chromatographed over 3 g of silica gel (ethyl acetate-hexane; first 4:96, then 8:92, then 10:90). The material from the column was concentrated in vacuo, dissolved in 20 mL of toluene and concentrated in vacuo to azetrop off residual pyridine to afford 165 mg (87%) of aldehyde 328 as a clear oil: IR (neat) 2247, 1726 cm⁻¹;¹H NMR (300 MHz, C₆D₆) δ -0.03 (s, 6 H, SiCH₃), 0.87
(±)-(αE,2R*,3S*,4S*,5S*)-1-Benzyl-3-[(tert-butyldimethylsiloxy)methyl]-4-(cyanomethyl)-5-vinyl-2-pyrrolidineacrylonitrile (329). To a solution of 162 mg (0.407 mmol) of aldehyde 328 in 10 mL of dichloromethane was added 245 mg (0.813 mmol) of (cyanomethylidene)triphenylphosphorane. The mixture was stirred for 18 h, and was then concentrated in vacuo. The residue was triturated with ethyl acetate-hexane (1:9), and the mother liquor was decanted and passed through a pad of 3 g of silica gel (ethyl acetate-hexane, 1:9) to afford 168 mg (97%) of α,β-unsaturated nitrile 329 as a clear oil: IR (neat) 2246, 2223 cm⁻¹; 1H NMR (300 MHz, CDCl₃) δ 0.01 (s, 3 H, SiCH₃), 0.02 (s, 3 H, SiCH₃), 0.85 (s, 9 H, SiC(CH₃)₃), 1.84 (m, 1 H, C₃H), 2.30 (m, 1 H, C₄H), 2.42 (m, 2 H, CH₂CN), 3.11 (t, J = 7.6 Hz, 1 H, C₂H), 3.37 (t, J = 7.6 Hz, 1 H, C₂H), 3.47-3.60 (m, 3 H, CH₂O and one NCH₂Ph), 3.78 (d, J = 13.9 Hz, 1 H, NCH₂Ph), 5.32 (m, 3 H, =CH₂ and =CHCN), 5.70 (m, 1 H, CH=CH₂), 6.48 (dd, J =
16.3, 7.8 Hz, 1 H, CH=CHCN), 7.13-7.29 (m, 5 H, ArH), a \(^1\)H NMR was also obtained in C\(_6\)D\(_6\) and appears in Appendix A; \(^{13}\)C NMR (75.5 MHz, C\(_6\)D\(_6\)) \(\delta\) -5.5 (q), -5.5 (q), 18.2 (s), 19.2 (t), 25.9 (q), 28.0 (s), 40.6 (d), 51.4 (d), 55.3 (t), 62.1 (t), 66.9 (d), 68.2 (d), 100.4 (d), 116.8 (s), 118.7 (s), 119.2 (t), 129.7 (d), 136.4 (d), 137.0 (s), 155.7 (d), one aromatic doublet is obscured by the solvent; mass spectrum, \(m/z\) (relative intensity) 421 (M\(^+\), 7), 330 (16), 276 (19), 91 (100), 73 (17); exact mass calcd. for C\(_{25}\)H\(_{35}\)N\(_3\)OSi \(m/z\) 421.2551, found \(m/z\) 421.2548.

\[ \text{OTBDMS} \]

\[ \text{Bn} \]

\[ \text{330} \]

(\(\pm\)-(2\(R^*\),3\(S^*\),4\(S^*\),5\(S^*\))-1-Benzyl-3-[(tert-butyldimethylsiloxy)methyl]-4-(cyanomethyl)-5-ethyl-2-pyrrolidineproponitrile (330). A solution of 145 mg (0.344 mmol) of olefin 329 and 20 mg of 10% palladium on carbon in 95% ethanol was stirred under 1 atmosphere of hydrogen. After 4 h, an additional 16 mg of 10% palladium on carbon was added and the mixture was stirred for 1.5 h. The mixture was then filtered through Celite, concentrated in vacuo, and the residue was chromatographed over 5 g of silica gel (ethyl acetate-hexane-triethylamine; 2:97:1, then 4:85:1, then 5:94:1, then 10:89:1) to afford 96 mg (65%) of pyrrolidine 330 as a viscous oil: IR (neat) 2246 cm\(^{-1}\); \(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)) \(\delta\) 0.00 (s, 3 H, SiCH\(_3\)), 0.02 (s, 3 H, SiCH\(_3\)), 0.49 (t, \(J = 7.3\) Hz, 3 H, CH\(_2\)CH\(_3\)), 0.71 (m, 1 H), 0.91 (s, 9 H, SiCCH\(_3\)), 1.11 (m, 1 H), 1.23 (m, 1 H), 1.32 (m, 1 H), 1.48 (m, 1 H), 1.65-1.89 (m, 5 H), 2.34 (m, 2 H), 3.30 (m, 4 H, NCH\(_2\)Ph and CH\(_2\)OSi), 7.03-7.18 (m, 5 H, ArH); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) -5.6 (q), 10.4 (q), 13.1 (t), 18.0 (t), 18.1 (s), 22.2 (t), 25.8 (q), 30.0 (t), 38.5 (d), 49.2 (d), 56.9 (t), 64.4 (t), 65.3 (d), 67.1 (d), 119.1 (s), 119.7 (s), 127.0 (d), 128.2 (d), 128.4 (d), 130.8 (s); \(^{13}\)C NMR (75.5 MHz, C\(_6\)D\(_6\)) \(\delta\) -5.4 (q), -5.3 (q), 10.5 (q), 13.0 (t), 18.0 (t), 18.4 (s), 22.4 (t), 26.1 (q), 30.1 (t), 38.6 (d), 49.3 (d), 57.0 (t), 64.5 (t), 65.4 (d), 67.5 (d), 119.2 (s), 119.7 (s), 127.2 (d), 128.5 (d), 128.7 (d), 139.7 (s); mass
spectrum, m/z (relative intensity) 425 (M+, 1), 396 (52), 368 (23), 91 (100); exact mass calcld. for
C_{25}H_{39}N_{3}OSi m/z 425.2864, found m/z 425.2850.

\[
\text{NO}_2 \begin{array}{c}
\text{SeCN}
\end{array}
\]

\text{o-Nitrophenylselenocyanate. To a solution of 50 g (362 mmol) of 2-nitroaniline in 400 mL of tetrahydrofuran cooled to -20 °C} \text{ was added 30 mL of concentrated aqueous hydrochloric acid in several portions followed by 72 g of 49% aqueous fluoboric acid in several portions. To the resulting suspension was then added a solution of 27.5 g (398 mmol) of sodium nitrite in 40 mL of water dropwise while maintaining the temperature at -20 °C. The addition of sodium nitrite is very exothermic and can result in decomposition of the diazonium salt if the exotherm is not controlled. The mixture was then stirred for 30 min, and filtered. The filter cake was washed with 200 mL of cold (0 °C) isopropanol followed by 200 mL of cold (0 °C) ether. The off white solid was dried by pulling house vacuum through the filter cake to provide 76 g of the diazonium tetrafluoroborate salt.}

To a stirred solution of 44.8 g (311 mmol) of potassium selenocyanate in 200 mL of water cooled to 5 °C with crushed ice was added the diazonium salt in several portions (vigorous N\textsubscript{2} evolution). The exothermic reaction was cooled by the addition of crushed ice. The resulting orange solid was then collected by filtration and washed with plenty of cold water. The still moist filter cake was dissolved in 800 mL of dichloromethane, dried (MgSO\textsubscript{4}), filtered and concentrated in vacuo. The residue was triturated with 200 mL of ether to provide 48 g (58%) of o-nitrophenylselenocyanate as an orange solid: mp 140-143 °C (lit\textsuperscript{38} 142 °C).
LIST OF REFERENCES


10. Gibson, M. S.; Robinson, R. Chem. Ind. 1951, 93, 93.


42. For a prep of ethyl (triphenylphosphoranylidene)acetate see: Denney, D. B.; Ross, S. T. J. Org. Chem. 1962, 27, 998.


48. We thank Dr. Judith Gallucci for performing the X-ray crystallographic analysis of compounds 186, 190, 212, and 250 at The Ohio State University Crystallography Facility.


50. Some methods include reductions with sodium cyanoborohydride under acidic conditions, and tri-n-butyltin hydride under neutral conditions.


APPENDIX A: $^1$H and $^{13}$C NMR Spectra of New Compounds
DK-VI-116 (300 MHz, CDCl₃)
DK-VI-116 (75.5 MHz, CDCl₃)
OCH₃

HO

NMMe

OMe

163

DK-V-124B (300 MHz, CDCl₃)
DK-V-124B (75.5 MHz, CDCl₃)
Me₃SiO

145 (crude)
DK-II-43 (200 MMz, CDCl₃)
INTEGRAL

1 46

DK-II-18B (200 MHz, CDCl₃)

*= EtOAc

OHNMe
INTE6RAL

MeO

M

164

DK-II-18A2 (200 MHz, CDCl₃)
164

DK-II-18A2 (62.5 MHz, CDCl₃)

* = impurity
147
DK-V-18A (250 MHz, CDCl_3)
INTEGRAL NMe 148
DK-II-52A (200 MHz, CDCl₃)
INTEGRAL

OEt

NMe

149

DK-V-37 (200 MHz, CDCl₃)
INTEGRAL

OEt

O NMe

°

OCH₃

150

DK-II-35 (200 MHz, CDCl₃)
166

DK-II-83 (200 MHz, CDCl₃)
DK-II-83 (75.5 MHz, CDCl₃)

166
DK-II-150B (75.5 MHz, CDCl₃)
151 (crude)

DK-V-46 (300 MHz, CDCl₃)
DK-V-45 & 46B (300 MHz, CDCl₃)
173.5 Q Q

V O H OEt

NMe  0

OBn

C 02Et

168

DK-II-154 (62.2 MHz, CDCl₃)
INTEGRAL

\[ f \frac{V}{T t f} \]

OCH, CO\text{Et}

DK-V-47B (200 MHz, CDCl\textsubscript{3})

153

DK-V-47B (200 MHz, CDCl\textsubscript{3})
DK-II-157 (300 MHz, CDCl₃)
DK-II-157 (75.5 MHz, CDCl₃)
154 (crude)

DK-V-51 (300 MHz, CDCl₃)
OMe
CH
CO₂Et

154
DK-V-51B (250 MHz, CDCl₃)
DK-II-160 (75.5 MHz, CDCl₃)
DK-III-5A (75.5 MHz, CDCl₃)
OCH$_3$

180

DK-V-65 (75.5 MHz, CDCl$_3$)
DK-V-65 (300 MHz, CDCl₃)
OBn
NMe
OH
181
DK-II-141C (300 MHz, CDCl₃)
DK-II-141C (75.5 MHz, CDCl₃)
DK-II-144A (300 MHz, CDCl₃)
DK-II-105 (75.5 MHz, CDCl₃)
DK-III-13A (300 MHz, CDCl₃)

* = instrument artifact
DK-II-118 (75.5 MHz, CDCl₃)
184

DK-II-126D (300 MHz, CDCl₃)
DK-III-29 (300 MHz, CDCl₃, 303 °K)
* = solvent
DK-III-29 (300 MHz, DMSO-d$_6$, 303 °K)
DK-III-29 (75.5 MHz, DMSO-d$_6$, 373 °K)
DK-III-38A (300 MHz, CDCl₃)
MOM
OBn
MOMO CH.
187
DK-VII-141B2 (300 MHz, CDCl₃)
DK-VII-141B2 (75.5 MHz, CDCl₃)
DK-VII-144 (75.5 MHz, CDCl₃)

* = instrument artifact
DK-VII-145 (75.5 MHz, CDCl₃)
MOM

190

DK-III-50A (62.2 MHz, CDCl₃)
MOM

DK-VII-154 (300 MHz, CDCl₃)

191

DK-VII-154 (300 MHz, CDCl₃)
MOM

DK-VII-154 (75.5 MHz, CDCl₃)

191
DK-IV-4A (300 MHz, CDCl₃)
* = impurities
DK-IV-4A (75.5 MHz, CDCl₃)

*= impurities
OBn
MOM-N
CH₃

194

DK-IV-10 (300 MHz, CDCl₃)
194

DK-IV-10 (75.5 MHz, CDCl₃)
DK-IV-15 (75.5 MHz, CDCl₃)
DK-III-123 (300 MHz, CDCl₃)
DK-III-123 (75.5 MHz, CDCl₃)

197

1. 197

DK-III-123 (75.5 MHz, CDCl₃)
OCH₃
OMe

198
DK-V-67 (300 MHz, CDCl₃)
198

DK-V-67 (75.5 MHz, CDCl₃)
DK-III-127 (300 MHz, CDCl₃)
199
DK-III-127 (75.5 MHz, CDCl₃)
DK-V-89 (75.5 MHz, CDCl₃)
201

DK-IV-25 (300 MHz, CDCl₃)
DK-VI-39A (300 MHz, CDCl₃)
MOMO — NMMe

Ph  Ph

OMe

202

DK-VI-39A (75.5 MHz, CDCl₃)
DK-III-141 (300 MHz, CDCl₃)
DK-III-131 (75.5 MHz, CDCl₃)
DK-V-108 (300 MHz, CDCl₃)
DK-V-108 (75.5 MHz, CDC\(_3\))
DK-VI-70 (300 MHz, CDCl₃, 303 °K)
DK-V-110 (300 MHz, DMSO-d$_6$, 303 °K)
DK-V-112 (300 MHz, DMSO-d$_6$, 370 °K)
208
DK-VI-76A (300 MHz, CDCl₃)
DK-VI-76A (75.5 MHz, CDCl₃)
209
DK-VI-76B (75.5 MHz, CDCl₃)
MOM

DK-III-152B (300 MHz, CDCl₃)
If $\text{c}$

MOM

$\text{OMe}$

$\text{DK-III-152B (75.5 MHz, CDCl}_3\text{)}$

211

DK-III-152B (75.5 MHz, CDCl$_3$)
MOM-\(\text{N}\)O
Ph Ph

DK-III-135A (300 MHz, CDCl\(_3\))

212

\(\text{P P M}\)
213
DK-III-135B (75.5 MHz, CDCl₃)
MOM

DK-VI-77 (300 MHz, CDCl₃)

214
215
DK-VI-79 (300 MHz, CDCl₃)
* = impurity
MOM

-OH

215

DK-VI-79 (75.5 MHz, CDCl₃)

* = impurities
218
DK-VI-95A (300 MHz, CDCl₃)
218

DK-VI-95A (75.5 MHz, CDCl₃)
MOMO
O
N
Br
219
DK-VII-146 (300 MHz, CDCl$_3$)
DK-VII-146 (75.5 MHz, CDCl₃)
MOMO
CH₂
220
DK-VII-149 (300 MHz, CDCl₃)

* = impurities
DK-VII-149 (75.5 MHz, CDCl₃)

* = geometrical isomer
DK-VI-108A (75.5 MHz, CDCl₃)
221

DK-VI-108A (300 MHz, CDCl₃)
MOMO

222

DK-VI-108B (300 MHz, CDCl₃)
MOMO
MOM

DK-VI-108B (75.5 MHz, CDCl₃)
MOM
223
DK-VII-151 (300 MHz, CDCl₃)
DK-VII-151 (75.5 MHz, CDCl₃)
DK-IV-37 (300 MHz, CDCl₃)
225
DK-IV-100 (300 MHz, DMSO-d$_6$, 303 °K)

* = Et$_2$O
225

DK-IV-100 (300 MHz, DMSO-d$_6$, 363 °K)

* = Et$_2$O
OBn — NMe

OMe

225

DK-IV-100 (75.5 MHz, DMSO-d$_6$, 373 °K)
DK-VI-33A (300 MHz, CDCl₃)

* = impurities
DK-VI-33A (75.5 MHz, CDCl₃)

* = instrument artifact
DK-VI-33B2 (300 MHz, CDCl₃)
• = impurities
227

DK-VI-33B2 (75.5 MHz, CDCl₃)

* = impurities
DK-IV-110B2 (300 MHz, CDCl₃)
DK-IV-110B2 (75.5 MHz, CDCl₃)
DK-V-2 (300 MHz, CDCl₃)
* = impurities
229
DK-V-2 (75.5 MHz, CDCl₃)
* = impurities
DK-V-3 (300 MHz, CDCl₃)
*
* = impurities
DK-V-3 (75.5 MHz, CDCl₃)

230
AcOBn-NEtAcO

DK-IV-53 (300 MHz, CDCl₃)

231

DK-IV-53 (300 MHz, CDCl₃)
DK-IV-53 (75.5 MHz, CDCl₃)
OBn NMe AcO

DK-VI-17 (300 MHz, CDCI₃)

DK-VI-17 (300 MHz, CDCI₃)
DK-VI-40 (300 MHz, CDCl₃)
DK-IV-150A (75.5 MHz, CDCl₃)

* = impurities
DK-VI-40B (300 MHz, CDCl₃)
234

DK-VI-40B (75.5 MHz, CDCl₃)
DK-VI-46 (300 MHz, CDCl₃)

*= impurity
DK-VI-46 (75.5 MHz, CDCl₃)
DK-VI-32A (300 MHz, CDC13)

* = impurity
DK-VI-32A (75.5 MHz, CDCl₃)
* = impurity
DK-VI-48A (300 MHz, CDCl₃)

* = hexane
DK-VI-48A (75.5 MHz, CDCl₃)

* = impurity
DK-V-23A (75.5 MHz, CDCl₃)
DK-V-31 (300 MHz, CDCl₃)
DK-V-31 (75.5 MHz, CDCl₃)
DK-V-69 (300 MHz, CDCl₃)
246
DK-V-69 (75.5 MHz, CDCl₃)
DK-V-79 (300 MHz, CDCl₃)

* = hexane
DK-V-79 (75.5 MHz, CDCl₃)
DK-V-116 (300 MHz, CDCl₃)

*= hexane

248
DK-V-116 (75.5 MHz, CDCl₃)
DK-V-119A (300 MHz, CDCl₃)
DK-V-119A (75.5 MHz, CDCl₃)
250 DK-IV-134 (300 MHz, DMSO-d₆)
* = impurities
DK-IV-134 (75.5 MHz, DMSO-d$_6$)
DK-VI-60 (300 MHz, CDCl₃)

*= impurities
DK-VI-60 (75.5 MHz, CDCl₃)
* = impurities
DK-IV-47 (300 MHz, CDCl₃)
Synthetic

2
2

(300 MHz, CDCl₃)

Authentic
From Dr. Cordell
DK-IV-47 (75.5 MHz, CDCl$_3$)
Synthetic
OBn
H -N
AcO
\(\text{DK-VI-45 (300 MHz, CDCl}_3\)
DK-VI-45 (75.5 MHz, CDCl₃)
DK-VI-59 (300 MHz, CDCl₃)

* = impurities
DK-VI-59 (75.5 MHz, CDCl₃)
DK-VI-61B (75.5 MHz, DMSO-$d_6$)
DK-VI-63A (300 MHz, CDCl₃)
DK-VI-63A (75.5 MHz, CDCl₃)
256

DK-VI-69 (300 MHz, DMSO-d6)

* = hexane
DK-VI-69 (75.5 MHz, DMSO-d$_6$)

H-N

OH

N

N

CH$_3$

256
DK-VI-72 (300 MHz, DMSO-d$_6$)

* = EtOAC
DK-VI-72 (75.5 MHz, DMSO-\textsubscript{d$_6$})
DK-VI-75 (300 MHz, CDC$_3$)
DK-VI-75 (75.5 MHz, CDCl₃)
JMB-I-118 (200 MHz, CDCl$_3$)

EtO$_2$C

Br

Br

CO$_2$Et

316a

JMB-I-118 (200 MHz, CDCl$_3$)
EtO₂C

316
DK-VI-142 (200 MHz, CDCl₃)

*= impurities
PhSO\textsubscript{C}H\textsubscript{3}COSPh

Et\textsubscript{2}C\textsubscript{N}C\textsubscript{0}2Et

Bn

315

DK-VII-122 (300 MHz, CDCl\textsubscript{3})
PhSOC - COSPh

EtO₂C - CO₂Et

Bn

315

DK-VII-122 (75.5 MHz, CDCl₃)
OH

DK-VI-149A (300 MHz, CDCl₃)

Bn

318

DK-VI-149A (300 MHz, CDCl₃)
DK-VI-149A (75.5 MHz, CDCl₃)

318
DK-VI-22 (300 MHz, CDCl₃)
DK-VI-22 (75.5 MHz, CDCl₃)
OTBDMS

HO

N

Bn

CO₂Et

320

DK-VII-32 (75.5 MHz, CDCl₃)

* = instrument artifact
DK-VII-79A (300 MHz, CDCl₃)
HO OTBDMS

321

DK-VII-79A (75.5 MHz, CDCl₃)
DK-VII-101 (300 MHz, CDCl₃)
HO OTBDMS

Bn

322

DK-VII-101 (75.5 MHz, CDCl₃)
MsO OTBDMS
CO₂Et
Bn
323
DK-VII-122 (300 MHz, CDCl₃)
MsO

OTBDMS

N

CO₂Et

Bn

323

DK-VII-122 (75.5 MHz, CDCl₃)
DK-VII-104 (300 MHz, CDCl₃)
172.671

MsO OTBDMS

C 02tBu

Bn

324

DK-VII-104 (75.5 MHz, CDCl₃)

PPM

3.1526
3.5192
8.118912

-0.13805
-0.13805

-1.20285
-1.20285

0.29483
0.29483

0.62033
0.62033

0.66883
0.66883

0.69683
0.69683

8.7454
8.7454

8.1564
8.1564

6.1594
6.1594

5.1254
5.1254

4.9743
4.9743

4.9423
4.9423

4.683
4.683

3.656
3.656

3.24
3.24

2.56
2.56

1.54
1.54

0.94
0.94

0.63
0.63

0.21
0.21

-0.13
-0.13

-0.37
-0.37

-0.89
-0.89

-1.97
-1.97

-3.16
-3.16

-4.36
-4.36

-5.74
-5.74

DK-VII-104 (75.5 MHz, CDCl₃)
OTBDMS

325

DK-VII-123 (300 MHz, CDCl₃)
DK-VII-123 (300 MHz, C₆D₆)
DK-VII-123 (75.5 MHz, C₆D₆)
CN OTBDMS
C02 tBu
Bn
326
DK-VII-106A (300 MHz, C6D6)
DK-VII-106A (75.5 MHz, C₆D₆)
DK-VII-124A (300 MHz, C₆D₆)
DK-VII-124A (75.5 MHz, C₆D₆)
DK-VII-126 (300 MHz, C₆D₆)
OTBDMS

Bn

328

DK-VII-126 (75.5 MHz, C₆D₆)
CN OTBDMS

Bn

329

DK-VII-127 (300 MHz, C₆D₆)
DK-VII-127 (75.5 MHz, C₆D₆)
CN OTBDMS

330

DK-VII-134 (300 MHz, C₆D₆)
APPENDIX B: X-Ray Crystallographic Data for Compound 186
Figure 12. ORTEP of Oxindole 186
<table>
<thead>
<tr>
<th>Atom</th>
<th>Atom</th>
<th>Distance</th>
<th>Atom</th>
<th>Atom</th>
<th>Distance</th>
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<td>O(2)</td>
<td>C(10)</td>
<td>1.202(14)</td>
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<td>C(9)</td>
<td>1.439(10)</td>
<td>O(3)</td>
<td>C(32)</td>
<td>1.398(14)</td>
</tr>
<tr>
<td>O(4)</td>
<td>C(32)</td>
<td>1.364(17)</td>
<td>O(4)</td>
<td>C(33)</td>
<td>1.416(19)</td>
</tr>
<tr>
<td>O(5)</td>
<td>C(34)</td>
<td>1.397(15)</td>
<td>O(5)</td>
<td>C(35)</td>
<td>1.402(16)</td>
</tr>
<tr>
<td>O(6)</td>
<td>C(36)</td>
<td>1.396(12)</td>
<td>O(6)</td>
<td>C(37)</td>
<td>1.411(15)</td>
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<td>C(4)</td>
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<td>C(5)</td>
<td>1.455(11)</td>
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<td>C(17)</td>
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<td>C(10)</td>
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<td>C(11)</td>
<td>1.389(16)</td>
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<td>C(34)</td>
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<td>1.561(11)</td>
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<td>C(10)</td>
<td>1.555(14)</td>
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<td>C(16)</td>
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<td>C(3)</td>
<td>1.541(11)</td>
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<td>C(8)</td>
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<td>C(44)</td>
<td>C(45)</td>
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</table>

Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.
Table 10. Bond Angles for Oxindole 186

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<th>Atom</th>
<th>Atom</th>
<th>Angle</th>
<th>Atom</th>
<th>Atom</th>
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<td>114.7(10)</td>
<td>C(36)</td>
<td>O(6)</td>
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Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.
APPENDIX C: X-Ray Crystallographic Data for Compound 190
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Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.
APPENDIX D: X-Ray Crystallographic Data for Compound 212
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Phenyl rings C(19)-C(24) and C(25)-C(30) are refined as rigid groups with a constrained C-C distance of 1.395 Å.

Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.
Table 14. Bond Angles for Oxindole 212

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Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.
APPENDIX E: X-Ray Crystallographic Data for Compound 250
Figure 15. ORTEP of Hexacyclic Cage 250
Table 15. Bond Lengths for 250

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Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.
Table 16. Bond Angles for 250

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Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.