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Approaches to a total synthesis of gelsemine

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The Ohio State University, 1991
APPROACHES TO A TOTAL SYNTHESIS OF GELSEMINE

DISSERTATION

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

By

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To My Parents
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CHAPTER I
BACKGROUND AND SYNTHETIC STUDIES

A. Introduction

The objective of this research was to explore and develop approaches to the synthesis of gelsemine (1) and two related natural products, gelsevirine (2), and 21-oxogelsemine (3) (Figure 1). The results of the study will be discussed in five chapters. To place this work in perspective the first chapter will focus on background information about the isolation, biological activity, structure determination and biosynthesis of gelsemine (1) followed by a survey of previous studies directed toward syntheses of gelsemine. A retrosynthetic analysis and preliminary studies will be presented in the second chapter. Chapters 3-5 will each be devoted to an approach to introducing the oxindole moiety of gelsemine.

B. Background

Gelsemine was first isolated by Wormley in 1870 from the rhizomes and roots of Gelsemium sempervirens (yellow jasmine) as an amorphous base and was later obtained pure in a crystalline form by Gerrard in 1883. In addition to the principal alkaloid gelsemine, a number of other alkaloids were also isolated from Gelsemium sempervirens, including gelsevirene (2), 21-oxogelsemine (3), and three pentacyclic alkaloids gelsedine (4), gelsemicine (5), and 14β-hydroxygelsedine (6). Gelsemium sempervirens has a long medicinal history for use in the treatment of neuralgia and migraine, but because of its toxicity, it is now very rarely used. The physiological activities of gelsemine have been studied for many years. In in vivo studies, the
hydrochloride salt of gelsemine exhibits antihypertensive, cardiovascular, and analgesic activities. Gelsemine is also a strong central nervous stimulant with strychnine-like activity.

![Chemical structures of gelsemine and its derivatives](image)

**Figure 1. Oxindole Alkaloids from *Gelsemium sempervirens***

The elemental composition of gelsemine was not established until 1910 as C\(_{20}\)H\(_{22}\)N\(_2\)O\(_2\) by Moore. Its melting point was found to be 178°C and its [\(\alpha\)]\(_D\) was +15.9° in chloroform. Moore also found that gelsemine had a basic nitrogen and the [\(\alpha\)]\(_D\) of the hydrochloride salt was +2.6° in water. During a period of the next 50 years, efforts to elucidate the structure of gelsemine resulted in confirming the presence of a spirooxindole, a tertiary basic nitrogen bearing one methyl group, a vinyl side chain, and a cyclic ether moiety. It was not until 1959 that the structure of gelsemine was suggested by Conroy on the basis of biosynthetic considerations, NMR spectral data, and chemical degradation. At the same time, the structure was independently confirmed by X-ray crystallography.
In Conroy's structural studies, the $^1$H NMR spectrum of gelsemine showed the presence of two ABX systems and one AB system. The vinylic protons account for one of the ABX systems. These resonances are comprised of three symmetrical doublets of doublets at $\delta$ 4.90 ($J = 17.8, 1.5$ Hz), 5.05 ($J = 11.3, 1.5$ Hz), and 6.18 ($J = 17.8, 11.3$ Hz). Two doublets of doublets, part of another ABX system, at $\delta$ 4.10 ($J = 11.5, 1.6$ Hz), and 3.80 ($J = 11.5, 0.9$ Hz) infer the presence of an OCH$_2$CH group. An AB system at $\delta$ 3.1 and 2.2 with a coupling constant of 10.6 Hz infers the presence of an NCH$_2$C group. In addition, two protons with very small coupling constants at $\delta$ 3.75 and 3.40 suggested the presence of a combination of OCH and NCH groups.

Conroy next obtained information about the nature of the olefin, which at one time was considered to be an allylic amine, by investigating degradation reactions of gelsemine derivative 8 (Scheme I). Thus, reduction of gelsemine using lithium aluminium hydride and protection of the resulting dihydroindole 7 as an acetamide gave 8. The amine was quaternized using iodomethane ($8 \rightarrow 9$). Oxidation of the olefin using alkaline potassium permanganate provided carboxylate 10 which underwent concerted decarboxylative $\beta$-elimination under high dilution conditions in N,N-dimethylformamide to give the basic pentacyclic olefin 11. The $^1$H NMR spectrum of 11 showed an uncoupled symmetrical pair of olefinic resonances. The presence of a terminal olefin in 11 was further confirmed by hydrogenation to provide dihydro derivative 12, whose $^1$H NMR spectrum showed an additional methyl group as a doublet. In addition, Johnson-Lemieux oxidation of 11 gave ketone 13. The infrared spectrum of 13 showed an absorbance at 1748 cm$^{-1}$, consistent with the presence of a cyclopentanone. The results of this degradation sequence suggested the presence of the homoallylic amine, including quaternary C(2) and the AB system discussed earlier.
A biosynthesis of gelsemine was then considered (Scheme II). Conroy suggested oxindole 14 might be a precursor of gelsemine. This compound displays a close structural
relationship to corynoline (15) and rhyncophylline (16), and might be derived from tryptamine and 3,4-dihydroxyphenylalanine. Oxidation of the tertiary amine was expected to give enamine 17. The enamine then could undergo Michael addition to the unsaturated aldehyde to afford 18. The intermediate iminium ion 18 is set for an intramolecular Mannich reaction to give a tricyclic substructure (19) of gelsemine. Finally, gelsemine could be derived from 19 by decarboxylation, formation of the tetrahydropyran and appropriate adjustment of oxidation states. Despite the incorrect nature of this biosynthesis (vide infra), it helped in the structure elucidation of gelsemine.

Scheme II. Conroy's Argument on Biosynthesis of Gelsemine

Conroy's structural study on gelsemine is very significant, because it stands as one of the first alkaloid structural determinations for which proton NMR provided crucial and decisive information. In addition, gelsemine was one of the last alkaloids to have its structure determined largely by classical methods. Finally, gelsemine was actually the first alkaloid whose $^{13}$C NMR
spectrum was assigned. The absolute configuration of gelsemine still remains uncertain, but on biosynthetic considerations 1a should represent the natural enantiomer (Scheme III).

Although Conroy's structure determination of gelsemine relied in part on his biosynthetic considerations, recent biosynthetic studies have proved his biosynthetic pathway to be unlikely and have shown that gelsemine is biosynthetically derived from strictosidine (20). Strictosidine is derived in turn from condensation of tryptamine (21) with secologanin (22). Zenk and coworkers have shown that strictosidine is, in fact, converted to gelsemine in vivo by *Gelsemium sempervirens*. Thus, condensation of (2-14C)-tryptamine with (7-3H)-secologanin (21a) under standard conditions led to the labelled strictosidine (20) and its C(3) epimer vincoside (23). The labelled secologanin was prepared by reduction of secologanin with sodium borotritiilide and oxidation of the resulting secologanol with Jones reagent. The epimers were separated by chromatography, or alternatively, strictosidine was prepared stereospecifically using an enzyme.

Scheme III. Zenk's Studies on Biosynthesis of Gelsemine

![Diagram of Scheme III](image-url)
catalyzed condensation. The labelled strictosidine was fed to the root system of *Gelsemium sempervirens* by a capillary technique and the plants were allowed to grow for 24 hours. The isolated and purified gelsemine showed the incorporation of the labelled carbon and proton at C(6) and H(3), respectively.

C. Synthetic Studies

Although the structure of gelsemine was reported thirty years ago, thus far it has not yielded to total synthesis. This has not, however, been due to a lack of effort. In fact, the

Scheme IV. Autrey and Tahk's Approach to Gelsemine

![Scheme IV. Autrey and Tahk's Approach to Gelsemine](image-url)
numerous studies that have been reported suggest this synthetic challenge will eventually be met with a variety of solutions. The first to embark upon the synthesis of gelsemine were Autrey and Tahk. The projected key step in the synthesis involved Michael addition of an enamine of type 25 to C(3) of N-benzylisatylidene 24 to give 3,3-disubstituted isatylidene 26 (Scheme IV). Reduction of the ester followed by intramolecular enamine condensation would afford tetracycle 27 (Scheme IV). Unfortunately, the Michael addition led to a mixture of products from which ethyl N-benzyloxindole-3-acetate (29) and N-benzyloxindole (31) were the two major products isolated. Autrey rationalized that 29 arose from proton abstraction of the initial enamine addition product 28. Addition of enamine 25 to other olefin termini followed by retro-Aldol condensation would explain 31 as a reaction product. This approach would be an elegant route to gelsemine, if the initial bond between the enamine and C(3) of the isatylidene could be made.

In 1970, Stevens and coworkers reported preliminary studies on the synthesis of relevant isoquinoline derivatives as possible precursors for gelsemine synthesis. This group realized

Scheme V. Stevens' Preliminary Study on Gelsemine
that gelsemine includes the skeleton of a spiro[indole-3,7'-isoquinoline]. Thus, oxindole 35 was constructed from N-methyloxindole (32) via Michael adduct 33 and intramolecular Dieckmann adduct 34 (Scheme V). Apparently this approach did not get too far, however, as no further progress has been reported.

In contrast to early synthetic studies, recent efforts have left introduction of the oxindole substructure of gelsemine to later stages of the synthesis. It appears that Stork and coworkers anticipate intermediate 36 to be a possible precursor to gelsemine (Scheme VI). A preliminary report suggests that 36 might be prepared from 37 using a rhodium catalyzed C-H insertion reaction. α-Diazoketone 37 might be available from 38, whose synthesis is outlined in Scheme VII. This synthesis involves a radical cyclization (39 → 40) and Claisen rearrangement (48 → 38) as key steps.

Scheme VI. Stork's Approach to Gelsemine

The synthesis of 38 began with a tributylstannane-initiated radical cyclization of bromohemiacetal 39 to give bicyclic hemiacetal ester 40 as a mixture diastereomers in 95% yield. Bromoacetal 39 was in turn prepared in four steps from diethyl cyclopentanone-2,5-dicarboxylate.
using a known procedure. The mixture of esters was converted to a 1:6 mixture of unsaturated esters 41 and 42, respectively, using a selenation-oxidation-elimination sequence.

Scheme VII. Stork's Synthesis of Tricyclic Intermediate 38

(a) n-Bu₃SnH, AIBN, PhH; (b) LDA, THF, PhSeSePh; (c) 1. MCPBA, CH₂Cl₂, 2. Et₃N; (d) Dibal-H ether; (e) phenylacetic acid, CH₂Cl₂, DCC, 4-DMAP; (f) Amberlite-H⁺, THF, H₂O; (g) Piv-Cl, CH₂Cl₂, 4-DMAP, Et₃N; (h) LDA, THF, TMSCl; (i) TMS-OTf; (j) LDA, THF, TMSCl (10eq); (k) Br₂, CH₂Cl₂.

The synthesis was next directed to preparation of Claisen rearrangement substrate 48. Thus, diisobutylaluminium hydride reduction of 42 gave allylic alcohol 43. Esterification of the
alcohol with phenylacetic acid gave 44. Hydrolysis of the ketal using amberlite followed by esterification of the corresponding hemiacetal gave 46. Construction of the crucial bond between the α-methylene of the phenylacetic ester and the anomeric center was accomplished by trimethylsilyl triflate catalyzed alkylation of trimethylsilyl ketene acetal 47, formed by silylation of 46, to give lactone 48 as a single diastereomer. Finally, preparation of 38 was accomplished by Claisen rearrangement of the silyl ketene acetal derived from lactone 48. The stereochemistry at C(4) was confirmed by formation of bromolactone 49 upon treatment of 38 with bromine. Stork's approach offers an efficient route to gelsemine, if a workable endgame can be developed.

Fleming's group revealed their interest in the total synthesis of gelsemine (1) in 1982 (Scheme VIII). A preliminary report suggests that gelsemine might be derived from 50, whose synthesis is outlined in Scheme IX. The last stage of this synthesis involved construction of the pyrrolidine using an N-acyliminium ion cyclization.

**Scheme VIII. Fleming's Approach to Gelsemine**

The synthesis started with a Diels-Alder reaction between cyclohexadiene 52 and methyl β-nitroacrylate to give a mixture of 1:1 ratio of endo-cycloadduct 53 and the corresponding exo-cycloadduct. The moderate yield (43%) was due to low endo stereoselectivity. Sequential reduction of the nitro group, acylation of the resulting amine, reduction of the ester, acylation of the resulting alcohol, and hydrolysis of the acetal gave 54 in an overall 81% yield. The olefin was
next oxidized to epoxide 55 (85%). When 55 was treated with 600 mol% of magnesium bromide, the bicyclo[2.2.2]octane skeleton rearranged to bicyclo[3.2.1]octane 56 in 78% yield. Construction
of the tetrahydropyran was then accomplished by sequential bromination of the ketone using phenyltrimethylammonium tribromide, protection of the alcohol as a tetrahydropyranyl ether, and removal of acetyl group using potassium carbonate. During the deacetylation cyclization also occurred. The ketone was immediately converted to ketal 57 (62% from 56).

The synthesis was next directed to construction of the pyrrolidine moiety using an N-acyliminium ion cyclization.\(^{19}\) Thus, oxidation of the alcohol using PCC on alumina followed by addition of vinylmagnesium bromide to the resulting ketone 51 gave allylic alcohol 58. The allylic alcohol was displaced in S\(_{N}2'\) fashion by chloride, using thionyl chloride, to yield allylic chloride 59. Chloride 59 was converted to allylic silane 60 using lithium bis(trimethylsilyl)cuprate and treatment of 60 with 1,3,5-trioxane in the present of formic acid resulted in tetracyclic pyrrolidine 50.

The remaining task of the synthesis is installing the oxindole group. Since it was impossible to predict the stereochemical outcome of nucleophilic additions to ketone 50, two stereochemically complementary oxindole syntheses were developed, as outlined in Scheme X.\(^{17a}\) Norbornanone was chosen to illustrate the two complementary routes. In the first route, an aryl group was introduced to norboranone in 37% yield using o-lithioformanilide, prepared by halogen-metal exchange of o-bromoformanilide with n-butyllithium. The low yield of this reaction was due to enolization of norboranone under the reaction conditions. This enolization, however, would not be a problem for ketone 50. The resulting alcohol 61 was treated with sodium cyanide in N,N-dimethylformamide to give the aminoindoline 62. The hydrochloride salt of the aminoindoline was heated in water to afford oxindole 63. In the second route, epoxide 64 was prepared in two steps. Thus, Wittig reaction of (o-bromobenzylidene)triphenylphosphorane and norbornanone followed by MCPBA oxidation yielded epoxide 64 in an overall 71% yield. Rearrangement of the epoxide using aluminium chloride or trifluoroacetic acid afforded both aryl migration (64 \(\rightarrow\) 66) and hydride migration (64 \(\rightarrow\) 65) products in about a 1:1 ratio. Treatment of aldehyde 66 with chromium trioxide followed by amidation of the resulting acid 67 gave 68 in an
overall 30% yield. Then cyclization was effected with sodium hydride in tetrahydrofuran to give oxindole 69 in 68%.

**Scheme X. Fleming's Oxindole Studies**

(a) o-bromoformanilide, n-BuLi, THF; (b) NaCN, DMF; (c) HCl, H₂O, Δ; (d) (o-fluorobenzylidene) triphenylphosphorane; (e) MCPBA; (f) AlCl₃, CH₂Cl₂; (g) CrO₃; (h) SOCl₂, NH₃; (i) NaH, diglyme

Diastereomers 63 and 69 were clearly distinguished by difference NOE experiments. Irradiation of Hₐ in 69 showed enhancement of an aromatic signal (Hₑ) whereas no aryl proton enhancement was observed upon irradiation of Hₐ in 63. Each of these routes was to provide different oxindole stereochemistry. Thus, the first route would provide synthesis of an oxindole in which the carbonyl group is to attach to the less sterically hindered diastereotopic face of ketone. In route two, the aryl group is to attach to the less sterically hindered face.¹⁷ᵃ

Attempts to use these two complementary routes to achieve a synthesis of gelsemine, however, resulted in failure. Neither oxindole synthesis provided gelsemine or its epimer. Fleming argued that the neighboring C-O bond might be involved in some way with the carbocation
chemistry. To circumvent this problem a new strategy was developed as outlined in Scheme XI. This report suggests that Kikugawa's N-methoxyoxindole synthesis might be of use in a synthesis of gelsemine. This chemistry was illustrated using adamantane. Thus, treatment of adamantane with nitromethane followed by conjugate addition of triphenylaluminum to the unsaturated nitro compound gave 71. Conversion of 71 to methyl hydroxamate 73 was accomplished by sequential dehydration of 71 using sodium methoxide and acetyl chloride, hydration of the resulting nitrile oxide 72, and methylation of the hydroxamic acid using sodium carbonate and iodomethane. Finally, treatment of 73 with t-butyl hypochlorite followed by reduction of the resulting N-methoxyoxindole 74 gave oxindole 75 in an overall 85% yield. To address stereochemical issues relevant to gelsemine, Fleming has shown that treatment of 76 with triphenylaluminum gives 77. Coordination of the aluminum reagent to the oxygen presumably

Scheme XI. Fleming's Recent Oxindole Studies

(a) CH₃NO₂, H₂NCH₂CH₂NH₂; (b) Ph₃Al, xylene; (c) NaOMe, MeOH; AcCl; (d) H₂SO₄, acetone; (e) Mel, Na₂CO₃, MeOH; (f) t-BuOCl, CH₂Cl₂; Zn(OAc)₂; (g) Na-Hg, MeOH
controls the stereochemistry. This approach is currently being explored to install the oxindole substructure in gelsemine.

Overman and coworkers recently reported a synthesis of oxindole 78 which might be a precursor to gelsemine.\textsuperscript{20} The retrosynthetic strategy is depicted in Scheme XI. The approach features a palladium catalyzed intramolecular alkene arylation (79 $\rightarrow$ 78). Aryl bromide 79 was in turn derived from 82 via a aza-oxy-Cope rearrangement and an intramolecular Mannich reaction.

\textbf{Scheme XII. Overman's Retrosynthetic Analysis}

The investigation began with a stereoselective synthesis of bicyclo[2.2.2]octenyl amine 82 by a Diels-Alder cycloaddition-Curtius rearrangement reaction sequence. Thus, cycloaddition of 1-triisopropylsiloxyl-3-methyl-1,3-cyclohexadiene (83) with methyl acrylate in the presence of aluminium chloride provided endo-cycloadduct 84 with high stereoselectivity. The vinyl group destined for the angular C(20) position of gelsemine was introduced by selenium dioxide oxidation
of the allylic methyl group followed by Wittig olefination of the corresponding enal 85 to give 86.

Ester 86 was converted to amine 87 under standard Curtius rearrangement conditions.

Scheme XIII. Overman's Synthesis of Oxindole 78

Amine 87 was converted to a cyanomethylamine and deprotection of the alcohol using tetrabutylammonium fluoride gave 82. A model study had suggested that base catalyzed aza-oxy-Cope rearrangement of 82 would proceed to the cis-perhydroisoquinoline without complications.
In fact, the anionic [3,3]-sigmatropic rearrangement (82 → 81) was accomplished by treating 82 with excess potassium hydride at room temperature followed by quenching with methyl chloroformate. To functionalize the C-16 position, a requirement for ultimate construction of the tetrahydrofuran moiety, enamine 81 was brominated in the presence of 1,2,2,6,6-pentamethylpiperidine to give β-bromoenecarbamate 87. This unstable bromide was immediately subjected to standard Mannich reaction conditions to afford tricyclic ketone 80.

The next stage of the synthesis involved elaboration of the oxindole. It had been previously demonstrated in a simple system that a Heck reaction would be useful for accomplishing this task. The cyclization substrate 79 was prepared in two steps. First, ketone 80 was converted to vinyl triflate 89. Carbonylation of 89 in the presence of o-bromoaniline followed by protection of the resulting amide gave 79. The palladium-catalyzed alkene arylation proceeded smoothly to give oxindole 78 as a mixture of diastereomers. The diastereoselectivity ranged from 1:1.2 to 1:3 depending on the amide protecting groups. Thus far, Overman's group is the only one to incorporate an oxindole group with the required stereochemistry into a gelsemine intermediate. Construction of the tetrahydrofuran group is apparently in progress.

Another effort directed at gelsemine was reported by Hiemstra and Speckamp in 1987. The approach is outlined in Scheme XIV. The oxindole and tetrahydrofuran moieties were to be introduced at a late stage of the synthesis from alcohol 90. The key step in this strategy mimics the biosynthetic pathway suggested by Conroy. Thus, construction of the C(5)-C(16) bond was to be accomplished by cyclization of N-acyliminium ion intermediate 91. The acyliminium ion was to be derived from ethoxyaminal 92 which, in turn, was to be prepared from perhydrophthalimide 93. The chemistry involved in the synthesis of ethoxylactam 92 is closely related to that used in our approach to gelsemine. Thus, the preparation of substances related to 92 will be discussed in detail in a later chapter. The remainder of Speckamp's approach to 90 is shown in Scheme XV. Ethoxylactam 92 was converted to cyclization precursor 93 by sequential oxidation
of the alcohol using PDC, silylation of the resulting aldehyde with triisopropylsilyl triflate in the presence of triethylamine, and alkylation of the lactam with 2-(phenylseleno)ethanal. Upon work-up the aldol condensation product was converted to the incipient C(20) angular vinyl group of gelsemine. The acyliminium ion cyclization was effected under Lewis acid conditions and reduction of the resulting aldehyde gave tricyclic alcohol 90 and its C(16) epimer in a 7:3 ratio.

**Scheme XIV. Hiemstra and Speckamp's Retrosynthetic Analysis**

![Scheme XIV](image)

respectively, in 70% yield from 93. It was next demonstrated that the tetrahydropyran could be constructed using an iodoetherification. Therefore, treatment of 90 with iodine in the presence of sodium carbonate furnished the tetracycle 94.22c

Next, construction of the oxindole moiety was investigated as outlined in Scheme XIV.22c Toward this end, Hiemstra and Speckamp employed Fleming's first strategy (Scheme X). Thus, protection of a 4:1 mixture of C-16 diastereomeric alcohols 90 as t-butyldimethylsilyl ethers followed by allylic oxidation using CrO₃ in the presence of 3,5-dimethylpyrazole gave enone 95. The dianion derived from o-bromoformanilide was added to the enone to give alcohol 96 as a
mixture of diastereomers. A small amount 1,4-addition product was present as a contaminant. Treatment of alcohol 96 with excess sodium cyanide in N,N-dimethylformamide gave a mixture of

Scheme XV. Hlemstra and Speckamp's Synthesis of 94 and Oxindole 98

(a) CrO3, Py, CH2Cl2; (b) i-Pr3SiOTf, Et3N, Et2O; (c) LDA, THF, PhSeCH2CHO; CH3SO2Cl, Et3N, CH2Cl2; (d) BF3OEt2, CH2Cl2; (e) NaBH4, EtOH; (f) I2, Na2CO3, CH3CN; (g) TBDMSCI imidazole, DMF. h) CrO3,3,5-dimethylpyrazole, CH2Cl2. i) NaH, THF, α-bromoformanilide; n-BuLi, HMPT; 83; (j) NaCN, DMF; (k) HCl-H2O, Δ
products from which aminoindolenine 97 was isolated in 28% yield. Hydrolysis of the
aminoindolenine with aqueous hydrochloric acid gave spirooxindole 98. However, the
stereochemistry at C(4) was proven not to be that required for gelsemine. Nevertheless,
Fleming's second route to introduce the oxindole moiety might offer an alternative approach from
92 to gelsemine (1). This tactic is currently been investigated by Hiemstra and Speckamp.

In addition to the approaches described above, we understand that the groups of
Curran,24 Johnson,25 and Jones26 are also working on syntheses of gelsemine. Their
approaches, however, are unknown to us although we understand that Johnson has apparently
completed a total synthesis of 1. The following chapter will begin to describe our approach to
gelsemine by presenting a retrosynthetic analysis as well as preliminary results that preceeded the
research to be described in chapters 3-5 of this thesis.
CHAPTER II
RETROSYNTHETIC ANALYSIS AND PRELIMINARY STUDIES

A. Introduction

In 1985 efforts directed toward a synthesis of gelsemine were initiated in our laboratories. This chapter will describe the synthetic plan that has been pursued and discuss results obtained by members who preceded my involvement with the project. Examination of the structure of gelsemine (1) reveals it has a tetracyclic nucleus with a spirooxindole group appended at the C(4) position and a vinyl group at the C(20) position. The tetracyclic substructure consists of tetrahydropyran, pyrrolidine, and bicyclo[3.2.1]octane substructures. The challenging structure of gelsemine (1) as well as its biological activities, render it a worthwhile target for synthesis.

B. Retrosynthetic Analysis

Our approach to gelsemine follows the retrosynthetic plan outlined in Scheme XVI. This analysis is related to that followed by Hiemstra and Speckamp,22 but involves radical intermediates for construction of the C(5)-C(16) bond. We anticipated gelsemine might be prepared from intermediate 99, where X, Y, and Z are suitable to introduce the oxindole, vinyl and tetrahydropyran moieties, respectively. It is well known that α-acylamino radical cyclizations are of some use in the construction of carbon-carbon bonds adjacent to nitrogen.27 Thus, we projected tricyclic intermediate 99 could be constructed by cyclization of α-acylamino radical 100. Two critical conformational issues arise when considering this projected cyclization (100 → 99). One
would expect radical 101 to be in conformational equilibrium with radical 100. If cyclization takes place from conformation 101, it will not provide the C(16) stereochemistry required for gelsemine. More importantly, one would also expect 100 and 101 to be in conformational equilibrium with 102. It is obvious that cyclization can not take place from conformation 102. Furthermore, it is reasonable to assume that 102 could be more stable than either 100 or 101. Thus, the success of the proposed construction of the C(5)-C(16) bond of gelsemine would depend on a balance of cyclization rates, conformational equilibria, and rates of other radical processes such as reduction.
Returning to the retrosynthesis, a radical of type 102 could be generated by homolysis of a carbon-sulfur bond such as in α-thiophenoxylactam 103. Radical precursor 103 could be derived from perhydrophthalimide 104 via a series of functional group transformations. Finally, diene 105 and N-methyImaleimide would serve as the building blocks to 104.

III. Preliminary Studies

Some studies designed to carry out the plan shown in Scheme XVI had been reported prior to the author's involvement with this synthesis. These studies are briefly reviewed here. Initial studies by Choi focused on construction of C(5)-C(16) bond of gelsem ine using the proposed α-acylamino radical cyclization. Choi was able to prepare 106 where X=Y=Z=H using a reaction sequence that will become apparent (vide infra). He found that treatment of 106 with tri-n-butyltin hydride and AIBN under high dilution conditions gave only reduction product 108 (90%). Thus, the aforementioned conformational problem appeared to be real.

Several strategies could be used to overcome this conformational problem. For example, one might be able to reduce the rate of reduction of radical 106 by using trialkylgermanium hydride in place of tri-n-butyltin hydride. The use of hydride free sources of tin radicals, such as hexamethylditin or bis(trimethylstannyl)benzopinacolate, might also have some merit. In yet another approach, Ramesh prepared α-thiophenoxylactam 109 in an attempt to increase the rate of the radical cyclization. He found that this compound did undergo cyclization to afford a 10:1 mixture of 113 and 114 in 75% yield. This result was encouraging, but indicated that it would be necessary to correct the C(16) stereochemistry at some stage of the synthesis. The
stereochemical outcome at C(16) indicated that cyclization took place principally through conformation 111 rather than 112. This was of interest because current transition-state models for 5-hexenyl radical cyclizations suggest that chair-like transition states (e.g. 112) are preferred over the corresponding boat-like transition states (e.g. 111). One explanation for this observation is that allylic 1,3-strain between the vinyl hydrogen next to carboxyl group and the C(3) and/or C(2) methylenes arises in conformation 112 but is absent in conformation 111.

Next, in studies designed to see if the strategy would accommodate an appropriate C(20) substituent, Lee prepared radical precursor 115 (Scheme XVII). It was no surprise that 115 gave 117 (73%) upon treatment with tri-n-butyltin hydride and AIBN. Once again, olefin activation led to desired cyclization. Thus, treatment of 118 gave a 12:1 mixture of 119 and 120, respectively.
Scheme XVII. Lee's Free Radical Cyclization Studies

Studies next turned toward incorporating C(3) functionality suitable for construction of tetrahydropyran substructure. Toward this end, Ha prepared α-thiophenoxy lactam 129 as outlined in Scheme XVIII. As the synthesis is presented, the chemistry used to prepare the other radical precursors mentioned above will become apparent. The synthesis of 129 began with preparation of enone 122 (81%) using a Wittig reaction between (2-oxopropylidene)triphenylphosphorane and 3-tetrahydropyran-4-ol (121). Sequential treatment of 122 with lithium disopropylamide and chlorotrimethylsilane gave diene 123 in 93% yield. Diels-Alder cycloaddition between 123 and N-methylmaleimide followed by hydrolysis of the resulting cycloadduct gave 124 in 95% overall yield. Ketolization of 124 using 2,2-dimethylpropane-1,3-diol and formal dehydration of the alcohol gave olefin 125 in 56% overall yield. Reduction of 125 with sodium borohydride followed by hydroxy-ethoxy exchange gave lactam 126 (84%). This remarkable regioselectivity will be discussed in the next chapter. Sequential treatment of 126 with lithium disopropylamide and chloromethyl methyl ether gave 127 (84%). Johnson-Lemieux oxidation of 127 and Wittig reaction of the resulting aldehyde with the appropriate phosphorane gave unsaturated ester 128 in 65% overall yield. Finally, radical precursor 129 (83%) was obtained by ethoxy-thiophenoxy exchange.
Scheme XVIII. Ha's Preparation of Radical Precursor 129

(a) LDA, THF; Me₃SiCl; (b) N-methylmaleimide, toluene; (c) Dowex-50(H⁺), MeOH;
(d) 2,2-dimethylpropanediol, Dowex-50(H⁺), PhH; (e) o-NO₂C₆H₄SeCN, n-Bu₃P, THF; H₂O₂;
(f) NaBH₄, MeOH; (g) EtOH, Dowex-50 (H⁺); (h) LDA, THF, -23°C; ClCH₂OCH₃, -78°C;
(i) NaIO₄, OsO₄(cat.),THF, t-BuOH, H₂O; (d) Ph₃P=CHCO₂Et; CH₂Cl₂; (e) PhSH, Dowex-50 (H⁺)

Ha next showed that when 129 was subjected to the same cyclization conditions as used before, 132 was obtained in 87% yield as 12:1 mixture of C(16) diastereomers (Scheme XIX).

This radical cyclization was sterically more demanding than those of 109 and 118 due to the additional axial substitution at C(3). Nevertheless, the cyclization still competed favorably with
bimolecular reduction. Since the diastereoselectivity was identical to that obtained in previous studies, this result suggested that substituents at C(3) had little or no effect on the stereochemical outcome at C(16). This observation was also supported by the result of 6:1 stereoselectivity at C(16) in the cyclization of ketone 133 to 134, a case where the aforementioned interaction between C(3) and the vinyl hydrogen is absent.

**Scheme XIX. Cyclization of C-3 Functionalized Precursor**

With a C(3) functionalized tricycle in hand, Ha proceeded to develop a protocol for adjusting the stereochemistry at C(16) and ultimately constructing the tetrahydropyran substructure. The plan was to degrade the C(16) acetate residue to an aldehyde and use a C(3) hydroxyl group to trap the aldehyde as a hemiacetal as shown in Scheme XX.\(^{23}\) Thus, hydrolysis of 132 followed by reduction of the resulting ketone 134 gave 135 (70%) and its C(3) epimer (20%). Alcohol 135 was protected as a silyl ether and sequential treatment of 136 with excess
phenylmagnesium bromide followed by an acidic workup gave 137. Ozonolysis of olefin 137 gave aldehyde 138. Treatment of aldehyde 138 with DBU in dichloromethane accomplished epimerization of the aldehyde which was trapped by C(3) hydroxy to afford hemiacetal 139 as a mixture diastereomers in 43% yield from 136. Reduction of 139 using triethylsilane and trifluoroacetic acid afforded tetrahydropyran 140.

Scheme XX. Construction of Tetrahydropyran 140

The author's involvement with the synthesis of gelsemine began with developing a streamlined preparation of 140 as outlined in Scheme XXI. Prior to hydrolysis of 130, the first stage of the Barbier-Wieland degradation was conducted. Thus, treatment of 130 with excess phenylmagnesium bromide followed by an acidic workup gave keto olefin 141 in 76% yield.
Reduction of the ketone with sodium borohydride gave 81% of alcohol 137 and along with 7% of its C(3) epimer. The remainder of the synthesis converged with steps carried out by Ha.

Scheme XXI. A Streamlined Preparation of Tetrahydropyran 140

(a) PhMgBr (excess), THF; Dowex-50(H+); (b) NaBH₄, MeOH; (c) O₃, MeOH; DMS; (d) DBU, CH₂Cl₂; (e) Et₃SiH, CF₃CO₂H, CH₂Cl₂

C. Summary

In this chapter, studies that ultimately led to the preparation of a tetracyclic substructure (140) of gelsemine were presented. A favorable feature of this approach is that it passes through intermediates in the ketone oxidation state at C(3). In principle, this should allow further functionalization at C(4) required for incorporating the oxindole substructure of gelsemine. The studies described in this chapter required about two man-years of effort as tremendous progress was made within a relatively short period of time. The remaining task of the synthesis was
incorporation of the oxindole substructure and at the time, we imagined that gelsemine was well within reach. However, as the discussion in next chapters will reveal, this turned out not to be the case.
I. Introduction

The proceeding chapter described our synthetic plan and preliminary studies directed toward gelsemine. The preliminary studies addressed conformational issues in the free radical cyclization, developed a protocol for incorporating the tetrahydropyran, and ultimately led to preparation of a tetracyclic gelsemine substructure (140) that incorporated a methoxymethyl group which might eventually become the C(20) vinyl group of gelsemine. The task that remained was incorporation of the oxindole substructure. To accomplish this objective, functionality had to be introduced at C(4). Two general approaches were in our mind. In one approach, we could take advantage of the chemistry used to prepare 141 and introduce C(4) functionality at a late stage of the synthesis. Alternatively, we could carry suitable C(4) functionality from the beginning of the synthesis. We decided to evaluate the latter approach by carrying an o-fluorophenyl group from the onset of the synthesis. We imagined that nucleophilic aromatic substitution chemistry developed by Fleming (Equation 3) might be used to complete construction the oxindole. Therefore, this chapter will describe studies directed toward the preparation and C(4)-functionalization of ketone 181.
II. Results and Discussion

The synthesis of 181 followed the general plan used by Ha to prepare 129 (Scheme XVIII). Thus, enone 146 became our initial target (Scheme XXII). The preparation of 146 (75%) was accomplished by a Wittig reaction between phosphorane 143 and 3-tetrahydropyranoyloxypropanal (121). A number of procedures were examined to prepare 143 from o-fluorophenylacetic acid. We eventually followed the reaction sequence shown in Scheme XXII. Thus, treatment of o-fluorophenylacetic acid to phenyl thioester using dicyclohexylcarbodiimide, 4,4-(dimethylamino)pyridine, and thiophenol followed by treatment of the resulting thioester 142 with two equivalents of (methylidene)triphenylphosphorane gave 143 in good yield (50% from the phenylacetic acid).37–67 Aldehyde 121 was prepared by either of two methods. Protection of 1,3-propanediol with dihydropyran gave a mixture of mono- and di-protected alcohols 144a and 144b. Separation of the mixture by a series of extractions followed by oxidation of 144b with pyridinium chlorochromate afforded 121.39,48 This procedure was not suitable for large scale use, however, due to difficulties in the pyridinium chlorochromate oxidation workup. An alternate procedure for the preparation of aldehyde 121 involved treatment of 3-buten-1-ol with dihydropyran in dichloromethane using acidic Dowex-50 as a catalyst. This gave 145 in 90% yield. Ozonolysis of olefin 145 in toluene at -78°C followed by reductive workup gave aldehyde 121 in 72% yield.38
The remainder of the synthesis of 181 closely paralleled the preparation of 130. However, the additional aryl group in the current case presented a stereochemical issue in the Diels-Alder cycloaddition, which was not relevant to studies discussed in the preceding chapter. Initially, the Diels-Alder diene was prepared by enolization of enone 146 using lithium diisopropylamide at -78°C in tetrahydrofuran and subsequent silylation with chlorotrimethylsilane. However, the Diels-Alder reaction between resulting diene and N-methylmaleimide afforded only a trace amount of the desired cycloadduct 151 after enol ether hydrolysis using acidic Dowex-50 in methanol (Scheme
XXIII). The failure of the Diels-Alder addition could be a result of $E,E$-diene geometry (149), which would discourage the diene from adopting the conformation required for cycloaddition. Although diene geometry was not proven, it is possible that deprotonation of enone 146 with lithium diisopropylamide proceeded through chair-like transition state 148 rather than 147. It is well preceded that the geometry of an enolate generated from an $\alpha$-substituted ketone under kinetic control depends on the substituents on the ketone and the base, and solvent coordination ability.\textsuperscript{40} Perhaps a steric interaction between the aryl group and the isopropyl group in 147 is greater than that between the aryl group and the vinyl group in 148. If this were the case, $E,E$-diene 149 would result from the aforementioned enolization process.

In a coordinating solvent system, the enolate anion geometry is controlled by intrinsic steric factors of ketones, perhaps a consequence of the absence of chair-like transition states. Thus, treatment of 146 with lithium diisopropylamide in tetrahydrofuran and hexamethylphosphoramide at -78°C followed by silylation using chlorotrimethylsilane gave Diels-Alder diene 152 in 85% yield. The Diels-Alder reaction of 152 with $N$-methylmaleimide proceeded in toluene at reflux and the resulting endo-cycloadduct 153 was immediately subjected to hydrolysis in methanol using acidic Dowex-50 as catalyst to give 151 in 59% yield (Scheme XXIII). The ring juncture stereochemistry assigned to 151 was based on analogy with earlier results obtained by Ha and Lee in similar systems. In addition, there is ample precedent for the endo selectivity in similar Diels-Alder reactions.\textsuperscript{19, 41} During hydrolysis, the tetrahydropyranly ether was also removed to give a primary alcohol. Finally, it is suspected that the $\alpha$-fluorophenyl group epimerized to the thermodynamically more stable isomer. The stereochemical assignment at C(4) was based on the appearance of H(4) as a doublet at $\delta$ 4.0 with a coupling constant of 7.0 Hz, an indication of a reasonably large dihedral angle between H(4) and the adjacent angular proton. Although this coupling constant is a bit small for a trans-diaxial relationship, the stereochemical assignment at C(4) was proven by X-ray crystallography at a later stage of synthesis.
Scheme XXIII. Preparation of Perhydrophthalimide 151

R = -CH₂CH₂OTHP
Ar = o-fluorophenyl
We focused next on dehydration of the primary alcohol as outlined in Scheme XXIV. Ha had previously found that it was necessary to protect the ketone before a formal dehydration could be efficiently accomplished. Thus, 151 was treated with 2,2-dimethyl-1,3-propanediol using Dowex-50 (H+) as an acid catalyst in benzene with continuous removal of water to give ketal 154 in 73% yield. Applying the Grieco dehydration sequence, alcohol 154 was treated with o-nitrophenylselenocyanate and tri-n-butylphosphine at room temperature in tetrahydrofuran to generate the o-nitrophenylselenide. Without purification, the corresponding selenide was oxidized using excess 30% aqueous hydrogen peroxide at 0°C and upon warming to room temperature the resulting selenoxide eliminated to afford olefin 155 in 71% yield.

**Scheme XXIV. Preparation of Olefin 155**

(a) 2,2-dimethyl-1,3-propanediol, Dowex-50(H+), benzene; (b) o-NO$_2$C$_6$H$_4$SeCN (2 eq.), tri-n-butylphosphine (2 eq.), THF; 30% H$_2$O$_2$ (excess), 0°C → 25°C

With olefin 155 in hand, we proceeded to differentiate the two carbonyls. Reduction of the imide with sodium borohydride in methanol provided only one reduction product (157) in very good yield (74%). This remarkable regioselectivity agreed with the results that were obtained by Ha (125 → 126). This regiochemical course was initially determined by $^1$H NMR spectroscopy and the connectivities of H(3)-H(3a)-H(4) were established by a series of decoupling experiments. The stereochemical assignment at C-3 was based on the appearance of H$_3$ as a doublet of doublets at δ 4.92 with coupling constants of 8.6 (J$_{CH-OH}$) and 5.5 (J$_{CH-CH}$) Hz, an indication of a cis relationship between H(3) and H(3a).
One explanation for the regiochemical course of imide reduction, put forth by Dunitz and coworkers, is that a "109° approach" of the nucleophile to the carbonyl leads to steric interactions that favor one approach over the other. For example, the substituents at C(3) in 3,3-disubstituted succinimides hinder approach of hydride to the C(5) carbonyl more than the C(2) carbonyl (Equation 4). However, this argument would not explain our result satisfactorily, because of the comparable steric environments of the two carbonyl groups.

An alternate explanation proposed by Kayser focuses on the importance of the antiperiplanar alignment of the HOMO of incoming nucleophile and \( \sigma^* \) of adjacent carbon-carbon
bonds during nucleophilic addition to a carbonyl. Our system, which has a conformationally biased hexahydroisoindoie ring system where most substituents occupy equatorial positions (155 vs. 158), is reduced at the equatorially disposed carbonyl whose π framework is orthogonal to the adjacent carbon-carbon bond of the cyclohexane ring [C(3a)-C(4)]. Similar results have been reported by Speckamp who observed that acid-catalyzed reduction of imide 161 with sodium borohydride followed by ethanolation gave ethoxylactam 162 in 60% yield (Equation 6). Our observation was also supported by two anhydride hydrolysis studies. Kraus and Hagen reported that hydrolysis of 163 with methanol afforded ester acid 164 in 95% yield (Equation 7). In Chen's studies toward a total synthesis of stenine (167), the two anhydride carbonyls of 165 were also differentiated upon hydrolysis with methanol to provide ester acid 166 (Equation 8).
To convert hydroxy lactam 159 to radical precursor 175 it was necessary to install an appropriate appendage at C(7a) that would become the C(20) vinyl group in gelsemine, to perform one carbon homologation of the olefin, and to exchange the hydroxy group for a thiophenoxy group (Scheme XXV). To accomplish these objectives, ethanolation of hydroxy lactam 159 was first conducted using Dowex-50 (H+) in ethanol to afford ethoxylactam 168 in 78% yield. The stereochemistry assigned at C(3) was apparent from the H(3) methine resonance which appeared as a singlet at δ 3.88, an indication of a 90° H(3)-C(3)-C(3a)-H(3a) dihedral angle. The structure of 168 was confirmed by X-ray crystallography (Figure 2), which also proved the regiochemical course of the reduction (157 → 159) and the endo-selectivity of Diels-Alder reaction (152 → 153 → 151).
In previous studies, Lee had successfully alkylated lactam 169 with chloromethyl methyl ether to give 170 (Scheme XXVI). He had also demonstrated that the methoxymethyl group could be converted to a vinyl group at a later stage of the synthesis by sequential deblocking of the methyl ether using boron tribromide,\textsuperscript{50} Swern oxidation of the resulting alcohol,\textsuperscript{51} and Wittig olefination of the corresponding aldehyde (119 $\rightarrow$ 171). With Lee's result in mind, we proceeded to alkylate the angular C(7a) position of 168. Thus, the lithium enolate of lactam 168 was generated using lithium diisopropylamide in tetrahydrofuran at -23\textdegree{}C followed by treatment with chloromethyl methyl ether at -78\textdegree{}C to give 172 (88%).
The one carbon homologation of the olefin was next accomplished by a one carbon degradation-two carbon homologation sequence. Following the Johnson-Lemieux oxidation procedure, olefin 172 was treated with sodium periodate and osmium tetroxide to afford aldehyde 173 in 62% yield. The structural assignment of 173 was initially based on $^1$H NMR spectra and later confirmed by X-ray crystallography. The X-ray crystallographic analysis of 173 clearly indicates that the cyclohexane ring of the molecule adopts a chair conformation despite much substitution. A Wittig reaction between (carbethoxy)methylidene)triphenylphosphorane and 173 afforded unsaturated ester 174 in 88% yield. Finally, ethoxy-thiophenoxy exchange proceeded smoothly with thiophenol in dichloromethane using Dowex-50 (H$^+$) to afford radical precursor 175 in 83% yield.

When radical precursor 175 was treated with tri-$n$-butyltin hydride and AIBN under the identical conditions as used before, about a 1:1 ratio of reduction product 179 and cyclization product 180 was obtained in 85% total yield (Equation 9). The appearance of the olefinic protons of the unsaturated ester at $\delta$ 5.85 ($J = 15.7$ Hz) and 7.78 ($J = 15.7, 9.8$ Hz) and the absence of thiophenoxy protons supported the structure assignment of 179. The structure of 180 was consistent with spectral data and proven by X-ray crystallography. This cyclization ($175 \rightarrow 179 + \cdots$)
180) is sterically more demanding than the cyclization of 129 due to an additional axial aryl substituent at C(4). Thus, one might expect the cyclization to occur through a boat-like conformation (178) than a chair-like conformation (177). It is obvious that multiple 1,3-diaxial interactions are avoided in 178. In support of this suggestion, it is notable that 180 crystallizes with the cyclohexane ring in a boat-like conformation (Figure 4). It is also notable that the C(16) epimer of 180 was not obtained from the cyclization of 175.
Figure 3. ORTEP of Aldehyde 173

Figure 4. ORTEP of Cyclization Product 180
We next focused our attention on incorporating the oxindole moiety. The plan of using nucleophilic aromatic substitution to accomplish this objective required an amide group at the C(4) position. We projected that the C(3) ketone oxidation state would allow attachment of this functionality. In accord with the methodology developed for constructing the tetrahydropyran portion of gelsemine, 180 was converted to 181 in 74% yield using phenyllithium followed by acidic work up. We next applied Mander's procedure for carbethoxylation of ketones to the problem at hand. Treatment of 181 with lithium diisopropylamide, hexamethylphosphoramide and ethyl cyanoformate gave a 2:1 mixture of starting material (181) and β-ketoester 182 (Scheme XXVII). The reaction, however, was capricious and the best yield of 182 was only 32%. In addition, starting ketone 181 and ketoester 182 were not readily separated by chromatography. When the aforementioned mixture of the 181 and 182 was subjected the same conditions three times, it was possible to obtain a low yield of 182 that was approximately 80% pure (contaminated by 181). The structure of 182 was tentatively assigned on the basis of ¹H NMR spectral data. The stereochemistry of carbethoxy group was inferred from a drastic chemical shift change of H(5) and a series of difference NOE experiments which revealed the proximate nature of the H(5), H(16), and an aryl proton. Although the regiochemistry of the acylation (C vs. O) was not rigorously determined.

Scheme XXVII. Preparation of Ketoester 182

(a) phenyllithium (excess), THF; p-toluensulfonic acid, C₆H₆; (b) LDA, THF, HMPA; ethyl cyanoformate
proven, one reduction of 182 was attempted. Unfortunately, treatment of 182 with sodium borohydride in methanol resulted in decarbethoxylation to give 181. Other endgames from 181 were examined (including use of the C(20) appendage as a handle to introduce the C(4)-functionality) but did not provide conclusive results. Due to difficulties associated with incorporating a functional group at C(4) and the inefficiency of this synthesis in term of material throughput, we eventually abandoned this route to gelsemine.

C. Summary

The research presented in this chapter described the preparation of ketone 180. During the course of our investigation, we demonstrated the versatility of free radical cyclizations for making carbon-carbon bonds adjacent to nitrogen and obtained some insight into the nature of tricyclic systems like 180, including conformational biases and diasteresoselectivity in arylations of the C(4) position of gelsemine. Although this approach was eventually abandoned, it led to a refinement of the synthetic strategy and provided background for later studies. Another venture addressing incorporation of the oxindole moiety will be presented in chapter four.
CHAPTER IV
C(4)-FUNCTIONALIZATIONS OF KETONE 141 USING A FISCHER-INDOLE SYNTHESIS AND ELECTROPHILIC AROMATIC SUBSTITUTIONS

A. Introduction

The preceding chapter described the preparation of a tricyclic gelsemine substructure (143) in which an o-fluorophenyl group was carried through the synthesis. The approach, however, was eventually abandoned because the preparation could not be easily scaled up. As an alternative, we moved to plans that involved introducing C(4)-functionality at a late stage of the synthesis. We decided that ketone 141 was an appropriate starting point for accomplishing this objective. Thus, this chapter will focus on studies directed toward C(4) arylation of ketone 141 using a Fischer-indole synthesis and further C(4)-functionalization using intramolecular electrophilic aromatic substitutions.

B. Results and Discussion

Our plan for this approach to gelsemine is outlined in Scheme XXVIII. We projected that indole 183 might be an appropriate intermediate in the synthesis of gelsemine and that it could be prepared from ketone 141 using a Fischer indole synthesis. The indole retains C(3) at the ketone
oxidation state and thus, we hoped that the strategy presented in Scheme XXI could still be used to construct the tetrahydropyran substructure. Moreover, we felt that the indole could serve as the ortho-substituted aniline portion required for construction of the oxindole moiety. We imagined the carboxy portion of the oxindole could be attached stereoselectively using intramolecular electrophilic substitution reactions and projected that the C(20) angular substituent would serve as a handle to direct the substitutions. Sequential ether cleavage (183 → 184), acylation of the resulting hydroxymethyl group using phosgene, and electrophilic aromatic substitutions were expected to give an indoline such as 185. The final stage of this approach was to be conversion of 185 to an oxindole such as 186. One plan that could accomplish this task might involve
opening of indoline 185 under thioketalization conditions followed by lactam formation between the liberated aniline and the carboxy group. Alternatively, a sequence involving oxidative cleavage of the C=N bond using sodium nitrite, substitution of the resulting aryldiazonium ion with azide, protection of the resulting ketone, and reduction of the azide was also expected to afford an oxindole related to 186. Completion of the synthesis of gelsemine from 186 was to be accomplished by construction of the tetrahydropyran group using the strategy described in Scheme XXI followed by appropriate adjustment of oxidation states.

The pseudo symmetry of ketone 141 presented a regiochemical problem in terms of introducing functionality at C(4). An early study, however, suggested that regioselective C(4)-functionalization of 141 should be possible. During an attempt to protect ketone 134 using methanol and trimethyl orthoformate and acidic Dowex-50 as catalyst under standard ketalization conditions, it was discovered that enol ether 187 was produced as the only regioisomer in 75% yield. The regiochemical assignment was based on the relationship between the vinylic proton and C(5) methine proton and a small allylic coupling between the C(2) equatorial proton and C(4) proton in ¹H NMR spectral data. The reluctance of 134 to form a ketal can be rationalized on steric grounds while the regiochemical course of the enol ether formation is most likely related to less torsional strain being introduced upon enolization toward C(4) than C(2). This result gave us hope that regioselective C(4)-functionalization of 141 could be accomplished.

\[
\text{(MeO)}_3\text{CH, MeOH, Dowex-50 (H\textsuperscript{+})} \rightarrow \begin{array}{c}
\text{134} \\
\rightarrow
\end{array} \begin{array}{c}
\text{187} \\
\end{array}
\]

Rather than immediately carry out the plan with ketone 141, initial studies were performed using trans-decalone 193. It was felt that this compound would be a good model for the rigid cyclohexane moiety of 141. Decalone 193 was prepared according to established procedures as
Treatment of 2-carbethoxycyclohexanone with methyl vinyl ketone in the presence of Triton B followed by treatment of the resulting conjugate adduct with sodium ethoxide in ethanol gave enone 188 in 72% yield. Catalytic hydrogenation of enone 188 over platinum oxide gave ketoester 189 in 89% yield. Our next task was to reduce the carboxethoxy group without disturbing the ketone. Thus, protection of the ketone using ethylene glycol in the presence of acidic Dowex-50 followed by reduction of the resulting ester 190 using lithium aluminum hydride gave hydroxy ketal 191 in 70% overall yield. Treatment of 191 with acidic Dowex-(50) in acetone surprisingly gave 192. The regiochemical assignment of 192 was proven by establishing the relationship between the angular methine proton and the C(6) methylene protons.

Scheme XXIX. Preparation of Decalone 193

(a) Triton-B; (b) EtONa, EtOH; (c) PtO/H₂, EtOH; (d) HOCH₂CH₂OH, Dowex-50 (H⁺); (e) LAH, THF; (f) acetone, Dowex-50 (H⁺); (g) HCl (aq), MeOH; (h) (MeO)₂CH₂, EtAlCl₂

Dowex-(50) in acetone surprisingly gave 192. The regiochemical assignment of 192 was proven by establishing the relationship between the angular methine proton and the C(6) methylene protons.
using $^1$H NMR spectral data. Since 192 undoubtedly was the product of an acid catalyzed aldol condensation, this result gave us hope that the electrophilic aromatic substitutions via an aldol condensation, in place of the originally proposed acylation, would be feasible.\textsuperscript{57} Hydrolysis of 191 to 193 was eventually accomplished using 2$\text{N}$ aqueous hydrochloric acid in methanol and we demonstrated that conversion of 193 to 192 (74\%) was also possible. Finally, treatment of 193 with ethylaluminum dichloride and dimethoxymethane gave 194 in 59\% yield, indicating that the aforementioned condensation might work with a variety of electrophiles.

With model hydroxy ketone 193 in hand, we turned to the Fischer-indole synthesis outlined in Scheme XXX.\textsuperscript{58} Thus, treatment of 193 with phenylhydrazine in the presence of boron trifluoride etherate as a catalyst afforded indole 195 in 70\% yield. A streamlined preparation of 195 was also developed. Application of a Fischer-indole synthesis to ketoester 189 followed by lithium aluminum hydride reduction of the resulting ester 196 gave 195 in 70\% overall yield. The regiochemical assignment of 195 was once again based on the relationship between the angular

\textbf{Scheme XXX. Preparation of Model Substitution Substrate 195}

\begin{equation}
\begin{align*}
193 & \xrightarrow{\text{PhNHNH}_2, \text{AcOH, BF}_3\text{•Et}_2\text{O}} 195 (76\%) \\
189 & \xrightarrow{1. \text{PhNHNH}_2, \text{AcOH, BF}_3\text{•Et}_2\text{O}, 2. \text{LAH, THF}} 195 (70\%)
\end{align*}
\end{equation}
methine proton and the C(6) methylene protons in $^1$H NMR spectral data. Since the regiochemical
course of a Fischer-indole synthesis is dictated by the direction of enolization of an intermediate
hydrazone, the regioselectivity of the reaction (193 $\rightarrow$ 195 and 189 $\rightarrow$ 195) was not surprising.

With 195 in hand, the intramolecular electrophilic aromatic substitution was examined as
shown in Equation 11. When 195 was treated with dimethoxymethane in the presence of
ethylaluminum dichloride as a catalyst cyclic ether 197 was obtained in 59% yield. One problem
with this approach is that opening of the cyclic ether to afford a useful C(20) substituent might be
difficult. Plans to deal with this problem will become apparent (vide infra).

It was clear from the model study that the desired electrophilic aromatic substitution might
be accomplished in a system like 184. Thus, ketone 141 was converted to indole 184. Treatment
of 141 with phenylhydrazine and boron trifluoride etherate gave indole 183 as the only regioisomer
in 72% yield.58 In a series of decoupling experiments, the relationship between the distinctive
C(1) methine proton and the C(2) methylene protons clearly established the regiochemical course
of the indole synthesis.59 This regioselectivity was consistent with the previously noted enol ether
preparation (134 $\rightarrow$ 187). Continuing with the synthesis, the methyl ether was next cleaved to
afford 184 (88%) using boron tribromide under surprisingly mild conditions.60 Demethylations
using this procedure normally occur at temperatures above -23°C as opposed to -78°C in this
case. The coordination of boron tribromide to both lactam and ether oxygens is suspected to
increase the rate of the deprotection of 183.
With 184 in our hand, we attempted the long awaited substitution reaction as shown in Scheme XXXI. Unfortunately, treatment of 184 with dimethoxymethane in the presence of ethylaluminum dichloride under variety of conditions only returned the starting indole. One possible reason for this failure was suspected to be the additional ring strain introduced upon going from 184 to 198 (relative to 195 → 197).

Considering ring strain, we imagined that a seven-membered ring lactone might be constructed using thionium ion electrophilic aromatic substitution reactions developed by Oikawa and Yonemitsu. These authors reported that thionium ions, intermediates in Pummerer rearrangements, would undergo electrophilic aromatic substitution at the 2-position of indole 199 (Equation 12). Magnus had demonstrated the synthetic value of this methodology for C(3) substitution of indoles. An example of this, used in the synthesis of 16-methoxytabersonine, is shown in Equation 13. We hoped to apply this methodology to the current problem by attaching an α-sulfinylacetate group to the angular hydroxymethyl appendage. The substitution was expected to proceed under Pummerer rearrangement conditions.
Once again, the initial electrophilic aromatic substitution studies were performed using indole 195. The preparation of α-sulfinylacetate 206 is outlined in Scheme XXXII. Treatment of 195 with α-thiophenoxyacetyl chloride and 4,4-(dimethylamino)pyridine followed by oxidation of the resulting sulfide (205) using m-chloroperbenzoic acid afforded 206 as a mixture of diastereomers in 60 % overall yield. Unfortunately, when 206 was treated with trifluoroacetic anhydride and 2,6-di-t-butyl-4-methylpyridine in toluene, none of the desired 207 was obtained. Nonetheless, we continued to a system more relevant to gelsemine.
Scheme XXXII. Preparation and Substitution Studies of 206

One problem with this approach is opening the intermediate lactone in a useful manner. A plan designed to deal with this problem and at the same time incorporate the angular vinyl group is outlined in Scheme XXXIII. Oxidation of 184 and addition of an appropriate nucleophile to the resulting aldehyde was expected to afford 209. The electrophilic aromatic substitution reaction was expected to give 210 and β-elimination would then afford 211. One-carbon degradation (211 → 212) was then to be performed using Trost's oxidative decarboxylation method. Subsequent manipulations of 212 were expected to eventually lead to gelsemine.
We next moved to the preparation of sulfoxide 214 from 184 using the same procedure for preparing 206 (Scheme XXXIV). Thus, acylation of 184 with α-thiophenoxyacetyl chloride and 4,4-(dimethylamino)pyridine followed by oxidation of the resulting sulfide 213 using m-chloroperoxybenzoic acid afforded 214 in 69% overall yield. To our disappointment, treatment of 214 with trifluoroacetic anhydride and 2,6-di-t-butyl-4-methylpyridine in toluene afforded a complex mixture of unidentified products. With the observation of the facile demethylation (183 → 184), we suspected the nucleophilic lactam oxygen might be responsible for the negative results in this system (214).
Scheme XXXIV. Preparation and Substitution Studies of 214

The lactam oxygen participation hypothesis could be tested using amines 216 and 217, prepared as shown in Scheme XXXV. Treatment of 184 with lithium aluminum hydride afforded 216 in 70% yield. To prepare 217, a selective oxidation problem is encountered if acylation-oxidation sequence (Scheme XXXII) were to be used. It was imagined that reversal of the sequence would circumvent this problem. Thus, oxidation of α-thiophenoxyacetic acid using m-chloroperoxybenzoic acid and esterification of the resulting acid with 216 provided 217 in 73% yield. A small amount of dicyclohexylurea was present as a contaminant. With these amine substrates in hand, substitution reactions of both substrates were attempted. Unfortunately, all
attempts to cyclize 216 and 217 again afforded complex mixtures of unidentified products. A decomposition pathway that resembles Conroy's degradative studies (Scheme I) might be responsible for the failure of these reactions. Both 216 and 217 could undergo Grob fragmentation to give an amine of type 220 and subsequent decomposition of 220 could then occur (Equation 14). Eventually we abandoned this route to the oxindole portion of gelsemine due to promising results using an alternate strategy. These results will be the focus of the next chapter.
C. Summary

In this chapter, approaches to gelsemine that involve \( \alpha \)-arylation of ketone 141 and intramolecular electrophilic aromatic substitutions to functionalize C(4) were described. The results of model studies were very encouraging, but for some unknown reasons the crucial bonds could not be constructed in systems relevant to the total synthesis. Development of another approach was forced upon us and this will be presented in the next chapter.
CHAPTER V
INCORPORATION OF THE OXINDOLE SUBSTRUCTURE
USING A FREE RADICAL CYCLIZATION

A. Introduction

The preceding chapter described the regioselective C(4) arylation of ketone 141 using a Fischer-indole synthesis and studies involving further C(4) functionalization using intramolecular electrophilic aromatic substitutions. A number of attempts to convert 184 to an indoline of type 185 using electrophilic aromatic substitutions met with failure and the route was eventually abandoned for the approach described in this chapter. This approach to construction of the oxindole substructure was based on an oxindole synthesis developed by Jones and features a bond construction similar to that used by Overman (Scheme XIII).20, 65 Jones' oxindole synthesis revolved around the cyclization of aryl radicals derived from o-bromo-N-acryloylanilides (221 → 222 and 221 → 223). This chapter will describe the introduction of the oxindole substructure into ketone 141 using a variant of Jones' procedure as well as studies directed toward completion of the gelsemine synthesis.

Scheme XXXVI. Jones' Oxindole Synthesis
B. Results and Discussion

Our plan for constructing the oxindole using an aryl radical cyclization is outlined in Scheme XXXVII. We imagined that cyclization of the radical derived from aryl bromide 224 would provide α-alkoxy radical 225. Our hope was that at least a 1:1 mixture of C(4)-diastereomers would be obtained based on Overman's studies where no stereoselectivity was observed in a related Heck arylation. Reduction of 225 was expected to give 226 on steric grounds.

Scheme XXXVII. Approach to Construction of Oxindole

Our initial study focused on the cyclization of o-bromo-N-acryloylanilide 229 which was prepared from 2-carbethoxycyclohexanone as outlined in Scheme XXXVIII. Sequential treatment of 2-carbethoxycyclohexanone with potassium hydride and dimethyl sulfate afforded enol ether 227 in 76% yield. Amidation of 227 using (o-bromophenyl)dimethylaluminum amide, derived from o-bromoaniline and trimethylaluminum, followed by methylation of the resulting amide 228 using
sodium hydride and iodomethane gave 229 in 65% overall yield.\(^6\) Treatment of a solution 229 in benzene at reflux with 1.2 equivalents of tri-\(n\)-butyltin hydride and 0.1 equivalent of AIBN under high dilution conditions gave a 1:1 mixture of oxindoles 230 and 231 in 95% yield. The assignment of stereochemistry to the two diastereomers was based on \(^1\)H NMR spectra data. For example, irradiation of the carbinol methine gave a 5% NOE at H\(_0\) in 230 whereas no enhancement of H\(_0\) was observed upon irradiation of the carbinol methine of 231. Appearance of the carbinol methine as a doublet of doublets (\(J = 11\) and 5 Hz) in both isomers indicated an axial disposition for this proton.

Scheme XXXVIII. Preparation and Cyclization Study of 229

We next decided to study a system more relevant to the synthesis of gelsemine. Toward this end, cyclization studies were conducted with 238, prepared from ketal alcohol 191 as outlined in Scheme XXXIX. Treatment of 191 with sodium hydride and iodomethane followed by hydrolysis of the ketal using hydrochloric acid in methanol gave 233 in 78% yield. Regioselective carboxethoxylation of ketone 233 was accomplished using potassium hydride and dimethyl
carbonate as β-ketoester 234 was obtained in 78% as a mixture of keto and enol tautomers.67

Warming a solution of 234 in methanol-trimethylorthoformate (7:3) in the presence of acidic Dowex-50 for 1 h at reflux gave 48% of 235 along with 46% of 236. Chromatographic separation

Scheme XXXIX. Preparation and Cyclization Study of 238

(a) NaH, CH₃I, THF; (b) HCl (aq), CH₃OH; (c) KH, (CH₃O)₂C=O, THF; (d) CH₃OH, HC(OCH₃)₃,
Dowex-50 (H⁺); (e) o-BrC₆H₄NH₂, Al(CH₃)₃, C₆H₆; (f) NaH, CH₃I, THF; (g) n-Bu₃SnH (1.2 equiv)
AIBN (0.1 equiv), C₆H₆
of 235 and 236 followed by subjecting 235 to the same conditions for four cycles provided 236 in 92% yield from 234. The conversion of 236 to cyclization substrate 238 (63%) was achieved by amidation using (o-bromophenyl)dimethylaluminum amide and methylation of the resulting amide 237 using sodium hydride and iodomethane. Treatment of 238 with tri-n-butyltin hydride and AIBN under the identical conditions with 229 gave a separable mixture of oxindoles 239 and 240, each in 42% yield. The assignment of C(3) stereochemistry in 239 and 240 was in each case based on appearance of the C(3) methine proton as a doublet of doublets \((J = 11.0 \text{ and } 4.0 \text{ Hz})\), indicating an axial disposition for this proton in both diastereomers. The assignment of C(4) stereochemistry in 239 and 240 was based on a series of NOE experiments. For example, irradiation of the diasterotopic protons of the angular methoxymethyl group showed an 18% enhancement at \(H_0\) in 240 where no such enhancement was observed for 239.

These studies gave us hope that cyclization of the radical derived from 224 would provide some material with C(4) stereochemistry appropriate for the synthesis of gelsemine. The C(3) stereochemistry remained to be seen, however, because 238 was not considered a suitable model for the steric environment of 225. Cyclization substrate 245 became our next target, and it was prepared from ketone 141 as outlined in Scheme XXXX. Our hope that regioselective carboxymethoxylation of 141 could be accomplished was once again based on the aforementioned propensity of 141 to enolize toward C(4) \((141 \rightarrow 183 \text{ and } 134 \rightarrow 187)\). Although 241 could be isolated and purified following treatment of 141 with potassium hydride and dimethyl carbonate, it was more convenient to add hexamethylphosphoram ide and dimethyl sulfate to the crude enolate. In this manner, vinylogous carbonate 242 was obtained in 74% overall yield from 141. The C-methylation product 243 was obtained if iodomethane was used in place of dimethyl sulfate. The stereochemical course of this alkylation was apparent from an NOE experiment which established the proximity of the C(4)-methyl and angular methoxymethyl groups. The significance of this result will become apparent. Treatment of 242 with the amide derived from o-bromoaniline and trimethylaluminum, followed by alkylation of the resulting amide 244 using
lithium diisopropylamide and chloromethyl methyl ether gave vinylogous urethane 245 in 58% overall yield. The $^1$H NMR spectra of 245 was complicated at room temperature due to the presence of amide geometrical isomers, although the signals did undergo coalescence at 420°K in dimethyl sulfoxide.

**Scheme XXXX. Preparation of Radical Cyclization Precursor 245**

(a) KH (3 equiv), (CH$_3$O)$_2$C=O, THF; (b) HMPA, (CH$_3$)$_2$SO$_4$; (c) KH, CH$_3$I, THF, HMPA; (d) o-BrC$_6$H$_4$NH$_2$, Me$_3$Al, C$_6$H$_6$; (e) LDA (1.2 equiv), CH$_3$OCH$_2$Cl, THF

Cyclization studies were next conducted as outlined in Scheme XXXXI. When 245 was treated with 1.2 equivalents of tri-$n$-butyltin hydride and 0.1 equivalent of AIBN under the identical conditions used in model studies, the reaction initially proceeded but eventually stopped with 85% recovery of 245. The failure of the cyclization could be a result of interruption of radical chain
propagation. To deal with this problem, a stoichiometric amount of AIBN was used. Treatment of a solution of 245 with 1.2 equivalents of tri-n-butyltin hydride and 0.5 equivalent of AIBN under identical conditions afforded oxindole 248 in 46% yield along with two other products that both contained oxindole moieties. The structure of 248 was initially assigned on the basis of spectroscopic data (Figure 5). For example, the assignment of stereochemistry at C(3) was based on the appearance of H(3) as a doublet of doublets \((J = 11.6 \text{ Hz}, 6.3 \text{ Hz})\), an indication of axial disposition for this proton. The stereochemistry of the olefin was assigned on the basis of NOE experiments that established the proximity of H(5) and H(17) and the C(4) stereochemical
Figure 5. NOE Experiments with Oxindole 248

<table>
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<tr>
<th>$^1$H Irradiated</th>
<th>Chemical Shift (CDC$_3$)</th>
<th>NOE Observed</th>
<th>Chemical Shift</th>
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</thead>
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<td>$H_{5'}$</td>
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<td>$H_{17}$ (11%)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>$H_{4a}$</td>
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<table>
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<tr>
<th>$^1$H Irradiated</th>
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<th>NOE Observed</th>
<th>Chemical Shift</th>
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<td></td>
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<td>2.65</td>
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<td></td>
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<td>$H_b$</td>
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<td>7.24</td>
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<td></td>
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<tr>
<td>oxindole OCH$_3$</td>
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<td></td>
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</table>
Figure 6. ORTEP of Oxindole 248

assignment was based on NOE experiments that established the proximate nature of H(4') and the angular C(20) methoxymethyl group. The structure of 248 was eventually confirmed by a X-ray crystallography (Figure 6).49 The stereochemical course of the oxindole formation was consistent with that of the aforementioned methylation (241 → 243). We imagine that 248 was derived from cyclization of the initially formed aryl radical to give 246, followed by 1,4-hydrogen atom transfer to form stabilized allylic radical 247, and subsequent reduction of 247.68 In accord with this proposal, deuterium incorporation at the benzylic position of 249 was observed when tri-n-butyltin deuteride was used in place of tri-n-butyltin hydride. In addition, one of the two unidentified products (250), isolated in 18% yield, had a molecular formula of C_{40}H_{43}N_{3}O_{5} (by HRMS) and was suspected to be the product derived from 1:1 coupling of radical 247 with an isobutyronitrile radical.
It was clear that the radical cyclization and subsequent reduction did not provide the appropriate C(4) and C(3) stereochemistry for a synthesis of gelsemine. Moreover, the 1,4-hydrogen atom transfer disturbed C(16) functionality required to construct the tetrahydropyran according our approach. Our plans to deal with these problems follow. We imagined that the 1,4-hydrogen atom transfer of 246 could be avoided by using a higher concentration of tri-n-butyltin hydride in the radical cyclization. Rather than attempt this radical cyclization with 245, initial studies were performed using 238 (Equation 15). Treatment of a solution of 238 in benzene at reflux with 10 equivalents of tri-n-butyltin hydride and 0.1 equivalent of AIBN gave a 4:3 mixture of 239 and 240, respectively, in 85% yield. No reduction of aryl radical 251 was observed. Even when the reaction was conducted in neat tri-n-butyltin hydride, 239 and 240 were isolated in 72% combined yield. The rate of this cyclization was remarkable and gave us hope that cyclization of 245 could be accomplished without disturbing the C(16) diphendylethylene moiety. In addition, the solvent effect on stereoselectivity was interesting and revived our hope that this cyclization could provide some material with C(4) stereochemistry appropriate for the synthesis of gelsemine.
With the above results in hand, cyclization of 245 was performed using ten equivalents of tri-\(n\)-butyltin hydride (Equation 16). These conditions gave a 2.5:1 mixture of oxindoles 248 and 252, respectively, in 60% yield along with 14% of 253. The structures of 252 and 253 were based on a series of NMR experiments (decoupling and difference NOE). Relevant difference NOE experiments are summarized Figures 7 and 8. For oxindole 252, C(4) stereochemistry was assigned on the basis of the proximity of \(\text{H}(5)\) and \(\text{H}(4')\) while the stereochemistry at C(3) was based on the observation that double bond migration had occurred. Olefin geometry was assigned based on the proximity of \(\text{H}(5)\) and \(\text{H}(17)\). For oxindole 253, the stereochemistry at C(4) was based on the small NOE observed at \(\text{H}(4')\) upon irradiation of one of the diastereotopic methylenes of the C-20 methoxymethyl group (\(\text{H}_b\)) and the absence of an NOE at \(\text{H}(4')\) upon irradiation of \(\text{H}(5)\) and \(\text{H}(16)\). A large NOE was not observed because 253 principally adopts a boat-like conformation. This is evident from the proximity of \(\text{H}(3)\) and the C-20 methoxymethyl group.
Figure 7. NOE Experiments with Oxindole 252

<table>
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<tr>
<th>H_17</th>
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<tr>
<td>H_5</td>
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<td>C(20)-OCH_3 (5%)</td>
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Figure 8. NOE Experiments with Oxindole 253

<table>
<thead>
<tr>
<th>H&lt;sub&gt;17&lt;/sub&gt;</th>
<th>Chemical Shift (CDCl&lt;sub&gt;3&lt;/sub&gt;)</th>
<th>NOE Observed</th>
<th>Chemical Shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.71</td>
<td>H&lt;sub&gt;16&lt;/sub&gt; (3%)</td>
<td></td>
<td>4.41</td>
</tr>
<tr>
<td></td>
<td>NCH&lt;sub&gt;3&lt;/sub&gt; (2%)</td>
<td></td>
<td>2.87</td>
</tr>
<tr>
<td></td>
<td>H&lt;sub&gt;1&lt;/sub&gt; (7%)</td>
<td></td>
<td>1.97</td>
</tr>
<tr>
<td>H&lt;sub&gt;16&lt;/sub&gt;</td>
<td>4.41</td>
<td>H&lt;sub&gt;17&lt;/sub&gt; (3%)</td>
<td>5.71</td>
</tr>
<tr>
<td></td>
<td>H&lt;sub&gt;5&lt;/sub&gt; (11%)</td>
<td></td>
<td>3.43</td>
</tr>
<tr>
<td></td>
<td>H&lt;sub&gt;2a&lt;/sub&gt; (8%)</td>
<td></td>
<td>1.74</td>
</tr>
<tr>
<td>H&lt;sub&gt;b'&lt;/sub&gt;</td>
<td>4.18</td>
<td>H&lt;sub&gt;b&lt;/sub&gt; (22%)</td>
<td>3.85</td>
</tr>
<tr>
<td></td>
<td>C(20)-OCH&lt;sub&gt;3&lt;/sub&gt; (5%)</td>
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<td>3.56</td>
</tr>
<tr>
<td>H&lt;sub&gt;3&lt;/sub&gt;</td>
<td>4.01</td>
<td>H&lt;sub&gt;4' &lt;/sub&gt;(9%)</td>
<td>7.42</td>
</tr>
<tr>
<td></td>
<td>H&lt;sub&gt;b&lt;/sub&gt; (10%)</td>
<td></td>
<td>3.85</td>
</tr>
<tr>
<td></td>
<td>C(3)-OCH&lt;sub&gt;3&lt;/sub&gt; (11%)</td>
<td></td>
<td>2.93</td>
</tr>
<tr>
<td>H&lt;sub&gt;b&lt;/sub&gt;</td>
<td>3.85</td>
<td>H&lt;sub&gt;4' &lt;/sub&gt;(4%)</td>
<td>7.42</td>
</tr>
<tr>
<td></td>
<td>H&lt;sub&gt;b'&lt;/sub&gt; (26%)</td>
<td></td>
<td>4.18</td>
</tr>
<tr>
<td></td>
<td>H&lt;sub&gt;3&lt;/sub&gt; (12%)</td>
<td></td>
<td>4.01</td>
</tr>
<tr>
<td></td>
<td>C(20)-OCH&lt;sub&gt;3&lt;/sub&gt; (1%)</td>
<td></td>
<td>3.56</td>
</tr>
<tr>
<td>H&lt;sub&gt;5&lt;/sub&gt;</td>
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<td>H&lt;sub&gt;16&lt;/sub&gt; (9%)</td>
<td>4.41</td>
</tr>
<tr>
<td></td>
<td>NCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
<td>2.87</td>
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<tr>
<td></td>
<td>H&lt;sub&gt;4a&lt;/sub&gt; (12%)</td>
<td></td>
<td>2.46</td>
</tr>
<tr>
<td>oxindole OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3.27</td>
<td>NCH&lt;sub&gt;2&lt;/sub&gt; (2%)</td>
<td>5.03</td>
</tr>
<tr>
<td>C(3)-OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>2.97</td>
<td>H&lt;sub&gt;3&lt;/sub&gt; (7%)</td>
<td>4.01</td>
</tr>
<tr>
<td>NCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>2.87</td>
<td>H&lt;sub&gt;17&lt;/sub&gt; (3%)</td>
<td>5.71</td>
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<tr>
<td></td>
<td>H&lt;sub&gt;5&lt;/sub&gt; (3%)</td>
<td></td>
<td>3.43</td>
</tr>
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</table>
group, an observation that also allowed assignment of stereochemistry at C(3). This interesting result indicated that although 1,4-hydrogen atom transfer was still competing with reduction of radical 246, reduction of 246 did occur to give the required stereochemistry (245 → 246 → 253). In addition the appearance of 252 indicated that, for some undetermined reason, these conditions gave some of the required C(4) stereochemistry in the aryl radical cyclization.

In an attempt to further increase the rate of reduction of 246, cyclization of 245 was conducted in neat tri-n-butyltin hydride (Equation 17). Thus, warming a solution of 245 in tri-n-butyltin hydride in the presence of 0.1 equivalent AIBN at 80°C for 1 h gave 253 in 57% yield along with 26% of 254. The structure assignment for 254 was also based on ¹H NMR spectra (Figures 9 and 10). For example, the C(4) stereochemistry of 254 was assigned based on the proximate nature of the H(4') and the C(5) methine and the C(3) stereochemistry of was assigned based on the appearance of C(3) methine as a doublet (J = 6.0 Hz), an indication of equatorial disposition for this proton. It is notable that 254 appears to adopt a chair-like conformation while
Figure 9. NOE Experiments with Oxindole 254 in Chloroform

<table>
<thead>
<tr>
<th>$^1$H Irradiated</th>
<th>Chemical Shift (CDCl$_3$)</th>
<th>NOE Observed</th>
<th>Chemical Shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_7'$</td>
<td>6.96</td>
<td>$H_6'$ (9%)</td>
<td>7.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$H_a$ (4%)</td>
<td>4.95</td>
</tr>
<tr>
<td>$H_5'$</td>
<td>6.86</td>
<td>$H_6'$ (8%)</td>
<td>7.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$H_4'$ (8%)</td>
<td>6.32</td>
</tr>
<tr>
<td>$H_4'$</td>
<td>6.32</td>
<td>$H_5'$ (13%)</td>
<td>6.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$H_{16}$ (11%)</td>
<td>3.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$H_5$ (7%)</td>
<td>3.23</td>
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<tr>
<td>$H_a'$</td>
<td>5.13</td>
<td>$H_a$ (27%)</td>
<td>4.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>oxindole OCH$_3$ (5%)</td>
<td>3.28</td>
</tr>
<tr>
<td>$H_a$</td>
<td>4.95</td>
<td>$H_7'$ (9%)</td>
<td>6.96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$H_a'$ (28%)</td>
<td>5.13</td>
</tr>
<tr>
<td>oxindole OCH$_3$</td>
<td>3.28</td>
<td>$H_a'$ (2%)</td>
<td>5.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$H_a$ (1%)</td>
<td>4.95</td>
</tr>
<tr>
<td>$H_5$</td>
<td>3.23</td>
<td>$H_4'$ (11%)</td>
<td>6.32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$H_{16}$ (7%)</td>
<td>3.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCH$_3$ (7%)</td>
<td>2.87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$H_{4a}$ (13%)</td>
<td>2.09</td>
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</tbody>
</table>
Figure 10. NOE Experiments with Oxindole 254 In Benzene

<table>
<thead>
<tr>
<th>1H Irradiated</th>
<th>Chemical Shift (C$_6$D$_6$)</th>
<th>NOE Observed</th>
<th>Chemical Shift</th>
</tr>
</thead>
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<tr>
<td>H$_b$ and H$_b'$</td>
<td>4.33</td>
<td>C(20)-OCH$_3$ (5%)</td>
<td>3.42</td>
</tr>
<tr>
<td>H$_{16}$</td>
<td>3.93</td>
<td>H$_4'$ (11%)</td>
<td>6.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H$_{17}$ (3%)</td>
<td>5.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H$_5$ (5%)</td>
<td>3.17</td>
</tr>
<tr>
<td>H$_3$</td>
<td>3.57</td>
<td>C(3)-OCH$_3$ (11%)</td>
<td>2.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H$_{2a}$ (5%)</td>
<td>2.30</td>
</tr>
<tr>
<td>C(20)-OCH$_3$</td>
<td>3.42</td>
<td>H$_b$ and H$_b'$ (3%)</td>
<td>4.33</td>
</tr>
<tr>
<td>H$_5$</td>
<td>3.17</td>
<td>H$_4'$ (6%)</td>
<td>6.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H$_{16}$ (4%)</td>
<td>3.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCH$_3$ (3%)</td>
<td>2.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H$_{4a}$ (8%)</td>
<td>2.31</td>
</tr>
<tr>
<td>NCH$_3$</td>
<td>2.55</td>
<td>H$_{17}$ (3%)</td>
<td>5.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H$_5$ (4%)</td>
<td>3.17</td>
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<td>H$_{4a}$ (1%)</td>
<td>2.31</td>
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<tr>
<td>C(3)-OCH$_3$</td>
<td>2.45</td>
<td>H$_4'$ (1%)</td>
<td>6.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H$_3$ (4%)</td>
<td>3.57</td>
</tr>
</tbody>
</table>
253 adopts a boat-like conformation. This may be due to steric compression between the aryl group and H(5)/H(16) in boat-like conformations of 254. In summary, cyclization of 245 in neat tri-n-butyltin hydride increased the rate of the reduction of radical 246 such that it competed favorably with the 1,4-hydrogen atom transfer and afforded, as anticipated, the appropriate stereochemistry at C(3). In addition, it provided some material with appropriate stereochemistry at C(4). Although the major product did not have the C(4) stereochemistry required for gelsemine, we felt it could still be used in the synthesis. For example, we imagined that the C(4)

Scheme XXXXII. Proposed End-Game

![Chemical structure]

stereochemistry of materials like 255 (or C(3)-epi-255) could be epimerized via a retroaldol-aldol process. Our plan to epimerize C(4) stereochemistry and construct the tetrahydropyran substructure of gelsemine is outlined in Scheme XXXXII. Oxidative cleavage of 255 (or C(3)-epi-
was expected to afford aldehyde 257 (or C(3)-epi-257) and our hope was that isomerization of C(3) and C(4) could then be accomplished by a retroaldol-aldol process to give 258 and its C(4) epimer. We recognized that C(3) isomer of 258 would be more stable than 258 but only the aldehyde derived from 258 would undergo cyclization to give hemiacetal 259. Similar plans were also to be used to convert 256, which has the required C(4) stereochemistry for gelsemine, to 259.

There are potential problems with this plan, such as hemiacetal formation prior to C(4) isomerization, but it was felt that this plan might allow us to recover from the poor stereoselectivity observed in the aryl radical cyclization. In principle, the epimerization-isomerization-cyclization sequence could be subject to thermodynamic control and the product ratio would depend on the relative stability of 259 and its C(4) epimer. Molecular mechanics calculations suggested that 259 is 1.1 kcal and 1.4 kcal/mol lower in energy than 4-epi-259 using Model and Macromodel, respectively, and thus Scheme XXXXII seemed to merit investigation.

Studies designed to eventually execute this plan were first conducted using oxindoles 270 and 271. Preparation of these compounds is describe in Scheme XXXXIII. Treatment of decalone 233 with potassium hydride and dimethyl carbonate followed by treatment of the crude enolate with hexamethylphosphoramide and chloromethyl methyl ether afforded 260 in 79% yield. Amidation of 260 using the appropriate dimethyl aluminum amide gave 261 in 47% overall yield along with 18% of the enamine 261a derived from amide attack at C(3) and 27% of starting 260. Treatment of 261 with sodium hydride and iodomethane followed by cyclization of the resulting vinylogous urethane 262 using tri-n-butyltin hydride and AIBN, under the conditions used with 238 afforded oxindoles 263 (41%) and 264 (39%). Hydrolysis of 263 to 270 was accomplished in 95% yield using hydrochloric acid. Hydrolysis of 264 under the same conditions was accompanied by epimerization to afford a separable 80:20 mixture of 271 and 270. The stereochemical assignments for 270 and 271 were based on arguments similar to those used to establish the structures of 239 and 240.
Scheme XXXIII. Preparation of 270 and 271

(a) KH, (CH$_3$O)$_2$C=O, THF; HMPA, CICH$_2$OCH$_3$; (b) KH, (CH$_3$O)$_2$C=O, THF; (c) t-BDMSCI, imidazole, DMF; (d) o-BrC$_6$H$_4$NH$_2$, Al(CH$_3$)$_3$, C$_6$H$_6$; (e) NaH, CH$_3$I, THF; (f) NaH, CICH$_2$OCl, THF; (g) n-Bu$_3$SnH (1.2 equiv), AIBN (0.1 equiv), C$_6$H$_6$; (h) HCl (aq), THF
With 270 and 271 in hand, epimerization studies were conducted under conditions used to convert 138 to 139 (Scheme XXI) as outlined in Scheme XXXXIV. Independently warming solutions of 270 and 271 with DBU in dichloromethane at reflux gave a 14:78:7:1 mixture of 270, 271, 271, and 273, respectively, with 85% recovery of material. The ratio was determined using analytical HPLC and the equilibrium was established after 16 hours. The structure of 272 was based on spectroscopic data. For example, the C(3) stereochemical assignment was based on the appearance of C(3) methine proton at δ 3.75 as a broad triplet that indicated an equatorial disposition for this proton. The C(4) stereochemical assignment was based on the analogy to 239. The structure of 273 is tentative and was based only on HPLC analysis. It was noted that axial alcohols (272 and 273) were eluted faster than equatorial alcohols (270 and 271) using an ISCO silica 0.5 μm column (ethyl acetate-hexane 15:85). This experiment indicated that the epimerization proposed in Scheme XXXXII was feasible. Furthermore, it indicated that the
spirooxindoles with equatorial aryl groups (270 and 272) were more stable than those with axial aryl groups (271 and 273). These observations were supported by molecular mechanics calculations which suggested that 270 was 2.9 kcal and 1.5 kcal/mol lower in energy than 271 using Model and Macromodel, respectively.\textsuperscript{69}

Before returning to gelsemine intermediates, additional C(3) and nitrogen protecting groups were examined. Thus, treatment of 234 with chloro-\textit{tert}-butyldimethylsilane and imidazole gave 265 in 82\% yield.\textsuperscript{70} Amidation of 265 using (o-bromophenyl)dimethylaluminum amide followed by N-alkylation of the resulting amide 266 using sodium hydride and chloromethyl methyl ether afforded 267 in 30\% overall yield. Treatment of 267 with tri-\textit{t}-butyltin hydride and AIBN gave a separable 1:1 mixture of 268 and 269. Although desilylation of 268 was not attempted, it was noted that treatment of 269 with tetra-\textit{t}-butylammonium fluoride gave 274 in 73\% yield. Thus, base promoted isomerization at C(4) accompanied deprotection the C(3) hydroxy group.

\begin{equation}
\begin{array}{c}
\text{OCH}_3 \quad \text{OCH}_3 \\
\text{TBSO} \quad \text{O} \\
\text{269}
\end{array} \quad \text{TBAF, THF} \quad \begin{array}{c}
\text{OCH}_3 \\
\text{274 (73\%)}
\end{array}
\end{equation}

Knowing that the desired epimerization could be accomplished with acid or base, the preparation of 257 was pursued as outlined in Scheme XXXXV. The preparation of 257, however, turned out not to be straightforward using the protocol developed for the preparation of 270 and 271. Vinlylogous carbonate 275 was prepared in 80\% from ketone 141 under the same conditions used to convert 233 to 260. Treatment of 273 with (o-bromophenyl)dimethylaluminum amide, however, afforded 231 in 85\% yield. Since the methoxymethyl protecting group appeared unsuitable, a silyl protecting group was examined. Thus, treatment of 241 with chloro-\textit{tert}-butyl-
dimethylsilane and imidazole gave vinylogous carbonate 276 in 59% yield. Unfortunately, treatment of 276 with the appropriate aluminum amide afforded a mixture of unidentified products.

Scheme XXXXV. Attempted Preparations of 257

(a) KH (3 equiv), (CH$_3$O)$_2$C=O, THF; HMPA, (CH$_3$)$_2$SO$_4$; (b) KH (3 equiv), (CH$_3$O)$_2$C=O, THF; (c) $t$-BDMSCI, imidazole, DMF; (d) $o$-BrC$_6$H$_4$NH$_2$, Me$_3$Al, C$_6$H$_6$; (e) $o$-BrC$_6$H$_4$N=C=O, KH, THF; (f) $t$-Pr$_2$NEt, CICH$_2$OCH$_3$, CH$_2$Cl$_2$
It was felt that constructing the amide prior to the protection of the enol should eliminate the deprotection problems. Toward this end, we demonstrated that treatment of ketone 141 with o-bromophenyl isocyanate and potassium hydride afforded vinylogous urethane 278 in 70\% yield.\(^{71}\) Protection of 278 using chloromethyl methyl ether under a variety of conditions afforded only the O-protected enol 279. The assignment of 279 was based on \(^1\)H NMR spectrum. For example, slow deuterium exchange of the singlet at δ 10.0 infer an amide proton. To our disappointment, attempts to to protect the enol using chloromethyl methyl ether or chloro-\textit{tert}-butyldimethylsilane under a variety of conditions met with failure.

These results suggest that it will be necessary to convert 279 to a vinylogous urethane derivative with an alkyl group (rather than trialkysilyl or methoxymethyl) on the amide nitrogen. This alkyl group, however, must be easily removed after conducting the aryl radical cyclization. Benzylic protecting groups might satisfy these requirements. In this regard, we have found that treatment of 280 with dimethyl sulfate gives 281 in 78\% yield (structure based on NMR only). Thus, it is our hope that 279 will undergo N-alkylation upon treatment with benzyl tosylate to afford 277 (where R = methoxymethyl and R' = benzyl) and allow us to examine the epimerization chemistry proposed in Scheme XXXII.

\[ \text{KH, (CH}_3\text{)}_2\text{SO}_4 \]

C. Summary

This chapter described studies that resulted in construction of the oxindole substructure of gelsemine. In the course of this investigation, we discovered that the rate of cyclizations
between an enol and aryl radical derived from o-bromo-N-acryloylanilide was extremely fast (245 → 253 + 254). Although this cyclization did not provide the required C(4) stereochemistry in high yield, model studies designed to epimerize the C(4) stereochemistry to that required for gelsemine were very encouraging. The preparation of 257 and the epimerization study outlined in Scheme XXXIX are currently being examined. We are hopeful that the synthesis of gelsemine will eventually be completed using the aforementioned approach.
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 dimethysulfoxide on the δ scale. The 1H NMR spectra are reported as follow: chemical shift [multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz, integration, interpretation]. 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 457 or 1600 instruments. Mass spectra were obtained on Kratos MS-30 or Kratos 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. High pressure liquid chromatographic analyses were performed on ISCO 2350. Combustion analysis were performed by Micro-Analysis, Inc., Wilmington, Delaware.

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. Reactions requiring an inert atmosphere were run under argon. Tri-n-butyltin hydride was prepared according a known procedure. Analytical thin-layer chromatography was conducted using EM Laboratories 0.25 mm thick precoated silica gel 60F-254 plates. Column chromatography was performed over EM Laboratories silica gel (70-230 or 230-400 mesh). Medium pressure liquid chromatography
(MPLC) was performed using EM laboratories Laboratories Lobar prepacked silica gel columns. All organometallic reagents (Grignard, and organic lithiums) were titrated prior to use with menthol using 1,10-phenanthroline as the indicator. The order of experimental procedures follow their order of appearance in the text.

\[
\text{(1a,3aβ,4α,7α,R*)-8-(2,2-Diphenylethenyl)hexahydro-3a-(methoxy-methyl)-2-methyl-1,4-methano-1H-Isolindol-3,6-(2H)-dione (141). To a solution of 150 mg (0.38 mmol) of ketal 132 in 30 mL of tetrahydrofuran cooled in a dry ice-acetone bath was added 2.3 mL (1.50 mmol) of 0.65 M of phenylmagnesium bromide in tetrahydrofuran over a 4-min period. The mixture was warmed to room temperature and stirred for 30 min. The resulting solution was concentrated in vacuo. The residue was diluted with 50 mL of dichloromethane and washed with 30 mL of saturated aqueous ammonium chloride. The aqueous wash was extracted with three 20-mL portions of dichloromethane. The combined organic phases were dried (MgSO}_4\) and concentrated in vacuo. The residue was chromatographed over 6 g of silica gel (ethyl acetate) to give 142 mg (78%) of tertiary alcohol as a clear oil. This material was dissolved in 30 mL of benzene and 50 mg (0.26 mmol) of p-toluenesulfonic acid was added. The mixture was warmed under reflux for 1.5 h, concentrated in vacuo, and the residue was chromatographed over 6 g of silica gel (ethyl acetate) to give 115 mg (76%) of ketone 141 as clear oil: IR (CH}_2Cl}_2 1705, 1690 cm\(^{-1}\); \text{^1H NMR (500 MHz, CDCl}_3\) \delta 2.05 (d, \textit{J} = 19 Hz, 1H, C5H), 2.09 (m, 1H, C7aH), 2.32 (dd, \textit{J} = 18.6, 2.9 Hz, 1H, C7H), 2.51 (dd, \textit{J} = 19, 6.9 Hz, 1H, C5H), 2.58-2.65 (m, 3H, C4H, C7H and C8H), 3.01 (s, 3H, NCH}, 3.35 (s, 3H, OCH}_3\), 3.44 (t, \textit{J} = 2.5 Hz, 1H, C1H), 3.74 (d, \textit{J} = 10.3 Hz, 1H, CH2OMe), 3.96 (d, \textit{J} = 10.3 Hz, 1H, CH2OMe), 5.82 (d, \textit{J} = 9.4 Hz, 1H, =CH), 7.1-7.4
(m, 10H, ArH); $^{13}$C NMR (CDCl$_3$) δ 30.5 (q), 39.1 (t), 41.5 (d), 42.5 (t), 49.0 (d), 50.2 (d), 55.0 (s), 59.4 (q), 68.0 (d), 69.4 (t), 126.5 (d), 126.8 (d), 127.6 (d), 127.7 (d), 128.2 (d), 128.6 (d), 129.1 (d), 139.2 (s), 140.9 (s), 144.4 (s), 175.6 (s), 208.0 (s); exact mass calcd. for C$_{26}$H$_{27}$NO$_3$ m/e 401.1992, found m/e 401.1966.

(1a,3ab,4a,6a,7ab,8R*)-(±)-8-(2,2-Diphenylethenyl)hexahydro-6-hydroxy-3a-(methoxymethyl)-2-methyl-1,4-methano-1H-isindol-3,6(2H)-dione (137). To a solution of 110 mg (0.27 mmol) of the ketone 141 in 5 mL of methanol cooled in ice bath was added 26 mg (0.69 mmol) of sodium borohydride in one portion. The mixture was stirred for 30 min at 0 °C and 1 h at room temperature. The resulting solution was concentrated in vacuo. The residue was diluted with 50 mL of dichloromethane and washed with 30 mL of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with three 20-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 6 g of silica gel (ethyl acetate-methanol, 15:1) to give 89 mg (81%) of alcohol 137 as white solid: mp 171-173 °C; IR (CHCl$_3$) 1685 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 1.34 (dd, $J = 15.6$, 4.4 Hz, 1H, C$_4$H$_2$), 1.49 (bs, 1H, OH), 1.50 (dt, $J = 14.9$, 2.8 Hz, 1H, C$_2$H), 1.79 (m, 1H, C$_4$A$^a$H), 2.13 (m, 2H, C$_4$H and C$_2$H), 2.35 (m, 1H, C$_1$H), 2.98 (s, 3H, NCH$_3$), 3.33 (t, $J = 2.5$ Hz, 1H, C$_5$H), 3.38 (s, 3H, OCH$_3$), 3.45 (d, $J = 10.0$ Hz, 1H, CH$_2$OMe), 3.48 (dt, $J = 9.9$, 2.5 Hz, 1H, C$_1$H$_2$H), 3.88 (d, $J = 10.0$ Hz, CH$_2$OMe), 4.00 (m, 1H, C$_3$H), 5.77 (d, $J = 9.9$ Hz, 1H, =CH$_2$), 7.15-7.45 (m, 10H, ArH); $^{13}$C NMR (CDCl$_3$) δ 30.6 (q), 31.6 (t), 35.8 (t), 41.3 (d), 47.3 (d), 48.1 (d), 55.5 (s), 59.6 (q), 62.2 (d), 67.1 (d), 68.8 (t), 126.8 (d), 127.2 (d), 128.2 (d), 128.3 (d), 128.7 (d), 129.7 (d), 140.0 (s), 141.3 (s), 143.1 (s), 176.7 (s); exact mass calcd. for C$_{26}$H$_{29}$NO$_3$
m/e 403.2147, found m/e 403.2124. Further elution gave 6.4 mg (7%) of an impure material suspected to be epimeric to 137 at C(3).

3-[(Tetrahydro-2'H-pyran-2'-yl)oxy]propanal (121).³⁸,³⁹,⁴⁸ Method A: To a suspension of 5.00 g (66 mmol) of 1,3-propanediol and 0.85 g (35 mmol) of pyridinium p-toluenesulfonate in 70 mL of dichloromethane was added 5.61 g (66 mmol) of 3,4-dihydropyran dropwise. The mixture was stirred for 2 h at room temperature until the solution was homogeneous. The solution was concentrated in vacuo, dissolved in 50 mL of hexane and washed with three 50-mL portions of water. The combined aqueous layers were extracted with three 50-mL portions of dichloromethane. The dichloromethane extracts were dried (Na₂SO₄) and concentrated in vacuo to give 6.6 g (62%) of 144b as a clear oil. This material was used in subsequent reactions without further purification.

To a suspension of 13.8 g (64 mmol) of pyridinium chlorochromate and 1 g (13 mmol) of sodium acetate in 100 mL of dichloromethane was added 6.6 g (43 mmol) of alcohol 144b in 10 mL of dichloromethane in one portion. The mixture was stirred at room temperature for 2 h and concentrated in vacuo. The residue was suspended in 100 mL of diethyl ether and filtered through Florisil. The filtrate was concentrated in vacuo and distilled to afford 3.5 g (53%) of aldehyde 121 as a clear oil: bp 66-67°C at 1.0 mm (lit.³⁹ bp 58-60°C at 0.1 mm).

Method B: To a solution of 5.0 g (69 mmol) of 3-buten-1-ol and 11.6 g (138 mmol) of 3,4-dihydropyran in 25 mL of hexane was added 1.8 g of Dowex-50 (H⁺). The mixture was stirred for 2 h at room temperature and filtered. The filtrate was concentrated in vacuo and distilled to give 7.7 g (74%) of 145 as a clear oil.
To a solution of 2 g (12.8 mmol) of olefin 145 in 15 mL of toluene cooled dry ice acetone bath was bubbled ozone for 2 h at -78°C. The solution was flushed with argon and 0.2 g of 10% palladium on charcoal was added. The mixture was hydrogenated under 15 psi of hydrogen for 12 h (Parr apparatus) and filtered through celite. The filtrate was concentrated in vacuo and distilled to afford 1.2 g (61%) of 121 as a clear oil: bp 68-69°C at 1.0 mm (lit.39 bp 58-60°C at 0.1 mm); δ ^1H NMR (250 MHz, CDCl3) δ 1.50-2.01 (m, 6H, CH2), 2.68 (dt, J = 6.1, 1.8 Hz, 2H, CH2O), 3.49 (m, 1H, CH20), 3.70 (m, 2H, CH2O), 4.10 (m, 1H, CH2O), 4.62 (m, 1H, OCHO), 9.75 (t, J = 1.8 Hz, 1H, CHO).

Phenyl α-(2-Fluorophenyl)thioacetate (142). To a solution of 5.0 g (32 mmol) of 2-fluorophenylacetic acid and 8.0 g (32 mmol) of thiophenol in 100 mL of dichloromethane was added 6.7 g (32 mmol) of dicyclohexylcarbodiimide and 50 mg (0.4 mmol) of 4,4-dimethylaminopyridine at room temperature. The mixture was stirred for 12 h at room temperature and washed with three 30-mL portions of saturated aqueous sodium bicarbonate. The organic layers were dried (MgSO4) and concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (ethyl acetate-hexane, 5:95) to give 6.45 g (81%) of thioester 142 as white solid: mp 44.2-45.0 °C; IR (CH2Cl2) 1704 cm⁻¹; ^1H NMR (250 MHz, CDCl3) δ 4.0 (d, J = 0.8 Hz, 2H, CH2), 7.15-7.42 (m, 9H, ArH); ^13C NMR (62.9 Hz, CDCl3) δ 43.00 (dt, J = 2.6 Hz), 115.49 (dd, J = 21.7 Hz), 120.61 (ds, J = 15.6 Hz), 124.21 (dd, J = 3.6 Hz), 127.53 (s) 129.12 (d), 129.39 (d), 129.55 (dd, J = 8.1 Hz), 131.77 (dd, J = 3.8 Hz), 134.43 (d), 161.09 (dd, J = 256.8 Hz), 194.41 (s); exact mass calcd for C14H11FOS m/e 246.0515, found m/e 246.0515.
1-Triphenylphosphoranylidene-3-(2-fluorophenyl)-2-propanone (143). To a suspension of 16.3 g (16.3 mmol) of methyl triphenylphosphonium bromide in 100 mL of tetrahydrofuran cooled in a dry ice-acetone bath was added 10.7 mL (16.3 mmol) of 1.52 \textit{M} \textit{n}-butyllithium in hexane. The mixture was stirred for 30 min at -75 °C and 2.0 g (8.1 mmol) of phenyl α-(2-fluorophenyl)thioacetate (142) in 10 mL of tetrahydrofuran was added over a 10-min period. The mixture was stirred for 30 min at -75 °C and for 1 h at room temperature. The mixture was concentrated in vacuo and the residue was diluted with 100 mL of ethyl acetate, filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed over 100 g of silica gel (eluted with 400 mL of ethyl acetate-hexane, 1:1, followed by 700 mL of ethyl acetate) to give 2.75 g of yellow solid. The solid was recrystallized from ethyl acetate-petroleum ether to give 2.51 g of phosphorane 143 (82%) as yellow solid: mp 113-115 °C; IR (\textit{CH}_2\textit{Cl}_2) 1687 cm\(^{-1}\); \textit{^1}H NMR (300 MHz, CDC\textit{D}_3) \delta 2.50 (b s, 1H, P=CH), 3.70 (s, 2H, ArCH\textit{D}_2), 7.0-7.3 (m, 4H, ArH), 7.3-7.9 (m, 15H, ArH); \textit{^13}C NMR (62.9 MHz, CDC\textit{D}_3) \delta 41.40 (dt, \textit{J} = 15.7 Hz), 51.30 (dd, \textit{J} = 108.2 Hz), 114.85 (dd, \textit{J} = 22.6 Hz), 123.62 (dd, \textit{J} = 3.7 Hz), 126.45 (ds, \textit{J} = 15.7 Hz), 127.31 (dd, \textit{J} = 7.5 Hz), 127.67 (d), 128.65 (dd, \textit{J} = 6.9 Hz), 128.95 (ds, \textit{J} = 335.8 Hz), 131.71 (dd, \textit{J} = 4.4 Hz), 132.94 (dd, \textit{J} = 6.9 Hz), 161.01 (dd, \textit{J} = 244.7 Hz), 189.81 (s); exact mass calcd. for C\textsubscript{27}H\textsubscript{22}FOP \textit{m/e} 412.1392, found \textit{m/e} 412.1385.

Anal. calcd. for C\textsubscript{27}H\textsubscript{22}FOP: C, 78.60; H, 5.38; P 7.52. Found C, 78.98; H, 5.35; P, 7.79.
6-(2-Fluorophenyl)-5-oxo-3(\(E\))-hexenyl Tetrahydropyran-2-yl Ether (146). A mixture of 9.56 g (23.2 mmol) of phosphorane 143 and 3.66 g (23.2 mmol) of 3-oxopropyl tetrahydropyran-2-yl ether (121) in 30 mL of dichloromethane was warmed under reflux for 21 h. The mixture was concentrated in vacuo, diluted with 500 mL of hexane, filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed over 300 g of silica gel (ethyl acetate-hexane, 1:4) to give 5.53 g (82\%) of enone 146 as yellow oil: IR (neat) 1690, 1680, 1630 cm\(^{-1}\); \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 1.45-1.90 (m, 6H, CH\(_2\)), 2.53 (qd, \(J = 6.5, 1.5\) Hz, 2H, =CCH\(_2\)), 3.54 (m, 2H, CH\(_2\)O), 3.85 (m, 2H, OCH\(_2\)), 3.89 (s, 2H, ArCH\(_2\)), 5.80 (m, 1H, OCHO), 6.21 (dt, \(J = 16.1, 6.8\) Hz, 1H, =CH), 6.97 (d, \(J = 16.1\) Hz, 1H, =CH), 6.90-7.30 (m, 4H, ArH); \(^13\)C NMR (62.85 MHz, CDCl\(_3\)) \(\delta\) 19.3 (t), 25.3 (t), 30.5 (t), 32.8 (t), 40.2 (t), 62.1 (t), 65.3 (t), 98.7 (d), 115.2 (dd, \(J = 22.0\) Hz), 121.6 (ds, \(J = 13.4\) Hz), 124.0 (dd, \(J = 3.8\) Hz), 128.7 (dd, \(J = 8.2\) Hz), 130.5 (d), 131.5 (dd, \(J = 4.4\) Hz), 145.0 (d), 160.9 (ds, \(J = 245.9\) Hz), 195.8 (s); exact mass calcd. for C\(_{12}\)H\(_{13}\)FO (M\(^+\)-C\(_5\)H\(_9\)O\(_2\)) \(m/e\) 191.0872, found \(m/e\) 191.0875. No parent ion was observed.

2-[[6-(2-Fluorophenyl)-5-trimethylsilyloxy-3(\(E\))-hexadienyl]oxy]tetrahydropyran (152). To a solution of 6.86 g (67.8 mmol) of diisopropylamine in 160 mL of tetrahydrofuran cooled in a dry-acetone bath was added 45.2 mL (67.8 mmol) of 1.50 \(M\) n-butyllithium in hexane.
The mixture was stirred for 30 min at -75 °C and 12.2 g (67.8 mmol) of hexamethylphosphoramide was added over a 5-min period. The solution was stirred for 15 min at -75 °C and 16.5 g (56.5 mmol) of enone 146 in 40 mL of tetrahydrofuran was added over a 30-min period. The resulting mixture was stirred for 15 min at -75 °C, 9.21 g (84.8 mmol) of trimethylsilyl chloride was added in one portion, the solution was warmed to room temperature, and concentrated in vacuo. The residue was flash chromatographed over 100 g of silica gel (ethyl acetate-hexane, 3:7) to give 17.5 g (85%) of 152 as yellow oil: IR (neat) 3040, 1735, 1620, 1605 cm⁻¹; ¹H NMR (90 MHz, CDCl₃) δ 0.00 (s, 9H, SiMe₃), 1.35-2.03 (m, 6H, CH₂), 2.40 (m, 2H, =CCH₂), 3.50 (m, 2H, CH₂O), 3.83 (m, 2H, OCH₂), 4.58 (b t, 1H, OCHO), 5.65 (br, 1H, =CHAr), 5.95-6.20 (m, 2H, CH=CH), 6.89-7.21 (m, 3H, ArH) 7.89 (td, 7.3, 1.5 Hz, 1H, ArH); ¹³C NMR (62.9 MHz, CDCl₃) δ 0.55 (q), 19.51 (t), 25.48 (t), 30.68 (t), 32.81 (t), 62.24 (t), 66.87 (t), 98.81 (d), 104.32 (dd, J = 5.2 Hz), 114.84 (dd, J = 22.1 Hz), 123.39 (dd, J = 3.1 Hz), 124.42 (ds, J = 12.7 Hz), 127.35 (dd, J = 8.1 Hz), 128.67 (d), 130.54 (dd, J = 3.1 Hz), 130.88 (d), 150.87 (s), 159.74 (dd, J = 247.7 Hz). Minor signals at δ 0.10 (s) in the ¹H NMR and δ 1.56 (q) in the ¹³C NMR of this material were attributed to the minor geometrical isomer (152). No mass spectrum was obtained due to sensitivity of the silyl enol ether.

(3α⁺,4α,7β,7αα)-(±)-Tetrahydro-4-(2-Fluorophenyl)-7-(2-hydroxyethyl)-2-methyl-1H-isolindole-1,3,5(2H,4H)-trione (151). A mixture of 17.51 g (48.1 mmol) of diene 152 and 5.34 g (48.1 mmol) of N-methylmaleimide in 35 mL of toluene was warmed under reflux for 40 h and
concentrated in vacuo. The residue was dissolved in 50 mL of methanol and 2 g of Dowex 50X8-100 ion exchange resin was added. The resulting mixture was warmed under reflux for 4 h, filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed over 300 g of silica gel (ethyl acetate-hexane, 7:3) to give 7.75 g (51%) of 151 as white solid: mp 138-139°C; IR (neat) 3690, 3600, 1705 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 1.41-1.52 (m, 1H, CH₂), 1.78-1.90 (m, 1H, CH₂), 2.34 (dd, J = 15.3, 8.6 Hz, 1H, C₆H), 2.47 (dd, J = 15.3, 4.1 Hz, 1H, C₆H), 2.62-2.76 (m, 1H, C₇H), 2.91 (s, 3H, NCH₃), 3.33-3.46 (m, 2H, C₃aH and C₇aH), 3.53-3.69 (m, 2H, CH₂O), 3.91 (d, J = 7.1 Hz, 1H, C₄H), 6.97-7.26 (m, 4H, ArH), the alcohol proton was not observed; ¹³C NMR (62.85 MHz, CDCl₃) δ 24.74 (q), 30.80 (d), 33.54 (t), 42.42 (t), 42.58 (d), 44.10 (d), 48.75 (d), 60.04 (t), 115.78 (dd, J = 21.8 Hz), 124.35 (dd, J = 3.1 Hz), 125.39 (ds, J = 13.9 Hz), 129.53 (dd, J = 12.2 Hz), 130.99 (dd, J = 4.1 Hz), 160.27 (ds, J = 246.1 Hz), 176.97 (s), 177.56 (s), 204.7 (s); exact mass calcd. for C₁₇H₁₈FNO₄ m/z 319.1220, found m/z 319.1315.

Anal. calcd. for C₁₇H₁₈FNO₄: C, 63.9; H, 5.68. Found C, 63.9; H, 5.8.

(3'α,4'α,7'β,7'α)-(±)-4'-[2-Fluorophenyl]-7'-[2-hydroxyethyl]tetrahydro-2',5,5-trimethylspiro[1,3-dioxane-2,5'-[5H]isindole]-1',3'-[2'H,4'H]-dione (154). A mixture of 12.89 g (57.3 mmol) of ketone 151, 5.97 g (57.3 mmol) of 2,2-dimethyl-1,3-propanediol, and 2.0 g of Dowex 50X8-100 ion exchange resin in 250 mL of benzene was warmed under reflux for 15 h with continuous removal of water using a Dean-Stark trap. The mixture was filtered and concentrated in vacuo. The residue was chromatographed over 200 g of silica gel (ethyl acetate) to give 12.9 g
(73%) of ketal 154 as a white solid: mp 169.5-171 °C; IR (neat) 3620, 1700 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.57 (s, 3H, CH₃), 0.64 (s, 3H, CH₃), 1.29 (t, J = 16.0 Hz, 1H, C₆H), 1.90-2.02 (m, 1H, CH₂), 2.28-2.46 (m, 2H, C₇H, CH₂), 2.31 (b s, 1H, OH), 2.78 (dd, J = 16.0, 3.8 Hz, 1H, C₆H), 2.90 (s, 3H, NCH₃), 3.13-3.25 (m, 3H, C₃aH, C₇aH, and OCH₂), 3.30-3.36 (m, 2H, C₄H, OCH₂), 3.56 (d, J =12.8 Hz, 1H, OCH₂), 3.64 (d, J = 12.8 Hz, 1H, OCH₂), 3.78-3.89 (m, 2H, CH₂0), 6.99 (t, J = 9.6 Hz, 1H, C₆-H), 7.11 (t, J = 5.4 Hz, 1H, C₄-H), 7.18-7.26 (m, 1H, C₃-H), 7.62 (dt, J = 7.1, 3.2 Hz, 1H, C₅-H); ¹³C NMR (62.85 MHz, CDCl₃) δ 22.08 (q), 22.28 (q), 24.33 (q), 29.43 (d), 29.58 (s), 31.22 (t), 34.89 (t), 43.21 (d), 44.53 (d), 46.01 (d), 61.02 (t), 69.82 (t), 70.10 (t), 97.82 (s), 114.30 (dd, J = 23.8 Hz), 123.19 (dd, 3.0 Hz), 124.36 (ds, J = 13.3 Hz), 128.35 (dd, J = 8.5 Hz), 131.06 (dd, J = 3.0 Hz), 162.00 (dd, J = 246.0 Hz), 177.41 (s), 177.70 (s); exact mass calcd. for C₂₂H₂₈FN₂O₅ m/z 405.1952, found m/z 405.1952.

Anal. calcd. for C₂₂H₂₈FN₂O₅: C, 65.2; H, 6.96. Found, 65.2; H, 7.08.

(3αα,4α,7β,7αα)-(±)-4′-(2-Fluorophenyl)-7′-ethenyltetrahydro-2′,5,5-trimethylspiro[1,3-dioxane-2,5′-[5H]Isolndole]-1′,3′-(2′H,4′H)-dione (155). To a solution of 1.35 g (3.3 mmol) of alcohol 154 and 1.51 g (6.6 mmol) of 2-nitrophenylselenocyanate in 22 mL of tetrahydrofuran at room temperature was added 1.66 mL (6.6 mmol) of tri-n-butylphosphine dropwise over a 15-min period. The mixture was stirred for 1 h, cooled in an ice-salt bath and 5.02 mL (52.8 mmol) of 30% of aqueous hydrogen peroxide was added over a 15-min period. The mixture was warmed to room temperature and stirred for 10 h, followed by addition of 20 mL of
water and concentration in vacuo. The residue was extracted with three 20-mL portions of diethyl ether. The combined organic layers were dried (MgSO₄), concentrated in vacuo and the residue was chromatographed over 100 g of silica gel (ethyl acetate-hexane, 4:6) to give 0.62 g (53%) of olefin 155 as white needles: mp 163-165 °C; IR (CH₂Cl₂) 1750 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.59 (s, 3H, CH₃), 0.65 (s, 3H, CH₃), 1.45 (dd, J = 13.2, 11.8 Hz, 1H, C₆⁻H), 2.75-2.84 (m, 2H, C₇⁻H and C₆⁻H), 2.90 (s, 3H, NCH₃), 3.13 (t, J = 6.7 Hz, 1H, C₇⁻H), 3.14 (dd, J = 11.4, 2.6 Hz, 1H, OCH₂), 3.24 (d, J = 9.7 Hz, 1H, C₄⁻H), 3.33-3.51 (m, 2H, C₃⁻H, OCH₂), 3.52 (d, J = 11.4 Hz, OCH₂), 3.63 (d, J = 11.4 Hz, 1H, OCH₂), 5.14-5.29 (m, 2H, =CH₂), 6.50 (dd, J = 18.3, 10.2, 8.3 Hz, 1H, =CH), 6.99-7.01 (m, 1H, C₆⁻H), 7.02-7.15 (m, 1H, C₄⁻H), 7.21-7.26 (m, 1H, C₃⁻H), 7.62 (dt, J = 1.6, 7.6 Hz, C₅⁻H); ¹³C NMR (125 MHz, CDCl₃) δ 22.10 (q), 22.29 (q), 24.41 (q), 29.67 (s), 30.42 (t), 37.26 (d), 43.82 (d), 45.21 (d), 45.67 (d), 69.89 (l), 70.17 (l), 97.87 (s), 114.59 (dd, J = 23.9 Hz), 115.26 (l), 123.22 (dd, J = 3.1 Hz), 124.39 (ds, J = 13.8 Hz), 128.39 (dd, J = 8.2 Hz), 130.99 (dd, J = 3.8 Hz), 139.10 (d), 161.97 (dd, J = 244.7 Hz), 176.80 (s), 177.26 (s); exact mass calcd. for C₂₂H₂₆FN₄Me 387.1846, found m/e 387.1824.

Anal. calcd. for C₂₂H₂₆FN₄O: C, 68.20; H, 6.77. Found C, 68.50; H, 7.19.

(3β,3'α,4α,7β,7αα)-(±)-4'-(2-Fluorophenyl)-7'-ethenyl-3'-hydroxyhexahydro-2',5,5-trimethylspiro[1,3-dioxane-2,5'-[5H]isolindole]-1'(4'H)-one (159). To a solution of 550 mg (1.42 mmol) of imide 155 in 30 mL of methanol cooled in an ice-salt bath was added 134 mg (3.55 mmol) of sodium borohydride in five portions over a 5-min period. The mixture was stirred for 1.5
h at 0°C, warmed to room temperature, and concentrated in vacuo. The residue was diluted with 80 mL of dichloromethane, washed with 120 mL of saturated aqueous sodium bicarbonate, and the aqueous layer was extracted with three 50-mL portions of dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 8 g of silica gel (ethyl acetate-hexane, 1:1) to give 402 mg (74%) of 159 as white solid: mp 130-130.5 °C; IR (CH₂Cl₂) 3450, 1700 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.43 (s, 3H, CH₃), 0.61 (s, 3H, CH₃), 1.65 (dd, J = 14.3, 8.5 Hz, 1H, C₆'H), 1.83 (d, J = 8.8 Hz, 1H, OH), 2.70 (dd, J = 14.5, 5.2 Hz, 1H, C₆'H), 2.81 (s, 3H, NCH₃), 2.78-2.85 (m, 2H, C₇'H, C₇₅'H), 3.13-3.21 (m, 1H, C₃₇₄'H), 3.13 (dd, J = 11.3, 2.6 Hz, 1H, OCH₂), 3.26 (dd, J = 11.3, 2.6 Hz, 1H, OCH₂), 3.35 (m, 1H, C₄H), 3.55 (d, J = 11.3 Hz, 1H, OCH₂), 3.62 (d, J = 11.3 Hz, 1H, OCH₂), 4.91 (dd, J = 8.8, 5.5 Hz, 1H, C₃'H), 5.13-5.25 (m, 2H, =CH₂), 6.46 (ddd, J = 18.5, 10.3, 7.4 Hz, 1H, =CH), 6.98-7.23 (m, 3H, ArH), 7.52 (dt, J = 8.2, 2.2 Hz, 1H, C₅₆'H); ¹³C NMR (62.85 MHz, CDCl₃) δ 21.90 (q), 22.04 (q), 26.29 (q), 29.60 (s), 29.88 (t), 34.73 (d), 37.12 (d), 41.75, (d), 45.22 (d), 69.82 (l), 69.85 (l), 84.05 (d), 98.83 (s), 114.60 (dd, J = 23.9 Hz), 115.20 (l), 123.03 (dd, J = 1.9 Hz), 126.66 (ds, J = 13.7 Hz), 127.79 (dd, J = 8.8 Hz), 131.14 (dd, J = 3.8 Hz), 140.72 (d), 161.71 (dd, J = 244.7 Hz), 173.34 (s); exact mass calcd. for C₄₂H₂₈FNO₄ m/e 389.2003, found m/e 389.1975.

To a solution of 289 mg (0.74 mmol) of 159 in 30 mL of absolute ethanol was added 100 mg of Dowex 50X-8-100 ion exchange resin. The mixture was stirred for 4.5 h at room temperature, filtered, and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (ethyl acetate-hexane, 1:2) to give 242 mg (78%) of 168 as white solid: mp 150-152 °C; IR (CH$_2$Cl$_2$) 1700 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 0.47 (s, 3H, CH$_3$), 0.55 (s, 3H, CH$_3$), 0.95 (t, $J = 7.0$ Hz, 3H, OCCH$_3$), 1.2 (t, $J = 13.4$ Hz, 1H, C$_6$H), 2.57-2.74 (m, 2H, C$_6$H, and C$_7$H), 2.78 (s, 3H, NCH$_3$), 2.82-3.16 (m, 5H, C$_3'$H, C$_4$H, C$_7$H, OCH$_2$Me), 3.05 (dd, $J = 11.4$, 2.6 Hz, 1H, OCH$_2$), 3.23 (dd, $J = 11.2$, 2.6 Hz, 1H, OCH$_2$), 3.46 (d, $J = 11.2$ Hz, 1H, OCH$_2$), 3.59 (d, $J = 11.4$ Hz, 1H, OCH$_2$), 3.88 (s, 1H, C$_3'$H), 5.07-5.16 (m, 2H, =CH$_2$), 6.60 (ddd, $J = 17.2$, 10.0, 8.3 Hz, 1H, =CH), 6.96 (dt, $J = 7.4$, 1.0 Hz, 1H, C$_6$H), 7.07 (t, $J = 7.4$ Hz, 1H, C$_4$H), 7.14-7.21 (m, 1H, C$_5$H), 7.60 (bt, 1H, C$_5$H); $^{13}$C NMR (62.85 MHz, CDCl$_3$) $\delta$ 12.55 (q), 22.03 (q), 22.34 (q), 28.37 (q), 29.65 (t), 29.71 (s), 37.77 (d), 42.24 (d), 43.17 (d), 43.63 (d), 63.08 (t), 69.65 (t), 70.02 (t), 93.23 (d), 98.23 (s), 113.81 (l), 114.47 (dd, $J = 23.9$ Hz), 123.38 (dd, $J = 4.4$ Hz), 125.66 (ds, $J = 13.2$ Hz), 128.23 (dd, $J = 8.2$ Hz), 130.86 (d), 140.39 (d), 162.33 (dd, $J = 244.0$ Hz), 174.60 (s); exact mass calcd. for C$_{24}$H$_{32}$FNO$_4$ m/z 417.23166, found m/z 417.2308. The structure of 168 was confirmed by X-ray crystallography.

Anal. calcd. for C$_{24}$H$_{32}$FNO$_4$: C, 69.0; H, 7.73. Found C, 69.1; H, 7.87.
(3′α,3′α,4′α,7′β,7′α)-4′-(2-Fluorophenyl)-7′-ethenyl-3′-ethoxyhexahydro-7′α-(methoxymethyl)-2′,5,5-trimethylspiro[1,3-dioxane-2,5′-[5H]isondole]-1′(4′H)-one (172). To a solution of 0.45 g (4.4 mmol) of diisopropylamine in 100 mL of tetrahydrofuran cooled in a dry ice-acetone bath was added 2.95 mL (4.4 mmol) of 1.50 M n-butyllithium in hexane over a 1-min period. The mixture was stirred for 30 minutes and 1.23 g (2.9 mmol) of 168 in 1 mL of tetrahydrofuran was added over a 5-min period. The mixture was stirred for 15 min at -78 °C, warmed to -20 °C, and stirred for 1.5 h in a dry ice-carbon tetrachloride bath. The mixture was cooled to -75 °C and 0.47 g (5.9 mmol) of chloromethyl methyl ether was added in one portion. The resulting mixture was stirred for 30 min at -75 °C, warmed to room temperature, and concentrated in vacuo. The residue was diluted with 20 mL of dichloromethane, washed with 100 mL of brine, and the aqueous wash was extracted with three 50-mL portions of dichloromethane. The combined organic layers were dried (MgSO₄), concentrated in vacuo, and the residue was chromatographed over 40 g of silica gel (ethyl acetate-hexane, 4:6) to give 1.19 g (88%) of 172 as a solid: mp 168-172 °C; ¹H NMR (500 MHz, CDCl₃) δ 0.52 (s, 3H, CH₃), 0.60 (s, 3H, CH₃), 0.96 (t, J = 7.0 Hz, 3H, OCH₃), 1.34 (m, J = 13.8 Hz, 1H, C₆H), 2.63 (dd, J = 13.8, 3.6 Hz, 1H, C₆H), 2.82 (s, 3H, NCH₃), 2.87-3.02 (m, 4H, C₃αH, C₄H, CH₂OMe, and C₇H), 3.09 (d, J = 11.4 Hz, 1H, CH₂OMe), 3.10 (d, J = 11.3 Hz, 1H, OCH₂), 3.32 (s, 3H, OCH₃), 3.34 (dd, J = 11.5, 2.7 Hz, 1H, CH₂OCH₂), 3.50 (d, J = 11.3 Hz, 1H, OCH₂), 3.60-3.64 (m, 3H, OCH₂Me, OCH₂), 3.96 (s, 1H, C₃H), 5.11-5.13 (m, 1H, CH=CH₂), 5.14 (m, 1H, =CH₂), 6.60-6.67 (m, 1H, =CH), 7.00-7.04 (m, 1H, C₆H), 7.13 (t, J = 7.4 Hz, 1H, C₄⁺H), 7.18-7.28 (m, 1H, C₄⁺H), 7.70 (t, J = 7.4 Hz, 1H, C₅⁺H).
\[^{13}\text{C}\) NMR (125.7 MHz, CDCl\(_3\)) \(\delta\ 14.87\ (q), 21.98\ (q), 22.29\ (q), 28.17\ (q), 29.62\ (s), 30.69\ (t), 39.46\ (d), 43.42\ (d), 43.78\ (d), 51.82\ (s), 59.00\ (q), 62.66\ (t), 69.82\ (t), 69.99\ (t), 73.98\ (t), 94.12\ (d), 97.53\ (s), 114.30\ (dd, \(J = 24.2\) Hz), 115.63\ (t), 123.27\ (d), 126.07\ (s), 128.20\ (dd, \(J = 8.1\) Hz), 131.54\ (d), 139.14\ (d), 162.24\ (dd, \(J = 243.7\) Hz), 175.08\ (s); exact mass calcd. for C\(_{26}\)H\(_{36}\)FNO\(_5\) \(m/e\ 461.2579\), found \(m/e\ 461.2557\).

Anal. calcd. for C\(_{26}\)H\(_{36}\)FNO\(_5\): C, 67.70; H, 7.86. Found C, 67.5; H, 7.95.

(3'\(\alpha\),3'\(\alpha\),4'\(\alpha\),7'\(\beta\),7'\(\alpha\))-\((\pm)-4'-(2-Fluorophenyl)-3'-ethoxy-7'-formylhexahydro-7'a-
(methoxymethyl)-2',5,5-trimethylspiro[1,3-dioxane-2,5'-[5\(H\)]isindole]-1'(4\'\(H\))-one (173). To a
solution 100 mg (0.24 mmol) of olefin 172 in 6 mL of tert-butanol, 3 mL of tetrahydrofuran, and 1
mL of water cooled in a salted ice bath was added 0.8 mL of 1% aqueous osmium tetroxide, and
102 mg (0.47 mmol) of sodium periodate in three portions over a 10-min period. The mixture was
stirred for 45 min at 0 °C and 5.5 h at room temperature and concentrated in vacuo. The residual
oil was diluted with 40 mL of water and the mixture was extracted with four 25-mL portions of
dichloromethane. The combined organic layers were washed with 60 mL of brine, dried (MgSO\(_4\)),
and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (ethyl
acetate-hexane, 4:6) to give 62 mg (62%) of aldehyde 173 as a white solid: mp 169-171.5 °C; IR
(CH\(_2\)Cl\(_2\)) 1700 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\ 0.49\ (s, 3H, CH\(_3\)), 0.54\ (s, 3H, CH\(_3\)), 0.90\ (t,
\(J = 8.0\) Hz, 3H, OC\(_{3}\)CH\(_3\)), 1.21\ (t, \(J = 13.4\) Hz, 1H, C\(_6\)\(^{\beta}\)H), 2.73-2.98\ (m, 4H, C\(_3\)^{\beta}H, C\(_4\)^{\alpha}H, C\(_6\)^{\alpha}H,
and C\(_7\)^{\beta}H), 2.80\ (s, 3H, NCH\(_3\)), 2.81-3.29\ (m, 3H, OCH\(_2\)Me, and OCH\(_2\)), 3.25\ (dd, \(J = 11.4, 2.7\)
(3′α,3′α,4′α,7′β,7′α)-(±)-Ethyl 3-[4′(2-Fluorophenyl)-3′-ethoxyoctahydro-7′-a-
(methoxymethyl)]-2’,5,5-trimethyl-1’-oxospiro[1,3-dioxane-2, 5′[5H]isindole]-7’yl]-2-
propenoate (174) A mixture of 0.80 g (1.71 mmol) of aldehyde 173 and 1.50 g (4.32 mmol) of
(carbethoxymethylidene)triphenylphosphorane in 10 mL of tetrahydrofuran was warmed under
reflux for 60 h. The mixture was concentrated and the residue was chromatographed over 30 g of
silica gel (ethyl acetate-hexane, 4:6) to give 0.90 g (90%) of 174 as clear oil: IR (CH_2Cl_2) 1700,
1695 cm^{-1}; ^1H NMR (300 MHz, CDCl_3) δ 0.52 (s, 3H, CH_3), 0.60 (s, 3H, CH_3), 0.96 (t, J = 7.0
Hz, 3H, OCCH_3), 1.32 (t, J = 7.1 Hz, 3H, CO_2CCH_3), 1.37 (t, J = 13.8 Hz, 1H, C_6H), 2.65 (dd, J =
13.8, 3.4 Hz, 1H, C_6H), 2.83 (s, 3H, NCH_3), 2.84-3.00 (m, 3H, C_3′aH, OCH_2Me), 3.03-3.14 (m,
4H, OCH₂, C₄H, C₇H), 3.33 (s, 3H, OCH₃), 3.46 (d, J = 11.5 Hz, 1H, OCH₂), 3.47 (d, J = 9.0 Hz, 1H, CH₂OMe), 3.59 (d, J = 11.5 Hz, 1H, OCH₂), 3.66 (d, J = 9.0 Hz, 1H, CH₂OMe), 3.97 (s, 1H, C₃H), 4.21 (dq, J = 7.1, 0.7 Hz, CO₂CH₂Me), 5.89 (d, J = 15.5 Hz, 1H, =CHCO₂Et), 7.02 (t, J = 9.7 Hz, 1H, C₆H⁺), 7.13 (d, J = 6.6 Hz, 1H, C₄H⁺), 7.22-7.25 (m, 1H, C₃H⁺), 7.72 (dd, J = 15.5, 9.6 Hz, 1H, =CH); ¹³C NMR (62.85 MHz, CDCl₃) δ 14.26 (q), 14.81 (q), 21.92 (q), 22.21 (q), 28.15 (q), 29.56 (t), 37.60 (d), 43.63 (d), 43.63 (d), 52.15 (s), 59.04 (q), 60.18 (t), 62.76 (t), 69.82 (t), 70.00 (t), 73.95 (t), 94.13 (t), 97.20 (S), 114.35 (dd, J = 23.9 Hz), 122.17 (d), 123.33 (dd, J = 3.14 Hz), 125.64 (ds, J = 14.5 Hz), 128.34 (dd, J = 10.7 Hz), 131.41 (d), 149.07 (d), 162.17 (dd, J = 244.0 Hz), 166.53 (s), 174.36 (s); exact mass calcld. for C₂₉H₄₀FNO₇ m/e 533.2790, found m/e 533.2761.

(3′α,3′αα,4′α,7′α,7′αα)-(+)-Ethyl 3-[4′(2-Fluorophenyl)-7′α-(methoxy-methyl)-2′,5,5-trimethyl-1′-oxo-3′-phenylthiospiro[1,3-dioxane-2,5′][5H]iso-indole]-7′-yl]-2-propenoate (175).

A mixture of 0.90 g (1.7 mmol) of 174, 0.22 g (2.0 mmol) of thiophenol, and 1 g of Dowex 50X8-100 ion exchange resin in 20 mL of dichloromethane was stirred for 30 h at room temperature. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (ethyl acetate-hexane, 3:7) to give 0.89 g of 175 as a white solid: mp 189.5-190 °C; IR (CH₂Cl₂) 1700 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.54 (s, 3H, CH₃), 0.60 (s, 3H, CH₃), 0.96 (t, 7.0 Hz, 3H, OCH₂CH₃), 1.33 (t, J = 7.1 Hz, 3H, CO₂CCH₃),
1.41 (t, J = 12.3 Hz, 1H, C6'H), 2.65 (dd, J = 13.2, 3.9 Hz, 1H, C6'H), 2.81 (s, 3H, NCH3), 2.84-3.00 (m, 3H, C32'H, OCH2Me), 3.02-3.13 (m, 4H, OCH2, C4'H, and C7'H), 3.34 (s, 3H, OCH3), 3.46 (d, J = 11.5 Hz, 1H, CH2O), 3.47 (d, J = 7.4 Hz, 1H, CH2OMe), 3.59 (d, J = 11.5 Hz, 1H, OCH2), 3.63 (d, J = 7.4 Hz, 1H, CH2OMe), 4.09 (s, 1H, C3'H), 4.13 (q, J = 7.1 Hz, 2H, CO2CH2Me), 5.91 (d, J = 15.7 Hz, 1H, =CHCO2Et), 6.75-7.28 (m, 8H, ArH), 7.66 (t, J = 7.0 Hz, 1H, C5'H), 7.74 (dd, J = 15.2, 3.2 Hz, 1H, CH=CH); 13C NMR (62.9 MHz, CDCl3) δ 14.34 (q), 22.00 (q), 22.32 (q), 28.44 (q), 29.65 (t), 29.85 (s), 38.18 (d), 45.89 (d), 48.24 (d), 52.44 (s), 59.16 (q), 60.31 (t), 69.87 (t), 70.09 (t), 73.20 (t), 76.80 (d), 97.12 (s), 114.34 (dd, J = 24.2 Hz), 122.49 (d), 123.64 (d), 125.27 (s), 127.76 (d), 128.16 (d), 129.05 (d), 131.61 (d), 132.97 (d), 134.82 (s), 148.71 (d), 162.23 (dd, J = 244.6 Hz), 166.42 (s), 172.97 (s); exact mass calcd. for C27H35NO6 (M+SC6H5) m/e 488.2448, found m/e 488.2445.

(3'α,3'aα,4'α,7'β,7'aα)-(±)-Ethyl 3-[4'(2-Fluorophenyl)-7'a-(methoxymethyl)-2',5,5-trimethyl-1'-oxo-spiro[1,3-dioxane-2,5'[5H]iso-indole]-7'y]-2-propenoate (179) and (1'α,3'aβ, 4'α,5'β,7'aβ,8'R')-(±)-Ethyl Hexahydro-5'-(2-fluorophenyl)-3'a-(methoxymethyl)-2',5,5-trimethyl-3'-oxospiro[1,3-dioxane-2,6'(2'H)-[1, 4]methano[1H]isoindole-8'-yl]acetate (180).

To a solution of 860 mg (1.4 mmol) of 175 in 75 mL of benzene warmed under reflux was added a solution of 550 mg (2.9 mmol) of tri-n-butyltin hydride and 10 mg of AIBN in 10 mL of benzene over a 20-h period using a syringe pump. The mixture was concentrated in vacuo and diluted with
50 mL of dichloromethane and 20 mL of 5% aqueous potassium fluoride. The mixture was stirred for 30 min at room temperature. The organic layer was separated, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (ethyl acetate-hexane, 2:1) to give 311 mg (45%) of 179 as white solid: mp 170-170.5 °C; IR (CH₂Cl₂) 1709, 1686, 1650 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 0.51 (s, 3H CH₃), 0.59 (s, 3H, CH₃), 1.31 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.47 (t, J = 13.6 Hz, 1H, C₆H₂), 1.79 (b s, 1H, C₃H₂), 2.54 (d, J = 11.2 Hz, 1H, CH₂OMe), 2.63 (dd, J = 13.7, 4.4 Hz, 1H, C₆H₂), 2.79 (s, 3H, NCH₃), 2.83-3.55 (m, 9H, C₃H₂, C₃H₂, C₄H, C₇H, OCH₂), 3.32 (s, 3H, OCH₃), 3.59 (d, J = 11.2 Hz, 1H, CH₂OMe), 4.21 (q, J = 7.1 Hz, 2H, OCH₂Me), 5.86 (d, J = 15.7 Hz, 1H, =CHCO₂Et), 7.00 (b t, J = 8.1 Hz, 1H, C₆H), 7.10 (b t, J = 7.8 Hz, 1H, C₄H), 7.19 (b t, J = 7.8 Hz, 1H, C₃H), 7.64 (b t, 1H, C₅H), 7.80 (dd, J = 15.7, 9.8 Hz, 1H, CH=CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 14.28 (q), 22.97 (q), 22.25 (q), 29.59 (s), 29.77 (t), 29.96 (q), 38.45 (d), 40.34 (d), 44.62 (d), 51.87 (t), 53.07 (S), 59.24 (q), 60.27 (t), 69.75 (t), 70.00 (t), 73.16 (t), 97.32 (s), 114.37 (dd, J = 24.2 Hz), 122.17 (d), 123.26 (dd, J = 3.0 Hz), 126.10 (ds, J = 14 Hz), 128.12 (dd, J = 8.5 Hz), 131.33 (d), 149.25 (d), 162.42 (dd, J = 244.0 Hz), 160.35 (s), 173.55 (s); exact mass calcd. for C₂₇H₃₅FNO₆ m/e 489.2518, found m/e 489.2522.

Further elution gave 280 mg (40%) of 180 as white solid: mp 89-91 °C; IR (CH₂Cl₂) 1725, 1695 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.44 (s, 3H, CH₃), 0.59 (s, 3H, CH₃), 1.27 (t, J = 7.2 Hz, 3H, CO₂CH₃), 1.79 (b s, 1H, C₇aH), 2.19 (dd, J = 14.1, 1.7 Hz, 1H, C₇H2), 2.30 (dd, J = 16.4, 8.9 Hz, 1H, CH₂CO₂), 2.40 (dd, J = 16.4, 8.9 Hz, 1H, CH₂CO₂), 2.59 (dd, J = 14.3, 5.6 Hz, 1H, C₇H), 2.68 (q, J = 2.1 Hz, 1H, C₄aH), 2.72-2.78 (m, 1H, C₈H), 2.86 (s, 3H, NCH₃), 3.14-3.24 (m, 2H, OCH₂), 3.45 (s, 3H, OCH₃), 3.54 (b s, 1H, C¹H), 3.54-3.57 (m, 2H, OCH₂), 3.93 (d, J = 9.0 Hz, 1H, CH₂OMe), 4.02 (d, J = 9.0 Hz, 1H, CH₂OMe), 4.15 (q, J = 7.2 Hz, 2H, CO₂CH₂Me), 6.94-6.98 (m, 1H, C₅H), 7.05 (dt, J = 1.1, 7.2 Hz, 1H, C₄H), 7.10-7.18 (m, 1H, C₃H), 7.50 (m, 1H, C₅H); ¹³C NMR (62.9 MHz, CDCl₃) δ 14.24 (q), 21.38 (q), 21.94 (q), 29.56 (s), 30.25 (q), 33.90 (t), 35.96 (t), 39.87 (d), 46.47 (d), 54.11 (d), 55.29 (s), 59.25 (q), 60.64 (t), 65.32 (d), 68.11 (t),
69.58 (t), 70.44 (t), 97.97 (s), 114.15 (dd, J = 24.3 Hz), 123.01 (dd, J = 3.3 Hz), 127.70 (dd, J = 8.4 Hz), 128.04 (s), 134.11 (dd, J = 3.9 Hz), 160.84 (dd, J = 245.4 Hz), 172.13 (s), 176.11 (s); exact mass calcd. for C_{27}H_{35}FNO_6 m/e 489.2518, found m/e 489.2515; The structure of 180 was confirmed by X-ray crystallography.

![Diagram of molecule 181](image.png)

(1α, 3αβ, 4α, 5β, 7αβ, β?-)-8-(2,2-Diphenylethenyl)-hexahydro-5-(2'-fluorophenyl)-3α-(methoxymethyl)-2-methyl-1,4-methano-[1H]isindole-3,6-[2H]dione (181) Method A: To a stirred solution of 30 mg (0.06 mmol) of the ester 180 in 2 mL of tetrahydrofuran at -75 °C was added 0.51 mL (0.31 mmol) of 0.60 M phenylmagnesium bromide in ether over a 1-min period. The mixture was stirred for 0.5 h at room temperature and concentrated in vacuo. The yellow residual oil was dissolved in 20 mL of dichloromethane and washed with three 10-mL portions of saturated aqueous ammonium chloride. The aqueous washes were extracted with three 20-mL portions of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate-hexane, 3:1) to yield 28 mg (74%) of tertiary alcohol as a clear oil. This material was used directly in the next reaction. The alcohol was dissolved in 20 mL of benzene and 20 mg (0.1 mmol) of p-toluenesulfonic acid was added. The resulting mixture was warmed under reflux for 10 h and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate-hexane, 3:1) to yield 18 mg (60%) of ketone 181 as a clear oil. Method B: To a stirred solution of 20 mg (0.04 mmol) of the ester 180 in 2 mL of tetrahydrofuran at -75 °C was added 50 μL (0.10 mmol) of 2.0 M phenyllithium in ether over a 1-min period. The mixture was stirred for
0.5 h at room temperature and concentrated in vacuo. The residual yellow oil was dissolved in 20 mL of dichloromethane and washed with three 10-mL portions of saturated aqueous ammonium chloride. The aqueous washes were extracted with three 20-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate-hexane, 3:1) to yield 28 mg (74%) of tertiary alcohol as a clear oil. This material was used without further purification. The alcohol was dissolved in 5 mL of benzene and 50 mg (0.25 mmol) of p-toluenesulfonic acid was added. The resulting mixture was warmed under reflux for 10 h and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate-hexane, 3:1) to yield 18 mg (74%) of ketone 181 as a clear oil: IR (CH$_2$Cl$_2$) 3040, 2980, 1730, 1700 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.20 (qu, $J = 2.5$ Hz, 1H, C$_7$H), 2.59 (dd, $J = 8.1$, 3.4 Hz, 1H, C$_7$H$_2$), 2.74 (dt, $J = 5.4$, 1.8 Hz, 1H, C$_4$H), 2.86-3.02 (m, 2H, C$_7$H$_2$ and C$_6$H), 2.91 (s, 3H, NCH$_3$), 3.15 (t, $J = 2.3$ Hz, 1H, C$_1$H), 3.45 (s, 3H, OCH$_3$), 3.93 (d, $J = 10.4$ Hz, 1H, CH$_2$OMe), 4.12 (d, $J = 10.4$ Hz, 1H, CH$_2$OMe), 4.19 (d, $J = 5.4$ Hz, 1H, C$_5$H), 5.82 (d, $J = 9.3$ Hz, 1H, =CH), 6.16, (br t, $J = 7.5$ Hz, 1H, C$_6$H), 6.90 (dt, $J = 7.5$, 1.0 Hz, 1H, C$_4$H), 7.00 (dt, $J = 8.6$, 1.0 Hz, 1H, C$_3$H), 7.13-7.51 (m, 11H, ArH); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 30.56 (q), 41.69 (d), 43.34 (t), 48.26 (d), 49.97 (d), 55.47 (d), 56.24 (s), 59.76 (q), 66.29 (d), 69.64 (t), 115.63 (dd, $J = 22.6$ Hz), 124.26 (d), 126.49 (d), 126.72 (d), 127.68 (dd, $J = 6.3$ Hz), 127.95 (s), 128.34 (d), 128.75 (d), 128.81 (d), 128.95 (d), 129.22 (d), 129.94 (d), 139.44 (s), 140.43 (s), 144.61 (s), 160.69 (dd, $J = 246.4$ Hz), 175.31 (s), 207.26 (s); exact mass calcd. for C$_{32}$H$_{30}$FNO$_3$ m/e 495.0212, found m/e 495.2212.
(1α, 3αβ, 4α, 5β, 7αβ, 8R)-(-)-8-(2,2-Diphenylethenyl)octahydro-5-(2'-fluorophenyl)-5-(ethoxycarbonyl)-3a-(methoxymethyl)-2-methyl-1,4-methano-[1H]isoindole-3,6-[2H]dione (182). To 130 µL (0.03 mmol) of 0.23 M of lithium diisopropylamide and 5 mg (0.03 mmol) hexamethylphosphoramide in 5 mL of tetrahydrofuran at -75 °C was added of 10 mg (0.02 mmol) of ketone 181 in 1 mL of tetrahydrofuran. The mixture was stirred for 0.5 h at -75 °C and 5 µL (0.03 mmol) of ethyl cyanoformate was added in one portion. The mixture was stirred for 15 min, warmed to room temperature, and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate-hexane, 3:1) to yield 11 mg of a 3:1 mixture of 181 and 182, respectively, as a yellow oil. The residue was subjected to the same reaction conditions two more times to yield 7 mg (61%) of a 4:1 mixture of 181 and 182, respectively, as a pale yellow oil. This material was not fully characterized and the structure assignment for 182 is only tentative. This assignment is based on the appearance of the following signals in the 1H NMR (300 MHz, CDCl3) of the mixtures δ 1.16 (t, J = 7.1 Hz, 3H, CH3), 2.04-2.17 (m, 2H, C7H and C7αH), 2.68 (dd, J = 18.2, 4.0 Hz, 1H, C7H), 2.85 (b qu, J = 1.7 Hz, 1H, C4H), 2.95 (s, 3H, NCH3), 3.20 (dt, J = 9.0, 2.3 Hz, 1H, C8H), 3.45 (s, 3H, OCH3), 3.71 (d, J = 9.7 Hz, 1H, CH2Ome), 3.77 (br t, 1H, C1H), 3.97 (d, J = 9.7 Hz, 1H, CH2Ome), 4.04 (q, J = 7.1 Hz, 2H, CO2CH2), 5.84 (d, J = 9.6 Hz, 1H, =CH), 6.83-7.50 (m, 14H, ArH).
(1α,3αβ,4α,7αβ,8R*)-(±)-Ethyl 2,3,3a,4,5,7α-Hexahydro-6-methoxy-3α-
(methoxymethyl)-2-methyl-3-oxo-1,4-methano-1H-Indole-8-acetate (187). A mixture of 24
mg (0.080 mmol) of ketone 134 and 300 mg (1.58 mmol) of p-toluenesulfonic acid in 4 mL of
trimethylorthoformate and 1 mL of methanol was warmed at reflux for 60 h. The resulting solution
was concentrated in vacuo. The mixture was diluted with 20 mL of dichloromethane and washed
with three 10-mL portions of saturated aqueous sodium bicarbonate followed by 10 mL of brine.
The organic layers were dried (MgSO$_4$), concentrated in vacuo and the residue was
chromatographed over 2 g of silica gel (ethyl acetate) to yield 19 mg (72%) of 187 as a clear oil: IR
(CH$_2$Cl$_2$) 1730, 1690,1650 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 1.25 (t, $J$ = 7 Hz, 3H, CH$_3$), 1.72
(qu, $J$ = 2.6 Hz, 1H, C$_7$αH), 2.20 (dd, $J$ = 17, 2.7 Hz, 1H, C$_7$H$_2$), 2.31 (m, 2H, CH$_2$CO$_2$Et), 2.41
(dd, $J$ = 17.5, 2.3 Hz, 1H, C$_7$H$_2$), 2.50 (m, 1H, C$_8$H), 2.70 (dt, $J$ = 6.8, 1.8 Hz, 1H, C$_4$H), 2.89 (s, 3H, NCH$_3$), 3.39 (s, 3H, OCH$_3$), 3.47 (d, $J$ = 9.5 Hz, 1H, CH$_2$OMe), 3.53 (s, 3H, =COCH$_3$), 3.68
(t, $J$ = 2.3 Hz, 1H, C$_1$H), 3.69 (d, $J$ = 9.5 Hz, 1H, CH$_2$OMe), 4.13 (q, $J$ = 7 Hz, 2H, OCH$_2$), 4.53 (d, $J$ = 6.8 Hz, 1H, C$_5$H); mass spectrum, m/e (relative intensity) 323 (M$^+$, 323), 309 (2), 291 (13), 278 (69), 264 (12), 250 (10); exact mass calcd. for C$_{17}$H$_{25}$NO$_3$ m/e 323.1734, found m/e 323.1724.
trans-10-Carbethoxy-2-decalone (189). To a solution of 25.2 g (0.15 mol) of ethyl cyclohexanone-2-carboxylate and 2 mL of 40% triton B in methanol in an ice bath was added 12.9 g (0.18 mol) of methyl vinyl ketone dropwise over a period of 30 min. The mixture was stirred for 12 h at room temperature and diluted with 100 mL of diethyl ether. The mixture was washed with 30 mL of 2 N aqueous hydrochloric acid and 30 mL of brine. The organic phase was dried (Na₂SO₄) and concentrated in vacuo. The yellow residue was distilled to give 18.3 g of Michael adduct: bp 129-140°C/0.5 mm (lit 138-140°C/0.5mm). The Michael adduct was dissolved in 20 mL of ethanol and added to a solution of sodium ethoxide, prepared by adding 5 g (0.21 mol) of sodium to 250 mL of ethanol. The mixture was stirred for 2 h at room temperature and 25 mL of acetic acid was added dropwise to neutralized the mixture. The mixture was filtered and concentrated in vacuo. The residue was dissolved in 60 mL of ethanol and 2 g of platinium oxide was added. The mixture was stirred under hydrogen for 3 h at room temperature, filtered through Celite and concentrated in vacuo. The residue was distilled to give 17.0 g (92%) of 189 as a clear oil: bp 85-94°C/0.3 mm (lit 115-135°C/1mm). The 1H NMR spectrum of this material was in agreement with that reported elsewhere.

(±)-(4α,6α,10α)-Octahydro-3,3-dimethyl-5H-4,10a-methano-1H2-benzoxocin-5-one (192). Method A: A solution of 6.2 g (27 mmol) of the hydroxy ketal 191 and 3 g of Dowex 50X8-
100 acid resin in 30 mL of acetone was stirred for 48 h at room temperature. The solution was filtered and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (ethyl acetate hexane, 1:1) to yield 5.03 g (83%) of 192 as a clear oil. Method B: A mixture of 0.2 g (1.1 mmol) of ketone 193 and 1 g of Dowex 50X8-100 acid resin in 20 mL of acetone was stirred for 4 h at reflux, cooled to room temperature, and filtered. The filtrate was concentrated in vacuo and the residue was chromatographed over 5 g of silica gel (ethyl acetate hexane, 1:1) to yield 210 mg (74%) of 192 as a clear oil: IR (neat) 2980, 2930, 2860, 1720 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 1.02-1.62 (m with singlets at δ 1.08 and δ 1.29, 15H, CH₂ and CH₃), 1.78 (m, 1H, C₆aH), 2.05 (dd, J = 14.5, 3.0 Hz, 1H, C₁₁H₂), 2.23 (bs, 1H, C₄H), 2.27 (dd, J = 14.7, 3.6 Hz, 1H, C₆H₂), 2.80 (dd, J = 14.7, 12.1 Hz, 1H, C₆H₂), 3.53 (d, J = 12.1 Hz, 1H, CH₂O), 4.26 (dd, J = 12.1, 2.7 Hz, 1H, CH₂O); ¹³C NMR (62.85 Hz, CDCl₃) δ 21.27 (t), 21.98 (q), 25.94 (t), 27.80 (q), 28.72 (t), 32.46 (s), 36.51 (t), 38.00 (t), 44.98 (d), 46.81 (t), 56.14 (d), 66.73 (t), 71.36 (s), 213.31 (s); mass spectrum, m/e (relative intensity) 222 (M⁺, 27), 207 (100); exact mass calcd. for C₁₄H₂₂O₂ m/e 222.1619, found m/e 222.1617.

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(±)-(4α, 6αa, 10αα)-Octahydro-5H-4,10a-methano-1H-2-benzoxocin-5-one (194). To a solution of 0.1 g (0.51 mmol) of decalone 193 in 5 mL of dichloromethane and 5 mL of dimethoxymethane in cooled dry ice-acetone bath was added 1.5 mL (1.5 mmol) of 1 M ethylaluminum dichloride in dichloromethane. The mixture was stirred for 4 h at -78 °C and 1 h at room temperature. The mixture was cooled to -78 °C and 20 mL of 2 N aqueous sodium hydroxide was added. The aqueous layer was extracted with three 20-mL portions of dichloromethane. The combined organic layers were dried (NaSO₄) and concentrated in vacuo.
The residue was chromatographed over 5 g of silica gel (ethyl acetate-hexane, 3:7) to give 63 mg (59%) of 194 as yellow oil: IR (neat) 2940, 2870, 1715 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 1.04-1.81 (m, 11H, CH and CH₂), 2.39 (dd, J = 15.6, 1.3 Hz, 1H, C₆H₂), 2.45 (b s, 1H, C₄H), 2.71 (dd, J = 15.6, 13.0 Hz, 1H, C₆H₂), 3.31 (dd, J = 11.7, 1.9 Hz, 1H, CH₂O), 3.58 (dd, J = 11.2, 2.1 Hz, 1H, CH₂O), 3.86 (d, J = 11.2 Hz, 1H, CH₂O), 4.49 (d, J = 11.7 Hz, 1H, CH₂O); mass spectrum, m/e (relative intensity) 194 (M⁺, 100), 153 (66); exact mass calcd. for C₁₂H₁₈O₂ m/e 194.1308, found m/e 194.1292.

![Image](196)

Ethyl (±)-trans-5,6,6a,7,8,9,10,11-Octahydro-5H-benzo[b]carbazol-10a-acetate (196). To a stirred solution of 3.0 g (14 mmol) of ketone 189 in 75 mL of acetic acid was added a solution of 1.5 g (14 mmol) of phenylhydrazine in 5 mL of acetic acid. The mixture was stirred for 30 min at 50°C and cooled to room temperature. To the mixture was added 3.50 g (24 mmol) of boron trifluoride etherate. The resulting green solution was stirred for 16 h at 80°C and cooled to room temperature. The mixture was diluted with 250 mL of dichloromethane, 100 mL of water was added, and the solution was neutralized with sodium bicarbonate. The organic layer was washed with three 50-mL portions of saturated aqueous sodium bicarbonate, dried (Na₂SO₄), and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (ethyl acetate-hexane, 1:1) to give 3.2 g (80%) of 196 as a yellow solid: mp 165-166.7°C; IR (CH₂Cl₂) 3430, 1722, 1615 cm⁻¹; ¹H NMR (250 MHz, CDCl₃), δ 1.28 (t, J = 7.1 Hz, 3H, CH₃), 1.41-2.22 (m, 8H, CH₂), 2.55 (bd, J = 12.1 Hz, 1H, CH), 2.68 (d, J = 15.4, 1H, C₁₁H₂), 2.79 (ddd, J = 16.3, 1.7, 1.1 Hz, 1H, C₆H₂), 3.27 (ddd, J = 16.3, 10.8, 1.4 Hz, 1H, C₆H₂), 3.51 (d, J = 15.5 Hz, 1H, C₁₁H₂), 4.07-4.25 (m, 2H, OCH₂), 7.21-7.31 (m, 2H, ArH), 7.39-7.43 (m, 1H, ArH), 7.59-7.63 (m, 1H, ArH),
7.87 (bs, 1H, NH); $^{13}$C NMR (62.9, CDCl$_3$) δ 14.08 (q), 23.58 (t), 26.43 (t), 28.29 (t), 29.65 (t),
34.22 (t), 38.23 (t), 41.11 (d), 47.06 (s), 59.73 (t), 107.92 (s), 110.30 (d), 117.62 (d), 118.96 (d),
120.87 (d), 127.49 (s), 133.97 (s), 135.91 (s), 175.10 (s); mass spectrum, m/e (relative intensity)
297 (M$^+$, 62), 283 (10), 268 (8), 238 (22), 222 (100); exact mass calcd. for C$_{19}$H$_{23}$NO$_2$ m/e
297.1729, found m/e 297.1721.

(±)-trans-5,6,6a,7,8,9,10,11-Octahydro-5-10aH-benzo[b]carbazole-10a-methanol

(195). To a suspension of 0.64 g (17 mmol) of lithium aluminum hydride in 30 mL of
tetrahydrofuran cooled in ice bath was added a solution 2 g (7 mmol) of ester 196 in 20 mL of
tetrahydrofuran. The mixture was stirred for 6 h at reflux and cooled to room temperature. To the
mixture was added sequentially 2 mL of water, 6 g of sodium hydroxide in 30% aqueous solution,
and 2 mL of water. The mixture was extracted with three 30-mL portions of dichloromethane. The
combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was
chromatographed over 20 g of silica gel (ethyl acetate-hexane, 1:4) to give 1.5 g (91%) of 195 as a
white solid: mp 241-242 °C; IR (CH$_2$Cl$_2$) 3625, 3463, 1605 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$-
DMSO) δ 0.68-1.71 (m, 8H, CH$_2$), 1.84 (d, J = 15.6 Hz, 1H, C$_{11}$H$_2$), 1.97 (bd, J = 13.2 Hz, 1H,
CH), 2.13 (dd, J = 16.7, 13.2 Hz, 1H, C$_6$H$_2$), 2.35 (dd, J = 16.7, 5.3 Hz, 1H, C$_6$H$_2$), 2.83 (d, J
=15.6 Hz, 1H, C$_{11}$H$_2$), 2.99 (b s, 1H, OH), 3.17 (d, J = 9.7 Hz, 1H, CH$_2$O), 3.50 (d, J = 9.7 Hz, 1H,
CH$_2$O), 6.74 (qu, J = 7.0 Hz, 1H, C$_3$H), 6.75 (qu, J = 7.0 Hz, 1H, C$_2$H), 7.01 (dd, J = 7.0, 1.3 Hz,
1H, C$_1$H), 7.15 (dd, J = 6.7, 1.3 Hz, 1H, C$_4$H), 9.12 (b s, 1H, NH); $^{13}$C NMR (62.9 Hz, CDCl$_3$-DMSO)
δ 21.37 (t), 26.03 (t), 26.99 (t), 28.65 (t), 30.58 (t), 34.06 (t), 37.30 (s), 40.44 (d), 57.36 (t), 107.58
(s), 109.92 (d), 117.05 (d), 117.68 (d), 119.68 (d), 127.40 (s), 132.71 (s), 135.58 (s); mass
spectrum, m/e (relative intensity) 255 (M+, 85), 236 (12), 224 (20); exact mass calcd. for C$_{17}$H$_{21}$NO m/e 255.1623, found m/e 255.1560.

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(±)-(4αα,7αα,13αα)-1,2,3,4,13,13α-Hexahydro-5H,7H-4α,7α-methano[2]-benzoxocino-
[5,4-b]indole (197). To a solution of 50 mg (0.2 mmol) of indole 195 in 8 mL of dichloromethane
in dry ice-acetone bath was added 0.3 mL (0.3 mmol) of 1M ethylaluminium dichloride in
dichloromethane. The mixture was stirred for 30 min at -78 °C and 1 mL of dimethoxymethane
was added. The mixture was stirred for 30 min at -78 °C and 16 h at room temperature. To the
mixture was added 20 mL of 2 N aqueous sodium hydroxide solution. The aqueous layer was
extracted with three 20-mL portions of dichloromethane. The combined organic layers were dried
(Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel
(ethyl acetate-hexane, 3:7) to give 31 mg (59%) of 197 as yellow oil: IR (neat) 2930, 2850 1540
cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) δ 1.05-1.88 (m, 10H, CH, CH$_2$, C$_{14}$H$_2$), 2.13 (d, J = 14.4 Hz,
1H, C$_{14}$H$_2$), 2.85 (dd, J = 14.6, 5.2 Hz, 1H, C$_{13}$H$_2$), 3.08 (dd, J = 14.6, 12.1 Hz, 1H, C$_{13}$H$_2$), 3.40
(d, J = 11.9 Hz, 1H, CH$_2$O), 3.44 (dd, J = 10.8, 2.3 Hz, 1H, CH$_2$O), 3.87 (d, J = 10.8 Hz, 1H,
CH$_2$O), 4.59 (dd, J = 11.9, 2.5 Hz, 1H, CH$_2$O), 7.24-7.14 (m, 2H, ArH), 7.35 (td, J = 7.0, 1.4 Hz,
1H, C$_1$H), 7.59 (d, J = 7.7 Hz, 1H, C$_4$H); $^{13}$C NMR (62.9 Hz, CDCl$_3$) δ 21.41 (t), 26.29 (t), 29.17
(t), 34.59 (s), 36.60 (t), 37.64 (t), 45.87 (d), 46.61 (t), 56.19 (s), 71.70 (t), 72.21 (t), 120.37 (d),
121.53 (d), 124.66 (d), 128.27 (d), 139.92 (s), 155.65 (s), 188.43 (s); mass spectrum, m/e (relative
intensity) 267 (M+, 100), 249 (15), 236 (82), 222 (27); exact mass calcd. for C$_{18}$H$_{21}$NO m/e
267.1623, found m/e 267.1570.
(±)-(1α,3αβ,4α,10cβ,11R*)-11-(2,2-Diphenylethenyl)-1,3α,4,5,6,10c-hexahydro-3α-(methoxymethyl)-2-methyl-1,4-methanopyrrolo[3,4-c]carbazol-3(2H)-one (183). To a solution of 60 mg (0.15 mmol) of ketone 141 in 5 mL of acetic acid was added a solution of 16 mg (0.15 mmol) of phenylhydrazine in 1 mL of acetic acid. The mixture was stirred for 30 min at 50°C and cooled to room temperature. Boron trifluoride etherate (42 mg, 0.3 mmol) was added and the mixture was stirred for 16 h at 80°C. The mixture was diluted with 50 mL of dichloromethane and washed with three 30-mL portions of saturated aqueous sodium bicarbonate. The combined aqueous washes were extracted with three 20-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (ethyl acetate) to yield 44 mg (73%) of indole 183 as a yellow oil: IR (CH₂Cl₂) 3390, 1680 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 2.25 (b qu, 1H, C₄H), 2.50 (dd, J = 16.8, 2.6 Hz, 1H, C₅H₂), 2.80 (dt, J = 10.1, 2.5 Hz, 1H, C₁₁H), 2.96 (dd, J = 16.8, 3.4 Hz, 1H, C₅H₂), 3.11 (s, 3H, NCH₃), 3.24 (s, 3H, OCH₃), 3.34 (d, J = 9.6 Hz, 1H, CH₂O), 3.51 (t, J = 1.7 Hz, 1H, C₁₀H), 3.71 (d, J = 9.6 Hz, 1H, CH₂O), 3.73 (qu, J = 1.9, 1H, C₁H), 5.90 (d, J = 10.1 Hz, 1H, =CH), 7.04-7.49 (m, 14H, ArH), 7.82 (bs, 1H, NH); ¹³C NMR (62.9 MHz, CDCl₃) δ 27.68 (t), 30.84 (q), 42.36 (d), 47.00 (d), 49.74 (d), 59.72 (q), 59.75 (s), 67.49 (t), 70.95 (d), 108.81 (s), 110.81 (s), 117.50 (d), 119.53 (d), 121.28 (d), 126.95 (d), 127.12 (s), 127.29 (d), 127.33 (d), 128.11 (d), 128.20 (d), 128.40 (d), 129.42 (d), 132.40 (s), 136.31 (s), 139.62 (s), 141.69 (s), 143.26 (s), 176.15 (s); mass spectrum, m/e (relative intensity) 474 (M⁺, 100), 442 (29), 429 (13); exact mass calcd. for C₃₂H₃₀N₂O₂ m/e 474.2307, found m/e 474.2332.
(±)-(1α,3αβ,4α,10cβ,11R*)-11-(2,2-Diphenylethenyl)-1,3a,4,5,6,10c-hexahydro-3a-(hydroxymethyl)-2-methyl-1,4-methanopyrrolo[3,4-c]carbazol-3(2H)-one (184). To a solution of 30 mg (0.06 mmol) of ether 183 in 2 mL of dichloromethane cooled in dry ice-acetone bath was added 0.15 mL (0.15 mmol) of 1 M boron tribromide in dichloromethane. The mixture was stirred for 15 min at -75°C, warmed to room temperature, and diluted with 10 mL of dichloromethane. The resulting solution was washed with 10 mL of brine solution. The aqueous wash was extracted with two 10-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (ethyl acetate) to yield 25 mg (88%) of alcohol 184 as a yellow oil: IR (CH$_2$Cl$_2$) 3320, 1675 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) δ 2.25 (b qu, 1H, C$_4$H), 2.55 (dd, J = 17.0, 2.7 Hz, 1H, C$_5$H$_2$), 2.86 (dt, J = 10.0, 2.5 Hz, 1H, C$_{11}$H), 3.06 (dd, J = 17.0, 3.3 Hz, 1H, C$_5$H$_2$), 3.13 (s, 3H, NCH$_3$), 3.38 (b s, 1H, C$_10$cH), 3.51 (d, J = 12.0 Hz, 1H, CH$_2$O), 3.75 (qu, J = 2.1 Hz, 1H, C$_1$H), 3.84 (d, J = 12.0 Hz, 1H, CH$_2$O), 5.90 (d, J = 10.0 Hz, 1H, =CH), 7.04-7.45 (m, 14H, ArH), 7.91 (bs, 1H, NH). The alcohol proton was not observed. Singlets at δ 3.09 and 3.21 were attributed to the starting methyl ether; $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 27.47 (l), 30.91 (q), 41.87 (d), 48.38 (d), 49.18 (d), 56.75 (s), 59.60 (l), 71.70 (d), 111.22 (d), 115.30 (s), 117.53 (d), 119.90 (d), 121.67 (d), 127.13 (s), 127.26 (d), 127.68 (d), 127.72 (d), 128.04 (d), 128.53 (d), 128.74 (d), 129.69 (d), 132.90 (s), 136.54 (s), 139.84 (s), 140.96 (s), 143.96 (s), 178.55 (s); mass specturm, m/e (relative intensity) 460 (M$^+$, 100), 442 (10), 428 (2); exact mass calcd. for C$_{31}$H$_{28}$N$_2$O$_2$ m/e 460.2151, found m/e 460.2150.
(±)-trans-5,6,6a,7,8,9,10,11-Octahydro-5-10H-benzo[b]carbazole-10a-methanol α-thiophenoxyacetate (205). To a solution of 200 mg (0.78 mmol) of alcohol 195 in 10 mL of dichloromethane and 1 mL of tetrahydrofuran was added 146 mg (0.78 mmol) of α-thiophenoxyacetyl chloride and 100 mg (0.78 mmol) of 4,4-dimethylaminopyridine. The mixture was stirred for 4 h at 35°C and cooled to room temperature. The mixture was washed with two 10-mL portions of saturated aqueous sodium bicarbonate. The aqueous washes were extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (ethyl acetate-hexane, 3:7) to give 285 mg (90%) of 205 as yellow oil: IR (CH$_2$Cl$_2$) 3396, 1726, 1650 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 1.13-2.01 (m, 9H, CH$_2$, CH), 2.21 (d, $J=15.8$ Hz, 1H, C$_{11}$H$_2$), 2.37 (dd, $J=16.6$, 12.0 Hz, 1H, C$_6$H$_2$), 2.62 (dd, $J=16.6$, 5.6 Hz, 1H, C$_6$H$_2$), 2.93 (d, $J=15.8$ Hz, 1H, C$_{11}$H$_2$), 3.60 (two s, 2H, CH$_2$S), 3.84 (d, $J=10.8$ Hz, 1H, CH$_2$O), 4.49 (dd, $J=20.8$, 1.2 Hz, 1H, CH$_2$O), 7.05-7.48 (m, 9H, ArH), 7.69 (bs, 1H, NH); $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 21.74 (t), 26.28 (t), 27.45 (t), 29.14 (t), 31.65 (t), 34.80 (t), 36.51 (t), 36.62 (s), 40.89 (d), 63.00 (t), 108.30 (s), 110.41 (d), 117.82 (d), 119.03 (d), 121.12 (d), 126.77 (d), 127.79 (s), 129.01 (d), 129.57 (d), 132.22 (s), 134.96 (s), 135.97 (s), 169.96 (s); mass spectrum, m/e (relative intensity) 405 (M$^+$, 100), 255 (29), 237 (43), 222 (28); exact mass calcd. for C$_{25}$H$_{27}$NO$_2$S m/e 405.1763, found m/e 405.1767.
(±)-trans-5,6,6a,7,8,9,10,11-Octahydro-5-10αH-benzo[b]carbazole-10α-methanol α-phenylsulfanylacetate (206). To a solution of 40 mg (0.1 mmol) of sulfide 205 in 3 mL of dichloromethane and 3 mL of 10% of aqueous sodium bicarbonate in an ice bath was added a solution of 25 mg (0.11 mmol) of m-chloroperoxybenzoic acid in 3 mL of dichloromethane over a period of 10 min. The mixture was stirred for 15 min at 0°C and 30 min at room temperature. The aqueous layer was extracted with two 10-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate-hexane, 6:4) to give 31 mg (72%) of diastereomeric sulfoxides 206 as yellow oil: IR (CH$_2$Cl$_2$) 3461, 1732 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.26-2.05 (m, 9H, CH$_2$, CH), 2.27-2.39 (m, 2H, C$_6$H$_2$ and C$_{11}$H$_2$), 2.65 (dt, $J = 16.3, 5.6$ Hz, 1H, C$_6$H$_2$), 2.93 and 3.00 (two d, $J = 15.8$ Hz, 1H, C$_{11}$H$_2$), 3.56 and 3.59 (two d, $J = 13.5$ Hz, 1H, CH$_2$S), 3.78 and 3.86 (two d, $J = 13.5$ Hz, 1H, C$_2$HS), 3.86 (d, $J = 10.9$ Hz, 1H, CH$_2$O), 4.47 (d, $J = 11.0$ Hz, 1H, CH$_2$O), 7.10-7.60 (m, 9H, ArH), 7.71 (b s, 1H, NH); mass spectrum, m/e (relative intensity) 421 (M$^+$, 0.79), 405 (3); exact mass calcd. for C$_{25}$H$_{27}$NO$_3$S m/e, found m/e
(±)-(1α,3αβ,4α,10cβ,11R+)·11-(2,2-Diphenylethenyl)-1,3a,4,5,6,10c-hexahydro-3-oxo-2-methyl-1,4-methanopyrrolo[3,4-c]carbazol-3a-methanol α-thiophenoxyacetate (213). To a solution of 21 mg (0.034 mmol) of alcohol 184 in 5 mL of dichloromethane was added 6 mg (0.034 mmol) of α-thiophenoxyacetyl chloride and 4 mg (0.034 mmol) of 4,4-dimethylaminopyridine. The mixture was stirred for 16 h at 35°C and cooled to room temperature. The mixture was diluted with 10 mL of dichloromethane and washed with two 10-mL portions of saturated aqueous sodium bicarbonate. The aqueous washes were extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na2SO4) and concentrated in vacuo. The residue was chromatographed over 1 g of silica gel (ethyl acetate) to give 25 mg (89%) of 213 as yellow oil: IR (CH2Cl2) 3460, 1730, 1695, cm⁻¹; ¹H NMR (250 MHz, CDCl3) δ 2.18 (b s, 1H, C4H), 2.44 (dd, J = 17.1, 2.6 Hz, 1H C5H2), 2.77 (dt, J = 10.7, 2.6 Hz, 1H, C11H), 2.84 (dd, J = 17.2, 3.4 Hz, 1H, C5H2), 3.08 (s, 3H, NCH3), 3.40 (t, J = 1.7 Hz, 1H, C10cH), 3.50 (two s, 2H, CH2S), 3.69 (dd, J = 1.8, 1.8 Hz, 1H, C11H), 4.05 (d, J = 11.3 Hz, 1H, CH2O), 4.40 (d, J = 11.4 Hz, 1H, CH2O), 5.83 (d, J = 10.4 Hz, 1H, =CH), 6.99-7.27 (m, 18 H, ArH), 7.37 (d, J = 7.0 Hz, 1H, ArH), 7.75 (s, 1H, NH); ¹³C NMR (62.9 MHz, CDCl3) δ 27.50 (t), 30.89 (q), 36.20 (t), 42.46 (d), 47.30 (d), 49.63 (d), 54.98 (s), 60.72 (t), 70.99 (d), 108.14 (s), 110.92 (d), 117.33 (d), 119.69 (d), 121.51 (d), 126.59 (d), 126.83 (s), 126.95 (d), 127.40 (d), 127.45 (d), 127.52 (d), 128.23 (d), 128.45 (d), 128.90 (d), 129.18 (s), 129.35 (d), 129.55 (d), 132.03 (s), 134.49 (s), 135.01 (s), 136.33 (s), 139.46 (s), 141.56 (s), 143.66 (s), 169.49 (s), 175.07 (s). Two extra singlets in the aromatic region were attributed to contaminants; mass spectrum, m/e (relative intensity) 610 (M⁺, 100), 502 (19), 460 (10), 442 (48); exact mass calcd. for C39H34N2O3S m/e 610.2290, found m/e 610.2293.
(±)-(1α,3αβ,4α,10cβ,11R*)-11-(2,2-Diphenylethenyl)-1,3a,4,5,6,10c-hexahydro-3-oxo-2-methyl-1,4-methanopyrrolo[3,4-c]carbazol-3a-methanol α-phenylsulfoxacetate (214). To a solution of 20 mg (0.03 mmol) of sulfide 213 in 3 mL of dichloromethane and 3 mL of 10% of aqueous sodium bicarbonate in an ice bath was added a solution of 7 mg (0.04 mmol) of m-chloroperoxybenzoic acid in 0.5 mL of dichloromethane over a period of 1 min. The mixture was stirred for 15 min at 0°C and 30 min at room temperature. The aqueous layer was extracted with two 10-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate) to give 18 mg (78%) of 214 as yellow oil: IR (CH₂Cl₂) 3470, 1750, 1710 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.28 and 2.34 (two b s, 1H, C₄H), 2.52 and 2.59 (two dd, J = 17.2, 2.5 Hz, 1H, C₅H₂), 2.82-3.02 (m, 2H, C₅H₂, C₁₁H), 3.13 and 3.14 (two s, 3H, NCH₃), 3.53 and 3.54 (two d, 13.5 Hz, 1H, CH₂S), 3.57 (s, 1H, C₁₀cH), 3.75 and 3.84 (two d, J = 13.5 Hz, 1H, CH₂S), 3.77 (s, 1H, C₁H), 4.06 and 4.08 (two d, J = 11.4 Hz, 1H, CH₂), 4.44 and 4.45 (two d, J = 11.4 Hz, 1H, CH₂), 5.88 and 5.90 (two d, J = 10.1 Hz, 1H, =CH), 7.04-7.58 (m, 19H, ArH), 7.86 and 7.88 (two s, 1H, NH); mass spectrum, m/e (relative intensity) 626 (M⁺, 3), 610 (40), 518 (16), 502 (22), 460 (70), 442 (54); exact mass calcd. for C₃₉H₃₄N₂O₄S m/e 626.2239, found m/e 626.2246.
(±)-(1α.3αβ,4α,10cβ,11R*)-11-(Diphenylethenyl)-1,3α,4,5,6,10c-hexahydro-3α-(hydroxymethyl)-2-methyl-1,4-methanopyrrolo[3,4-c]carbazole (216). To a solution of 25 mg (0.06 mmol) of amide 184 in 5 mL of tetrahydrofuran in ice bath was added 8 mg (0.2 mmol) of lithium aluminum hydride. The mixture was stirred for 2 h at room temperature and 2 mL of H2O was added dropwise. The mixture was extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na2SO4) and concentrated in vacuo. The residue was chromatographed over 1 g of silica gel (ethyl acetate-methanol, 4:1) to give 17 mg (70%) of 216 as a yellow oil: IR (CH2Cl2) 3616, 3459 cm⁻¹; ¹H NMR (300 MHz, C6D6) δ 1.77 (dd, J = 16.5, 2.4 Hz, 1H, C5H2), 1.80 (bs, 1H, C4H), 2.50 (dd, J = 16.5, 3.6 Hz, 1H, C5H2), 2.50 (s, 3H, NCH3), 2.70 (d, J = 10.3 Hz, 1H, CH2N), 2.68-2.71 (m, 1H, C11H), 3.09 (d, J = 10.3 Hz, 1H, CH2N), 3.24 (bs, 1H, C10cH), 3.25 (d, J = 10.8 Hz, 1H, CH2OH), 3.28 (bs, 1H, C1H), 3.33 (d, J = 10.8 Hz, 1H, CH2OH), 6.23 (bs, 1H, NH), 6.2-7.53 (m, 14H, ArH), 7.44, (d, J = 7.0 Hz, 1H, =CH). The alcohol proton was not observed; ¹³C NMR (62.9 MHz, CDCl3) δ 28.34 (t), 39.42 (d), 44.72 (q), 45.14 (d), 46.51 (d), 53.05 (s), 61.35 (t), 61.83 (t), 75.62 (d), 108.08 (s), 110.70 (d), 117.19 (d), 119.26 (d), 120.96 (d), 127.76 (s), 126.81 (d), 127.08 (d), 127.49 (s), 128.01 (d), 128.24 (d), 129.82 (d), 132.28 (s), 136.34 (s), 140.81 (s), 142.43 (s). Two aromatic doublets were not resolved; mass spectrum, m/e (relative intensity) 446 (M⁺, 100), 415 (8); exact mass calcd. for C31H30N2O m/e 446.2358, found m/e 446.2358.
(±)-(1α,3αβ,4α,10cβ,11R∗)-11-(2,2-Diphenylethynyl)-1,3α,4,5,6,10c-hexahydro-2-methyl-1,4-methanopyrrolo[3,4-c]carbazol-3a-methanol α-phenylsulfoxycacetate (ester) (217). To a solution of 15 mg (0.03 mmol) of alcohol 216 in 5 mL of dichloromethane was added 7 mg (0.03 mmol) of α-phenylsulfinylacetic acid, 7 mg (0.03 mmol) of dicyclohexylcarbodiimide, and 1 mg (0.008 mol) of 4,4-dimethylaminopyridine at room temperature. The mixture was stirred for 2 h at room temperature and 5 mL of saturated aqueous sodium bicarbonate was added. The aqueous wash was extracted with two 5-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over 1 g of silica gel (ethyl acetate-methanol, 9:1) to give 13 mg (65%) of 217 as a mixture of diastereomers, contaminated with a small amount of dicyclohexylurea: IR (CH₂Cl₂) 1732, 1712 cm⁻¹; ¹H NMR (300 MHz, C₆D₆) δ 1.83 and 1.88 (two b t, 1H, C₄H), 1.98 (dd, J = 16.1, 7.9 Hz, 1H, C₅H₂), 2.49 and 2.52 (two s, 3H, NCH₃), 2.55 and 2.61 (two d, J = 7.0 Hz, 1H, CH₂N), 2.64 (2d, J = 16.4, 8.8 Hz, 1H, C₅H₂), 2.75 (m, 1H, C₁₁H), 3.09 and 3.11 (two d, J = 13.3 Hz, 1H, CH₂S), 3.10-3.20 (m, 1H, C₁₀cH), 3.24 (b t, 1H, C₁H), 3.26 and 3.30 (two d, J = 7.0 Hz, 1H, CH₂N), 3.29 (d, J = 13.3 Hz, 1H, CH₂S), 3.86 and 3.93 (two d, J = 11.5 Hz, 1H, CH₂O), 4.20, 4.24 (d, J = 11.5 Hz, 1H, CH₂O), 6.29 (two b s, 1H, NH), 6.88-7.549 (m, 19H, ArH), 7.45 (bd, J = 7.5 Hz, 1H, =CH); mass spectrum (FAB), m/e (relative intensity) 613 (M⁺+1, 45), 597 (4), 489 (20); exact mass calcd. for C₃₉H₃₆N₂O₃S+H m/e 613.2525, found m/e 613.2565.
(227). To a solution of 0.5 g (3 mmol) of ethyl cyclohexanone-2-carboxylate in 40 mL of tetrahydrofuran was added 0.14 g (3.5 mmol) of potassium hydride. The mixture was stirred for 30 min at reflux, cooled to room temperature and 4 mL of HMPA was added. The resulting mixture was stirred for 30 min at room temperature and 0.44 g (3.5 mmol) of dimethyl sulfate was added dropwise over a period of 5 min. The mixture was stirred for another 30 min at room temperature and 20 mL of saturated aqueous ammonium chloride was added dropwise. The mixture was concentrated in vacuo and the residue was extracted with four 20-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (ethyl acetate-hexane, 1:9) to yield 0.41 g (76%) of vinylogous carbonate 227 as a clear oil: IR (neat) 1715, 1628 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.19 (t, $J = 7.1$ Hz, 3H CH$_3$), 1.42-1.67 (m, 4H, CH$_2$), 2.17-2.24 (m, 4H, CH$_2$), 3.60 (s, 3H, OCH$_3$), 4.80 (q, $J = 7.1$ Hz, 2H, OCH$_2$Me); $^{13}$C NMR (62.9 MHz,C$_6$D$_6$) $\delta$ 6.33 (t), 14.50 (q), 22.40 (t), 22.70 (t), 26.02 (t), 55.72 (q), 59.50 (t), 108.91 (s), 161.65 (s), 167.47 (s); mass spectrum, m/e (relative intensity) 184 (M$^+$, 11), 169 (21), 139 (27), 123 (52), 111 (67); exact mass calcd. for C$_{10}$H$_{16}$O$_3$ m/e 184.1099, found m/e 184.1085.

(228). To a solution of 0.25 g (1.4 mmol) of ester 227 in 15 mL of benzene in ice bath was added a solution of (o-bromophenyl)dimethylaluminum amide, prepared by adding 0.8 mL (1.6 mmol) of 2 $M$ trimethylaluminum in hexane to 0.28 g (1.6 mmol) of o-bromoaniline in 1 mL of
benzene) with cooling in an ice bath. The mixture was stirred for 1 h at reflux, cooled to room temperature, and 20 mL of 2 N aqueous sodium hydroxide was added over a period of 2 min. The aqueous phase was extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate-hexane, 1:9) to yield 0.44 g (73%) of vinylogous urethane 228 as yellow oil: IR (neat) 3405, 3308, 1658 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 1.51-1.66 (m, 2H, CH$_2$), 1.71-1.80 (m, 2H, CH$_2$), 2.37-2.46 (m, 4H, CH$_2$), 3.86 (s, 3H, OCH$_3$), 6.90 (ddd, $J$ = 8.0, 7.5, 1.6 Hz, 1H, ArH), 7.51 (dd, $J$ = 8.0, 1.6 Hz, 1H, ArH), 7.57 (tt, $J$ = 7.5, 1.6 Hz, 1H, ArH), 8.68 (dd, $J$ = 8.4, 1.6 Hz, 1H, ArH), 10.31 (b s, 1H, NH); $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 22.10 (t), 22.63 (t), 24.58 (t), 25.53 (t), 55.14 (q), 110.89 (s), 112.76 (s), 121.85 (d), 123.87 (d), 128.13 (d), 132.15 (d), 137.60 (s), 159.56 (s), 165.49 (s); mass spectrum, m/e (relative intensity) 311 (M$^+$, 6), 309 (5), 230 (4), 139 (100), 112 (16); exact mass calcd. for C$_{14}$H$_{16}$BrNO$_2$ m/e 311.0316 and 309.0348, found m/e 311.0330 and 309.0357.

![229](image)

(229). To a solution of 100 mg (0.32 mmol) of anilide 228 in 5 mL tetrahydrofuran was added 12 mg (0.48 mmol) of sodium hydride at room temperature. The mixture was stirred for 30 min at reflux, cooled to room temperature, and 46 mg (0.32 mmol) of iodomethane was added dropwise. The resulting mixture was stirred for 30 min at room temperature and 10 mL of saturated aqueous ammonium chloride solution was added. The mixture was concentrated, and the residue was extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate-hexane, 1:4) to yield 98 mg (92%) of vinylogous urethane 229 as
yellow oil: IR (neat) 1649 cm\(^{-1}\); \(^1\)H NMR (250 MHz, CD\(_6\)D\(_6\)), \(\delta\) 0.83-1.64 (m, 6H, CH\(_2\)), 2.23-2.27 (m, 2H, CH\(_2\)), 3.17 (s, 3H, NCH\(_3\)), 3.24 (s, 3H, OCH\(_3\)), 6.59 (td, \(J = 7.9, 1.6\) Hz, 1H, ArH), 6.79 (td, \(J = 7.6, 1.4\) Hz, 1H, ArH), 7.24-7.29 (m, 2H, ArH). The presence of a minor geometrical isomer (10%) was apparent from small singlets at \(\delta\) 3.31 and \(\delta\) 3.01; \(^{13}\)C NMR (62.9 MHz, CD\(_6\)D\(_6\)) \(\delta\) 22.17 (t), 22.69 (t), 24.21 (t), 26.25 (t), 35.62 (q), 55.22 (q), 114.53 (s), 127.31 (d), 128.59 (d), 130.60 (d), 133.18 (d), 143.90 (s), 150.85 (s), 170.31 (s) one singlet was not observed due to resonances from CD\(_6\)D\(_6\); mass spectrum, \(m/e\) (relative intensity) 325 (M\(^+\), 0.2), 323 (0.2), 244 (13), 212 (1), 139 (100); exact mass calcd. for C\(_{15}\)H\(_{18}\)BrNO\(_2\) \(m/e\) 325.0500 and 323.0521, found \(m/e\) 325.0484 and 323.0521.

(230) and (231). To a solution of 0.1 g (0.22 mmol) of the amide 229 in 15 mL of benzene under reflux was added 96 mg (0.33 mmol) of n-Bu\(_3\)SnH and 5 mg (0.03 mmol) of AIBN in 1 mL of benzene. The mixture was stirred for 30 min at reflux, cooled to room temperature, and 10 mL of saturated aqueous potassium fluoride was added. The mixture was stirred for 30 min at room temperature. The aqueous phase was extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate-hexane, 3:7) to yield 34 mg (41%) of 230 as clear oils: IR (neat) 1612 cm\(^{-1}\); \(^1\)H NMR \(\delta\) 1.25-2.28 (m, 8H, CH\(_2\)), 3.03 (s, 3H, NCH\(_3\)), 3.19 (s, 3H, OCH\(_3\)), 3.48 (dd, \(J = 11.5, 4.5\) Hz, 1H, CHOMe), 6.79 (d, \(J = 7.7\) Hz, 1H, ArH), 7.04 (td, \(J = 7.5, 1.0\) Hz, 1H, ArH), 7.17 (dd, \(J = 7.4, 1.1\) Hz, 1H, ArH), 7.25 (td, \(J = 7.6, 1.3\) Hz, 1H, ArH); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 20.05 (t), 24.55 (t), 25.54 (t), 25.93 (q), 34.54 (t), 52.12 (s), 57.71 (q), 84.20 (d), 107.49 (d), 121.27(d), 121.94 (d), 127.55 (d), 134.21 (s), 143.95 (s), 177.95 (s); mass

\[
\begin{align*}
\text{MeO} & \quad \text{Me} \\
\text{230} & \quad \text{MeO} \\
\text{N} & \quad \text{Me}
\end{align*}
\]
spectrum, m/e (relative intensity) 245 (51), 230 (2), 213 (65); exact mass calcd. for m/e C_{15}H_{19}NO_2 245.2426, found m/e 245.1407.

Continued elution afforded 32 mg (39%) 231 as clear oil: IR (neat) 1611 cm^{-1}; ^1H NMR (250 MHz, CDCl_3) δ 1.49-2.22 (m, 8H, CH_2), 3.19 (s, 3H, CH_3), 3.23 (s, 3H, OCH_3), 3.66 (dd, J = 11.4, 4.4 Hz, 1H, CHOMe), 6.87 (d, J = 7.7 Hz, 1H, ArH), 7.05 (td, J = 7.6, 1.1 Hz, 1H, ArH), 7.30 (td, J = 7.7, 1.2 Hz, 1H, ArH), 7.54 (d, J = 7.6 Hz, 1H, ArH); ^13C NMR (62.9 MHz, CDCl_3) δ 20.69 (t), 23.79 (t), 26.19 (t), 26.36 (q), 33.47 (t), 53.80 (s), 57.26 (q), 82.25 (d), 108.00 (d), 121.82 (d), 125.30 (d), 127.70 (d), 131.47 (s), 143.90 (s), 179.77 (s); mass spectrum, m/e (relative intensity) 245 (M^+, 56), 230 (4), 213 (72); exact mass calcd. for C_{15}H_{19}NO_2 m/e 245.2426, found m/e 245.1395.

(233). To a solution of 2.4 g (10.6 mmol) of ketal alcohol 191 in 80 mL of tetrahydrofuran was added 0.38 g (16.0 mmol) of sodium hydride. The mixture was stirred for 30 min at reflux, cooled to room temperature, and 1.81 g (12.7 mmol) of iodomethane was added dropwise. The resulting yellow solution was stirred for 2h at reflux, cooled to room temperature, 2 mL of methanol was added, and the mixture was concentrated in vacuo. The residue was dissolved in 50 mL of dichloromethane and washed with 30 mL of saturated aqueous ammonium chloride. The aqueous wash was extracted with three 20-mL portions of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Without further purification, the residue was dissolved in 30 mL of methanol and 2 mL of 6 N aqueous hydrochloric acid. The solution was stirred for 1h at reflux, cooled to room temperature, and concentrated. The residue was dissolved in 30 mL of dichloromethane and washed with 20 mL of saturated aqueous sodium bicarbonate.
The aqueous wash was back extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (ethyl acetate-hexane, 1:9) to give 1.4 g (71%) of decalone 233 as a clear oil: IR (neat) 1713 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.79-1.70 (m, 9H, CH$_2$), 1.86 (d, $J$ = 13.4 Hz, 1H, C$_4$H$_2$), 2.19-2.00 (m, 2H, C$_4$H$_2$), 2.25-2.20 (m, 2H, C$_2$H$_2$), 2.41 (td, $J$ = 13.9, 7.0 Hz, 1H, CH), 3.29 (s, 3H, CH$_2$OMe), 3.51 (s, 2H, CH$_2$OMe); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 21.24 (t), 25.71 (t), 28.52 (t), 34.85 (t), 35.53 (t), 36.52 (s), 38.19 (t), 44.31 (d), 44.56 (t), 59.34 (q), 69.51 (t), 211.28 (s); mass spectrum, m/e (relative intensity) 196 (M$^+$, 23), 164 (81), 151 (69); exact mass calcd. for C$_{12}$H$_{20}$O$_2$ m/e 196.1464, found m/e 194.1464.

(234). To a solution of 1.5 g (7.6 mmol) of decalone 233 and 2.3 g (76.5 mmol) of dimethyl carbonate in 150 mL of tetrahydrofuran was added 0.92 g (23.0 mmol) of potassium hydride. The mixture was stirred for 3 h at reflux, cooled to room temperature, and 10 mL of methanol was added dropwise over a period of 1 min. The mixture was concentrated in vacuo and the residue was dissolved in 40 mL of dichloromethane and washed with 30 mL of saturated aqueous ammonium chloride. The aqueous phase was extracted with three 30-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (ethyl acetate-hexane, 1:9) to yield 1.5 g (78%) of 234 as a clear oil: IR (neat) 3649, 1712, 1614 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 0.82-2.18 (m, 12H, CH$_2$, CH), 2.56 (d, $J$ = 16.0 Hz, 1H, C$_4$H$_2$), 3.20 (d, $J$ = 9.1 Hz, 1H, CH$_2$OMe), 3.28 (s, 3H, OCH$_3$), 3.42 (dd, $J$ = 9.1, 1.4 Hz, 1H, CH$_2$OMe), 3.73 (s, 3H, CO$_2$CH$_3$), 12.11 (s, 1H,
OH); mass spectrum, m/e (relative intensity) 254 (M+, 3), 222 (12), 190 (8); exact mass calcd. for C_{14}H_{22}O_{4} m/e 254.1518, found m/e 254.1555.

(236). To a solution of 0.8 g (3.0 mmol) of β-ketoester 234 in 25 mL of methanol-trimethylorthoformate (3:7) was added 1 g of Dowex-50 (H+). The mixture was stirred for 3 h at reflux, cooled to room temperature, and filtered. The filtrate was concentrated in vacuo and the residue was chromatographed over 10 g of silica gel (ethyl acetate-hexane, 1:4) to give 406 mg (48%) of vinylogous carbonate 236 as a pale yellow oil and 412 mg (43%) of 235. Diketal 235 was subjected to the same conditions (4 cycles) yield a total of 774 mg (92%) of 236 as a pale yellow oil: IR (neat) 1715, 1624 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 0.76-2.02 (m, 11H, CH₂, CH), 2.24 (dd, J = 17.7, 6.9 Hz, 1H, C₂H₂), 2.58 (d, J = 17.7 Hz, 1H, C₄aH₂), 3.11 (d, J = 9.2 Hz, 1H, CH₂OMe), 3.23 (s, 3H, CH₂OCH₃), 3.38 (d, J = 9.1 Hz, 1H, CH₂OMe), 3.64 (s, 6H, OCH₃, CO₂CH₃); ¹³C NMR (62.9 MHz, C₆D₆) δ 22.01 (t), 26.45 (t), 28.42 (t), 30.67 (t), 35.01 (t), 35.92 (s), 36.99 (t), 39.84 (d), 50.66 (q), 55.65 (q), 59.19 (q), 69.73 (t), 102.12 (s), 160.37 (s), 167.67 (s). One singlet was suspected to be obscured by the C₆D₆ resonance; mass spectrum, m/e (relative intensity) 268 (M⁺, 22), 253 (22), 236 (100), 221 (75), 208 (24), 191 (59), 177 (36), 163 (87); exact mass calcd. for C₁₅H₂₄O₄ m/e 268.1674, found m/e 268.1655.
(237). To a solution of 0.88 g (3.2 mmol) of the β-ketoester 236 in 20 mL of benzene in ice bath was added a solution of (o-bromophenyl)dimethylaluminum amide, prepared by adding 3.3 mL (6.6 mmol) of 2 M trimethylaluminum in hexane to 1.12 g (6.6 mmol) o-bromoaniline in 5 mL of benzene) with cooling in an ice bath. The mixture was stirred for 1 h at reflux, cooled to room temperature, and 50 mL of 2 N aqueous sodium hydroxide solution was added over a period of 2 min. The aqueous phase was extracted with four 30-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄), concentrated in vacuo, and the residue was chromatographed over 10 g of silica gel (ethyl acetate-hexane, 1:4) to yield 0.967 g (71%) of vinylogous urethane 237 as yellow oil: IR (CH₂Cl₂) 3316, 1654 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 0.84-2.13 (m, 11H, CH₂, CH), 2.49 (dd, J = 17.7, 6.9 Hz, 1H, C₂H₂), 2.90 (d, J = 17.1 Hz, 1H, C₄aH₂), 3.14 (d, J = 9.0 Hz, 1H, CH₂OMe), 3.28 (s, 3H, CH₂OCH₃), 3.45 (dd, J = 9.1, 1.1 Hz, 1H, CH₂OCH₃), 3.87 (s, 3H, OCH₃), 6.91 (td, J = 7.9, 1.6 Hz, 1H, ArH), 7.27 (td, J = 8.4, 15 Hz, 1H, ArH), 7.52 (dd, J = 8.0, 1.5 Hz, 1H, ArH), 8.62 (dd, J = 8.4, 1.6 Hz, 1H, ArH), 10.35 (s, 1H, NH); ¹³C NMR (62.9 MHz, CDCl₃) δ 21.61 (t), 26.06 (t), 28.09 (t), 29.80 (t), 34.73 (t), 35.37 (s), 35.46 (t), 39.87 (d), 55.23 (q), 59.49 (q), 69.87 (t), 109.22 (s), 112.54 (s), 121.64 (d), 123.76 (d), 128.10 (d), 132.08 (d), 137.58 (s), 158.03 (s), 165.35 (s); mass spectrum, m/e (relative intensity) 409 (M⁺, 5), 407 (M⁺, 5), 237 (100), 209 (4), 177 (14); exact mass calcd. for C₂₀H₂₆BrNO₃ m/e 409.1086 and 407.1114, found m/e 409.1085 and 407.1105.
To a solution of 891 mg (2.2 mmol) of anilide 237 in 30 mL tetrahydrofuran was added 79 mg (3.3 mmol) of sodium hydride at room temperature. The mixture was stirred for 30 min at reflux, cooled to room temperature, and 370 mg (2.6 mmol) of iodomethane was added dropwise over a period of 1 min. The resulting mixture was stirred for 30 min at reflux, cooled to room temperature, and 10 mL of methanol was added. The mixture was concentrated in vacuo and the residue was dissolved in 30 mL of dichloromethane and washed with 20 mL of saturated aqueous ammonium chloride. The aqueous phase was extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (ethyl acetate-hexane, 1:1) to yield 983 mg (92%) of vinylogous urethane 238 as yellow oil: IR (neat) 1643 cm$^{-1}$; $^1$H NMR (250 MHz, DMSO) At 420K, this material gave a complicated spectrum due to a mixture of geometrical isomers: m/e (relative intensity) 423 (M$^+$, 3), 421 (M$^+$, 2), 342 (7), 237 (100), 209 (5), 177 (16); exact mass calcd. for C$_{21}$H$_{28}$BrN$_3$O$_3$ m/e 423.1230 and 421.1259.

To solution of 350 mg (0.8 mmol) of amide 238 in 16 mL of benzene under reflux was added 290 mg (0.33 mmol) of tri-$n$-butyltin hydride and 10 mg (0.03 mmol) of
AIBN in 2 mL of benzene. The mixture was stirred for 30 min at reflux, cooled to room temperature, and 10 mL of saturated aqueous potassium fluoride was added. The mixture was stirred for 30 min at room temperature and the aqueous phase was extracted with three 20-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$), concentrated in vacuo and the residue was chromatographed over 5 g of silica gel (ethyl acetate-hexane, 1:1) to yield 118 mg (41%) of 239 as white solid: mp 202.5-203.5°C; IR (CH$_2$Cl$_2$) 1705 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 0.79 (td, J = 14.4, 5.2 Hz, 1H, CH), 1.38-1.84 (m, 9H, CH$_2$, CH), 1.17 (d, J = 14.7 Hz, 1H, C$_4$H$_2$), 2.14 (d, J = 14.7 Hz, 1H, C$_4$H$_2$), 2.49 (dd, J = 23.9, 11.8 Hz, 1H, C$_2$H$_2$), 3.05 (s, 3H, NCH$_3$), 3.15 (s, 3H, OCH$_3$), 3.29 (s, 3H, CH$_2$OCH$_3$), 3.49-3.59 (m, 2H, CH$_2$OMe, CHOMe), 4.49 (d, J = 8.9 Hz, 1H, CH$_2$OMe), 6.71 (d, J = 7.7 Hz, 1H, ArH), 7.00 (t, J = 7.5 Hz, 1H, ArH), 7.16-7.20 (m, 2H, ArH); $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 21.23 (t), 25.89 (q), 26.51 (t), 27.84 (t), 29.34 (t), 36.33 (t), 37.86 (s), 43.42 (t), 44.08 (d), 53.48 (s), 57.79 (q), 58.44 (q), 68.43 (t), 85.02 (d), 107.16 (d), 121.35 (d), 121.81 (d), 127.53 (d), 134.89 (s), 143.70 (s), 177.69 (s); mass spectrum, m/e (relative intensity) 343 (M$^+$, 31), 328 (3), 312 (1), 296 (2), 266 (7); exact mass calcd. for C$_2$IH$_2$gNO$_3$ m/e 343.2143, found m/e 343.2146.

Anal. Calcd. for C$_2$IH$_2$gNO$_3$: C, 73.44; H, 8.51. Found: C, 73.41; H, 8.53.

Continued elution afforded 121 mg (42%) of oxindole 240 as white solid: mp 132-132.5°C; IR (CH$_2$Cl$_2$) 1704 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 0.62-1.97 (m, 13H, CH$_2$, CH), 3.05 (s, 3H, CH$_2$OCH$_3$), 3.09 (s, 3H, OCH$_3$), 3.20 (s, 3H, NCH$_3$), 3.56 (d, J = 9.5 Hz, 1H, CH$_2$OMe), 3.76 (d, J = 9.5 Hz, 1H, CH$_2$OMe), 3.83 (dd, J = 11.0, 5.2 Hz, 1H, CHOMe), 6.84 (d, J = 7.7 Hz, 1H, ArH), 7.02 (t, J = 7.6 Hz, 1H, ArH), 7.24 (t, J = 7.7 Hz, 1H, ArH), 7.52 (d, J = 7.6 Hz, 1H, ArH); $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 21.24 (t), 26.30 (t), 26.50 (q), 27.77 (t), 31.36 (t), 36.10 (t), 37.54 (s), 43.50 (d), 43.79 (t), 55.48 (s), 57.08 (q), 58.35 (q), 68.79 (t), 81.84 (d), 108.18 (d), 121.18 (d), 125.89 (d), 127.35 (d), 131.37 (s), 143.91 (s), 181.26 (s); mass spectrum, m/e (relative intensity) 343 (M$^+$, 24), 328 (2), 312 (1), 296 (1), 266 (8); exact mass calcd. for C$_2$IH$_2$gNO$_3$ m/e 343.2143, found m/e 343.2143.
Anal. Calcd. for C$_2$H$_{29}$NO$_3$: C, 73.44; H, 8.51. Found: C, 73.54; H, 8.49.

![Chemical Structure](image)

(241). To a solution of 131 mg (0.32 mmol) of ketone 141 and 300 mg (3.2 mmol) of dimethyl carbonate in 15 mL of tetrahydrofuran was added 24 mg (0.96 mmol) of potassium hydride. The mixture was stirred for 3 h at reflux, cooled to room temperature, and 10 mL of methanol was added dropwise over a period of 1 min. The mixture was concentrated in vacuo and the residue was dissolved in 20 mL of dichloromethane and washed with 10 mL of saturated aqueous ammonium chloride. The aqueous phase was extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (ethyl acetate) to give 103 mg (78%) of enol 241 as yellow oil: 1731, 1697, 1654, 1611 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$), 2.00 (qu, $J = 2.6$ Hz, 1H, C$_1$H), 2.11 (dd, $J = 18.9$, 2.6 Hz, 1H, C$_2$H$_2$), 2.56 (dd, $J = 18.9$, 3.6 Hz, 1H, C$_2$H$_2$), 2.68 (dt, $J = 10.0$, 2.5 Hz, 1H, C$_{16}$H), 3.02 (s, 3H, NCH$_3$), 3.10 (t, $J = 2.0$ Hz, 1H, C$_4$H$_2$), 3.38 (s, 3H, CH$_2$OCH$_3$), 3.44 (d, $J = 9.9$ Hz, 1H, CH$_2$OMe), 3.54 (d, $J = 2.9$, 2.0 Hz, 1H, C$_5$H), 3.71 (d, $J = 9.9$ Hz, 1H, CH$_2$OMe), 3.73 (s, 3H, CO$_2$CH$_3$), 5.79 (d, $J = 9.9$ Hz, 1H, =CH), 7.11-7.42 (m, 10H, ArH), 12.10 (b s, 1H, OH); $^{13}$C NMR (75.5 MHz, CDCl$_3$) 30.63 (q), 34.10 (t), 40.35 (d), 47.29 (d), 49.75 (d), 51.66 (q), 55.09 (s), 59.82 (q), 67.34 (t), 70.01 (d), 96.29 (s), 126.92 (d), 127.10 (d), 127.45 (d), 127.56 (d), 128.22 (d), 128.56 (d), 129.39 (d), 139.51 (s), 141.36 (s), 143.72 (s), 171.79 (s), 172.66 (s), 175.17 (s); mass spectrum, m/e (relative intensity) 459 (M$^+$, 4), 427 (5), 413 (2), 395 (2); exact mass calcd. for C$_{28}$H$_{29}$NO$_3$ m/e 459.2045, found m/e 450.2043.
(242). To a solution of 163 mg (0.41 mmol) of ketone 141 and 382 mg (4.1 mmol) of dimethyl carbonate in 30 mL of tetrahydrofuran was added 48 mg (1.2 mmol) of potassium hydride. The mixture was stirred for 15 h at reflux, cooled to room temperature, and 2 mL of HMPA was added. The mixture was stirred for 30 min at room temperature and 59 mg (0.41 mmol) of dimethyl sulfate was added. The mixture was stirred for another 30 min at room temperature and 20 mL of saturated aqueous ammonium chloride was added dropwise over a period of 5 min. The solvent was removed in vacuo and the residue was extracted with four 20-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (ethyl acetate) to yield 141 mg (74%) of vinylogous carbonate 242 as a clear oil: IR (CH$_2$Cl$_2$) 1731, 1697, 1612 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) δ 2.05 (b qu, 1H, C$_1$H), 2.14 (dd, J = 18.1, 2.8 Hz, 1H, C$_2$H$_2$), 2.53 (dd, J = 18.1, 2.7 Hz, 1H, C$_2$H$_2$), 2.69 (dt, J = 9.8, 2.4 Hz, 1H, C$_{16}$H), 3.04 (s, 3H, NCH$_3$), 3.14 (t, J = 2.1 Hz, 1H, C$_{4a}$H), 3.37 (s, 3H, OCH$_3$), 3.37 (t, J = 5.1 Hz, 1H, C$_5$H), 3.46 (d, J = 9.0 Hz, 1H, CH$_2$OMe), 3.58 (s, 3H, CH$_2$OCH$_3$), 3.65 (d, J = 9.1 Hz, 1H, CH$_2$OMe), 3.67 (s, 3H, CO$_2$CH$_3$), 5.84 (d, J = 9.8 Hz, 1H, =CH), 7.12-7.43 (m, 10H, ArH). Singlets at δ 3.75, δ 3.34, and δ 3.69 indicated the presence of a small amount of β,γ-unsaturated ester; $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 30.66 (q), 31.47 (t), 40.67 (d), 49.46 (d), 50.16 (d), 51.23 (q), 53.86 (s), 55.64 (q), 59.76 (q), 67.39 (t), 70.29 (d), 102.70 (s), 126.81 (d), 127.02 (d), 127.44 (d), 127.54 (d), 128.22 (d), 128.53 (d), 129.46 (d), 139.74 (s), 141.16 (s), 143.76 (s), 164.75 (s), 166.18 (s), 175.37 (s); mass spectrum, m/e (relative intensity) 473 (M$^+$, 7), 441 (3), 409 (2), 396 (3), 382 (2); exact mass calcd. for C$_{29}$H$_{31}$NO$_5$ m/e 473.2201, found m/e 473.2199.
(243). To a solution of 15 mg (0.03 mmol) of enol 241 in 2 mL of tetrahydrofuran and 0.1 mL of hexamethylphosphoramide was added 1 mg (0.04 mmol) of sodium hydride. The mixture was stirred for 30 min at reflux, cooled to room temperature, and 5 mg (0.04 mmol) of iodomethane was added. The resulting yellow solution was stirred for 1 h at reflux, cooled to room temperature, and 2 mL of methanol was added dropwise. Solvent was removed in vacuo and the residue was dissolved in 10 mL of dichloromethane and washed with 10 mL of 2 N aqueous hydrochloride. The aqueous wash was extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate-methanol, 20:1) to give 8 mg (42%) of vinylogous carbonate 242 and 7 mg (41%) of slightly impure of 243 as a yellow oil: 

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.41 (s, 3H, CH$_3$), 2.06 (qu, $J = 2.3$ Hz, 1H, C$_1$H), 2.50 (dd, $J = 18.3, 2.5$ Hz, 1H, C$_2$H$_2$), 2.60 (t, $J = 2.0$ Hz, 1H, C$_4$H), 2.61 (dd, $J = 18.3, 4.4$ Hz, 1H, C$_2$H$_2$), 2.93-2.99 (m, 1H, C$_6$H), 3.02 (s, 3H, NCH$_3$), 3.28 (s, 3H, CH$_2$OCH$_3$), 3.38 (s, 3H, CO$_2$CH$_3$), 3.46 (dd, $J = 3.0, 2.0$ Hz, 1H, C$_5$H), 3.51 (d, $J = 10.2$ Hz, 1H, CH$_2$OMe), 3.98 (d, $J = 10.2$ Hz, 1H, CH$_2$OMe), 5.76 (d, $J = 9.5$ Hz, 1H, =CH), 7.08-7.45 (m, 10H, ArH); $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 24.41 (q), 30.79 (q), 40.84 (d), 41.93 (t), 49.98 (d), 52.39 (q), 56.14 (s), 56.57 (s), 57.56 (d), 59.30 (q), 66.53 (d), 68.14 (t), 126.84 (d), 126.91 (d), 127.56 (d), 127.66 (d), 128.30 (d), 128.73 (d), 129.35 (d), 139.52 (s), 141.00 (s), 144.28 (s), 171.89 (s), 174.53 (s), 206.75 (s); IR and mass spectra were not obtained.
To a solution of 93 mg (0.2 mmol) of the ester 242 in 2 mL of benzene in ice bath was added a solution of (o-bromophenyl)dimethylaluminum amide, prepared by adding 145 μL (0.29 mmol) of 2 M trimethylaluminum in hexane to 50 mg (0.29 mmol) of 2-bromoaniline in 1 mL of benzene) with cooling in an ice bath. The mixture was stirred for 12 h at reflux, cooled to room temperature, and 10 mL of 2N aqueous sodium hydroxide was added over a period of 1 min. The aqueous phase was extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (ethyl acetate) to yield 102 mg (83%) of amide 244 as yellow oil: IR (CH₂Cl₂) 3328, 1697, 1655 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 2.14 (b qu, 1H, C₁H), 2.16 (dd, J = 18.7, 2.8 Hz, 1H, C₂H₂), 2.63 (dd, J = 18.6, 4.6 Hz, 1H, C₂H₂), 2.71 (dt, J = 10.9, 1.7 Hz, 1H, C₁₆H), 3.05 (s, 3H, NCH₃), 3.40 (s, 3H, CH₂OCH₃), 3.43 (l, J = 2.0 Hz, 1H, C₄₅H), 3.53 (d, J = 10.0 Hz, 1H, CH₂OMe), 3.64 (d, J = 10.0 Hz, 1H, CH₂OMe), 3.71 (s, 3H, OCH₃), 3.72 (dd, J = 3.0, 0.8 Hz, 1H, C₅H), 5.88 (d, J = 9.0 Hz, 1H, CH=), 6.93 (td, J = 7.9, 1.6 Hz, 1H, ArH), 7.09-7.43 (m, 11H, ArH), 7.52 (dd, J = 8.0, 1.4 Hz, 1H, ArH), 8.53 (dd, J = 8.4, 1.5 Hz, 1H, ArH), 9.97 (s, 1H, NH). Singlets at δ 3.75, δ 3.69, and δ 3.34 indicated the presence of a small amount of β,γ-unsaturated ester; ¹³C NMR (62.9 MHz, CDCl₃) δ 30.66 (q), 31.27 (t), 40.97 (d), 49.56 (d), 49.64 (d), 53.89 (s), 55.95 (q), 59.87 (q), 67.66 (l), 70.37 (d), 107.93 (s), 112.68 (s), 121.61 (d), 124.31 (d), 126.85 (d), 127.06 (d), 127.44 (d), 127.48 (d), 128.26 (d), 128.53 (d), 129.60 (d), 132.25 (d), 137.12 (s), 139.92 (s), 141.15 (s), 143.81 (s), 160.30 (s), 163.89 (s), 175.51 (s). (one aromatic carbon (d) was unresolved); mass spectrum, m/e (relative intensity) 614
(245). To a solution of lithium diisopropylamide (prepared by adding 144 µL (0.36 mmol) of 2.5 M n-butyl lithium in hexane to 37 mg (0.36 mmol) of diisopropylamine in 1 mL of tetrahydrofuran in dry ice acetone bath) was added 113 mg (0.18 mmol) of amide 244 in 4 mL of tetrahydrofuran at -78 °C. The mixture was stirred for 1 h at -78 °C and 29 mg (0.36 mmol) of chloromethyl methyl ether was added dropwise. The mixture was stirred for 1 h at -78 °C, warmed to room temperature, and 10 mL of saturated aqueous ammonium chloride was added. The solvent was removed in vacuo and the residue was extracted with four 20-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate) to yield 18 mg (15%) of starting amide 244 and 84 mg (71%) of vinylogous urethane 245 as yellow oil: IR (CH₂Cl₂) 1697, 1655 cm⁻¹; ¹H NMR (250 MHz, DMSO-d₆, 420 K) δ 1.84-1.92 (m, 2H, C₂H₂, C₁H), 2.30 (dd, J = 16.1, 3.6 Hz, 1H, C₂H₂), 2.61 (bd, J = 9.6 Hz, 1H, C₁₆H), 2.69 (t, J = 1.8 Hz, 1H, C₄₃H), 2.91 (s, 3H, NCH₃), 3.23 (s, 3H, CH₂OCH₃), 3.26 (s, 3H, CH₂OCH₃), 3.32 (s, 3H, OCH₃), 3.28-3.35 (m, 2H, CH₂OMe), 3.64 (t, J = 2.0 Hz, 1H, C₅H), 4.86 (b s, 2H, CH₂NAr), 5.72 (d, J = 9.6 Hz, 1H, =CH), 7.13-7.46 (m,13H, ArH), 7.62 (d, J = 8.2 Hz, 1H, ArH); mass spectrum (FAB, m/e (relative intensity), 658 (M⁺, 31), 656 (29), 614 (11), 576 (6) 531 (6), 442 (37), 409 (100); exact mass calcd. for C₃₆H₃₇BrN₂O₅ + H m/e 658.1899 and 656.1881, found m/e 658.1882 and 658.1883.
(248) and (250). To a solution of 60 mg (0.09 mmol) of amide 245 in 5 mL of benzene under reflux was added 40 mg (0.13 mmol) of tri-n-butyltin hydride and 8 mg (0.05 mmol) of AIBN in 1 mL of benzene. The mixture was stirred for 2 h at reflux, cooled to room temperature and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate-hexane, 6:4) and at medium pressure (Lobar size A; ethyl acetate-hexane, 6:4) to yield 23 mg (46%) of 248 as white solid: mp 195-195.5°C; IR (CH2Cl2) 1713, 1612 cm⁻¹; ¹H NMR (500 MHz, CD6D6) 8 1.87 (t, J = 13.3 Hz, 1H, C2H2), 2.12, (dt, J = 13.0, 5.9 Hz, 1H, C2H2), 2.35 (s, 3H, NCH3), 2.49 (b t, 1H, C1H), 2.57 (s, 3H, OCH3), 2.65 (m, 1H, C4aH), 3.00 (s. 3H, OCH3), 3.06 (s, 3H, CH2OCH3), 3.86 (d, J = 9.5 Hz, 1H, CH2OME), 4.22 (d, J = 9.6 Hz, 1H, CH2OME), 4.25 (d, J = 1.5 Hz, 1H, C5H), 4.27 (dd, J = 11.6, 1H, 7.3 Hz, CHOMe), 4.72 (d, J = 10.2 Hz, 1H, CHPh2), 4.79 (d, J = 10.8 Hz, 1H, CH2N), 4.89 (d, J = 10.8 Hz, 1H, CH2N), 5.99 (dd, J = 10.2, 1.4 Hz, 1H, =CH), 6.86 (d, 7.5 Hz, 1H, ArH), 6.91 (td, J = 7.7, 1.0 Hz, 1H, ArH), 6.97-7.11 (m, 10H, ArH); ¹³C NMR (62.9 MHz, CDCl3) δ 27.60 (q), 29.57 (t), 37.12 (d), 50.72 (d), 54.76 (d), 55.40 (s), 56.30 (q), 56.86 (q), 57.33 (s), 58.64 (q), 65.18 (d), 67.60 (t), 71.62 (t), 75.40 (d), 109.66 (d), 121.95 (d), 125.16 (d), 126.46 (d), 126.70 (d), 127.65 (d), 128.00 (d), 128.08 (s), 128.19 (d), 128.62 (d), 128.85 (d), 139.31 (s), 141.37 (s), 143.03 (s), 144.24 (s), 177.57 (s), 179.93 (s); mass spectrum (FAB) m/e (relative intensity), 579 (M+1, 100), 563 (4), 547 (10); exact mass calcd. for C36H38N2O5 + H m/e 579.2859, found m/e 579.2847.
Continued elution afforded 11 mg (16%) of oxindole 250 as white solid: mp 117-121°C; IR (CH$_2$Cl$_2$) 3053, 2929, 1711, 1612 cm$^{-1}$; $^1$H NMR (250 MHz, C$_6$D$_6$) $\delta$ 0.72 (s, 1H, C$_1$H), 0.74 (b s, 3H, CH$_3$), 1.08 (s, 3H, CH$_3$), 1.52 (t, $J = 13.0$ Hz, 1H, C$_2$H$_2$), 1.72 (dd, $J = 12.0$, 6.7 Hz, 1H, C$_2$H$_2$), 2.37 (b t, 1H, C$_4$aH), 2.79 (s, 3H, OCH$_3$), 2.88 (s, 3H, CH$_2$OCH$_3$), 2.93 (b s, 3H, NCH$_3$), 3.06 (s, 3H, NCH$_2$OCH$_3$), 3.38 (d, $J = 9.5$ Hz, 1H, CH$_2$OME), 3.73 (d, $J = 9.6$ Hz, 1H, CH$_2$OME), 4.38 (d, $J = 1.5$ Hz, 1H, C$_5$H), 4.48 (dd, $J = 11.5$, 6.7 Hz, 1H, CHOME), 4.84 (d, $J = 10.7$ Hz, 1H, NCH$_2$), 4.94 (d, $J = 10.6$ Hz, 1H, NCH$_2$), 6.62 (b s, 1H, =CH$_2$), 7.83-6.81 (m, 14H, ArH); $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 24.06 (q), 26.61 (q), 28.06 (q), 30.67 (l), 35.84 (d), 41.74 (s), 54.24 (d), 55.28 (s), 56.44 (q), 57.06 (q), 57.06 (s), 58.37 (s), 58.38 (q), 67.29 (l), 68.05 (d), 71.75 (l), 75.17 (d), 77.20 (s), 109.60 (d), 121.91 (d), 126.89 (d), 127.21 (s), 127.63 (d), 127.87 (d), 127.93 (d), 127.94 (s), 128.03 (d), 128.29 (d), 130.10 (d), 130.43 (d), 141.20 (s), 141.53 (s), 144.30 (s), 176.48 (s), 180.48 (s); mass spectrum (FAB), m/e (relative intensity) 646 (M+1, 100), 614 (9.1), 578 (49.4), 563 (13), 546 (5.2), 516 (5.3); exact mass calcd. for C$_{40}$H$_{43}$N$_3$O$_5$ m/e 645.3202, found m/e 642.3205.

(248) and (250). To a solution of 60 mg (0.09 mmol) of amide 245 in 5 mL of benzene under reflux was added 40 mg (0.13 mmol) of tri-$n$-butyltin deuteride and 8 mg (0.05 mmol) of AIBN in 1 mL of benzene. The mixture was stirred for 2 h at reflux, cooled to room temperature and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate-
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NCH₂OMe), 5.70 (d, J = 8.9 Hz, 1H, CH), 6.89 (d, J = 7.1 Hz, 1H, ArH), 7.06 (td, J = 7.6, 1.0 Hz, 1H, ArH), 7.16-7.45 (m, 12H, ArH); ¹³C NMR (62.9 MHz, CDCl₃) δ 30.96 (q), 33.09 (t), 40.85 (d), 50.87 (d), 55.12 (s), 56.14 (q), 56.35 (d), 58.27 (q), 59.12 (s), 59.40 (q), 65.71 (d), 70.56 (t), 71.19 (t), 78.85 (d), 108.47 (d), 123.23 (d), 123.67 (d), 127.15 (d), 127.24 (d), 127.29 (d), 128.08 (d), 128.12 (d), 128.30 (d), 129.60 (d), 129.89 (d), 136.67 (s), 139.62 (s), 141.00 (s), 142.29 (s), 143.74 (s), 174.69 (s), 175.20 (s); mass spectrum m/e 578 (M⁺, 50), 547 (15), 502 (18), 469 (6); exact mass calcd. for C₃₆H₃₈N₂O₅ m/e 578.2794, found m/e 578.2779.

Continued elution sequentially gave 29 mg (41%) of oxindole 248 and 13 mg (18%) of oxindole 252 as white solid: mp 154.3-160.5°C; IR (CH₂Cl₂) 1731, 1701, 1610 cm⁻¹;¹H NMR (250 MHz, CDCl₃) δ 2.20-2.24 (m, 2H, C₂H₂), 2.37 (b s, 1H, C₄H), 2.52 (s, 3H, OCH₃), 2.64 (s, 3H, NCH₃), 2.90 (b s, 1H, C₁H), 3.27 (s, 3H, CH₂OCH₃), 3.35 (s, 3H, NCH₂OCH₃), 3.75 (t, J = 9.1 Hz, 1H, CHOMe), 3.89 (d, J = 1.4 Hz, 1H, C₅H), 4.04 (d, J = 7.5 Hz, 1H, CH₃OMe), 4.51 (d, J = 7.5 Hz, 1H, CH₂OMe), 4.86 (d, J = 9.2 Hz, 1H, CHPh₂), 5.03 (d, J = 11.0 Hz, 1H, NCH₂), 5.14 (d, J = 11.0 Hz, 1H, NCH₂), 6.25 (dd, J = 10.0, 1.4 Hz, 1H, C₁₇H), 6.98 (d, J = 7.9 Hz, 1H, ArH), 7.08-7.42 (m, 13H, ArH), singlets at δ 2.79, 2.91, 3.32 indicated the presence of a small amount of 254;¹³C NMR (62.9 MHz, CDCl₃) δ 27.43 (t), 27.54 (q), 37.40 (d), 50.63 (d), 53.45 (d), 54.16 (s), 55.76 (q), 57.62 (q), 57.78 (s), 58.72 (q), 66.36 (d), 67.61 (t), 70.90 (t), 109.57 (d), 122.44 (d), 122.82 (d), 125.52 (d), 126.60 (d), 126.86 (d), 127.56 (d), 128.09 (d), 128.66 (d), 129.02 (d), 131.59 (s), 139.73 (s), 142.08 (s), 142.92 (s), 143.72 (s), 175.79 (s), 177.81 (s), one doublet was obscured by CDCl₃ and one aromatic doublet was not resolved; mass spectrum m/e 578 (M⁺, 100), 547 (11), 533 (22), 501 (7); exact mass calcd. for C₃₆H₃₈N₂O₅ m/e 578.2794, found m/e 578.2773.
To a mixture of 52 mg (0.07 mmol) of amide 245 and 1.2 mg (0.007 mmol) of AIBN was added 1 mL of tri-n-butyltin hydride at room temperature. The mixture was stirred for 4 h at 80 °C, cooled to 0 °C, and 10 mL of carbon tetrachloride was added over a period of 1 min, followed by 20 mL of saturated aqueous potassium fluoride. The mixture was stirred for 30 min at room temperature and aqueous phase was extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (ethyl acetate-hexane, 1:1) and at medium pressure (Lobar size A; ethyl acetate-hexane, 1:1) to sequentially give 26 mg (57%) of oxindole 253 as white solid and 14 mg (26%) of oxindole 254 as clear oil: IR (CH$_2$Cl$_2$) 1710, 1697, 1607 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.04 (qu, $J = 1.4$ Hz, 1H, $C_1$H), 2.08-2.11 (m, 1H, $C_2$H$_2$), 2.08 (t, $J = 1.7$ Hz, 1H, $C_4$H), 2.40 (ddd, $J = 15.6, 6.9, 1.7$ Hz, 1H, $C_2$H$_2$), 2.70 (s, 3H, OCH$_3$), 2.87 (s, 3H, NCH$_3$), 3.23 (dd, $J = 3.1, 1.7$ Hz, 1H, $C_5$H), 3.28 (s, 3H, NCH$_2$OCH$_3$), 3.34 (s, 3H, CH$_2$OCH$_3$), 3.55 (d, $J = 5.9$ Hz, 1H, CHOMe), 3.92 (ddd, $J = 9.2, 1.7, 1.5$ Hz, 1H, $C_1$H), 4.00 (d, $J = 8.8$ Hz, 1H, CH$_2$OMe), 4.10 (d, $J = 8.8$ Hz, 1H, CH$_2$OMe), 4.95 (d, $J = 11.0$ Hz, 1H, NCH$_2$OMe), 5.13 (d, $J = 11.0$ Hz, 1H, NCH$_2$OMe), 5.84 (d, $J = 9.2$ Hz, 1H, =CH), 6.32 (d, $J = 7.1$ Hz, 1H, ArH), 6.86 (td, $J = 7.7, 1.1$ Hz, 1H, ArH), 6.95 (d, $J = 7.3$ Hz, 1H, ArH), 7.18-7.57 (m, 11H, ArH); $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 30.68 (q), 31.02 (t), 39.54 (d), 45.13 (d), 53.81 (d), 54.46 (s), 56.01 (q), 57.68 (s), 57.83 (q), 58.85 (q), 65.85 (d), 68.08 (t), 71.24 (t), 75.12 (d), 109.18 (d), 122.29 (d), 126.60 (d), 127.23 (d), 127.42 (d), 127.85 (d), 127.92 (s), 128.07 (d), 128.29 (d),
128.56 (d), 128.62 (d), 129.73 (d), 140.14 (s), 140.63 (s), 141.41 (s), 143.65 (s), 176.10 (s), 179.90 (s); mass spectrum, \( m/e \) (relative intensity) 578 (M⁺, 10), 546 (16), 514 (15), 482 (5); exact mass calcld. for \( C_{36}H_{38}N_2O_5 \) \( m/e \) 578.2794, found \( m/e \) 578.2787.

(260). To a solution of 0.1 g (0.5 mmol) of decalone 233 and 0.45 g (5.0 mmol) of dimethyl carbonate in 10 mL of tetrahydrofuran was added 61 mg (1.5 mmol) of potassium hydride. The mixture was stirred for 2 h at reflux, cooled to room temperature, and 1 mL of hexamethylphosphoramide was added. The mixture was stirred for 15 min at room temperature and 50 mg (0.61 mmol) of chloromethyl methyl ether was added. The resulting mixture was stirred for another 15 min at room temperature and 10 mL of saturated aqueous ammonium chloride was added dropwise. The aqueous layer was extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (ethyl acetate-hexane, 1:4) to give 0.12 g (79%) of vinylogous carbonate 260 as yellow oil: IR (neat) 1721, 1636 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 0.85 (td, \( J = 11.8, 4.5 \) Hz, 1H, CH), 1.23-2.06 (m, 10H, CH₂), 2.23 (ddd, \( J = 18.1, 5.6, 1.7 \) Hz, 1H, C₂H₂), 2.62 (d, \( J = 14.9 \) Hz, 1H, C₄aH₂), 3.14 (d, \( J = 9.1 \) Hz, 1H, CH₂OMe), 3.27 (s, 3H, CH₂OCH₃), 3.42 (d, \( J = 9.1 \) Hz, 1H, CH₂OMe), 3.45 (s, 3H, OCH₂OCH₃), 3.68 (s, 3H, CO₂CH₃), 4.94 (d, \( J = 6.8 \) Hz, 1H, OCH₂OMe), 4.97 (d, \( J = 6.8 \) Hz, 1H, OCH₂OMe); ¹³C NMR (62.9 Hz, CDCl₃) δ 21.61 (t), 26.06 (t), 28.15 (t), 30.96 (t), 34.41 (t), 35.56 (s), 36.09 (t), 39.65 (d), 51.11 (q), 56.37 (q), 59.47 (q), 69.37 (t), 93.77 (t), 109.29 (s), 158.47 (s), 167.63 (s); mass spectrum, \( m/e \) (relative intensity) 298 (M⁺, 2), 267 (15), 253 (39), 221 (100); exact mass calcld. for \( C_{16}H_{26}O_5 \) \( m/e \) 298.1780, found \( m/e \) 298.1777.
To a solution of 0.1 g (0.34 mmol) of enol 260 in 5 mL of benzene in ice bath was added a solution of (o-bromophenyl)dimethylaluminum amide in ice bath [prepared by adding 0.25 mL (0.5 mmol) of 2 M trimethylaluminum in hexane to 86 mg (0.5 mmol) o-bromoaniline in 1 mL of benzene at 0°C]. The mixture was stirred for 1 h at reflux, cooled to room temperature, and 10 mL of 2 N aqueous sodium hydroxide solution was added over a period of 1 min. The aqueous phase was extracted with four 10-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$), concentrated in vacuo, and the residue was chromatographed over 2 g of silica gel (ethyl acetate-hexane, 1:4) to yield 41 mg (47%) of vinylogous urethane 261 as a yellow oil: IR (neat) 3326, 1656 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) δ 0.94 (td, J = 12.2, 4.5 Hz, 1H, CH), 1.28-2.19 (m, 10H, CH$_2$), 2.40 (dd, J = 17.7, 5.4 Hz, 1H, C$_2$H$_2$), 2.94 (d, J = 17.4 Hz, 1H, C$_4$H$_2$), 3.15 (d, J = 9.2 Hz, 1H, CH$_2$OMe), 3.28 (s, 3H, CH$_2$OCH$_3$), 3.49 (s, 3H, OCH$_2$OCH$_3$), 3.50 (d, J = 9.2 Hz, 1H, CH$_2$OMe), 5.23 (d, J = 7.1 Hz, 1H, CH$_2$OMe), 5.91 (td, J = 7.8, 1.6 Hz, 1H, ArH), 7.30 (td, J = 7.2, 1.4 Hz, 1H, ArH), 7.52 (dd, J = 8.0, 1.5 Hz, 1H, ArH), 8.66 (dd, J = 8.5, 1.5 Hz, 1H, ArH), 10.29 (b s, 1H, NH); $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 21.66 (t), 26.13 (t), 28.12 (t), 29.98 (t), 34.75 (l), 35.53 (s), 35.72 (l), 39.90 (d), 57.04 (q), 59.58 (q), 69.96 (l), 92.45 (l), 111.80 (s), 112.48 (s), 121.70 (d), 123.97 (d), 128.27 (d), 132.16 (d), 137.54 (s), 155.60 (s), 165.20 (s); mass spectrum, m/e (relative intensity) 439, (M$^+$, 5), 437 (M$^+$, 5), 407 (10), 405 (10), 326 (7), 267 (100); exact mass calcd. for C$_{21}$H$_{28}$BrNO$_4$ m/e 437.1202 and 439.1181, found m/e 437.1207 and 439.1179.
Continued elution afforded 41 mg (18%) of enamine 261a as yellow oil: IR (neat) 3227, 3161, 1731, 1657 cm⁻¹; ¹H NMR (250MHz, CDCl₃) δ 0.90 (td, J = 12.1, 4.6 Hz, 1H, CH), 1.19-1.96 (m, 10H, CH₂), 2.06 (dd, J = 13.3, 1.4 Hz, 1H, C₂H₂), 2.74 (d, J = 16.1 Hz, 1H, C₄H₂), 3.31 (d, J = 9.0 Hz, 1H, CH₂OMe), 3.33 (s, 3H, OCH₃), 3.44 (d, J = 9.0 Hz, 1H, CH₂OMe), 3.73 (s, 3H, CO₂CH₃), 7.01 (td, J = 7.0, 1.8 Hz, 1H, ArH), 7.15 (dd, J = 7.5, 1.7 Hz, 1H, ArH), 7.25 (td, J = 7.5, 1.5 Hz, 1H, ArH), 7.59 (dd, J = 7.0, 1.5 Hz, 1H, ArH), 10.47 (b s, 1H, NH); ¹³C NMR (62.9 MHz, CDCl₃) δ 21.76 (t), 26.23 (t), 28.25 (t), 31.62 (t), 35.01 (t), 35.03 (t), 35.50 (s), 39.37 (d), 50.82 (q), 59.57 (q), 70.72 (t), 93.41 (s), 121.24 (s), 126.22 (d), 127.63 (d), 127.67 (d), 133.08 (s), 138.73 (s), 154.52 (s), 171.21 (s); mass spectrum, m/e (relative intensity) 409 (M⁺, 92), 407 (M⁺, 92), 394 (21), 392 (21), 322 (83), 320 (83); exact mass calcd. for C₂₀H₂₆BrN₃O₃ m/e 407.1094 and 409.1053, found m/e 407.1095 and 409.1064. Further elution gave 21 mg (27%) of starting enol 260.

(263) and (264). To a solution of 45 mg (0.10 mmol) of anilide 261 in 6 mL tetrahydrofuran was added 111 mg (0.45 mmol) of sodium hydride at room temperature. The mixture was stirred for 30 min at reflux, cooled to room temperature, and 66 mg (0.45 mmol) of iodomethane was added dropwise. The resulting mixture was stirred for 30 min at reflux, cooled to room temperature, and 5 mL of methanol was added. The mixture was concentrated in vacuo and the residue was dissolved in 20 mL of dichloromethane and washed with 20 mL of saturated aqueous ammonium chloride. The aqueous phase was extracted with three 20-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo.
The residue was chromatographed over 5 g of silica gel (ethyl acetate-hexane, 1:1) to yield 114 mg (82%) of vinylogous urethane 262 as yellow oil: this material gave a complicated $^1$H NMR spectrum due to a mixture of geometrical isomers and was used without further characterization.

To solution of 100 mg (0.22 mmol) of amide 262 in 15 mL of benzene under reflux was added 90 mg (0.26 mmol) of tri-$n$-butyltin hydride and 5 mg (0.03 mmol) of AIBN in 1 mL of benzene. The mixture was stirred for 30 min at reflux, cooled to room temperature, and 10 mL of saturated aqueous potassium fluoride was added. The mixture was stirred for 30 min at room temperature and the aqueous phase was extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$), concentrated in vacuo, and the residue was chromatographed over 2 g of silica gel (ethyl acetate-hexane, 1:1) to yield 34 mg (41%) of oxindole 263 as clear oil: IR (neat) 1713, 1611 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 0.75 (td, $J = 11.8$, 5.1 Hz, 1H, CH), 1.20 (dd, $J = 14.7$, 7.1 Hz, 1H, C$_4$H$_2$H$_2$), 1.36-1.89 (m, 9H, CH$_2$), 2.18 (d, $J = 14.8$ Hz, 1H, C$_4$H$_2$H$_2$), 2.48 (ddd, $J = 12.1$, 12.1, 12.1 Hz, 1H, C$_2$H$_2$), 2.74 (s, 3H, NCH$_3$), 3.17 (s, 3H, CH$_2$OCH$_3$), 3.30 (s, 3H, OCH$_2$OCH$_3$), 3.52 (d, $J = 9.0$ Hz, 1H, CH$_2$OMe), 3.98 (dd, $J = 11.5$, 4.7 Hz, 1H, CHO), 4.15 (d, $J = 7.1$ Hz, 1H, OCH$_2$OMe), 4.47 (d, $J = 7.1$ Hz, 1H, OCH$_2$OMe), 4.50 (dd, $J = 9.0$, 1.0 Hz, 1H, CH$_2$OMe), 6.71 (d, $J = 7.7$ Hz, 1H, ArH), 7.02 (td, $J = 7.4$, 1.0 Hz, 1H, ArH), 7.16-7.23 (m, 2H, ArH); $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 21.23 (t), 26.06 (q), 26.49 (t), 27.78 (t), 30.24 (t), 36.34 (t), 37.72 (s), 43.23 (t), 44.06 (d), 53.31 (s), 54.71 (q), 58.49 (q), 68.48 (t), 79.67 (d), 94.19 (t), 107.04 (d), 121.96 (2d), 127.65 (d), 134.46 (s), 143.81 (s), 177.77 (s); mass spectrum, $m/e$ (relative intensity) 373 (M$^+$, 19), 328 (4), 296 (4); exact mass calcd. for C$_{22}$H$_{31}$NO$_4$ $m/e$ 373.2258, found $m/e$ 373.2254.

Continued elution afforded 32 mg (39%) of oxindole 264: IR (neat) 1713, 1612 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 0.89-1.90 (m, 12H, CH$_2$CH), 1.97 (d, $J = 13.9$ Hz, 1H, C$_4$H$_2$H$_2$), 3.00 (s, 3H, NCH$_3$), 3.06 (s, 3H, OCH$_3$), 3.19 (s, 3H, OCH$_2$OCH$_3$), 3.56 (d, $J = 9.5$ Hz, 1H, CH$_2$OMe), 3.77 (d, $J = 9.5$ Hz, 1H, CH$_2$OMe), 4.16 (dd, $J = 11.2$, 5.5 Hz, 1H, CHO), 4.38 (d, $J = 6.9$ Hz, 1H, OCH$_2$OMe), 5.49 (d, $J = 6.9$ Hz, 1H, OCH$_2$OMe), 6.84 (d, $J = 7.7$ Hz, 1H, ArH), 7.03 (td, $J = 7.6$,
1.1 Hz, 1H, ArH), 7.25 (td, J = 7.7, 1.1 Hz, 1H, ArH), 7.67 (d, J = 7.6 Hz, 1H, ArH); ¹³C NMR (62.9 MHz, CDCl₃) δ 21.25 (t), 26.29 (t), 26.45 (q), 27.71 (t), 32.77 (t), 36.11 (t), 37.41 (s), 43.58 (d), 43.69 (t), 55.18 (q), 55.68 (s), 58.40 (q), 68.85 (t), 78.86 (d), 95.73 (l), 108.13 (d), 121.08 (d), 125.90 (d), 127.36 (d), 131.73 (s), 144.17 (s), 181.01 (s); mass spectrum, m/e (relative intensity) 373 (M⁺, 15), 328 (4), 296 (2); exact mass calcd. for C₂₂H₃₁NO₄ m/e 373.2258, found m/e 373.2255.

![Compound 270](image)

(270). To a solution of 34 mg (0.09 mmol) of oxindole 263 in 2 mL of tetrahydrofuran was added 2 drops of 37% aqueous hydrochloric acid. The mixture was stirred for 2.5 h at reflux, cooled to room temperature and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate-hexane, 1:1) to give 29 mg (100%) of oxindole 270 as white solid: mp 203.5-205°C; IR (CH₂Cl₂) 3715, 1703, 1609 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 0.78 (td, J = 12.3, 4.6 Hz, 1H, CH), 1.17 (dd, J = 14.7, 2.1 Hz, 1H, C₄₃H₂), 1.41-1.87 (m, 9H, CH₂), 2.17 (d, J = 14.7 Hz, 1H, C₄₃H₂), 2.37 (ddd, J = 12.0, 12.0, 12.0 Hz, 1H, C₂H₂), 3.17 (s, 3H, NCH₃), 3.29 (s, 3H, OCH₃), 3.51 (d, J = 9.0 Hz, 1H, CH₂OMe), 4.01 (dd, J = 12.3, 4.8 Hz, 1H, CHO), 4.42 (dd, J = 9.1, 1.2 Hz, 1H, CH₂OMe), 6.75 (dd, J = 7.6, 1.3 Hz, 1H, ArH), 7.05 (td, J = 7.5, 0.9 Hz, 1H, ArH), 7.17 (dd, J = 7.6, 0.9 Hz, 1H, ArH), 7.23 (td, J = 7.5, 1.3 Hz, 1H, ArH), the alcohol proton signal was not observed; ¹³C NMR (62.9 MHz, CDCl₃) δ 21.22 (t), 26.01 (q), 26.44 (t), 27.66 (t), 33.87 (t), 36.19 (t), 37.87 (s), 43.42 (t), 44.39 (d), 54.86 (s), 58.46 (q), 68.44 (t), 75.46 (d), 107.51 (d), 121.81 (d), 122.36 (d), 127.90 (d), 134.03 (s), 143.66 (s), 178.20 (s); mass spectrum, m/e (relative intensity) 329 (M⁺, 17), 296 (2); exact mass calcd. for C₂₀H₂₇NO₃ m/e 329.1971, found 329.1980.
To a solution of 32 mg (0.09 mmol) of oxindole 264 in 2 mL of tetrahydrofuran was added 2 drops of 37% aqueous hydrochloric acid. The mixture was stirred for 2.5 h at reflux, cooled to room temperature and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate-hexane, 1:1) to give 5 mg (20%) of oxindole 270 as white solid. Continued elution afforded 23 mg (80%) of oxindole 271 as a white solid: mp 188-191°C; IR (CH$_2$Cl$_2$) 3607, 1708, 1611 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 0.88-1.89 (m, 12H, CH$_2$, CH), 2.02 (d, $J$ = 14.3 Hz, 1H, C$_6$H$_2$), 3.10 (s, 3H, NCH$_3$), 3.21 (s, 3H, OCH$_3$), 3.59 (d, $J$ = 9.6 Hz, 1H, CH$_2$OMe), 3.74 (d, $J$ = 9.6 Hz, 1H, CH$_2$OMe), 4.19 (dd, $J$ = 11.6, 5.0 Hz, 1H, CHO), 6.88 (dd, $J$ = 7.7, 1.1 Hz, 1H, ArH), 7.05 (td, $J$ = 7.6, 1.1 Hz, 1H, ArH), 7.28 (td, $J$ = 7.8, 1.1 Hz, 1H, ArH), 7.55 (dd, $J$ = 7.7, 1.0 Hz, 1H, ArH), the alcohol proton signal was not observed; $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 21.32 (t), 26.25 (t), 26.56 (q), 27.65 (t), 35.78 (t), 36.17 (t), 37.28 (s), 42.77 (t), 43.80 (d), 56.84 (s), 58.49 (q), 69.08 (t), 73.20 (d), 108.61 (d), 121.40 (d), 125.55 (d), 128.14 (d), 129.87 (s), 144.81 (s), 180.70 (s); mass spectrum, $m/e$ (relative intensity) 329 (M$^+$, 13), 296 (2); exact mass calcd. for C$_{20}$H$_{27}$NO$_3$ $m/e$ 329.1971, found $m/e$ 329.1979.
To a solution of 15 mg (0.05 mmol) of oxindole 270 in 5 mL of dichloromethane was added 3 mg (0.02 mmol) of DBU in one portion. The mixture was stirred for 36 h at reflux until equilibrium was reached [the reaction was monitored by analytical HPLC using an ISCO silica 0.5 μm column (ethyl acetate-hexane, 15:85)]. A sample of oxindole 271 (15 mg, 0.05 mmol) was treated in an identical manner. The mixtures were combined and washed with 10 mL of 2N aqueous hydrochloric acid. The aqueous wash was extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate-hexane, 4:6) to give 2 mg (7%) of oxindole 272 as a white solid: mp 131-133°C; IR (CH$_2$Cl$_2$) 3715, 1703, 1609 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 0.92-2.00 (m, 11H, CH$_2$, CH), 1.97 (d, $J = 14.3$ Hz, 1H, C$_4$H$_2$), 2.47 (td, $J = 13.8$, 2.8 Hz, 1H, C$_2$H$_2$O), 3.17 (s, 3H, NCH$_3$), 3.29 (s, 3H, OCH$_3$), 3.54 (d, $J = 9.0$ Hz, 1H, CH$_2$OMe), 3.75 (b t, 1H, CHO), 4.42 (d, $J = 9.0$ Hz, 1H, CH$_2$OMe), 6.78 (d, $J = 7.6$ Hz, 1H, ArH), 7.05 (td, $J = 7.5$, 1.0 Hz, 1H, ArH), 7.27 (td, $J = 7.6$, 1.2 Hz, 1H, ArH), 7.39 (d, $J = 7.5$ Hz, 1H, ArH), the alcohol proton signal was not observed; $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 21.36 (t), 26.16 (q), 26.71 (t), 27.46 (t), 32.03 (t), 36.59 (d), 36.68 (t), 37.74 (s), 38.07 (t), 53.30 (s), 58.56 (q), 68.50 (d), 68.81 (t), 107.68 (d), 122.18 (d), 125.44 (d), 128.16 (d), 132.63 (s), 143.15 (s), 178.32 (s); mass spectrum, m/e (relative intensity) 329 (M$^+$, 19), 296 (2); exact mass calcd. for C$_{20}$H$_{27}$NO$_3$ m/e 329.1971, found m/e 329.1978.

Continued elution afforded 20 mg (67%) of oxindole 270 and 4 mg (14%) of oxindole 271, both as white solids.
(265). To a solution 0.7 g (2.7 mmol) of enol 234 in 8 mL of N,N-dimethylformamide was added 1.1 g (16.4 mmol) of imidazole and 1.2 g of (8.2 mmol) of chloro-tert-butylidimethylsilane. The mixture was stirred for 16 h at 80°C, cooled to room temperature, and diluted with 50 mL of dichloromethane. The resulting solution was washed with 30 mL of saturated aqueous sodium bicarbonate. The aqueous wash was extracted with three 20-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (ethyl acetate-hexane, 1:4) to give 0.81 g (82%) of silyl enol ether 265 as yellow oil: IR (neat) 1720, 1694, 1620 cm⁻¹;¹H NMR (250 MHz, CDCl₃) δ 0.15 (s, 3H, SiCH₃), 0.16 (s, 3H, SiCH₃), 0.93 (s with underlying m, 10H, three CH₃ and CH), 1.18-2.05 (m, 11H, CH₂), 2.63 (d, J = 16.0 Hz, 1H, C₄aH₂), 3.14 (d, J = 9.0 Hz, 1H, CH₂OMe), 3.27 (s, 3H, CH₂OCH₃), 3.43 (dd, J = 9.0, 1.0 Hz, 1H, CH₂OMe), 3.66 (s, 3H, CO₂CH₃);¹³C NMR (62.9 MHz, CDCl₃) δ 3.4 (t), 3.9 (t), 5.0 (q), 10.5 (t), 12.5 (t), 16.9 (t), 24.0 (q), 25.7 (q), 26.1 (t), 28.1 (t), 34.6 (t), 35.6 (s), 36.2 (t), 36.4 (t), 39.9 (d), 50.9 (q), 59.5 (q), 69.8 (t), 107.9 (s), 157.2 (s), 168.1 (s); mass spectrum, m/z (relative intensity) 368 (M⁺, 0.5), 353 (12), 312 (100), 279 (14); exact mass calcd. for C₂₆H₃₆O₄Si m/z 368.2363, found m/z 368.2341.
(266). To a solution of 1.0 g (2.7 mmol) of enol 265 in 30 mL of benzene in ice bath was added a solution of (o-bromophenyl)dimethylaluminum amide [prepared by adding 2 mL (4.1 mmol) of 2 M trimethylaluminum in hexane to 0.7 g (4.1 mmol) o-bromoaniline in 5 mL of benzene at 0°C]. The mixture was stirred for 3 h at reflux, cooled to room temperature, and 20 mL of 2 N aqueous sodium hydroxide was added over a period of 2 min. The aqueous phase was extracted with four 20-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄), concentrated in vacuo, and the residue was chromatographed over 20 g of silica gel (ethyl acetate-hexane, 1:4) to yield 0.2 g (21%) of 265 and 0.89 g (64%) of vinylogous urethane 266 as yellow oil: IR (neat) 3376, 1667 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 0.15 (s, 3H, SiCH₃), 0.18 (s, 3H, SiCH₃), 0.90 (s, 9H, three CH₃), 1.25-2.10 (m, 12H, CH₂, CH), 2.82 (d, J = 16.8 Hz, 1H, C₄aH₂), 3.18 (d, J = 9.1 Hz, 1H, CH₂OMe), 3.31 (s, 3H, OCH₃), 3.49 (d, J = 9.1 Hz, 1H, CH₂OMe), 6.91 (td, J = 7.9, 1.6 Hz, 1H, ArH), 7.27 (td, J = 7.2, 1.2 Hz, 1H, ArH), 7.50 (dd, J = 7.2, 1.5 Hz, 1H, ArH), 8.34 (dd, J = 8.0, 1.2 Hz, 1H, ArH), 8.88 (b s, 1H, NH); ¹³C NMR (62.9 MHz, CDCl₃) δ -3.55 (q), -3.46 (q), 18.36 (s), 21.74 (t), 25.80 (q), 26.12 (t), 28.11 (t), 34.85 (t), 35.70 (s), 35.94 (l), 36.07 (l), 40.23 (d), 59.62 (q), 70.29 (l), 112.92 (s), 113.42 (s), 122.67 (d), 124.48 (d), 128.06 (d), 132.21 (d), 136.35 (s), 153.31 (s), 166.28 (s); mass spectrum, m/e (relative intensity) 509 (M⁺, 0.5), 507 (M⁺, 0.5), 494 (3), 492 (3), 452 (36), 450 (41); exact mass calcd. for C₂₅H₂₈BrNO₃Si m/e 509.1761 and 507.1756, found m/e 509.1773 and 507.1780.
To a solution lithium diisopropylamide, prepared by addition of 0.73 mL (1.2 mmol) of 1.6 M n-butyllithium in hexane to a solution of 0.12 g (1.2 mmol) of diisopropylamine in 2 mL of tetrahydropyran in a dry ice-acetone bath, was added a solution of 0.4 g (0.78 mmol) of amide 266 in 4 mL of tetrahydrofuran. The mixture was stirred for 30 min at -75°C and 0.1 g (1.2 mmol) of chloromethyl methyl ether was added dropwise. The resulting yellow solution was stirred for 30 min at -75°C, warmed to room temperature, and 30 mL of saturated aqueous ammonium chloride was added. The aqueous wash was extracted with four 20-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (ethyl acetate-hexane, 15:85) to give 0.23 g (53%) of vinylogous urethane 267 as yellow oil: The $^1$H NMR spectrum was a complicated due to geometrical isomerism and the material was used without further charaterization.

A solution of 160 mg (0.29 mmol) of amide 267 in 1 mL of tri-n-butyltin hydride and 5 mg (0.03 mmol) of AIBN and was stirred for 30 min at 80°C, cooled to room temperature, and 10 mL of carbon tetrachloride and 20 mL of saturated aqueous potassium fluoride were added. The mixture was stirred for 30 min at room temperature and the aqueous phase was extracted with three 20-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$), concentrated in vacuo, and the residue was chromatographed over 5 g of silica gel (ethyl acetate-hexane, 1:1) to yield 52 mg (38%) of oxindole 268 as clear oil: IR (neat) 1726, 1613 cm$^{-1}$; $^1$H NMR (250 MHz, CDC$_3$) δ -0.57 (s, 3H, SiCH$_3$), -0.12 (s, 3H, SiCH$_3$), 0.58 (s, 9H, CCH$_3$), 0.82 (td, $J = 11.9, 5.6$ Hz, 1H, CH), 1.18 (dd, $J = 14.8, 0.9$ Hz, 1H, C$_{4a}$H$_2$), 1.37-1.88 (m, 9H, CH$_2$), 2.25 (d, $J = 14.8$ Hz, 1H, C$_{4a}$H$_2$), 2.41 (ddd, $J = 12.1, 12.1, 11.3$ Hz, 1H, C$_2$H$_2$), 3.26 (s, 3H, CH$_2$OCH$_3$).
3.34 (s, 3H, NCH$_2$OCH$_3$), 3.52 (d, $J$ = 9.0 Hz, 1H, CH$_2$OMe), 3.98 (dd, $J$ = 11.1, ,4.6 Hz, 1H, CHO), 4.46 (dd, $J$ = 9.0, 1.0 Hz, 1H, CH$_2$OMe), 4.96 (d, $J$ = 11.0 Hz, 1H, NCH$_2$), 5.17 (d, $J$ = 11.0 Hz, 1H, NCH$_2$), 6.90 (d, $J$ = 7.8 Hz, 1H, ArH), 7.06 (dd, $J$ = 7.4, 1.0 Hz, 1H, ArH), 7.12-7.23 (m, 2H, ArH); $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ -5.73 (q), -4.71 (q), 17.62 (s), 21.26 (t), 25.35 (q), 26.48 (t), 27.74 (t), 34.38 (t), 36.38 (t), 37.57 (s), 42.77 (t), 44.10 (d), 55.19 (s), 56.11 (q), 58.23 (q), 68.42 (t), 71.01 (t), 76.90 (d), 108.45 (d), 122.01 (d), 127.77 (d), 134.23 (s), 142.35 (s), 178.47 (s); mass spectrum, $m/e$ (relative intensity) 473 (M$^+$, 1), 458 (1), 442 (4), 416 (100), 386 (6), 354 (3); exact mass calcd. for C$_{27}$H$_{43}$NO$_4$Si $m/e$ 473.2949, found $m/e$ 473.2955.

Continued elution afforded 40 mg (28%) of oxindole 269 as clear oil: IR (neat) 1715, 1613 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) δ -0.20 (s, 3H, SiCH$_3$), -0.07 (s, 3H, SiCH$_3$), 0.47 (s, 9H, CCH$_3$), 0.80-0.99 (m, 2H, CH$_2$, CH), 1.25-1.95 (m, 10H, CH$_2$), 2.05 (d, $J$ = 14.2 Hz, 1H, C$_4$H$_2$), 3.10 (s, 3H, CH$_2$OCH$_3$), 3.33 (s, 3H, NCH$_2$OCH$_3$), 3.58 (d, $J$ = 9.0 Hz, 1H, CH$_2$OMe), 3.62 (d, $J$ = 9.0 Hz, 1H, CH$_2$OMe), 4.21 (dd, $J$ = 11.9, 5.7 Hz, 1H, CHO), 4.91 (d, $J$ = 10.7 Hz, 1H, NCH$_2$), 5.22 (d, $J$ = 10.7 Hz, 1H, NCH$_2$), 6.97-7.08 (m, 2H, ArH), 7.20 (td, $J$ = 7.4, 1.1 Hz, 1H, ArH), 7.54 (d, $J$ = 7.4 Hz, 1H, ArH); $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ -5.44 (q), -4.01 (q), 17.39 (s), 21.33 (t), 25.13 (q), 26.32 (t), 27.93 (t), 36.10 (t), 36.18 (t), 37.26 (s), 43.00 (t), 43.32 (d), 56.30 (q), 57.48 (s), 58.47 (q), 68.97 (t), 71.61 (t), 73.39 (d), 109.04 (d), 121.43 (d), 126.36 (d), 127.15 (d), 131.57 (s), 142.56 (s), 182.04 (s); mass spectrum, $m/e$ (relative intensity) 473 (M$^+$, 3), 458 (1), 442 (5), 416 (100), 386 (26), 354 (3); exact mass calcd. for C$_{27}$H$_{43}$NO$_4$Si $m/e$ 473.2957, found $m/e$ 473.2963.
(274). To a solution of 7 mg (0.016 mmol) of oxindole 269 in 2 mL of tetrahydrofuran was added 0.5 mL (0.5 mmol) of a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran. The mixture was stirred for 8 h at room temperature and concentrated in vacuo. The residue was dissolved in 10 mL of dichloromethane and washed with 10 mL of saturated aqueous ammonium chloride. The aqueous wash was extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over 1 g of silica gel (ethyl acetate-hexane, 4:6) to give 4 mg (73%) of oxindole 274: IR (CH₂Cl₂) 3612, 1704, 1611 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 0.80 (td, J = 11.8, 5.3 Hz, 1H, CH), 0.82-0.89 (m, 1H, CH₂), 1.20 (dd, J = 14.3, 1.9 Hz, 1H, C₄aH₂), 1.24-1.88 (m, 8H, CH₂), 2.26 (d, J = 14.7 Hz, 1H, C₄aH₂), 2.39 (ddd, J = 12.1, 12.1, 12.3 Hz, 1H, C₂H₂), 3.25 (s, 3H, CH₂OCH₃), 3.32 (s, 3H, NCH₂OCH₃), 3.50 (dd, J = 8.9, 0.6 Hz, 1H, CH₂OMe), 4.05 (ddd, J = 11.4, 6.1, 5.0 Hz, 1H, CHO), 4.37 (dd, J = 8.9, 1.1 Hz, 1H, CH₂OMe), 5.08 (d, J = 11.0 Hz, 1H, NCH₂), 5.17 (d, J = 11.0 Hz, 1H, NCH₂), 6.97 (d, J = 7.8 Hz, 1H, ArH), 7.09 (td, J = 7.4, 1.0 Hz, 1H, ArH), 7.11-7.25 (m, 2H, ArH), the alcohol proton was not observed; ¹³C NMR and mass spectrum were not obtained.
To a solution of 0.1 g (0.25 mmol) of ketone 141 and 224 mg (2.5 mmol) of dimethyl carbonate in 30 mL of tetrahydrofuran was added 30 mg (0.75 mmol) of potassium hydride. The mixture was stirred for 2 h at reflux, cooled to room temperature, and 2 mL of hexamethyldiphosphoramide was added. The mixture was stirred for 15 min at room temperature and 60 mg (0.75 mmol) of chloromethyl methyl ether was added. The resulting mixture was stirred for another 15 min at room temperature and 10 mL of saturated aqueous ammonium chloride was added dropwise and concentrated in vacuo. The residue was extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (ethyl acetate-hexane, 1:4) to give 0.12 g (79%) of vinylogous carbonate 275 as yellow oil: IR (neat) 3450, 1701, 1680, 1649 cm$^{-1}$; $^1$H NMR (250 MHz, C$_6$D$_6$) $\delta$ 2.00 (b qu, $J = 2.4$ Hz, 1H, C$_1$H), 2.10 (dd, $J = 18.2$, 2.7 Hz, 1H, C$_2$H$_2$), 2.44 (dd, $J = 18.1$, 3.6 Hz, 1H, C$_2$H$_2$), 2.78 (s, 3H, NCH$_3$), 2.87 (dt, $J = 9.9$, 2.6 Hz, 1H, C$_{16}$H), 3.16 (s, 3H, CH$_2$OCH$_3$), 3.31 (s, 3H, OCH$_2$OCH$_3$), 3.39 (s, 3H, CO$_2$CH$_3$), 3.52 (t, $J = 2.0$ Hz, 1H, C$_{4a}$H), 3.55 (d, $J = 9.7$ Hz, 1H, CH$_2$OMe), 3.61 (dd, $J = 3.0$, 2.0 Hz, 1H, C$_5$H), 3.87 (d, $J = 9.7$ Hz, 1H, CH$_2$OMe), 4.60 (d, $J = 6.7$ Hz, 1H, OCH$_2$OMe), 4.67 (d, $J = 6.7$ Hz, 1H, OCH$_2$OMe), 5.97 (d, $J = 9.9$ Hz, 1H, =CH), 7.00-7.30 (m, 10H, ArH); Singlets at $\delta$ 2.81, 3.17, 3.27 and a doublet at $\delta$ 5.92 are due to the $\beta,\gamma$-unsaturated ester derived from 275; mass spectrum, $m/e$ (relative intensity) 503 (M$^+$, 9), 472 (s), 458 (18), 426 (12), 394 (8); exact mass calcd. for C$_{30}$H$_{33}$NO$_6$ $m/e$ 503.2319, found $m/e$ 503.2313.
To a solution 64 mg (0.14 mmol) of enol 241 in 2 mL of N,N-dimethylforamide was added 37 mg (0.54 mmol) of imidazole and 81 mg (0.54 mmol) of chloro-tert-butylidimethylsilane. The mixture was stirred for 3 h at 40°C, cooled to room temperature and diluted with 20 mL of dichloromethane. The resulting solution was washed with 10 mL of saturated aqueous sodium bicarbonate. The aqueous wash was extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 1 g of silica gel (ethyl acetate) to give 31 mg (39%) of silyl enol ether 276 as yellow oil: IR (CH$_2$Cl$_2$) 3417, 1698, 1614 cm$^{-1}$; $^1$H NMR (250 MHz, C$_6$D$_6$), $\delta$ 0.01 (s, 3H, SiCH$_3$), 0.04 (s, 3H, SiCH$_3$), 0.95 (s, 9H, CCH$_3$), 1.81 (dd, J = 18.2, 2.6 Hz, 1H, C$_2$H$_2$), 1.94 (qu, J = 2.3 Hz, 1H, C$_1$H), 2.41 (dd, J = 18.2, 3.5 Hz, 1H, C$_2$H$_2$), 2.69 (s, 3H, NCH$_3$), 2.81 (dt, J = 9.9, 2.5 Hz, 1H, C$_{16}$H), 3.23 (s, 3H, CH$_2$OCH$_3$), 3.29 (s, 3H, CO$_2$CH$_3$), 3.47 (t, J = 2.0 Hz, 1H, C$_{4a}$H), 3.50 (d, J = 9.7 Hz, 1H, CH$_2$OMe), 3.56 (dd, J = 3.0, 2.0 Hz, 1H, C$_5$H), 3.80 (d, J = 9.8 Hz, 1H, CH$_2$OMe), 5.91 (d, J = 9.9 Hz, 1H, =CH), 7.00-7.21 (m, 10H, ArH); $^{13}$C NMR (62.9 MHz, C$_6$D$_6$) $\delta$ -3.94 (q), -3.61 (q), 18.50 (s), 25.94 (q), 30.14 (q), 38.20 (t), 41.42 (d), 50.58 (d), 50.73 (d), 54.98 (s), 59.52 (q), 68.09 (t), 70.73 (d), 107.55 (s), 127.32 (d), 127.61 (d), 128.38 (d), 128.61 (d), 128.76 (d), 128.83 (d), 140.30 (s), 141.94 (s), 143.57 (s), 160.70 (s), 165.97 (s), 174.91 (s), one aromatic doublet was obscured by benzene signals and one quartet apparently was not resolved; mass spectrum, m/e (relative intensity) 573 (M$^+$, 8), 541 (10), 516 (95), 484 (38); exact mass calcd. for C$_{34}$H$_{43}$NO$_5$ m/e 573.2887, found m/e 573.2898. Continued elution afforded 20% of starting 241.
(278). To a solution of 28 mg (0.07 mmol) of ketone 141 and 68 mg (0.34 mmol) of o-bromophenyl isocyanate was added 6 mg (0.14 mmol) of potassium hydride. The mixture was stirred for 18 h at reflux, cooled in ice bath, and 10 mL of saturated ammonium chloride was added. The mixture was concentrated in vacuo and the residue was extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate-hexane, 95:5) to give 29 mg (70%) of slightly impure 278 as yellow oil: IR (CH$_2$Cl$_2$) 3410, 1701, 1611 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) δ 2.03 (b qu, $J = 0.9$ Hz, 1H, C$_1$H), 2.16 (dd, $J = 18.7, 2.5$ Hz, 1H, C$_2$H$_2$), 2.59 (dd, $J = 18.7, 3.5$ Hz, 1H, C$_2$H$_2$), 2.82 (dt, $J = 9.5, 2.2$ Hz, 1H, C$_{16}$H), 3.00 (m, 1H, C$_{4a}$H), 3.08 (s, 3H, NCH$_3$), 3.39 (s, 3H, OCH$_3$), 3.46 (d, $J = 9.7$ Hz, 1H, CH$_2$OMe), 3.74 (t, $J = 2.7$ Hz, 1H, C$_5$H), 3.83 (d, $J = 9.7$ Hz, 1H, CH$_2$OMe), 5.81 (d, $J = 9.5$ Hz, 1H, =CH), 5.97-7.76 (m, 14H, ArH and NH), 8.23 (dd, $J = 8.2$ Hz, 1H, ArH), 13.8 (b s, 1H, OH); Singlets at δ 2.95 and 3.41 and a doublet at δ 5.71 suggested the presence of a small amount of an isomeric amide; $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 30.84 (q), 34.41 (t), 40.02 (d), 47.85 (d), 50.19 (d), 56.08 (s), 59.83 (q), 66.99 (t), 69.41 (d), 96.85 (s), 114.57 (s), 122.48 (d), 125.67 (d), 126.52 (d), 126.95 (d), 127.57 (d), 127.75 (d), 128.26 (d), 128.44 (d), 128.68 (d), 129.31 (d), 132.30 (d), 134.71 (s), 139.32 (s), 141.28 (s), 144.23 (s), 169.32 (s), 172.60 (s), 174.80 (s); mass spectrum, m/e (relative intensity) 598 (M$^+$-2, 7), 596 (M$^+$-2, 7 ), 514 (85); exact mass calcd. for C$_{33}$H$_{31}$BrN$_2$O$_4$·H$_2$ m/e 598.1290 and 596.1311, found m/e 598.1300 and 596.1306.
(279). To a solution of 148 mg (0.25 mmol) of amide 278 and 63 mg (0.50 mmol) of diisopropyl ethylamine in 5 mL of dichloromethane was added 39 mg (0.50 mmol) of chloromethyl methyl ether. The mixture was stirred for 24 h at room temperature and washed with 5 mL 2N aqueous hydrochloric acid. The aqueous wash was extracted with two 10-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate) to give 141 mg (89%) of 279 as yellow oil: IR (CH₂Cl₂) 3420, 1690, 1624 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 2.13 (b s 1H, C₁H), 2.42 (dd, J = 18.2, 2.7 Hz, 1H, C₂H₂), 2.69-2.77 (m, 2H, C₂H₂ and C₁₆H), 3.03 (s, 3H, NCH₃), 3.30 (s, 3H, OCH₂OCH₃), 3.40 (s, 3H, NCH₂OCH₃), 3.45 (t, J = 2.3 Hz, 1H, C₄₈H), 3.52 (d, J = 10.0 Hz, 1H, OCH₂OMe), 3.68 (d, J = 10.0 Hz, 1H, OCH₂OMe), 3.74 (dd, J = 2.9, 2.1 Hz, 1H, C₅H), 5.01 (d, J = 7.0 Hz, 1H, NCH₂OMe), 5.18 (d, J = 7.0 Hz, 1H, NCH₂OMe), 5.81 (d, J = 10.1 Hz, 1H, =CH), 6.93 (td, J = 7.4, 1.6 Hz, 1H, ArH), 7.12-7.41 (m, 11H, ArH), 7.52 (dd, J = 8.0 Hz, 1H, ArH), 8.58 (dd, J = 7.4, 1.5 Hz, 1H, ArH), 10.03 (b s, 1H, OH); ¹³C NMR (62.9 MHz, CDCl₃) δ 30.60 (q), 31.30 (t), 40.69 (d), 49.59 (d), 49.63 (d), 54.27 (s), 56.99 (q), 59.89 (q), 67.67 (t), 70.63 (d), 93.09 (t), 110.12 (s), 112.57 (s), 121.57 (d), 124.45 (d), 126.95 (d), 127.14 (d), 127.29 (d), 127.44 (d), 128.22 (d), 128.36 (d), 128.51 (d), 129.55 (d), 132.29 (d), 137.08 (s), 139.71 (s), 141.35 (s), 143.66 (s), 158.10 (s), 163.71 (s), 175.43 (s); mass spectrum, m/e (relative intensity) 644 (M⁺, 16), 642 (M⁺, 16), 599 (5), 597 (5); exact mass calcd. for C₃₅H₃₅BrN₂O₅ m/e 644.1709 and 642.1729, found m/e 644.1709 and 642.1733.
(281). To a solution of 15 mg (0.03 mmol) of enol 280 in 3 mL of tetrahydrofuran was added 1.6 mg (0.04 mmol) of potassium hydride. The mixture was stirred for 30 min at reflux, cooled to room temperature, and 5 mg (0.04 mmol) of dimethyl sulfate was added. The solution was warmed for 1 h at reflux, cooled to room temperature, and 1 mL of methanol was added dropwise. The solvent was removed in vacuo and the residue was dissolved in 20 mL of dichloromethane and washed with 10 mL of saturated aqueous ammonium chloride. The organic layer was dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (ethyl acetate) to give 12 mg (78%) of 281 as clear oil: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 1.91 (b s, 1H, C$_1$H), 2.00 (t, $J$ = 17.8 Hz, 2H, C$_2$H$_2$), 2.63 (s, 1H, C$_{4a}$H), 2.64 (d, $J$ = 10.2 Hz, 1H, C$_{16}$H) 2.97 (s, 3H, NCH$_3$), 3.12 (s, 3H, OCH$_3$), 3.18-3.40 (m with singlet at $\delta$ 3.29 and 3.39, 8H, CH$_2$OMe, CH$_2$OCH$_3$, NCH$_2$OCH$_3$), 3.51 (b s, 1H, C$_5$H), 4.41 (d, $J$ = 8.2 Hz, 1H, NCH$_2$), 4.50 (d, $J$ = 8.2 Hz, 1H, NCH$_2$), 5.73 (d, $J$ = 10.2 Hz, 1H, =CH), 7.00-7.41 (m, 15H, ArH).
REFERENCES


24. Personal communication from Dr. D. Curran.

25. Personal communication from Dr. P. A. Johnson.


34. This result suggests that 5-hexenyl radical constrained such that a substituent must occupy an axial site at C-4 in the traditional "chair" transition state will cyclize predominantly via "boat" transition state. See: Rajanbabu, T. V. J. Am. Chem. Soc. 1987, 109, 609. Rajanbabu, T. V. J. Org. Chem. 1988, 53, 4522.


49. We thank Dr. Judith Gallucci for determining this structure at the Ohio State University Chemistry Department X-ray crystallography facility.


55. Ketone 134 was extremely reluctant to return to sp³ hybridization at C-3 as enol ether 187 was generated in high yield under standard ketalization conditions. This was supported by MM2 calculations which indicated that I was at least 0.7 kcal/mol lower in energy than II.

\[
\begin{align*}
\text{I} & \quad \text{II} \\
\text{OCH}_3 & \quad \text{OCH}_3 \\
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et}
\end{align*}
\]


59. A very distinct C(1) methine proton resonance, δ ~2.0 ppm, was observed in all compounds after radical cyclization.


69. We thank Ram Krishnamurthy for performing the calculations.


71. A method describing reactions between lithium enolates and isocyanates (Hendi, S. B.; Hendi, M. S.; Wolfe, J. F. Syn. Commun 1987, 17, 13) failed in this system. We are evaluating the generality of our procedure.

APPENDIX A: $^1$H and $^{13}$C NMR Spectra of New Compounds
SCW-1-252 (500 MHz, CDCl₃)

* = impurities
SCW-1-252 (62.9 MHz, CDCl₃)

* = impurities
SCW-2021 (300 MHz, CDCl₃)
SCW-2021 (62.9 MHz, CDCl₃)
INTEGRAL

SCW-1-069A (250 MHz, CDCl₃)

142
142

SCW-1-069A (62.9 MHz, CDCl₃)
SCW-1-300 (300 MHz, CDCl₃)
SCW-1-300 (62.9 MHz, CDCl₃)
146
SCW-1-293 (250 MHz, CDCl₃)
SCW-1-293 (250 MHz, CDCl₃)
SCW-1-283 (62.9 MHz, CDC)
SCW-2-066 (250 MHz, CDCl₃)
SCW-2-066 (62.9 MHz, CDCl₃)
SCW-2-094A (300 MHz, CDCO)
SCW-2-094A (62.9 MHz, CDCl₃)
SCW-1-126A (62.9 MHz, CDCl₃)
SCW-2-014 (500 MHz, CDCl₃)

155

CH₂Cl₂
SCW-2-097A (250 MHz, CDCl₃)
159

SCW-2-097A (62.9 MHz, CDCl₃)

* = impurities
SCW-1-111A (250 MHz, CDCl₃)

* = impurities
172
SCW-2-027 (500 MHz, CDCl₃)
* = H₂O
SCW-2-027 (125 MHz, CDCl₃)
SCW-2-032 (500 MHz, CDCl₃)
SCW-2-032 (62.9 MHz, CDCl₃)
SCW-1-135A (250 MHz, CDCl₃)
174
SCW-1-135A (62.9 MHz, CDCl₃)
175
SCW-1-136 (300 MHz, CDCl₃)
* = H₂O
SCW-1-136 (75.5 MHz, CDCl₃)
INTEGRAL
NMe
OMe
CO_2Et

179
SCW-2-108A (250 MHz, CDCl_3)
SCW-2-108B (62.9 MHz, CDCl₃)
OMe - NMe - CPh₂

SCW-2-291A (500 MHz, CDCl₃)

*= impurities

H₂O

CH₂Cl₂

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
SCW-2-291A (125 MHz, CDCl₃)

181
SCW-2-117 (300 MHz, CDCl₃)

* = impurities
# = ethyl acetate

182
INTEGRAL

OMe - NMe = CPh₂

182
SCW-2-117 (250 MHz, CDCl₃)
SCW-2-117 (250 MHz, CDCl₃)
SCW-1-209B (500 MHz, CDCl₃)
SCW-3-051A (250 MHz, CDCl₃)

**Chemical Structure:**

![Chemical Structure](image)

**Resonance Peak:**

CH₂Cl₂

**P P H**

**PPM:**

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
196
SCW-3-056A (250 MHz, CDCl₃)
196

SCW-3-056A (62.9 MHz, CDCl₃)
SCW-3-057A (250 MHz, CDCl₃)

* = impurities  o = Et₂O
197
SCW-3-58C (250 MHz, CDCl₃)
* = CH₃OCH₂OCH₃
o = impurities

CH₂Cl₂

...
197

SCW-3-58C (62.9 MHz, CDCl₃)
183
SCW-3-076A (250 MHz, CDCl₃)
* = impurities
SCW-3-076A (62.9 MHz, CDCl₃)
SCW-3-080A (300 MHz, CDCl₃)

* = impurities  o = 183
SCW-3-080A (62.9 MHz, CDCl₃)

$^1$H = 183
SCW-110A (62.9 MHz, CDCl₃)
SCW-3-119B (250 MHz, CDCl₃)

* = Impurities
SCW-3-121A (300 MHz, CDCl₃)

* = impurities  O = EtOAc

H₂O

spectroscopic peaks at 7.5 to 5.0 ppm
SCW-3-138A (300 MHz, C₆D₆)

* = Impurities
SCW-3-138A (62.9 MHz, CDC13)

* = impurities
217
SCW-4017A (300 MHz, C₆D₆)

* = Impurities

o = Dicyclohexylurea
SCW-5-048A (200 MHz, CDCl$_3$)
SCW-5-048A (62.9 MHz, C₆D₆)
OMe O Me

228
SCW-5-049A (250 MHz, CDCl$_3$)

* = impurities
SCW-5-049A (62.9 MHz, CDCl₃)

* = impurities
INTEGRAL

SCW-5-053A (250 MHz, C₆D₆)

229
SCW-5-053A (62.9 MHz, C₆D₆)
SCW-5-057A (250 MHz, CDCl₃)
230

SCW-5-057A (75.5 MHz, CDCl₃)
SCW-4-044A (75.5 MHz, CDCl$_3$)
OMe
H
233
SCW-4-044A (300 MHz, CDCl₃)
SCW-5-026C (250 MHz, CDC6)
SCW-5-026C (62.9 MHz, C₆D₆)
237
SCW-4-065A (200 MHz, CDCl₃)
237
SCW-4-065A (62.9 MHz, CDCl₃)
SCW-5-030A (250 MHz, CDCl₃)
239
SCW-5-030A (62.9 MHz, CDCl₃)
SCW-5-030B (250 MHz, CDCl₃)

H₂O

CH₂Cl₂
SCW-5-030B (250 MHz, CDCl₃)
SCW-5-030B (62.9 MHz, CDCl₃)
SCW-4088B (300 MHz, CDCl₃)

* = impurities
INTEGRAL

OMe

MeO

i-NMe

242

SCW-5-024A (250 MHz, CDCl₃)

*= impurities

7.5 6.0 5.5 5.0 4.0

P P M 3.5 2.5 3.0 2.0

255

H₂O
SCW-4-131B (300 MHz, CDCl₃)
* = impurities

243
INTEGRAL

OMe
-NMe
ScPh!

243

SCW- 4-131B (250 MHz, CDCl₃)
SCW-4-123B (250 MHz, CDCl₃)

* = impurities
244

SCW-4-138B (62.9 MHz, CDCl₃)
SCW-5-008A (250 MHz, DMSO, 420 K)
SCW-5-003B (500 MHz, C₆D₆)

* = impurities
SCW-5-003B (62.9 MHz, CDCl₃)
250
SCW-5009C (250 MHz, CDCl₃, 363ºK)
SCW-5009C (62.9 MHz, CDCl₃)
QUANTNARY CARBONS ONLY

SCW-5009C (62.9 MHz, CDCl$_3$)
SCW-5009C (62.9 MHz, CDCl₃)
SCW-5-056A (300 MHz, CDCl₃)
* = impurities
SCW-5-081A (62.9 MHz, CDCl₃)
INTEGRAL

MeO

OMe

MeO

NMe

252

SCW-5-056C (250 MHz, CDCl₃)

* = impurities
MeO

OMe

MeO

NMe

OMe

MeO

H

Ph

Ph

252

SCW-5-056C (62.9 MHz, CDCl₃)
254
SCW-5-081B (300 MHz, CDCl₃)
* = impurities
SCW-5-081B (62.9 MHz, CDCl$_3$)
SCW-5-035A (250 MHz, CDCl₃)
INTEGRAL

SCW-5-038A (250 MHz, CDCl₃)

261

Br
HN
ONO
H
CH₂O
O
H

CH₂Cl₂
SCW-5-038A (62.9 MHz, CDCl₃)
261a

SCW-5-038B (250 MHz, CDCl₃)
INTEGRAL

H

SCW-5-042A (250 MHz, CDCl₃)

263
263
SCW-5-042A (62.9 MHz, CDCl3)
SCW-5-042B (62.9 MHz, CDCl₃)
SCW-5-045A (300 MHz, CDCl₃)
271

SCW-5-044A (250 MHz, CDCl₃)

* = EtOAc

CH₂Cl₂
SCW-5-044A (62.9 MHz, CDCl₃)

* = impurities
272
SCW-5-052A (250 MHz, CDCl₃)
272
SCW-5-052A (62.9 MHz, CDCl₃)
* = impurities
SCW-5-068 (62.9 MHz, CDCl₃)
SCW-5-070A (250 MHz, CDCl₃)
SCW-5-070A (62.9 MHz, CDCl₃)
I N T E G R A L

CH₂O

OMe

H

268

SCW-5-076A (250 MHz, CDCl₃)
SCW-5-076A (62.9 MHz, CDCl₃)
SCW-5-076B (62.9 MHz, CDCl₃)
SCW-5-077A (300 MHz, CDCl₃)
* = CH₂Cl₂
INTEGRAL

OCH.

NMe

CPh.

275

SCW-5-085A (250 MHz, CDCl₃)

* = impurities

7.0 6.5 6.0 5.5 5.0 4.5 4.0

PPM/

H₂O

3.0 2.5 I 3.5 3.0 2.5 2.0 1.5 1.0 .5
SCW-5-087A (250 MHz, C₆D₆)
This sample contains minor impurities.
SCW-5-089A (250 MHz, CDCl₃)

*= impurities

° = EtOAc

H₂O

CH₂Cl₂

O
This sample contains minor impurities.
SCW-5099A (250 MHz, CDCl₃)

* = impurities
APPENDIX B: X-Ray Crystallographic Details for Compound 168
Figure 2. ORTEP of Ethoxylactam 168
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Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.
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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 Details for Compound 173
### Intramolecular Distances Involving the Nonhydrogen Atoms

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Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.
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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 Details for Compound 180
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Distances are in angstroms. Estimated standard deviations in the least significant figure(s) are given in parentheses.
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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 Details for Compound 248
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Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.
## Final Bond Angles for C16 H38 N2 O5

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