RICE UNIVERSITY

STEREOCONTROLLED TOTAL SYNTHESIS OF (±)-GELSEMINE

by

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Abstract

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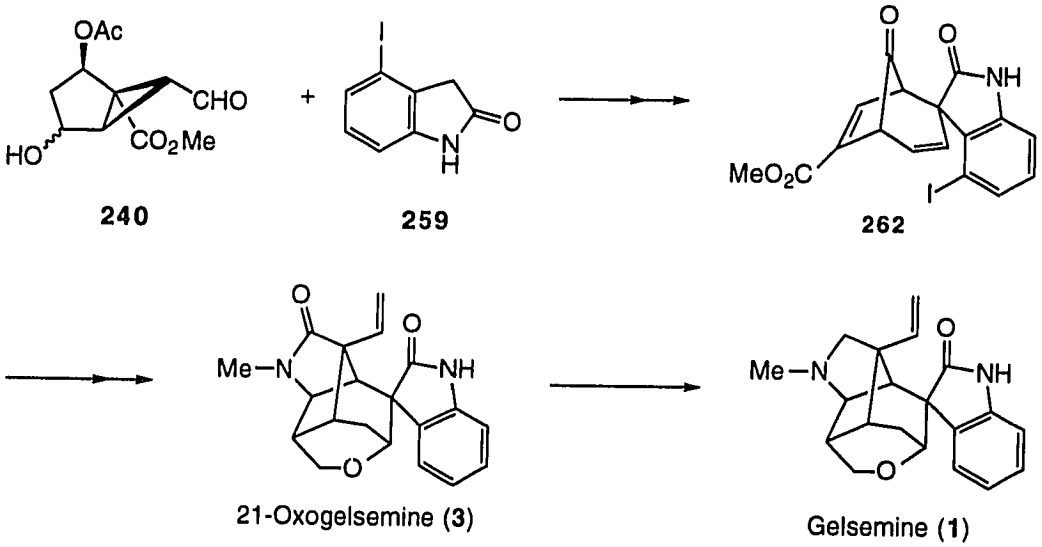
Gelsemine (**1**) has been recognized as the major alkaloid component of *Gelsemium sempervirens* since 1870. It has attracted numerous synthetic efforts since 1960s due to its unique rigid, hexacyclic cage structure. The first completely stereocontrolled total synthesis of gelsemine (**1**) via 21-oxogelsemine (**3**) is described herein. This synthesis features a stereospecific condensation between cyclopropyl carboxaldehyde (**240**) and 4-iodo-oxindole (**259**), facile construction of the tetracyclic intermediate (**262**) through a novel application of divinylcyclopropane-cycloheptadiene rearrangement, and an unprecedented silver-mediated cyclization between carbamoyl chloride and ene-carbamate.



240 **259** **262**

21-Oxogelsemine (**3**) Gelsemine (**1**)

Acknowledgments

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TABLE OF CONTENTS

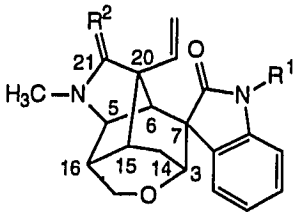
To my parents and Feng

Chapter I

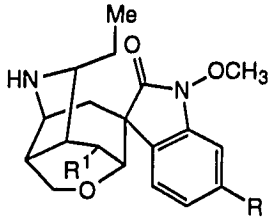
Introduction

The presence of gelsemine (**1**) as the principal alkaloid component of *Gelsemium sempervirens* Ait, better known as Carolina jasmine, was first established in 1870 (Figure 1).[1] Since then, some other gelsemine-type alkaloids have been isolated. Gelsevirine (**2**) was first isolated in 1953 from *G. sempervirens* by Schwarz and Marion.[2] The minor alkaloid, 21-oxogelsemine (**3**), was isolated in 1974 from *G. sempervirens* by a combination of column chromatography, TLC, and preparative gas chromatography.[3] 21-Oxogelsevirine (**4**) was isolated as the principal alkaloid from a methanol extract of the stem of *Gelsemium rankinii* Small.[4] Over the years, other constituents of *Gelsemium* alkaloids continued to be reported. Representative examples (**5-18**)[5] are shown in Figure 1.

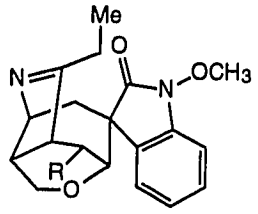
The structural elucidation of gelsemine required great efforts due to its complexity. This process also demonstrated the development of modern techniques for structural analysis of complex molecules. Early chemical investigation of gelsemine had provided only peripheral information on the complex structure. Little progress could be made in attempts to fully elucidate it. Attempted Hofmann degradation,[6] for example, simply led to N_b-demethylation of gelsemine methohydroxide. The presence of a vinyl group was deduced by the periodic acid-osmium tetroxide cleavage of N_a-methylgelsemine to a carbonyl compound **19**, shown to be an aldehyde by the dehydration of its oxime to a nitrile **20** (Scheme 1).[7]



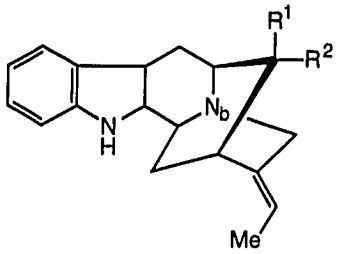
	R^1	R^2
Gelsemine (**1**)	H	H_2
Gelsevirine (**2**)	OCH_3	H_2
21-Oxogelsemine (**3**)	H	O
21-Oxogelsevirine (**4**)	OCH_3	O



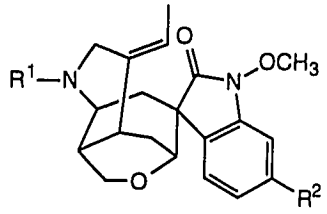
	R	R^1
Gelsemicine (**5**)	OCH_3	H
Gelsedine (**6**)	H	H
Hydroxygelsemicine (**7**)	OCH_3	OH
14β-Hydroxygelsedine (**8**)	H	OH(β)



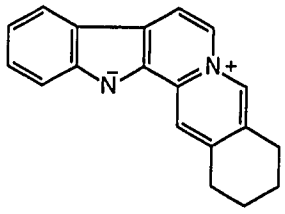
	R
Gelsenicine (**9**)	H
Humantenidine (**10**)	OH



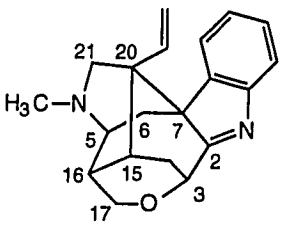
	R^1	R^2	N_b
Koumicine (**11**)	CO_2Me	CH_2OH	—
Akuammidine *N*-oxide (**12**)	CO_2Me	CH_2OH	→ O
Koumidine (**13**)	CH_2OH	H	—



	R^1	R^2
Humantenine (**14**)	CH_3	H
Humamtenirine (**15**)	H	OCH_3
Rankinidine (**16**)	H	H



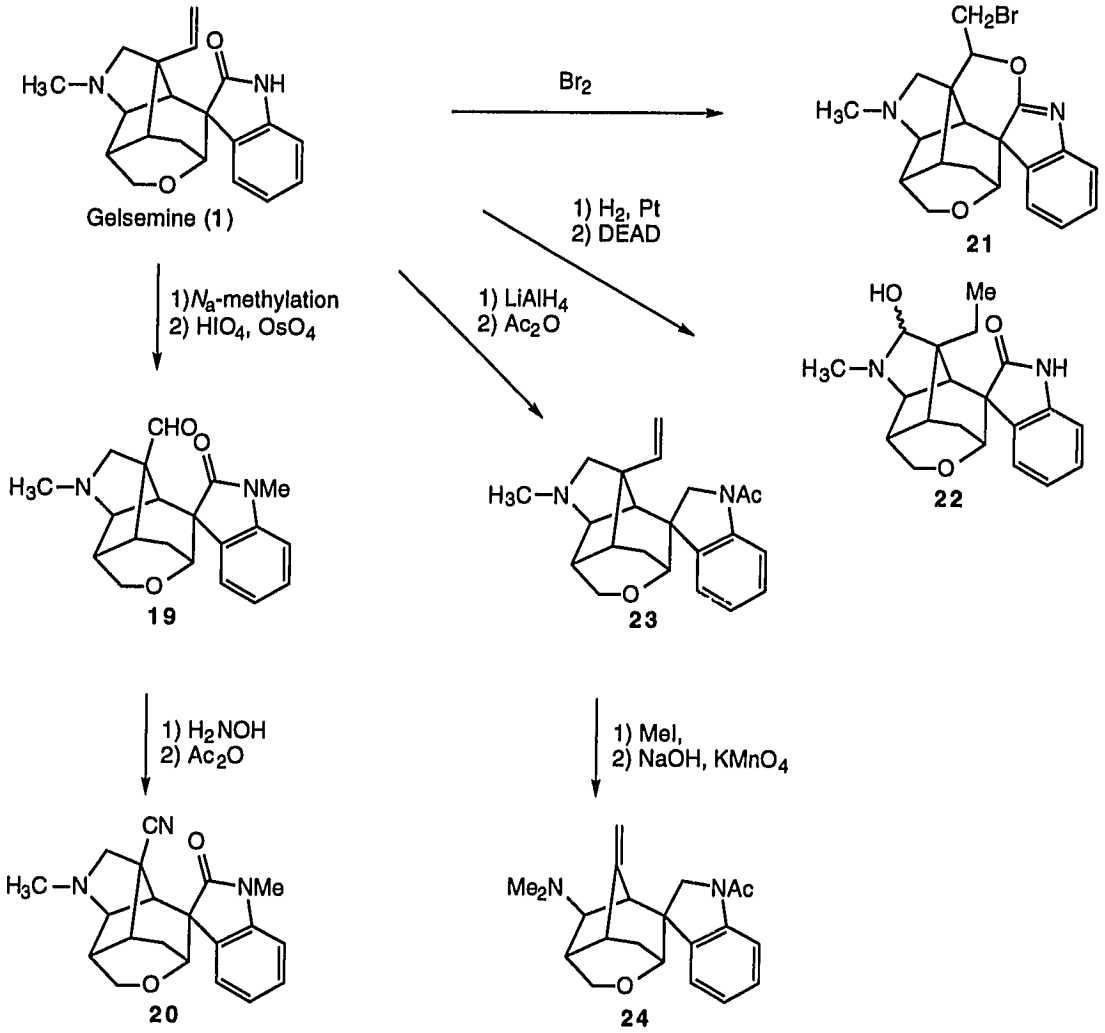
Sempervirine (**17**)



Koumine (**18**)

Figure 1

Reaction of gelsemine with bromine gave bromoallogelsemine **21**, which suggested steric proximity of the indolinone oxygen and the vinyl group, but provided no direct skeletal information.[8] Oxidation of 18,19-dihydrogelsemine with ethyl azodicarboxylate gave carbinolamine **22**. Further oxidation with chromium trioxide (CrO_3), provided a lactam, whose carbonyl absorption was typical of a 2-pyrrolidinone. This experiment provided evidence about the size of the ring containing N_b.[9]



Scheme 1

The scant structural information to emerge from early chemical investigations, together with UV and IR measurements, amounts to no more than the expression shown in Figure 2.

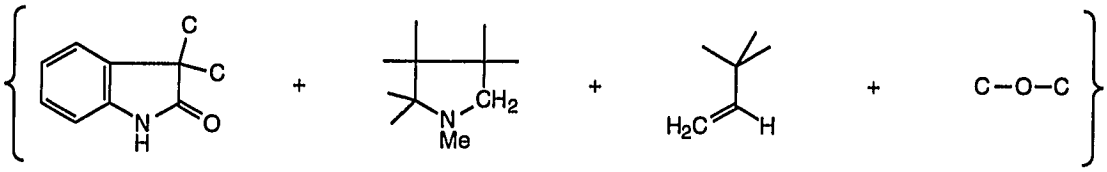
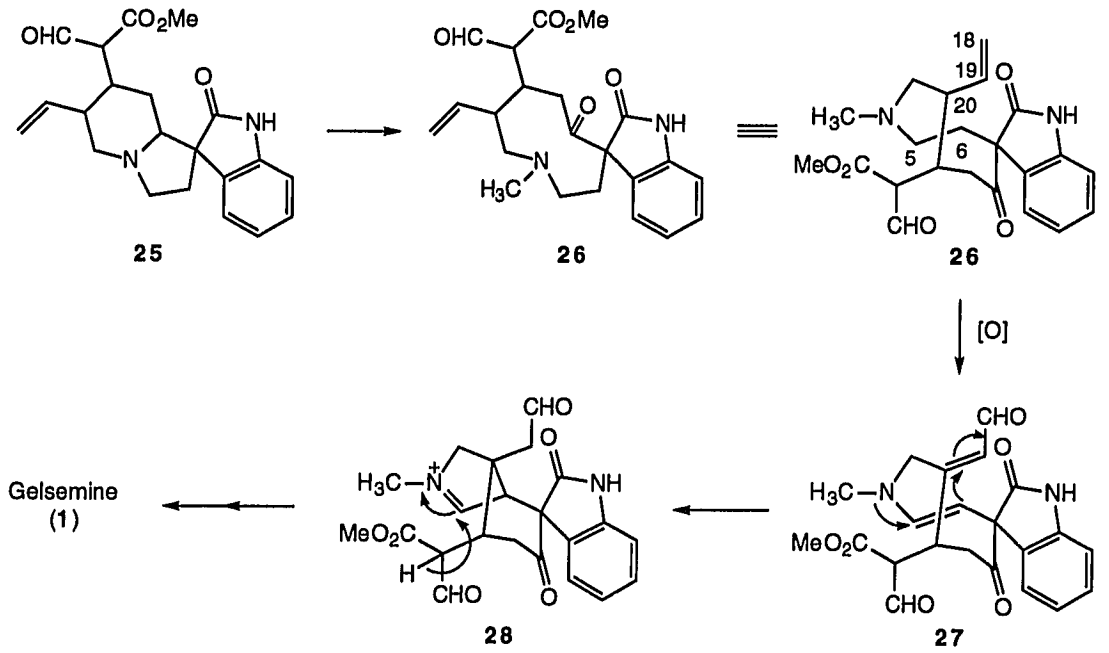


Figure 2

Thanks to the development of spectroscopic tools in the 1950s, the elucidation of the structure of gelsemine was tremendously facilitated. Proton NMR at 60MHz[10a] was able to confirm easily the presence of a vinyl group and its connection to a quaternary carbon, thus implying the novel quaternary carbon at C-20. The geminally coupled 21-methylene protons adjacent to nitrogen and the groups OCH_2CH, $OCH(C)_2$, and $N_bCH(C)_2$ were also discernible from the 60MHz spectrum. The relationship between vinyl group and basic nitrogen atom, which was predictable on the biogenetic grounds, was confirmed by one of the few helpful chemical degradation studies shown in Scheme 1. Oxidation of N_a-acetyldihydrodeoxy gelsemine **23** methohydroxide with alkaline potassium permanganate gave the unsaturated base **24**.

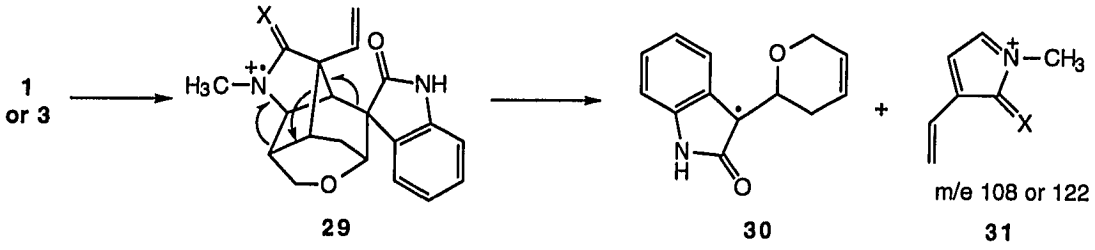
Armed with these data and a cleverly conceived, chemically rational modification of a standard biosynthetic pathway as shown in Scheme 2, Conroy and Chakrabarti deduced the correct structure of gelsemine in 1959.[10a] The key to the formation of the crucial 6,20 bond in their suggestion is the postulated oxidation at the 5,6 position of **26**, to give an enamine, and at the 18,19 and 20 positions of **26** to give an unsaturated aldehyde **27**. The required 6,20 bond formation then occurs in a Michael mode.



Scheme 2

An independent structural elucidation was also achieved in 1959 by Lovell and co-workers on the basis of an X-ray analysis of the hydrochloride and hydroiodide salts of gelsemine. This study defined the relative, but only presumed absolute, stereochemistry of (**1**).[10b]

The mass spectrum of gelsemine is dominated by an ion at *m/e* 108, for which the structure **31** was assigned (Scheme 3). A direct comparison with the fragmentation pattern of the minor 21-oxogelsemine supported structure of the proposed fragment, the base peak now being seen at *m/e* 122.

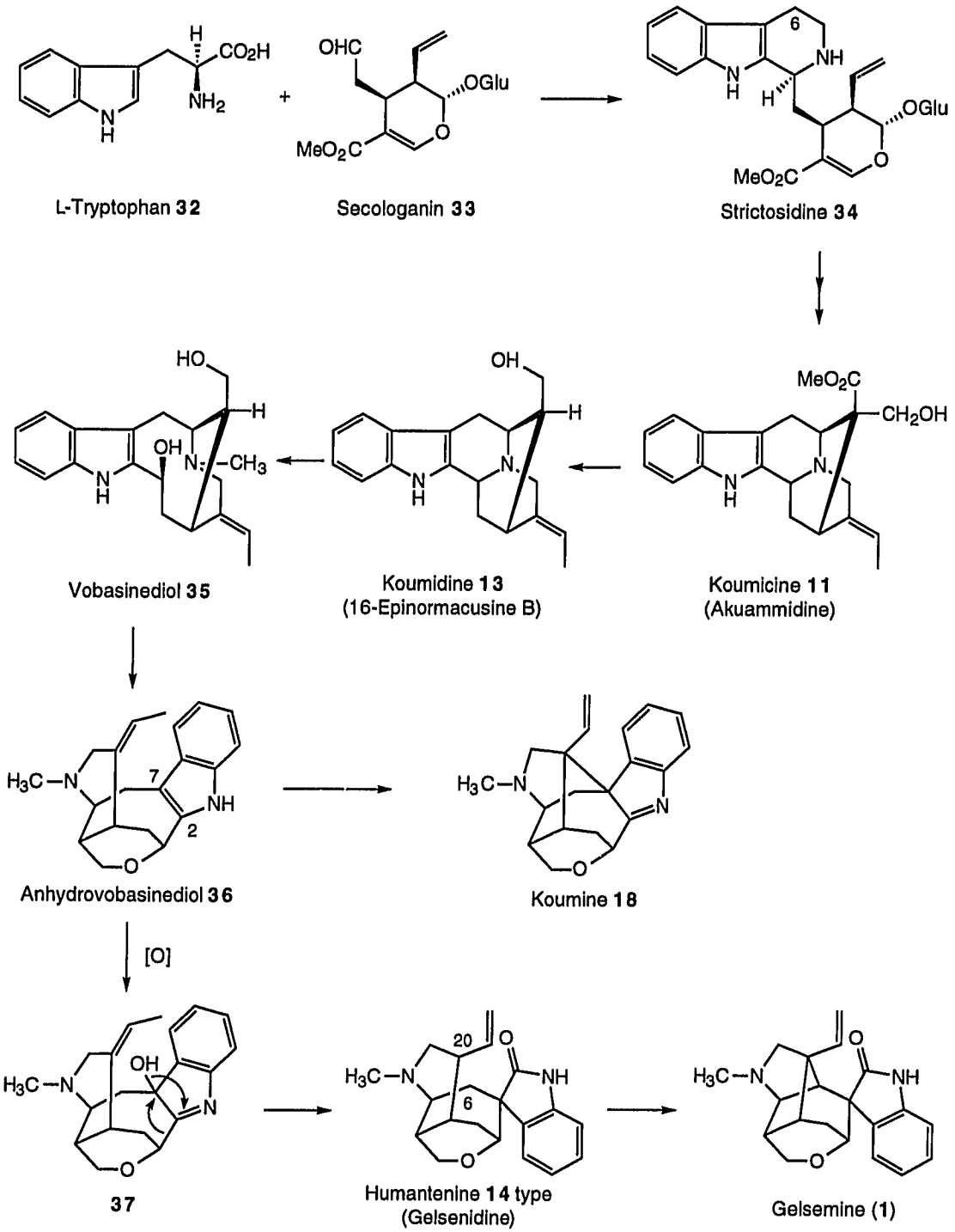


Scheme 3

Gelsemine-type bases are the only indole alkaloids known to have a 6,20 bond. This feature is not present in other alkaloids isolated from *G. sempervirens*. Thus gelsemine emerges as one of the most highly evolved among all the indole alkaloids. Meanwhile, koumine **18**, the principal alkaloid of the Chinese medicinal plant *Kou-Wen* (*G. elegans* Benth.),[11] is the only alkaloid known to have a 7,20 bond.

The biosynthesis of monoterpenoid indole alkaloids has been extensively studied. Zenk and co-workers reported incorporation of 0.47% of [6-^{14}C]strictosidine to gelsemine into *Gelsemium sempervirens*.[12] This has provided further experimental support to the proposal that strictosidine is a central intermediate in the biosynthesis of monoterpenoid indole alkaloids, although the detailed pathway of this biosynthetic process still remains obscure.

Battersby and co-workers established[13] that secologanin, **33**, is the ultimate precursor to the C-9/C-10, non-tryptamine carbon skeleton common to the majority of indole alkaloids. The crucial enzyme that catalyzes the condensation of tryptophan **32** and secologanin **33** to yield exclusively the α-epimer of strictosidine **33**, has been discovered and named strictosidine synthase.[14] The isolation and identification of humantenine **10**, koumicine **11**, and koumidine **12** from *G. elegans*, coupled with facile biomimetic transformation of vobasinediol **35** to koumine **18**,[15] shed some light on the biosynthetic pathway. Meanwhile, the transformation of koumidine **12** to vobasinediol **35** and then to anhydrovobasinediol **36** appears to involve conventional processes only. The proposed *in vivo* transformation of anhydrovobasinediol **36** to gelsemine (**1**) involves a series of alterations to the molecular skeleton which, presumably would include (1) oxidation of the


L-Tryptophan 32
Secologanin 33
Strictosidine 34
Koumicine 11
(Akuammidine)
Koumidine 13
(16-Epinormacusine B)
Vobasinediol 35
Anhydrovobasinediol 36
Koumine 18
[O]
37
Humantenine 14 type
(Gelsenidine)
Gelsemine (1)

Scheme 4

2,7 double bond, (2) an acid-induced 2,7 shift of **37**, and (3) allylic rearrangement of the C-20 ethylidene side chain to a C-20 vinyl to form a humantenine-type precursor, **14**.[5] Subsequent oxidative coupling between C-6 and C-20 would afford gelsemine (**1**).

Physiological study of gelsemine was reported as early as 1914 by Chillingsworth,[16] who concluded that the alkaloid acted on the central nervous system, and that the action on the heart was secondary via the vagus. The analgesic action of gelsemine was first reported by Eichler et al. in 1957.[17] Later, in the course of study of the analgesic activity of a mixture of gelsemine and aspirin, some detailed results were reported:[18] (1) the oral acute LD_{50} of gelsemine in mice is 1240 mg/kg (intraperitoneally 405 mg/kg, intravenously 133 mg/kg); (2) gelsemine does not have a curare like action, it is not a central nervous system sedative, and it has a very weak serotonin action. It strengthens the hypertensive action of adrenalin but it is hypotensive in large doses. It does not act on the heart and is not potentiated by barbiturates. It is interesting to note that gelsemicine (**5**) has much higher toxicity (MLD 0.05-0.06 mg/kg in rabbits, intravenous injection) in comparison to gelsemine (**1**) (MLD 180 mg/kg), and it has been considered to be mainly responsible for the characteristic effects of *Gelsemium* extracts.

Symptoms of intoxication in humans caused by accidental ingestion of *Kou-Wen* plants have been described as:[19] (1) loss of appetite and turn of the stomach, with eventual severe abdominal pain and intestinal bleeding, (2) breathing difficulties which finally lead to death by respiratory failure, (3) generalized muscular weakness and paralysis of the limbs, (4) arrhythmia and

drop in blood pressure, but heart failure is not a common cause of death, (5) dilation of pupils, drop in body temperature and proliferation of white blood cells.

The traditional and effective emergency treatment of this kind of poisoning in China includes administration of fresh sheep blood as well as Chinese cinnamon oil. Of course immediate detoxification measures such as gastric lavage, application of emetics or laxatives, and administration of active charcoal also prove effective.

It is interesting to note that the toxicity of *Gelsemium* species depends not only on the individual alkaloids present, but also on the route of administration as well as on the animal used. For example, the LD_{50} values of gelsemine in mice are 1240, 405, and 133 mg/kg, respectively, depending on whether the drug is administered orally, intraperitoneally, or intravenously.[18] Toxicity also depends on the animals used and on the method of drug administration, as can be seen clearly from Table 1.[20]

Animal	Route of administration	MLD (mg/kg)
Frog	Injection to abdominal lymph bladder	20-30
Rat	Intraperitoneal or abdominal cavity injection	0.1-0.12
Rabbit	Intravenous injection	0.05-0.06
Dog	Intravenous injection	0.5-1.0

Table 1

The toxic *Gelsemium* alkaloids in crude form have been used as analgesic and antispasm agents for a long time. They were also applied in

traditional Chinese medicine as a remedy for dangerous skin ulcers, such as miliary vesicles under the nose. In recent years, pure gelsemine has been used in an analgesic composition (0.5-2 mg gelsemine in 300-500 mg aspirin), and it was claimed that this preparation "has an onset of action of about 15 minutes and lasts for about 8 hours. The action of the combination is greater than either drug used alone."[18]

More recently, a preparation of the total alkaloids, which consists of seven individual *Gelsemium* alkaloids (as shown by TLC) with an LD_{50} in mice of 0.275 mg/kg (intravenous injection), has been used as analgesic for the palliation of various acute cancer pains, including hepatic cancer. It was claimed that good analgesic activity usually lasted for 4-6 h with a rating of remarkably effective (66%), effective (24%), and not effective (10%), thus confirming the analgesic activity of *Gelsemium* alkaloids. Furthermore, the preparation does not show any side effect of addiction and therefore has been recommended as a substitute for morphine or dolantin.[21]

Preliminary observation on 16 cancer patients who have been treated with the aforementioned total alkaloid preparation indicates that their conditions improved. Thus hepatic cancer patients have claimed disappearance of pain, improvement of appetite, and reduction of ascites; patients suffering from esophageal cancer claimed relaxation of pain and disappearance of vomiting and upset stomach, as well as improved appetite. These preliminary results are quite encouraging, but certainly more extensive investigations are needed before the pharmacological profile of *Gelsemium* alkaloids can be fully established. In particular, safety remains a concern. Thus, not only should the dosage itself be strictly controlled, but also further investigations of suitable

methods for administration and of application of combination forms, should be initiated.

Chapter II

Synthetic Background

The unique hexacyclic cage structure of gelsemine (**1**) has attracted numerous synthetic studies by chemists around the world since 1960s. It soon became apparent that the problem posed by structural features of gelsemine was far more challenging than anticipated. While construction of the cage system proved troublesome, the most difficult problem encountered was the construction of the spiro-indolinone in the presence of the sterically demanding cage structure, not to mention stereocontrol at the level of the critical spiro center.

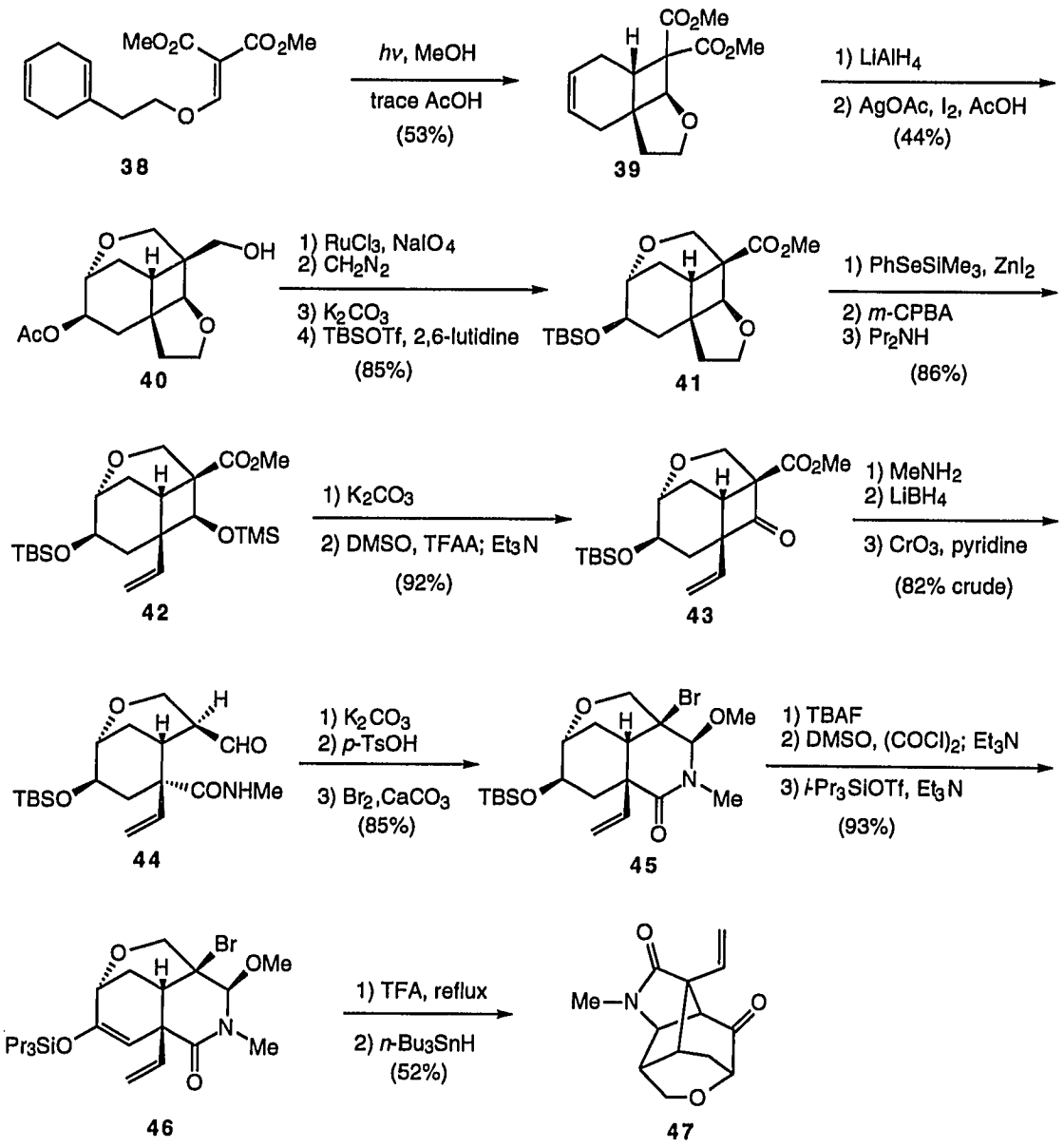
When we started our synthetic project in early 1993, no successful total synthesis of gelsemine has been reported. However, the monumental efforts of other chemists have culminated in three total syntheses since then. These syntheses and most of the synthetic studies will be reviewed in this chapter. Emphasis will be placed on synthetic strategies, instead of individual transformations.

Our own efforts in this area have recently led to the stereocontrolled synthesis of racemic gelsemine (**1**) via 21-oxogelsemine (**3**) by novel application of cyclopropane-cycloheptadiene rearrangement. Details of this project are described in the next two chapters.

Johnson's Total Synthesis[22]

The first two syntheses of gelsemine were reported by Johnson et al. and Speckamp et al. in 1994 respectively. Johnson's strategy was to construct the

tetracyclic ketone intermediate **47** first. The spiro-indolinone was then installed by a photochemical reaction.



Scheme 5

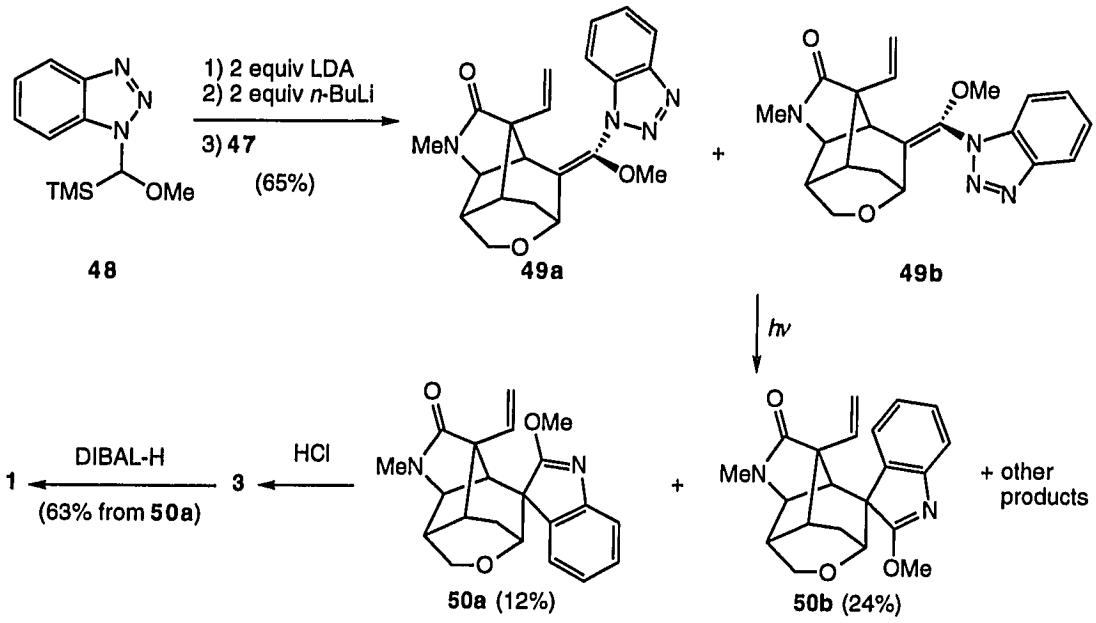
The synthesis of the tetracyclic intermediate **47** is outlined in Scheme 5. Photoinduced intramolecular cycloaddition of the triene **38** gave the tricyclic diester **39** which contains not only 12 of the 13 carbon atoms present in the

target ketone, but also has the masked vinyl group in the required *cis* relationship with the hydrogen at the ring fusion. Reduction of the diester **39** to the corresponding diol, followed by silver acetate-iodine treatment generated tetrahydropyranyl acetoxy alcohol **40**. After the alcohol **40** was oxidized to the corresponding acid, which was then esterified, the acetoxy group was exchanged with a silyl protecting group to give the methyl ester **41**. Cleavage of the tetrahydrofuran ring with phenyl trimethylsilyl selenide in the presence of a catalytic amount of zinc iodide gave a tricyclic selenide, which was subjected to oxidative deselenylation to yield the alkene **42**.

Careful desilylation of **42** under basic conditions gave an unstable cyclobutanol, which was immediately oxidized to the cyclobutane-β-ketoester **43**. Retro Claisen cleavage of the cyclobutane ring with methylamine followed by selective reduction and reoxidation of the resulting ester afforded the aldehyde **44**. Epimerization of aldehyde **44** allowed cyclization to occur to give the hydroxyl lactam, which readily dehydrated to an enamide. The tertiary methoxy bromide **45** was obtained by treatment of the enamide with methanolic bromine in the presence of suspended calcium carbonate buffer, to prevent potential cleavage of the tetrahydropyran ring. Desilylation and oxidation of **45** gave a ketolactam, which was then converted into its silyl enol ether **46**. The acyliminium ion-mediated variation of the intramolecular Mannich reaction proceeded cleanly in hot trifluoroacetic acid to give the normally disfavored *5-endo-trig* cyclization product, which was further transformed to the tetracyclic ketone **47** by radical debromination.

The conversion of sterically hindered ketone **47** to 21-oxogelsemine (**3**) and gelsemine (**1**) proved to be a nontrivial task. Johnson adopted a variation of Wender's photochemical indole synthesis, which involves C-C bond

formation by a biradical recombination that requires very low activation energy. Condensation of the ketone **47** with lithiated 1-(methoxytrimethylsilylmethyl)benzotriazole **48** gave a mixture of the (*E*)- and (*Z*)-methoxymethylene isomers **49** (Scheme 6). Photolysis of this mixture in acetonitrile generated four products, from which the desired imino-ether isomer **50a** was isolated in only 12% yield along with its epimer **50b** obtained in 24% yield. Imino-ether **50a** was converted to gelsemine (**1**) by hydrolysis to 21-oxogelsemine (**3**), followed by selective reduction of the tertiary amide.

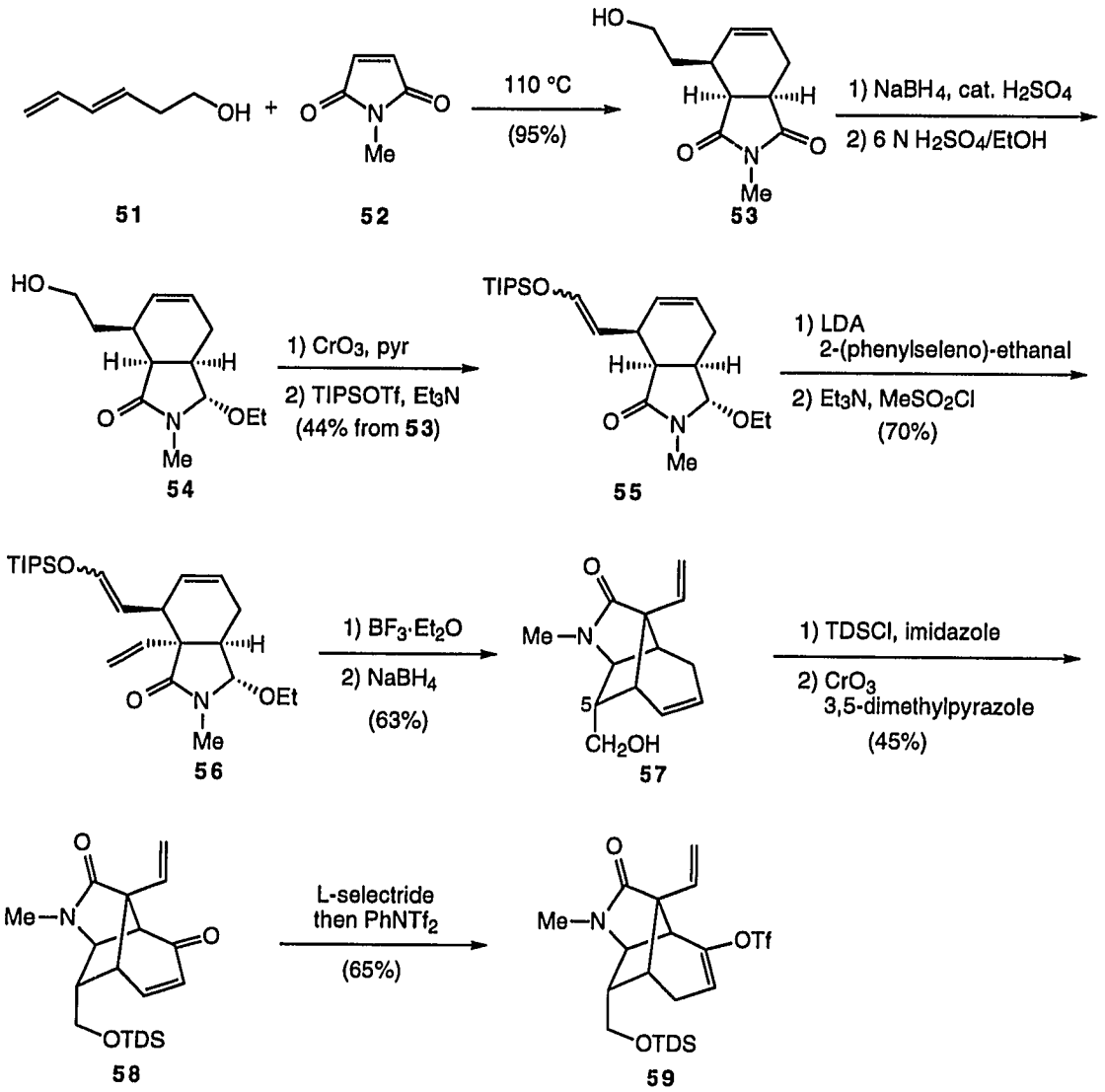


Scheme 6

This elegant but lengthy total synthesis did not finish strong for the critical indolinone construction, but nevertheless it demonstrated the high degree of difficulty in the synthesis of such a compact and complicated molecule.

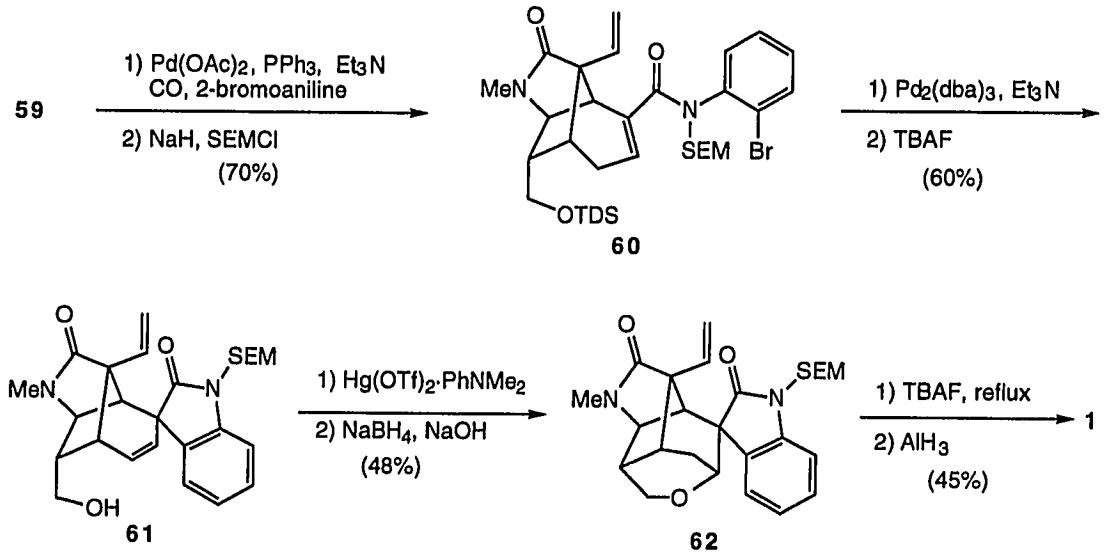
Speckamp's Total Synthesis[23]

Speckamp and co-workers reported the second total synthesis of gelsemine as back-to-back communications with Johnson's synthesis. Their approach was to construct the cage substructure by *N*-acyliminium ion-mediated cyclization, as in Johnson's synthesis, and to built the spiro-indolinone by intramolecular Heck reaction.



Scheme 7

Diels-Alder reaction of (*E*)-hex-3,5-dien-1-ol **51** with *N*-methylmaleimide **52** afforded the imide **53** (Scheme 7). Acid-assisted partial reduction of imide **53** followed by ethanolysis furnished a 3:7 mixture of the desired ethoxy lactam **54** and a tricyclic ether byproduct. Oxidation of crude primary alcohol **54** to an aldehyde, followed by treatment with triisopropylsilyl triflate and triethylamine (Et_3N), generated silyl enol ether **55** as a 3:1 mixture of (*E*), (*Z*) isomers. Vinylation of **55** was effected by quenching its enolate with 2-(phenylseleno)-ethanal, and by treating the mixture of aldol products with MsCl to induce elimination to **56**. Lewis acid treatment of **56** resulted in a facile cyclization to give a separable 3:1 mixture of diastereomeric aldehydes (at C-5) favoring the desired isomer, which was reduced to tricyclic alcohol **57** after chromatographic separation. The alcohol **57** was first protected as thexyldimethylsilyl (TDS) ether and then subjected to an allylic oxidation to yield the enone **58**. 1,4-Reduction of the enone with L-selectride and subsequent trapping of the resultant lithium enolate with *N*-phenyltrifluoromethanesulfonimide furnished



Scheme 8

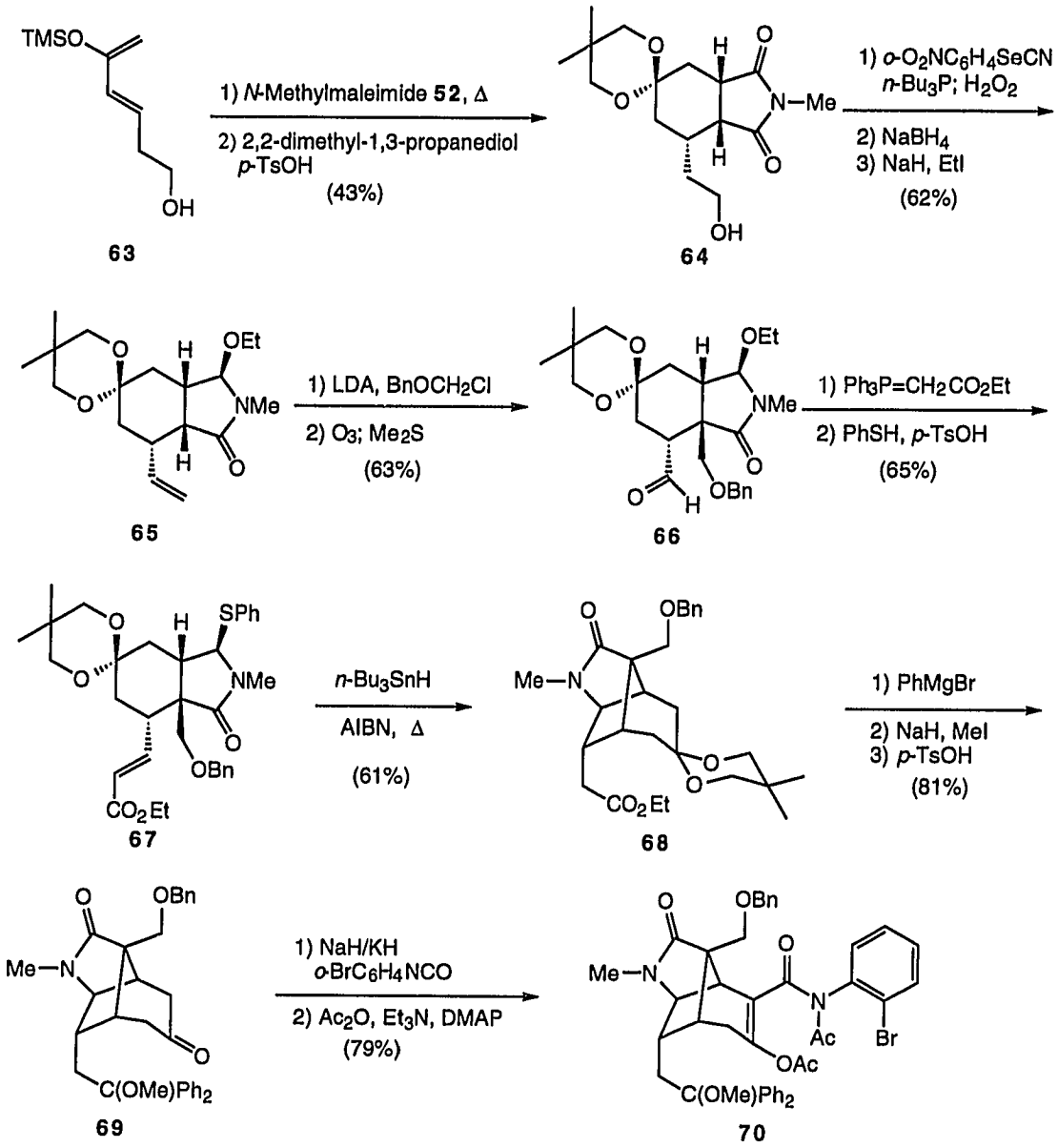
enol triflate **59**.

Palladium-catalyzed carbonylation of **59** in the presence of 2-bromoaniline gave the corresponding anilide, which was protected as its trimethylsilylethoxymethyl (SEM) derivative **60** (Scheme 8). When compound **60** was subjected to Overman's modified Heck reaction conditions, the desired spiro-indolinone **61** was obtained in 60% overall yield after removal of the TDS protecting group. In addition, the epimeric spiro-indolinone was also obtained in 30% yield. The remaining tetrahydropyran ring formation was achieved by exposure of alcohol **61** to the complex formed from mercury(II) triflate and *N*,*N*-dimethylaniline. Reduction of the resultant organomercurial with alkaline sodium borohydride ($NaBH_4$) afforded SEM-protected 21-oxogelsemine **62**. Treatment of **62** with tetrabutylammonium fluoride gave 21-oxogelsemine (**3**). Selective reduction of lactam moiety of **3** was achieved with aluminum hydride to give (±)-gelsemine. The availability of enantiopure alcohol **57** from (*R*)-malic acid should allow the synthesis of the natural alkaloids according to Speckamp's claim.

Even though Speckamp's total synthesis of gelsemine was accomplished in a more reasonable fashion than Johnson's synthesis, there are still rooms for improvement in terms of stereoselectivity.

Hart's Total Synthesis[24]

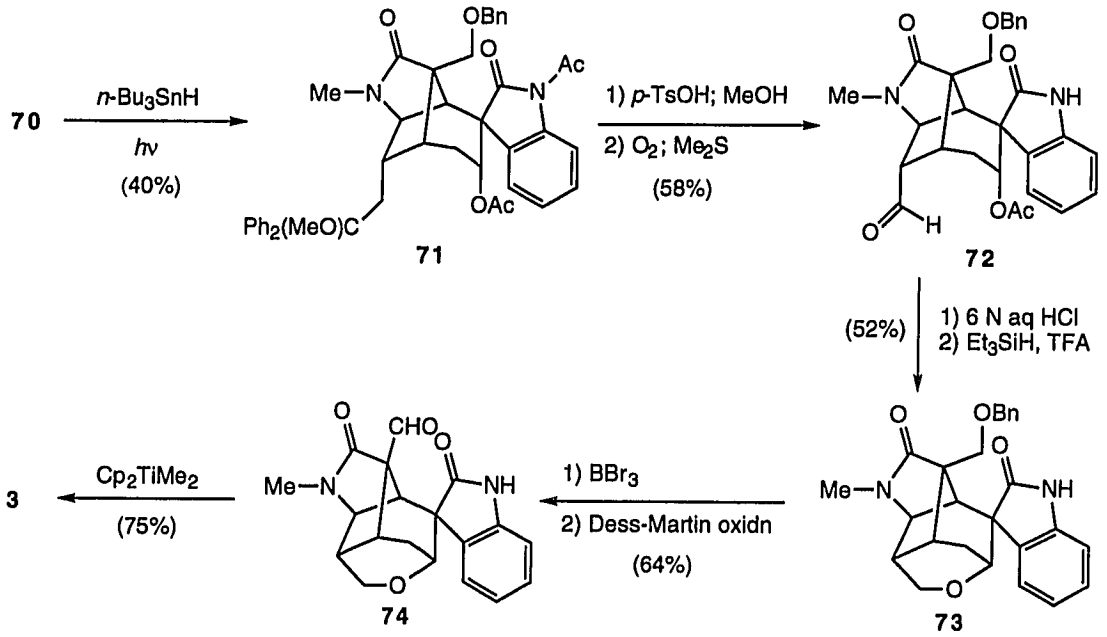
A few months after the publication of the first two total syntheses of gelsemine, Hart and co-workers disclosed their version of the total synthesis of (±)-21-oxogelsemine. Their plan revolved around preparation of the tricyclic gelsemine substructure **68**, followed by sequential introduction of the indolinone by radical cyclization.



Scheme 9

Similar to Speckamp's approach, Diels-Alder reaction between *N*-methylmaleimide **52** and diene **63** followed by ketalization of the resultant ketone afforded perhydroisoindole **64** (Scheme 9). Formal dehydration of **64** according to the Grieco protocol gave a vinyl compound. Selective reduction of

imide followed by ethylation of the resultant alcohol yielded the ethoxylactam **65**. Alkylation of the lithium enolate of **65** with benzyl chloromethyl ether followed by ozonolysis of the olefin generated crystalline aldehyde **66**. Wittig olefination and ethoxy-thiophenoxy exchange afforded compound **67**. Free-radical cyclization of **67** gave the gelsemine substructure **68**. Treatment of the ester with a Grignard reagent, methylation of the resulting alcohol, and deblocking of the ketal gave ketone **69**. Acylation of the resultant ketone **69** with *o*-bromophenyl isocyanate gave an anilide. Transformation of the ketone to enol acetate **70** maximizes diastereoselectivity in the desired sense during indolinone formation.



Scheme 10

Thus, treatment of bromide **70** with tributyltin hydride under photochemical conditions gave the desired indolinone **71** in 40% yield, along with 25% of the undesired stereoisomers (Scheme 10). Acid treatment of **71** gave an olefin, which was converted to aldehyde **72** by ozonolysis in 65%

yield. Interestingly, an epoxide derived from the alkene was also obtained (15%). Hydrochloric acid treatment of **72** afforded a mixture of diastereomeric hemiacetals. Reduction of this mixture with triethylsilane-trifluoroacetic acid gave tetrahydropyran ring of **73**. Removal of the benzyl protecting group followed by oxidation of the resulting alcohol with periodinane gave aldehyde **74**. Methylenation of the aldehyde using bis(cyclopentadienyl)dimethyltitanium afforded 21-oxogelsemine (**3**).

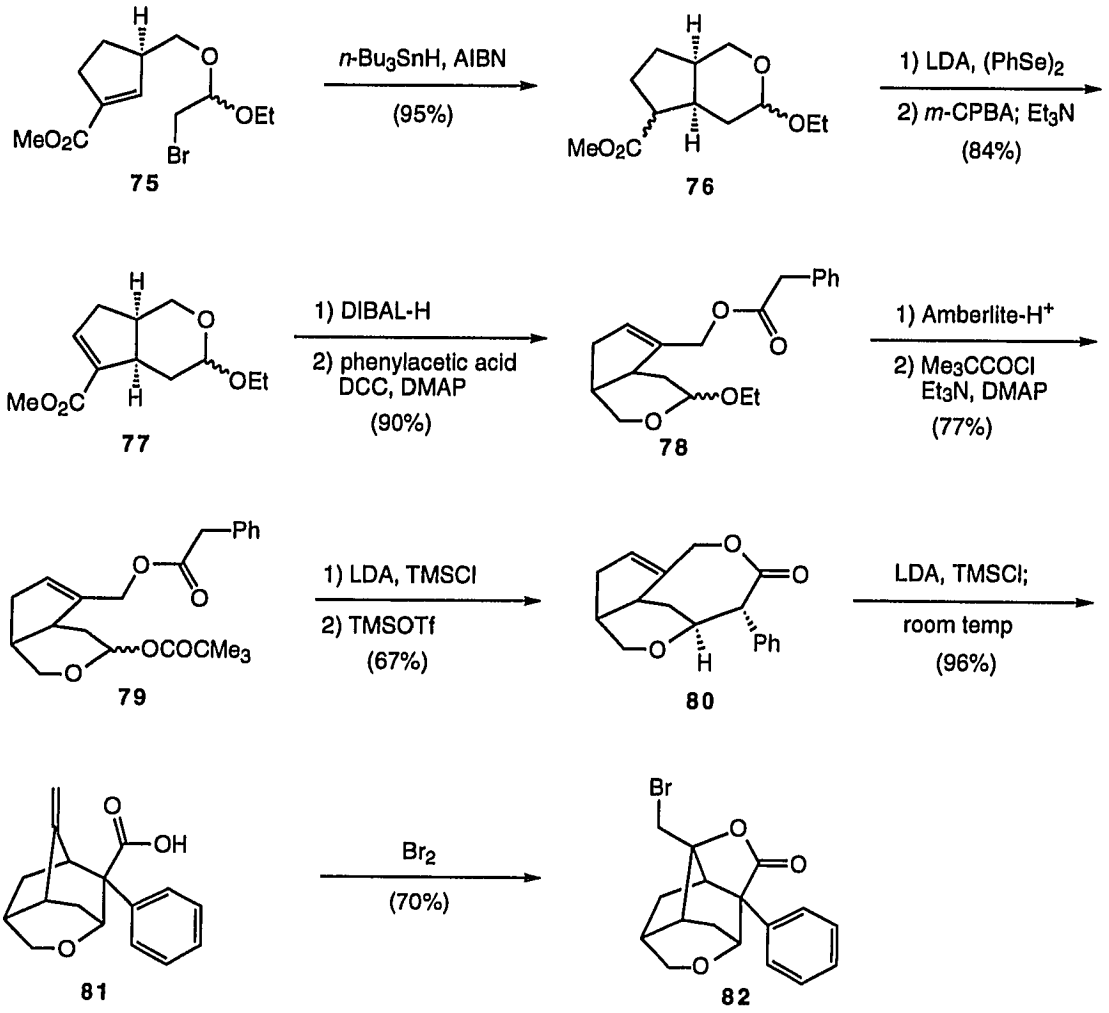
In summary, a total synthesis of (±)-21-oxogelsemine (**3**) was accomplished in 23 steps from diene **63**. This synthesis features two free-radical cyclization and a new protocol for construction of the tetrahydropyran after installation of the indolinone substructure.

Stork's Approach[25]

Stork's approach towards gelsemine still remains at the preliminary stage. Radical cyclization of a mixed acetal and a tandem transannular alkylation—Claisen rearrangement construct a sophisticated substructure **81** of gelsemine.

Tributylstannane-initiated radical cyclization of **75** gave bicyclic ester **76** (Scheme 11). Selenation of the ester **76** followed by selenoxide elimination led to a 1:6 mixture of the isomeric tetra- and tri-substituted (desired) α,β–unsaturated esters **77**. Ester **77** was reduced to an allylic alcohol, which was then esterified with phenylacetic acid to give **78**. The ethyl ether in **78** was replaced with a pivaloate ester, a better leaving group, through hydrolysis of acetal to hemiacetal, followed by esterification with trimethylacetyl chloride. The transannular alkylation was carried out by forming a silyl ketene acetal followed by cyclization using trimethylsilyl triflate to give a single isomer of the lactone

80. Claisen rearrangement was achieved easily via the silyl enol ether of the lactone to give acid **81**. The stereochemistry of acid **81** was confirmed by the formation of a single bromolactone **82** upon treatment with bromine.



Scheme 11

This highly stereoselective assembly of **81**, which represents a significant portion of the carbon skeleton of gelsemine, has not been followed up with an answer to the challenge of introducing the two amine functions necessary for the synthesis of (**1**).

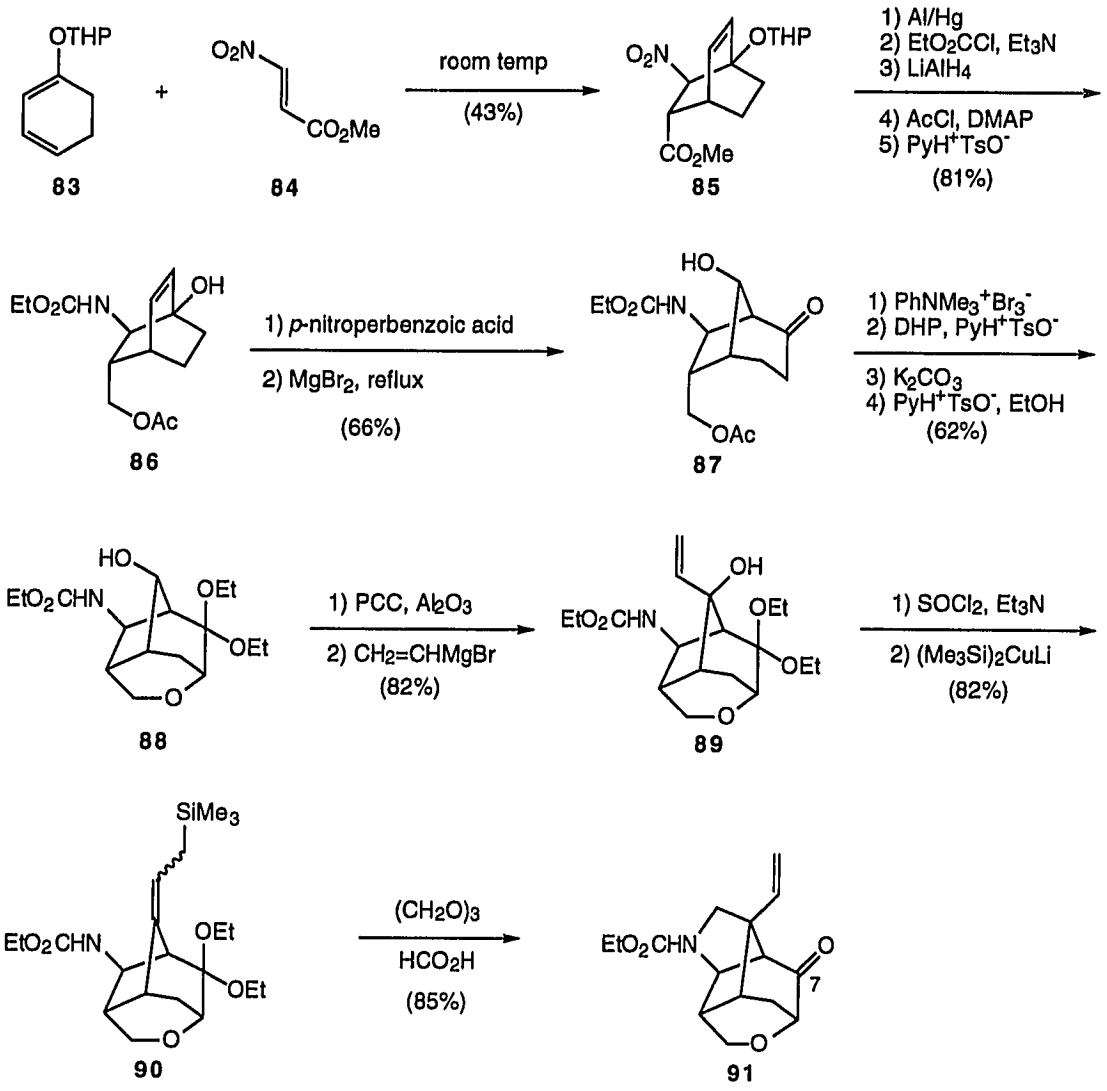
Fleming's Approach[26]

Ian Fleming could be acclaimed as one of the pioneers who systematically pursued the total synthesis of gelsemine. His efforts convincingly demonstrate the effectiveness of organosilicon chemistry for the construction of quaternary centers in complicated molecular structures.

Fleming's central intermediate was obtained starting with a Diels-Alder reaction between β-nitroacrylate **83** and the tetrahydropyranyl (THP) enol ether **84** to give crystalline adduct **85** (Scheme 12). The nitro group of **85** was reduced with aluminum amalgam, and the resulting amine was protected as the ethyl carbamate. The methyl ester was reduced to alcohol, which was blocked as its acetate, and the THP group was removed to give tertiary alcohol **86**. The rearrangement of the bicyclo[2.2.1]octane framework (**86**) to the bicyclo[3.2.1]octane system (**87**) was accomplished by successive epoxidation of **86** and treatment of the resulting epoxide with magnesium bromide. Formation of the tetrahydropyran ring was achieved in a four step sequence: α–bromination of the ketone, THP protection of the secondary alcohol, hydrolysis of acetate, and acid treatment in the presence of ethanol, to give the tricyclic ketal **88**. Oxidation of the secondary alcohol **88** followed by treatment of the resulting ketone with vinylmagnesium bromide provided tertiary alcohol **89**. Chlorination of **89** with thionyl chloride gave an allyl chloride, which was then converted to allylsilane **90** to set the stage for pyrrolidine ring formation. Reaction of silane **90** with trioxane in formic acid yielded the tetracyclic ketone **91** in good yield.

The assembly of the spiro-indolinone on ketone **91** has been addressed in two model studies, however, conversion of **91** to the target gelsemine has not

yet been worked out. As observed by Fleming, "It seems that we had no luck



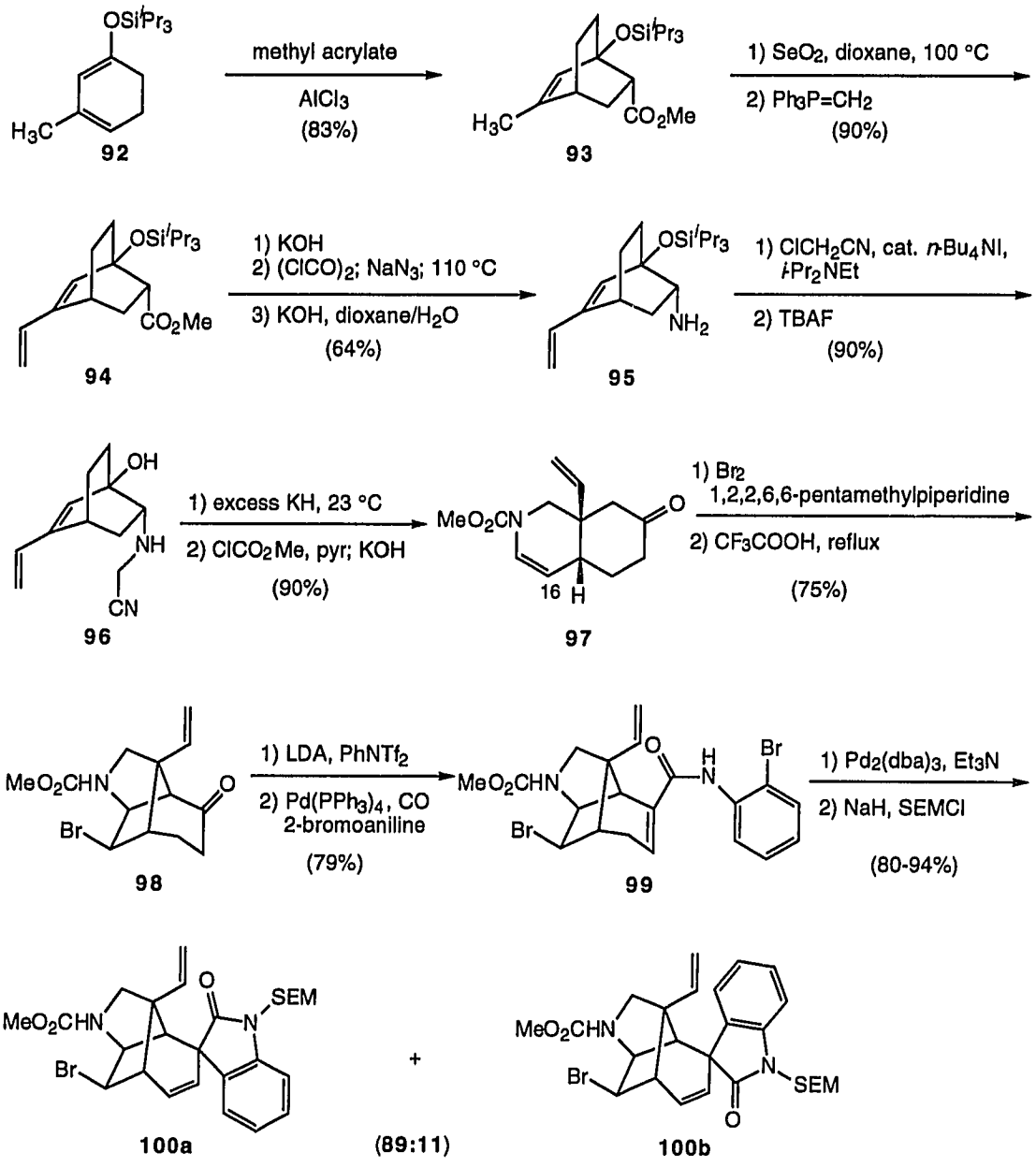
Scheme 12

in this work: every step has been a hard won battle." This underscores the difficulties associated with the approach of introducing the indolinone moiety through C-7 ketone in the presence of the cage system, as demonstrated also in Johnson's synthesis.

Overman's Approach[27]

Overman has made tremendous contributions to the synthesis of complicated alkaloids by discovering the aza-Mannich-Cope rearrangement. The utility of this reaction was demonstrated in his synthetic studies on gelsemine. He also developed intramolecular variation of the Heck reaction for stereoselective construction of the spiro-indolinone unit. It will be recalled that this transformation was utilized by Speckamp in his gelsemine synthesis.

Aluminum chloride-catalyzed stereoselective Diels-Alder reaction of cyclohexadiene **92** with methyl acrylate afforded the bicyclo[2.2.1] compound **93** (Scheme 13). The terminal vinyl group was readily introduced by selenium dioxide oxidation of **93**, followed by Wittig methylenation of the resulting aldehyde to give **94**. Then, hydrolysis of the ester, acid chloride formation, sodium azide treatment, and Curtius rearrangement of the acyl azide furnished the primary amine **95**. Cyanomethylation of **95** followed by removal of the silyl protecting group set the stage for the anionic aza-Cope rearrangement of bicyclo[2.2.1] system **96**, achieved by treatment with excess potassium hydride at room temperature. The reaction mixture was quenched with ethyl chloroformate, and selective cleavage of the enol carbonate furnished the bicyclic keto ene-carbamate **97**. Bromine was introduced at the electron-rich C-16 position to allow eventual elaboration of the tetrahydropyran ring of gelsemine. Immediate cyclization of the bromide afforded the tricyclic product **98**. Conversion of ketone **98** to enol triflate followed by carbonylation in the presence of 2-bromoaniline provided acrylamide **99**. The amide **99** was then protected as its SEM derivative to optimize the stereoselectivity of the following Heck reaction. This step was best conducted under catalysis by



Scheme 13

tris(dibenzylideneacetone)dipalladium without added phosphine ligand, in toluene, to afford spiro-indolinones **100a** and **100b** in a ratio of 9:1. In related studies, Overman and co-workers also reported the asymmetric synthesis of

simple spiro-indolinones by palladium-catalyzed cyclization in the presence of a chiral ligand, (*R*)-(+)-BINAP.

Overman's brilliant approach remains to be parlayed into a total synthesis, seemingly because of various obstacles encountered after the stage of **100**, even though it produced the most advanced gelsemine intermediate prior to the publication of the three successful total syntheses.

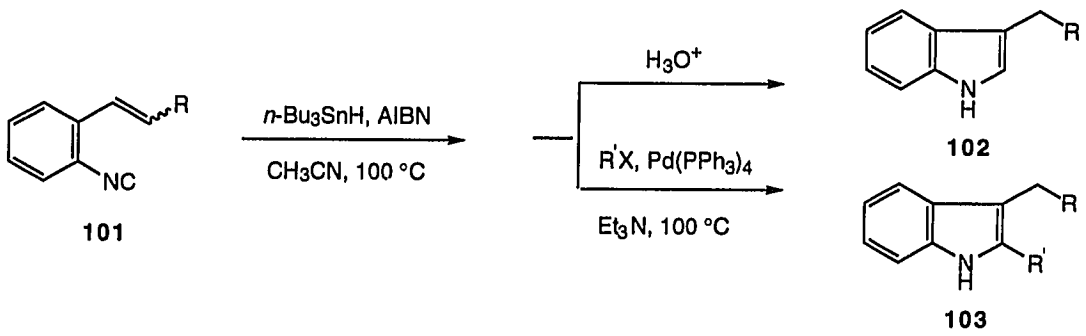
In summary, none of the three known total syntheses of (**1**) address the issue of controlling the stereochemistry of the spiro center of the indolinone in a satisfactory manner. Our goal, therefore, was to achieve a completely stereocontrolled total synthesis of gelsemine.

Chapter III

Stereocontrolled Total Synthesis of (±)-Gelsemine

Two major challenges faced us at the onset of our synthetic studies on gelsemine (**1**) in early 1993: the stereoselective construction of the critical spiro center of the indolinone, and the difficulty of performing intermolecular reactions in the sterically demanding cage system. Accordingly, it seemed adorable to incorporate most of the structural fragments in the earlier stage of the synthesis.

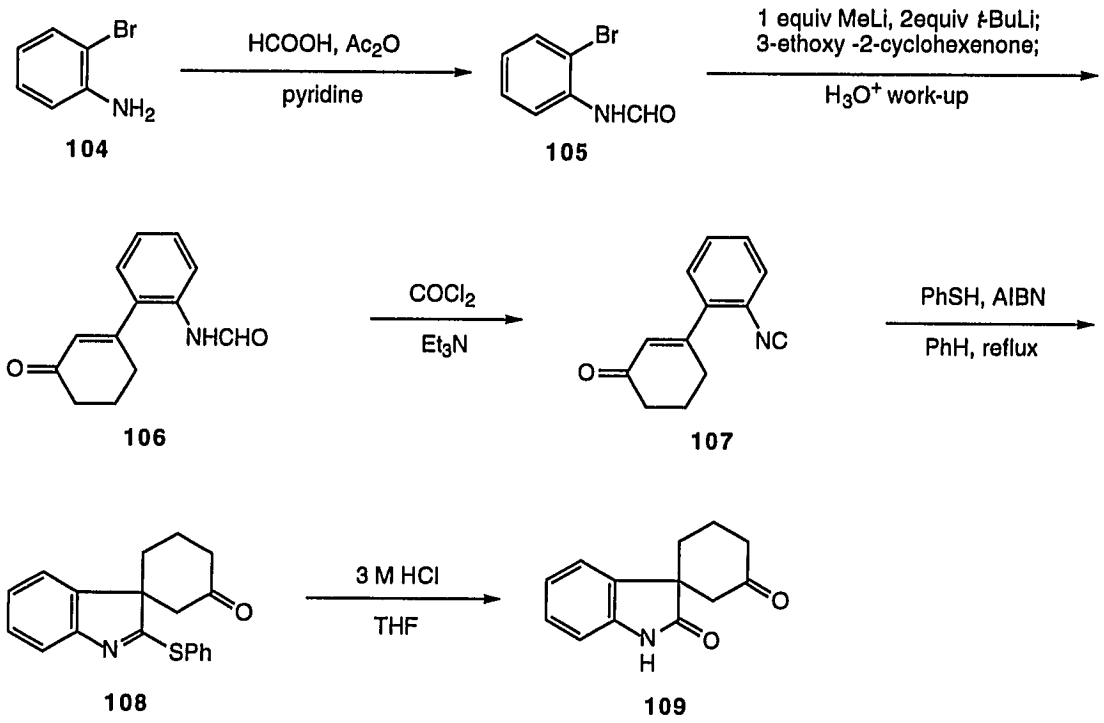
In 1994, a novel tin-mediated indole synthesis was reported from our laboratory.[28] Reaction of *o*-isocyano styrene derivatives **101** with tributyltin hydride and a catalytic amount of AIBN gave 3-substituted indoles **102**, upon acidic work-up, in good to excellent yield (Scheme 14). This cyclization could also be utilized for the synthesis of 2,3-disubstituted indoles **103** through one-pot palladium-mediated Stille coupling of 2-stannylindole intermediates with reactive halides.



Scheme 14

In a separate, unpublished result, we found that this type of radical cyclization could also be applied to spiro-indolinone synthesis, as illustrated in Scheme 15. Formylation of commercially available 2-bromoaniline **104** gave

formamide **105**. An aryllithium species, generated from sequential treatment of bromide **105** with methyl lithium and *t*-butyl lithium,[29] was quenched with 3-ethoxy-2-cyclohexenone to give an alcohol. Upon acidic work-up, elimination of ethanol furnished the enone **106**. Conventional dehydration of formamide **106** with phosgene afforded the isocyanide **107** for the designated radical cyclization, which occurred to give **108** upon refluxing isocyanide **107** with thiophenol in the presence of catalytic AIBN. This radical reaction is believed to proceed as the tin-mediated indole synthesis. Upon acidic hydrolysis, the desired spiro-indolinone **109** was obtained.

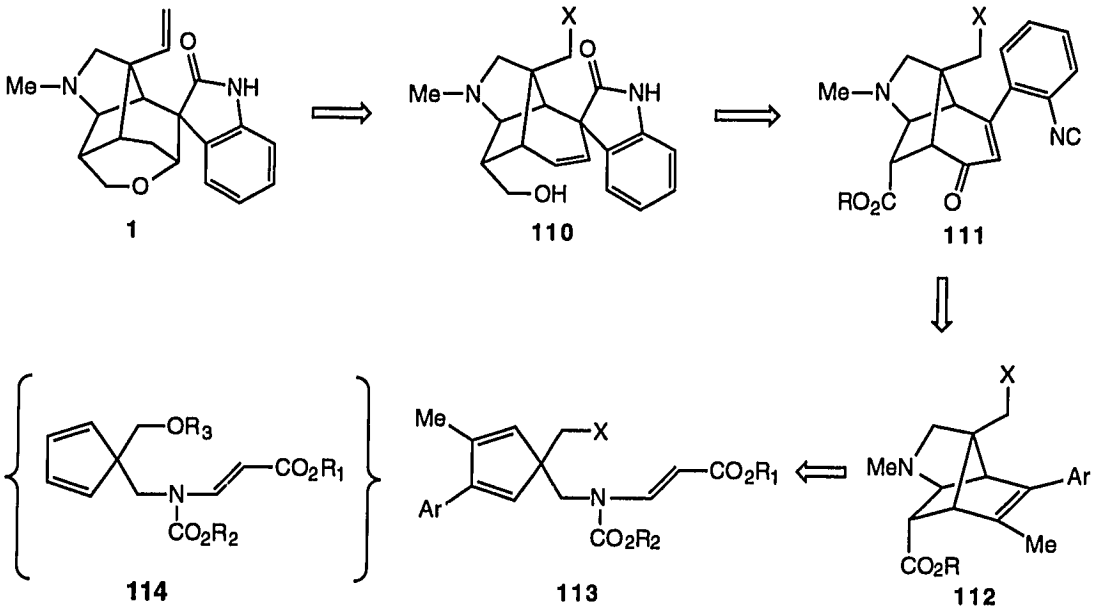


Scheme 15

This radical cyclization for simple spiro-indolinone synthesis has a definite advantage over the existing procedure published by Jones and co-workers[30], which affords only moderate selectivity in favor of indolinone over 2-

dihydroquinolone formation. We envisioned that our newly developed spiro-indolinone synthesis could be instrumental in gelsemine synthesis, even though we did not know how stereoselective the cyclization would be in the real gelsemine system.

Our first retrosynthetic analysis was formalized based on the above model studies, as shown in Scheme 16. The vinyl group of gelsemine (**1**) can be obtained from an alcohol. The tetrahydropyran ring can be formed through oxymercuration of olefin **110**,[23] while the spiro-indolinone would be synthesized through radical cyclization of *o*-isocyanophenyl enone **111**. The bicyclo[3.2.1]enone can be derived from ring cleavage and ring reclosure of the bicyclo[2.2.1] compound **112**. Clearly, tetracyclic intermediate **112** can be obtained from intramolecular Diels-Alder reaction of the 5,5-disubstituted cyclopentadiene derivative **113**.

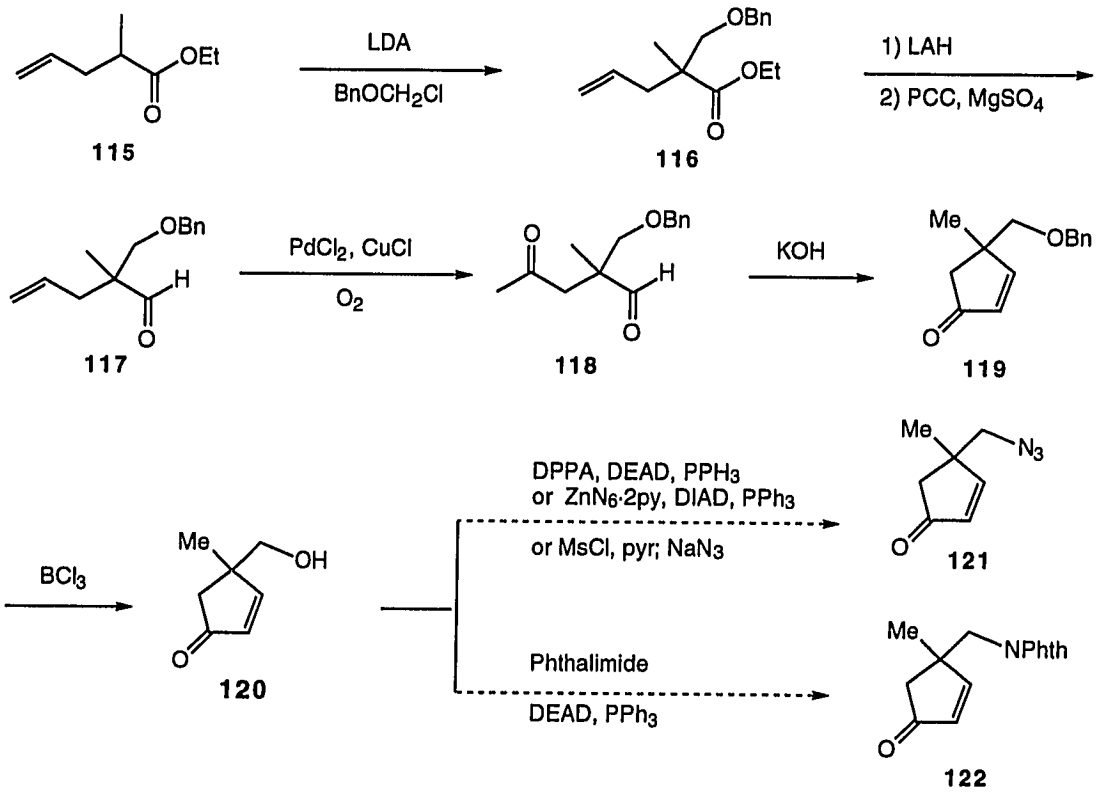


Scheme 16

At the outset of our studies, our primary efforts were focused on the synthesis of the substrate **113** for Diels-Alder reaction, and the less complicated molecule **114** was chosen as the substrate for model studies.

Model Studies I

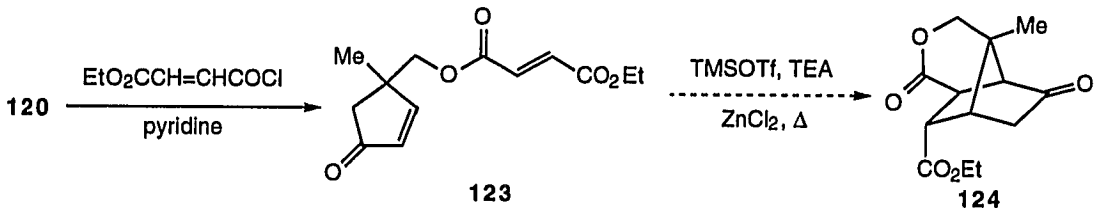
Cyclopentenone **119** was prepared starting with the readily available ethyl 2-methyl-4-pentenoate, **115**, as shown in Scheme 17. Formal hydroxymethylation of the lithium enolate of ester **115** with chloromethyl benzyl ether introduced the quaternary carbon in **116**. Reduction of the ester followed by pyridinium chlorochromate (PCC) oxidation of the resulting alcohol gave aldehyde **117**. Wacker oxidation[31] of olefin **117** with $PdCl_2$ and



Scheme 17

molecular oxygen furnished γ-ketoaldehyde **118**. Intramolecular aldol condensation gave the cyclopentenone **119**. To our disappointment, all attempts to introduce nitrogen functions at the neopentyl position of the alcohol **120** after removal of the benzyl group failed, including Mitsunobu reactions and alcohol activation followed by substitution.

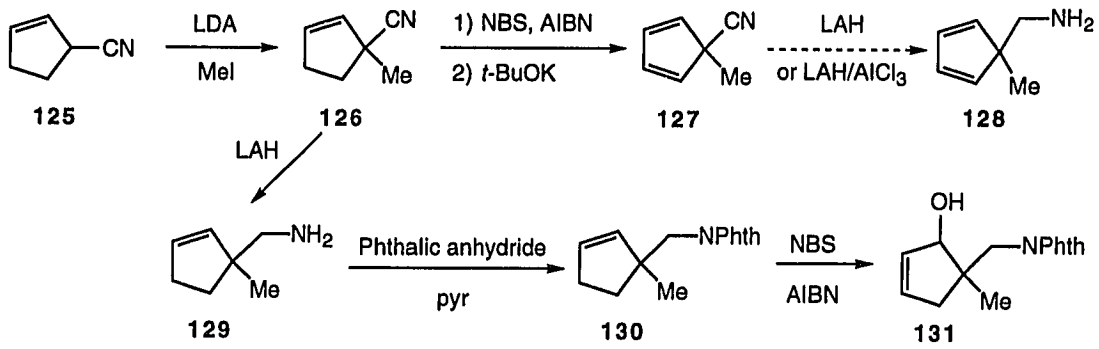
We then turned our attention to intermediates of the type **124**, with the hope that the δ-lactone could be converted to a pyrrolidine ring later on. Condensation of alcohol **120** with ethyl fumaryl chloride gave ester **123**, a plausible substrate for intramolecular Diels-Alder reaction (Scheme 18). Unlike the facile cyclization reported by Snowden,[32] prolonged heating of enone **123** with trimethylsilyl triflate and Et_3N did not yield any cycloadduct **124**. The failure of the cyclization might be attributed to the strained transition state of the cycloaddition involving the ester, which was different from the simple carbon tether used in Snowden's total synthesis of (±)-sativene.[32]



Scheme 18

The failure of the functionalization of the neopentyl position of alcohol **120** implied that it might be better to start with a nitrogen function already attached to the cyclopentane ring. We explored the route shown in Scheme 19. Methylation of readily available cyanide **125**[33] yielded a mixture of regioisomers, from which the desired nitrile **126** could be secured by fractional distillation. Although allylic bromination of **126** apparently gave a mixture of the regio- and stereo-isomers, dehydrobromination of the mixture with potassium *t*-

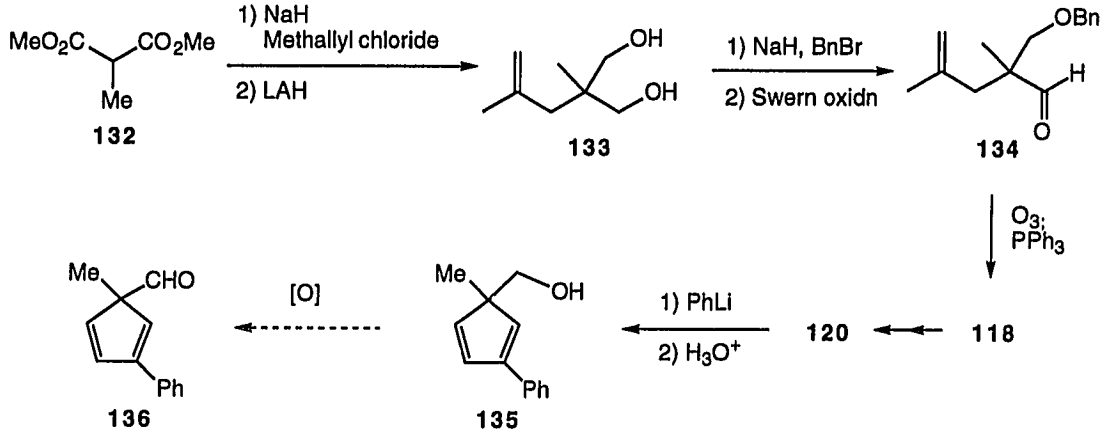
butoxide (*t*-BuOK) provided exclusively the desired 5,5-disubstituted cyclopentadiene **127**. Attempts at reducing nitrile **127** to amine **128** were unsuccessful, presumably due to the instability of the resulting aminomethyl cyclopentadiene. An alternative way to make the amine was also sought (Scheme 19). Reduction of nitrile **126** gave a stable amine **129**, which was blocked as phthalimide **130**. Attempted bromination of **130** with *N*-bromosuccinimide (NBS) failed to give the desired bromide, producing instead allyl alcohol **131**.



Scheme 19

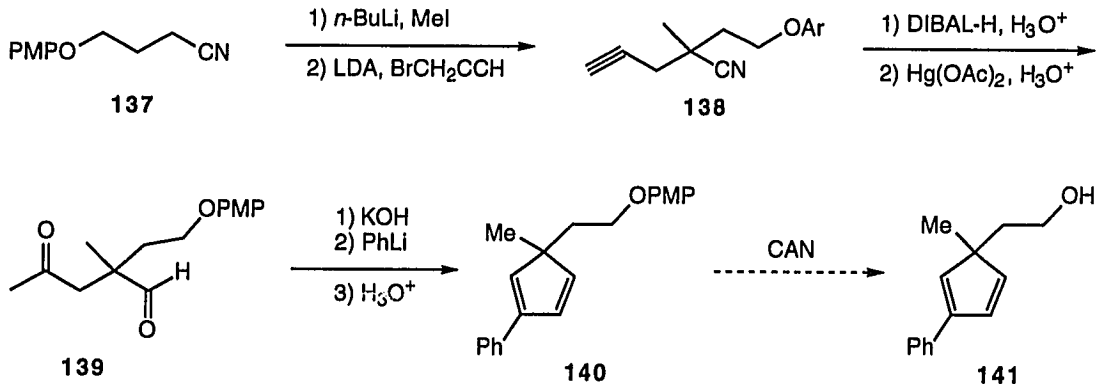
We also attempted to secure cyclopentadiene **114** from dimethyl methylmalonate **132** (Scheme 20). Alkylation of malonate with methallyl chloride followed by reduction of the methyl esters gave diol **133**. Monoprotection of the diol proceeded with a fair degree of selectivity, and a subsequent Swern oxidation[34] gave aldehyde **134**. This aldehyde interfered somewhat during ozonolysis of olefin **134**, however, cyclopentenone **120** was obtained through normal aldol condensation from ketoaldehyde **118**. The encouraging news was that the 1,2-addition of phenyl lithium to the enone and the subsequent dehydration gave the appropriately substituted cyclopentadiene **135**. We were hoping that the nitrogen function could be introduced through reductive amination of the aldehyde **136**, but it seemed that the

cyclopentadiene **135** was too reactive to be further manipulated. In particular, attempted oxidation of alcohol **135** caused extensive decomposition.



Scheme 20

Since the cyclopentadiene carboxaldehyde was very difficult to handle, the next logic thought was to change it to acetaldehyde, namely a homolog of **136**, and this idea was quickly tested. Successive alkylation of butyronitrile **137** with methyl iodide and propargyl bromide gave nitrile **138** (Scheme 21). After the reduction of nitrile to aldehyde, mercury-assisted hydration of the acetylene provided γ-ketoaldehyde **139**. Aldol condensation followed by

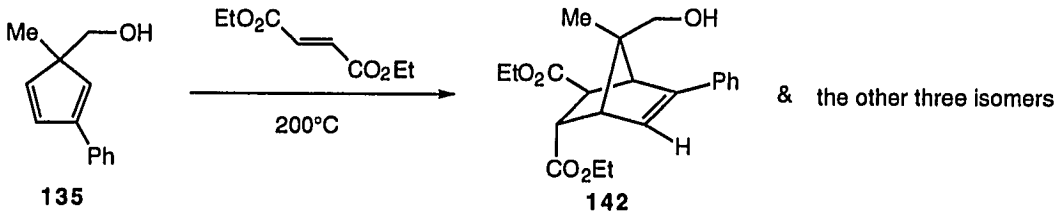


Scheme 21

phenyllithium addition and elimination furnished cyclopentadiene **140**. Unfortunately, removal of the *p*-methoxyphenyl (PMP) group in **140** caused extensive decomposition. The exchange of the PMP ether with a benzyl ether did not make a difference in the overall result.

Model Studies II

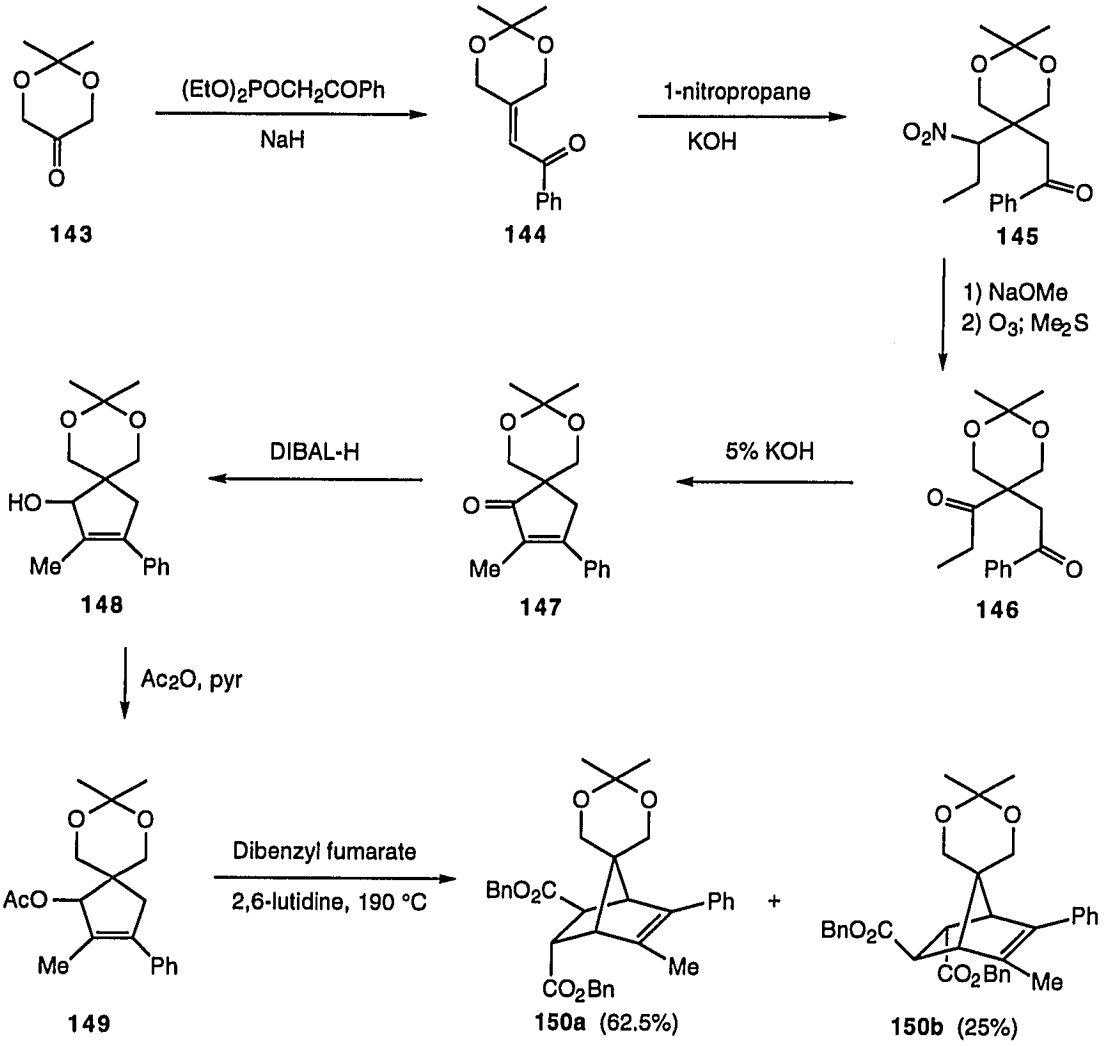
At this stage, the lability of the cyclopentadiene substrate forced us to change our initial synthetic plan from intramolecular to intermolecular Diels-Alder reaction. Simple Diels-Alder reaction with diene **135** provided very promising results (Scheme 22). Four possible cyclization products, including **142**, were obtained as an unseparable mixture. The next issue became how to improve the stereoselectivity of the Diels-Alder reaction. We conceived that introduction of mirror symmetry in the diene would reduce the number of possible Diels-Alder products down to two.



Scheme 22

Horner-Emmons reaction of the readily available 2,2-dimethyl-1,3-dioxan-5-one **143**[35] with a phosphonate derived from phenacyl bromide gave enone **144**. In order to minimize the isomerization of the exocyclic enone to the endocyclic olefin, enone **144** was immediately subjected to a Michael addition with 1-nitropropane to establish the quaternary carbon of **145**. Conversion of nitro to nitronate followed by ozonolysis[36] furnished diketone **146**, aldol condensation of which provided enone **147**. 1,2-Reduction of **147** with

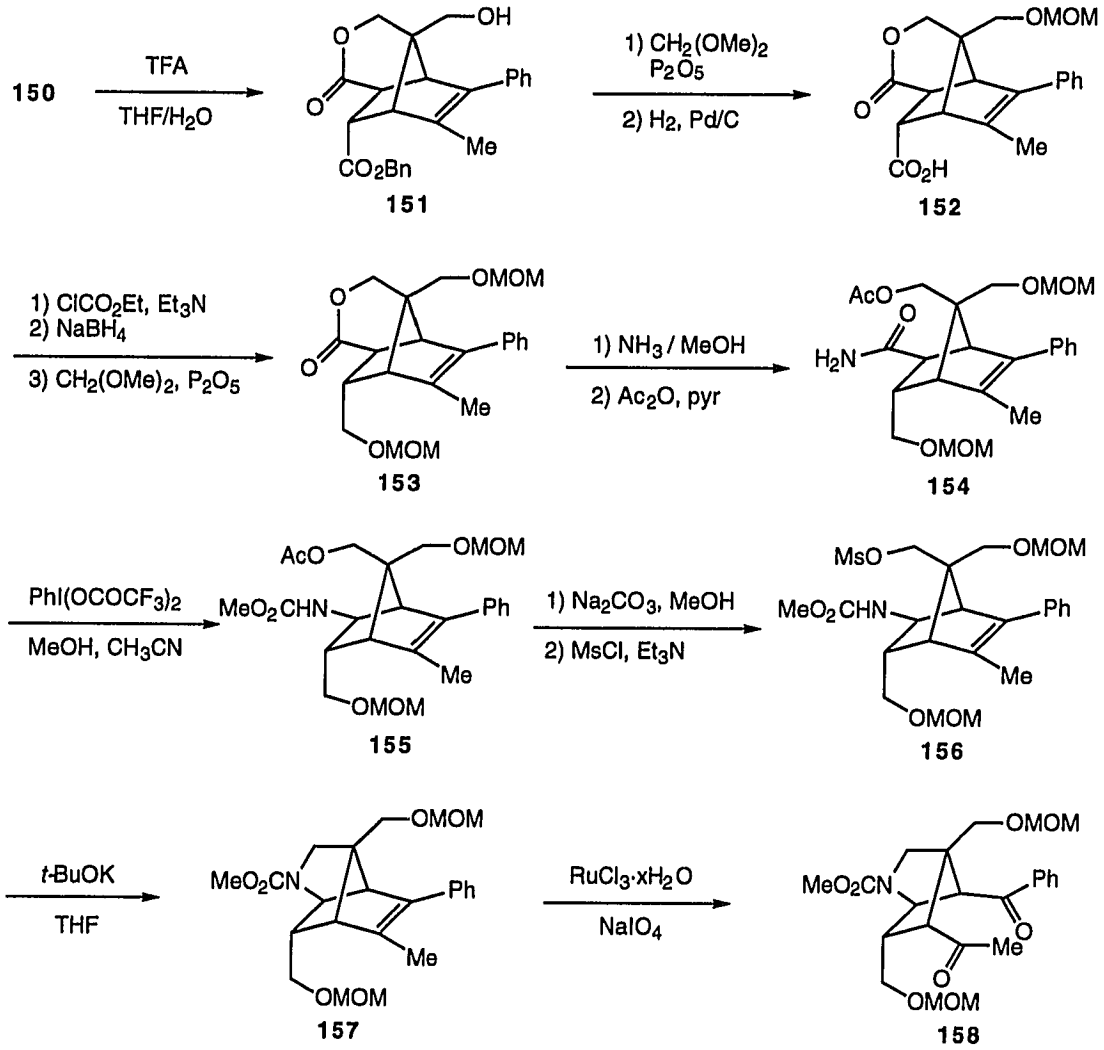
diisobutylaluminum hydride[37] (DIBAL-H) gave allylic alcohol **148** cleanly. Even though conventional dehydration could directly provide the desired cyclopentadiene, we anticipated instability problems with the resulting diene. A one-pot reaction protocol was thus developed. The alcohol was first moderately activated as its acetate **149**. When **149** was heated with dibenzyl fumarate and 2,6-lutidine at 190 °C, elimination followed by *in situ* Diels-Alder reaction



Scheme 23

gave two stereoisomeric cycloadducts in a ratio of 2.5 to 1 favoring the desired isomer.

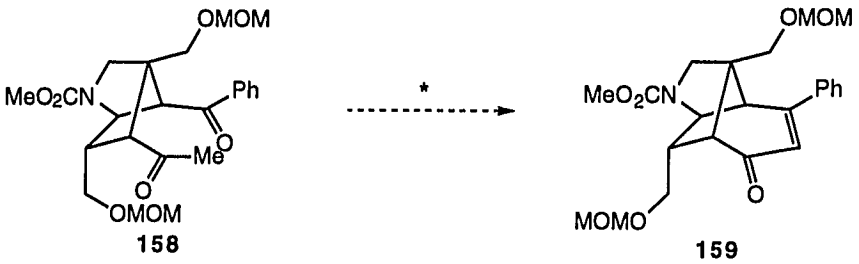
Further manipulation of compound **150** was rather straightforward. Acidic hydrolysis of acetonide **150** caused facile lactonization to give hydroxymethyl lactone **151** (Scheme 24). Then the alcohol was protected as its methoxymethyl ether,[38] and the benzyl ester was removed by hydrogenolysis. Fortunately, the two isomeric acids **152** could be separated at



Scheme 24

this stage by fractional crystallization from ethanol. The desired carboxylic acid **152** was then reduced through its mixed anhydride,[39] and the resulting primary alcohol was also blocked as its methoxymethyl ether **153**.

The tetra-substituted olefin in **153** was readily oxidized to the diketone by ruthenium tetroxide, but the subsequent aldol reaction of the resultant diketone was hampered by the presence of the base-sensitive lactone. Accordingly, the lactone was first converted to a pyrrolidine ring (Scheme 24). The lactone was cleaved with ammonia and the resultant alcohol was trapped as its acetate **154**, as mesylation of the alcohol regenerated the δ-lactone. Modified Hofmann rearrangement of primary amide **154** using *I,I*-bis(trifluoroacetoxy)iodobenzene[40] in the presence of methanol gave the methyl carbamate **155**. The acetate was hydrolyzed, and the emerging alcohol was activated by mesylation. When compound **156** was treated with *t*-BuOK, smooth ring closure took place to give tricyclic intermediate **157**. Diketone **158** was secured using Sharpless oxidative cleavage of the olefin **157**,[41] which set the stage for the critical ring reclosure.



* Conditions tried for ring closure:
1)Basic: NaOH/EtOH; K_2CO_3/MeOH; BaO/MeOH; KOH/DMSO; Al_2O_3/tol; DBU/CH_2Cl_2; NaH/DMSO; *t*-BuOK/DMSO; KH/THF; *t*-BuOK/THF, -78 °C; LDA, -78 °C.
2) Acidic: TFA/C_6H_6; AcOH/H_2SO_4; *p*-TsOH/C_6H_6; pyrrolidine/AcOH
3) Silyl enol ether formation: LDA, TMSCl or TBSOTf; Et_3N, TMSOTf

Scheme 25

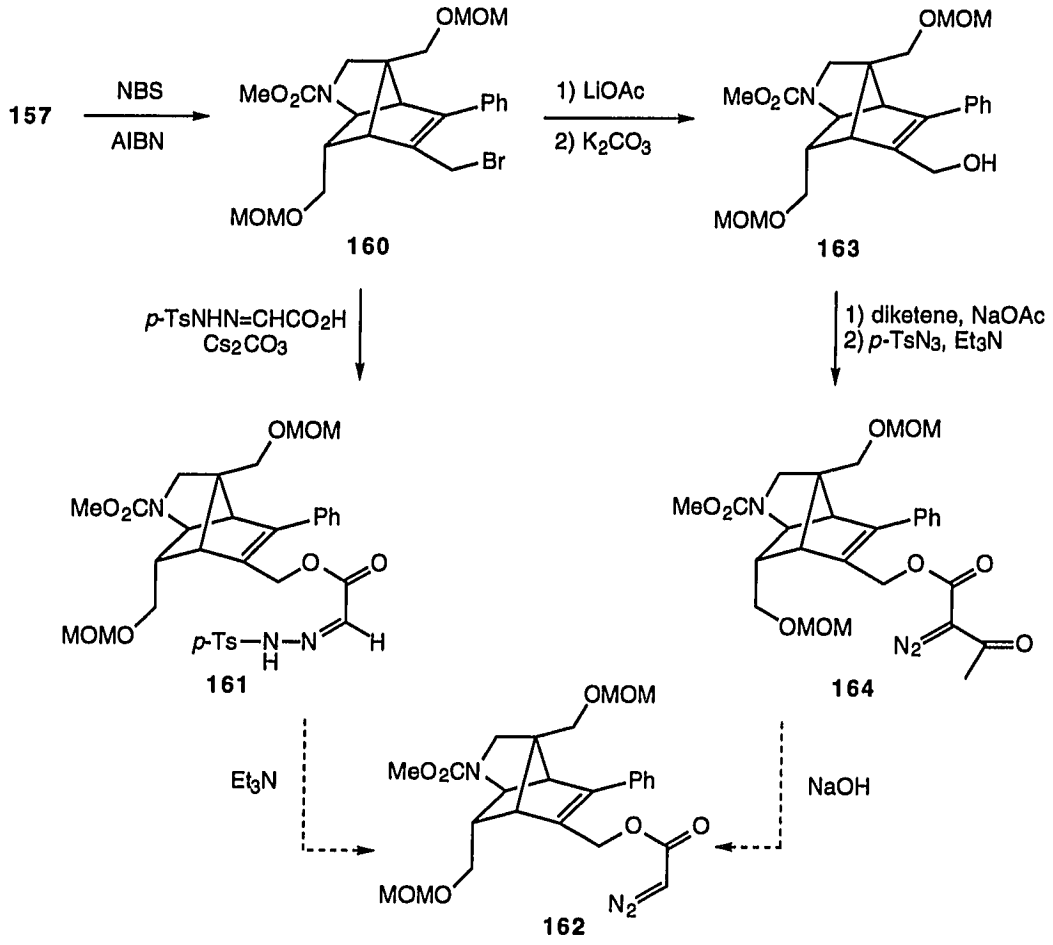
To our great disappointment, under all the conditions summarized in Scheme 25, the intramolecular aldol condensation of **158** to **159** could not be realized. The major reaction that occurred instead was a rapid epimerization of the two ketones to the thermodynamically more stable configuration. Furthermore, there was no evidence of equilibration back to the original isomer, precluding cyclization even after prolonged reaction time. Attempts to form a kinetic silyl enol ether of the methylketone **158** with lithium diisopropylamide (LDA) or Et_3N led to either no reaction or partial epimerization.

Model Studies III

Tempted by the possibility of effecting a ring expansion via a cyclopropane, we were delighted to find that allylic oxidation of **157** could be easily achieved (Scheme 26). Radical bromination of **157** under standard conditions gave bromide **160**. Treatment of **160** with the cesium salt of glyoxylic acid tosylhydrazone[42] afforded the hydrazone **161**. Unfortunately, we were unable to eliminate the tosyl group to generate diazoacetate **162** with base. The bromide **160** was therefore transformed into allylic alcohol **163** through its acetate. Subsequent condensation with diketene produced an acetoacetate ester, which upon Regitz diazo transfer reaction with *p*-toluenesulphonyl azide,[43] yielded the diazo keto-ester **164**. The subsequent deacetylation to form diazoacetate **162** was unsuccessful.

It was felt that ring expansion could also be achieved through bimolecular cyclopropanation of the olefin and subsequent rearrangement. We then prepared Diels-Alder adduct **166** from **144**, following almost the same synthetic pathway of Schemes 23 and 24 (Scheme 27). A notable exception is

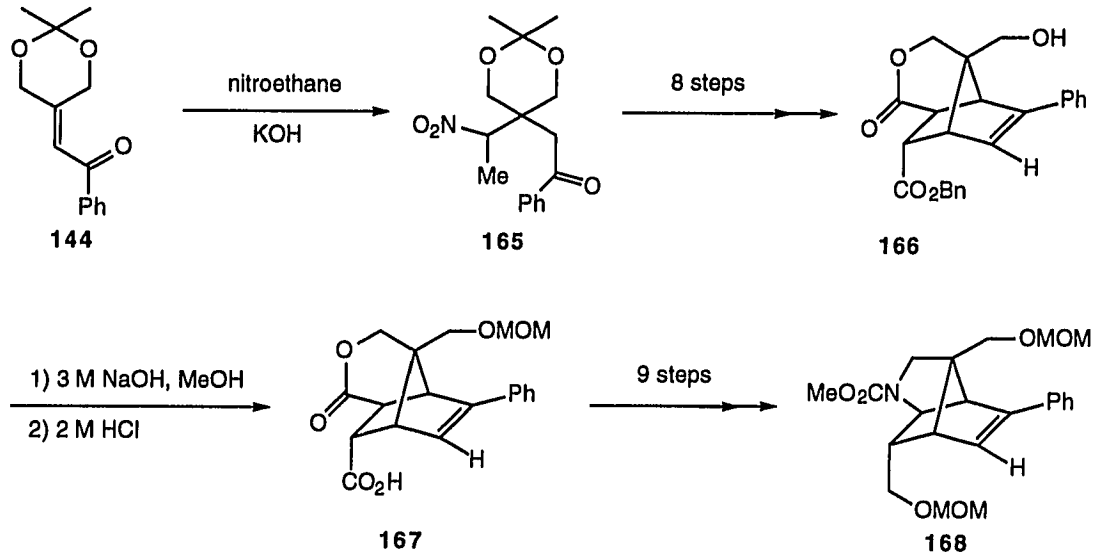
that nitroethane was used in this sequence instead of 1-nitropropane. This time



Scheme 26

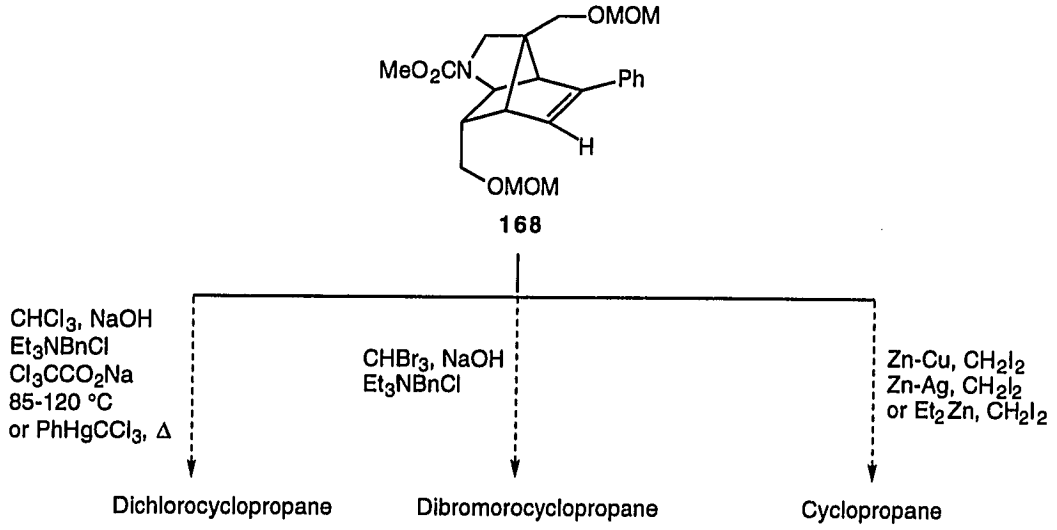
the stereoselectivity of the [4+2] cycloaddition improved from 2.5/1 to 4/1, suggesting that the selectivity stemmed, at least partially, from the steric difference between phenyl and methyl (hydrogen). Since hydrogenolysis would reduce the olefin, the benzyl ester was removed by hydrolysis to give carboxylic acid **167**. Desmethyl tetracyclic compound **168** was synthesized in nine steps from acid **167**. Along the reaction scheme towards the cage compound **168**, we tried a variety of reactions, such as carbene insertion and

cyclopropanation. In most cases, either no change or decomposition of starting materials was observed.



Scheme 27

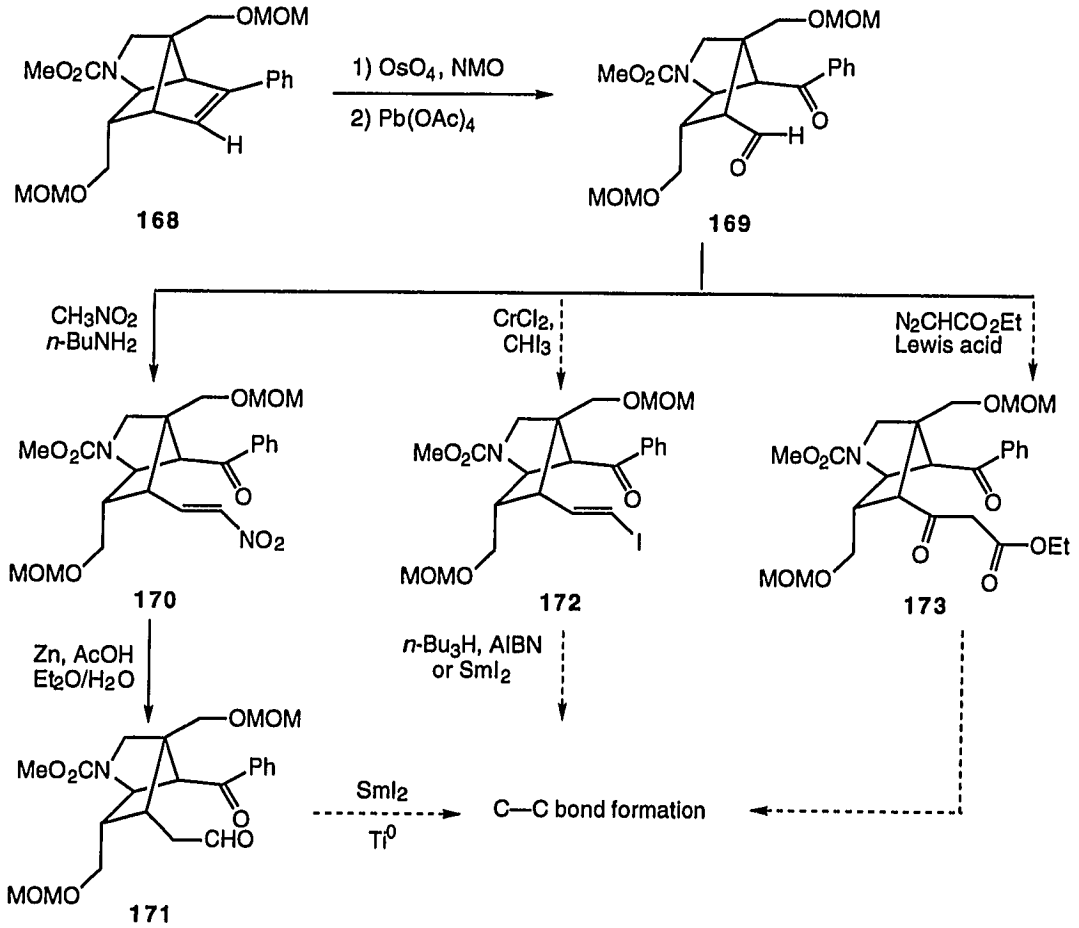
Much attention was focused on the important model compound **168**. Carbene insertion protocols were tested first. Phase transfer conditions with



Scheme 28

either chloroform or bromoform gave ambiguous results (Scheme 28). The starting material decomposed during thermolytic generation of dichlorocarbene. Simmons-Smith cyclopropanation, under various conditions, also failed to yield any desired products.

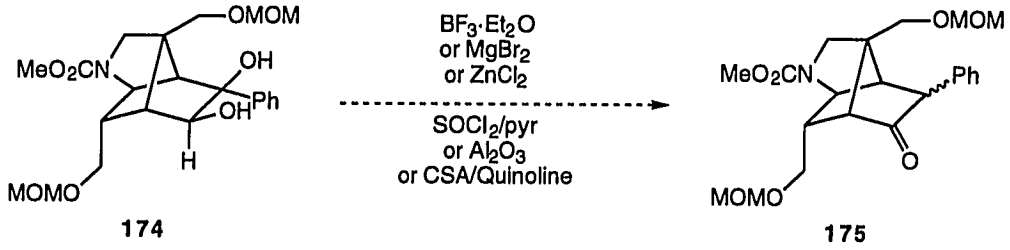
We then envisioned that homologation of the aldehyde **169** derived from ring cleavage could pave new ways for cyclizations other than aldol condensation. Unfortunately, Lemieux-Johnson oxidation cleavage[44] of olefin **168** failed, probably due to over-oxidization. Ozonolysis tended to form an epoxide from the olefin as the major product. Upjohn cis-dihydroxylation using



Scheme 29

osmium tetroxide (OsO_4) in the presence of *N*-methylmorpholine *N*-oxide (NMO)[45] followed by Criegee glycol cleavage[46] gave keto-aldehyde **169** in good yield (Scheme 29). Primary amine-catalyzed conversion of aldehyde **169** to nitroalkene **170** followed by reductive hydrolysis did yield some homologated aldehyde **171**. However, the intended pinacol-type coupling[47] could not be realized: samarium(II) iodide (SmI_2) treatment gave no reaction and low valent titanium treatment caused decomposition of the starting material. Vinyl iodide **172** was obtained from aldehyde **169** using Takai's procedure.[48] Unfortunately, neither radical cyclization nor Barbier-type cyclization[49] promoted by SmI_2 gave any of the desired product. We also failed to convert the aldehyde to a β-ketoester using the chemistry developed by Roskamp.[50]

At that moment, our attention was shifted to the preparation of the bicyclo[2.2.1]heptanone **175** as a substrate for ring enlargement. Pinacol-type rearrangement[51] of *cis*-diol **174** with Lewis acids, as listed in Scheme 30, failed to yield the desired ketone **175**. We were also unable to eliminate the benzylic alcohol under various conditions shown in Scheme 30.

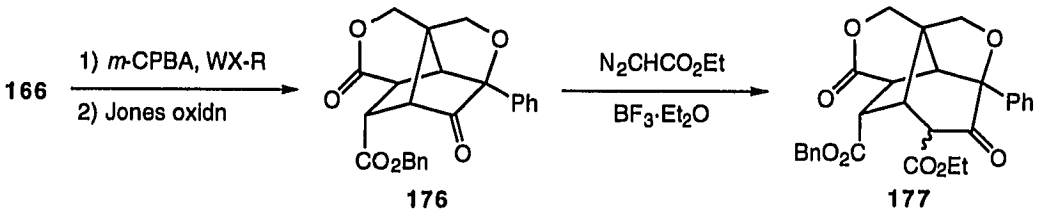


174 **175**

Scheme 30

Ketone **176** was successfully prepared from homoallylic alcohol **166** (Scheme 31). Cyclic ether formation with *meta*-chloroperbenzoic acid (*m*-CPBA) gave tetrahydrofuranyl alcohol, which was oxidized to its corresponding ketone **176** with the Jones reagent. When the ketone was treated with ethyl diazoacetate and Lewis acid, several products were isolated. The

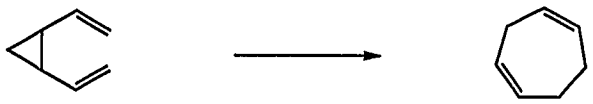
spectroscopic data of the major product **177** were consistent with the desired ring expansion compound. However, this process was not synthetically useful, due to its poor yield.



Scheme 31

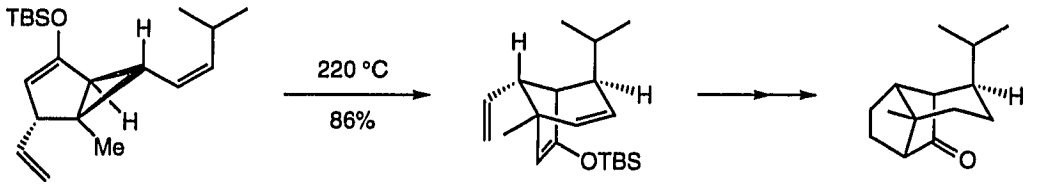
Model Studies IV

Our failure to convert the bicyclo[2.2.1]heptene system to bicyclo[3.2.1]octenone system, as we had intended in our initial synthetic plan, led us to ponder the possibility of making the required bicyclo[3.2.1] compound directly, without going through a bicyclo[2.2.1] intermediate. During this frustrating period, we came up with an interesting idea of applying the well-known divinylcyclopropane-cycloheptadiene rearrangement (Scheme 32) to the construction of the requisite bicyclo[3.2.1] system.



Scheme 32

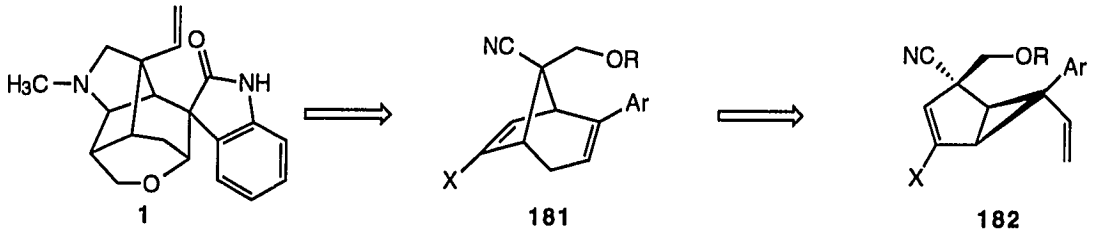
This rearrangement was first reported by Vogel in 1960 and has been shown to have great synthetic utility.[52] A typical example of the construction of the bicyclo[3.2.1] system using this rearrangement was reported by Piers in his synthesis of (±)-sinularene (**180**).[53] Thus, the silyl enol ether **178** rearranged to bicyclo[3.2.1] compound **179** in 88% yield during 4 h at 220 °C (Scheme 33).



178 179 Sinularene (180)

Scheme 33

Tempted by the prospect of synthesizing the long-sought bicyclo[3.2.1] system directly, we revised our initial synthetic strategy. The new retrosynthetic analysis is illustrated in Scheme 34. The gelsemine skeleton could be simplified to bicyclic compound **181**, which has all the functional groups needed for the construction of the target molecule. Bicyclo[3.2.1]octadiene **181** could be synthesized by thermal rearrangement of bicyclic compound **182**.

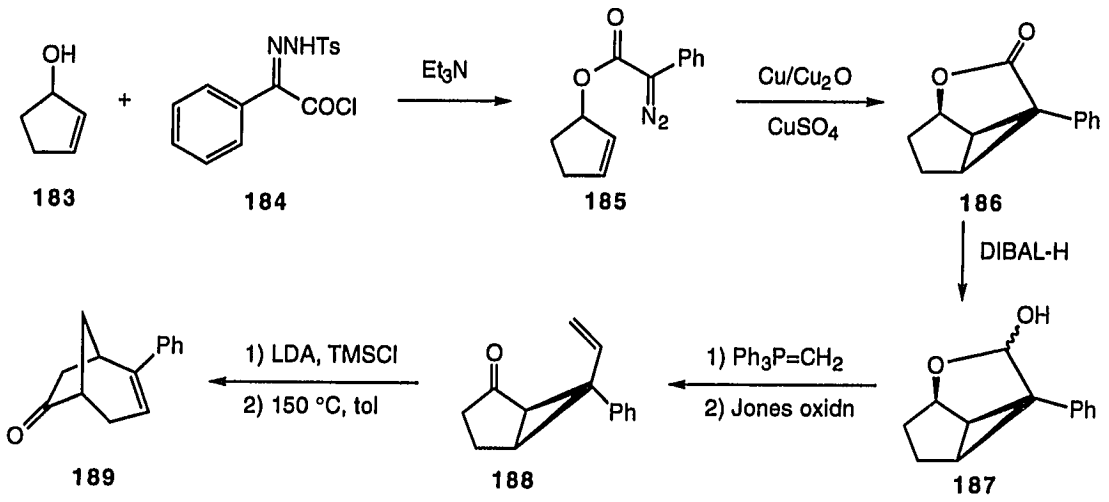


1 181 182

Scheme 34

To test the feasibility of this plan, a simple model study was designed. Treatment of cyclopent-2-en-1-ol **183** with the *p*-toluenesulfonylhydrazone **184** of phenylglyoxalyl chloride[54] and Et_3N gave phenyl diazoacetate **185** (Scheme 35). Copper-catalyzed cyclopropanation provided the tricyclic compound **186**. The lactone **186** was then carefully reduced to lactol **187** with DIBAL-H. After the smooth Wittig olefination of the lactol, Jones oxidation of the resulting alcohol yielded cyclopentanone **188**, which was transformed to its corresponding silyl enol ether under standard conditions. As expected, the

divinylcyclopropane underwent facile rearrangement at 150 °C to give bicyclo[3.2.1]octenone **189**.

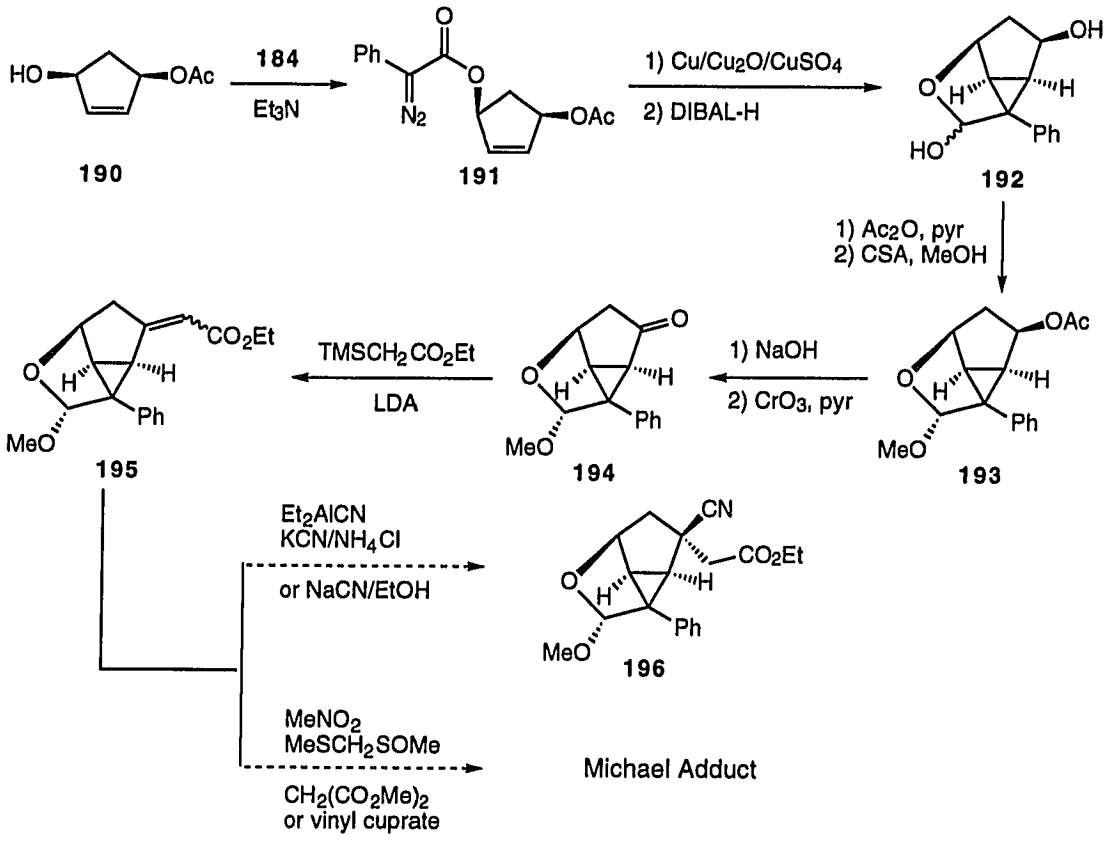


183 **184** **185** **186** **187** **188** **189**

Scheme 35

After this encouraging model study, we focused on the functionalization of the apical carbon with an asymmetric synthesis in mind. Deardorff's 3-acetoxy-5-hydroxycyclopent-1-ene[55] (**190**) was our first choice as the starting material (Scheme 36). Thus, intramolecular cyclopropanation of diazo compound **191** provided a lactone, which could not be selectively cleaved in the presence of acetate. Accordingly, both lactone and acetate were reduced to give **192**. After protection of the alcohols as their acetates, acid catalyzed methanolysis of lactol ester **192** gave mixed acetal **193**. Hydrolysis of acetate followed by Collins oxidation[56] of the resulting alcohol gave cyclopentanone **194**. Peterson-type olefination[57] was the best option for the homologation of the ketone to α,β-unsaturated ester **195**. In contrast, neither Horner-Emmons reaction nor oxidation of the vinyl carbinol prepared by addition of vinylmagnesium bromide to the ketone gave the desired product. Unfortunately, our attempted construction of the quaternary carbon by means of

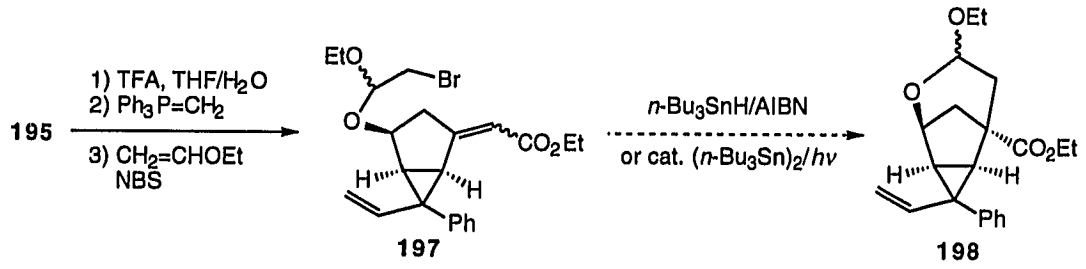
hydrocyanation of α,β-unsaturated ester **195** did not afford any cyanide **196**. Conjugate addition of other nucleophiles was also unsuccessful. The result of these reactions was either cleavage of the ethyl ester or epimerization of the acetal, which could derive from the cleavage and reclosure of the acetal-containing ring.



Scheme 36

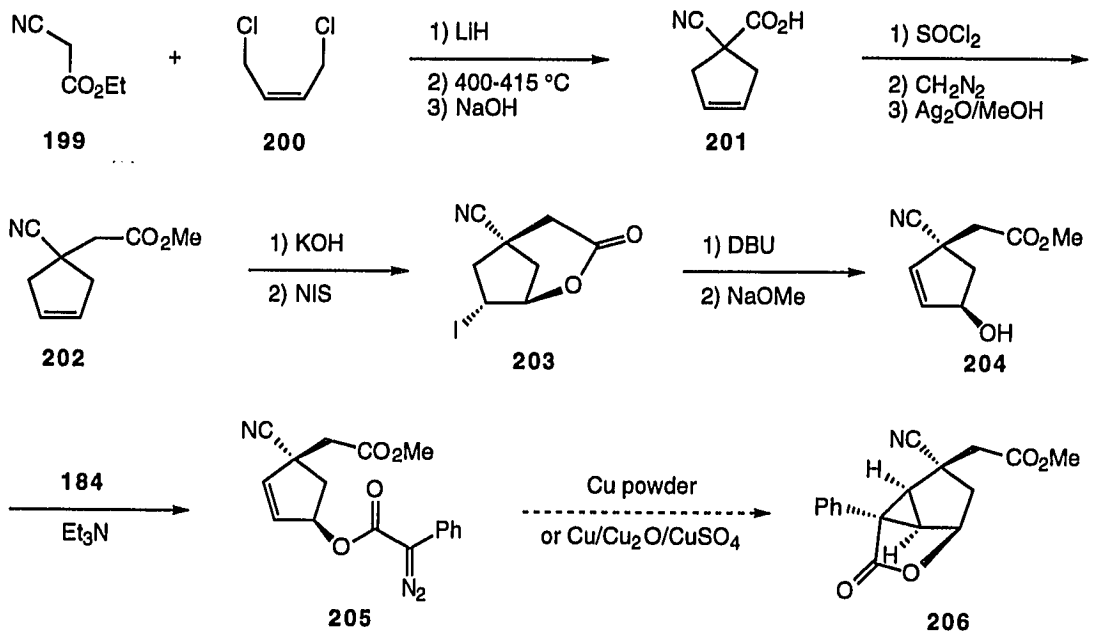
In the hope that intramolecular reaction might overcome the steric hindrance of the β,β-disubstituted olefin, we also tried to form the quaternary carbon through Stork's radical cyclization of a bromoketal[58] (Scheme 37). Hydrolysis of the mixed acetal **195** followed by Wittig olefination of the resultant lactol gave an alcohol, which was treated with ethyl vinyl ether and NBS to give

α-bromoketal **197**. Unfortunately, radical cyclization with tributyltin hydride or with hexabutylditin, under thermal or photochemical conditions, respectively, failed to produce the desired **198**.



Scheme 37

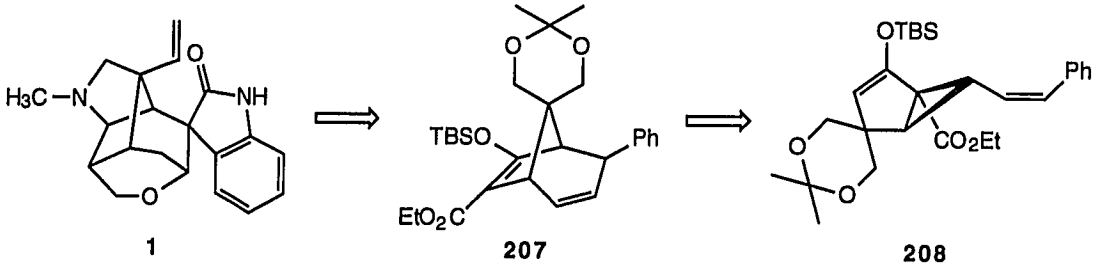
After the failure of nucleophilic and radical addition to the α,β-unsaturated ester, we felt that the establishment of the quaternary carbon should be carried out first. A quick model study was therefore set up (Scheme 38). Condensation between ethyl cyanoacetate **199** and 1,4-dichlorobutene **200** gave a mixture of vinyl cyclopropane and cyclopentene. The mixture could be easily converted to a single cyclopentene by thermolysis at 400-415 °C. Hydrolysis of the ethyl ester gave carboxylic acid **201**. Arndt-Eistert homologation of acid **201** gave methyl cyclopentenylacetate **202**. After hydrolysis of the methyl ester, iodolactonization with excess *N*-iodosuccinimide gave lactone **203** in poor yield. Elimination of iodide with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and subsequent methanolysis of the lactone furnished cyclopentenol **204**. Condensation of alcohol **204** with acid chloride **184** in the presence of Et_3N yielded phenyl diazoacetate **205**. Unlike previous case, no cyclopropanation product **206** could be isolated upon treatment of **205** with $Cu/Cu_2O/CuSO_4$ or copper powder.



Scheme 38

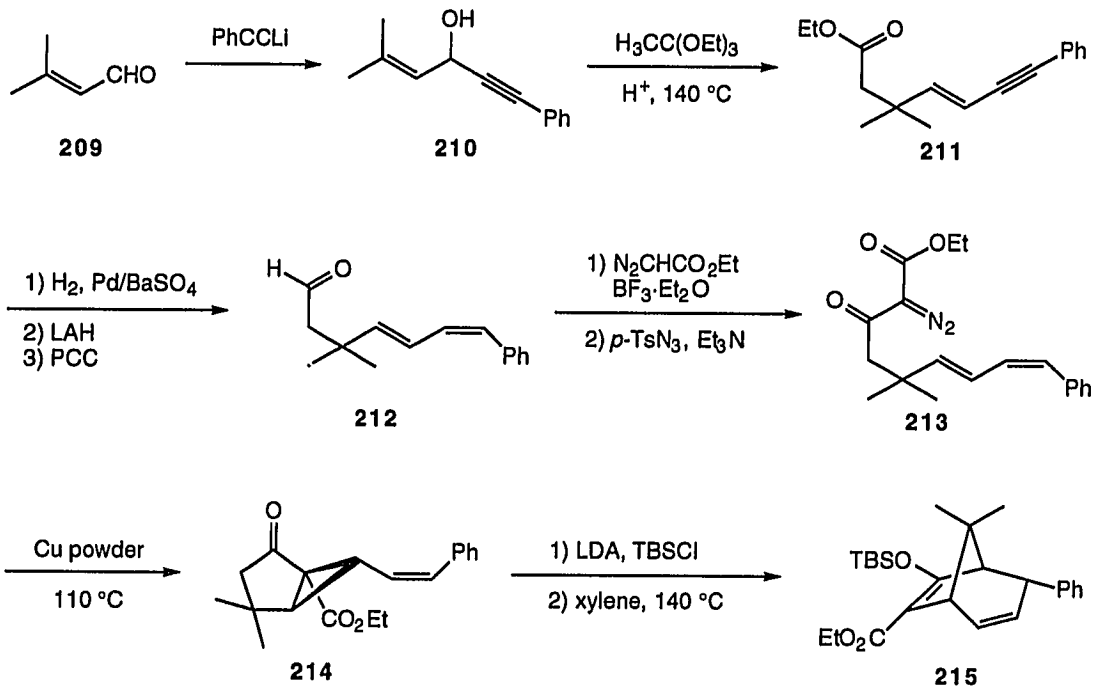
Model Studies V

Lack of success in the above cyclopropanation forced us to modify the synthetic plan to the one illustrated in Scheme 39. The symmetrically protected diol in **207** could be differentiated through intramolecular functional group manipulation, and serve well as the precursor for the pyrrolidine ring and the vinyl group of gelsemine (**1**). Bicyclo[3.2.1]cycloheptadiene **207** would be prepared from **208** by the aforementioned Cope rearrangement.



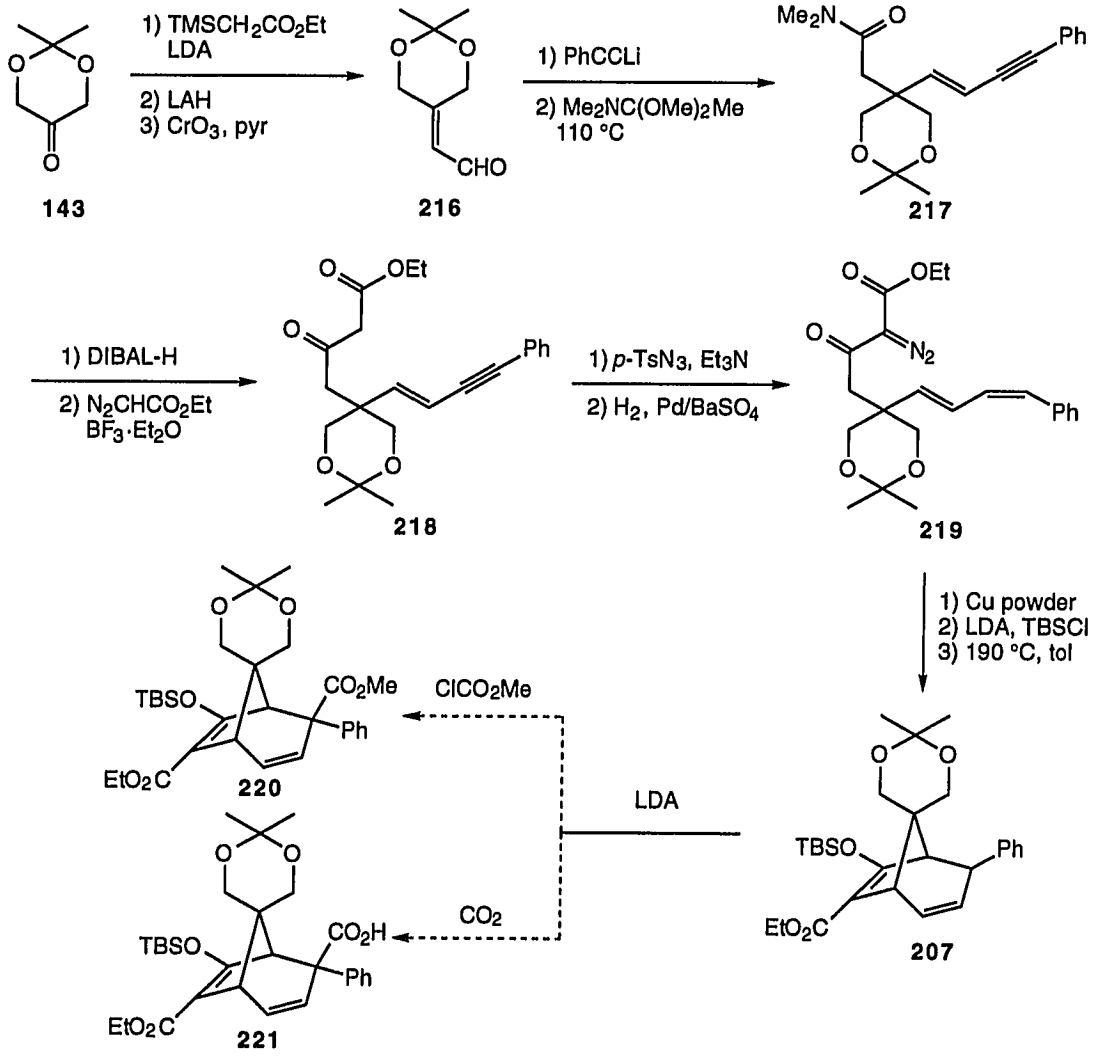
Scheme 39

A simple model study, involving a modification of Piers' synthesis of sinularene, was performed. Reaction of lithium phenylacetylide with 3-methyl-2-butenal **209** gave a relatively unstable propargyl alcohol **210** (Scheme 40), which was subjected to Claisen-Johnson rearrangement. Partial hydrogenation of the resulting ene-yne **211** over $Pd/BaSO_4$ gave a *cis-trans* diene. Reduction of the ethyl ester followed by oxidation of the resulting alcohol furnished aldehyde **212**. Treatment of the aldehyde with ethyl diazoacetate in the presence of boron trifluoride-etherate provided a β-ketoester, which was subjected to standard diazo transfer reaction. The resulting diazo compound **213** was refluxed with copper powder in toluene to give the bicyclic ketone **214**. Conversion of the ketone to the corresponding *t*-butyldimethylsilyl enol ether, followed by thermolysis at 140 °C, gave bicyclo[3.2.1]octadiene **215**.



Scheme 40

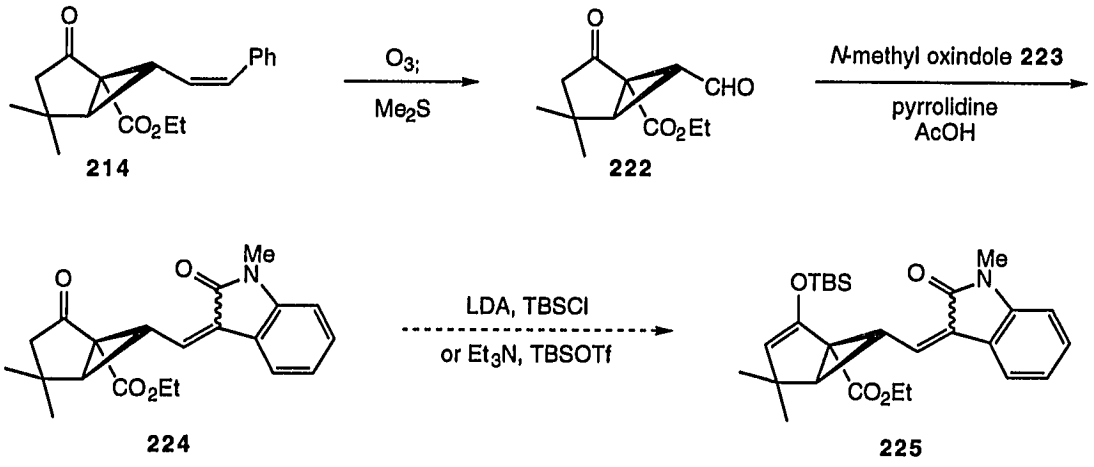
With a successful model compound in hand, we then focused our attention on the preparation of the real intermediate **207**. Two-carbon homologation of the ketone **143** by Peterson-type olefination gave an α,β-unsaturated ester (Scheme 41). Reduction of the ester and Collins oxidation of the resulting alcohol gave aldehyde **216**. Introduction of phenylacetylenyl fragment and Eschenmoser-Claisen rearrangement of the allylic alcohol with *N,N*-dimethyl acetamide dimethyl acetal[59] gave ene-yne **217**.



Scheme 41

Reduction of the dimethylamide under carefully controlled conditions followed by elongation of the resulting aldehyde gave β-ketoester **218**. Diazo transfer reaction followed by partial hydrogenation of the acetylene gave diazo compound **219**. The rearrangement precursor **208** was secured through copper-mediated cyclopropanation and silyl enol ether formation. Thermolysis of **208** at 190 °C cleanly gave the bicyclo[3.2.1]octadiene **207**.

Compound **207** has almost all the functional groups at proper positions as required for gelsemine (**1**). The problem remaining to be addressed was how to incorporate an indolinone into the bicyclic system. Attempted functionalization of the benzylic position by treatment of **207** with LDA and subsequent quenching the anion with different electrophiles, such as chloroformate and carbon dioxide, was unsuccessful, giving no desired product **220** or **221** (Scheme 41). This failure was attributed to the severely hindered environment and low acidity of the benzylic position.



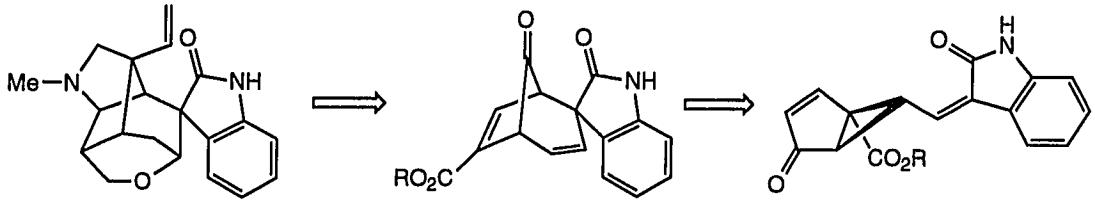
Scheme 42

Another possible solution was to incorporate the indolinone into the thermolysis precursor. A quick test gave mixed results (Scheme 42). Cyclopropyl carboxaldehyde **222** was prepared by ozonolysis of olefin **214**.

Pyrrolidium acetate-catalyzed Knoevenagel condensation[60] of **222** with *N*-methyloxindole[61] **223** gave a mixture of *E*- and *Z*- alkylidene indolinones **224** in poor yield. The immediate problem associated with compounds **224** was their instability under basic conditions required to form crucial enol derivative of the ketone, in preparation for the key rearrangement. LDA treatment only led to severe decomposition of the starting material, while treatment with Et_3N and TMSCl failed to give any silyl enol ether **225**.

Total Synthesis of (±)-Gelsemine

The synthetic plan then underwent further refinement according to the new development (Scheme 43). The silyl enol ether in the thermolysis precursor was replaced with an enone system **227**, which would lead to the same type of bicyclo[3.2.1]octadiene skeleton **226** with the bridgehead ketone as the handle for construction of the second quaternary carbon. The second amine function in gelsemine (**1**) can be introduced by Michael addition of methyl amine to the α,β-unsaturated ester. In this protocol, it is also possible to control the stereochemistry of the spiro center, as rearrangement of the *Z*-isomer of **227** is expected to give the desired spiro-indolinone exclusively.

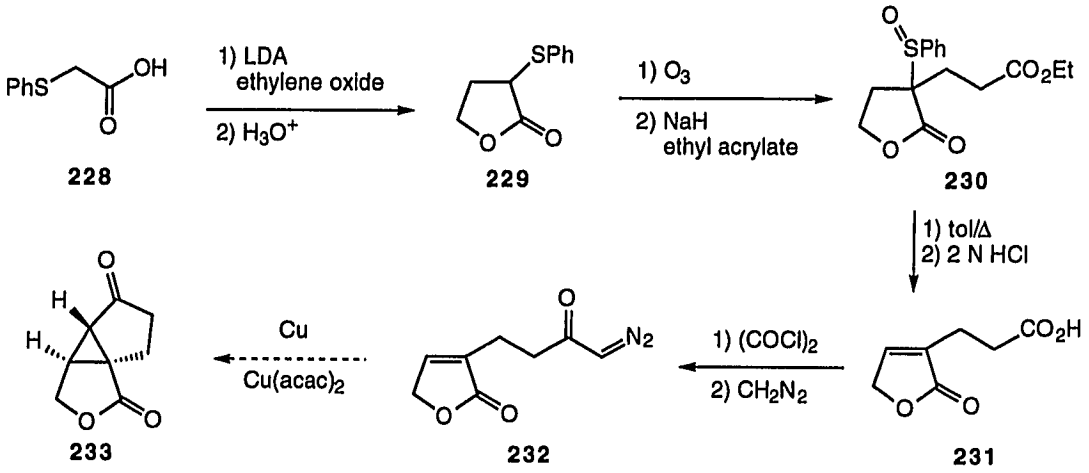


1 **226** **227**

Scheme 43

Synthesis of intermediate **227** therefore became our top priority. The initial approach started from simple phenylthioacetic acid **228** (Scheme 44).

Treatment of **228** with LDA and ethylene oxide gave an α-hydroxyethyl acid, which cyclized to lactone **229** upon acidic work-up. Oxidation of the phenyl sulfide to sulfoxide by ozone at low temperature, followed by Michael addition of the sulfoxide anion to ethyl acrylate, yielded lactone **230**. Thermal elimination of sulfoxide gave a butenolide and subsequent hydrolysis of the ester gave carboxylic acid **231**. Formation of an acid chloride from **231** and treatment with diazomethane provided diazoketone **232**. Unfortunately, subsequent thermolysis of **232** in the presence of copper powder or cupric acetylacetonate produced ambiguous results. First, it was not clear that the desired **233** had formed; second, the reaction was not reproducible.

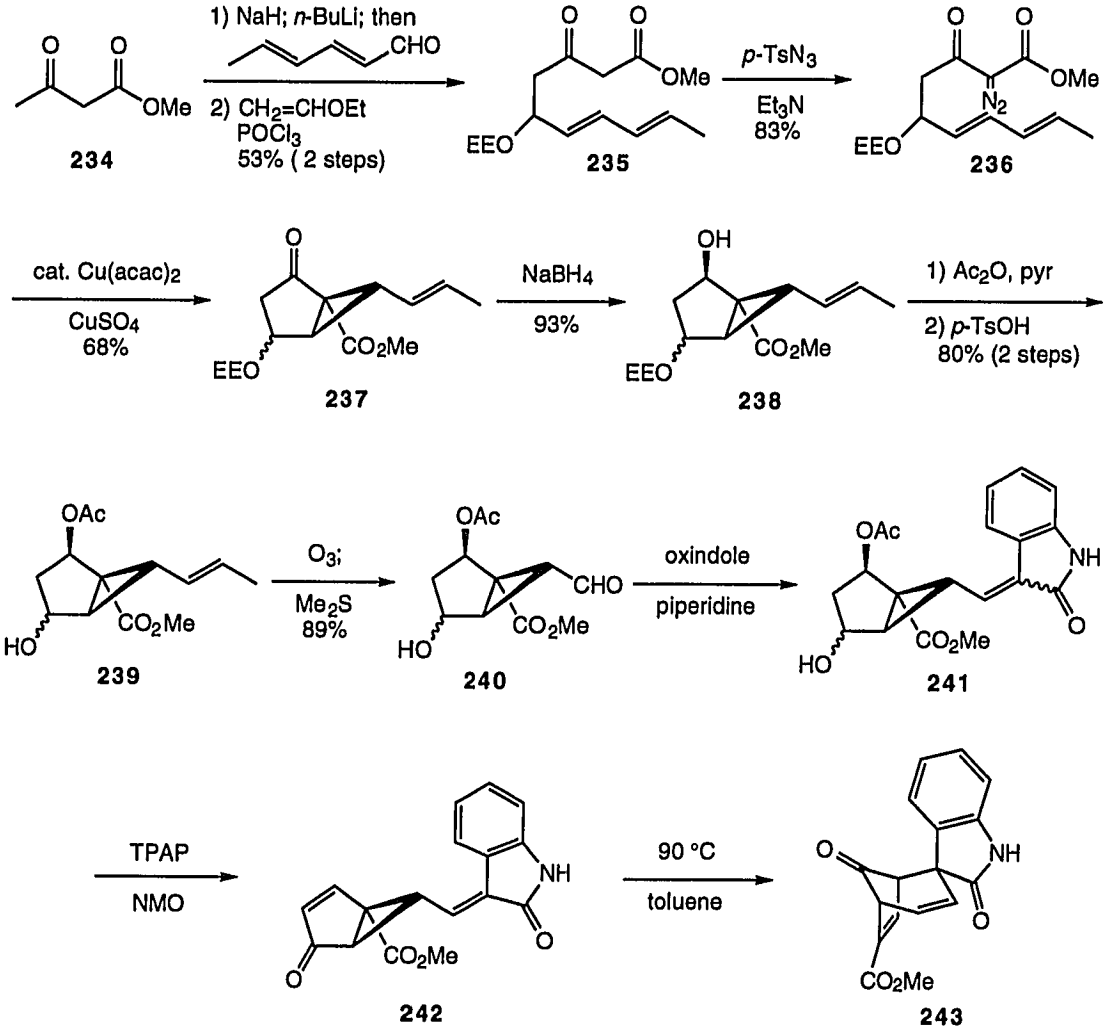


228 229 230 231 232 233

Scheme 44

A more reliable approach to the synthesis of the requisite intermediate **227** was adopted from Kondo's synthesis of prostaglandin $F_{2\alpha}$.[62] Successive treatment of methyl acetoacetate **234** with sodium hydride and *n*-butyllithium generated the dianion,[63] which was quenched with sorbic aldehyde to give an aldol adduct (Scheme 45). Since the resulting alcohol was relatively unstable, it was immediately protected as its ethoxyethyl ether **235** in 55% yield over two

steps. Standard diazo transfer reaction gave the diazo compound **236** in 83% yield. Cyclopropanation was best carried out with a catalytic amount of copper acetylacetonate and more than a stoichiometric amount of anhydrous copper sulfate in refluxing benzene, to give bicyclic ketone **237** in 68% yield. Stereoselective reduction of cyclopentanone **237** with $NaBH_4$ took place from the less hindered, α-face to give β-alcohol **238** in 93% yield. Protection of the alcohol **238** as its acetate followed by hydrolysis of the



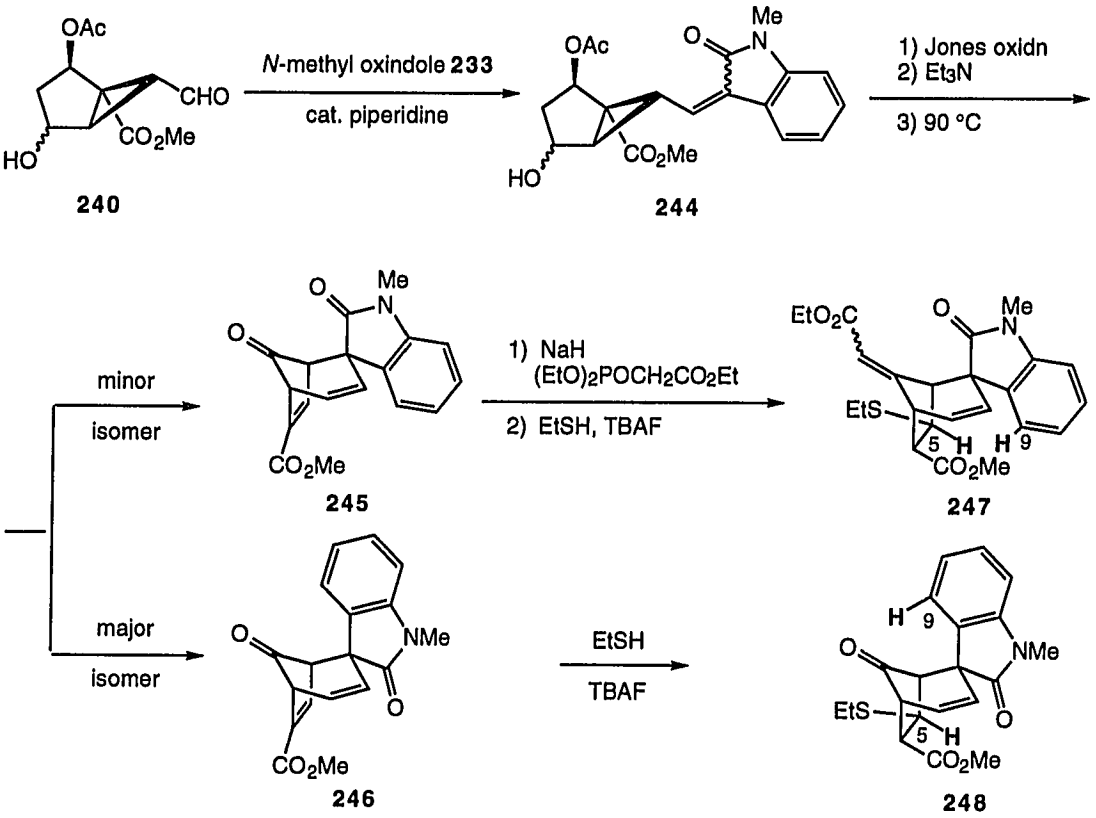
Scheme 45

ethoxyethyl ether furnished alcohol **239** in 80% yield. Ozonolysis of the olefin provided cyclopropyl carboxaldehyde **240** in 89% yield.

Nonstereoselective condensation of aldehyde **240** with oxindole in methanol in the presence of piperidine gave a mixture of the *E*- and *Z*-alkylidene indolinones **241** in low yield (Scheme 45). The major isomer was separated and subjected to tetrapropylammonium perruthenate (TPAP) oxidation[64] in the presence of NMO to give a β-acetoxyketone. Slow elimination of acetic acid promoted by morpholine proceeded simultaneously to give enone **242**. The enone-alkylidene indolinone system **242** was very prone to rearrange to the bicyclo[3.2.1]octadiene system. Brief heating of **242** yielded compound **243** as the dominant product. It needs to point out that the structure of **243** was characterized as the one shown in Scheme 45 only later. By contrast, if the allylic alcohol instead of enone was used, no rearrangement occurred, even after prolonged heating at 200 °C.

Even though we only obtained a small amount of **243**, we were very excited by the early success of this approach. At this stage, the assignment of the stereochemistry of the spiro center became our top priority. In order to secure more material for in-depth study, a few minor changes were made. The condensation step leading to **241** was conducted with a catalytic, instead of stoichiometric, amount of piperidine (Scheme 46). Also, replacement of oxindole with *N*-methyloxindole greatly improved the yield of the condensation reaction, because of the increased stability of the resulting alkylidene indolinone **244**. The condensation furnished, as in the previous sequence, a mixture of four products with a 4 to 1 ratio between the two olefinic isomers. The *E*, *Z*-isomers were separated and subjected to same chemical sequence. Secondary alcohols **244** were stable enough to withstand Jones oxidation.

Elimination and thermolysis of the resulting enone gave rearranged products in reasonable yield. The minor alkylidene indolinone gave one stereoisomer of spiro-indolinone **245** exclusively, regardless of the solvent and temperature, while major alkylidene indolinone consistently gave the other isomer **246** as the dominant product, along with a small amount of **245**.



Scheme 46

Until this stage we had no conclusive evidence for the relative stereochemistry of the spiro center. One of the most powerful tools to study the relative stereochemistry is the nuclear Overhauser effect (NOE) difference spectroscopy. Michael addition of ethyl mercaptan to the major stereoisomer **246** provided **248** (Scheme 46). The stereochemistry of adduct **248** was predicted on the assumption that addition of ethyl mercaptan as well as

protonation of the intermediate enolate, would occur from the less hindered

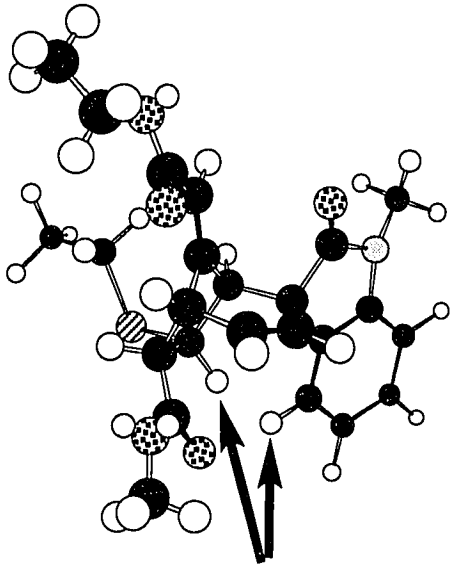


Figure 5

exo-face of the molecule. Similarly, ethyl mercaptan adduct **247** was prepared from the Horner-Emmons product of the minor isomer **245**. Of the two possible stereoisomers of the spiro-indolinone, the desired isomer **247** is the one with the two protons at C-5 and C-9 close enough (<2.5 Å) to cause substantial NOE enhancement, as shown in Figure 5. Unfortunately, we did not observe appreciable NOE enhancement between the protons at C-5 and C-9 of the major isomer **248**, while strong NOE enhancement was observed between the C-5 and C-9 protons (2.13 Å) of the minor isomer **247** (Figure 6). This was not a particularly encouraging result, because the minor isomer **245**, derived from *Z*-isomer of the alkylidene indolinone based on the concerted nature of the rearrangement process, is the one leading to gelsemine. At this stage, preparation of the desired spiro-indolinone **245** as the exclusive, or at least dominant product became an imperative task.

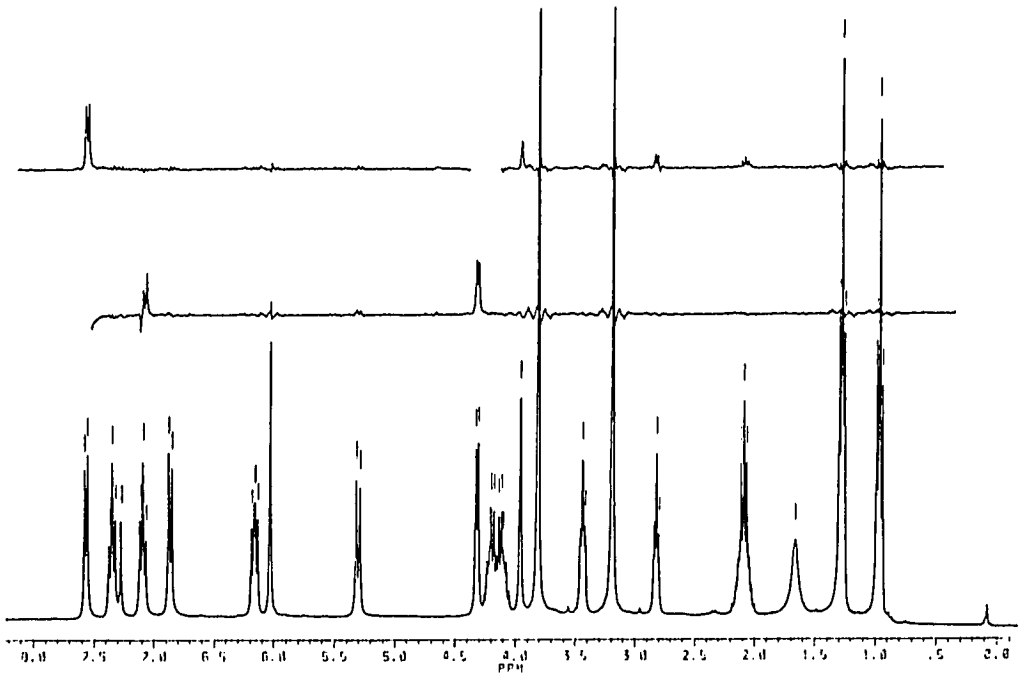
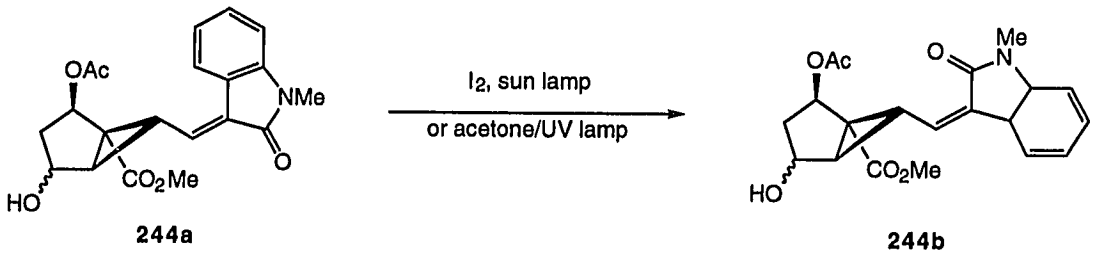


Figure 6

Neither changes in solvent or thermolysis temperature, nor the use of Lewis acid catalysts, altered the outcome of the rearrangement. We then turned our attention to the isomerization of the undesired *E*-isomer **244a**. Iodine-catalyzed photochemical isomerization using a sun lamp worked to some extent (Scheme 47). Photosensitized isomerization using a UV lamp gave a thermodynamic equilibrium mixture of *E*- and *Z*-isomers. The rate of the

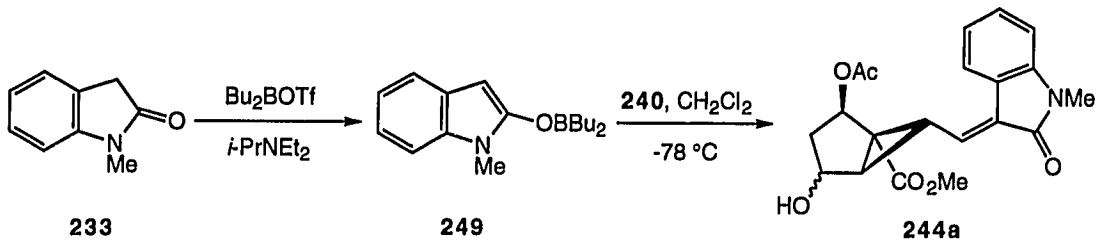


244a **244b**

Scheme 47

conversion was extremely slow, especially for large scale preparations. The UV spectra of the two isomers turned out to be almost identical, posing a serious problem in both theoretical and technical terms for isomerization of the olefin.

We then sought a way to control the stereochemical outcome of the condensation. Initially, the method reported by Kende for the synthesis of (±)-7-*epi*-20-desethylgelsedine[65] was tested. Unfortunately, treatment of aldehyde **240** with *N*-methyloxindole boron enolate **249** seemed to give only the undesired isomer **244a** (Scheme 48).



233 249 244a

Scheme 48

We felt that, instead of tuning the condensation conditions, reversal of the stereoselectivity of the condensation could also be accomplished by increasing the energy gap between the resulting *E*- and *Z*-isomers. We used our CAChe molecular modeling system to calculate the energy difference of the molecules and the interesting results are listed in Table 2. The difference in heat of formation between *E*- and *Z*-isomers of ordinary alkylidene indolinone is -0.53 kcal/mol, according to MOPAC (molecular orbital package) PM3 calculation using model compound **250**. Introduction of bromine at the 4-position of the oxindole increases the difference in heat of formation between *E*- and *Z*-isomers to 3.9 kcal/mol, which should dramatically change the stereochemical outcome of the thermodynamically controlled condensation. The steric

energies obtained from classical molecular mechanics calculation gave comparable results, as shown in Table 2.

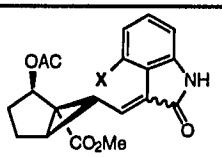
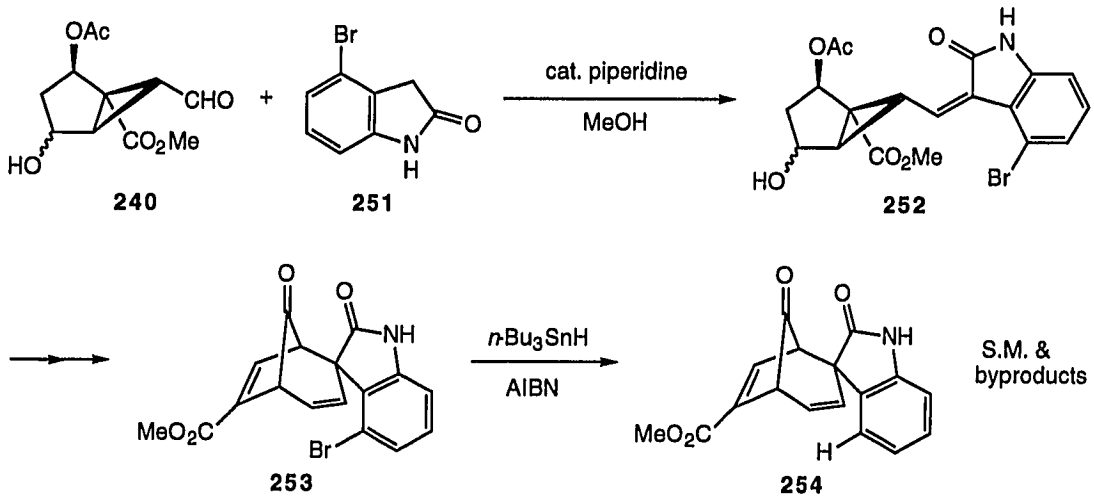
 250	steric energy (kcal/mol)	heat of formation (kcal/mol)
250-*E*	127.553	-140.298
250-*E*-Br	135.664	-125.442
250-*E*-I	137.194	-101.958
250-*Z*	125.822	-139.773
250-*Z*-Br	128.591	-129.383
250-*Z*-I	128.997	-110.866

Table 2

Experimental results fully reflected our anticipation. 4-Bromo-oxindole **251** was synthesized according to a literature procedure from 2-bromo-6-nitrotoluene.[66] Condensation of aldehyde **240** with **251** gave exclusively the *Z*-isomer of alkylidene indolinone **252** in good yield (Scheme 49). Highly crystalline rearrangement product **253** was isolated after the same sequence of reactions described earlier (oxidation, elimination, and rearrangement). To confirm the stereochemistry of the spiro center, the bromide **253** was subjected to a single crystal X-ray analysis, which unequivocally indicated that we had the desired stereoisomer (see Appendix).

After the stereoselective construction of the bicyclo[3.2.1] system, next on the agenda was the introduction of the second nitrogen atom required in gelsemine. To our surprise, addition of ammonia to the α,β-unsaturated ester in **253** was very messy and inconsistent. We then decided to remove the bromide

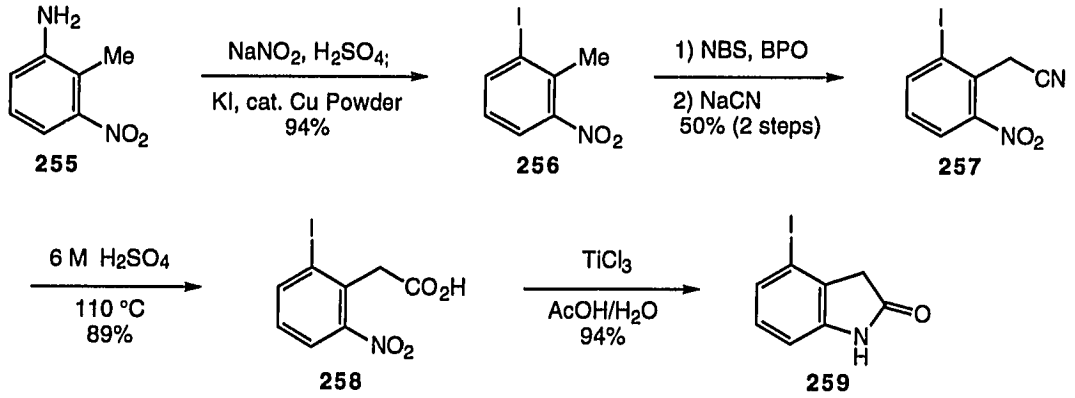


Scheme 49

prior to the addition of ammonia. However, radical debromination of **253** with tributyltin hydride was extremely slow, and gave substantial amount of byproducts in addition to the desired product **254** (Scheme 49). Hydrogenolysis with palladium or nickel catalyst only gave an unidentified byproduct. Attempts to remove the bromide before the rearrangement also failed.

Our failure to reduce the bromide **253** induced us to employ the more readily removable 4-iodo-oxindole **259**. As shown in Table 2, the *Z*-isomer (**250-*Z*-I**) is 8.9 kcal/mol more stable than the *E*-isomer (**250-*E*-I**) by comparison of the calculated heat of formation. Accordingly, it was expected that *Z*-alkylidene indolinone would be even more favored in this case. 4-Iodo-oxindole **259** was successfully synthesized as shown in Scheme 50. Sandmeyer reaction of 2-methyl-3-nitroaniline **255** followed by potassium iodide treatment gave iodotoluene **256** in 94% yield. Benzylic bromination of the toluene under normal radical conditions stalled at fifty percent conversion.

Fortunately, the benzyl cyanide **257** obtained from treatment of the resulting

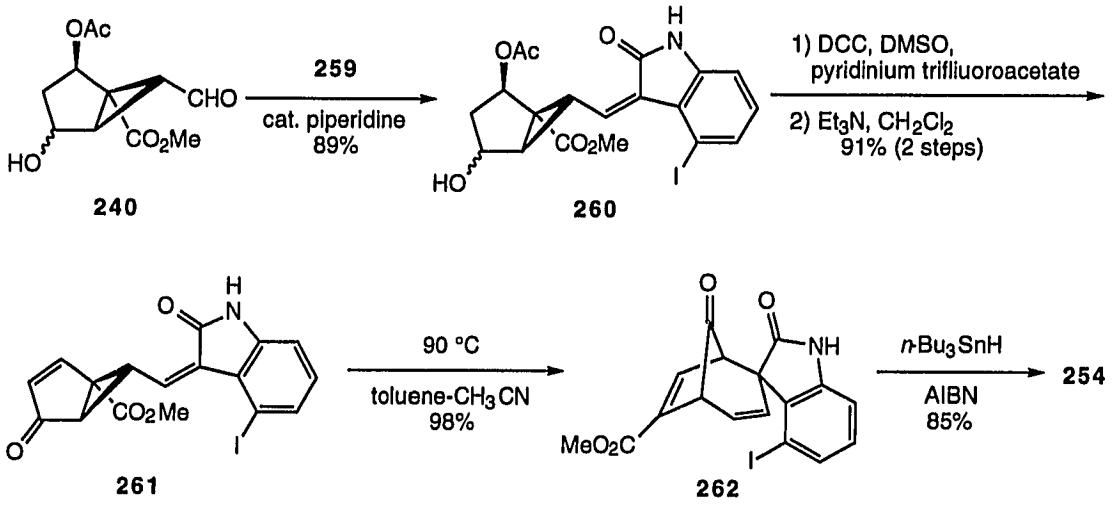


Scheme 50

bromide with sodium cyanide could be separated in 50% yield from the unreacted toluene **256** by crystallization. Hydrolysis of nitrile **257** in 6 M sulfuric acid gave phenylacetic acid **258** in 89% yield. Reduction of the nitro group without affecting the iodide was best achieved by using 20% aqueous Ti(III) chloride in $AcOH/H_2O(3:1)$.[67] The 4-iodo-oxindole **259** thus emerged as a crystalline precipitate in 94% yield.

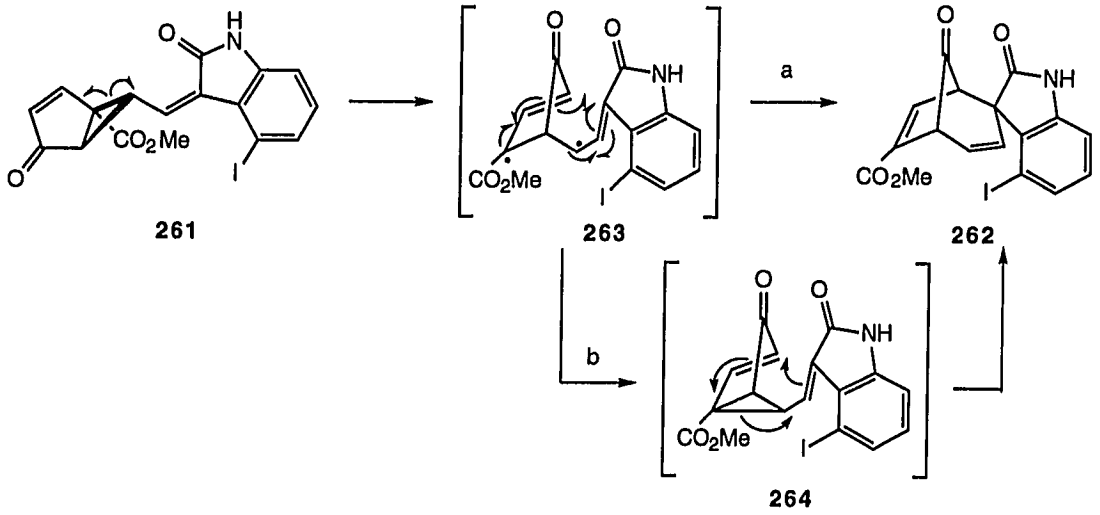
With a large quantity of **259** in hand, the condensation product **260** was secured in the same manner as bromide **252** (Scheme 51). The subsequent oxidation of alcohol **260** required substantial improvement, because Jones oxidation caused partial cleavage of the alkylidene indolinone to 4-iodoisatin. An attempted one-pot oxidation and elimination under Swern conditions gave mainly uncharacterized byproducts. However, mild Pfitzner Moffatt oxidation[68] of secondary alcohol **260** worked very well. Acetate elimination with Et_3N yielded the alkylidene indolinone enone **261** in 91% yield over two steps. When heated at 90 °C for 30 min, compound **261** smoothly rearranged to the bicyclo[3.2.1] compound **262**, a highly crystalline solid, in 98% yield. Facile

radical deiodination with tributyltin hydride cleanly gave the tetracyclic gelsemine core **254** in 85% yield.



Scheme 51

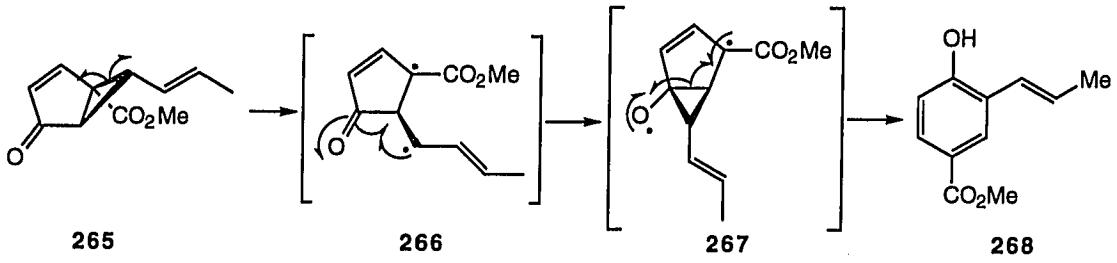
Some interesting aspects of the rearrangement process deserve further discussion. Thermolysis of **261** should proceed with initial homolytic cleavage of the cyclopropane to biradical **263** (Scheme 52). Two possible fates await



Scheme 52

263. Path (a) is the direct ring closure of the biradical to afford final product **262**. Path (b) is the recombination of the biradical to give *cis*-cyclopropane **264**, which should undergo a concerted sigmatropic rearrangement to give the desired product **262**.

Our results support the former process. First of all, isolation of some desired spiro-indolinone **245** from rearrangement of the *E*-isomer of alkylidene indolinone **244** (Scheme 46) demonstrated that the thermolysis was not a concerted process. More substantial evidence came from the rearrangement of model compound **265** (Scheme 53). Thermolysis of **265** did not give any of the desired bicyclo[3.2.1] compound, providing instead the aromatic compound **268**. Evidently, formation of biradical **266** resulted in attack of the allylic radical into the ketone to give oxygen radical **267**. Cyclopropane cleavage then gave phenol **268**. We felt fortunate that there was no stereochemical scrambling of the alkylidene indolinone **261** during the radical process.

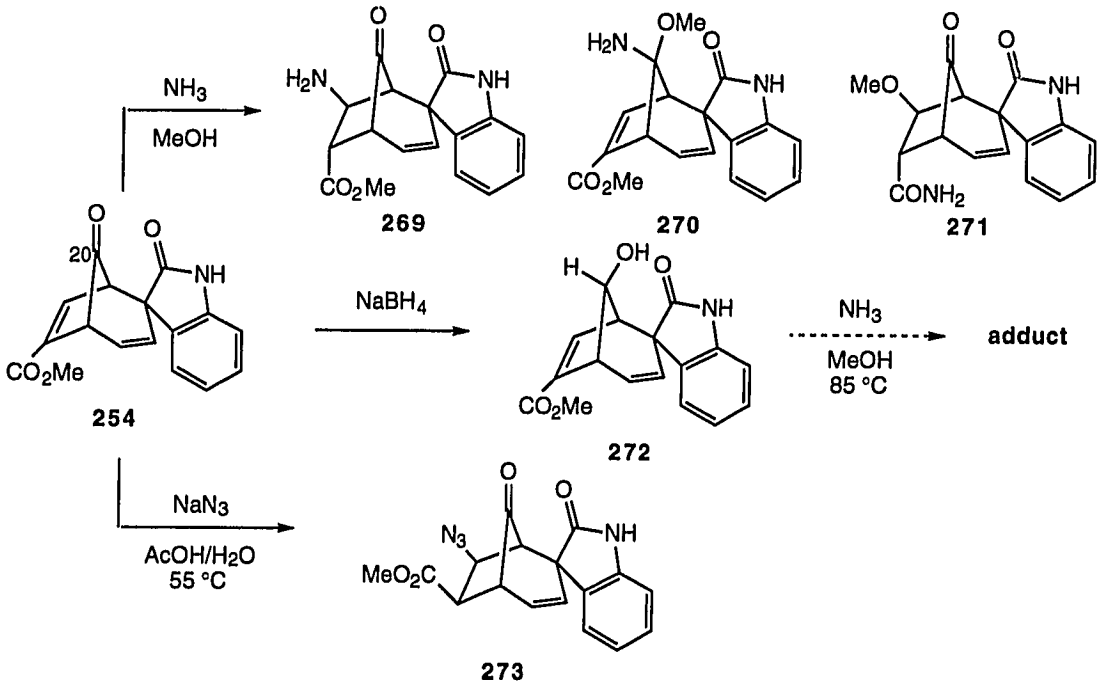


265 **266** **267** **268**

Scheme 53

With tetracyclic intermediate **254** available on a multigram scale, the remaining problems were the construction of the pyrrolidine and tetrahydropyran rings to finish the synthesis of gelsemine. We soon found that the construction of the second quaternary carbon was nowhere near trivial. Ideally, we would have introduced the second nitrogen function by a Michael addition to the α,β-unsaturated ester prior to manipulation of the ketone.

Surprisingly, treatment of **254** with ammonia in methanol gave only small amounts of desired amine **269**, along with many byproducts, including methoxyamine (**270**) and methoxy amide (**271**) (Scheme 54). It seemed that the success of the Michael addition depends upon the sp^2 character of C-20. No addition of nucleophiles to the α,β-unsaturated ester could be observed once the ketone **254** was reduced to alcohol **272**, even under such drastic conditions as heating **272** with ammonia at 85 °C in a bomb. Other ammonia equivalents were also tried without success. Addition of azide under forcing conditions gave epimeric methyl ester **273**.

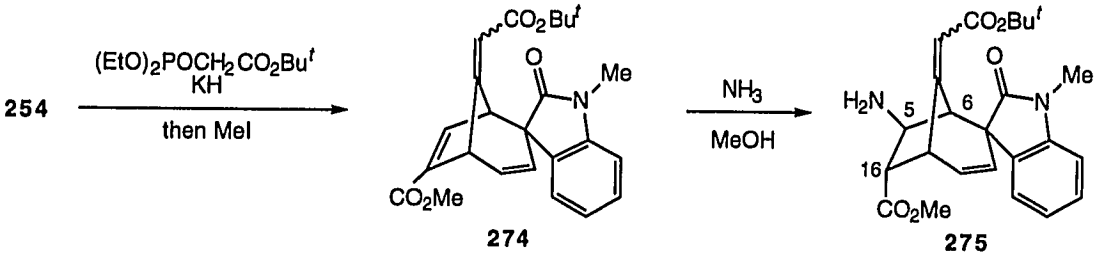


Scheme 54

In order to avoid interference by the ketone during Michael addition, we attempted to protect it. Normal ketal formation conditions did not give any protected product. Tentative masking the ketone as its methylene derivative using Wittig olefination or Takai's reagent afforded no desired compound.

Alcohol **272** was not a viable intermediate because of the extremely slow oxidation back to ketone **254** and the lack of sp^2-character at C-20.

It seemed that only choice left was to functionalize ketone **254** first. The behavior of the ketone was really puzzling. It was not particularly reactive towards various type of nucleophiles. For instance, vinylmagnesium bromide attacked the ketone to afford some tertiary alcohol, but it also reacted with the methyl ester. A phosphonium ylide reacted only with the α,β-unsaturated ester to give a cyclopropane. Elongation of the ketone could only be properly achieved using the Horner-Emmons reaction with *t*-butyl diethylphosphonoacetate to give the bis(α,β-unsaturated) esters as a 4:1 mixture of geometric isomers (Scheme 55). Tentatively, the major isomer was assigned as (*Z*) isomer. To simplify the situation, the indolinone was blocked by one-pot methylation to give **274**. The less sterically hindered α,β-unsaturated methyl ester proved to be an excellent Michael acceptor, which reacted smoothly with different nucleophiles, such as benzylamine, nitromethane, and even ammonia, while the *t*-butyl unsaturated ester was totally inert to nucleophiles.

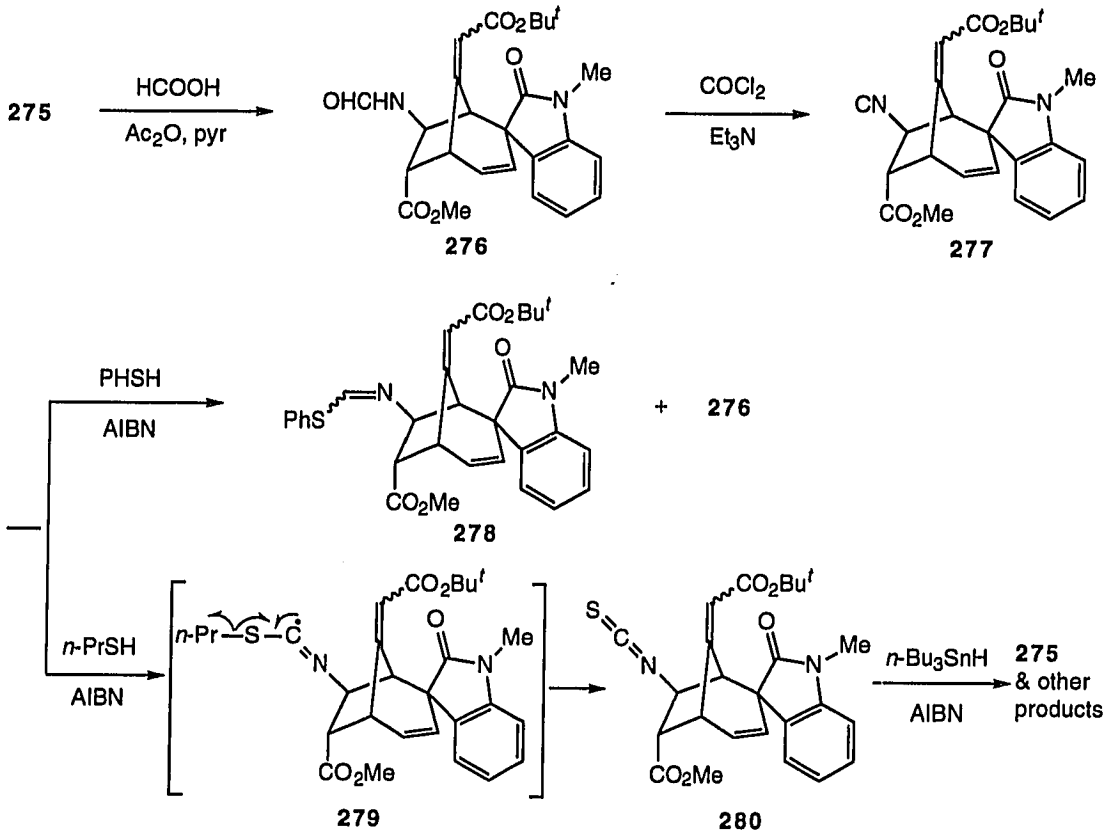


Scheme 55

The stereochemistry of ammonia adduct **275** was found to be of no concern. The *endo*-side of the bicyclo[3.2.1] system **274** was completely blocked by the indolinone, allowing the nucleophile to approach entirely from

the more open *exo*-side. Either concomitant or ensuing protonation occurred also from the less hindered *exo*-side to give the *trans*-amino ester **275** with the required stereochemistry for gelsemine. The ^{1}H NMR spectrum of adduct **275** was fully consistent with this rationale. The proton attached to C-5 appears as a doublet at δ = 4.41 ppm, while H-6 is a singlet at δ = 3.75 ppm. This suggested a nearly 90 °C dihedral angle between these two neighboring protons, therefore there was no coupling between H-5 and H-6.

Our initial approach to the construction of the pyrrolidine ring revolved about the tin-mediated radical cyclization between isocyanide and olefin developed for indole synthesis in our laboratory. Amine **275** was treated with acetic formic anhydride to give formamide **276**, which was dehydrated to isocyanide **277** with phosgene (Scheme 56). When isocyanide **277** was refluxed with thiophenol and catalytic AIBN in toluene, thioimidate **278** and formamide **276** were the only isolable products, and no desired cyclized material was obtained. In order to avoid any ionic addition to the isocyanide, thiophenol was replaced with the less acidic *n*-propylmercaptan as the radical source. This time the attempted radical reaction gave isothiocyanate **280** as the sole product. It is believed that this peculiar reaction proceeded through the mechanism shown in Scheme 56. Addition of *n*-propylthio radical to the isocyanide generated thioimidoyl radical **279**. Radical **279** did not attack the double bond to form the 5-membered ring; instead, it fragmented to give isothiocyanate **280** with extrusion of the more energetic *n*-propyl radical. Subsequent attempts at radical cyclization with isothiocyanate **280** using Bachi's condition[69] led to no cyclization product: only reduction of isothiocyanate was observed.

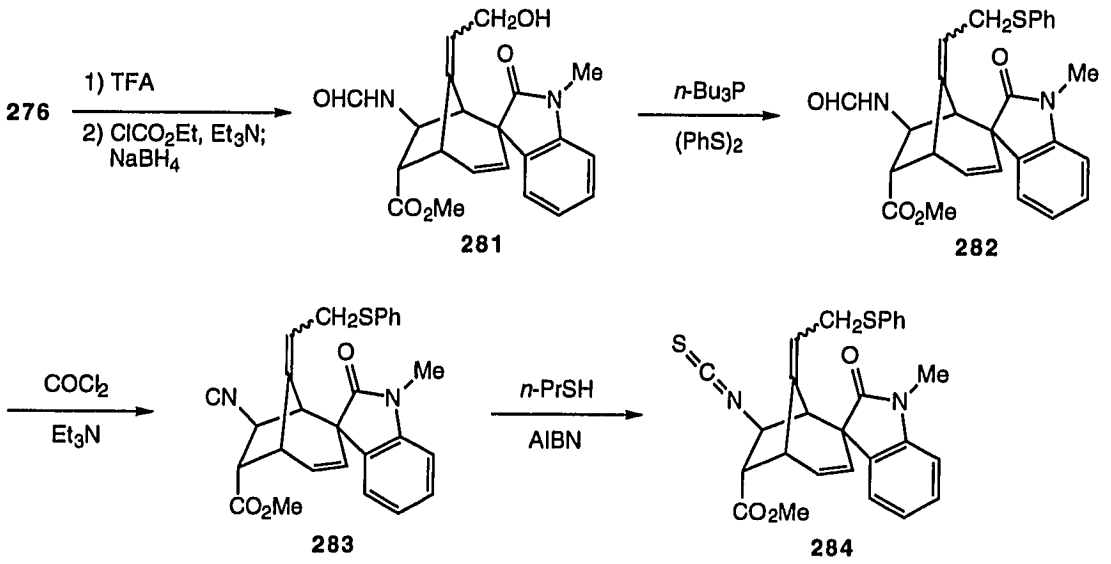


Scheme 56

Examination of the computer-optimized structure of the thioimidoyl radical **279** revealed that there was good orbital overlap between the imidoyl radical and the α,β-unsaturated ester. Thus, the failure of the radical cyclization might be attributed to the unfavorable ring strain of the newly formed 5-membered ring. In another respect, the desired C-C bond formation might have taken place reversibly. Before the stable ester radical was reduced, it might have reverted back to α,β-unsaturated ester and imidoyl radical, which then underwent fragmentation.

Gravel's strategy[70] provided a possible way to circumvent such problems. Briefly, the reversibility of imidoyl radical cyclization into the olefin may be nullified if the resulting radical intermediate can fragment with expulsion

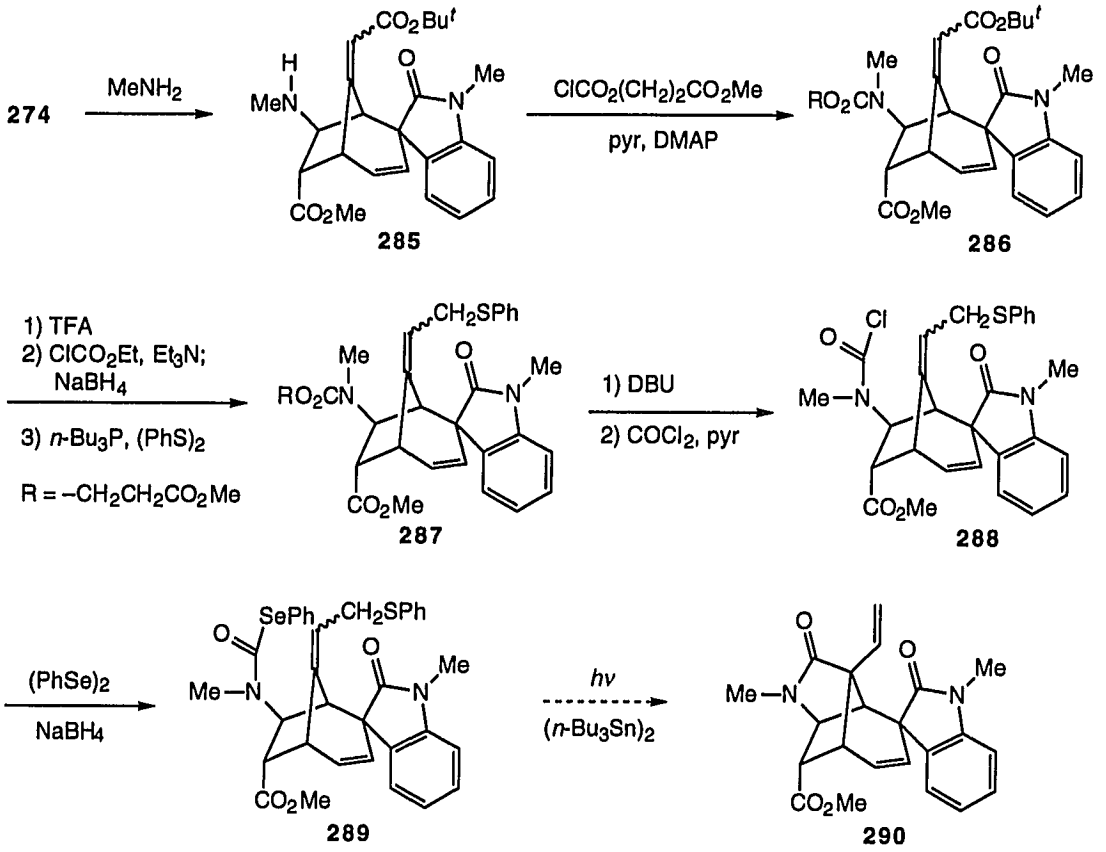
of phenylthio radical. This type of β-fragmentation is exceedingly fast, and it competes effectively with reversible ring opening. To that end, *t*-butyl ester **276** was converted to a carboxylic acid by treatment with trifluoroacetic acid. Reduction to alcohol **281** through the mixed anhydride set the stage for creation of phenyl sulfide **282** by treatment with tributylphosphine and diphenyl disulfide. After the formation of isocyanide **283**, the attempted radical cyclization under normal conditions provided only the isothiocyanate **284**, as in the case of *t*-butyl ester. This experiment surrendered substantial evidence for the unusually high transition state energy of the radical cyclization step.



Scheme 57

In addition to imidoyl radical, an acyl radical was also tried for the formation of the γ-lactam. One attempted route involves the phenylselenenylcarbamate **289** as a radical precursor (Scheme 58). Facile Michael addition of methylamine to **274** gave amine **285**, which was protected as 2-carbomethoxyethyl carbamate **286**. Cleavage of the *t*-butyl ester, reduction of the resulting acid, and sulfide formation provided **287**.

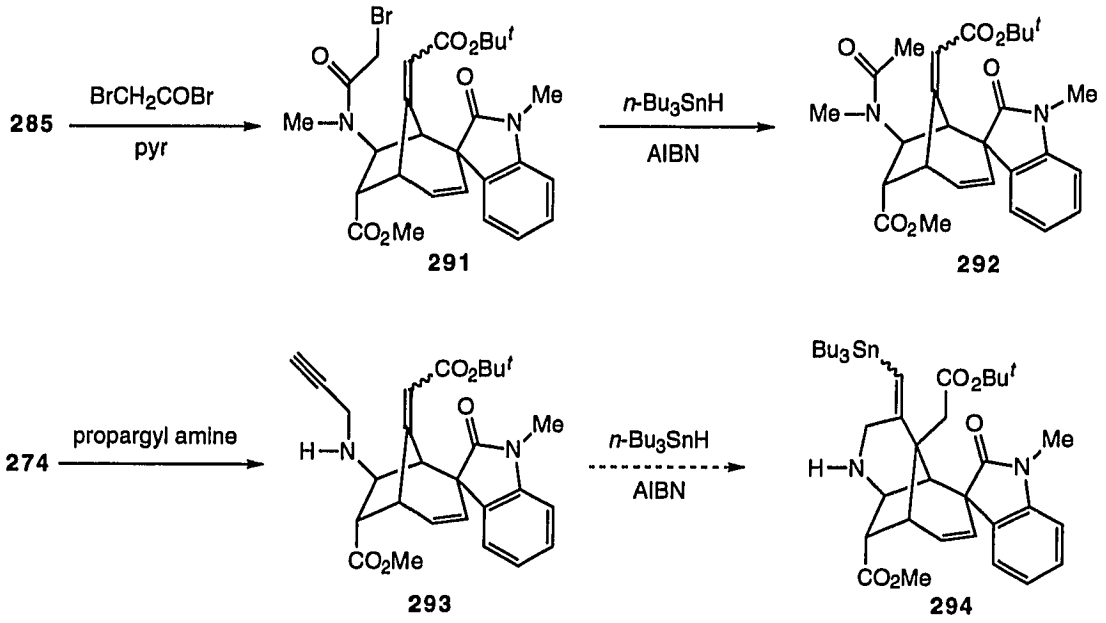
Deprotection of the carbamate with DBU followed by phosgene treatment yielded stable chloride **288**, which was treated with diphenyl diselenide and $NaBH_4$ to give **289**. Unfortunately, atom transfer radical reaction with hexabutylditin under photochemical conditions did not lead to cyclization product **290**.



Scheme 58

As an extension of the radical C-C bond formation strategy, we tried to form a six-membered ring first and convert it to a pyrrolidine ring later on. Thus, condensation of amine **285** with bromoacetyl bromide gave bromoacetamide **291** (Scheme 59). Standard radical conditions gave only the reduced acetamide **292**. The same type of reduction occurred when

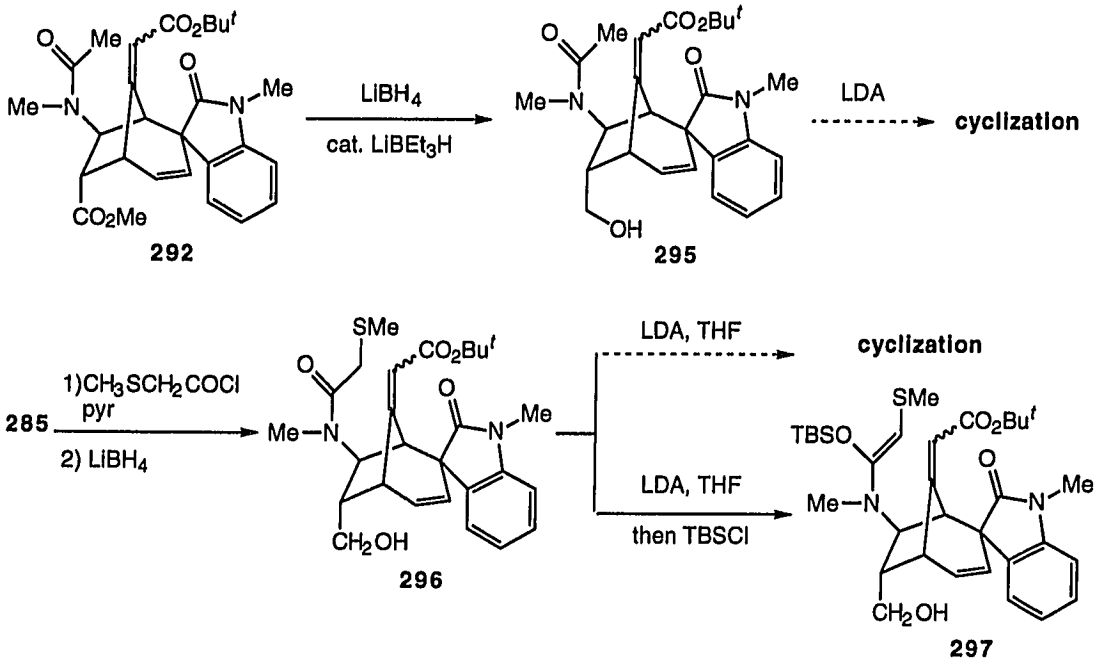
phenylselenoethylamine was used. Meanwhile, Michael addition of propargylamine to **274** and subsequent tributyltin hydride treatment of the resulting adduct **293** did not yield any cyclization product **294** either.



Scheme 59

The failure of carbon-carbon bond formation through radical reactions led us to consider C-C bond formation through ionic processes. Intramolecular Michael addition to the α,β-unsaturated *t*-butyl ester was obviously the first choice. Reduction of methyl ester **292** with lithium borohydride in the presence of a trace of super hydride[71] gave alcohol **295** (Scheme 60). Treatment of **295** with LDA at different temperatures led to no cyclization. Reformatsky reaction of bromo acetamide **291** using zinc or SmI_2 caused only debromination to give acetamide **292**. More greatly stabilized, "softer" anions also gave disappointing results. For instance, coupling of amine **285** with (methylthio)acetyl chloride followed by reduction of the methyl ester gave amide **296**. LDA treatment of **285** did not afford any cyclization product. The

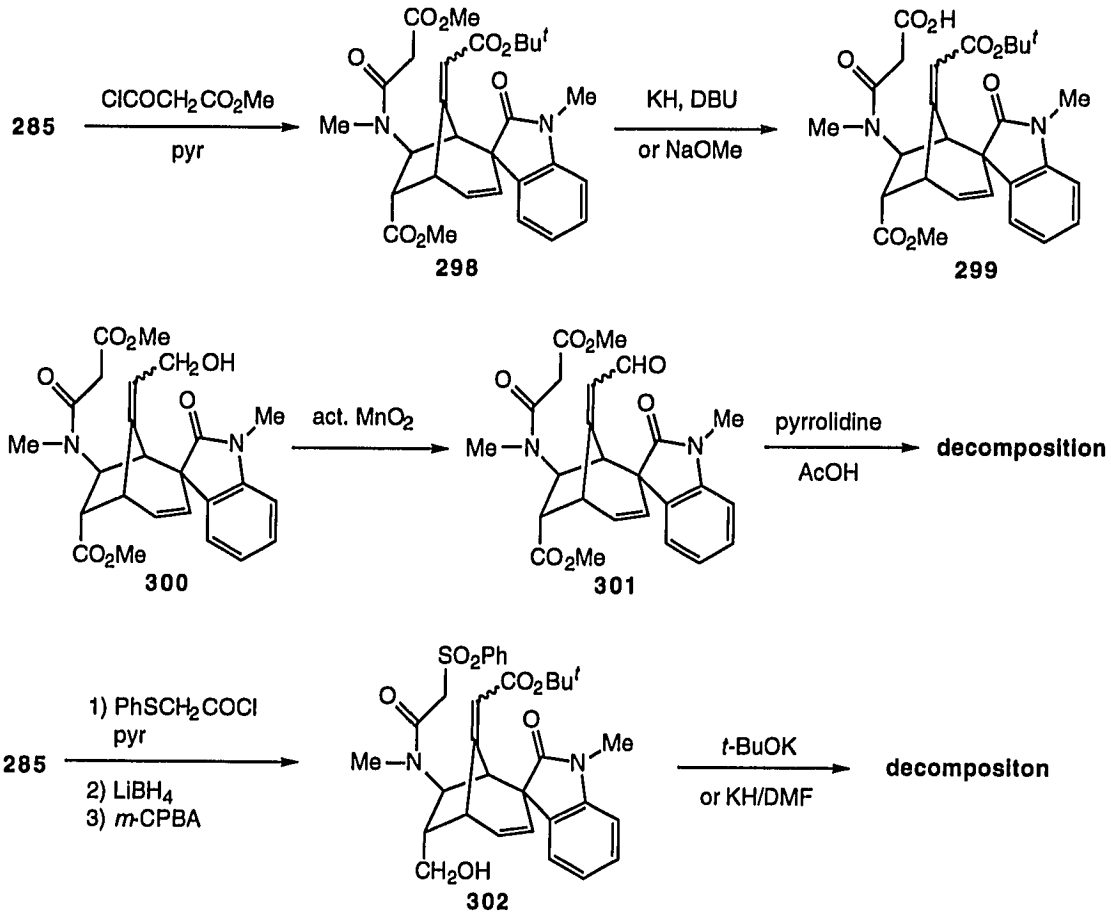
formation of enolate was confirmed by trapping with *t*-butyldimethylsilyl chloride (TBSCl) and subsequent isolation of silyl enol ether **297**.



Scheme 60

A more reactive soft-nucleophile was prepared by coupling the amine **285** with methyl malonyl chloride to give the malonamide **298** (Scheme 61). Treatment of **298** with bases, such as DBU, potassium hydride (KH), and sodium methoxide (NaOMe), did not lead to any C-C bond formation. In most cases, hydrolysis of the ester to acid **299** was effected by the bases used. The α,β-unsaturated ester was then changed to the aldehyde **301** through the oxidation of the alcohol **300** to increase the reactivity of the conjugate system. However, standard Knoevenagel conditions led to extensive decomposition. Sulfonamide **302** was then prepared by condensing the amine **285** with phenylthioacetyl chloride, reduction of the methyl ester to alcohol, and oxidation of the sulfide to sulphone with *m*-CPBA. Compound **302** was treated with *t*-

BuOK or KH at elevated temperature. Neither set of conditions could yield the cyclization product, but instead caused decomposition of the starting material.



Scheme 61

These studies showed that the intramolecular conjugate addition, either in a radical or ionic mode, is a highly disfavored process. This might be

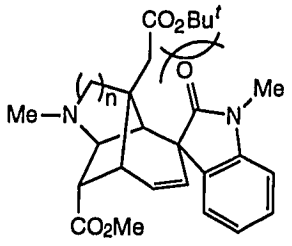
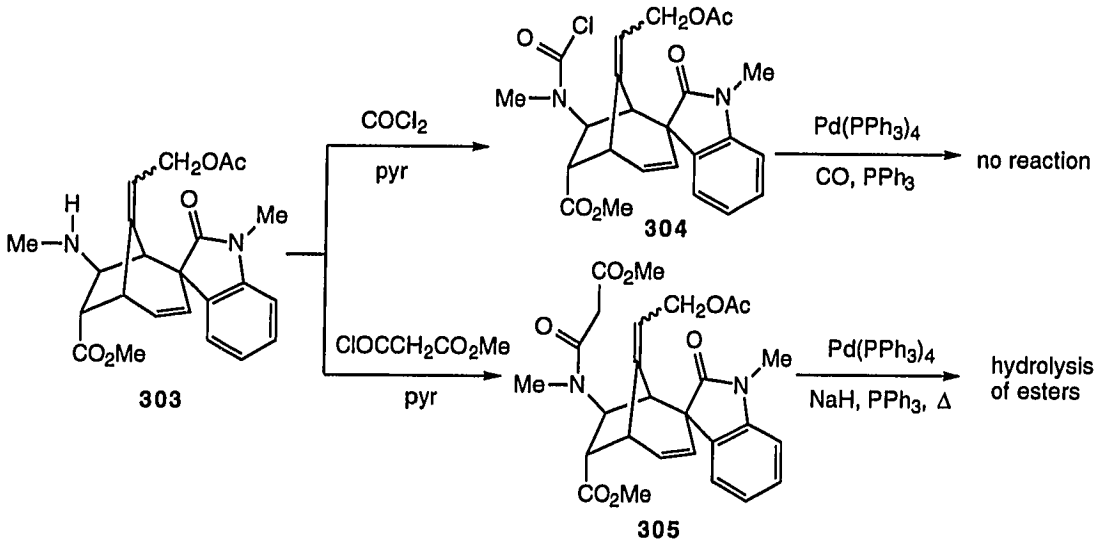


Figure 7

explained in terms of the severe steric compression between the carboxylate and indolinone carbonyl as a result of C-C bond formation, as shown in Figure 7.

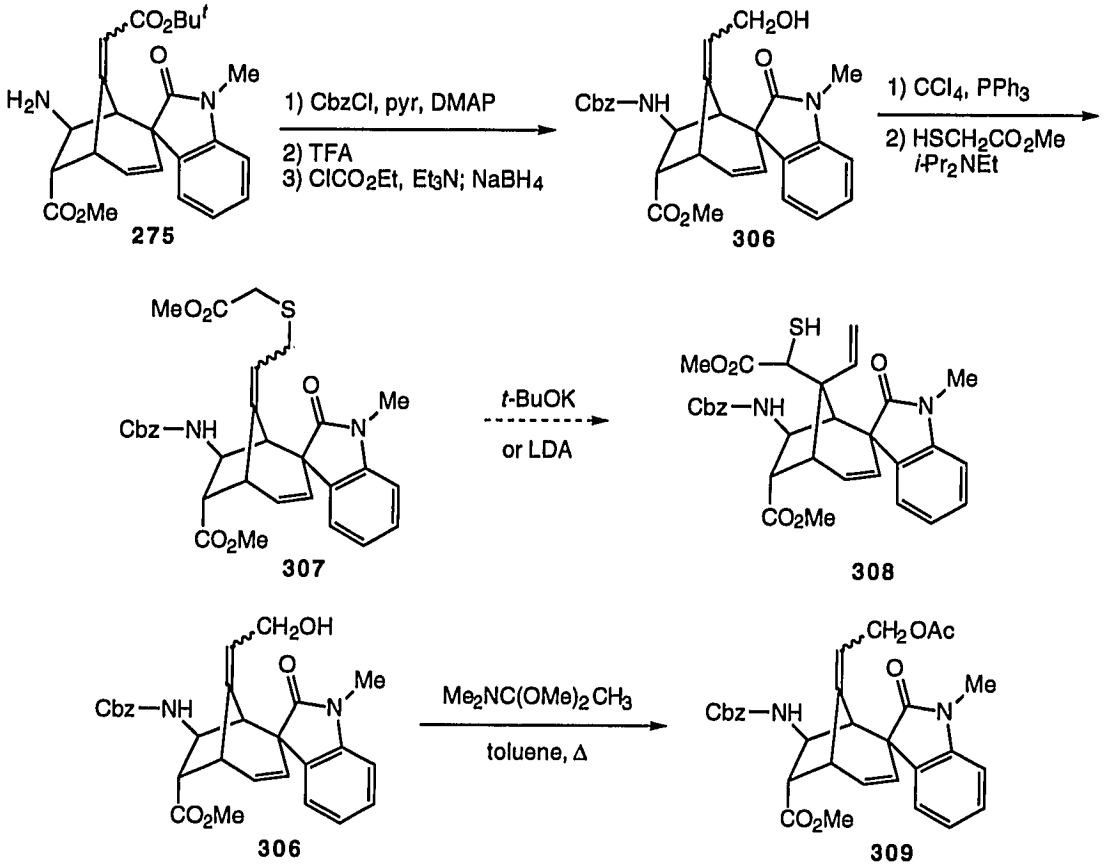
The possibility of palladium-mediated C-C bond formation was also explored. Treatment of amine **303** with phosgene gave the chromatographically stable carbamoyl chloride **304**, which was treated with Pd(0) and triphenylphosphine under a carbon monoxide atmosphere (Scheme 62). There was no change detected after prolonged reaction time. We then attempted the six-membered ring formation. Coupling of the amine **303** with methyl malonyl chloride gave the malonamide **305**. When **305** was subjected to the meticulously controlled Pd(0) and NaH conditions, only hydrolysis of the methyl ester and acetate was observed.



Scheme 62

Because of the ready availability of the allylic alcohol through reduction of carboxylic acid, we explored the possibility of forming the C-20 quaternary carbon through a sigmatropic process. The [2,3] Wittig rearrangement[72] was

first attempted. Protection of amine **275** as its benzyl carbamate, cleavage of the *t*-butyl ester, and reduction of the resulting acid generated alcohol **306** (Scheme 63). Conversion of alcohol **306** to an allyl chloride, followed by substitution of the resulting chloride with methyl thioglycolate, provided the thioether **307**. When this carboxylate was subjected to deprotonation

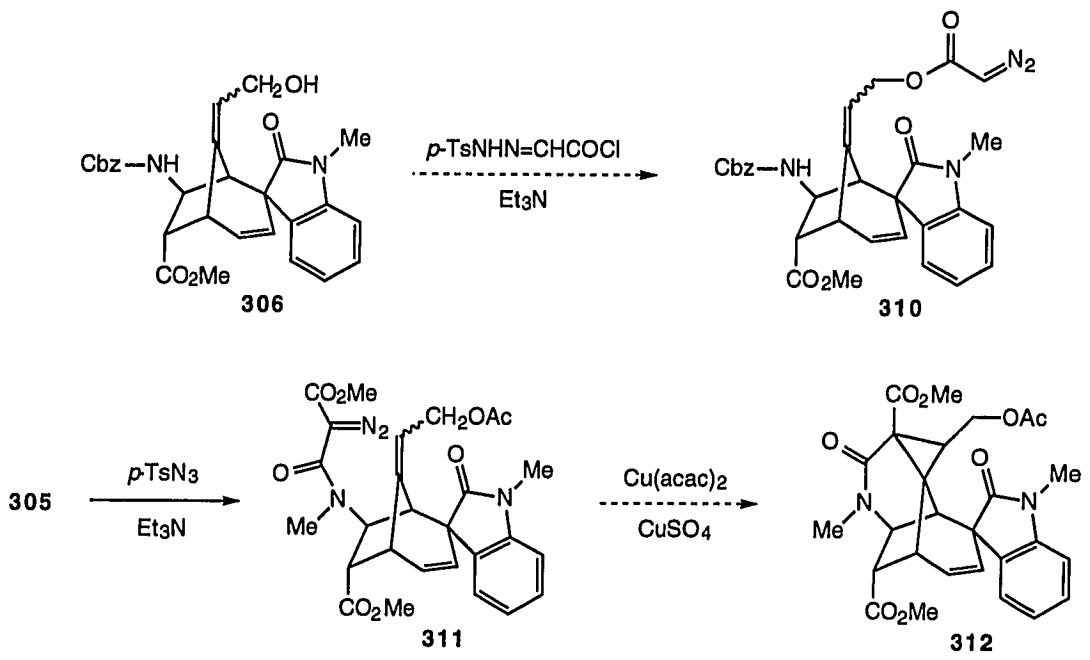


Scheme 63

conditions, such as *t*-BuOK or LDA, no rearranged product **308** was obtained. We also attempted Eschenmoser's modification of the Claisen rearrangement. Allyl alcohol **306** cleanly reacted with *N,N*-dimethylacetamide dimethylacetal in refluxing toluene to give a less polar product, which was found to be the allyl acetate **309** (Scheme 63). No rearrangement took place after the initial

condensation between the alcohol and the reagent. Attempts to form a vinyl ether of the allyl alcohol through ether exchange were also unsuccessful, precluding the feasibility of a classical Claisen rearrangement.

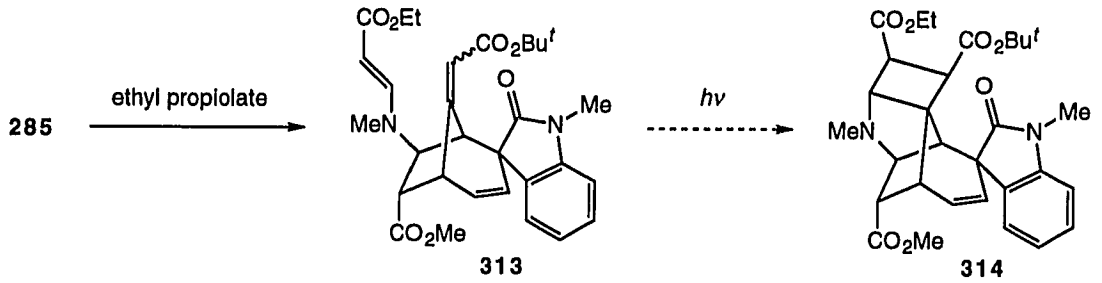
Cyclopropanation is regarded as a powerful method for C-C bond formation. Therefore, we considered the possible intramolecular cyclopropanation of **310** and **311** as sensible alternatives. Significant difficulties affected the preparation of diazoester **310** through condensation of alcohol **306** with the chloride of glyoxylic acid tosylhydrozone and subsequent elimination (Scheme 64). However, standard diazo transfer reaction of **305** provided the diazo compound **311**, but subsequent ring closure under the usual conditions did not afford any desired product **312**.



Scheme 64

Other conceptually different C-C bond forming methods were also explored. Conjugate addition of methylamine **285** to ethyl propiolate was

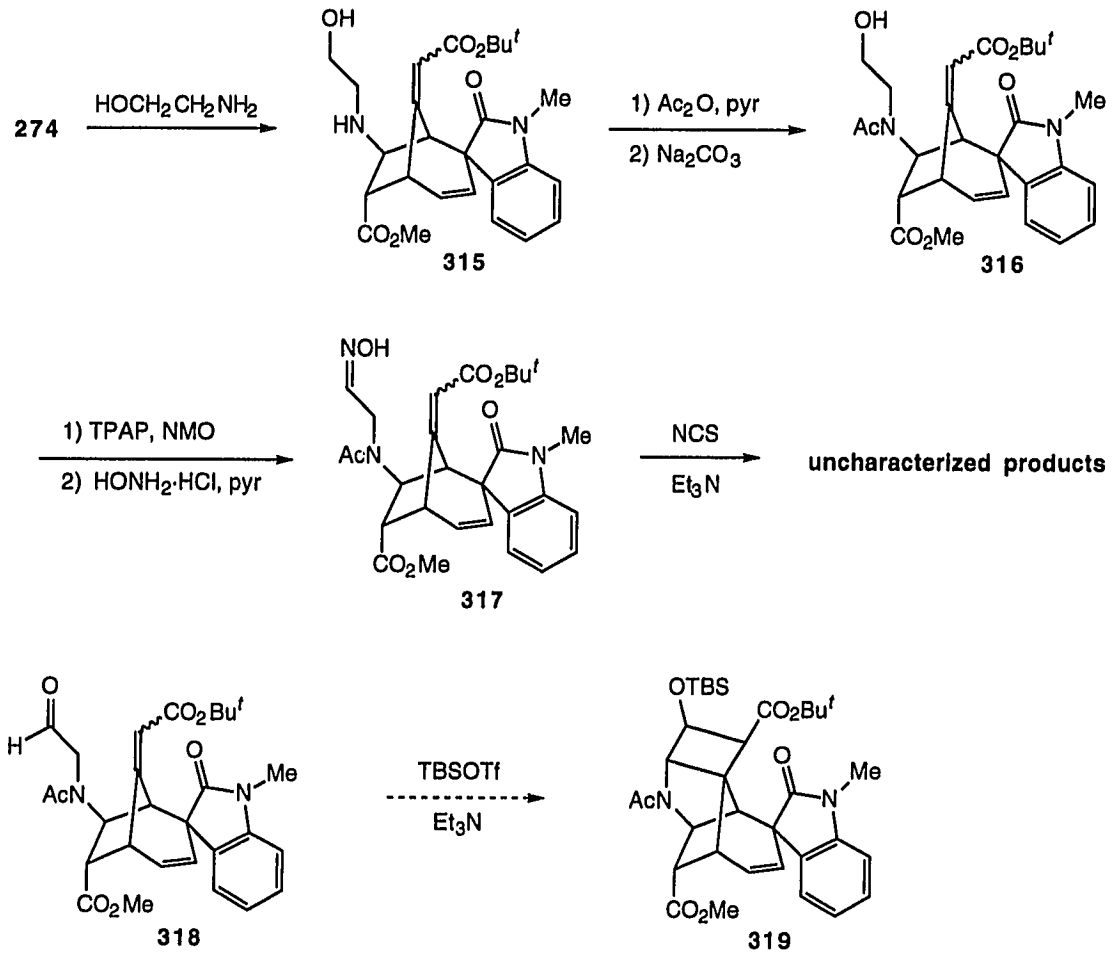
found to be rather facile. This reaction allowed us to run a quick test of [2+2] photocycloaddition[73] (Scheme 65). Irradiation of vinylogous carbamate **313** using medium pressure Hg lamp with Pyrex filter in toluene induced a smooth transformation. Unfortunately, this new product was not the cyclobutane **314**, but rather a product of extensive skeletal rearrangement.



Scheme 65

A [1,3] dipolar addition of nitrile oxide to the neighboring double bond was also tried. The whole sequence started with the Michael addition of ethanolamine to the α,β-unsaturated ester **274** (Scheme 66). Acetylation of both amine and alcohol in **315**, followed by selective hydrolysis of acetate, gave the hydroxyethyl acetamide **316**. Oxidation of alcohol **316** with TPAP and NMO followed by condensation of the resulting aldehyde with hydroxylamine gave the aldoxime **317**. Chlorination of the oxime followed by Et_3N treatment furnished a product which seemed to be neither the nitrile oxide nor the [1,3] dipolar addition product. Fukumoto's tandem intramolecular Michael-aldol reaction[74] for cyclobutane ring formation was also tried. Treatment of aldehyde **318** with TBSOTf and Et_3N did not lead to the desired product **319**.

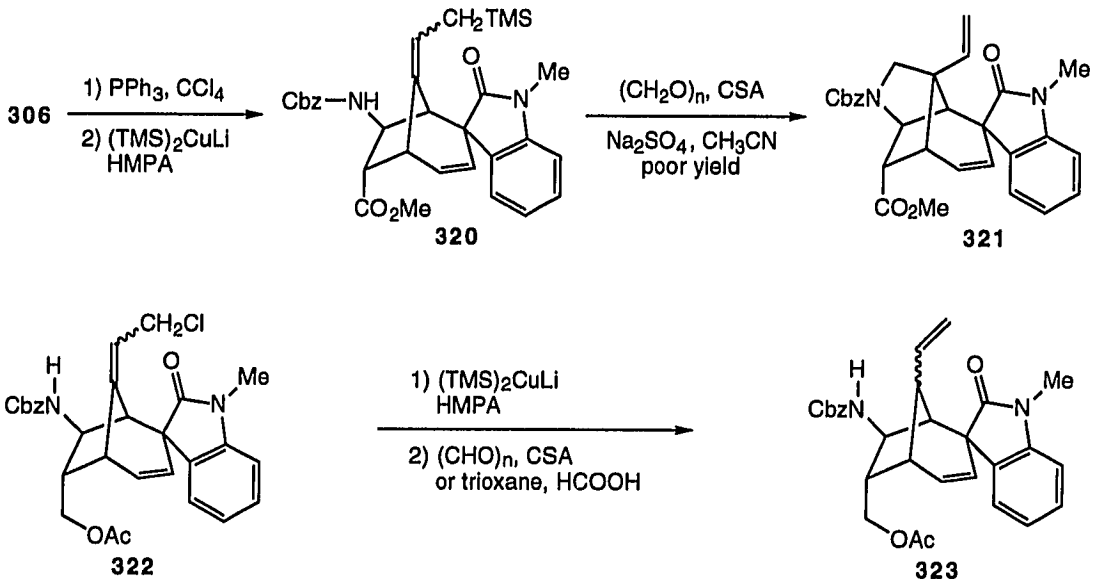
In all our previous C-C bond formation attempts, the amine moiety was used to carry a nucleophile, and the α,β-unsaturated ester served as the



Scheme 66

electrophile. It was envisaged that reversal of the electronic nature of these two moieties might lead to some positive outcome. We first explored Fleming's allylsilane-acyliminium ion intramolecular cyclization. Allylic alcohol **306** was transformed to the allyl chloride, which was treated with lithium bis(trimethylsilyl)cuprate to yield allylsilane **320** (Scheme 67). When **320** was heated with paraformaldehyde and camphorsulfonic acid (CSA), some cyclization product **321** was obtained, but this whole process proved to be rather capricious. First of all, some unknown byproducts formed during

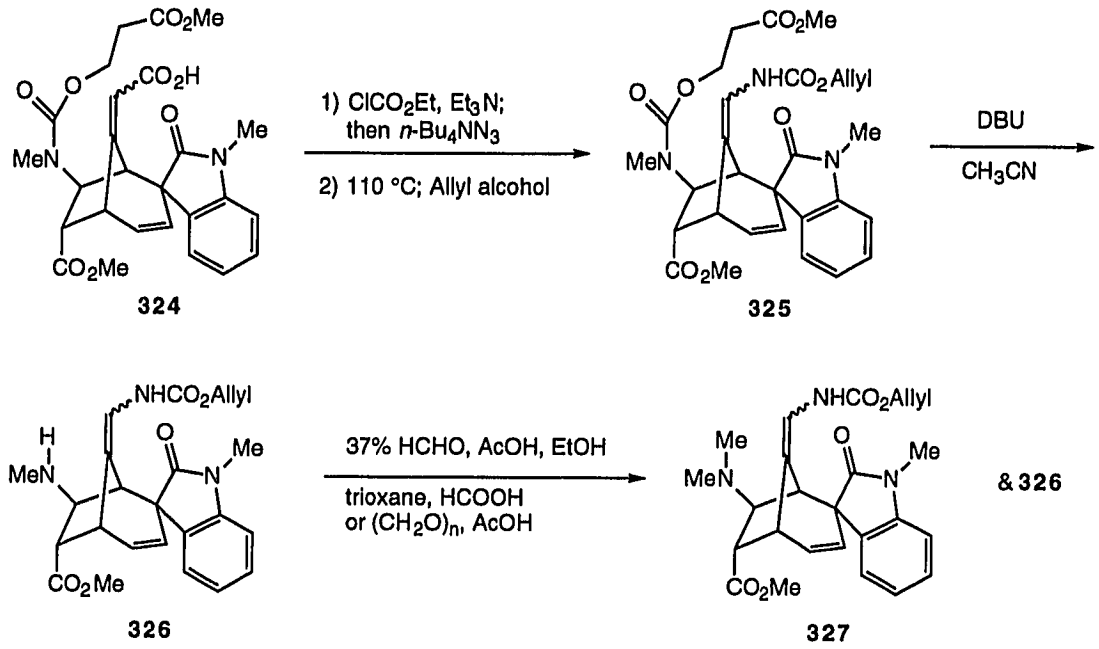
allylsilane formation. When the methyl ester was changed to acetate **322**



Scheme 67

through reduction and acetylation, allylsilane formation was relatively clean (Scheme 67). Secondly, the combination of paraformaldehyde and CSA worked to some extent, but did not give satisfactory results. The trioxane and formic acid conditions worked only in the case of methyl ester, but gave the protiodesilylation product **323** in the acetate series.

Since it is known that an ene-carbamate has comparable, or even stronger, nucleophilicity than an allylsilane, we decided to perform the Mannich-type reaction on an ene-carbamate. The α,β-unsaturated acid **324** was converted to the ene-carbamate **325** in a three-step sequence (Scheme 68). Mixed anhydride formation from carboxylic acid **324** followed by treatment with tetrabutylammonium azide generated the acyl azide, which underwent Curtius rearrangement in refluxing toluene containing allyl alcohol to give the allyl carbamate **325**. Deprotection of the 2-carbomethoxyethyl carbamate with DBU



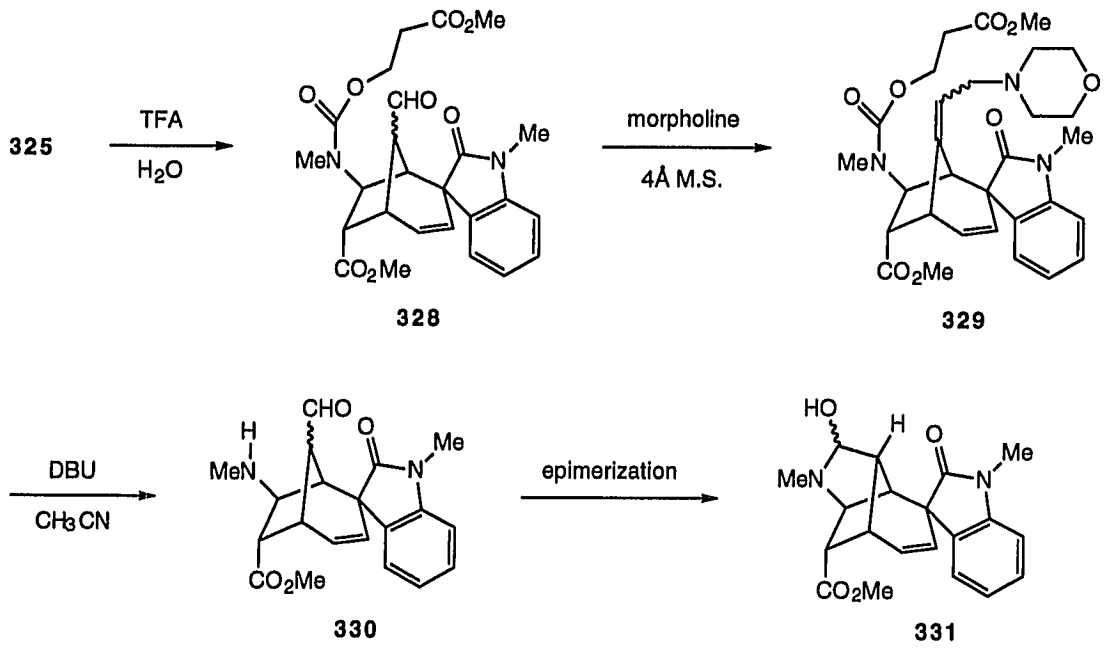
324 **325** **326** **327**

Scheme 68

gave the secondary amine **326**. When amine **326** was subjected to the cyclization conditions as in the allylsilane case, no cyclization product was obtained. Only methylation of the amino group **327**, besides recovery of starting material, was observed. Dimethyl formamide dimethyl acetal was also used as a formaldehyde equivalent, but only formylation of the amine **326** was observed.

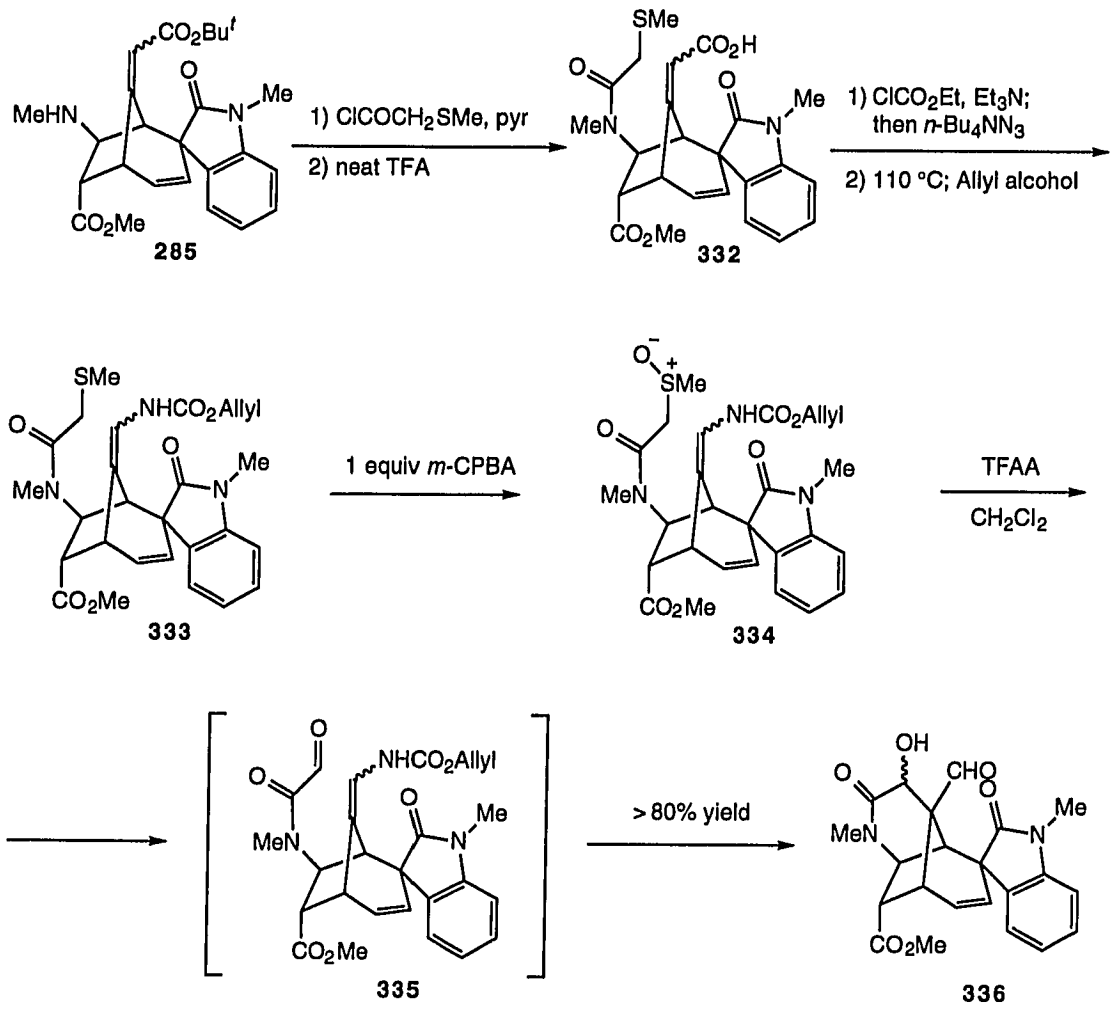
The possibility of engaging enamine **329** as the nucleophile was also explored. Ene-carbamate **325** was hydrolyzed to aldehyde **328** in aqueous trifluoroacetic acid (Scheme 69). Condensation of aldehyde **328** with morpholine in the presence of molecular sieves gave enamine **329**. Removal of carbamate caused hydrolysis of the enamine to aldehyde **330**. Epimerization of the aldehyde caused spontaneous cyclization to aminal **331**.

The real breakthrough came when we tried to form a six-membered ring



Scheme 69

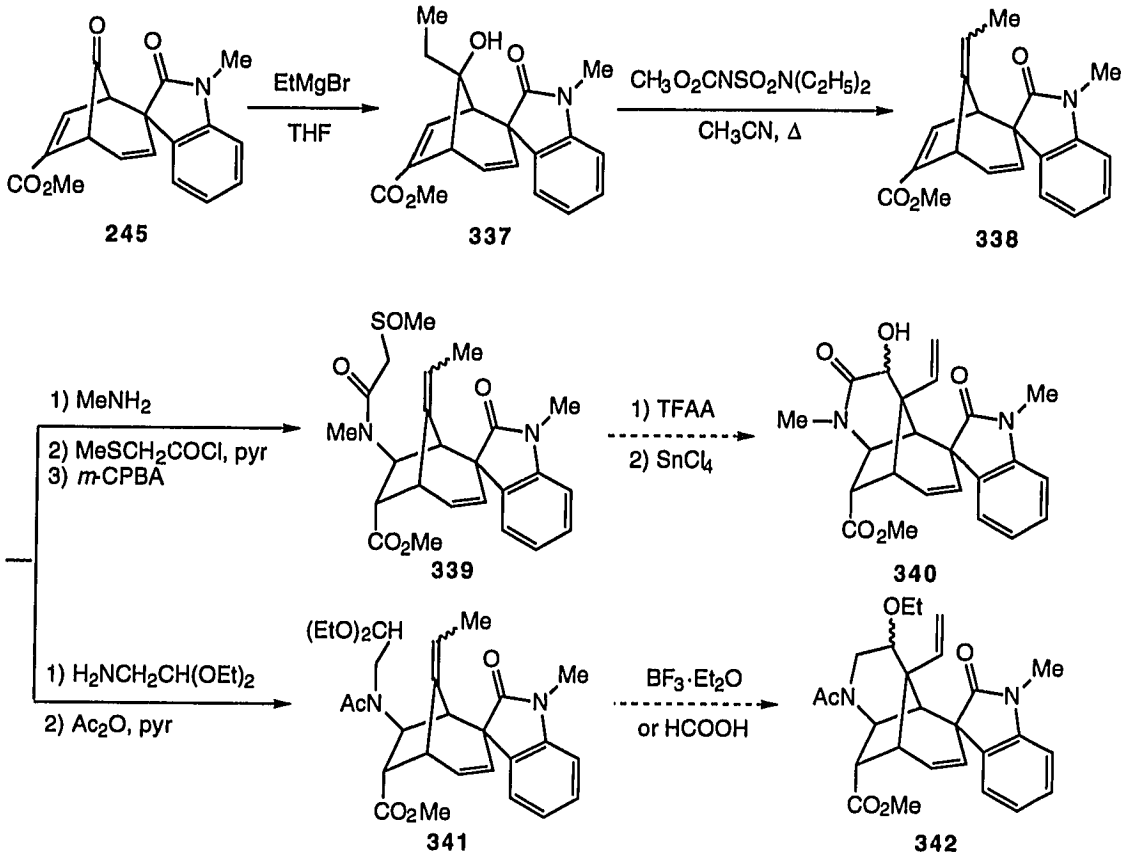
using the ene-carbamate as the nucleophile. The highly reactive intermediate of the Pummerer rearrangement was chosen as the electrophile for the cyclization.[75] Condensation of amine **285** with (methylthio)acetyl chloride followed by hydrolysis of the *t*-butyl ester provided carboxylic acid **332** (Scheme 70). As illustrated in Scheme 68, the conjugate acid **332** was transformed to ene-carbamate **333** through mixed anhydride, acyl azide, and Curtius rearrangement in the presence of allyl alcohol. The sulfide **333** was then oxidized carefully to sulfoxide **334** with *m*-CPBA. When sulfoxide **334** was subjected to Pummerer rearrangement conditions, the hydroxyaldehyde **336** was obtained in more than 80% yield after work-up. we believe that compound **336** forms through nucleophilic attack of the ene-carbamate into the formyl group of glyoxylic amide **335**, which, in turn, arises through reaction of the Pummerer intermediate with adventitious moisture.



Scheme 70

The success of the new mode of C-C bond formation tempted us to explore the possibility of forming the requisite vinyl function of (**1**) directly from during cyclization. To that end, we required olefin **338**. It will be recalled that introduction of a two carbon unit to the apical ketone through Wittig reaction or Julia olefination of **245** did not give any positive results. However, ethylmagnesium bromide did attack the ketone **245** to give some of the tertiary alcohol **337** (Scheme 71). Dehydration of **337** to the olefin could be effected only by refluxing in acetonitrile in the presence of the Burgess salt[76]. Other

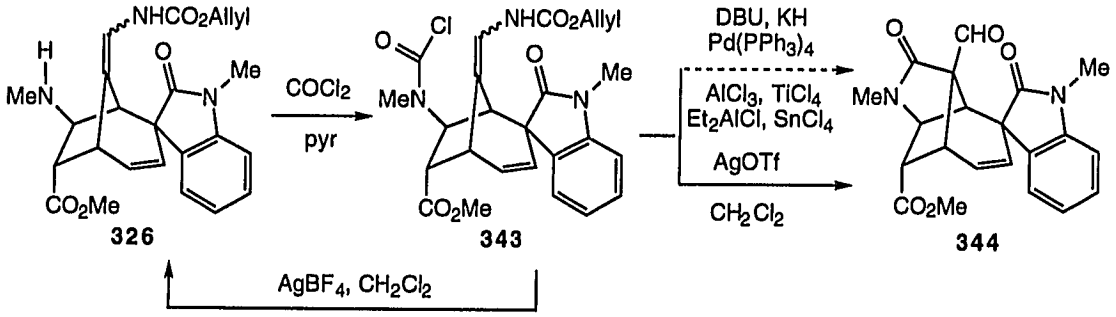
standard procedures involving alcohol activation/elimination failed. Compound **338** was advanced to sulfoxide **339** as described earlier. Subsequent treatment of **339** with trifluoroacetic anhydride and stannic chloride did not yield any cyclization product **340**. Similarly, Lewis acid treatment of acetal **341** failed to induce any cyclization to **342**, underscoring the need for a much more reactive nucleophile in the present C-C bond formation.



Scheme 71

While the six-membered hydroxylactam **325** could theoretically be converted to a γ-lactam by treatment with lead(IV) acetate (LTA),[77] we wished to carry out the direct formation of the five-membered ring. The question then became one of finding a one carbon lower homolog of the 2-oxoacetamide in

the cyclization step. A carbamoyl chloride met this criterion. Since application of this type of chloride is not well documented, we decided to design the experiments by analogy with ordinary acid chlorides. Condensation of amine **326** with phosgene provided stable chloride **343** (Scheme 72). Treatment of ene-carbamate **343** under basic conditions, such as DBU or KH, gave none of the cyclization product **344**. Activation of chloride **343** with tetrakis(triphenylphosphine) palladium met with failure. While treatment with mild Lewis acids led to no activation, stronger ones caused decomposition of the chloride.

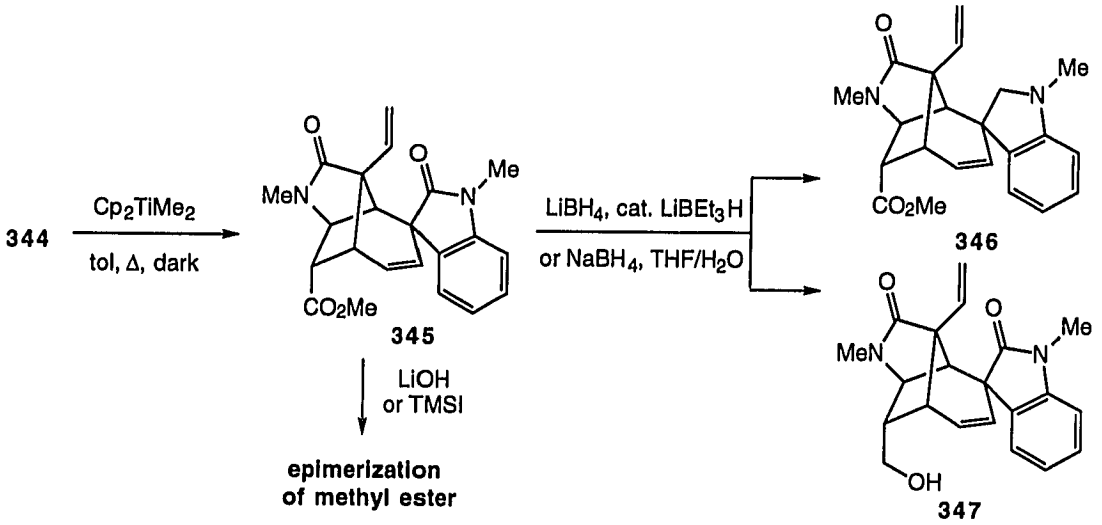


Scheme 72

Since the ability of various silver salt to activate acid chloride is well known,[78] we decided to explore such possibility. Treatment of chloride **326** with silver tetrafluoroborate at low temperature gave no reaction, while elevated temperature caused decomposition of **343** to amine **326** (Scheme 72). This reaction showed that silver ion did activate the chloride, but for unknown reason, there was no C-C bond formation. We were thrilled when **343** was treated with reactive silver triflate in methylene chloride. After simple filtration of the silver chloride precipitate, aldehyde **344** was isolated in ca. 30% yield after chromatography. To the best of our knowledge, this type of lactam formation is

unprecedented, but clearly, it may have great utility for the synthesis of complicated heterocyclic natural products.

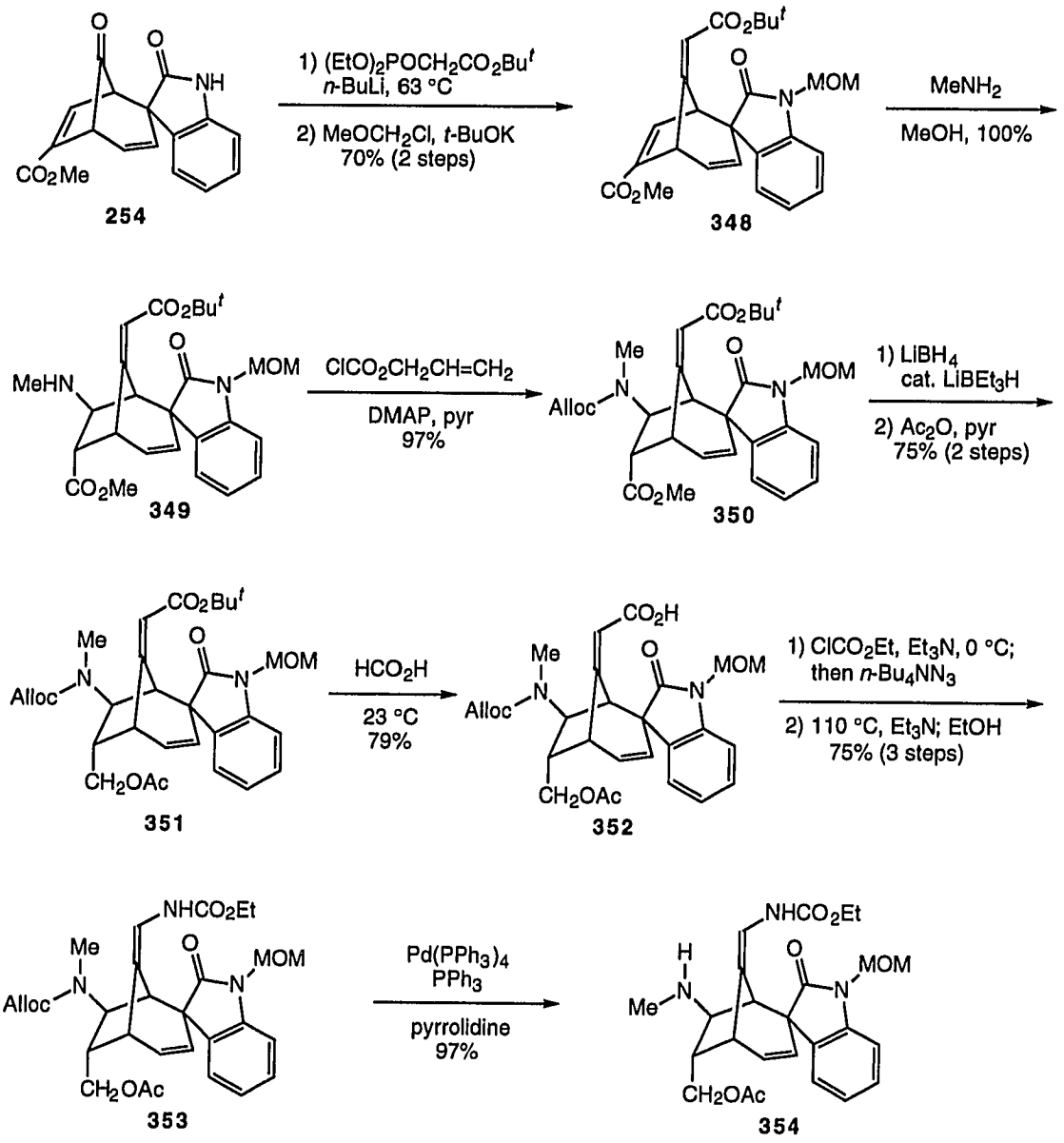
Methylenation of the hindered aldehyde **344** could be performed using bis(cyclopentadienyl)dimethyltitanium[79] to give vinyl compound **345** (Scheme 73). A problem arose during the subsequent reduction of the methyl ester: lithium borohydride and catalytic super hydride reduced the indolinone to give indoline **346**. Sodium borohydride in aqueous THF gave some desired alcohol **347**, in addition to the over-reduced indoline. Attempts to reduce the methyl ester through the carboxylic acid met with unexpected obstacles, in that hydrolysis of ester **345** with either lithium hydroxide or trimethylsilyl iodide (TMSI) caused facile epimerization.



Scheme 73

At this stage, most of the chemistry for the synthesis of gelsemine had been worked out. The problem associated with reduction of methyl ester could be alleviated by reducing it at an earlier stage, as it had been demonstrated in the model study. Thus, Horner-Emmons reaction of **254** using KH gave a mixture of geometric isomers of the *t*-butyl ester. Since reduction of the methyl

ester of the minor isomer was much slower than that of the major one, some efforts were directed toward complete elimination of



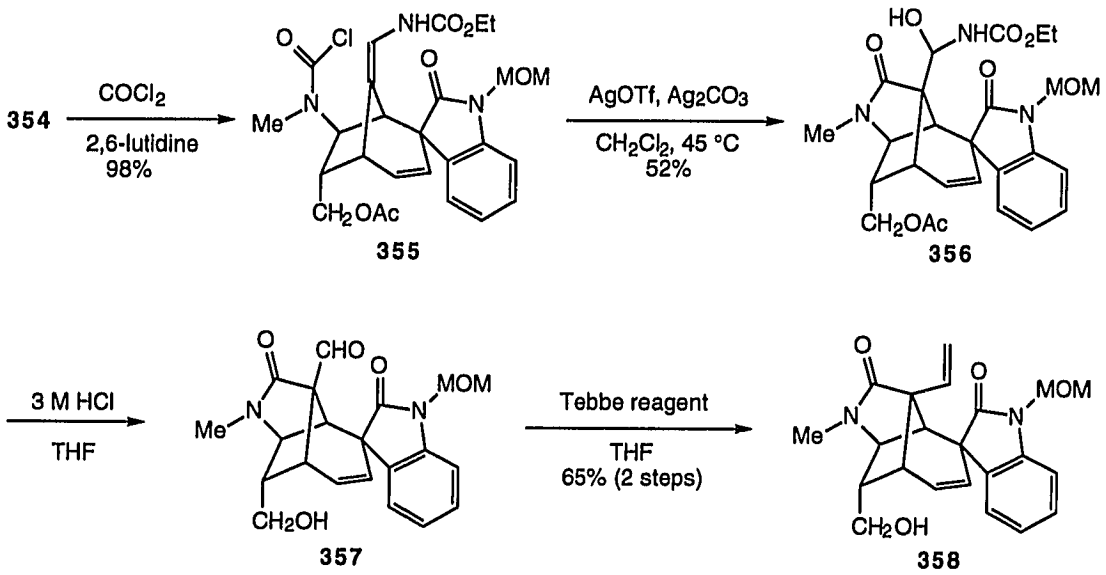
Scheme 74

the minor isomer. Because we could not prepare the *t*-butyl version of Still's phosphonate,[80] which is known to give excellent (*Z*) selectivity, we tried to

change the *E*, *Z* ratio by varying counterion and reaction temperature. Eventually, we found that the lithium salt of the phosphonate at 60 °C gave cleanly a single isomer (Scheme 74). The indolinone was protected by one-pot treatment with chloromethyl methyl ether to give *N*-MOM diester **348** in 70% yield over two steps.

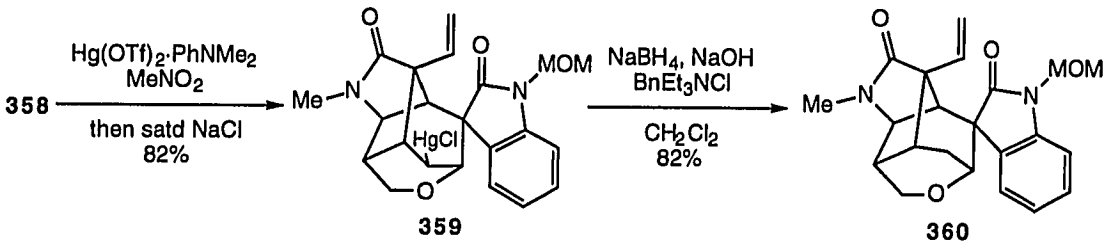
Conjugate addition of methylamine to ester **348** gave amino ester **349** in quantitative yield (Scheme 74). The amine **349** was then protected as allyl urethane **350** in 97% yield. The methyl ester in **350** was selectively reduced with lithium borohydride and catalytic super hydride. The alcohol was isolated as the acetate **351** in 75% yield over two steps. The *t*-butyl ester of **351** was selectively hydrolyzed to carboxylic acid **352** by treatment with neat formic acid in 79% yield, while keeping the *N*-MOM group intact. As in the model study, the acid **352** was transformed to ethyl carbamate **353** through conventional Curtius rearrangement in 75% yield over three steps. Removal of the allyl urethane by Pd(0) and pyrrolidine according to Deziel's procedure[81] gave secondary amine **354** in 97% yield.

Treatment of amine **354** with phosgene in the presence of 2,6-lutidine gave carbamoyl chloride **355** in 98% yield (Scheme 75). The subsequent cyclization was improved by buffering the reaction solution with silver carbonate and by running the reaction in refluxing methylene chloride. Under the optimized conditions, lactam **356** was obtained in 52% yield along with 18% of amine **354**, which resulted from simple decomposition. Hydrolysis of both the aminal derivative and the acetate of **356** using dilute acid gave hydroxyl aldehyde **357**. Methylenation could be better achieved using Tebbe's reagent[82] to give the hydroxyl vinyl compound **358** in 65% yield over two steps.



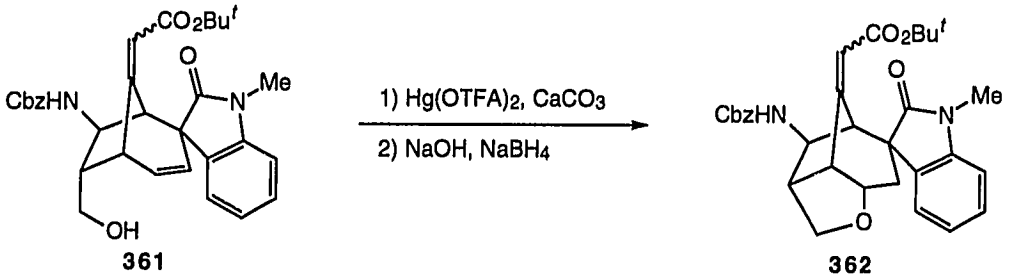
Scheme 75

As shown by Speckamp, the tetrahydropyran ring was formed by subjecting alcohol **358** to mercury(II) triflate-aniline complex in nitromethane[83] (Scheme 76). Upon treatment with sodium chloride, organomercury chloride **359** was isolated in 82% yield. The reduction of mercurial **359** was achieved by two-phase reaction with alkaline $NaBH_4$ in the presence of a large amount of benzyltriethylammomium chloride[84] to give *N*-MOM protected 21-oxogelsemine **360** in 82% yield. The success of the reduction critically depends on a high concentration (0.4 M) of the substrate, according to a private communication from Professor Speckamp.



Scheme 76

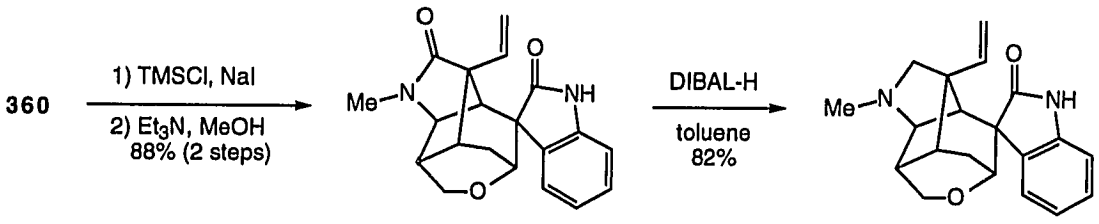
The excellent regioselectivity of cyclic ether formation was believed to be related to the conformation of the substrate. We found that oxymercuration /demercurization of alcohol **361**, wherein no lactam was yet present, gave only the 5-membered tetrahydrofuran **362**, whose structure was confirmed by COSY-2D NMR (Scheme 77). Use of phenylselenenyl chloride did not change the outcome of the cyclization. Contrary to expectation, the steric effect was not a decisive factor in the regioselectivity of cyclic ether formation.



361 **362**

Scheme 77

The *N*-MOM group of **360** was removed by treatment with TMSI followed by methanolysis of the resulting hydroxymethyl group to give 21-oxogelsemine (**3**) in 88% yield (Scheme 78). Selective reduction of the lactam with DIBAL-H in toluene yielded gelsemine (**1**) in 82% yield. Both synthetic 21-oxogelsemine and gelsemine are identical to natural samples, kindly provided by Professor Cordell at the University of Illinois, Chicago, by comparison of TLC, ^1H,



21-Oxogelsemine (3) **Gelsemine (1)**

Scheme 78

^{13}C NMR and HRMS.

In summary, we have accomplished the first stereocontrolled total synthesis of (±)-gelsemine (**1**) through 21-oxogelsemine (**3**) by novel application of divinylcyclopropane-cycloheptadiene rearrangement and by taking advantage of the steric hindrance of the bicyclo[3.2.1] system. This synthesis can also be applied to synthesis of enantiopure gelsemine. Asymmetric cyclopropanation of diazo compound **236** with appropriate chiral catalyst[85] would lead to natural gelsemine.

Chapter IV

Experimental

Technical notes

Melting points (mp), determined on a Mel-Temp, were uncorrected.

Infrared (IR) spectra were recorded on Nicolet 205 Infrared Spectrophotometer and are reported in wavenumbers (cm^{-1}).

^{1}H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) spectra were determined on a Bruker AC250 instrument unless otherwise noted. Chemical shifts for ^{1}H NMR are reported in parts per million (δ) downfield from tetramethylsilane as the internal standard and coupling constants are in hertz(Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, sex = sextet, m = multiplet and b = broad. When d^{6}-DMSO was used as solvent, ^{1}H NMR spectra were reported in ppm relative to the center line of a septet at 2.49 ppm for deuteriomethyl sulfoxide. ^{13}C NMR spectra were reported in ppm relative to the center line of a triplet at 77.0 ppm for deuteriochloroform or a septet at 39.7 ppm for deuteriomethyl sulfoxide.

Mass spectra (MS) were obtained on a Finnigan 3300 quadrupole at 70eV, unless otherwise noted, using direct probe insertion at temperature of 100 to 300 °C. High resolution mass spectra were obtained on a Finnigan Mat95 with electronic impact ion source at 70 eV, unless otherwise noted, using probe insertion at temperatures of 50 to 300 °C.

Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F_{254}. Preparative TLC separations were made on 10 x 20 cm or 20 x 20 cm plates prepared with a 2

mm layer of Merck silica gel 60 F_{254}. Compounds were eluted from the adsorbent with 10% methanol in dichloromethane.

All evaporations were performed under reduced pressure on a rotary evaporator.

Column chromatography was performed on Woelm silica gel, 230-400 mesh, packed in ACE columns on a flash chromatography system.

Commercial grades reagents and solvents were used as supplied with the following exceptions:

Dichloromethane and diethyl ether:
distilled through a 24 inch Snyder column.

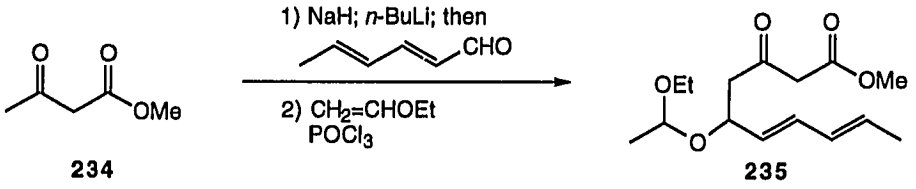
Tetrahydrofuran (dry):
distilled from sodium benzophenone ketyl.

Pyridine, triethylamine, and *N,N*-diisopropylethylamine:
dried over potassium hydroxide pellets.

t-Butanol: distilled from calcium hydride.

N, N-dimethylformamide, benzene, toluene, acetonitrile, and methanol:
dried over 4Å molecular sieves.

All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.



234 235

Methyl (6*E*, 8*E*)-5-ethoxyethyloxy-3-oxo-6,8-decadienoate (**235**)

Sodium hydride 18.9 g (0.473 mol), as a 60% mineral oil dispersion, was weighed into a 1-L flask, into which 400 mL of tetrahydrofuran was directly distilled. The flask was capped with septum cap, flushed with argon, and cooled in an ice bath. To above stirred slurry was added dropwise 46.5 mL (0.431 mol) of methyl acetoacetate **234**. After the addition was complete, the resulting mixture was stirred at 0 °C for additional 10 min. To above mixture was then added 182 mL (0.453 mol) of *n*-butyllithium, a 2.49 M solution in hexane, in a dropwise manner. The orange colored reaction mixture was stirred for additional 10 min before 54.7 mL (0.496 mol) of sorbic aldehyde was added in one portion. The reaction mixture was then allowed to warm to room temperature and stirred for additional 30 min before it was quenched by slow addition of 77.2 mL (cat. 0.926 mol) of concentrated hydrochloric acid. The biphasic mixture was poured to 50 mL of water and extracted with 500 mL of ethyl ether. The aqueous layer was extracted thoroughly with ethyl ether. The ethereal extracts were combined, washed with 2x50 mL of saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to give a brown oily residue.

To an ice-cold, stirred solution of the above residue and 65.8 mL (0.688 mol) of ethyl vinyl ether in 250 mL of dichloromethane was added 0.41 mL (0.0287 mmol) of phosphorus oxychloride in 2.0 mL of dichloromethane. The reaction was then allowed to warm to room temperature and stirred for 1 h. The

mixture was concentrated *in vacuo* to half of its original volume, diluted by addition of 350 mL of ethyl ether, and then poured into 25 mL of a saturated aqueous sodium bicarbonate solution. The aqueous layer was removed after partition and the extract was washed with 25 mL of brine, dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The residue was then separated by flash chromatography eluting with 5-25% ether in hexanes to give 64.9 g (53%) of **235** as a yellow oil.

IR (thin film): 2984, 2938, 1749, 1722, 1656, 1629, 1437, 1324, 1244, 1131, 1091, 992

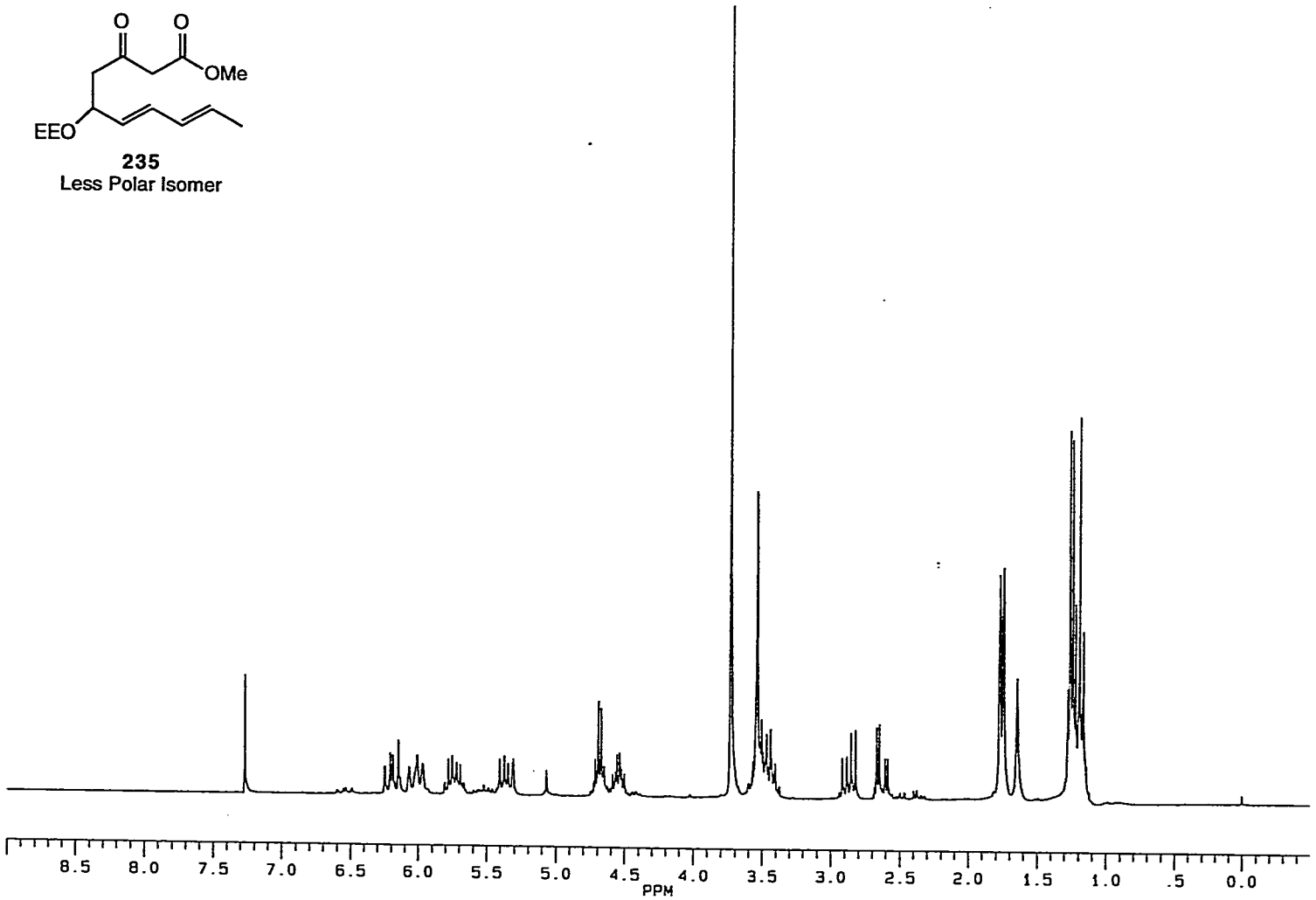
^{1}H NMR ($CDCl_3$): less polar isomer
1.25 (3H, d, 5.2 Hz), 1.76 (3H, d, 7.0 Hz), 1.89 (3H, t, J = 7.1 Hz), 2.63 (1H, dd, J_1 = 4.9 Hz, J_2 = 15.4 Hz), 2.87 (1H, dd, J_1 = 8.3 Hz, J_2 = 15.4 Hz), 3.40 - 3.57 (2H, m), 3.54 (2H, s), 3.73 (3H, s), 4.54 (1H, td, J_1 = 4.9 Hz, J_2 = 8.2 Hz), 4.68 (1H, q, J = 5.3 Hz), 5.36 (1H, dd, J_1 = 8.2 Hz, J_2 = 15.1 Hz), 5.74 (1H, dd, J_1 = 6.7 Hz, J_2 = 14.8 Hz), 6.01 (1H, ddd, J_1 = 1.45 Hz, J_2 = 10.3 Hz, J_3 = 14.8 Hz), 6.20 (1H, J_1 = 10.3 Hz, J_2 = 15.1 Hz)

more polar isomer
1.13 (3H, t, J = 7.1 Hz), 1.24 (3H, d, J = 5.3 Hz), 1.74 (3H, d, J = 6.6 Hz), 2.59 (1H, dd, J_1 = 4.5 Hz, J2 = 15.9 Hz), 2.88 (1H, dd, J_1 = 8.1 Hz, J_2 = 15.9 Hz), 3.36 (1H, dd, J_1 = 7.2 Hz, J_2 = 9.2 Hz), 3.48 (2H, s), 3.61 (1H, dd, J_1 = 7.2 Hz, J_2 = 9.1 Hz), 3.72 (3H, s), 4.38 (1H, td, J_1 = 4.7 Hz, J_2 = 8.1 Hz), 4.65 (1H, q, J = 5.3 Hz), 5.48 (1H, dd, J_1 = 8.0 Hz, J_2 = 15.0 Hz), 5.71 (1H, dd, J_1 = 6.8 Hz, J_2 = 14.7 Hz), 6.00 (1H, ddd, J_1 = 1.23 Hz, J_2 = 10.3 Hz, J_3 = 14.8 Hz), 6.17 (1H, dd, J_1 = 10.3 Hz, J_2 = 15.0 Hz)

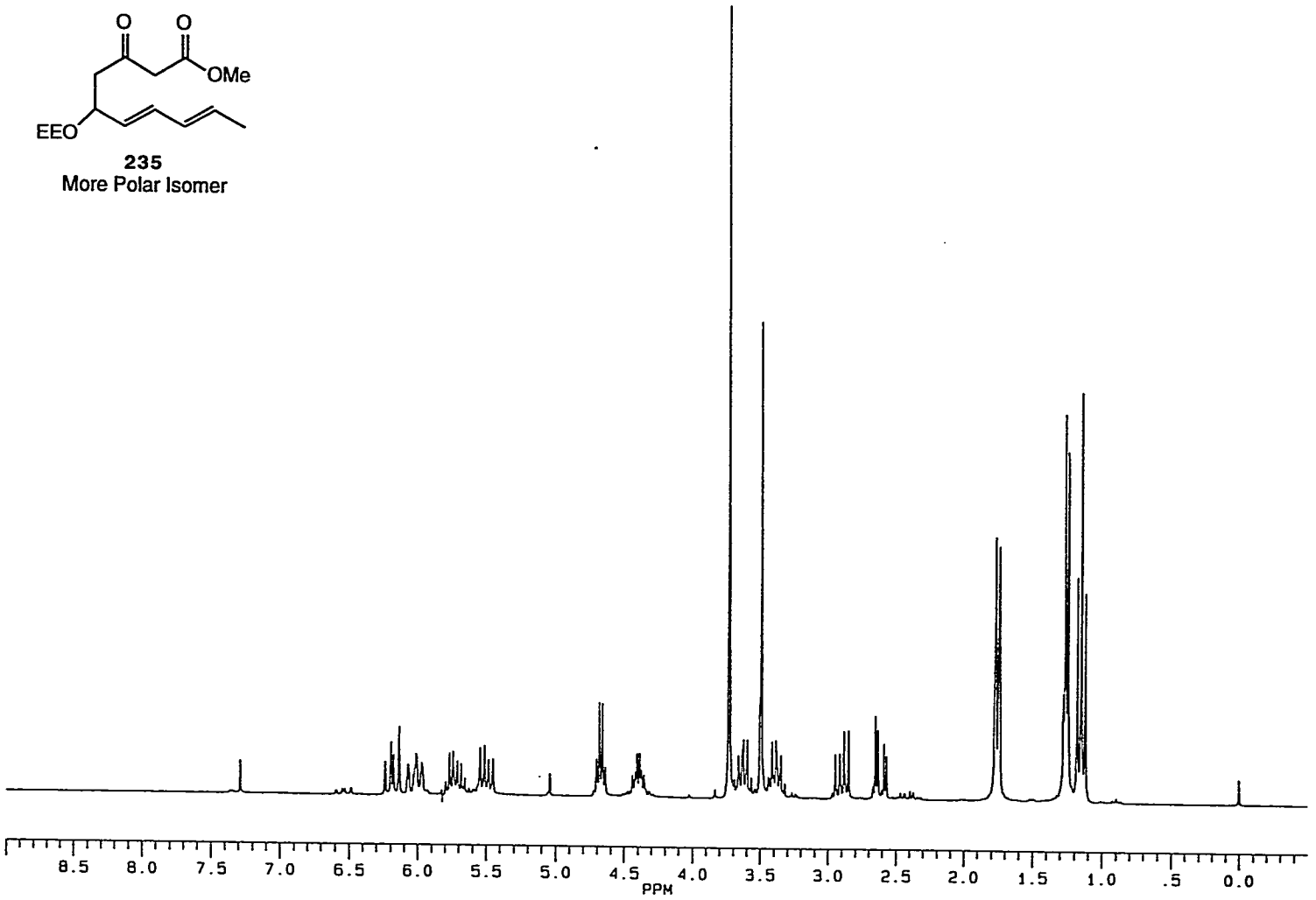
^{13}C NMR ($CDCl_3$): 14.90, 15.11, 17.87,17.87, 20.11, 20.13, 48.76, 49.90, 50.04, 52.01, 59.60, 61.18, 72.45, 73.26, 96.91, 96.91, 99.33, 99.33, 128.72, 129.68, 130.16, 130.28, 130.43, 130.77, 132.00, 133.30, 167.16, 167.29, 200.37, 200.44

MS (40 eV): 285 (<1, M+1), 284 (<1, M^+), 238 (14), 211 (27), 190 (38), 163 (31), 121 (100), 101 (80), 79 (80), 59 (85), 44 (72)

Exact Mass:	Calculated for $C_{15}H_{24}O_5$	284.1624
	Found	284.1615

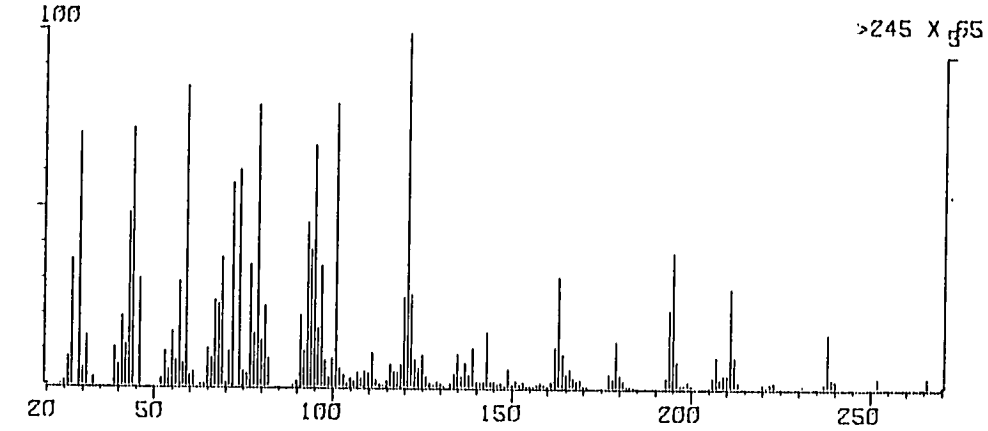


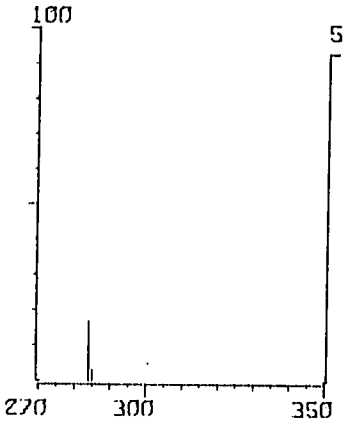
235
Less Polar Isomer

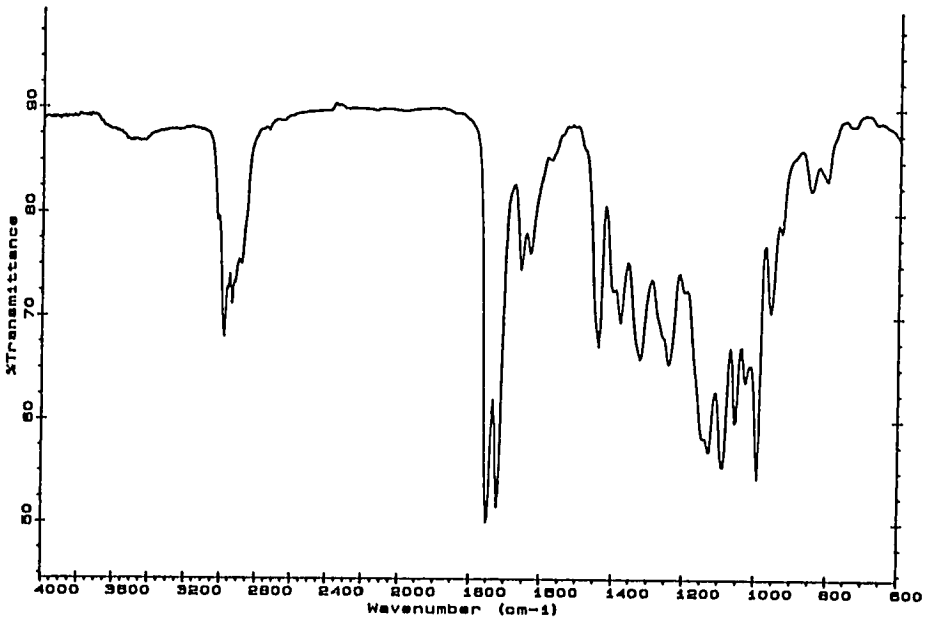


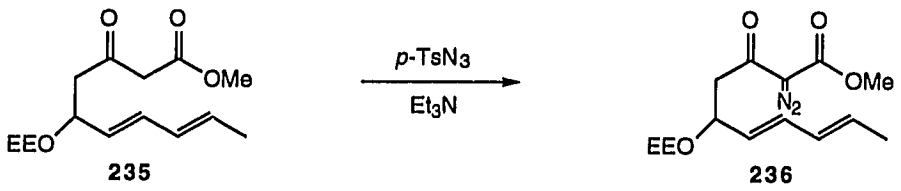
235
More Polar Isomer

Compound **235** continued:









235 236

Methyl (6*E*, 8*E*)-5-ethoxyethloxy-3-oxo-2-diazo-6,8-decadienoate (**236**)

To a stirred solution of 35.0 g (0.123 mol) of β-keto ester **235** and 18.7 mL (0.123 mol) of *p*-toluenesulphonyl azide in 200 mL of dichloromethane at 0 °C was added 42.9 mL (0.308 mol) of triethylamine through dropping funnel over a period of 30 min. After the addition of triethylamine, the reaction was allowed to warm to room temperature and stirred for additional 1 h. The mixture was evaporated to a small volume and partitioned between 350 mL of ethyl ether and 2x50 mL of 3 M hydrochloric acid. The aqueous layer was extracted thoroughly with ethyl ether. The extracts were combined, washed with a saturated aqueous sodium bicarbonate solution and brine, dried over sodium sulfate, filtered and evaporated *in vacuo*. The semi-solid residue was taken up in 100 mL of 40% ether-hexanes and filtered through celite. The solid was washed with 100 mL of 40% ether-hexanes. The filtrate and washings were combined and evaporated under reduced pressure. A flash silica gel column chromatography with 5-30% ether-hexanes as eluent afforded 31.7 g (83%) of **236** as a yellow oil.

IR (film): 2984, 2938, 2134, 1729, 1663, 1437, 1370, 1317, 1224, 1198, 1131, 1098, 1058, 1032, 992, 746

^{1}H NMR ($CDCl_3$): less polar isomer
1.18 (3H, t, 7.1 Hz), 1.25 (3H, d, 5.4 Hz), 1.75 (3H, d, 6.8 Hz), 2.96 (1H, dd, J_1 = 5.42 Hz, J_2 = 15.8 Hz), 3.28 (1H, dd, J_1 = 7.6 Hz, J_2 = 15.8 Hz), 3.47 (1H, dd, J_1 = 9.2 Hz, J_2 = 16.3 Hz), 3.57 (1H, dd, J_1 = 7.2 Hz, J_2 = 9.2 Hz), 3.83 (3H, s), 4.62 (1H, dt, J_1 = 5.5 Hz, J_2 = 8.0 Hz), 4.70 (1H, q, J =

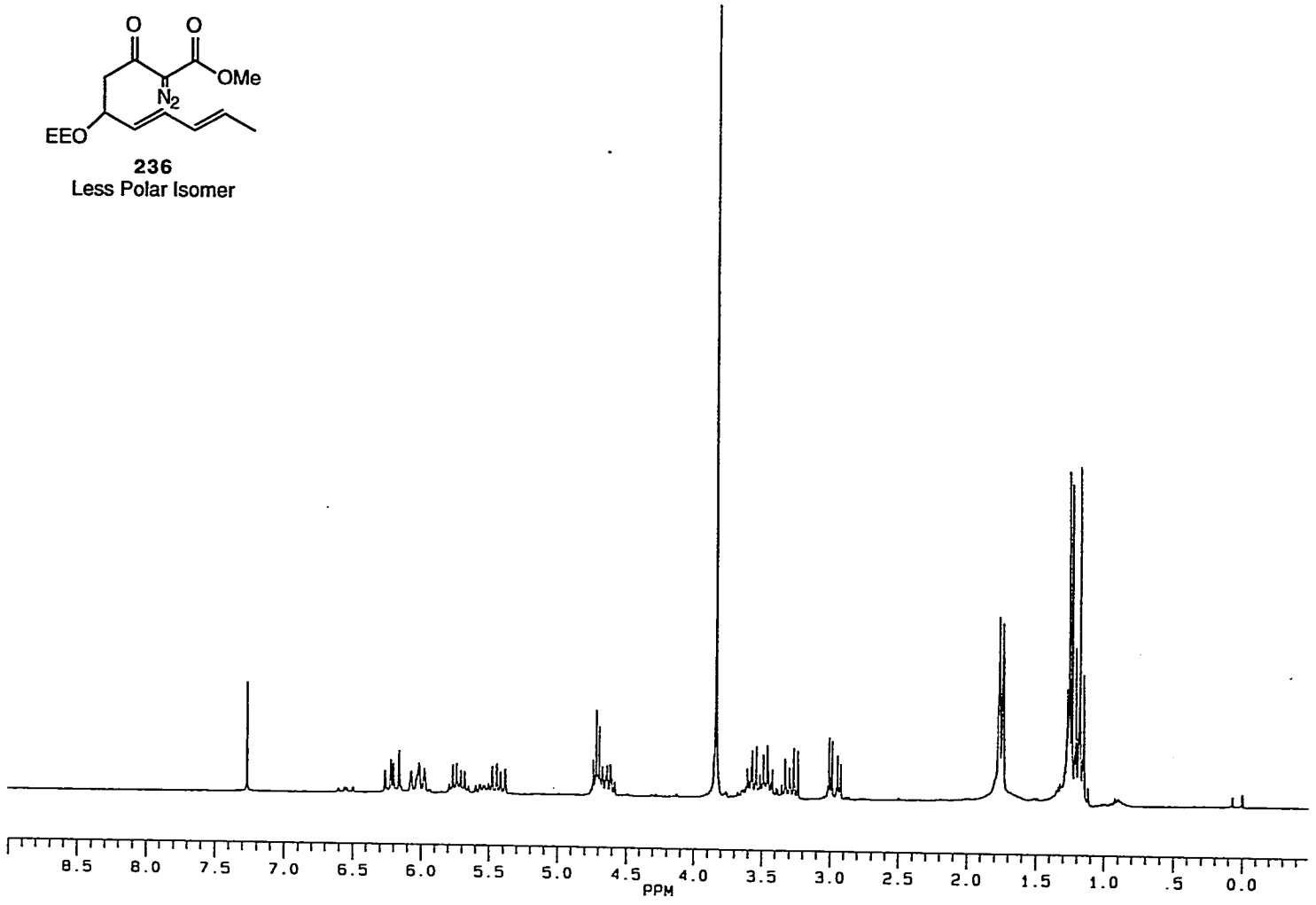
5.4 Hz), 5.43 (1H, dd, J_1 = 8.2 Hz, J_2 = 15.1 Hz), 5.72 (1H, dd, J_1 = 6.7, J_2 = 14.8 Hz), 6.02 (1H, ddd, J_1 = 1.36 Hz, J_2 = 10.5 Hz, J_3 = 14.8 Hz), 6.21 (1H, dd, J_1 = 10.4 Hz, J_2 = 15.1 Hz)

more polar isomer
1.15 (3H, t, J = 7.0 Hz), 1.27 (3H, d, J = 5.3 Hz), 1.75 (3H, d, 6.8 Hz), 2.94 (1H, dd, J_1 = 5.0 Hz, J_2 = 16.1 Hz), 3.33 (1H, dd, J_1 = 7.8 Hz, J_2 = 16.4 Hz), 3.38 (1H, dd, J_1 = 4.5 Hz, J_2 = 6.6 Hz) , 3.64 (1H, dd, J_1 = 6.9 Hz, J_2 = 9.3 Hz), 4.50 (dt, J_1 = 5.2 Hz, J_2 = 7.8 Hz), 4.71 (1H, q, J = 5.3 Hz), 5.55 (1H, dd, J_1 = 7.9 Hz, J_2 = 15.2 Hz), 5.71 (1H, dd, J_1 = 6.7 Hz, J_2 = 14.8 Hz), 6.02 (1H, ddd, J_1 = 1.34 Hz, J_2 = 10.2 Hz, J_3 = 14.8 Hz), 6.19 (1H, dd, J_1 = 10.4 Hz, J_2 = 15.1 Hz)

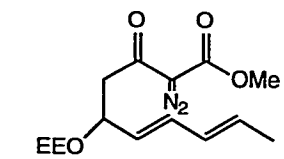
^{13}C NMR ($CDCl_3$): 14.63, 14.81, 17.59, 17.59, 19.90, 19.90, 45.71, 51.68, 58.87, 60.61, 72.15, 72.64, 75.69, 75.69, 96.69, 96.69, 98.87, 98.87, 129.29, 129.63, 129.95, 130.07, 130.18, 130.31, 131.43, 132.62, 161.02, 161.02, 188.90.188.99

MS (40 eV): 310 (<1, M^+), 279 (<1), 259 (2), 237 (21), 221 (25), 209 (62), 161 (33), 113 (25), 121 (24), 113 (40), 105 (64), 95 (89), 79 (90), 44 (100), 29 (88)

Exact Mass:		
	Calculated for $C_{15}H_{22}N_2O_5$	310.1528
	Found	310.1521

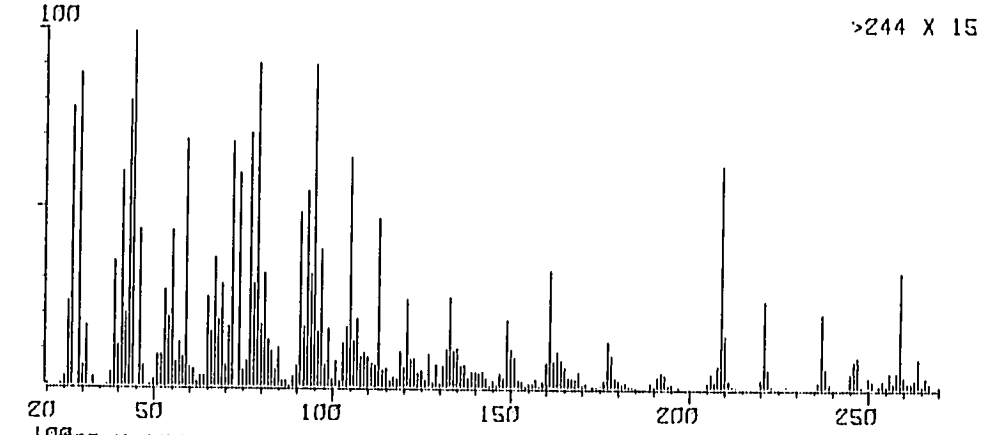


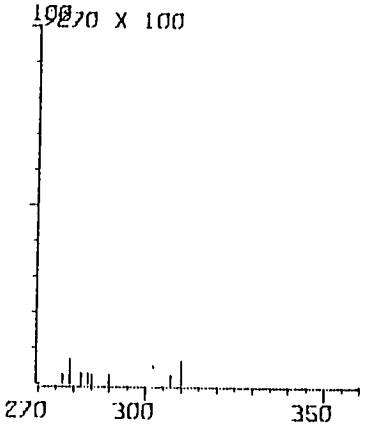
236
Less Polar Isomer

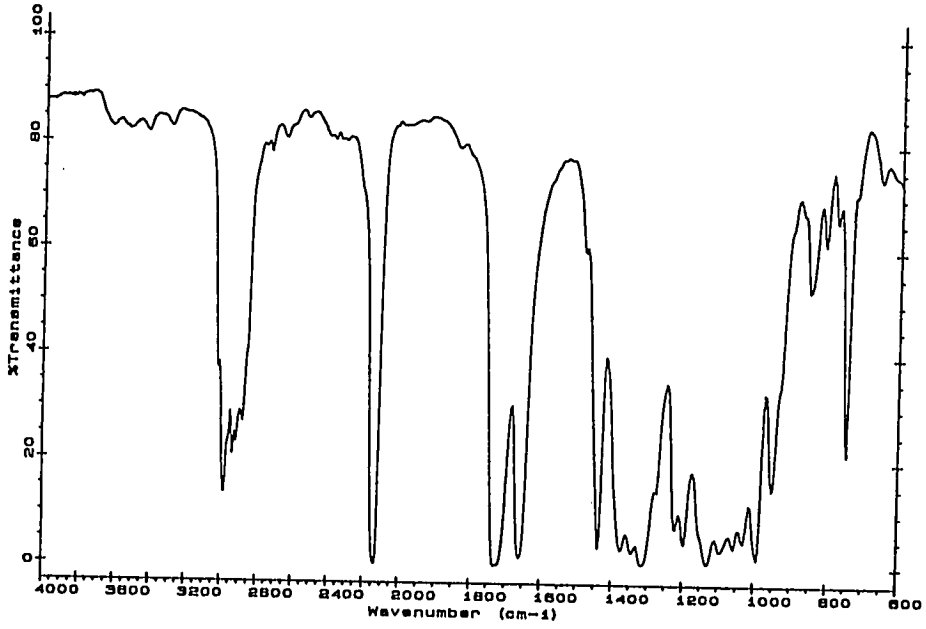


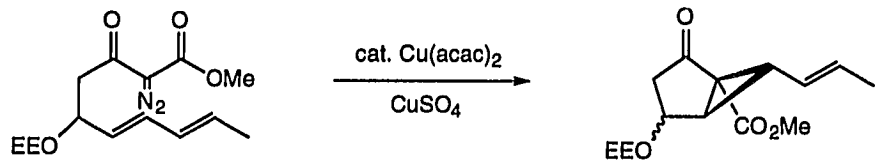
236
More Polar Isomer

Compound **236** continued:









236 **237**

1-Carbomethoxy-4-ethoxyethyloxy-6-exo[(*E*)-1-propenyl]bicyclo[3.1.0]-hexan-2-one (**237**)

To a stirred solution of 1.31 g (5.00 mmol) of cupric acetylacetonate and 23.9 g (150 mmol) of anhydrous copper(II) sulfate in 250 mL of benzene at 85 °C under argon was added slowly 31.0 g (99.9 mmol) of diazo ester **236** in 100 mL of benzene over a period of 2 h. The resulting mixture was heated at 85 °C for an additional 1.5 h. The reaction mixture was then allowed to cool to room temperature and filtered through celite. The solid was washed thoroughly with ethyl ether. The filtrate and washings were condensed to dryness *in vacuo.* The crude product was separated through flash silica gel chromatography eluting with 40% to 60% ether-hexanes to give 28.2 g (68.4%) of **237** as a light yellow oil.

IR (film): 2984, 2944, 1736, 1437, 1357, 1331, 1257, 1231, 1171, 1125, 1098, 1038, 972, 932, 832, 813

^{1}H NMR ($CDCl_3$): isomers from less polar isomer of **225**
1.20 (3H, t, J = 7.0 Hz), 1.22 (3H, t, J = 7.8 Hz), 1.33 (3H, d, J = 5.2 Hz), 1.33 (3H, overlapping), 1.70 (3H, d, J = 6.4 Hz), 1.70 (3H, overlapping), 1.74 (1H, ddd, J_1 = 1.7 Hz, J_2 = 6.8 Hz, J_3 = 12.3 Hz), 2.16 (1H, dd, J_1 = 5.6 Hz, J_2 = 8.8 Hz), 2.29 (1H, dd, J_1 = 7.7 Hz, J_2 = 18.9 Hz), 2.34 (1H, s), 2.25-2.40 (1H, m), 2.54 (1H, dd, J_1 = 5.7 Hz, J_2 = 18.7 Hz), 2.57 (1H, dd, J_1 = 4.5 Hz, J_2 = 18.6 Hz), 2.67 (1H, dd, J_1 = 5.6 Hz, J_2 = 8.9 Hz), 2.84 (1H, d, J = 5.5 Hz), 2.90 (1H, t, J = 5.2 Hz), 3.45 (1H, dd, J_1 = 7.1 Hz, J_2 = 14.2 Hz), 3.49 (1H, dd, J_1 = 7.0 Hz, J_2 = 14.1 Hz), 3.64 (1H, dd, J_1 = 6.8 Hz, J_2 = 9.1 Hz), 3.67 (1H, dd, J_1 = 6.1 Hz, J_2 = 9.3 Hz), 3.77 (3H, s), 3.78 (3H, s), 4.40 (1H, d, J =5.7 Hz), 4.68 (1H, td, J_1 = 5.4

Hz, J_2 = 7.8 Hz), 4.84 (1H, q, J = 5.4 Hz), 4.88 (1H, q, J = 5.4 Hz), 5.22 (1H, ddd, J_1 = 1.2 Hz, J_2 = 7.6 Hz, J_3 = 15.0 Hz), 5.29 (1H, ddd, J_1 = 1.6 Hz, J_2 = 8.9 Hz, J_3 = 15.2 Hz), 5.73 (1H, dd, J_1 = 6.4 Hz, J_2 = 12.9 Hz), 5.83 (1H, ddd, J_1 = 1.6 Hz, J_2 = 6.6 Hz, J_3 = 15.4 Hz)

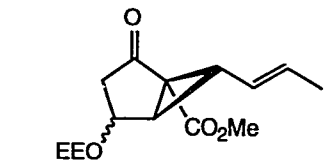
isomers from more polar isomer of **225**
1.19 (3H, t, J = 6.9 Hz), 1.21 (3H, t, J = 6.9 Hz), 1.33 (3H, d, J =5.3 Hz), 1.34 (3H, d, J = 5.3 Hz), 1.69 (3H, d, J = 6.5 Hz), 1.70 (3H, d, J =6.6 Hz), 1.74 (1H, ddd, J_1 = 1.6 Hz, J_2 = 7.0 Hz, J_3 = 12.6 Hz), 2.17 (1H, dd, J_1 = 5.6 Hz, J_2 = 8.7 Hz), 2.25 (1H, dd, J_1 =7.9 Hz, J_2 = 18.7 Hz), 2.25 (1H, d, J = 19.1 Hz), 2.49 (1H, dd, J_1 =5.6 Hz, J_2 = 19.3 Hz), 2.57 (1H, dd, J_1 = 9.2 Hz, J_2 = 18.6 Hz), 2.70 (1H, dd, J_1 =5.4 Hz, J_2 = 8.8 Hz), 2.89 (1H, d, J = 5.3 Hz), 2.92 (1H, dd, J_1 = 5.3 Hz, J_2 = 10.3 Hz), 3.49 (1H, td, J_1 = 2.3 Hz, J_2 = 6.8 Hz), 3.54 (1H, dd, J_1 = 6.4 Hz, J_2 = 13.2 Hz), 3.61 (1H, dd, J_1 = 5.0 Hz, J_2 = 7.0 Hz), 3.65 (1H, dd, J_1 = 5.0 Hz, J_2 = 7.0 Hz), 3.77 (3H, s), 3.78 (3H, s), 4.38 (1H, d, J =5.4 Hz), 4.60 (1H, dd, J_1 = 5.3 Hz, J_2 = 8.3 Hz), 4.79 (1H, dd, J_1 = 1.9 Hz, J_2 = 5.4 Hz), 4.75-4.82 (1H, m), 5.24 (1H, ddd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, J_3 = 15.1 Hz), 5.29 (1H, ddd, J_1 = 1.4 Hz, J_2 = 8.8 Hz, J_3 = 14.9 Hz), 5.73 (1H, dd, J_1 = 6.4 Hz, J_2 = 13.0 Hz), 5.84 (1H, dd, J_1 = 6.5 Hz, J_2 = 15.2 Hz)

^{13}C NMR ($CDCl_3$): 13.26, 15.07, 15.07, 15.07, 17.87, 17.87, 17.90, 17.90, 19.99, 20.08, 20.19, 20.06, 35.15, 35.40, 36.42, 36.47, 37.23, 38.01, 39.74, 40.22, 40.78, 40.86, 41.98, 42,05, 42.65, 42.70, 44.04, 44.12, 52.11, 52.15, 52.15, 52.24, 59.78, 60.02, 60.36, 60.96, 67.13, 68.28, 68.72, 69.43, 98.43, 98.54, 98.57, 99.23, 123.41, 123.45, 123.48, 123.51, 131.19, 131.24, 131.30, 131.33, 165.55, 165.90, 165.97, 165.97, 201.27, 201.45, 203.16, 203.24

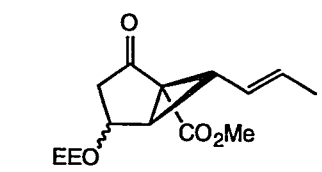
MS (40 eV): 283 (<1, M+1), 282 (<1, M^+), 251 (3), 211 (53), 192 (56), 161 (63), 133 (72), 105 (92), 91 (66), 77 (92), 72 (100), 44 (100), 29 (90)

Exact Mass:

Calculated for $C_{15}H_{22}O_5$	282.1467
Found	282.1463

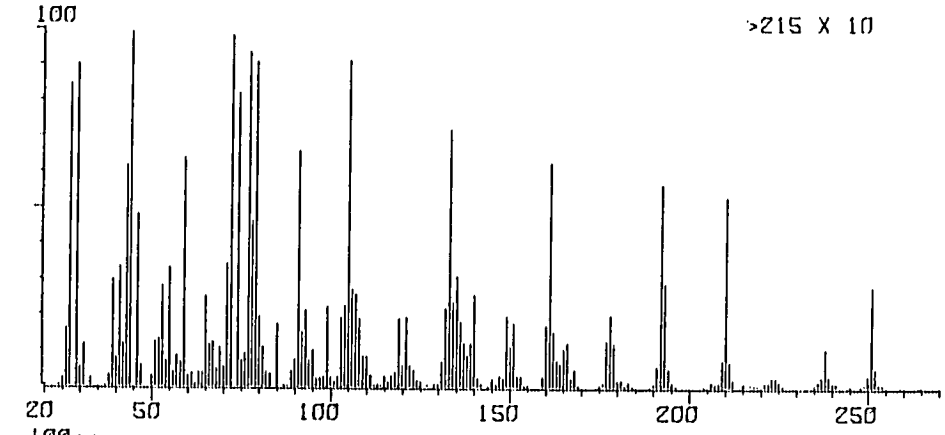


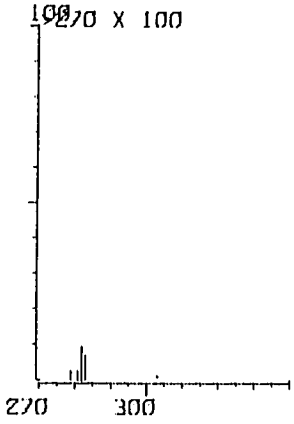
237
From Less Polar Isomer of **236**

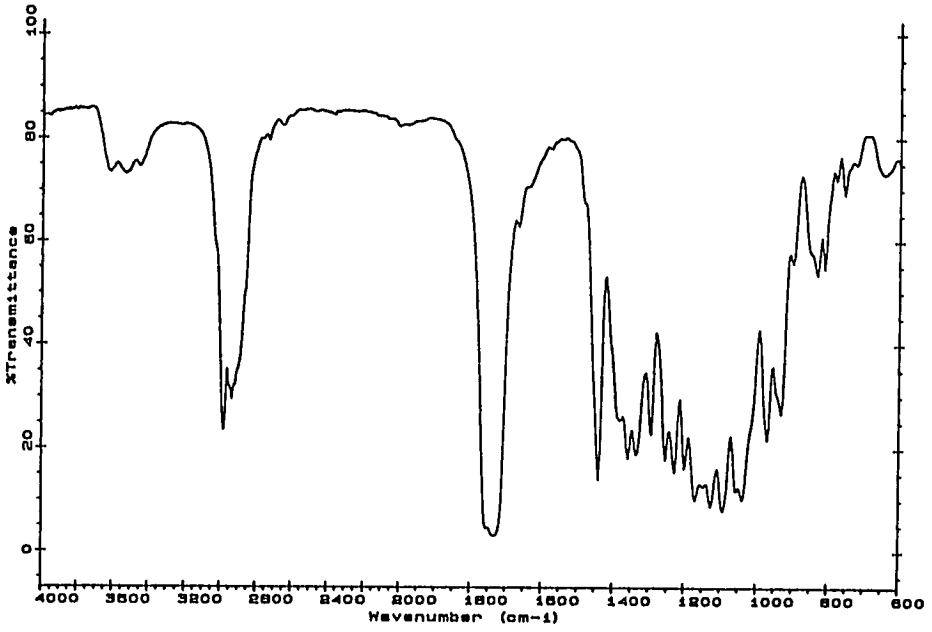


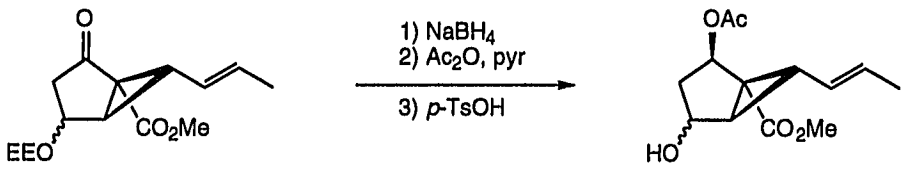
237
From more Polar Isomer of **236**

Compound **237** continued:









237 239

1-Carbomethoxy-2-acetoxy-6-exo[(*E*)-1-propenyl]bicyclo[3.1.0]-hexan-4-ol (**239**)

To a stirred solution of 17.8 g (63.0 mmol) of ketone **237** in 100 mL of methanol at 0 °C was added in portions 0.95 g (25.1 mmol) of sodium borohydride over a period of 15 min. The progress of the reaction was monitored by TLC. After starting material was consumed, the reaction mixture was condensed to half of its original volume, poured into 30 mL of a saturated sodium bicarbonate solution and thoroughly extracted with ethyl ether. The extracts were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure.

The above residue was dissolved in 13.8 mL (146 mmol) of acetic anhydride and 11.8 mL (146 mmol) of pyridine. The resulting mixture was heated at 50 °C for 1 h. The solution was then evaporated *in vacuo* with toluene to give a brown oil.

To the stirred solution of above oil in 80 mL of 2-propanol and 20 mL of water was added 0.21 g (1.10 mmol) of *p*-toluenesulfonic acid monohydrate. Stirring was continued for 3h while the progress of the reaction was monitored with TLC. The solution was then condensed to small volume under reduced pressure and the resulting biphasic mixture was extracted thoroughly with dichloromethane. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, evaporated and purified on silica gel

column (eluted with 40-70% ether-hexanes) to give 11.6 g (72.5%) of **239** as a colorless oil.

IR (film): 3449, 2957, 1722, 1443, 1317, 1257, 1171, 1045, 972, 925, 733

^{1}H NMR ($CDCl_3$): less polar isomer
1.21 (1H, dt, J_1 = 8.6 Hz, J_2 = 13.8 Hz), 1.71 (3H, dd, J_1 = 1.2 Hz, J_2 = 6.3 Hz), 2.07 (3H, s), 2.25 (1H, t, 5.1 Hz), 2.58 (1H, dd, J_1 = 5.1 Hz, J_2 = 8.9 Hz), 2.63 (1H, dt, J_1 = 8.1 Hz, J_2 = 13.6 Hz), 3.69 (3H, s), 4.51 (1H, td, J_1 = 4.9 Hz, J_2 = 8.4 Hz), 5.44-5.55 (1H, dd, overlapping), 5.52 (1H, t, J = 8.2 Hz), 5.79 (1H, dq, J_1 = 6.5 Hz, J_2 = 13.1 Hz)

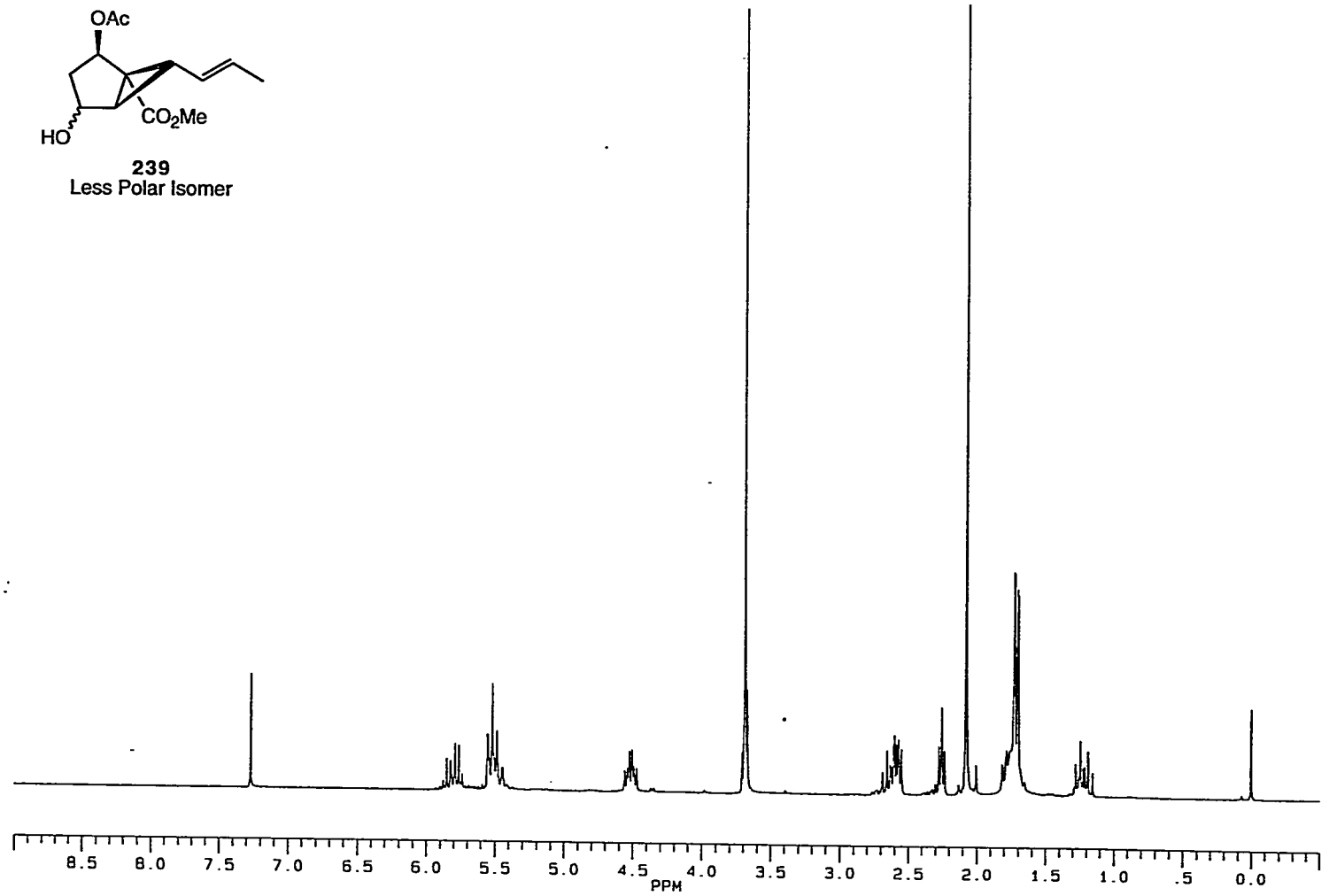
more polar isomer
1.44 (1H, ddd, J_1 = 5.3 Hz, J_2 = 8.3 Hz, J3 = 13.8 Hz), 1.71 (1H, dd, J_1 = 1.2 Hz, J_2 = 6.3 Hz), 2.07 (3H, s), 2.13 (2H, s), 2.34 (1H, dd, J_1 = 8.3 Hz, J_2 = 15.2 Hz), 3.71 (3H, s), 4.36 1H, d, 5.2 Hz), 5.53 (1H, dd, J_1 = 7.2 Hz, J_2 = 14.1 Hz), 5.70 (1H, dd, J_1 = 6.2 Hz, J_2 = 12.5 Hz), 5.90 (1H, t, 8.2 Hz)

^{13}C NMR ($CDCl_3$): 17.74, 17.78, 20.78, 20.83, 28.19, 30.99, 35.00, 38.06, 38.16, 38.60, 38.95, 40.88, 51.76, 51.76, 68.32, 71.16, 72.25, 75.00, 125.40, 125.56, 128.07, 128.16, 170.56, 170.73, 170.91, 170.91

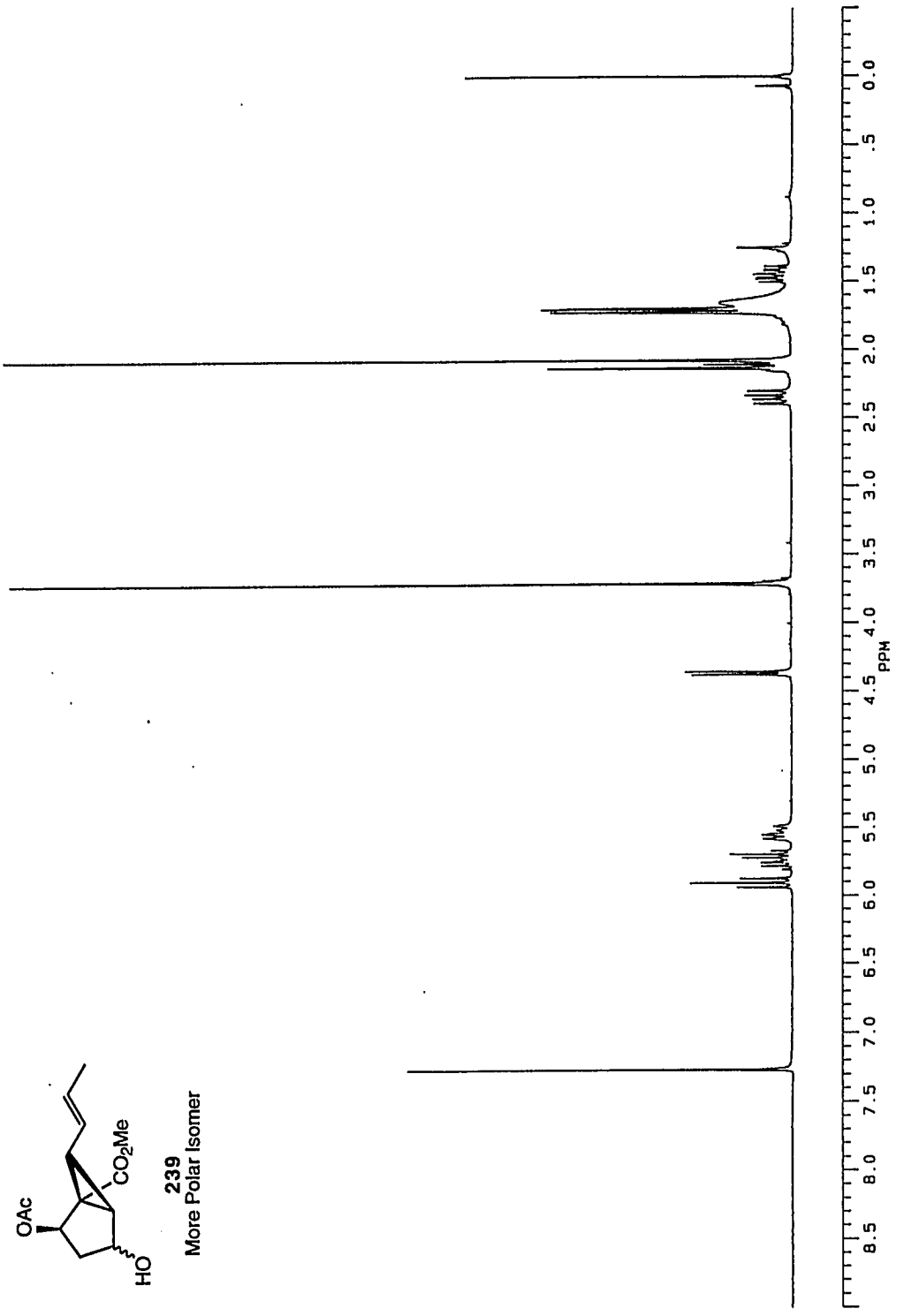
MS: 254 (1, M^+), 253 (<1, M-1), 194 (17), 162 (45), 151 (42), 134 (59), 124 (85), 118 (71), 107 (100), 91 (93), 79 (100), 43 (100)

Exact Mass:

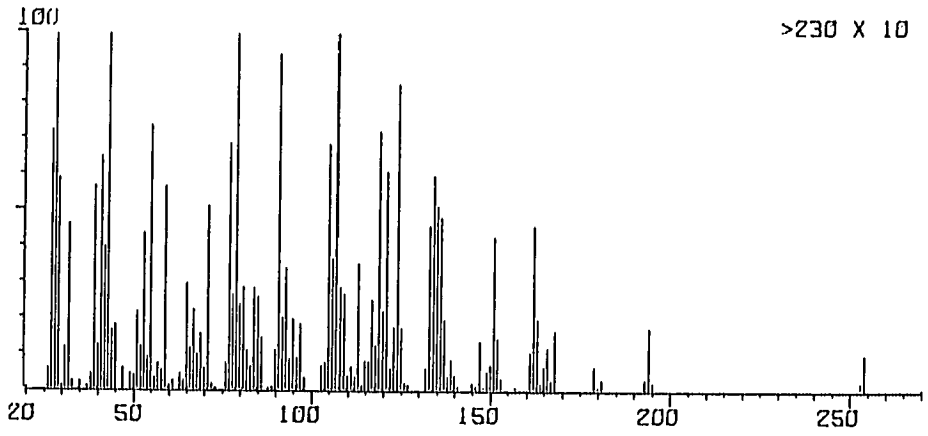
Calculated for $C_{13}H_{18}O_5$	254.1154
Found	254.1153

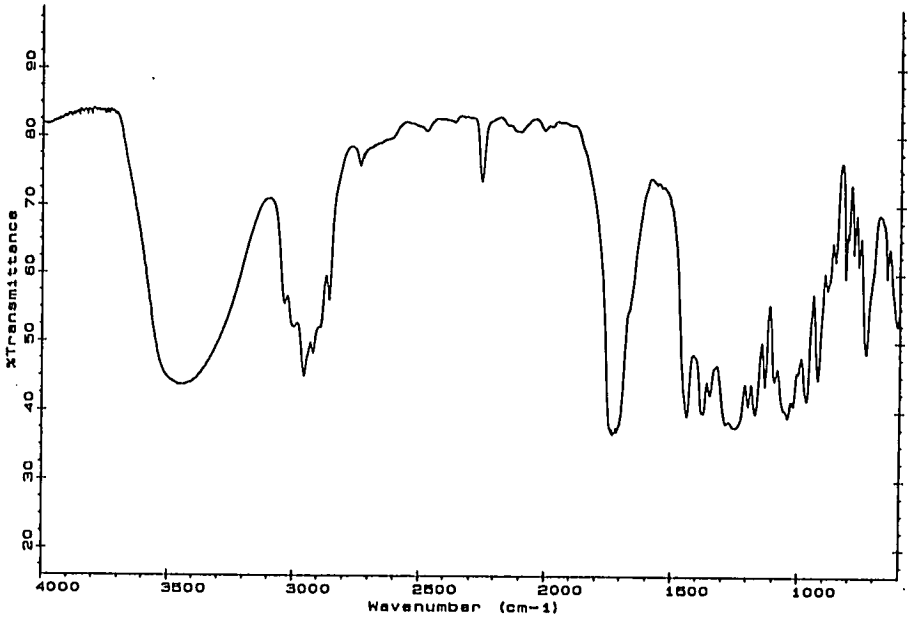


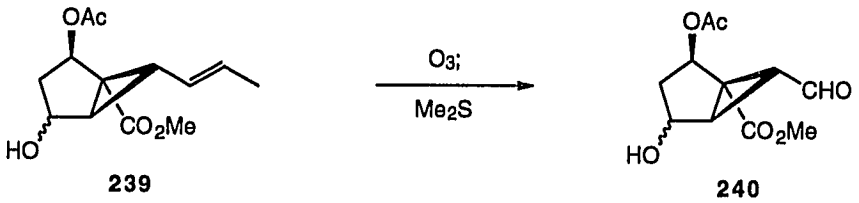
239
Less Polar Isomer


OAc
CO2Me
HO
239
More Polar Isomer
8.5 8.0 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
PPM

Compound **239** continued:







239 240

1-Carbomethoxy-2-acetoxy-6-exo(carboxaldehyde)bicyclo[3.1.0]-hexan-4-ol (**240**)

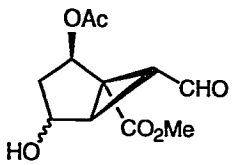
To a solution of 11.4 g (44.9 mmol) of olefin **239** in 100 mL of dichloromethane-methanol (9:1) cooled at -78 °C was bubbled with ozone. The progress of the reaction was carefully monitored by TLC. After the consumption of the starting material, the reaction mixture was purged with nitrogen for 10 min. To the above stirred solution was added 50 mL (mmol) of methyl sulfide and the mixture was then allowed to warm to room temperature slowly. The reaction mixture was stirred for 30 min at room temperature before the solvent was removed *in vacuo*. The residue was purified by flash chromatography employing a solvent gradient of 70-90% ether in hexanes to yield 9.69 g (89%) of **240** as a colorless oil.

IR (film): 3415, 2957, 1729, 1443, 1377, 1337, 1291, 1244, 1171, 1038, 766

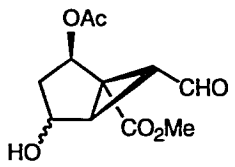
^{1}H NMR ($CDCl_3$): less polar isomer
1.14 (1H, dt, J_1 = 8.6 Hz, J2 = 13.9 Hz), 2.07 (3H, s), 2.63 (1H, dd, J_1 = 6.1 Hz, J_2 = 8.0 Hz), 2.67 (1H, dd, J_1 = 8.0 Hz, J_2 = 13.5 Hz), 2.90 (1H, t, J = 4.7 Hz), 3.74 (3H, s), 4.64 (1H, dt, J_1 = 4.5 Hz, J_2 = 12.9 Hz), 5.60 (1H, t, J = 8.3 Hz), 9.47 (1H, d, J = 5.6 Hz)

more polar isomer
1.39 (1H, ddd, J_1 = 5.4 Hz, J_2 = 8.4 Hz, J_3 = 15.0 Hz), 2.07 (3H, s), 2.23 (1H, t, J = 5.4 Hz), 2.39 (1H, ddd, J_1 = 0.94 Hz, J_2 = 8.4 Hz, J_3 = 15.2 Hz), 2.81 (1H, d, J = 5.0 Hz), 3.77 (1H, s), 4.56 (1H, d, J = 5.3 Hz), 6.00 (1H, t, J = 8.2 Hz), 9.48 (1H, d, J = 5.9 Hz)

^{13}C NMR ($CDCl_3$):	20.57, 20.62, 33.15, 34.21, 35.98, 37.29, 37.57, 39.43, 41.43, 41.64, 52.56, 52.56, 67.88, 70.94, 71.90, 74.85, 169.12, 169.61, 170.37, 170.57, 197.15, 197.69
MS (40 eV):	242 (<1, M^+), 241 (<1, M-1), 225 (<1), 213 (3), 153 (18), 150 (18), 139 (12), 126 (17), 121 (18), 94 (21), 67 (11), 59 (12), 44 (25), 43 (100)
Exact Mass:	Calculated for $C_{11}H_{14}O_6$ 242.0790 Found 242.0789

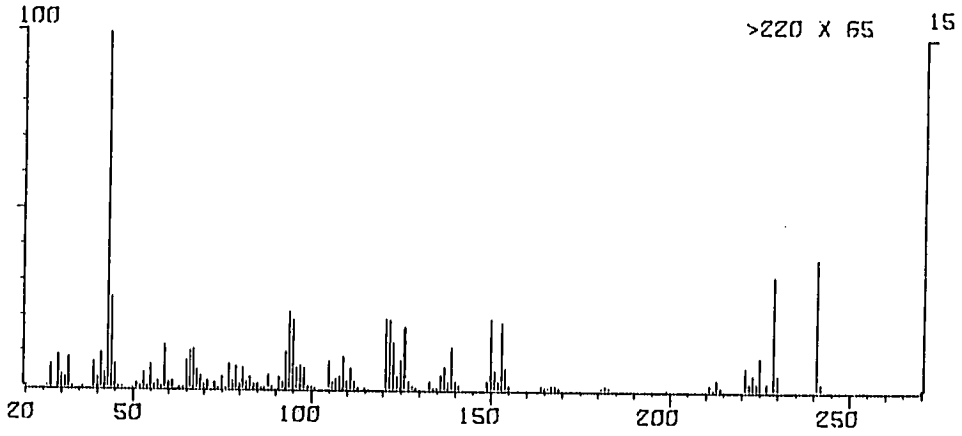


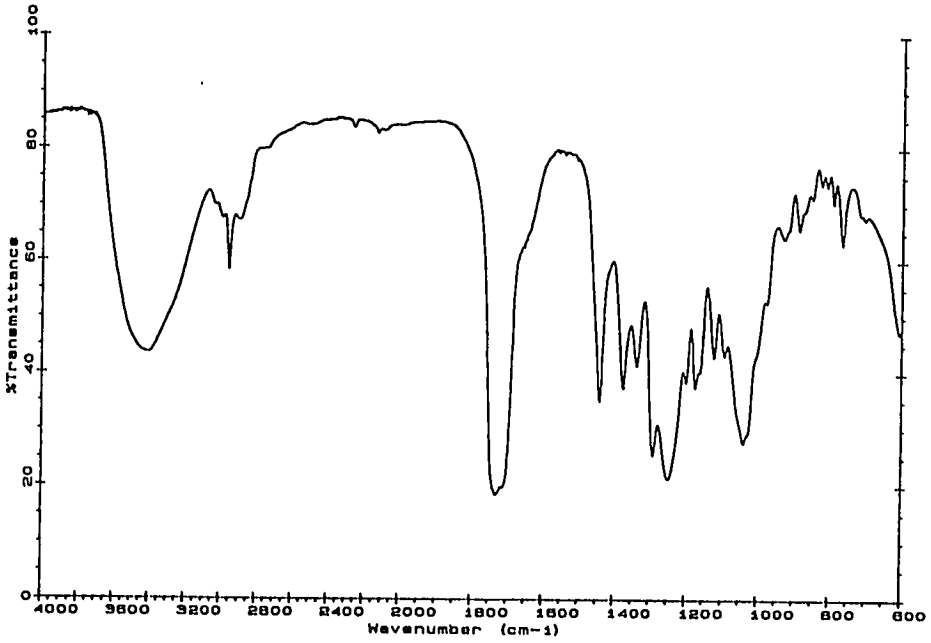
240
Less Polar Isomer

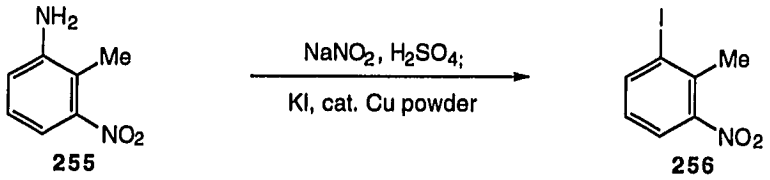


240
More Polar Isomer

Compound **240** continued:







255 256

2-Iodo-6-nitrotoluene (**256**)

To a stirred solution of 63.5 g (0.417 mol) of 2-methyl-3-nitroaniline **255**, 50 g of crushed ice chips in 200 mL of water was added 27.2 mL (0.521 mol) of concentrated sulfuric acid. The suspension was cooled in an ice bath and 33.1 g (0.480 mol) of sodium nitrite in 70 mL of water was added through dropping funnel over a period of 30 min. The mixture was allowed to stir at 0 °C for additional 20 min before it was filtered through a Büchner funnel directly to a vigorously stirred solution of 86.7 g (0.521 mol) of potassium iodide in 80 mL of water at 0 °C. The resultant brown mixture was allowed to warm to room temperature, to which 0.43 g (6.72 mmol) of copper powder was then added. The reaction mixture was then heated at 90 °C for 30 min before it was cooled to room temperature and partitioned between ethyl ether and a saturated sodium bicarbonate solution. The aqueous layer was thoroughly extracted with ethyl ether. The combined extracts were washed with brine, dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo* to give 103.7 g (94.4%) of **256** as light brown crystals.

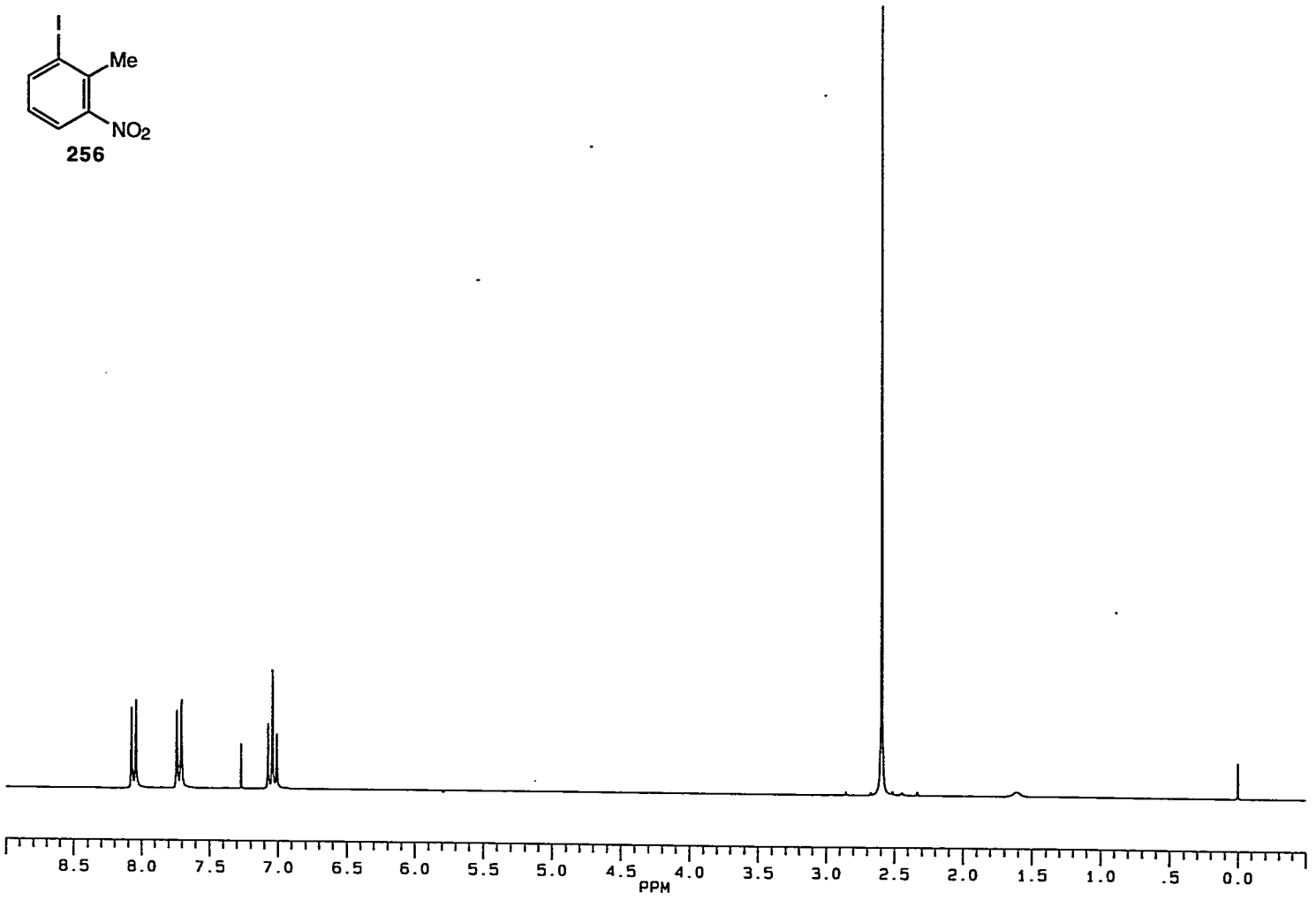
mp (Et_2O/hexanes) 33.0 °C

IR (film): 3084, 3004, 2977, 2931, 2864, 1530, 1443, 1357, 1277, 1085, 1005, 859, 799, 739, 699

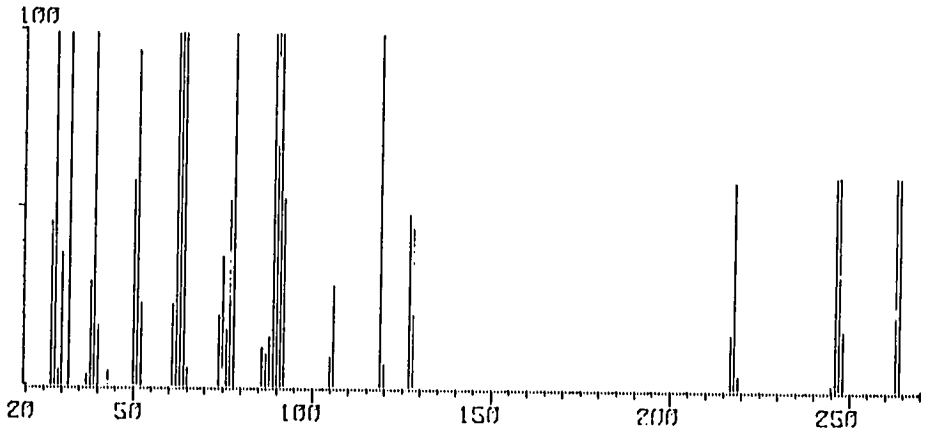
^1H NMR ($CDCl_3$): 2.59 (3H, s) 7.04 (1H, t, J = 8.0 Hz) 7,72 (1H, d , J = 8.0 Hz), 8.06 (1H, d, J = 8.0 Hz)

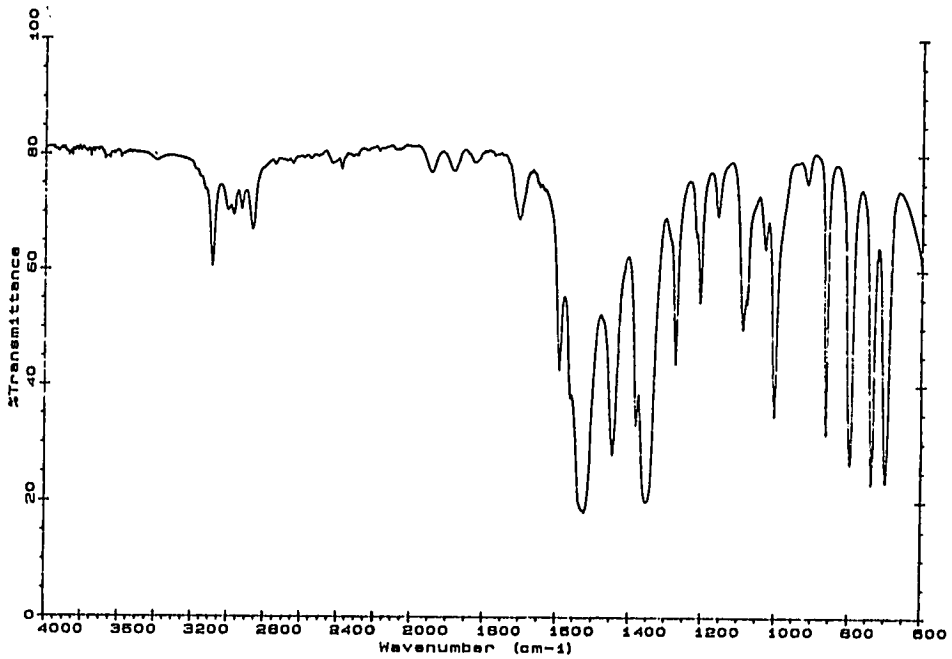
^{13}C NMR ($CDCl_3$): 24.8, 103.4, 123.7, 127.8, 134.8, 142.9, 150.1

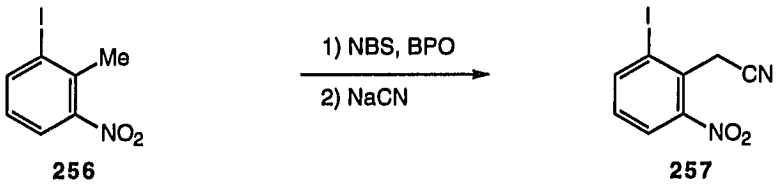
MS:	264 (58, M+1), 263 (58, M^+), 247 (58), 246 (58), 218 (58), 127 (48), 119 (100), 90 (100), 78 (100), 63 (100), 51 (95), 39 (100)	
Exact Mass:	Calculated for $C_7H_6I_1N_1O_2$	262.9443
	Found	262.9440


I
Me
NO2
256
8.5
8.0
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
PPM

Compound **256** continued:







256 257

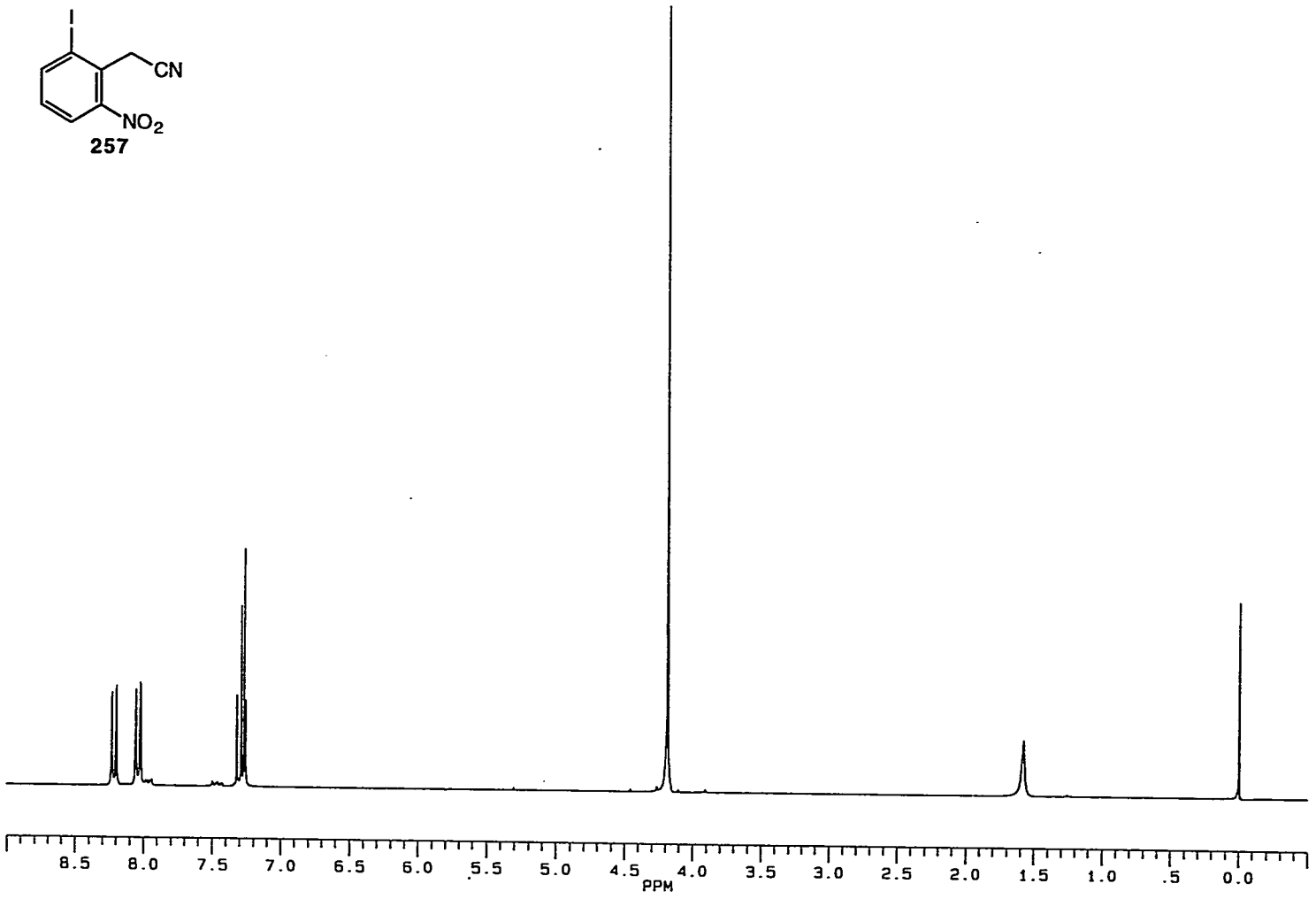
2-Iodo-6-nitro-benzyl cyanide (**257**)

A solution of 63.7 g (0.242 mol) of **256**, 107.8 g (0.656 mol) of *N*-bromosuccinimide and 8.85 g (0.0365 mol) of benzoyl peroxide in 300 mL of carbon tetrachloride was heated at 80 °C under argon for 4 days. The resulting mixture was cooled to room temperature and carefully filtered through celite in well ventilated fuming hood. The solid was washed with ethyl ether and the filtrate and washings were evaporated under reduced pressure.

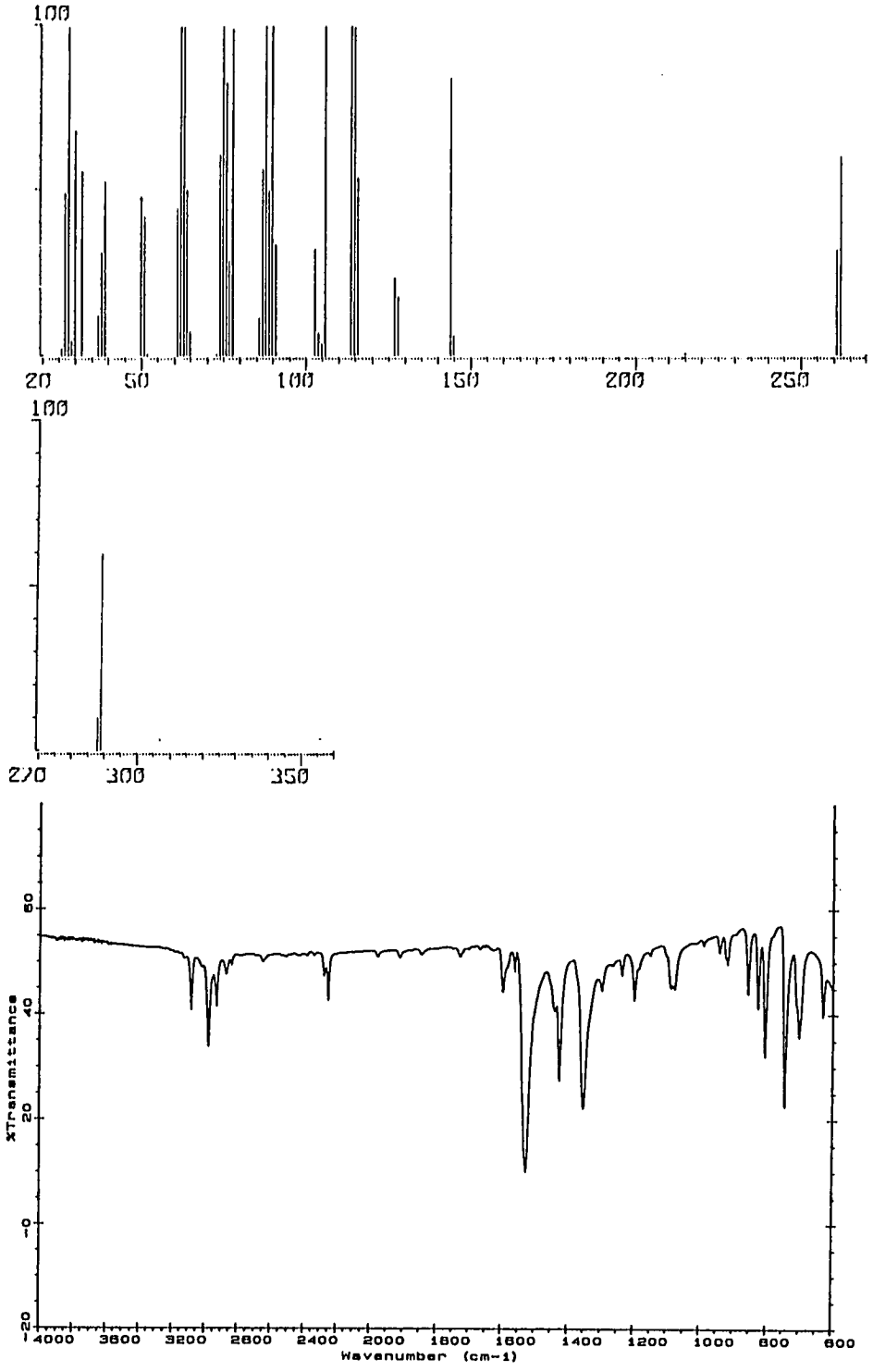
To a stirred solution of 23.7 g (0.484 mol) of sodium cyanide in 50 mL of methyl sulfoxide-water (1:1) was added slowly solution of the above residue in 100 mL of methyl sulfoxide. The temperature of the exothermic reaction was carefully controlled by water bath. The reaction mixture was stirred at room temperature for 30 min before it was poured into 100 mL of water. The aqueous layer was extracted thoroughly with ethyl ether. The ethereal extracts were washed with water and brine sequentially, dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The crude product was crystallized from ethyl acetate and hexanes to give 34.9 g (50%) of **257** as light yellow crystals.

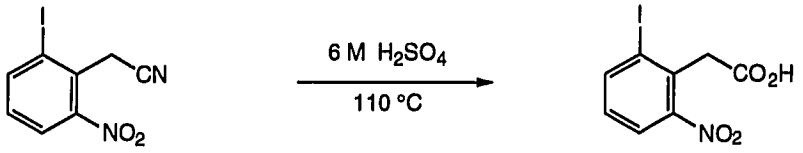
mp (EtOAc/Hexanes)	94.5-95.5 °C
IR (film):	3078, 2979, 2932, 2868, 2275, 2251, 1597, 1527, 1427, 1352, 1197, 1084, 854, 805, 743, 702
^{1}H NMR ($CDCl_3$):	4.18 (2H, s), 7.28 (1H, t, J = 8.1 Hz), 8.04 (1H, d, J = 8.1 Hz), 8.22 (1H, d, J = 8.1 Hz)
^{13}C NMR ($CDCl_3$):	27.8, 103.1, 115.0, 125.4, 130.9, 138.1, 144.8, 149.4

MS:	289 (60, M+1), 288 (10, M^+), 262 (60), 261 (30), 144 (85), 115 (100), 106 (100), 90 (100), 78 (100), 62 (100),	
Exact Mass:	Calculated for $C_8H_5I_1N_2O_2$	287.9395
	Found	287.9395


I
CN
NO2
257
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

Compound **257** continued:



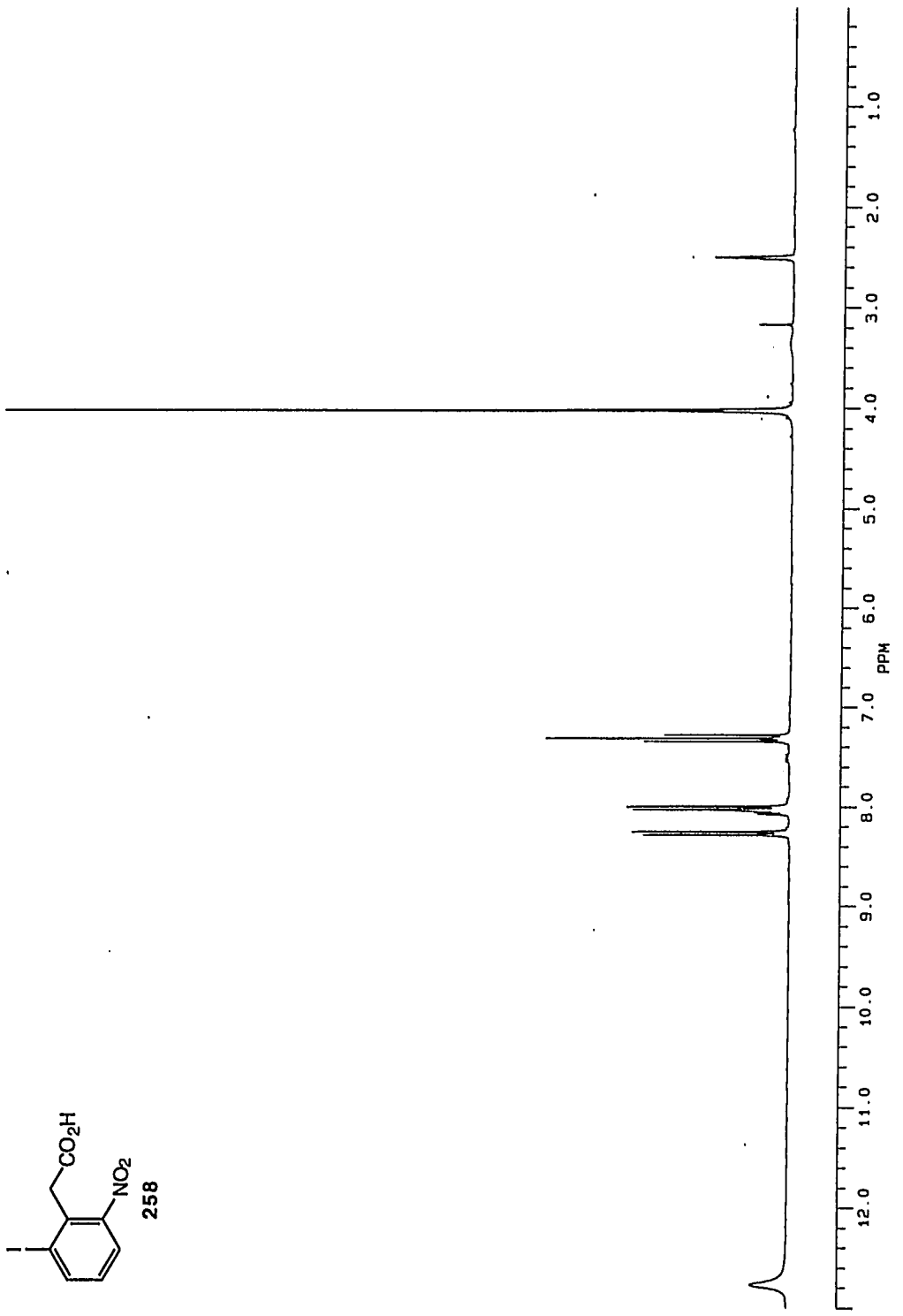


257 **258**

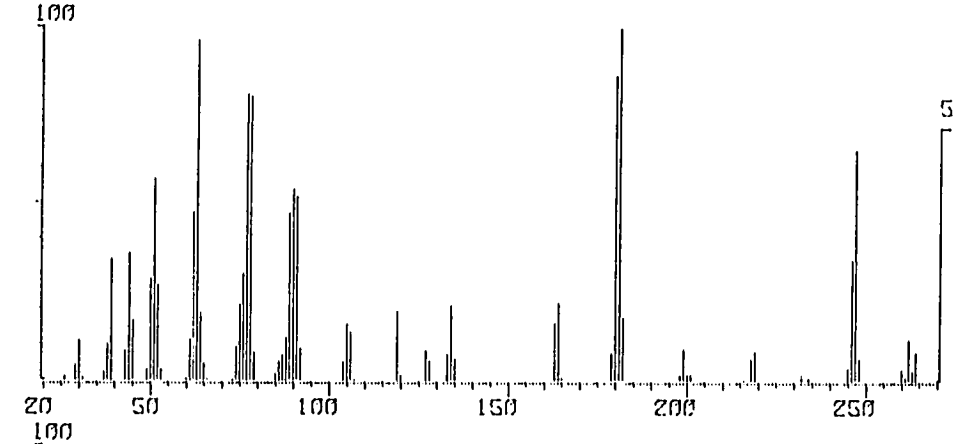
2-Iodo-6-nitro-phenylacetic acid (**258**)

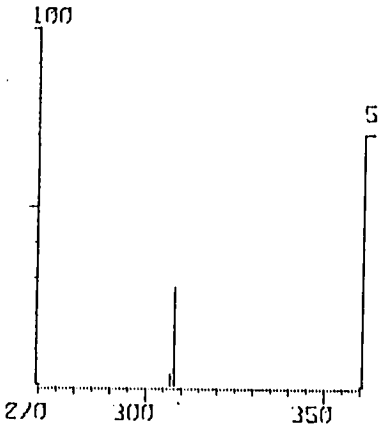
A mixture of 18.1 g (62.8 mmol) of nitrile **257** and 100 mL of 6 M sulfuric acid was heated at 110 °C over night. After cooling to room temperature, the crystalline acid **258** was filtered off the solution, washed with ice water and dried in a vacuum desiccator to give 17.1 g (89%) of **258** as light brown crystals.

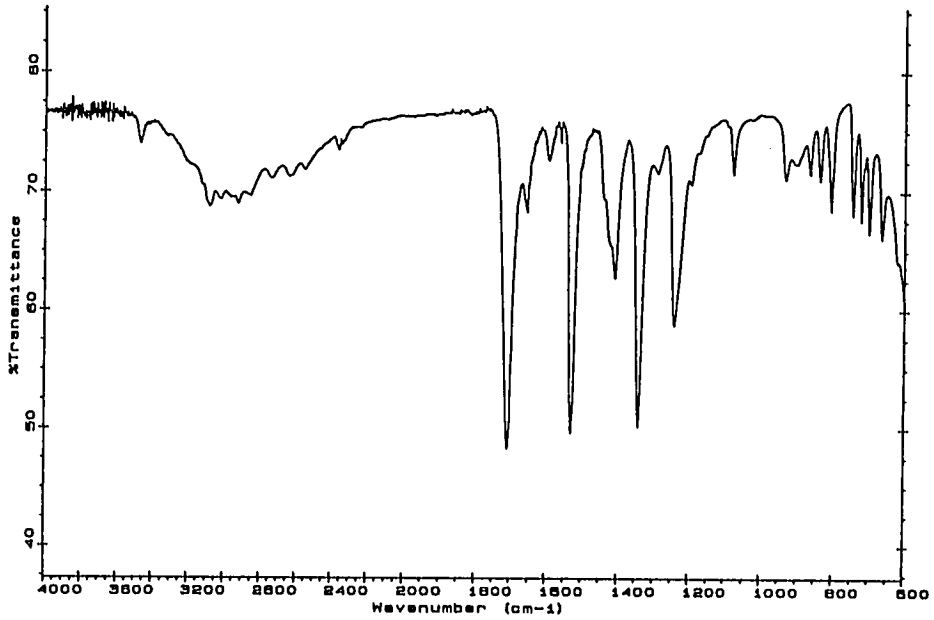
mp ($EtOH/H_2O$)	177-178 °C	
IR (film):	3090, 3017, 2924, 2858, 2738, 2639, 2552, 1709, 1530, 1410, 1344, 1244, 1078, 932, 805, 746, 720, 699, 666	
^1H NMR (d^6-DMSO):	4.02 (2H, s), 7.31 (1H, t, J = 8.0 Hz), 8.01 (1H, dd, J_1 = 0.93 Hz, J_2 = 8.0 Hz), 8.26 (1H, d, J = 8.0 Hz), 12.75 (1H, s)	
^{13}C NMR (d^6-DMSO):	43.5, 105.6, 124.7, 130.0, 132.2, 144.0, 149.8, 170.0	
MS:	308 (28, M+1), 307 (3, M^+), 262 (11), 247 (64), 181 (100), 180 (85), 90 (55), 77 (80), 63 (95), 51 (55)	
Exact Mass:	Calculated for $C_8H_6I_1NO_4$	306.9343
	Found	306.9341

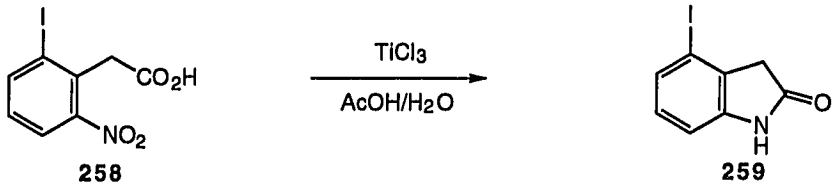

CO2H
NO2
I
258
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

Compound **258** continued:







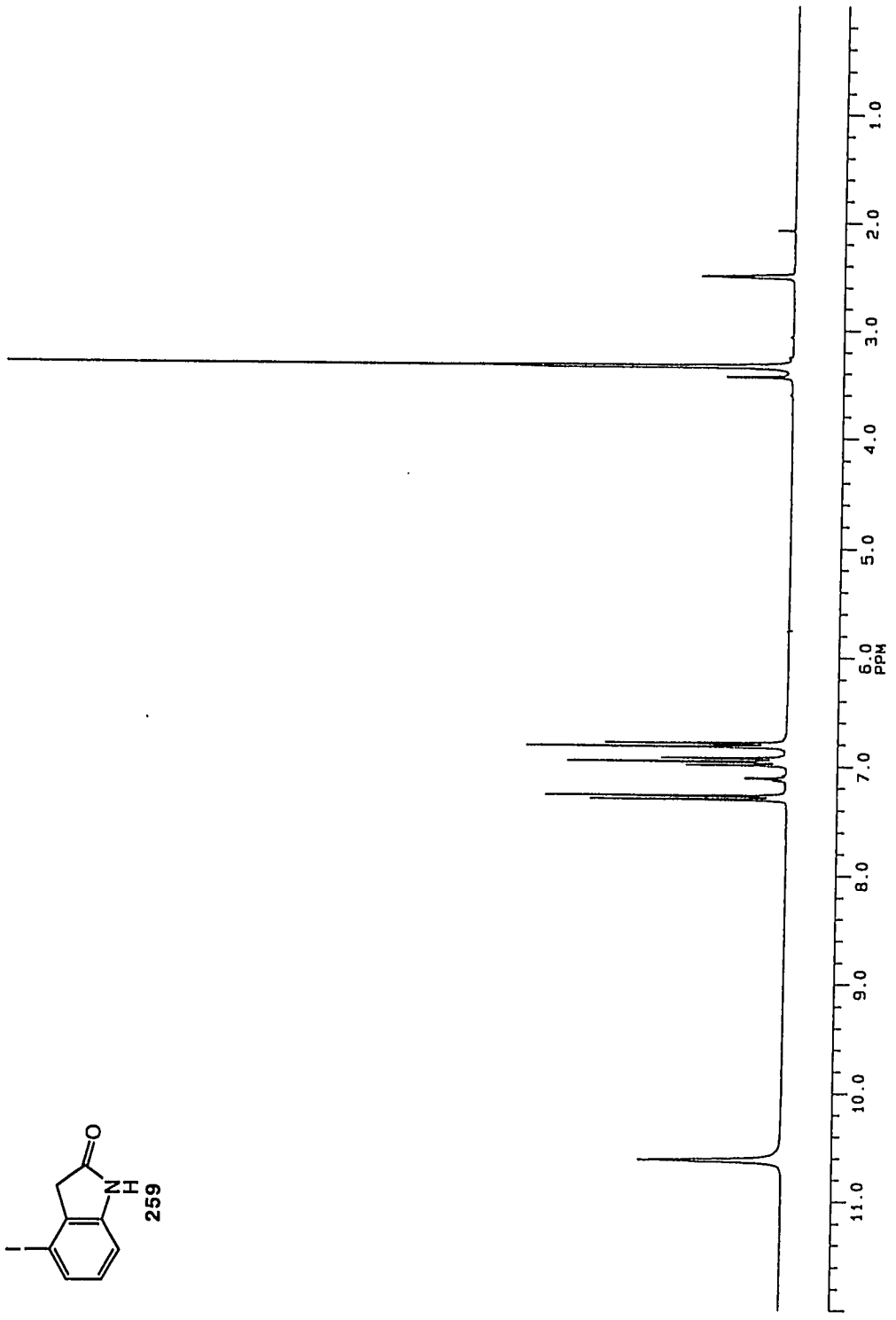


258 **259**

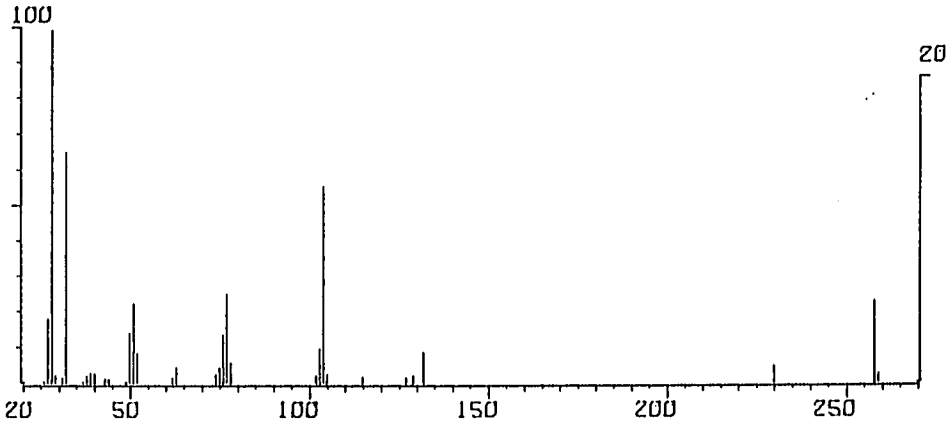
4-Iodo-oxindole (**259**)

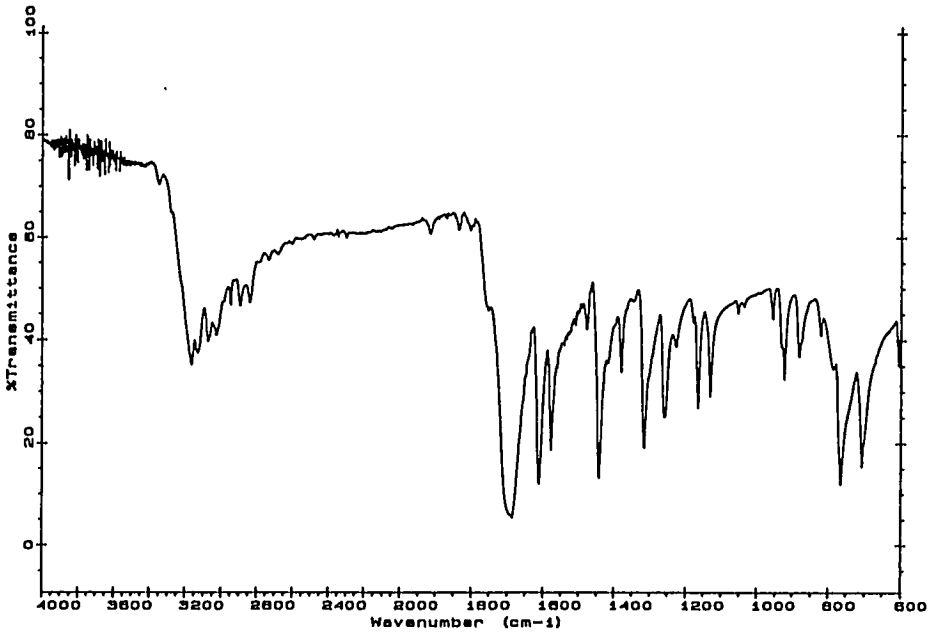
To a stirred solution of 16.6 g (54.1 mmol) of acid **258** in 100 mL of acetic acid and 30 mL of water was added through dropping funnel 190 mL (ca. 231 mmol) of 20% aqueous titanium(III) chloride. The resulting mixture was allowed to stir at room temperature for 30 min. The crystalline product was then filtered, washed with ice water and dried in a vacuum desiccator to give 13.2 g (94%) of **259** as light yellow crystals.

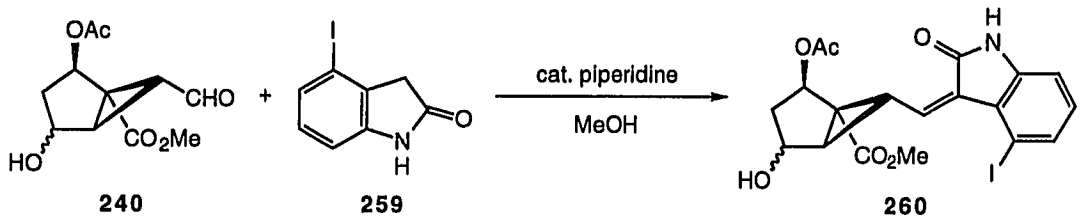
mp ($AcOH/H_2O$)	210-212 °C (decomposition)	
IR (KBr):	3164, 3132, 3074, 3027, 2946, 2894, 2839, 1689, 1611, 1578, 1444, 1316, 1259, 1165, 1130, 924, 764, 707	
^1H NMR (d^6-DMSO):	3.33 (2H, s), 6.80 (1H, d, J = 7.8 Hz), 6.96 (1H, t, 7.8 Hz), 7.29 (1H, d, J = 7.8 Hz), 10.62 (1H, s)	
^{13}C NMR (d^6-DMSO):	40.3, 92.5, 108.8, 129.6, 129.6, 130.8, 143.9, 174.3	
MS:	259 (3, M^+), 258 (25, M-1), 230 (6), 132 (9), 104 (55), 77 (25), 51 (22), 32 (65), 28 (100)	
Exact Mass:	Calculated for $C_8H_6I_1N_1O_1$	258.9495
	Found	258.9492


O
N
H
259
11.0
10.0
9.0
8.0
7.0
6.0
PPM
5.0
4.0
3.0
2.0
1.0

Compound **259** continued:







240 259 260

1-Carbomethoxy-2-acetoxy-6-exo[(*Z*)-alkylidene-(4'-iodo-indolinone)]bicyclo [3.1.0]-hexan-4-ol (**260**)

To a stirred solution of 9.68 g (40.0 mmol) of aldehyde **240** and 11.7 g (45.2 mmol) of oxindole **259** in 100 mL of methanol was added 0.22 mL (2.22 mmol) of piperidine at room temperature. The reaction mixture was stirred for 1 h before it was filtered through funnel. The crystalline product was washed with ethyl ether and dried *in vacuo* to give 9.5 g of **260** as pale yellow crystals. The filtrate and washing were combined and evaporated to dryness under reduced pressure. The resulting residue was separated by flash silica gel chromatography eluted with 50-65% ethyl acetate-hexanes to afford additional 7.8 g of **260** as light yellow crystals. The combined yield of **260** was 89.5%.

mp ($MeOH/Et_2O$): 251-254 °C (decomposition)

IR (film): 3502, 3170, 3084, 3017, 2951, 2878, 1722, 1609, 1570, 1437, 1364, 1331, 1244, 1171, 1052, 1012, 925, 759, 700

^1H NMR (d^6-DMSO): less polar isomer
1.11 (1H, dt, J_1 = 8.7 Hz, J_2 = 13.2 Hz), 2.00 (3H, s), 2.37 (1H, dd, J_1 = 7.8 Hz, J_2 = 15.6 Hz), 2.44 (1H, d, J = 9.2 Hz), 3.67 (1H, s), 4.44 (1H, sep, J = 4.1 Hz), 4.72 (1H, dd, J_1 = 5.1 Hz, J_2 = 10.5 Hz), 5.14 (1H, d, J = 4.6 Hz), 5.50 (1H, t, J = 8.2 Hz), 6.86 (1H, dd, J_1 = 1.1 Hz, J_2 = 7.8 Hz), 6.92 (1H, t, J = 7.7 Hz), 7.43 (1H, dd, J_1 = 1.1 Hz, J_2 = 7.4 Hz), 8.02 (1H, d, J = 10.5 Hz), 10.73 (1H, s)

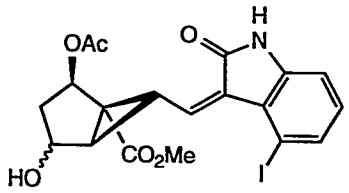
more polar isomer

1.41 (1H, ddd, J_1 = 5.6 Hz, J_2 = 7.8 Hz, J_3 = 14.1 Hz), 2.01 (3H, s), 2.15 (1H, dd, J_1 = 8.1 Hz, J_2 = 14.3 Hz), 2.33 (1H, d, J = 5.0 Hz), 3.72 (3H, s), 4.23 (1H, bs), 4.37 (1H, q, J = 5.0 Hz), 5.29 (1H, bs), 5.82 (1H, t, J = 8.1 Hz), 6.88 (1H, t, J = 7.6 Hz), 6.93 (1H, t, J = 7.6 Hz), 7.43 (1H, d, J = 7.5 Hz), 8.05 (1H, d, J = 10.3 Hz), 10.74 (1H, s)

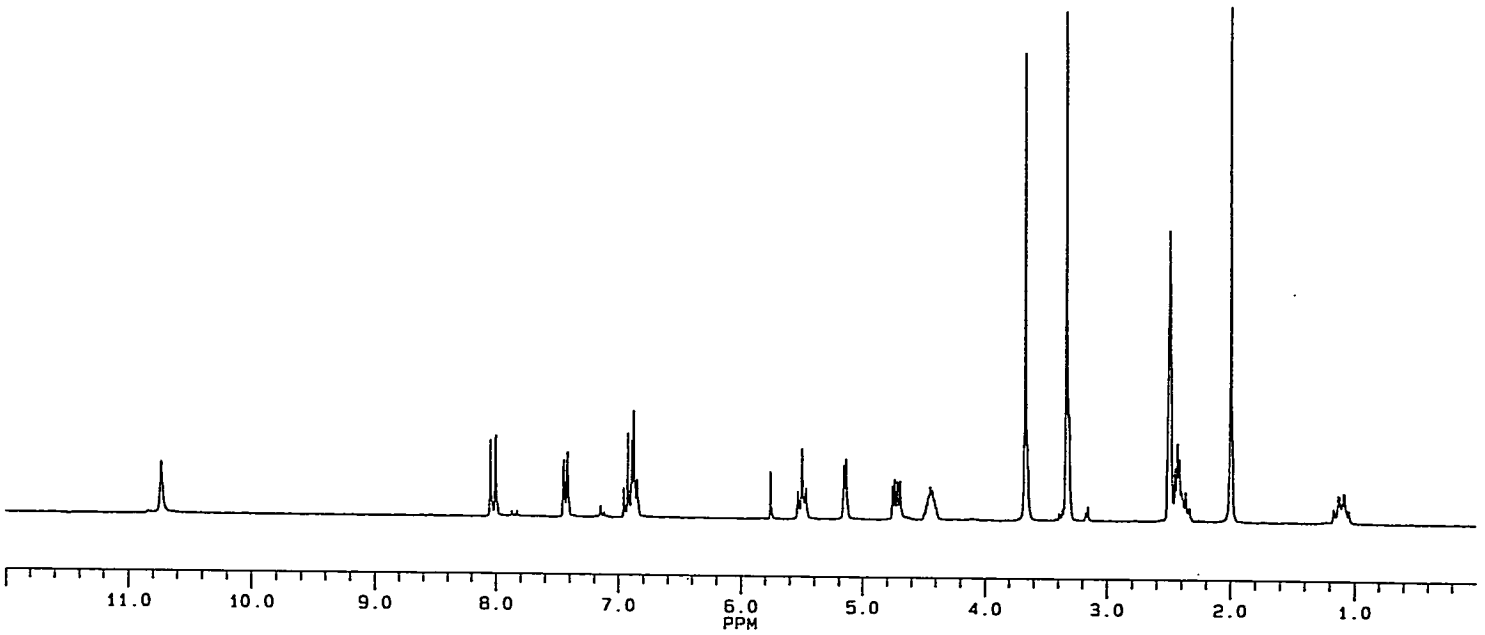
^{13}C NMR (d^6-DMSO): 20.80, 20.91, 23.28, 24.93, 34.84, 41.65, 41.65, 41.77, 42.09, 42.10, 44.41, 52.36, 52.45, 67.17, 70.39, 72.20, 74.07, 88.32, 88.64, 109.42, 109.51, 122.49, 122.76, 128.16, 128.79, 129.82, 130.07, 132.84, 132.84, 137.92, 140.16, 142.02, 142.12, 167.82, 167.91, 168.38, 169.46, 169.85, 169.88

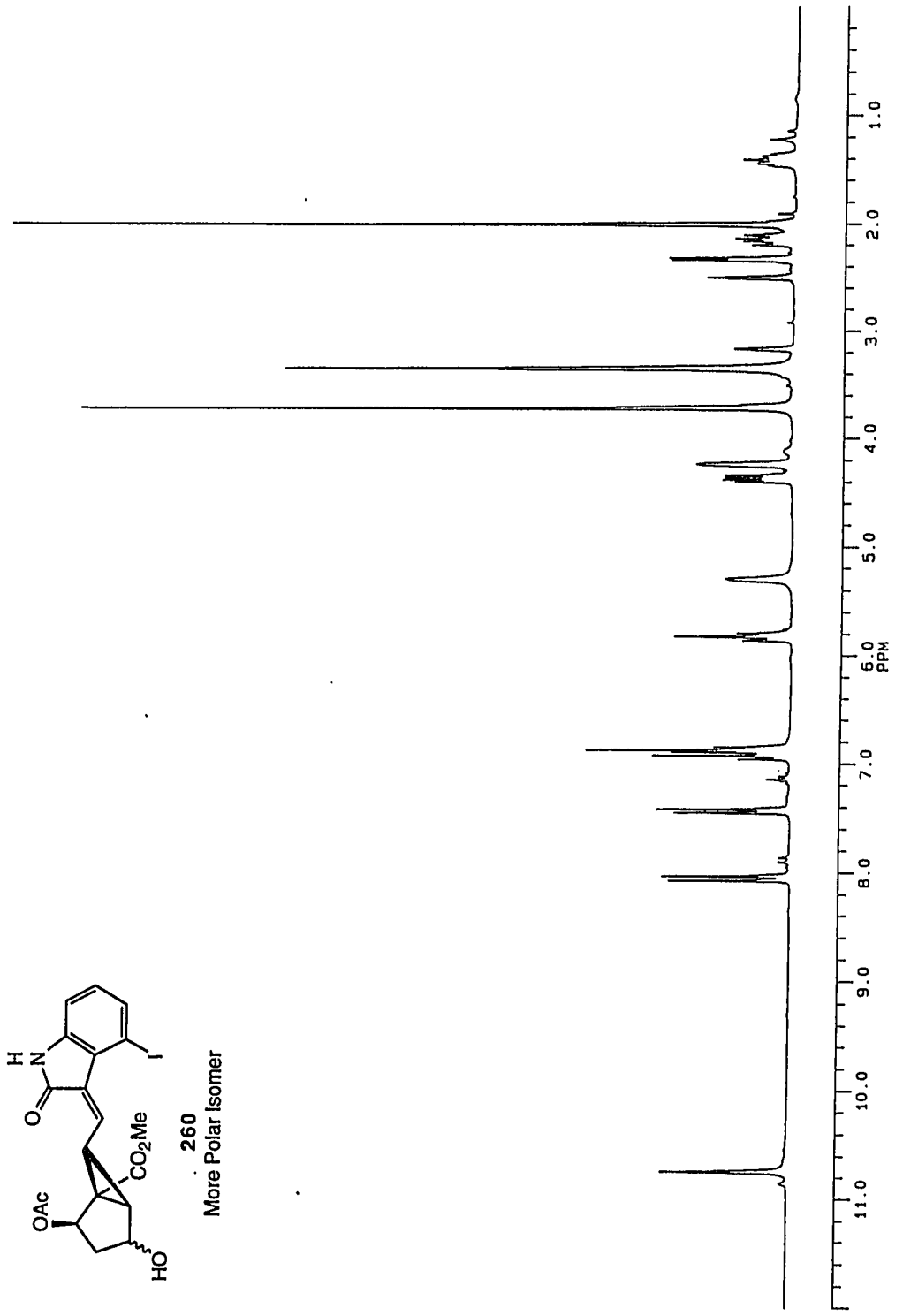
MS: 484 (<1, M+1), 483 (4, M^+), 482 (<1, M-1), 423 (14), 391 (20), 363 (10), 335 (10), 296 (13), 283 (26), 271 (25), 264 (40), 236 (49), 208 (25), 153 (20), 127 (34), 48 (100)

Exact Mass:		
	Calculated for $C_{19}H_{18}I_1N_1O_6$	483.0179
	Found	483.0161



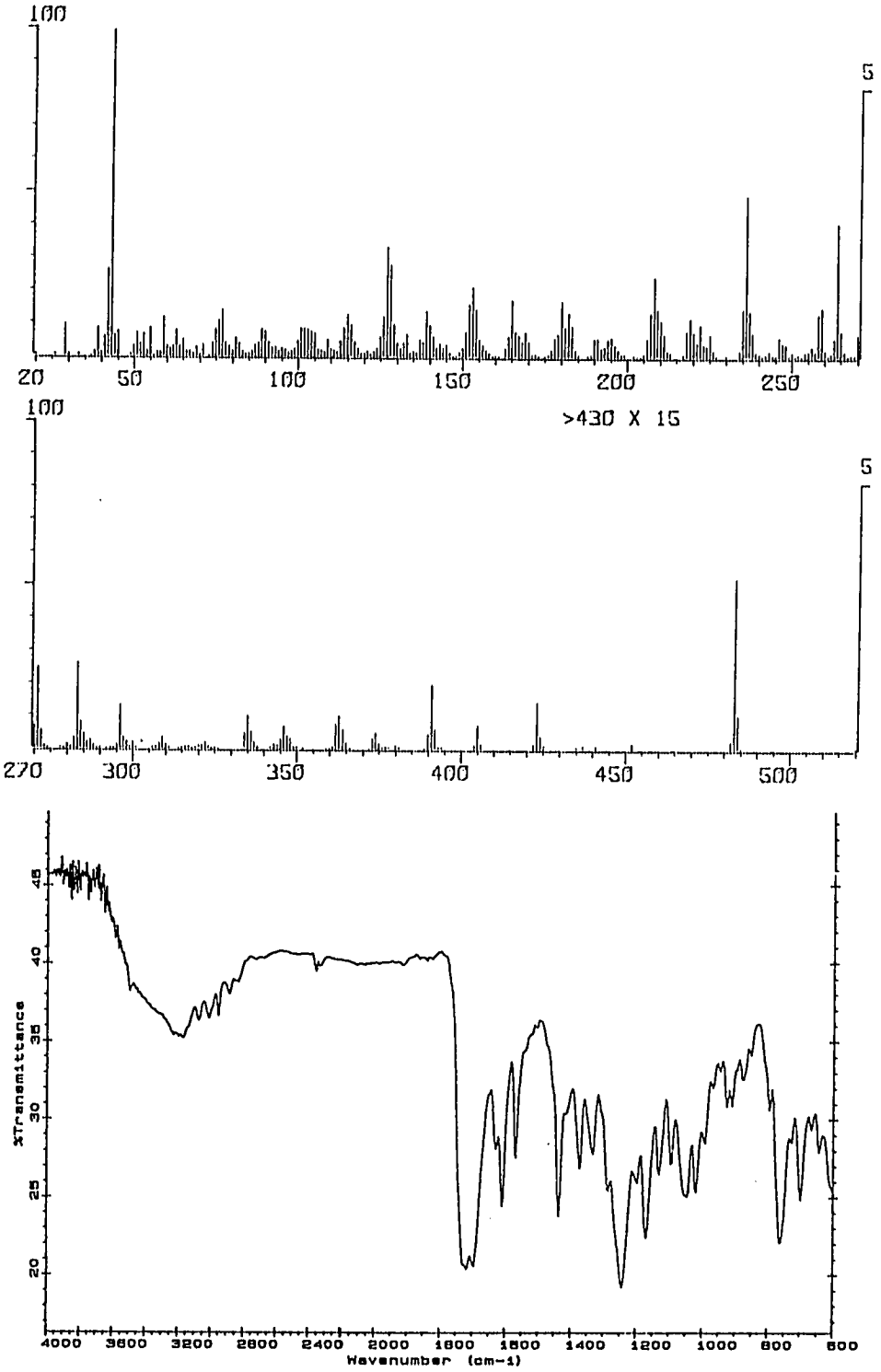
260
Less Polar Isomer

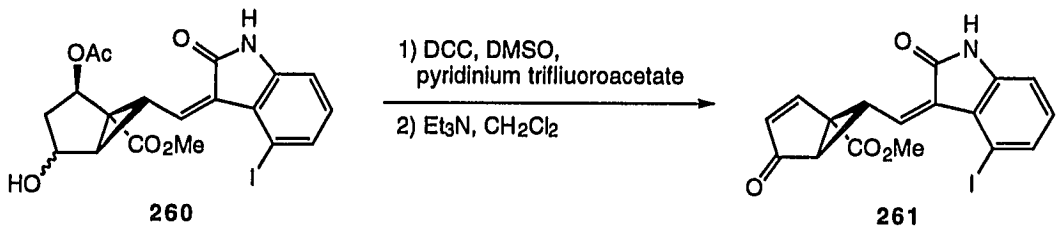




260
More Polar Isomer

Compound **260** continued:





260 **261**

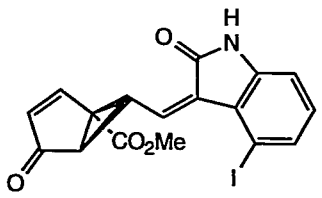
5-Carbomethoxy-6-exo[(*Z*)-alkylidene-(4'-iodo-indolinone)]bicyclo[3.1.0]-3-hexen-2-one (**261**)

To a stirred solution of 6.86 g (14.2 mmol) of alcohol **260** and 1.18 mL (14.6 mmol) of pyridine in 35 mL of methyl sulfoxide under argon were added 0.56 mL (7.3 mmol) of trifluoroacetic acid and 9.06 g (43.9 mmol) of 1,3-dicyclohexylcarbodiimide sequentially. The progress of the reaction was monitored by TLC. After the disappearance of the starting material, the reaction mixture was filtered through celite and the urea was washed with ethyl ether. The combined filtrate and washings were partitioned between ethyl acetate and water. The aqueous layer was thoroughly extracted with ethyl acetate. The extracts were combined, washed with a dilute sodium chloride solution and dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude product was purified through flash silica gel chromatography eluting with 30-45% ethyl acetate-hexanes to give 6.24 g (91%) of ketone as pale yellow crystals.

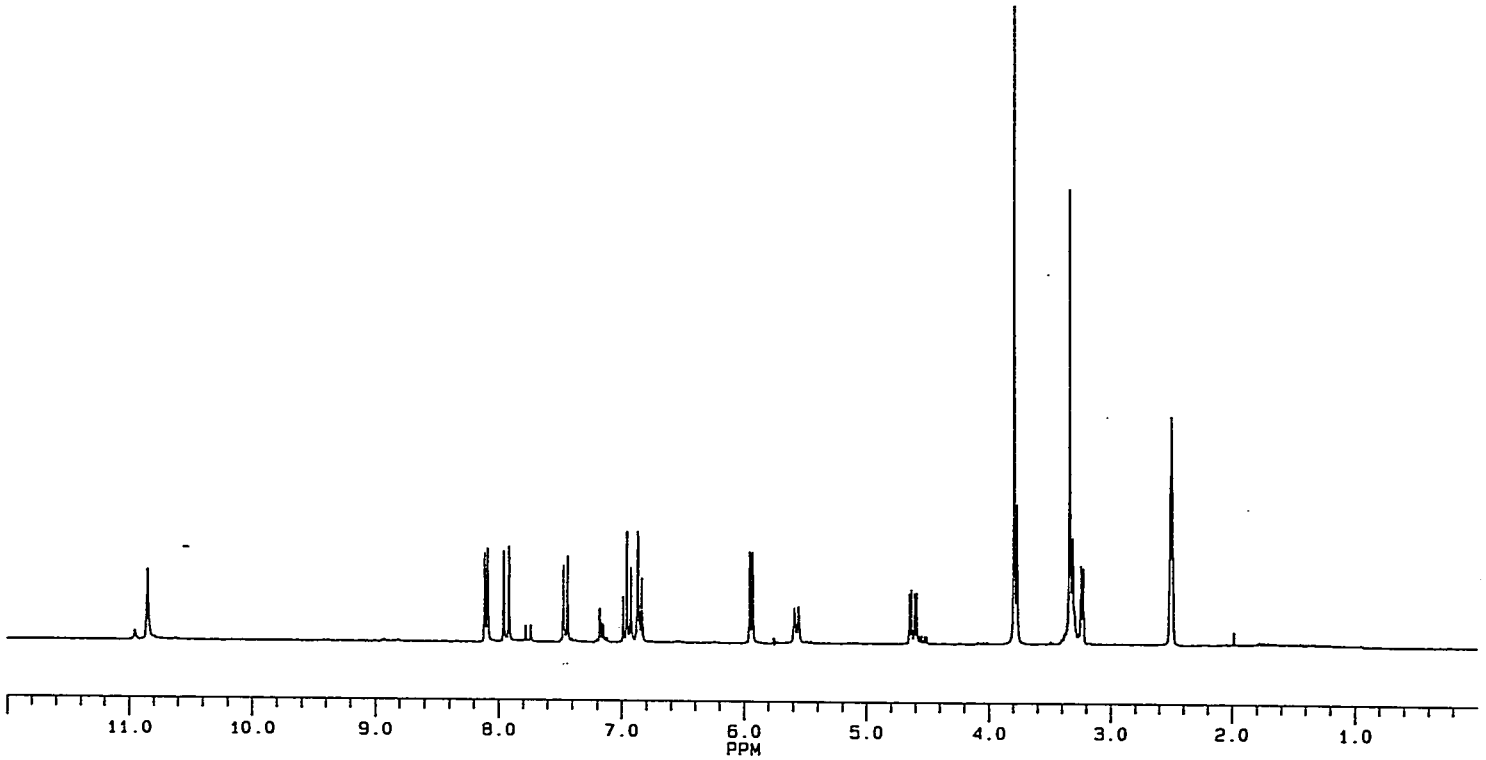
The above crystals were dissolved in 50 mL of dichloromethane, to which 2.72 mL (19.5 mmol) of triethylamine were added. The reaction mixture was stirred at room temperature for 30 min and then poured into a 3 M hydrochloric acid solution. The aqueous layer was thoroughly extracted with ethyl acetate. The combined extracts were washed with a saturated aqueous sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate,

filtered and evaporated under reduced pressure to afford 5.52 g (100%) of **261** as yellow crystals.

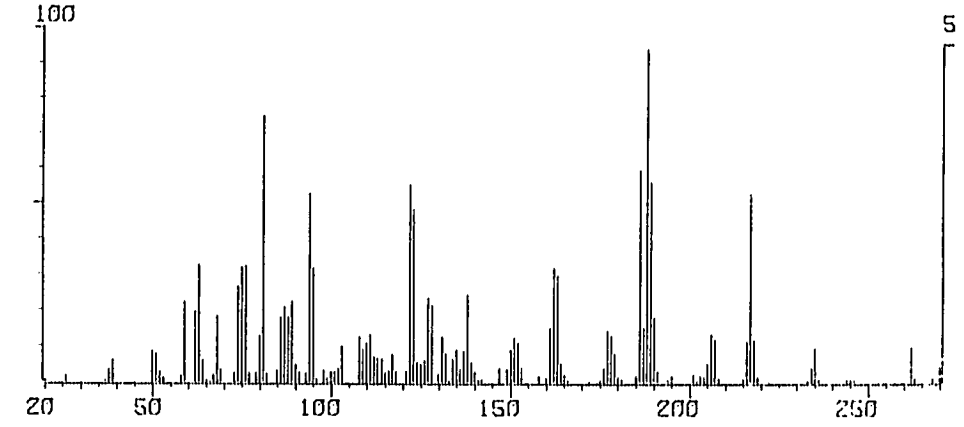
mp (CH_2Cl_2)	198-199 °C (decomposition)
IR (film):	3162, 3133, 3071, 3015, 2950, 2886, 2841, 1728, 1702, 1607, 1567, 1436, 1321, 1248, 1202, 1163, 1099, 943, 892, 772, 695
^{1}H NMR (d^6-DMSO):	3.23 (1H, d, J = 4.5 Hz), 3.79 (3H, s), 4.61 (1H, dd, J_1 = 4.4 Hz, J_2 = 10.4 Hz), 5.94 (1H, d, J = 5.7 Hz), 6.9 (1H, d, 7.6 Hz), 6.96 (1H, t, J = 7.8 Hz), 7.45 (1H, d, J = 7.8 Hz), 7.93 (1H, d, J = 10.4 Hz), 8.1 (1H, d, J = 5.6 Hz), 10.85 (1H, s)
^{13}C NMR (d^6-DMSO):	39.0, 43.2, 51.0, 53.0, 89,4, 109.7, 122.3, 128.6, 130.4, 130.8, 133.1, 134.5, 142.8, 160.0, 166.9, 167.7, 200.6
MS:	422 (2, M+1), 421 (12, M^+), 420 (3, M-1), 404 (32), 403 (100), 372 (16), 355 (13), 294 (48), 276 (68), 217 (52), 198 (100), 162 (32), 122 (55), 94 (52), 81 (75)
Exact Mass:	Calculated for $C_{17}H_{12}I_1N_1O_4$ 420.9813 Found 420.9823

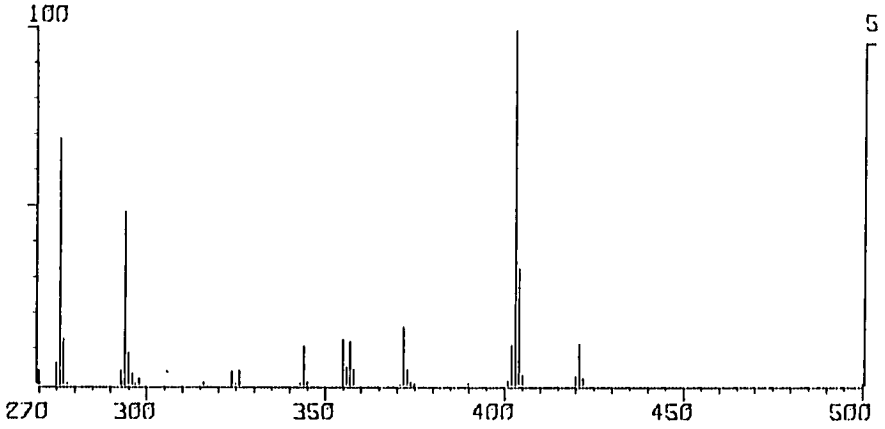


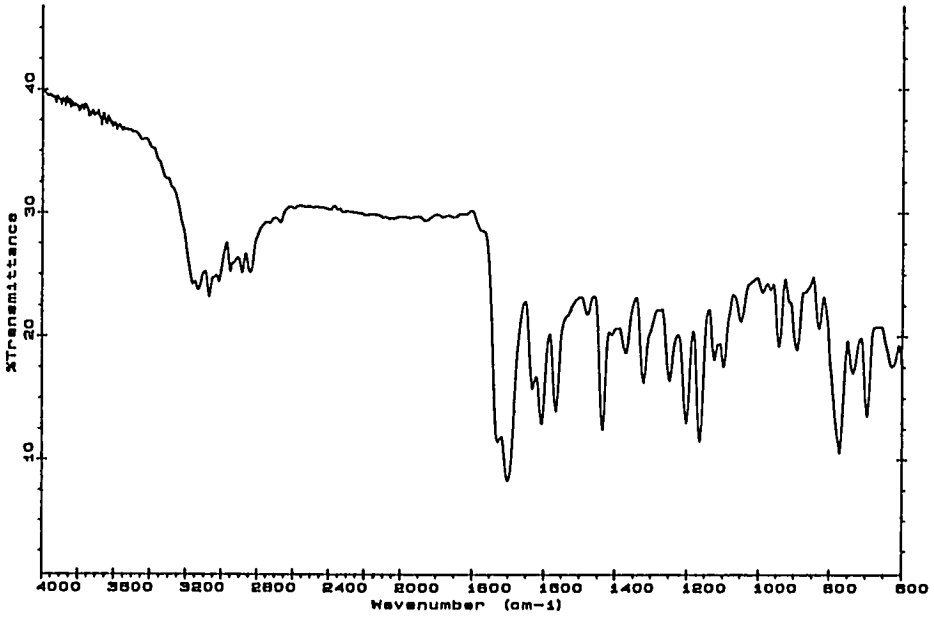
261

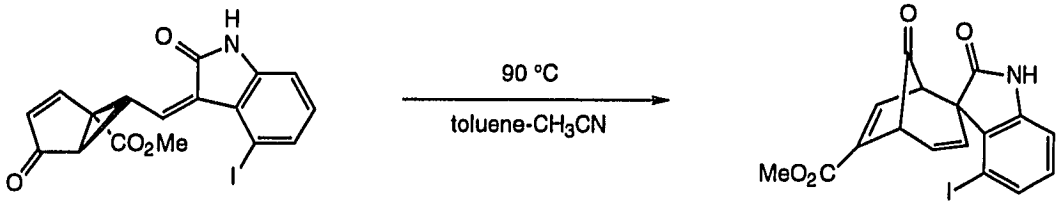


Compound **261** continued:









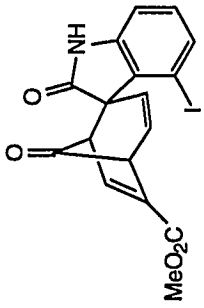
261 **262**

2,2-Spiro-(4'-iodo-indolinone)-6-carbomethoxy-bicyclo[3.2.1]octa-3,7-dien-8-one (**262**)

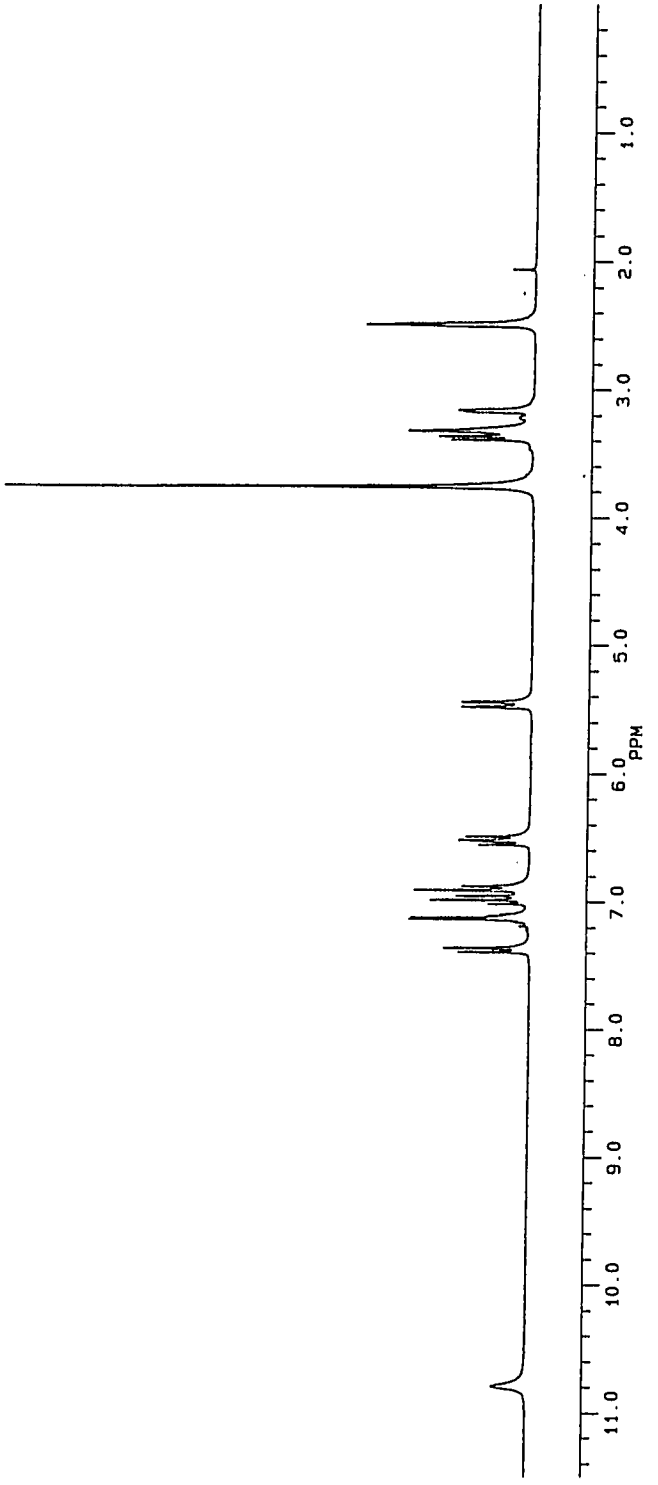
A solution of 2.73 g (6.48 mmol) of enone **261** in 40 mL of toluene-acetonitrile (1:1) under argon was heated at 90 °C for 45 min. The mixture was cooled in ice bath, then filtered and the solid was washed with ethyl ether to give 2.48 g of **262** as pale yellow crystals. The combined filtrate and washing were evaporated to dryness *in vacuo*. The residue was purified on a silica gel column employing 0.5-1% methanol-dichloromethane as eluent to afford 0.19 g of **262** as pale yellow crystals with a combined yield of **262** as 98%.

mp (tol/CH_3CN)	194-194.5 °C
IR (KBr):	3183, 3148, 3085, 2946, 2879, 2827, 1784, 1711, 1605, 1571, 1438, 1342, 1249, 1211, 1092, 987, 910, 875, 777, 741, 723
^{1}H NMR (d^6-DMSO):	3.16 (1H, d, J = 3.6 Hz), 3.37 (1H, d, J = 6.6 Hz), 3.76 (3H, s), 5.46 (1H, dd, J_1 = 1.3 Hz, J_2 = 9.4 Hz), 6.52 (1H, dd, J_1 = 6.9 Hz, J_2 = 9.4 Hz), 6.89 (1H, d, J = 7.5 Hz), 6.98 (1H, t, J = 7.8 Hz), 7.13 (1H, d, J = 3.6 Hz), 7.37 (1H, d, J = 7.8 Hz), 10.79 (1H, J = 7.8 Hz)
^{13}C NMR (d^6-DMSO):	46.3, 52.1, 58.2, 58.4, 93.1, 110.0, 125.5, 130.9, 131.3, 132.1, 133.2, 140.2, 141.7, 143.2, 162.2, 175.1, 198.4
MS:	422 (<1, M+1), 421 (4, M^+), 420 (<1, M-1), 404 (28), 403 (77), 372 (20), 344 (15), 294 (18), 276 (72), 217 (56), 188 (100), 162 (22), 122(50), 94 (38), 81 (61)

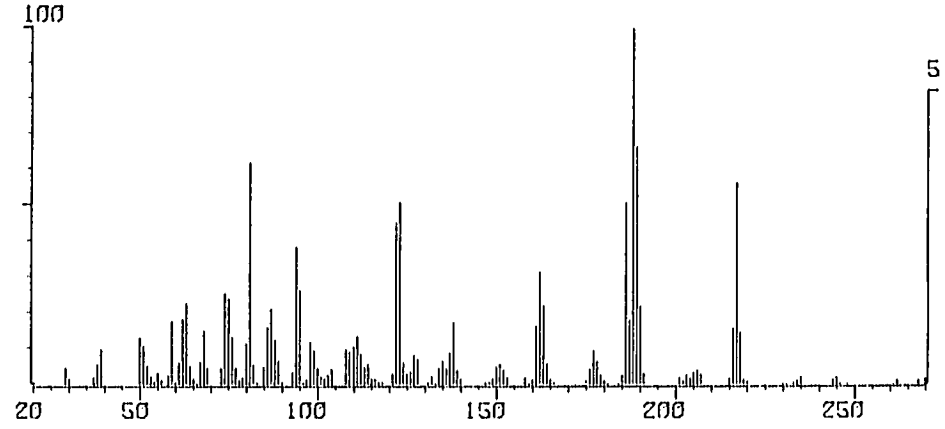
Exact Mass:	Calculated for $C_{17}H_{12}I_1N_1O_4$	420.9811
	Found	420.9814

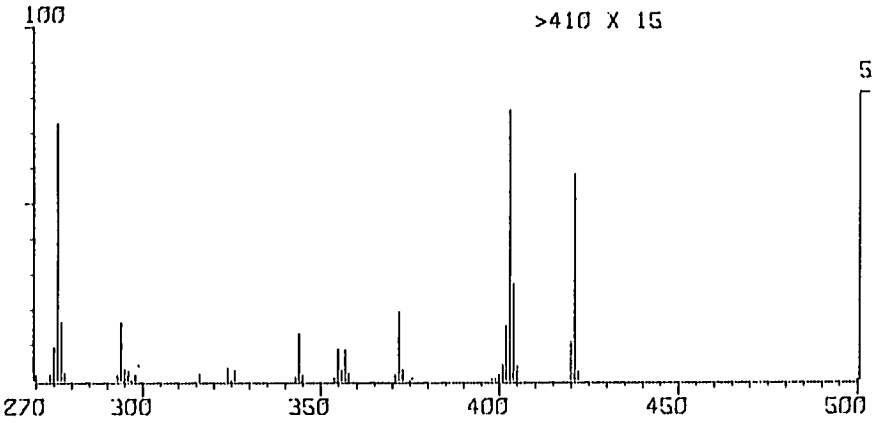


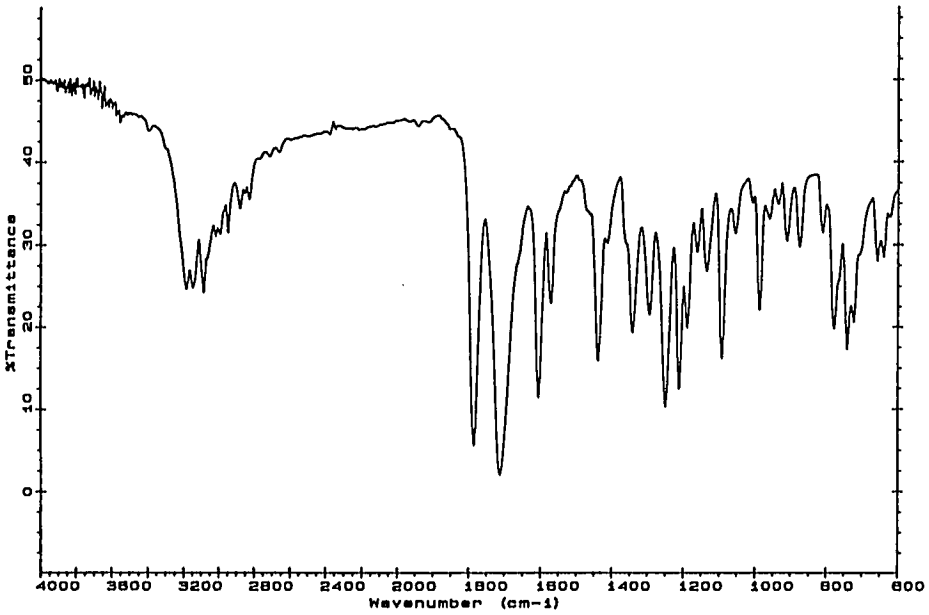
262

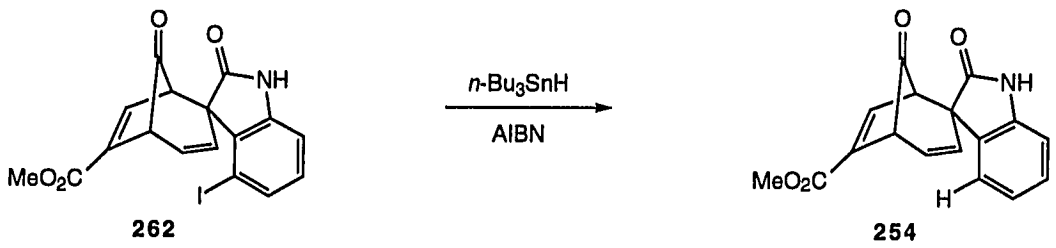


Compound **262** continued:









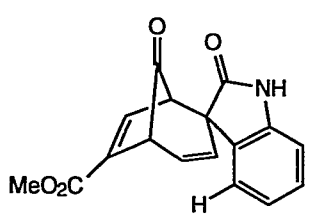
262 **254**

2,2-Spiro-indolinone-6-carbomethoxy-bicyclo[3.2.1]octa-3,7-dien-8-one (**254**)

A suspension of 2.44 g (5.80 mmol) of crystalline **262**, 3.90 mL (14.5 mmol) of tributyltin hydride and 95 mg (0.58 mmol) of 2,2'-azobisisobutyronitrile in 40 mL of toluene in culture tube was bubbled with argon for 10 min. The tube was then capped and heated at 90-95 °C for 1 h. The solution became clear after a while before the product precipitated out. Upon cooling to room temperature, the precipitate was collected by filtration and washed with ethyl ether to give 1.15 g of **254** as white crystals. The filtrate and the washings were combined and condensed to small volume under reduced pressure. The residue was partitioned between acetonitrile and hexanes three times. The acetonitrile extracts were combined and evaporated to dryness *in vacuo*. The resulting residue was partitioned between ethyl acetate and a diluted aqueous potassium fluoride solution. The aqueous layer was extracted thoroughly with ethyl acetate. The extracts were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. Flash silica gel chromatography separation of the crude product eluted with 0.5-1% methanol-dichloromethane afforded additional 0.31 g of **254** as light yellow crystals with a combined 85.4 % yield of **254**.

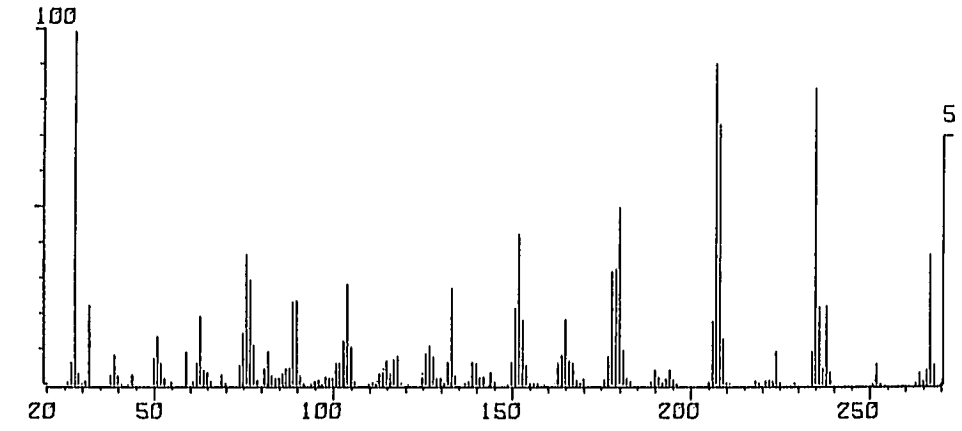
mp (toluene) 190-190.5 °C

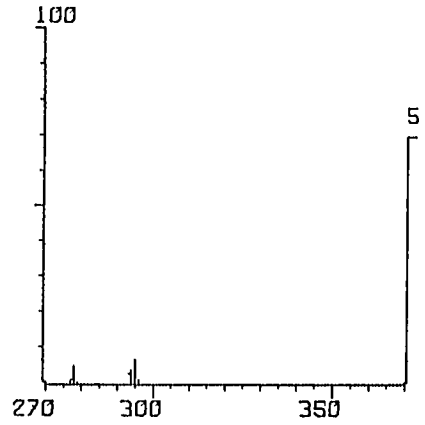
IR (film):	3270, 3084, 1782, 1722, 1616, 1470, 1317, 1264, 1211, 1091, 912, 733	
^{1}H NMR ($CDCl_3$):	2.28 (1H, d, J = 3.4 Hz), 3.52 (1H, d, J = 7.2 Hz), 3.88 (1H, s), 5.36 (1H, dd, J_1 = 1.4 Hz, J_2 = 9.3 Hz), 6.70 (1H, dd, J_1 = 7.2 Hz, J_2 = 9.3 Hz), 6.98 (1H, d, J = 7.9 Hz), 7.05 (1H, d, J = 7.2 Hz), 7.11 (1H, d, J = 3.5 Hz), 7.12 (1H, t, J = 7.8 Hz), 7.29 (1H, dt, J_1 = 1.2 Hz, J_2 = 7.5 Hz), 8.50 (1H, s)	
^{13}C NMR ($CDCl_3$):	46.3, 52.3, 55.6, 56.7, 111.0, 122.7, 125.3, 127.6, 128.4, 129.7, 135.1, 138.8, 139.9, 146.2, 162.7, 178.1, 200.8	
MS:	296 (<1, M+1), 295 (7, M^+), 294 (4, M-1), 267 (37), 235 (83), 207 (90), 180 (50), 152 (43), 133 (28), 104 (30), 76 (36), 28 (100)	
Exact Mass:	Calculated for $C_{17}H_{13}N_1O_4$	295.0844
	Found	295.0844

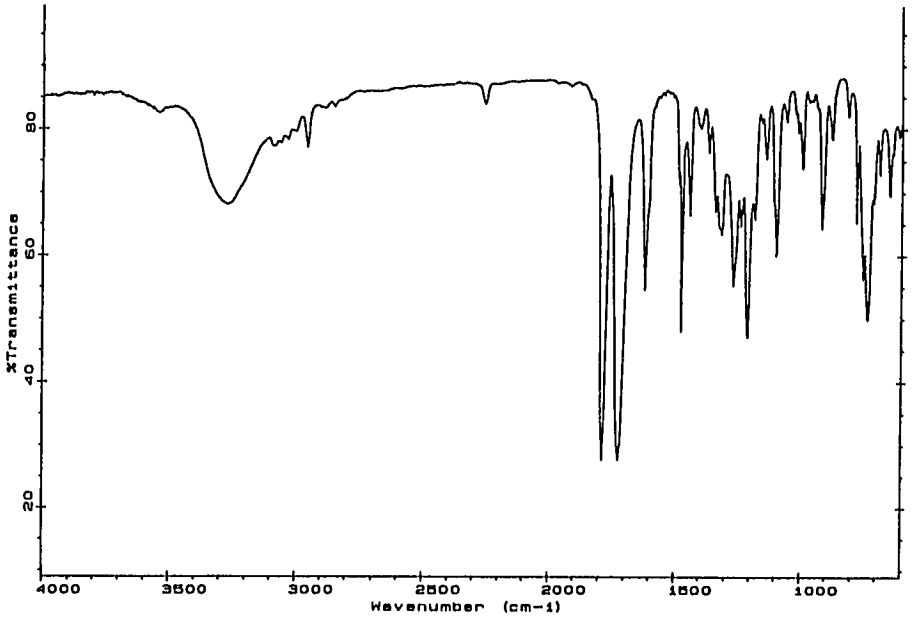


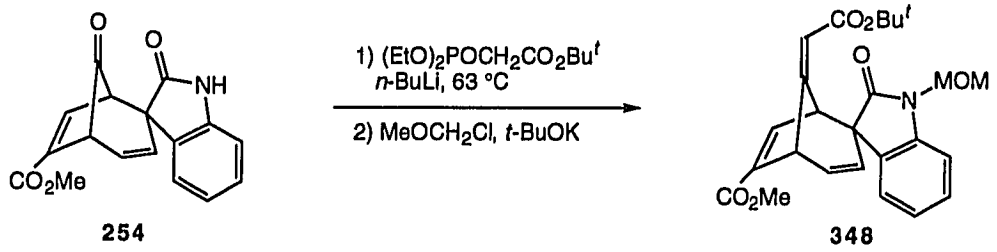
254

Compound **254** continued:









254 348

N-MOM-spiro-indolinone-(*Z*)-α,β-unsaturated-*t*-butyl ester (**348**)

To a stirred solution of 4.91 mL (22.4 mmol) of *t*-butyl diethylphosphonoacetate in 15 mL of tetrahydrofuran at 0 °C under argon was added dropwise 9.43 mL (22.1 mmol) of 2.34 M of *n*-butyllithium in hexanes. After the addition of *n*-butyllithium, the mixture was stirred at 0 °C for 10 min before it was added slowly to a solution of 2.10 g (7.12 mmol) of ketone **254** in 20 mL of tetrahydrofuran under argon at 63 °C. After the addition of the Horner-Emmons reagent, the resulting mixture was then cooled to room temperature and stirred for additional 15 min.

To above reaction mixture was added freshly distilled 1.42 mL (18.7 mmol) of chloromethylmethyl ether. The progress of the reaction was monitored with TLC. Some potassium *t*-butoxide may be needed to complete the reaction. Upon disappearance of the starting material, the reaction mixture was poured into water and partitioned with ethyl acetate. The aqueous layer was extracted thoroughly with ethyl acetate. The extracts were combined, washed with brine, dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude product was purified by flash silica gel chromatography to afford 2.18 g (70%) of **348** as white crystals.

mp (Et_2O) 147-149°C

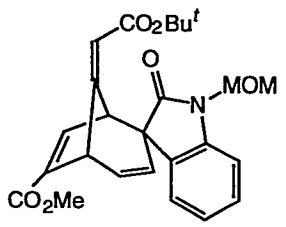
IR (film): 2977, 2938, 1716, 1609, 1483, 1364, 1337, 1244, 1218, 1164, 1125, 1091, 985, 919, 733

^{1}H NMR ($CDCl_3$): 1.45 (9H, s), 3.37 (3H, s), 3.55 (1H, d, J = 6.5 Hz), 4.75 (1H, d, J = 1.1 Hz), 5.05 (1H, d, J = 10.7 Hz), 5.17 (1H, d, J = 10.7 Hz), 5.72 (1H, s), 6.72 (1H, ddd, J_1 = 0.94 Hz, J_2 = 6.7 Hz, J_3 = 9.0 Hz), 6.82 (1H, d, J = 3.1 Hz), 7.05 (2H, m), 7.30 (1H, dt, J_1 = 1.6 Hz, J_2 = 8.4 Hz)

^{13}C NMR ($CDCl_3$): 21.0, 38.0, 41.7, 44.9, 47.0, 49.2, 64.5, 72.8, 102.7, 103.1, 115.6, 117.9, 119.3, 120.7, 122.1, 129.8, 134.3, 134.7, 141.7, 152.9, 156.4, 158.4, 168.6

MS: 438 (<1, M+1), 437 (1, M^+), 406 (2), 405 (3), 364 (1), 349 (26), 305 (8), 276 (19), 217 (10), 201 (14), 145 (4), 86 (78), 79 (100), 57 (32), 45 (60)

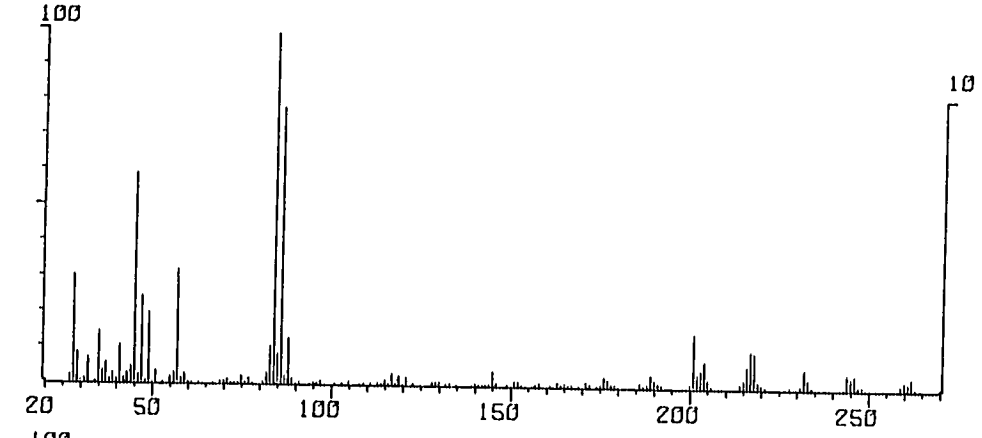
Exact Mass:		
	Calculated for $C_{25}H_{27}N_1O_6$	437.1838
	Found	437.1839

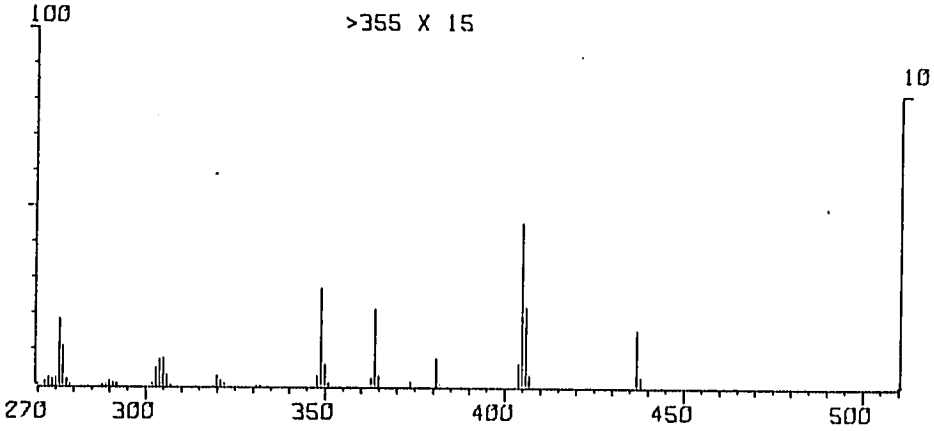

CO2Bu^t
O
N
MOM
CO2Me

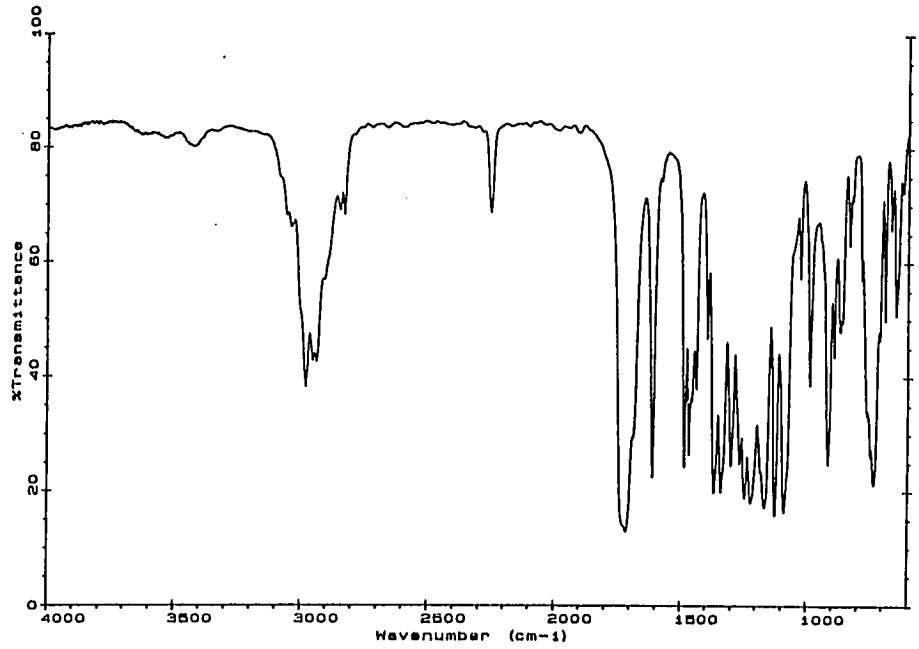
348

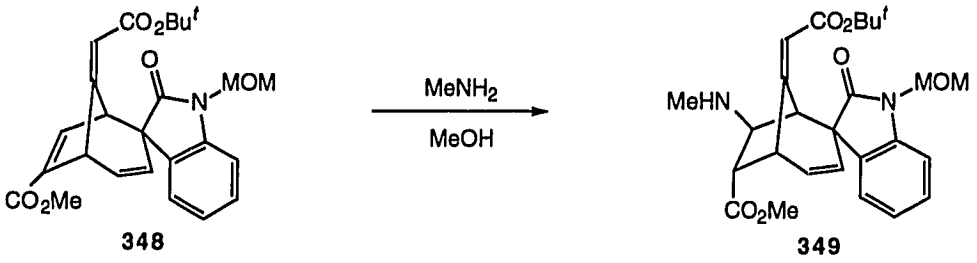
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

Compound **348** continued:







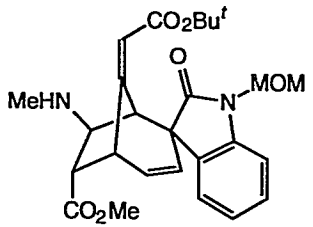


348 349

trans-Amino methyl ester (**349**)

A solution of 1.90 g (4.35 mmol) of **348** and 21.8 mL (43.6 mmol) of 2M methyl amine in methanol was stirred at room temperature for 45 min. The solvent was then removed under reduced pressure to give 2.03 g (100%) of **349** as white foams.

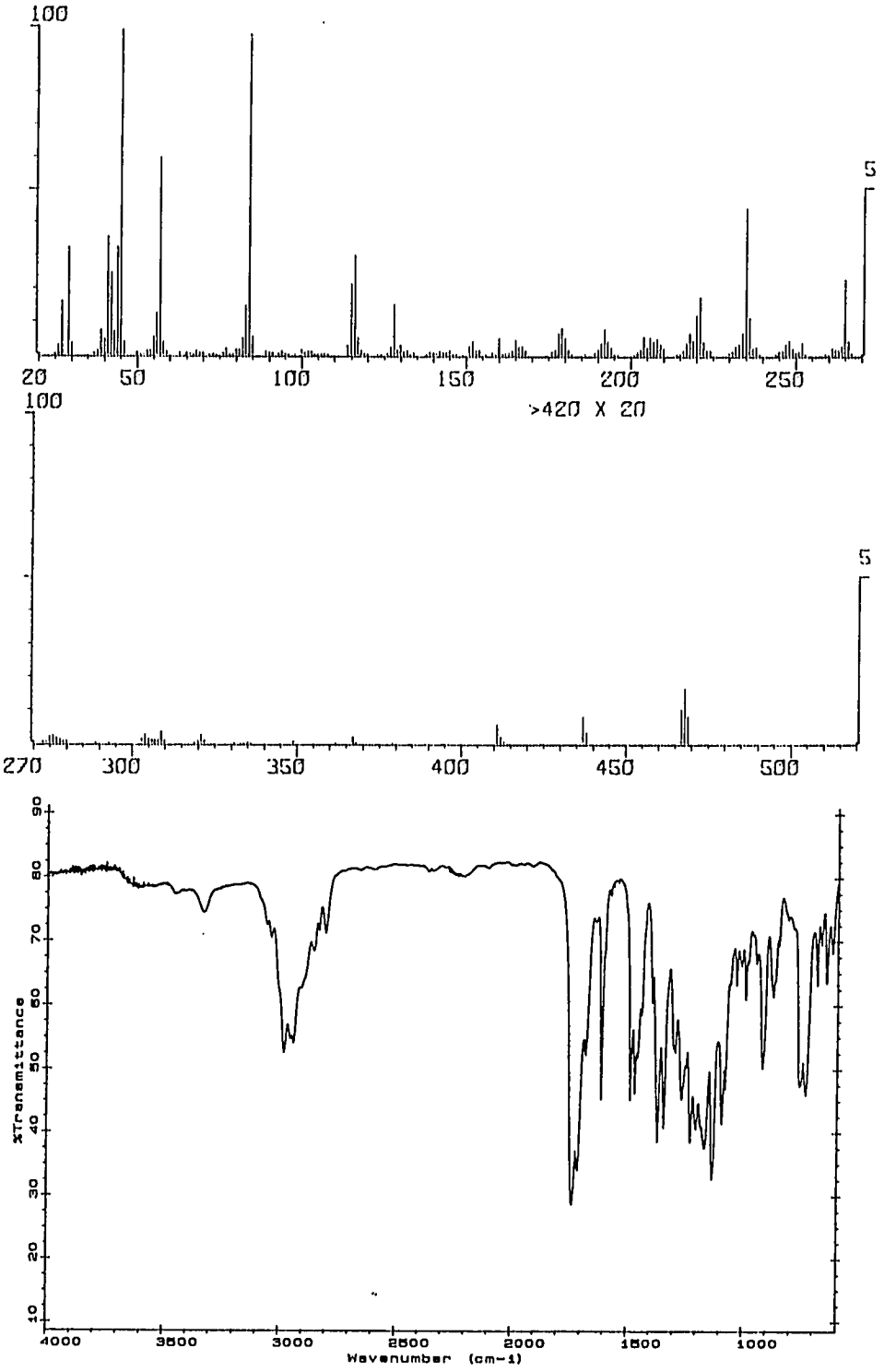
mp (methanol)	73-74 °C
IR (film):	3336, 2977, 2944, 1736, 1069, 1483, 1364, 1343, 1264, 1231, 1164, 1131, 1091, 919, 766, 733
^{1}H NMR ($CDCl_3$):	1.45 (9H, s), 2.07 (3H, s), 2.72 (3H, t, J = 5.7 Hz), 3.35 (3H, s), 3.37 (1H, dt, J_1 = 1.2 Hz, J_2 = 6.5 Hz), 3.79 (3H, s), 3.90 (1H, s), 4.17 (1H, d, J = 5.3 Hz), 5.02 (1H, d, J = 10.9 Hz), 5.14 (1H, d, J = 10.9 Hz), 5.26 (1H, dd, J_1 = 1.2 Hz, J_2 = 9.2 Hz), 5.96 (1H, s), 6.20 (1H, dd, J_1 = 6.5 Hz, J_2 = 9.2 Hz), 7.07 (1H, d, J = 7.8 Hz), 7.12 (1H, dt, J_1 = 0.95 Hz, J_2 = 7.3 Hz), 7.33 (1H, dt, J_1 = 0.95 Hz, J_2 = 7.3 Hz), 7.57 (1H, d, J = 7.4 Hz)
^{13}C NMR ($CDCl_3$):	28.0, 33.8, 45.4, 48.3, 52.0, 56.3, 56.9, 58.6, 61.4, 71.7, 79.7, 109.6, 112.3, 114.4, 125.9, 126,2, 128.9, 129.8, 134.4, 142.0, 156.5, 165.6, 172.1, 175.5
MS:	469 (<1, M+1), 468 (1, M^+), 467 (<1, M-1), 437 (<1), 411 (6), 265 (23), 235 (45), 221 (18), 128 (17), 116 (30), 84 (96), 57 (60), 45 (100)
Exact Mass:	Calculated for $C_{26}H_{32}N_2O_6$ 468.2260 Found 468.2262

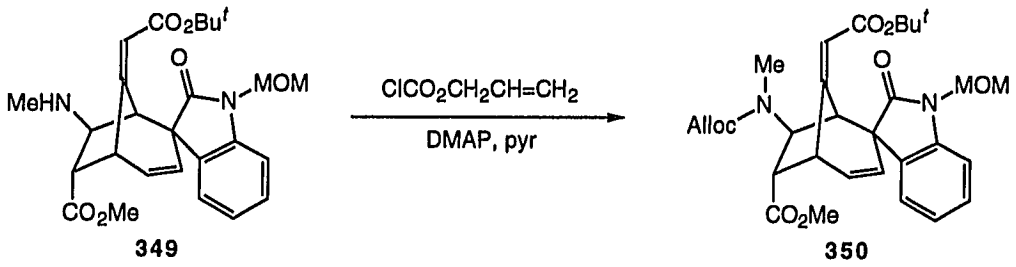

CO2But
O
MeHN
N
MOM
CO2Me

349

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

Compound **349** continued:





349 **350**

Allylurethane (**350**)

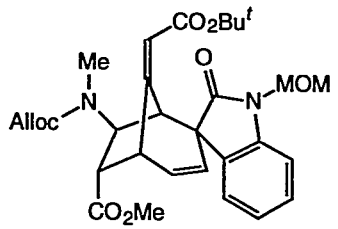
To a stirred solution of 2.03 g (4.34 mmol) of methyl amine **349**, 0.70 mL (8.65 mmol) of pyridine and 2.6 mg (0.021 mmol) of *N,N*-dimethylamino pyridine in 20 mL of dichloromethane at 0 °C was added 0.69 mL (6.50 mmol) of allyl chloroformate. The reaction mixture was stirred at 0 °C for 15 min before it was poured into ethyl acetate and partitioned with 3 M hydrochloric acid. The ethyl acetate layer was then washed with a saturated aqueous sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate and evaporated *in vacuo*. Flash silica gel chromatography separation of the crude product eluting with 50% ether-hexanes afforded 2.33 g (97%) of **350** as a colorless oil.

IR (film): 2984, 2944, 1736, 1709, 1609, 1470, 1364, 1344, 1164, 1131, 1091, 919, 766, 733

^{1}H NMR ($CDCl_3$): 1.44 (9H, s), 2.68 (3H, s), 3.13 (1H, bt), 3.36 (3H, s), 3.43 (1H, dt, J_1 = 1.5 Hz, J_2 = 6.1 Hz), 3.78 (3H, s), 3.98 (1H, s), 4.43 (1H, bs), 4.52 (1H, bs), 5.00 (1H, d, J = 10.9 Hz), 5.13 (1H, d, J = 10.9 Hz), 5.23-5.38 (2H, m), 5.28 (1H, dd, J_1 = 1.4 Hz, J_2 = 9.1 Hz), 5.70 (1H, d, J = 6.4 Hz), 5.9 (1H, bm), 5.95 (1H, s), 6.21 (1H, dd, J_1 = 6.4 Hz, J_2 = 9.1 Hz), 7.06 (1H, d, J = 7.7 Hz), 7.08 (1H, bm), 7.32 (1H, dt, J_1 = 0.89 Hz, J_2 = 7.9 Hz), 7.64 (1H, bs)

^{13}C NMR ($CDCl_3$): 28.1, 29.6, 46.1, 49.6, 52.1, 53.2, 56.4, 57.8, 59.0, 66.0, 71.8, 79.9, 106.5, 113.3, 117.3, 122.5, 126.1, 126.5, 129.0, 129.4, 132.9, 134.2, 141.9, 155.0, 156.6, 165.3, 171.5, 175.0

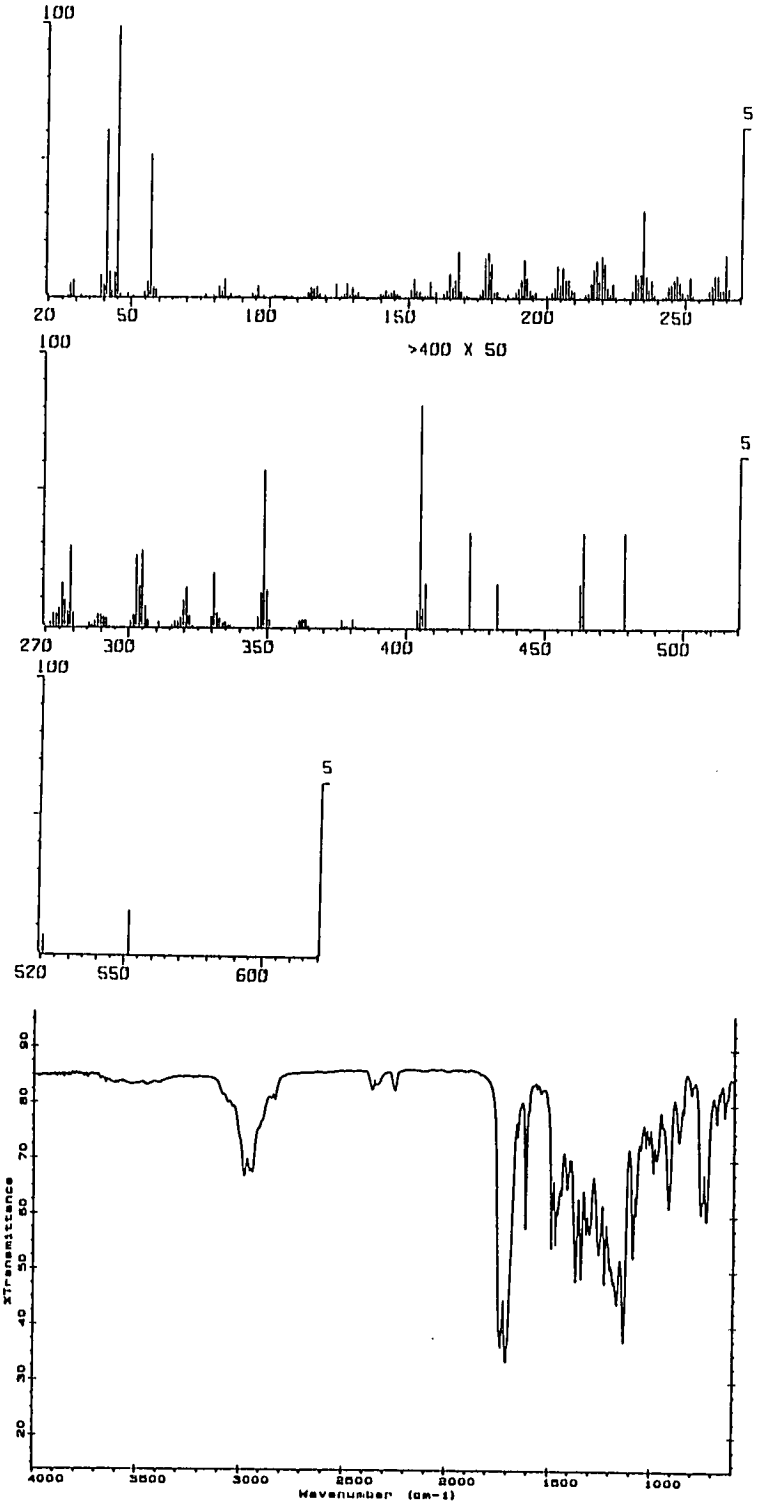
MS:	552 (<1, M^+), 521 (<1), 479 (<1), 464 (<1), 423 (<1), 405 (2), 349 (58), 305 (28), 279 (30), 235 (31), 179 (16), 57 (52), 50 (100), 46 (60)	
Exact Mass:	Calculated for $C_{30}H_{36}N_2O_8$	552.2472
	Found	552.2477

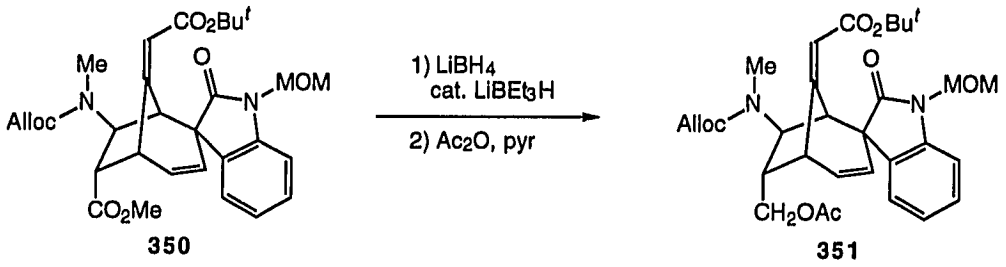

CO2Bu^t
Me
O
N
MOM
Alloc
N
CO2Me

350

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

Compound **350** continued:





350 351

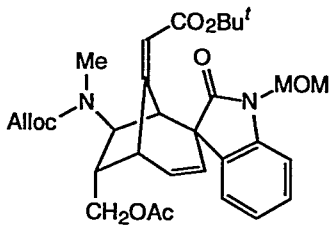
Allylurethane hydroxymethyl acetate (**351**)

To a stirred solution of 2.33 g (4.22 mmol) of **350** in 30 mL of anhydrous tetrahydrofuran at room temperature under argon was added sequentially 3.22 mL (6.44 mmol) of 2.0 M lithium borohydride in tetrahydrofuran and 0.20 mL (0.2 mmol) of 1.0 M of lithium triethylborohydride in tetrahydrofuran. The progress of the reaction was carefully monitored with TLC. Upon disappearance of the starting material, a 3 M hydrochloric acid solution was added slowly to above reaction mixture at 0 °C and the resulting biphasic mixture was poured into a saturated ammonium chloride solution and thoroughly extracted with dichloromethane. The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness *in vacuo*.

The residue was dissolved in 0.93 mL (9.86 mmol) of acetic anhydride and 0.79 mL (0.977 mmol) of pyridine and placed at room temperature for 15 min. The reagents were then removed under reduced pressure with toluene. The crude product was purified through flash silica gel chromatography eluting with 60% ether-hexanes to give 1.80 g (75%) of **351** as white crystals.

mp (Et_2O)	147-148 °C
IR (film):	2977, 2944, 1742, 1709, 1616, 1477, 1370, 1311, 1231, 1138, 1091, 1038, 979, 925, 753

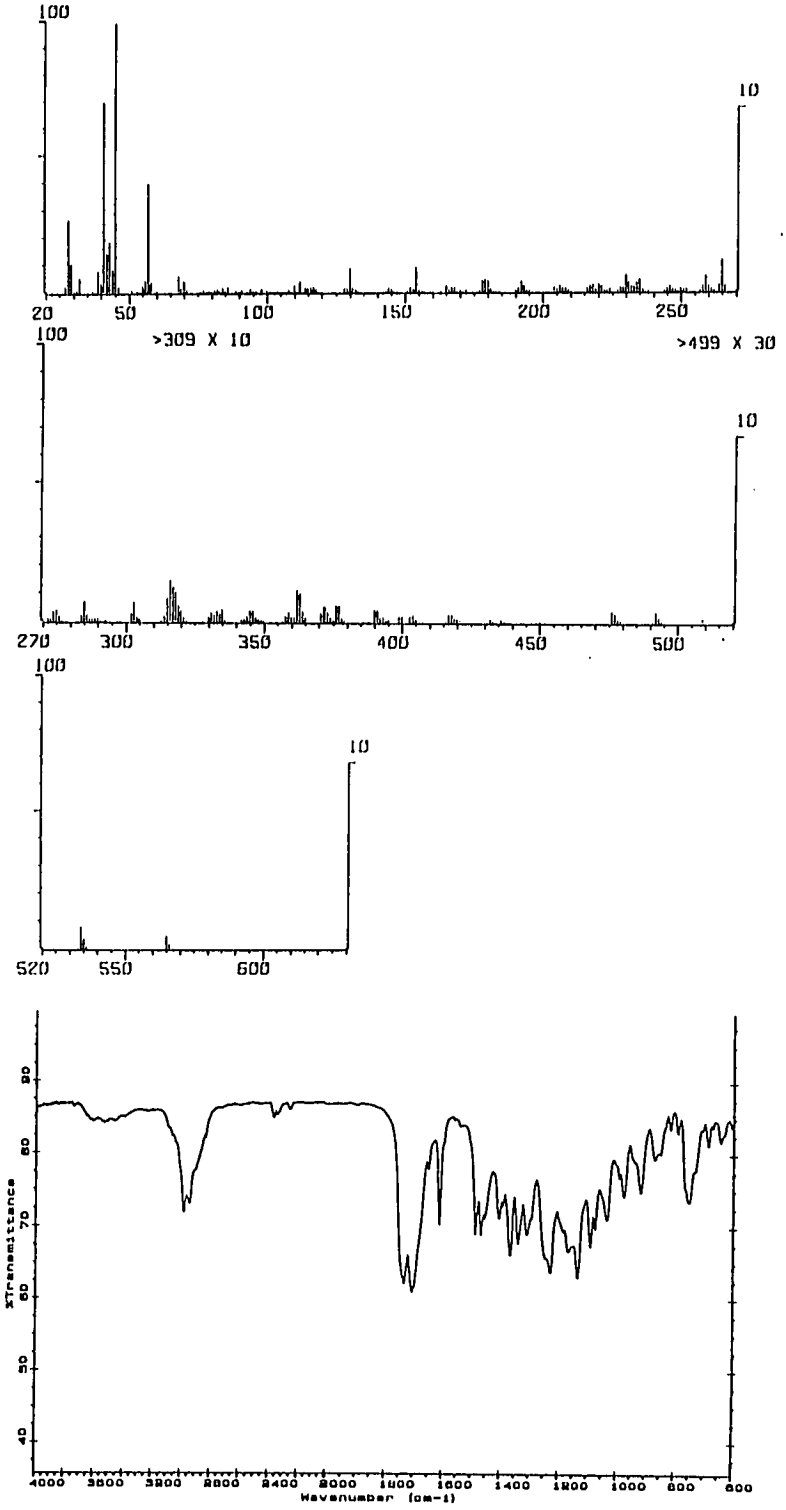
^{1}H NMR ($CDCl_3$):	1.44 (9H, s), 2.08 (3H, s), 2.44 (1H, d, J = 5.2 Hz), 2.66 (3H, s), 3.15 (1H, t, J = 5.2 Hz), 3.35 (3H, s), 3.96 (1H, s), 4.37 (2H, dd, J_1 = 11.4 Hz, J_2 = 20.2 Hz), 4.39-4.64 (1H, bm), 4.47 (1H, d, J = 5.5 Hz), 4.96-5.15 (2H, bm), 5.01 (1H, d, J = 10.8 Hz), 5.13 (1H, d, J = 10.8 Hz), 5.24-5.37 (2H, bm), 5.92 (1H, bm), 5.94 (1H, s), 6.24 (1H, dd, J_1 = 6.2 Hz, J_2 = 9.2 Hz), 7.06 (2H, bm), 7.31 (1H, t, J = 8.0 Hz), 7.38 and 7.65 (1H, d, J = 7.1 Hz)
^{13}C NMR ($CDCl_3$):	20.8, 28.0, 28.4, 45.5, 48.6, 53.1, 56.3, 57.7, 59.0, 63.3, 66.2, 71.8, 79.8, 109.5, 113.0, 117.6, 122.5, 126.0, 126.2, 129.0, 129.4, 132.7, 134.3, 141.9, 155.0, 157.0, 165.4, 170.7, 174.8
MS:	566 (<1, M^+), 565 (<1, M-1), 534 (<1), 492 (<1), 476 (<1), 362 (1), 316 (2), 303 (7), 285 (7), 265 (20), 154 (10), 80 (10), 57 (40), 50 (100), 41 (70)
Exact Mass:	Calculated for $C_{31}H_{38}N_2O_8$ 566.2628 Found 566.2630

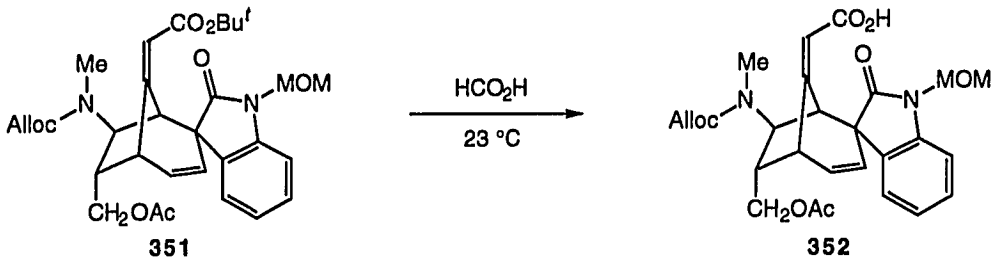

CO2Bu^t
Me
O
N
MOM
Alloc
N
CH2OAc

351

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

Compound **351** continued:





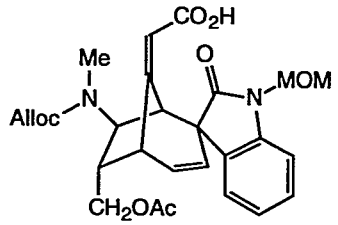
351 352

α,β-Unsaturated carboxylic acid (**352**)

A solution of 1.78 g (3.14 mmol) of *t*-butyl ester **351** and 10 mL of formic acid was stirred at room temperature. The progress of the reaction was carefully monitored by TLC. Upon disappearance of the starting material, the solution was carefully evaporated to dryness *in vacuo* at room temperature. The crude product was purified through flash silica gel chromatography eluted with 1% methanol-dichloromethane to give 1.28 g (79%) of **352** as white crystals.

mp ($MeOH/Et_2O$)	126-128 °C
IR (film):	3449, 3197, 3057, 2944, 2665, 2559, 1702, 1616, 1470, 1410, 1344, 1244, 1145, 1032, 759
^1H NMR ($CDCl_3$):	2.09 (3H, s), 2.47 (1H, bs), 2.66 (3H, s), 3.24 (1H, s), 3.32 (3H, s), 3.89 (1H, s), 4.30-4.60 (2H, bm), 4.38 (1H, d, J = 8.7 Hz), 4.47 (1H, d, J = 4.9 Hz), 4.80-5.30 (3H, bm), 5.03 (1H, d, J = 11.0 Hz), 5.14 (1H, d, J = 11.0 Hz), 5.37 (1H, d, J = 9.1 Hz), 5.92 (1H, bm), 6.04 (1H, s), 6.26 (1H, dd, J_1 = 6.1 Hz, J_2 = 9.1 Hz), 7.06 (2H, bm), 7.33 (1H, t, J = 7.7 Hz), 7.37 and 7.65 (1H, bm)
^{13}C NMR ($CDCl_3$):	20.8, 28.5, 45.6, 48.1, 49.2, 56.3, 57.6, 59.5, 63.1, 66.3, 71.7, 109.7, 111.3, 117.3, 118.3, 122.5, 123.0, 125.5, 126.2, 129.2, 132.5, 134.2, 141.7, 155.0, 160.6, 170.9, 175.1
MS:	510 (<1, M^+), 479 (<1), 391 (<1), 377 (<1), 363 (<1), 333 (<1), 318 (1), 303 (10), 285 (10), 265 (10), 230 (10), 179 (10), 154 (13), 130 (10), 45 (100), 41 (70), 28 (62)

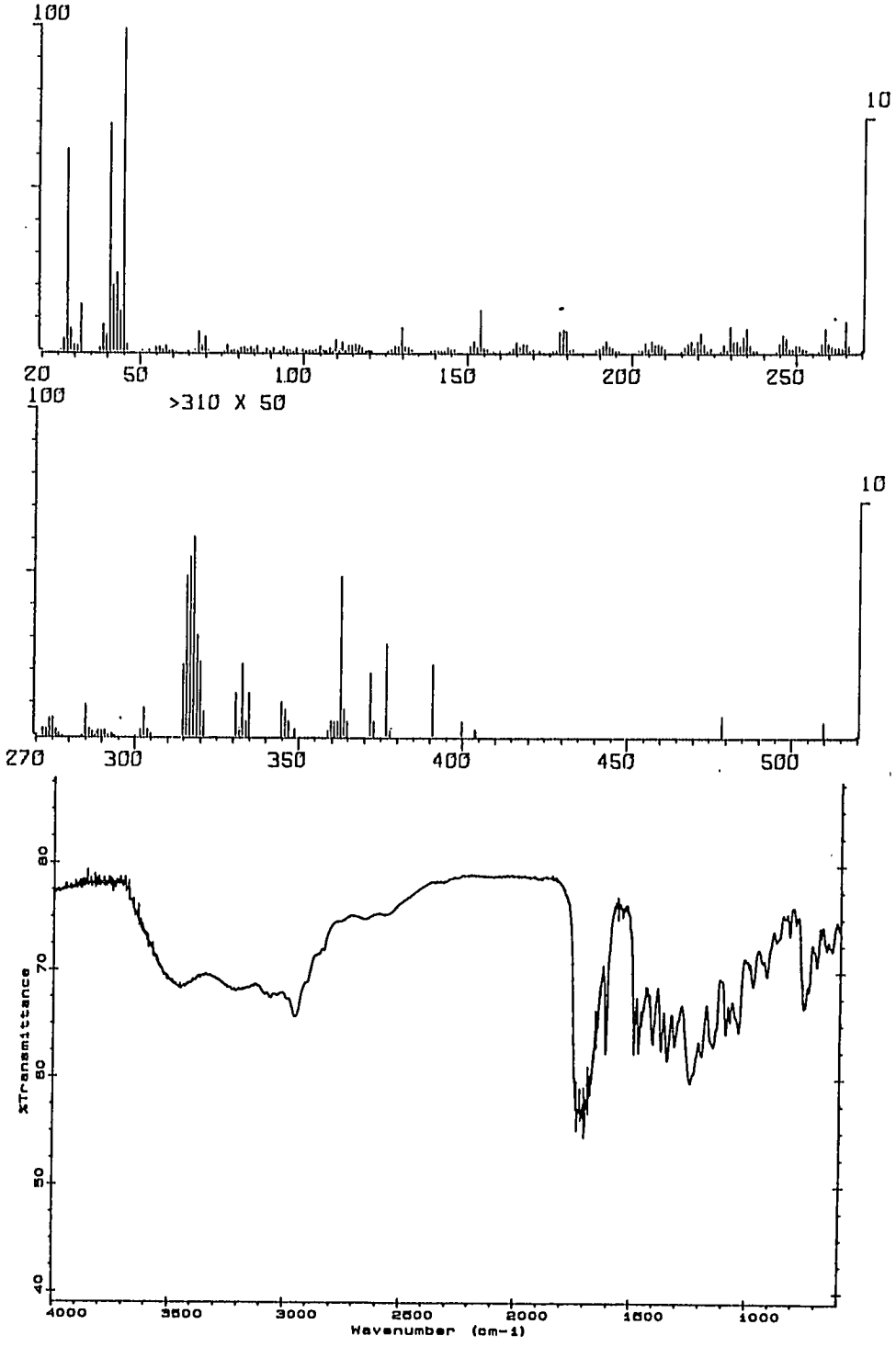
Exact Mass:	Calculated for $C_{27}H_{30}N_2O_8$	510.2002
	Found	510.2000

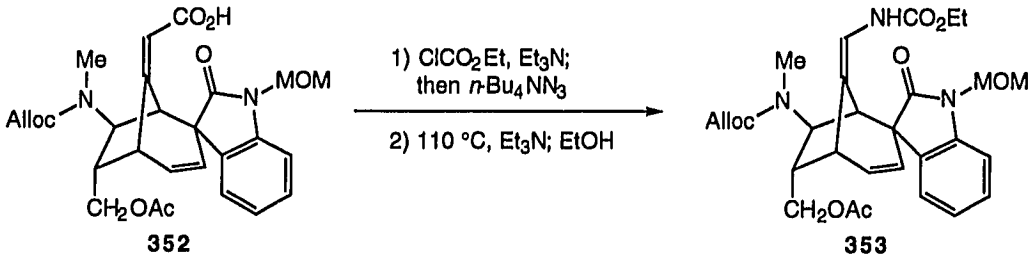

CO2H
Me
O
MOM
N
Alloc
N
CH2OAc

352

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

Compound **352** continued:





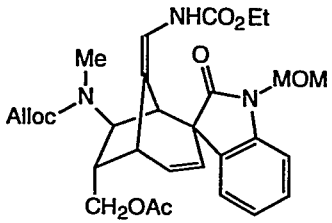
Ethyl ene-carbamate (**353**)

To a ice-cold, stirred solution of 1.24 g (2.43 mmol) of acid **352** in 15 mL of tetrahydrofuran was added 0.51 mL (3.66 mmol) of triethylamine and 0.29 mL (3.03 mmol) of ethyl chloroformate (purified by passing through alumna). The triethylamine hydrochloride settled in almost immediately. Upon the complete consumption of the starting material, to above mixture was then added 1.73 g (6.09 mmol) of tetrabutylammonium azide. The progress of the reaction was monitored by TLC. After disappearance of mixed anhydride, the reaction mixture was poured into water and the biphasic mixture was thoroughly extracted with ethyl ether. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The crude product was subjected to a quick flash column chromatography eluting with 70% of ether-hexane to give 1.14 g (88%) of acyl azide as white foams.

The above azide was dissolved in 15 mL of toluene and the resulting solution was flushed with argon for 5 min before 5 uL (0.04 mmol) of triethylamine was added. The resulting mixture was refluxed under argon for 45 min before 0.625 mL (11.1 mmol) of ethanol was added. The reaction mixture was then allowed to cool to room temperature and stirred for additional 90 min. The solution was then evaporated *in vacuo* to give a yellow oil. The crude

product was purified through silica gel flash column chromatography employing 80-90% of ether-hexanes as eluent to afford 1.02 g (76% from **352**) of **353** as colorless crystals.

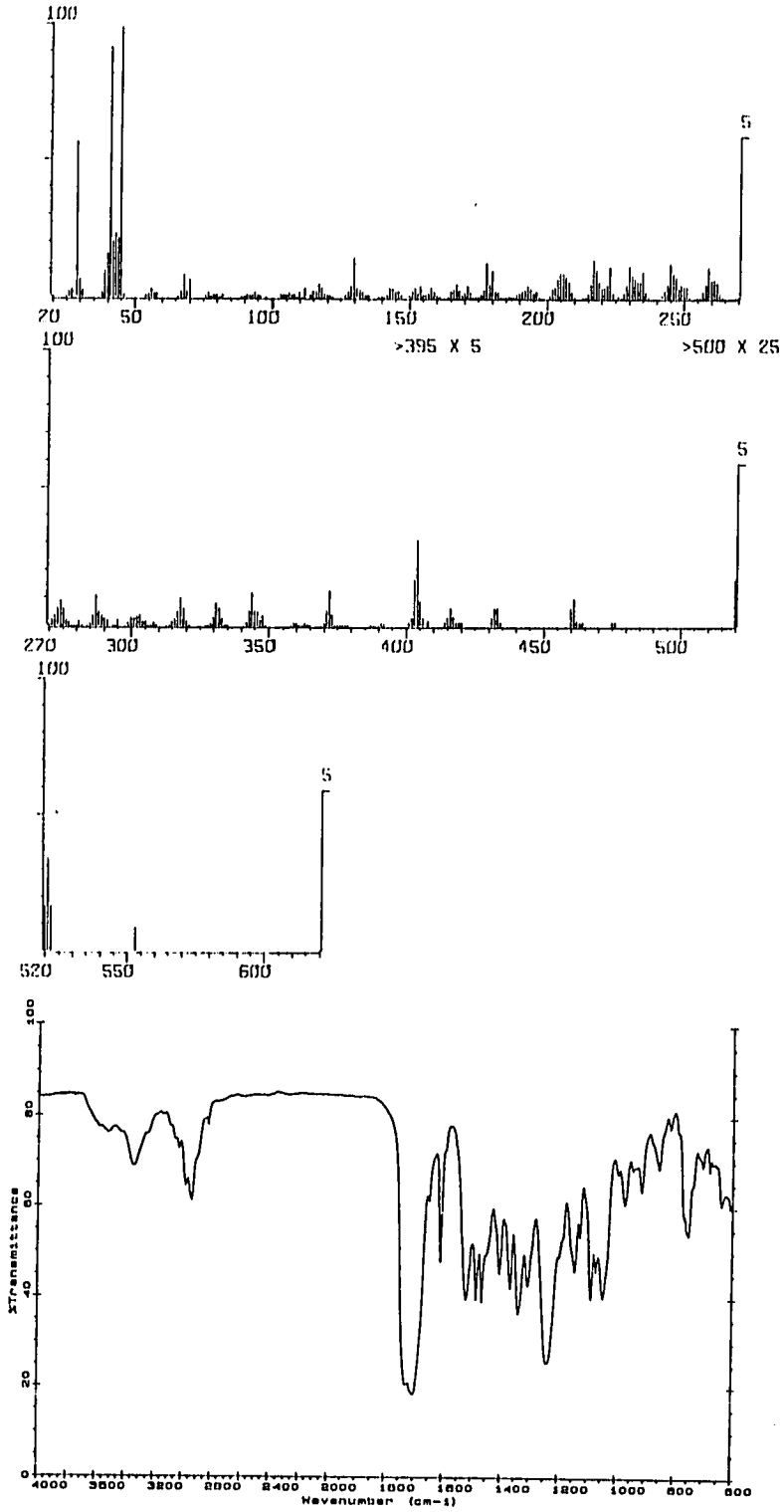
mp ($MeOH/Et_2O$)	105-106 °C
IR (film):	3529, 3343, 2991, 2944, 1709, 1609, 1523, 1470, 1410, 1370, 1337, 1311, 1238, 1151, 1091, 1045, 972, 919, 859, 753
^1H NMR ($CDCl_3$):	1.25 (3H, t, J = 7.0 Hz), 2.08 (3H, s), 2.48 (1H, bs), 2.63 (3H, s), 2.77 (1H, s), 3.21 (1H, s), 3.37 (3H, s), 4.14 (2H, q, J = 7.0 Hz), 4.32 (1H, dd, J_1 = 11.0 Hz, J_2 = 20.7 Hz), 4.44 (3H, bm), .4.98-5.30 (2H, m), 5,14 (1H, s), 5.08 (1H, d, J = 10.6 Hz), 5.22 (1H, d, J = 10.6 Hz), 5.26 (1H, d, J = 9.1 Hz), 5.86 (1H, bs), 6.35 (1H, d, J = 8.5 Hz), 6.33 (1H, dd, J_1 = 6.6 Hz, J_2 = 9.1 Hz), 6.59 (1H, d, J = 8.5 Hz), 7.05 (1H, d, J = 7.7 Hz), 7.18-7.62 (2H, bm), 7.33 (1H, t, J = 7.7 Hz)
^{13}C NMR ($CDCl_3$):	14.3, 20.7, 28.1, 42.1, 48.4, 49.5, 56.2, 57.2, 58.1, 61.2, 63.7, 66.3, 71.7, 109.4, 114.2, 117.0, 118.0, 122.9, 125.6, 126.3, 128.9, 129.4, 132.6, 136.3, 141.4, 154.4, 154.9, 170.7, 177.6
MS:	553 (<1, M^+), 521 (<1), 461 (2), 433 (2), 416 (2), 404 (6), 372 (15), 344 (15), 318 (10), 287 (10), 259 (12), 245 (13), 230 (12), 217 (15), 178 (15), 130 (16), 45 (100), 41(92), 29 (57)
Exact Mass:	Calculated for $C_{29}H_{35}N_3O_8$ 553.2424 Found 553.2426

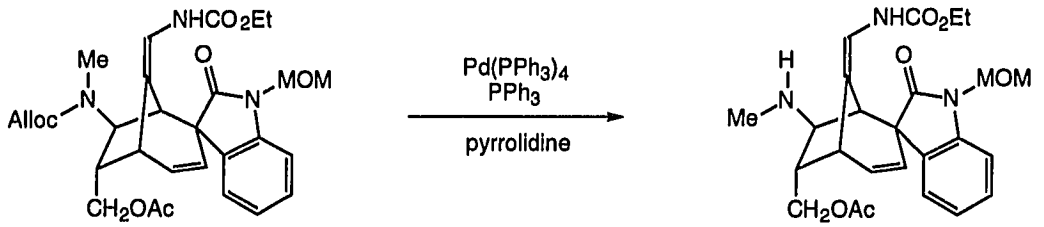

NHCO2Et
Me
O
MOM
Alloc
N
N
CH2OAc

353

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

Compound **353** continued:





Ene-carbamate methyl amine (**354**)

To a stirred solution of 0.92 g (1.66 mmol) of amine **353** in 20 mL of dichloromethane with 76.9 mg (0.067 mmol) of tetrakis(triphenylphospine) palladium and 43.6 mg (0.166 mmol) of triphenylphosphine under argon at room temperature was added 181 uL (2.17 mmol) of pyrrolidine through a micro syringe. After stirred for 10 min at room temperature, the solution was condensed under reduced pressure. The crude product was purified through silica gel flash chromatography eluting with 5% methanol-dichloromethane to give 0.75 g (97%) of **354** as white crystals.

mp ($MeOH/CH_2Cl_2$) 96-98 °C

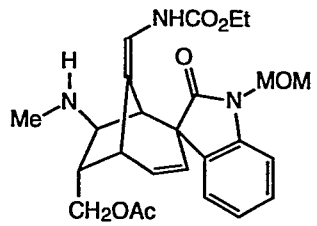
IR (film): 3542, 3316, 2944, 1722, 1609, 1523, 1483, 1370, 1337, 1238, 1091, 1045, 912, 733

^1H NMR ($CDCl_3$): 1.25 (3H, t, J = 7.1 Hz), 2.03 (3H, s), 2.11 (3H, s), 2.14 (1H, m), 2.72 (1H, s), 3.15 (1H, t, J = 5.6 Hz), 3.29 (1H, d, J = 5.4 Hz), 3.37 (3H, s), 4.14 (2H, q, J = 7.1 Hz), 4.22 (1H, dd, J_1 = 10.2 Hz, J_2 = 20.8 Hz), 4.49 (1H, dd, J_1 = 5.8 Hz, J_2 = 10.9 Hz), 5.12 (1H, d, J = 10.8 Hz), 5.23 (1H, d, J = 10.8 Hz), 5.28 (1H, dd, J_1 = 1.1 Hz, J_2 = 10.2 Hz), 6.33 (1H, dd, J_1 = 6.5 Hz, J_2 = 9.2 Hz), 6.40 (1H, d, J = 8.7 Hz), 6.62 (1H, d, J = 8.7 Hz), 7.08 (1H, d, J = 7.8 Hz), 7.11 (1H, t, J = 7.6 Hz), 7.30 (1H, d, J = 7.6 Hz), 7.34 (1H, t, J = 7.6 Hz)

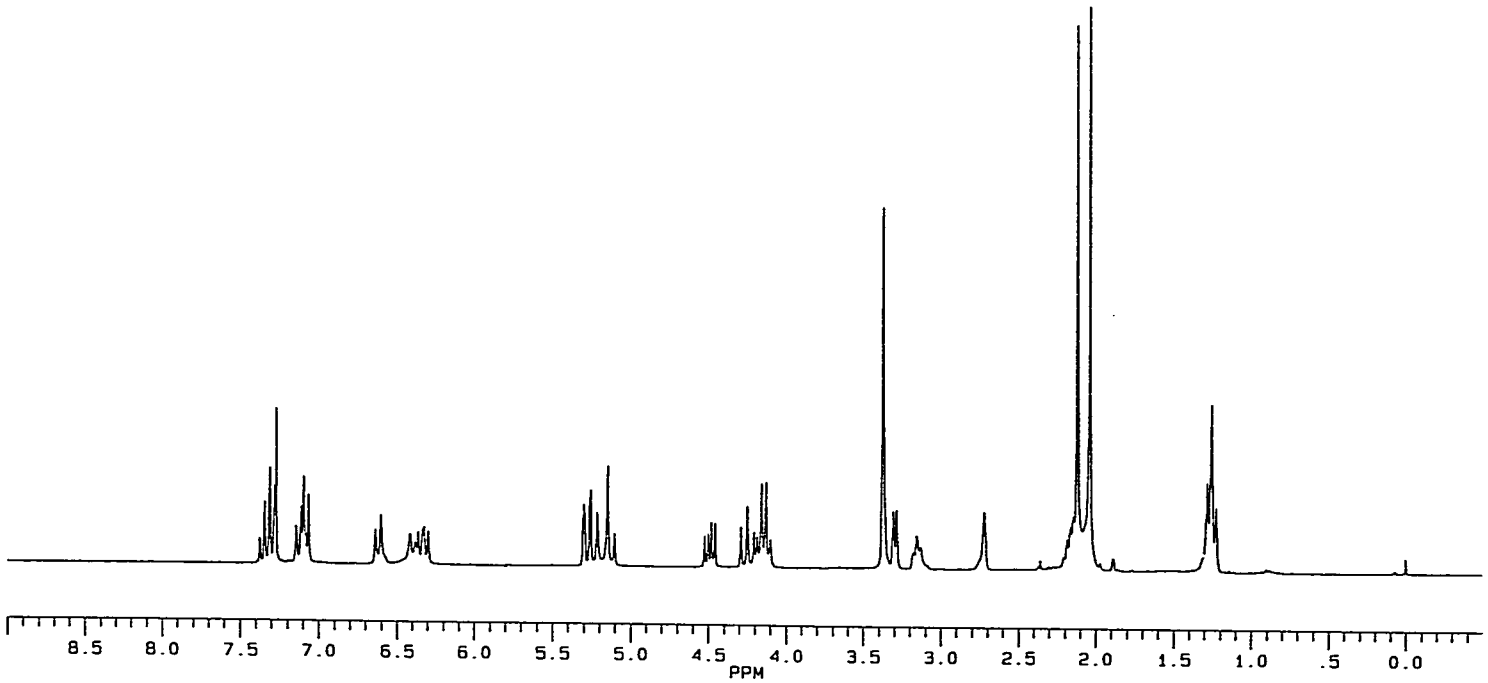
^{13}C NMR ($CDCl_3$): 14.4, 20.9, 34.0, 42.0, 48.7, 53.1, 56.2, 57.4, 61.1, 63.4, 64.4, 71.5, 109.8, 115.3, 122.7, 123.9, 125.2, 126.1, 129.0, 130.1, 136.9, 141.6, 154.5, 171.0, 178.3

MS: 470 (<1, M+1), 469 (1, M^+), 468 (2, M-1), 467 (1, M-2), 438 (1), 408 (1), 392 (1), 365 (1), 320 (12), 308 (20), 295 (11), 261 (20), 235 (18), 223 (30), 178 (23), 70 (98), 45 (95), 28 (100)

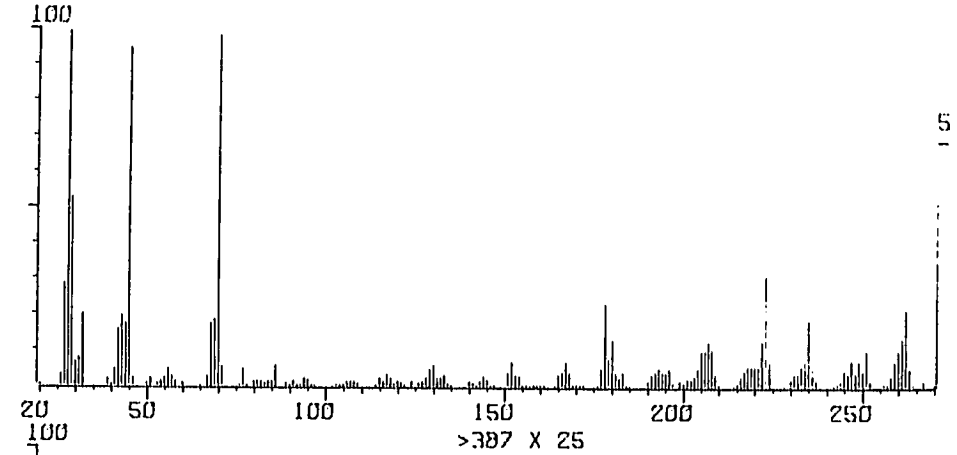
Exact Mass:		
	Calculated for $C_{25}H_{31}N_3O_6$	469.2213
	Found	469.2212

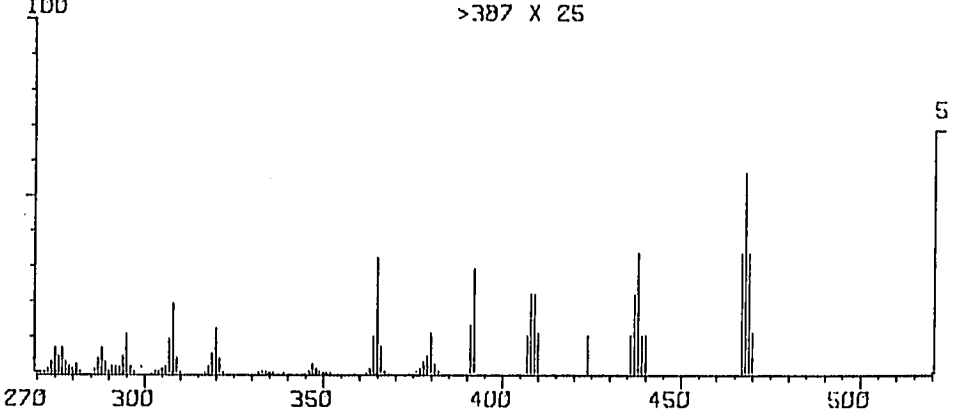

NHCO2Et
H
N
Me
O
N
MOM
CH2OAc

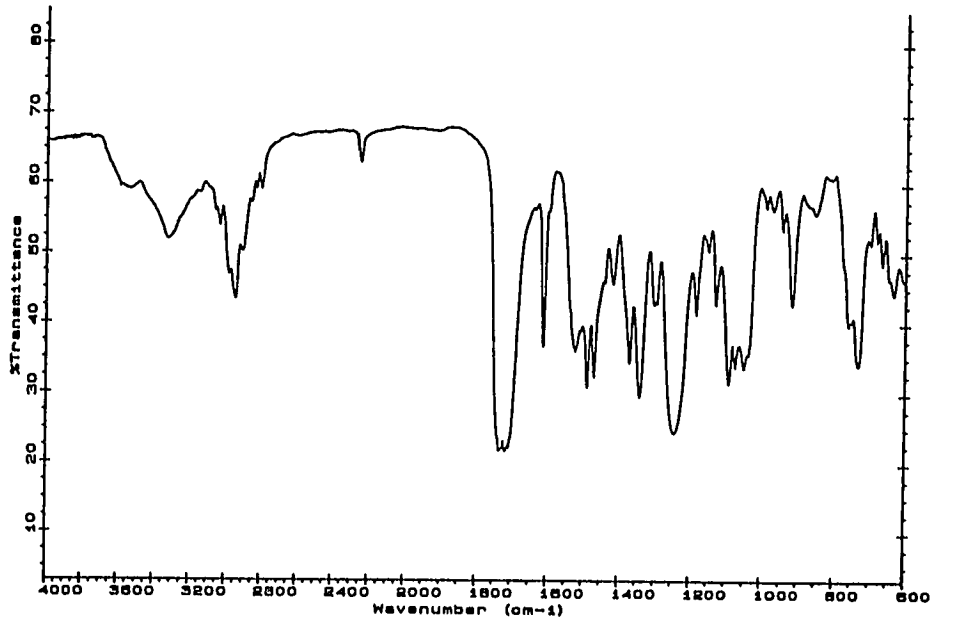
354

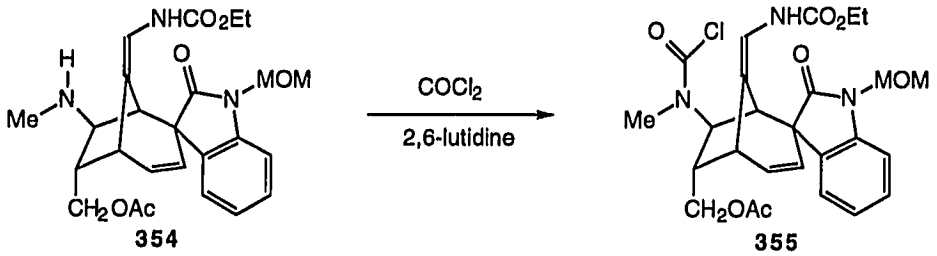

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

Compound **354** continued:







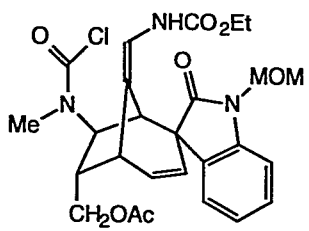


Ene-carbamate carbamoyl chloride (**355**)

To a stirred solution of 0.75 g (1.60 mmol) of amine **354** and 0.29 mL (2.49 mmol) of 2,6-lutidine in 15 mL of dichloromethane at 0 °C was added 0.6 mL (0.46 g/mL) of phosgene-dichloromethane solution. After stirring for 10 min at 0 °C, the reaction mixture was poured into a 3 M hydrochloric acid solution, and the biphasic solution was partitioned thoroughly with ethyl acetate. The combined extracts were washed with a saturated sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The crude product was purified through flash silica gel chromatography eluting with 0.5-1.5% methanol-dichloromethane to give 0.83 g (98%) of **355** as white crystals.

mp ($MeOH/Et_2O$)	175-176.5 °C
IR (film):	3349, 3031, 2984, 2938, 2825, 1729, 1609, 1523, 1490, 1470, 1370, 1344, 1297, 1238, 1091, 1072, 1045, 912, 759, 693, 666
^1H NMR ($CDCl_3$):	1.26 (3H, t, J = 7.1 Hz), 2.10 (3H, s), 2.52 (1H, sex, J = 6.5 Hz), 2.79 (1H, s), 2.84 (3H, s), 3.23 (1H, bt), 3.39 (3H, s), 4.15 (2H, q, J = 7.1 Hz), 4.31 (1H, dd, J_1 = 11.0 Hz, J_2 = 19.4 Hz), 4.45 (1H, dd, J_1 = 7.0 Hz, J_2 = 11.0 Hz), 5.08-5.23 (2H, overlapping), 5.24 (1H, d, J = 6.5 Hz), 5.29 (1H, dd, J_1 = 1.6 Hz, J_2 = 9.2 Hz), 6.32 (1H, d, J = 9.3 Hz), 6.39 (1H, dd, J_1 = 9.5 Hz, J_2 = 19.4 Hz), 6.62 (1H, dd, J = 8.3 Hz), 7.07 (1H, d, J = 7.5 Hz), 7.18 (1H, t, J = 7.8 Hz), 7.36 (1H, t, J = 7.7 Hz), 7.52 (1H, d, J = 7.4 Hz)

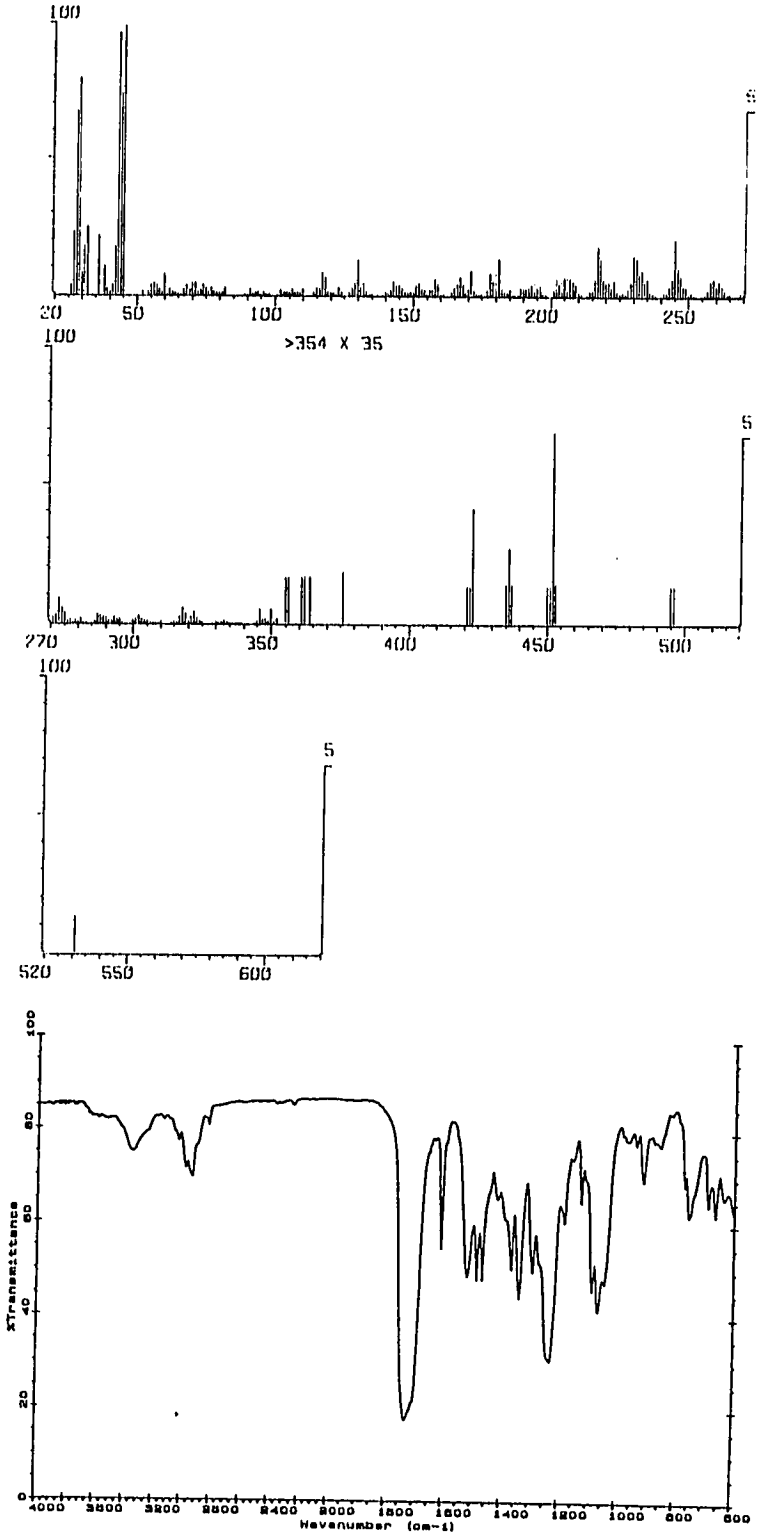
^{13}C NMR ($CDCl_3$):	14.4, 20.9, 32.5, 42.1, 48.7, 49.7, 56.5, 57.3, 60.8, 61.5, 63.0, 63.7, 71.7, 109.6, 114.9, 123.8, 124.2, 126.1, 126.7, 128.9, 129.4, 136.0, 141.2, 149.7, 154.6, 170.8	
MS:	531 (<1, M^+), 495 (<1), 452 (2), 436 (1), 423 (2), 366 (<1), 245 (20), 217 (18), 181 (15), 130 (15), 45 (100), 43 (96), 29 (80)	
Exact Mass:	Calculated for $C_{26}H_{30}Cl_1N_3O_7$	531.1772
	Found	531.1777

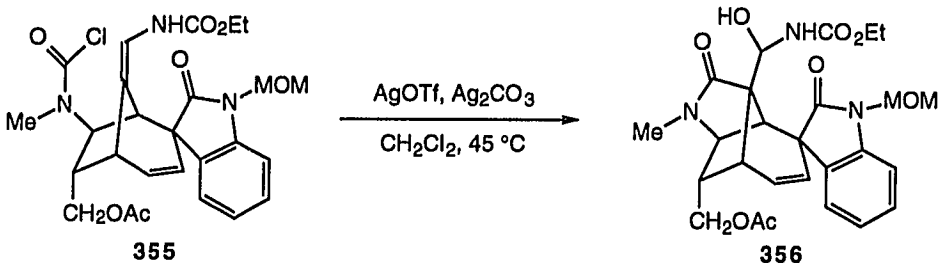

O
Cl
NHCO2Et
O
MOM
N
Me
N
CH2OAc

355

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

Compound **355** continued:





355 356

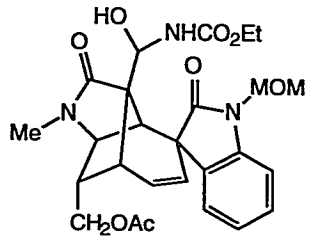
Lactam aminal (**356**)

A stirred solution of 100 mg (0.188 mmol) of chloride **355** and 56.9 mg (0.297 mmol) of silver carbonate in 10 mL of dichloromethane was bubbled with argon for 10 min and was then heated at 45 °C. To above solution was added dropwise 48.3 mg (0.188 mmol) of silver triflate in 0.4 mL of benzene. The resulting mixture was then allowed to cool to room temperature and stirred for additional 30 min before it was filtered through celite and washed thoroughly with dichloromethane. The filtrate and washings were combined and evaporated *in vacuo.* The crude product was separated on a preparative silica gel TLC (3% methanol-ether) to give 49.8 mg (52%) of **356** as a colorless oil in addition to 15.9 mg (18%) of amine **354**.

IR (film): 3502, 3382, 2977, 2931, 1702, 1609, 1503, 1377, 1344, 1304, 1231, 1125, 1072, 1032, 919, 859, 753

^{1}H NMR ($CDCl_3$): 1.26 (3H, t, J = 7.1 Hz), 2.14 (3H, s), 2.29 (1H, dd, J_1 = 7.1 Hz, J_2 = 14.5 Hz), 2.46 (1H, s), 2.76 (3H, s), 2.82 (1H, t, J = 7.8 Hz), 3.32 (3H, s), 3.71 (1H, s), 4.16 (2H, q, J = 7.1 Hz), 4.15 (1H, m), 4.49 (2H, d, J = 8.4 Hz), 5.13 (2H, d, J = 1.1 Hz), 5.62 (1H, dd, J_1 = 1.2 Hz, J_2 = 9.2 Hz), 6.23 (1H, dd, J_1 = 7.3 Hz, J_2= 9.2 Hz), 6.33 (1H, dd, J_1 = 5.3 Hz, J_2 = 10.3 Hz), 7.05 (1H, dd, J_1 = 1.1 Hz, J_2 = 7.9 Hz), 7.09 (1H, t, J = 7.9 Hz), 7.13 (1H, m), 7.38 (1H, t, J = 7.9 Hz), 7.43 (1H, d, 7.9 Hz)

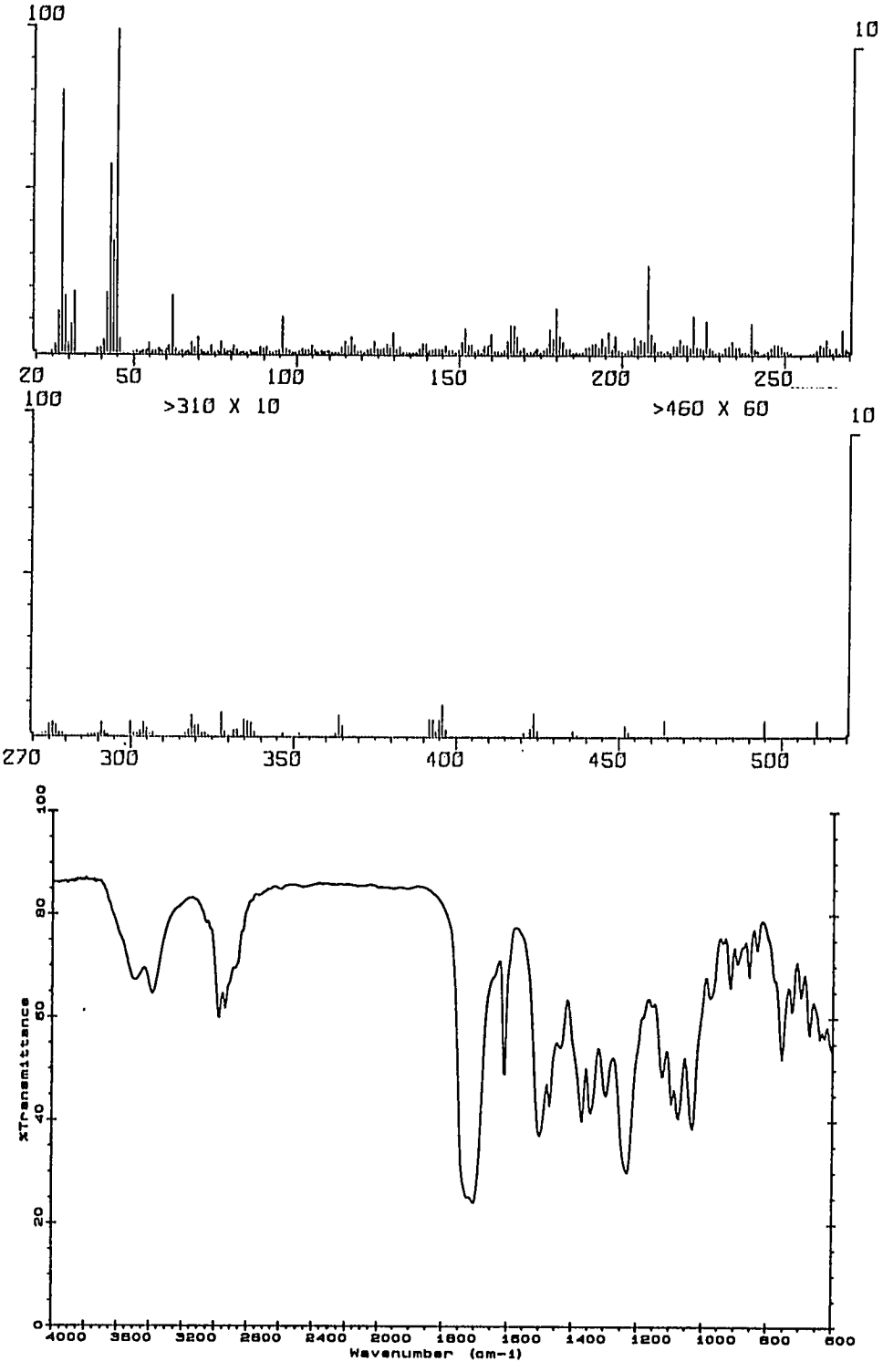
^{13}C NMR ($CDCl_3$):	14.5, 20.7, 27.2, 36.8, 50.1, 52.1, 54.5, 56.4, 60.7, 62.8, 63.5, 63.9, 71.6, 74.2, 110.6, 123.4, 124.8, 127.0, 127.9, 129.4, 131.6, 141.9, 170.2, 170.5, 177.4, 177.9
MS:	511 (<1, M-2), 495 (<1), 464 (<1), 424 (<1), 396 (1), 364 (<1), 328 (<1), 300 (4), 268 (7), 240 (10), 222 (10), 208 (26), 180 (12), 96 (11), 67 (16), 45 (100), 43 (58), 28 (80)
Exact Mass:	Calculated for $C_{23}H_{24}N_2O_6$(M-NH_2CO_2Et) 424.1634 Found 424.1623


HO
NHCO2Et
O
O
MOM
N
Me
N
CH2OAc

356

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

Compound **356** continued:



356 358

Vinyl alcohol (**358**)

A solution of 38.3 mg (0.0747 mmol) of **356** and 1.0 mL of 3 M hydrochloric acid solution in 3 mL of tetrahydrofuran was stirred at room temperature over night. The resulting solution was then adjusted to pH 6 by a slow addition of 3 M sodium hydroxide aqueous solution. The resulting biphasic solution was extracted with dichloromethane thoroughly. The extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to give 34.9 mg of crude aldehyde **357**.

The above residue was dissolved in 4 mL of anhydrous tetrahydrofuran, cooled to -40 °C under argon, and 360 uL (0.18 mmol) of 0.5 M Tebbe reagent was introduced dropwise. The resulting reddish mixture was allowed to warm to 0 °C slowly over 30 min and stirred at 0 °C for additional 2 h. The reaction mixture was then quenched with a saturated aqueous ammonium chloride solution and the resulting biphasic mixture was extracted thoroughly with dichloromethane. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude product was purified on a preparative silica gel TLC to give 18.5 mg (65% from **356**) of **358** as colorless crystals.

mp (CH_2Cl_2/Et_2O) 222-223 °C

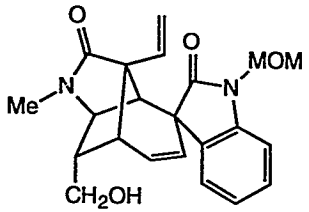
IR (film): 3416, 2998, 2938, 2825, 1729, 1689, 1616, 1470, 1344, 1304, 1244, 1125, 1091.4, 919, 733

^{1}H NMR ($CDCl_3$): 1.77 (1H, t, J = 4.1 Hz), 2.18 (1H, ddd, J_1 = 1.2 Hz, J_2 = 7.4 Hz, J_3 = 15.3 Hz), 2.41 (1H, t, J = 1.2 Hz), 2.77 (3H, s), 2.96 (1H, td, J_1 = 1.4 Hz, J_2 = 7.2 Hz), 3.31 (3H, s), 3.82 (1H, d, J = 1.1 Hz), 4.06 (2H, dtd, J_1 = 4.1 Hz, J_2 = 7.8 Hz, J3 = 19.2 Hz), 5.09 (2H, s), 5.29 (1H, dd, J_1 = 0.98 Hz, J_2 = 17.7 Hz), 5.49, (1H, dd, J_1 = 1.3 Hz, J_2 = 9.2 Hz), 5.51 (1H, dd, J_1=0.9 Hz, J_2 = 11.1 Hz), 6.32 (1H, dd, J_1 = 7.0 Hz, J_2 = 9.2 Hz), 6.34 (1H, dd, J_1 = 11.1 Hz, J_2 = 17.7 Hz), 7.07 (1H, d, J = 7.4 Hz), 7.12 (1H, dt, J_1 = 1.0 Hz, J_2 = 7.4 Hz), 7.29 (1H, d, J =7.8 Hz), 7.35 (1H, t, J = 7.8 Hz)

^{13}C NMR ($CDCl_3$): 27.7, 36.7, 53.1, 54.2, 55.3, 56.3, 61.9, 62.2, 63.6, 71.5, 110.1, 117.7, 123.2, 125.4, 126.4, 128.4, 129.1, 132.8, 134.8, 142.2, 176.9, 178.1

MS: 381 (3, M+1), 380 (14, M^+), 349 (2), 321 (1), 260 (3), 244 (6), 226 (13), 196 (13), 168 (6), 158 (8), 122 (40), 45 (40), 28 (100)

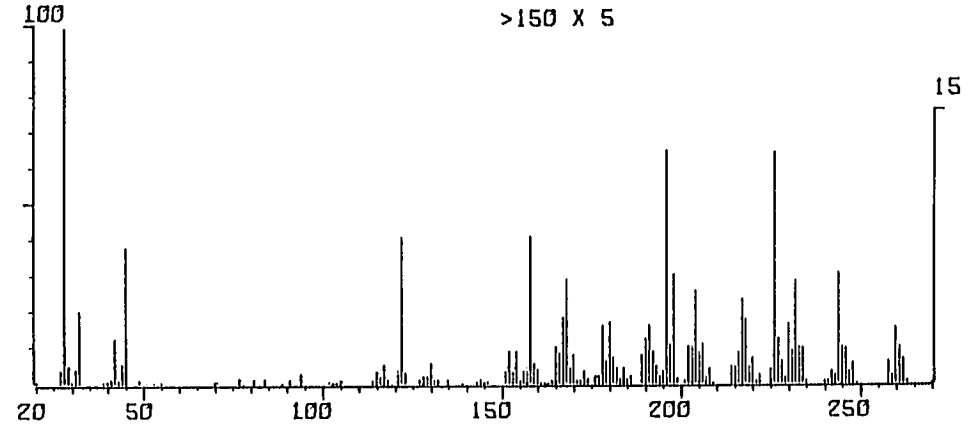
Exact Mass: Calculated for $C_{22}H_{24}N_2O_4$ 380.1736
Found 380.1737

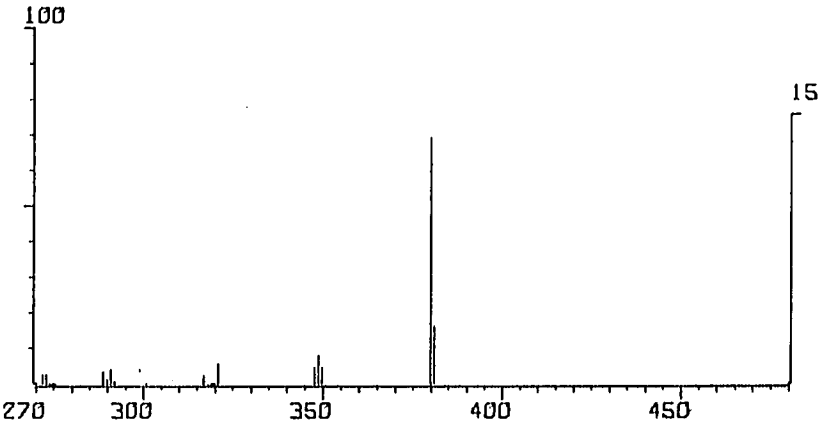

O
O
MOM
N
Me
N
CH2OH

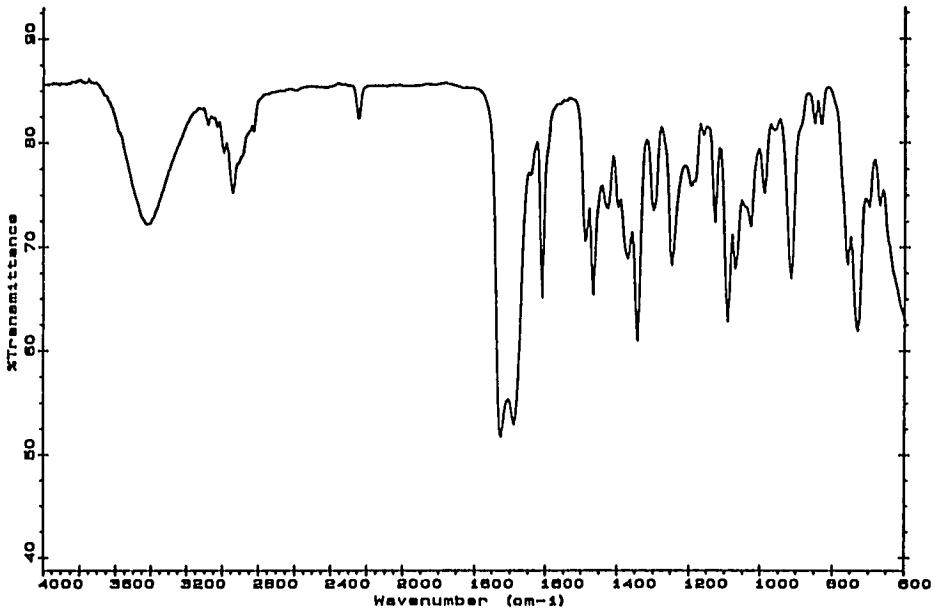
358

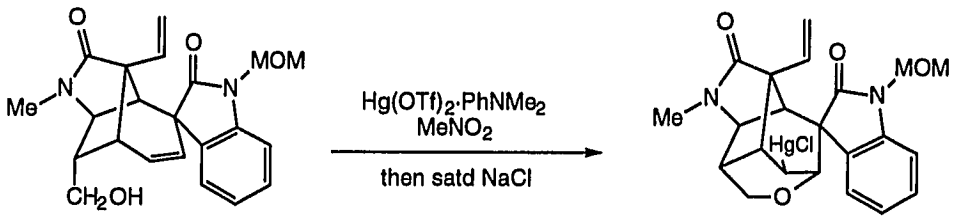
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

Compound **358** continued:









358 359

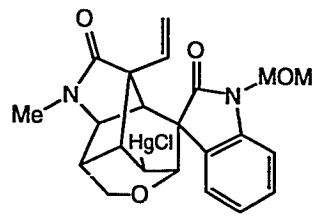
Tetrahydropyranyl mercury chloride (**359**)

To a stirred solution of 18.0 mg (0.0474 mmol) of alcohol **358** in 2 mL of freshly distilled nitromethane under argon at room temperature was added 0.464 mL (0.0711 mmol) of a 0.153 M mercuric triflate dimethylaniline complex solution in nitromethane. The reaction mixture was stirred at room temperature for 30 min before a saturated aqueous sodium chloride was added. The resulting biphasic mixture was stirred at room temperature for 15 min before it was poured into brine. The aqueous layer was extracted thoroughly with dichloromethane. The extracts were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product was purified on a preparative silica gel TLC to give 29.1 mg (82%) of **359** as white crystals.

mp (Et_2O/MeOH)	273-276 °C (decomposition)
IR (film):	3489, 3057, 2918, 1696, 1609, 1470, 1350, 1251, 1091, 919, 759, 686
^1H NMR ($CDCl_3$):	2.08 (1H, s), 2.39 (1H, d, J = 8.2 Hz), 2.69 (1H, dd, J_1 = 4.7 Hz, J_2 = 8.2 Hz), 2.80 (3H, s), 3.15 (1H, d, J = 3.3 Hz), 3.32 (3H, s), 3.49 (1H, d, J = 4.7 Hz), 3.96 (1H, s), 4.04 (1H, dd, J_1 = 1.8 Hz, J_2 = 11.8 Hz), 4.28 (1H, dd, J_1 = 1.8 Hz, J_2 = 11.8 Hz), 5.06 (1H, d, J = 10.6 Hz), 5.25 (1H, d, J = 10.6 Hz), 5.45 (1H, d, J = 18.0 Hz), 5.87 (1H, d, J = 11.0 Hz), 6.12 (1H, dd, J_1 = 11.0 Hz, J_2 = 18.0 Hz), 7.09 (1H, d, J = 7.8 Hz), 7.17 (1H, t, J = 7.8 Hz), 7.36 (1H, t, J = 7.8 Hz), 7.45 (1H, d, J = 7.8 Hz)

^{13}C NMR ($CDCl_3$):	28.2, 37.0, 39.5, 45.9, 52.5, 53.8, 56.3, 59.7, 60.1, 65.7, 71.5, 72.3, 110.0, 122.3, 123.2, 128.3, 129.0, 136.1, 140.9, 175.7, 177.7
MS:	621 (<1, M+5), 620 (<1, M+4), 619 (1, M+3), 618 (1, M+2), 617 (3, M+1), 616 (2, M^+), 615 (2, M-1), 614 (1, M-2), 613 (<1, M-3), 587 (7), 586 (6), 585 (18), 584 (12), 583 (20), 582 (9), 581 (5), 380 (67), 348 (9), 319 (13), 265 (20), 226 (18), 202 (21), 148 (32), 122 (100), 94 (20), 45 (100)

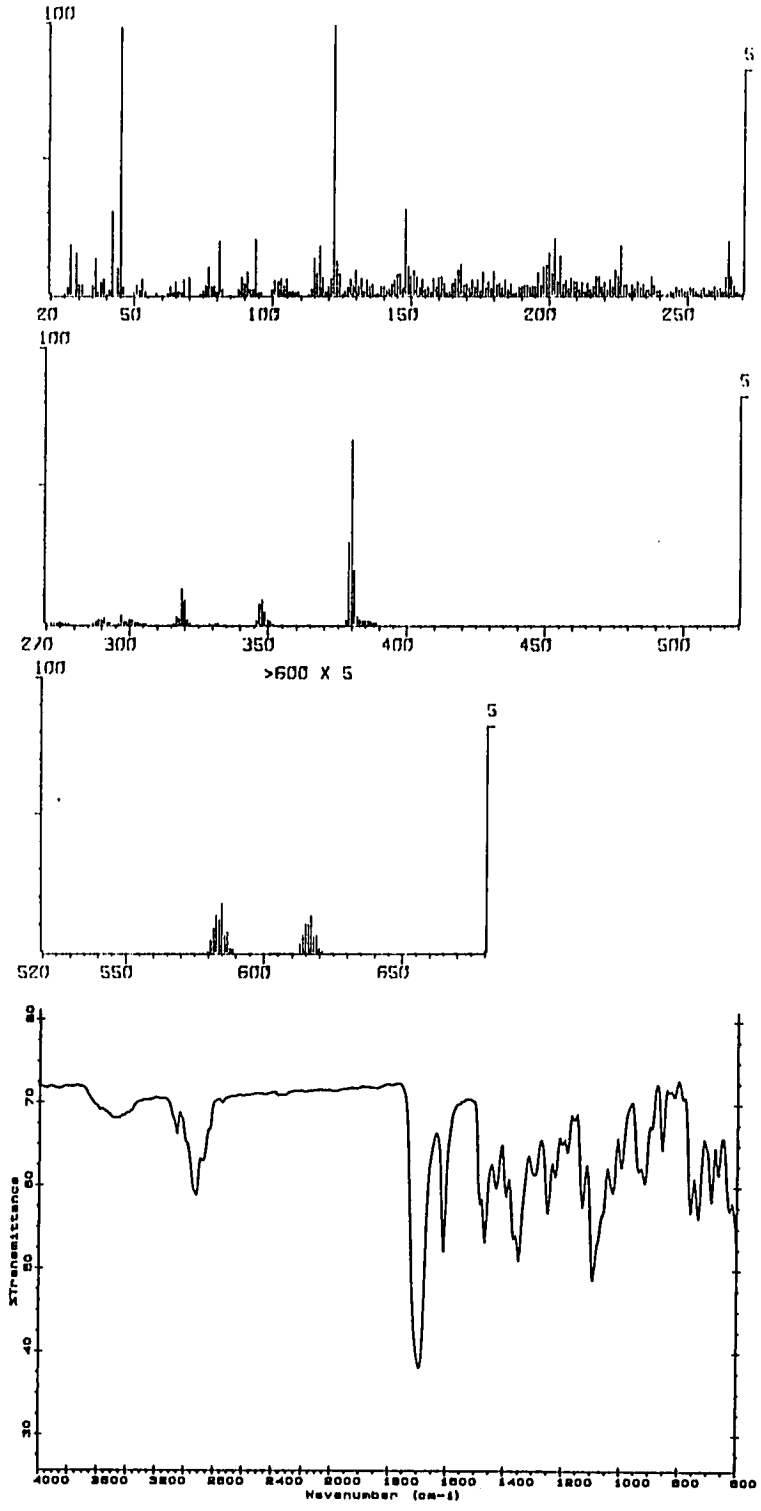
Exact Mass:	Calculated for $C_{22}H_{23}Cl_1Hg_1N_2O_4$	616.1052
	Found	616.1055

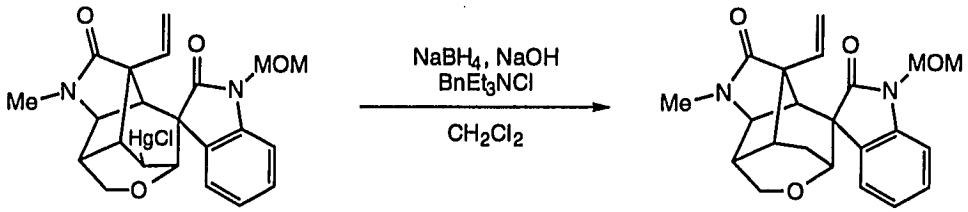

O
O
N
MOM
Me
HgCl
O

359

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

Compound **359** continued:





359 360

N-MOM-21-oxogelsemine (**360**)

To a two phase system of 14.4 mg (0.0234 mmol) of organomercurial **359** in 58.5 uL of dichloromethane and 117 uL of a 10% aqueous sodium hydroxide was added at room temperature 18.7 mg (0.0821 mmol) of benzyltriethylammonium chloride. The mixture was stirred for 10 min before 0.71 mg (0.0188 mmol) of sodium borohydride in 37 uL of 10 % aqueous sodium hydroxide was introduced. The demercurization set in immediately and the reaction was complete within 10 min. The reaction mixture is quenched with a saturated aqueous ammonium chloride solution and the aqueous layer was extracted thoroughly with dichloromethane. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by means of preparative TLC with 3% methanol-dichloromethane to afford 7.3 mg (82%) of **360** as colorless crystals.

mp (Et_2O/MeOH) 179-180 °C

IR (film): 3436, 2924, 2851, 1716, 1609, 1470, 1344, 1251, 1231, 1091, 912, 759

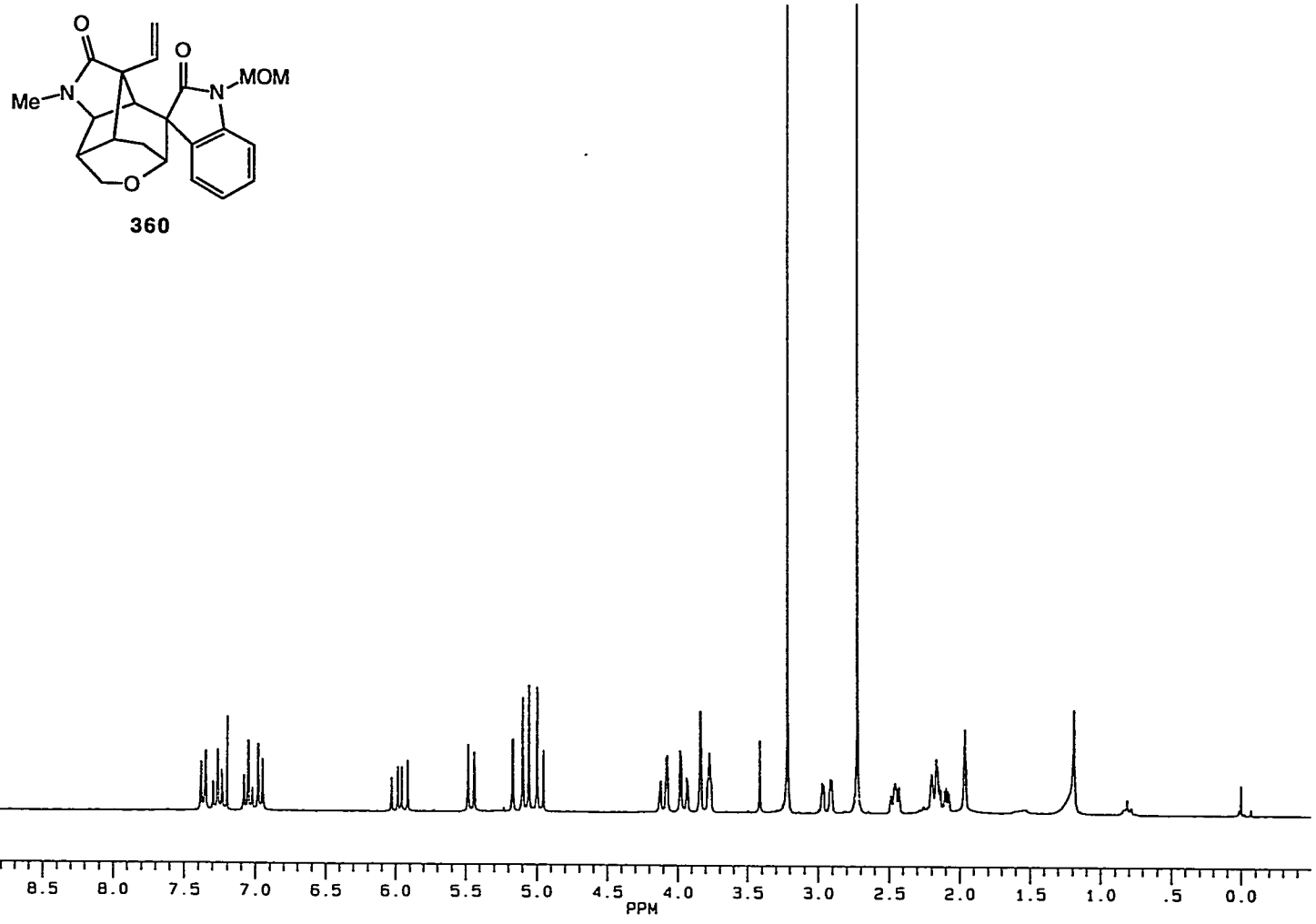
^{1}H NMR ($CDCl_3$): 1.96 (1H, d, J = 0.88 Hz), 2.12 (1H, ddd, J_1 = 2.7 Hz, J_2 = 5.6 Hz, J3 = 14.6 Hz), 2.18 (1H, d, J = 7.7 Hz), 2.45 (1H, t, J = 6.3 Hz), 2.72 (3H, s), 2.94 (1H, dd, J_1 = 2.7 Hz, J_2 = 14.6 Hz), 3.21 (3H, s), 3.77 (1H, s), 3.83 (1H, d, J = 1.5 Hz), 3.95 (1H, dd, J_1 = 2.0 Hz, J_2 = 11.5 Hz), 4.10 (1H, dd, J_1 = 2.0 Hz, J_2 = 11.5 Hz), 4.97 (1H, d, J = 10.8 Hz), 5.07 (1H, d, J = 10.8 Hz), 5.13 (1H, dd, J_1 = 0.97 Hz, J_2 = 18.0 Hz), 5.46

(1H, d, J = 11.0 Hz), 5.97 (1H, dd, J_1 = 11.0 Hz, J_2 = 18.0 Hz), 6.96 (1H, d, J = 7.6 Hz), 7.05 (1H, dt, J_1 = 1.1 Hz, J_2 = 7.6 Hz), 7.26 (1H, dt, J_1 = 1.1 Hz, J_2 = 7.6 Hz), 7.36 (1H, d, J = 7.6 Hz)

^{13}C NMR ($CDCl_3$): 23.2, 27.9, 31.7, 42.7, 53.4, 54.1, 56.1, 60.6, 60.7, 66.2, 69.3, 71.2, 109.4, 117.3, 122.6, 127.7, 128.7, 129.3, 133.2, 141.4, 176.2, 176.8

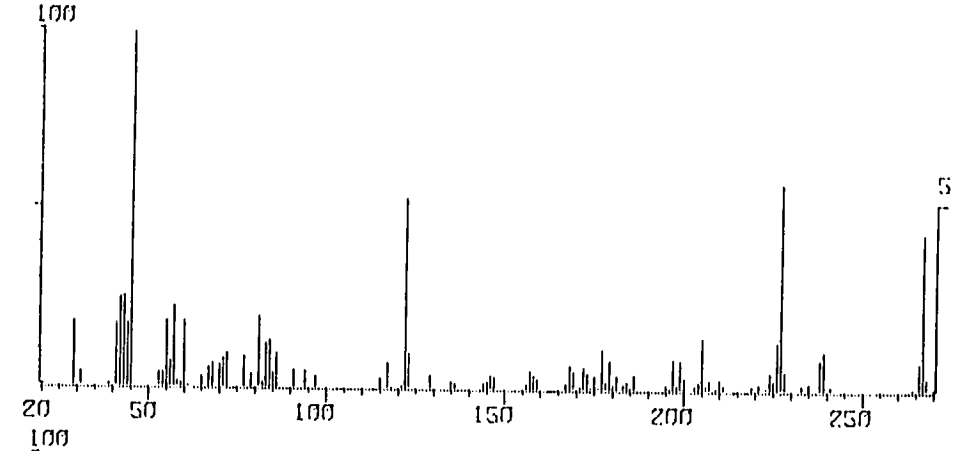
MS: 382 (82, M+2), 381 (79, M+1), 380 (22, M^+), 267 (43), 227 (58), 205 (15), 122 (52), 81 (20), 45 (100)

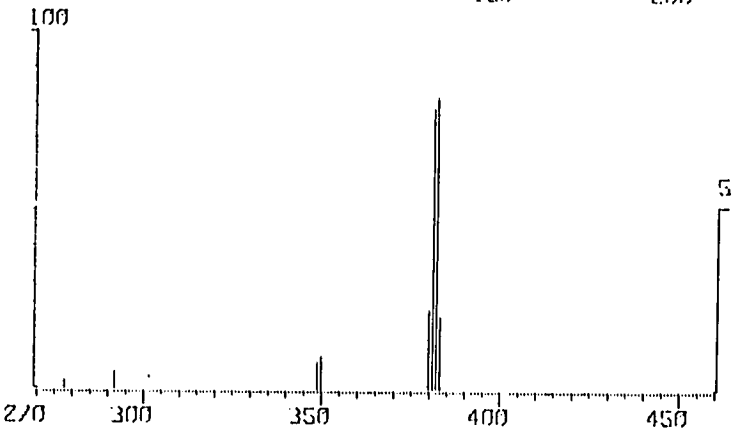
Exact Mass:		
	Calculated for $C_{22}H_{24}N_2O_4$	380.1736
	Found	380.1741

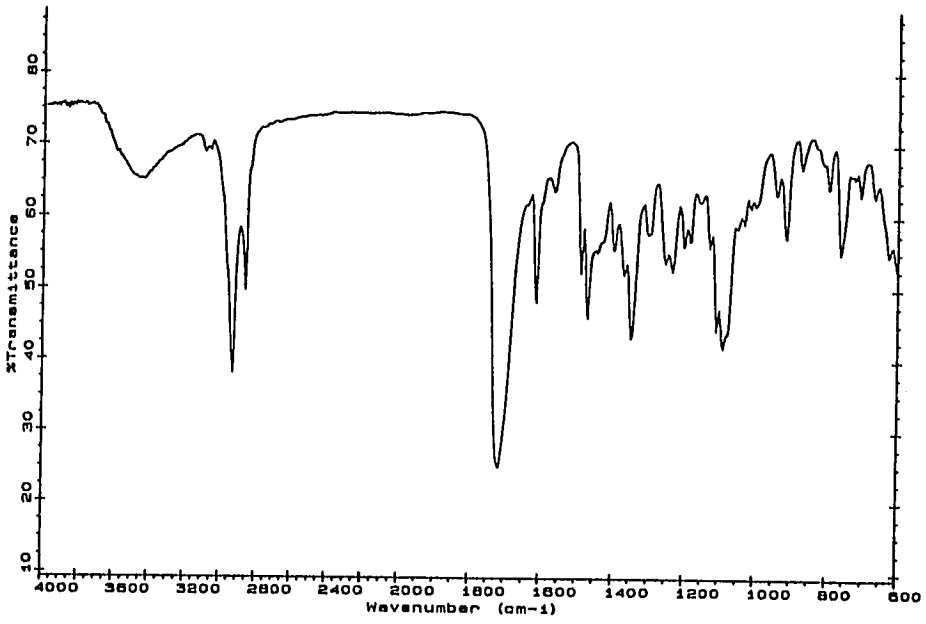


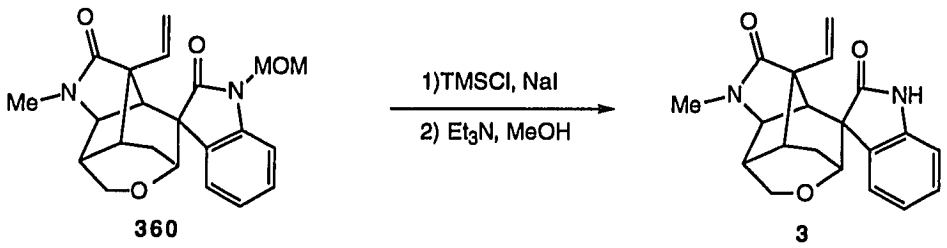
360

Compound **360** continued:









360 3

(±)-21-Oxogelsemine (3)

To an ice-cold, solution of 6.4 mg (0.0168 mmol) of **360** and 6.4 mg (0.0427 mmol) of anhydrous sodium iodide in 1.0 mL of acetonitrile was added 4.6 uL (0.0427 mmol) of chlorotrimethylsilane. The reaction mixture was then allowed to warm to room temperature and stirred for 1 h. The mixture was then poured into a saturated sodium chloride solution and the aqueous layer was thoroughly extracted with dichloromethane. The extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness *in vacuo*.

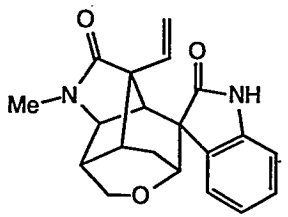
The residue was dissolved in 1.0 mL of methanol and 25 uL of triethylamine was introduced. The reaction mixture was heated at 55 °C for 40 min before the solvent was evaporated under reduced pressure. The crude product was separated on a silica gel TLC (3% methanol-ether) to give 5.0 mg (88.4 %) of 21-oxogelsemine (**3**) as colorless crystals.

mp ($MeOH/CH_2Cl_2$) 149-151 °C

IR (film): 3223, 3097, 2964, 1918, 1858, 1702, 1616, 1470, 1397, 1324, 1257, 1231, 1105, 1038, 793, 746

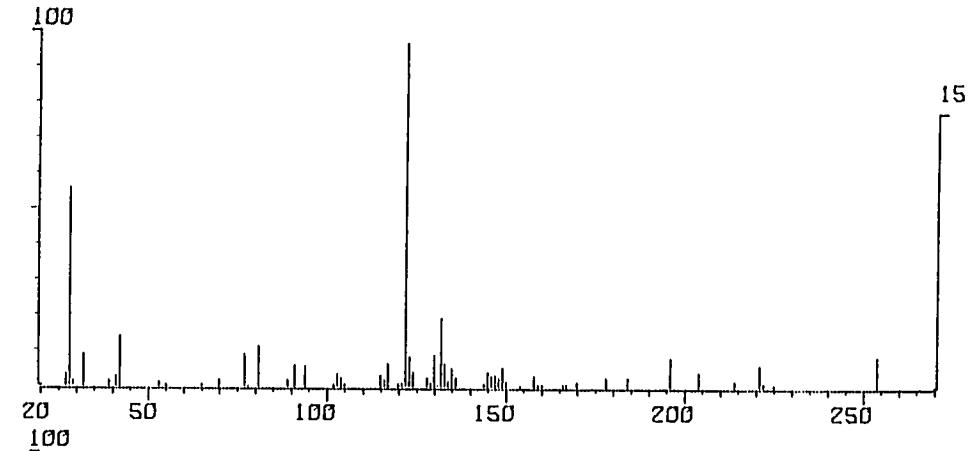
^1H NMR ($CDCl_3$): 2.00 (1H, s), 2.10 (1H, ddd, J_1 = 2.8 Hz, J_2 = 5.7 Hz, J_3 = 14.6 Hz), 2.16 (1H, d, J = 7.6 Hz), 2.43 (1H, t, J = 6.9 Hz), 2.72 (3H, s), 2.90 (1H, dd, J_1 = 2.8 Hz, J_2 = 14.6 Hz), 3.80 (1H, s), 3.81 (1H, s), 3.94 (1H, dd, J_1 = 2.0 Hz, J_2 = 11.5 Hz), 4.09 (1H, dd, J_1 = 2.0 Hz, J_2 = 11.5 Hz), 5.14 (1H, dd, J_1 = 0.94 Hz, J_2 = 17.7 Hz), 5.43 (1H, J_1 = 0.86

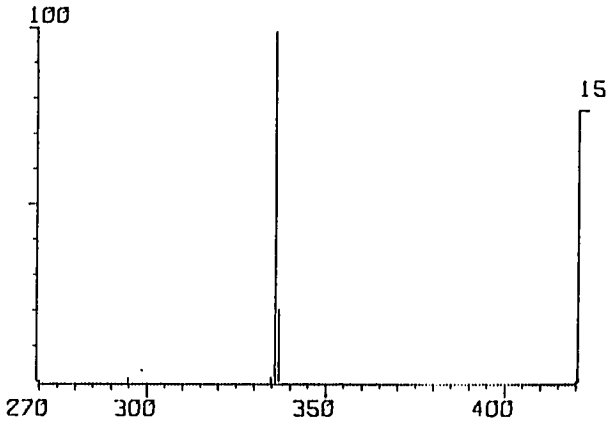
	Hz, J_2 = 11.0 Hz), 6.00 (1H, dd, J_1 = 11.0 Hz, J_2 = 17.7 Hz), 6.79 (1H, d, J = 7.5 Hz), 6.98 (1H, dt, J_1 = 0.88 Hz, J_2 = 7.5 Hz), 7.19 (1H, dt, J_1 = 0.92 Hz, J_2 = 7.5 Hz), 7.32 (1H, d, J = 7.5 Hz), 7.90 (1H, s)
^{13}C NMR ($CDCl_3$):	23.2, 27.9, 31.7, 42.7, 53.3, 53.8, 60.5, 60.7, 66.2, 69.0, 109.5, 117.4, 122.0, 127.9, 128.5, 130.4, 133.2, 140.3, 177.0, 177.5
MS:	337 (21, M+1), 336 (100, M^+), 254 (9), 221 (7), 196 (9), 132 (20), 122 (100), 81 (12), 42 (14)
Exact Mass:	Calculated for $C_{20}H_{19}N_2O_3$ 336.1474 Found 336.1474

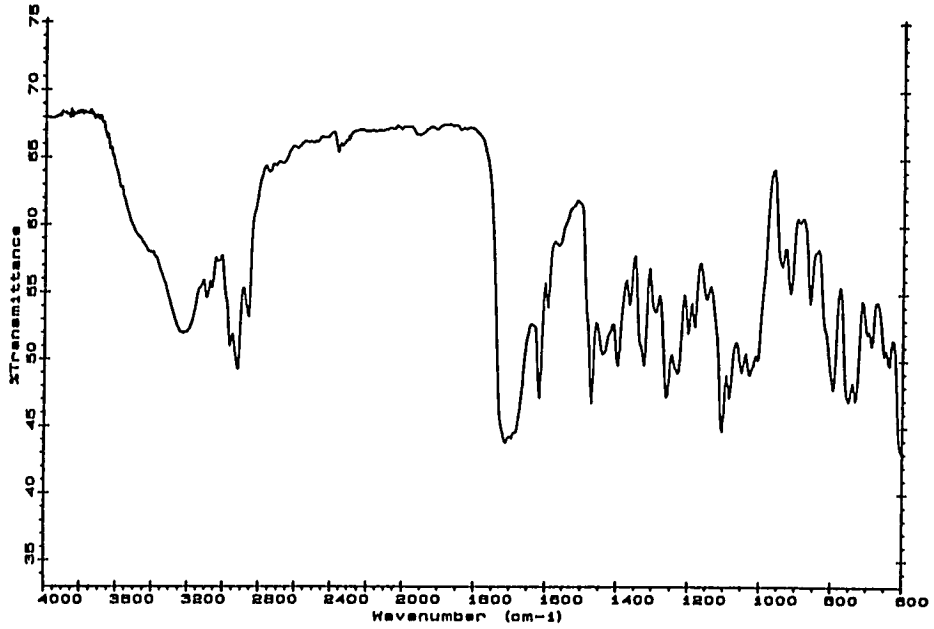


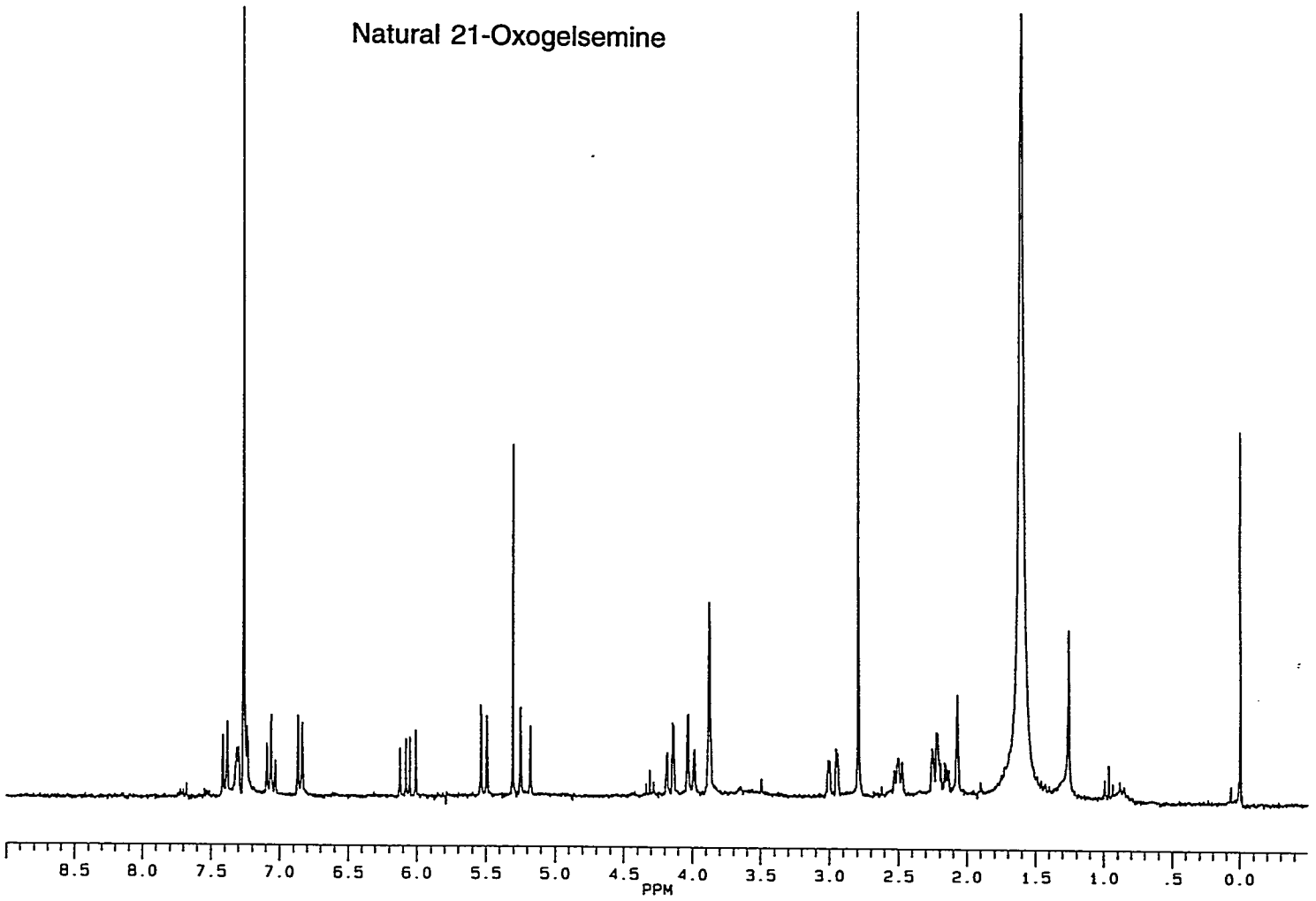
3

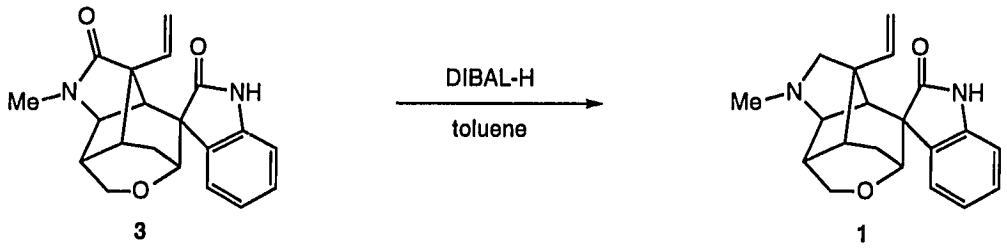
Compound **3** continued:








Natural 21-Oxogelsemine
8.5
8.0
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
PPM



3 1

(±)-Gelsemine (1)

To a stirred solution of 2.8 mg (0.0083 mmol) of 21-oxogelsemine (**3**) in 1.0 mL of toluene with 0.15 mL of dichloromethane at 0 °C was added 55.6 uL (0.083 mmol) of diisobutylaluminum hydride. The reaction mixture was stirred between 0 °C and room temperature for 1 h before 0.3 mL of methanol was added. The resulting mixture was partitioned between chloroform and a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted thoroughly with chloroform. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The crude product was purified on a silica gel TLC (8% methanol-dichloromethane) to afford 2.2 mg (82%) of gelsemine (**1**) as white crystals.

mp ($MeOH/CH_2Cl_2$) 234-235 °C

IR (film): 3203, 3078, 2918, 2859, 1712, 1617, 1471, 1323, 1233, 1182, 1100, 989, 907, 854, 759, 746, 683, 657, 643, 613

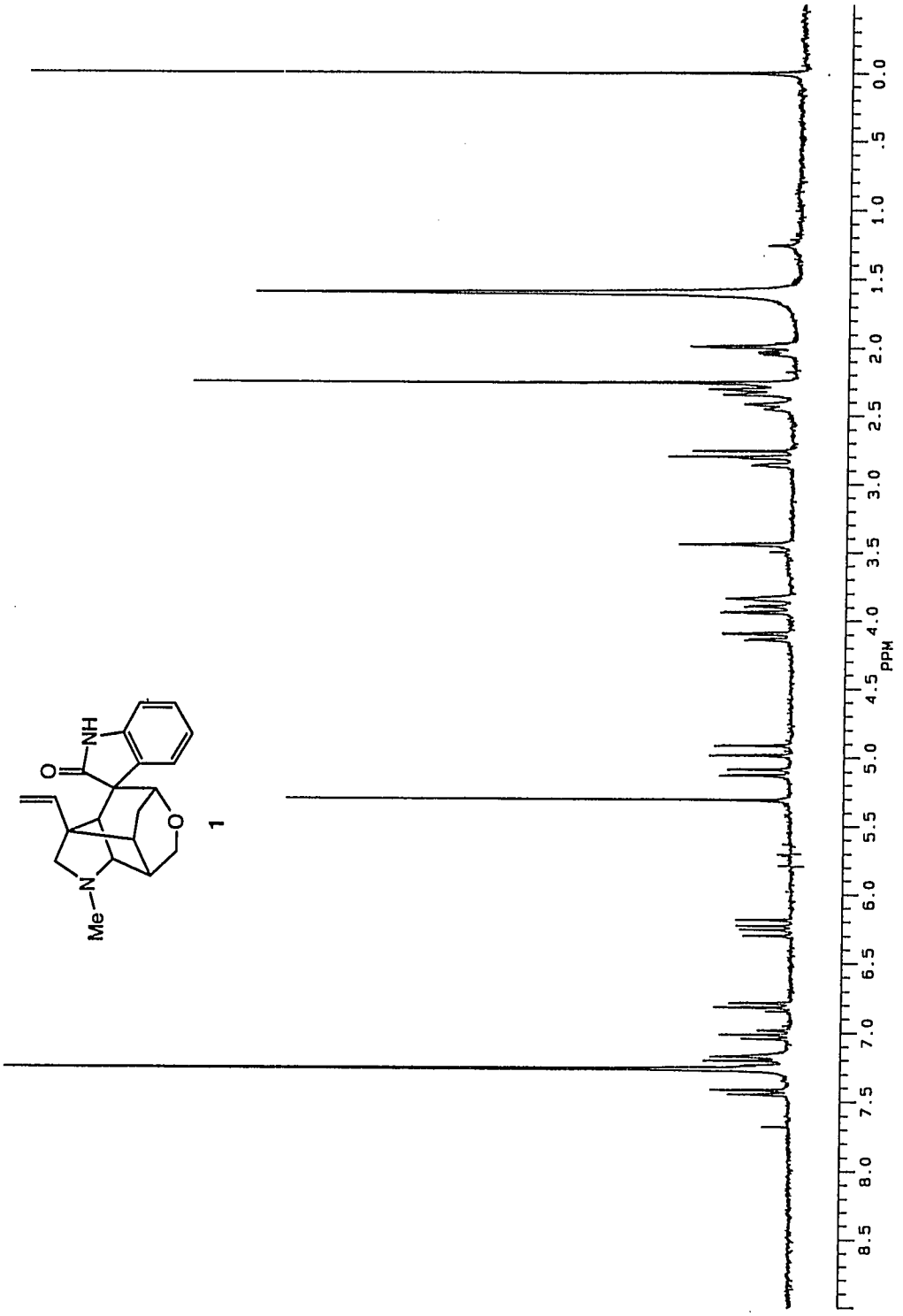
^1H NMR ($CDCl_3$): 1.99 (1H, d, J = 1.3 Hz), 2.00 (1H, ddd, J_1 = 2.8 Hz, J_2 = 5.7 Hz, J_3 = 14.2 Hz), 2.25 (3H, s), 2.30 (overlapping), 2.32 (1H, d, J = 10.3 Hz), 2.43 (1H, d, J = 8.3 Hz), 2.77 (1H, d, J = 10.3 Hz), 2.83 (1H, dd, J_1 = 2.5 Hz, J_2 = 14.2 Hz), 3.44 (1H, s), 3.83 (1H, s), 3.91 (1H, dd, J_1 = 2.0 Hz, J_2 = 11.1 Hz), 4.11 (1H, dd, J_1 = 2.0 Hz, J_2 = 11.1 Hz), 4.94 (1H, dd, J_1 = 1.2 Hz, J_2 = 17.7 Hz), 5.10 (1H, dd, J_1 = 1.2 Hz, J_2 = 11.1 Hz), 6.24 (1H, dd, J_1 = 11.1 Hz, J_2 = 17.7 Hz), 6.80 (1H, d, J = 7.7 Hz), 7.01 (1H, dt, J_1 = 1.0 Hz, J_2 =

7.7 Hz), 7.20 (1H, dt, J_1 = 1.0 Hz, J_2 = 7.7 Hz), 7.42 (1H, d, J = 7.7 Hz)

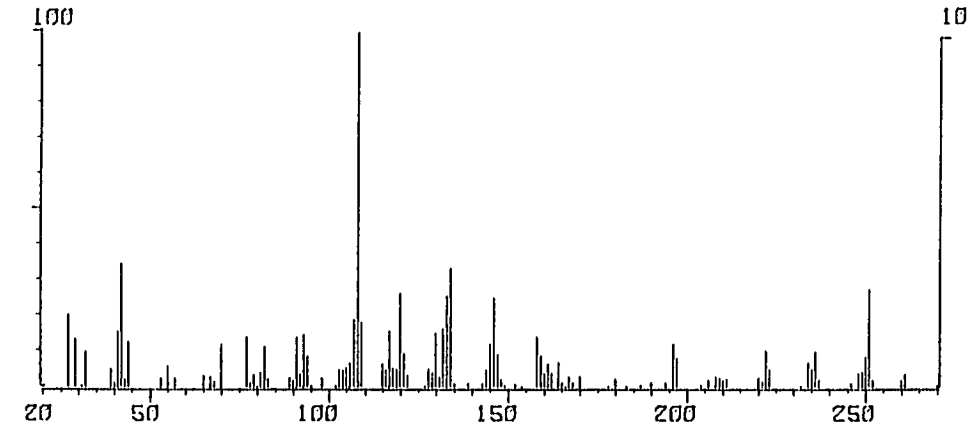
^{13}C NMR ($CDCl_3$): 22.79, 35.58, 38.43, 40.95, 50.30, 53.90, 53.93, 61.44, 65.63, 69.92, 72.14, 109.01, 112.88, 122.12, 128.14, 128.39, 131.65, 137.93, 139.98, 178.45

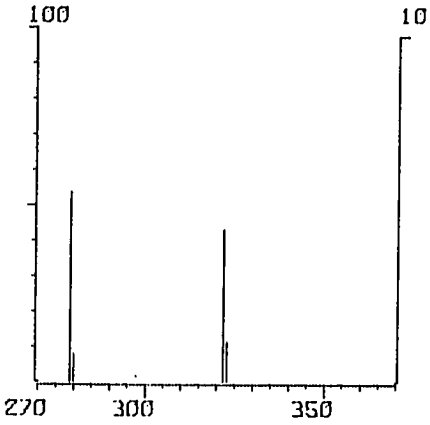
MS: 323 (12, M+1), 322 (43, M^+), 279 (54), 251 (27), 236 (10), 222 (10), 196 (12), 158 (20), 146 (25), 134 (33), 120 (26), 108 (100), 93 (14), 77 (14), 47 (34)

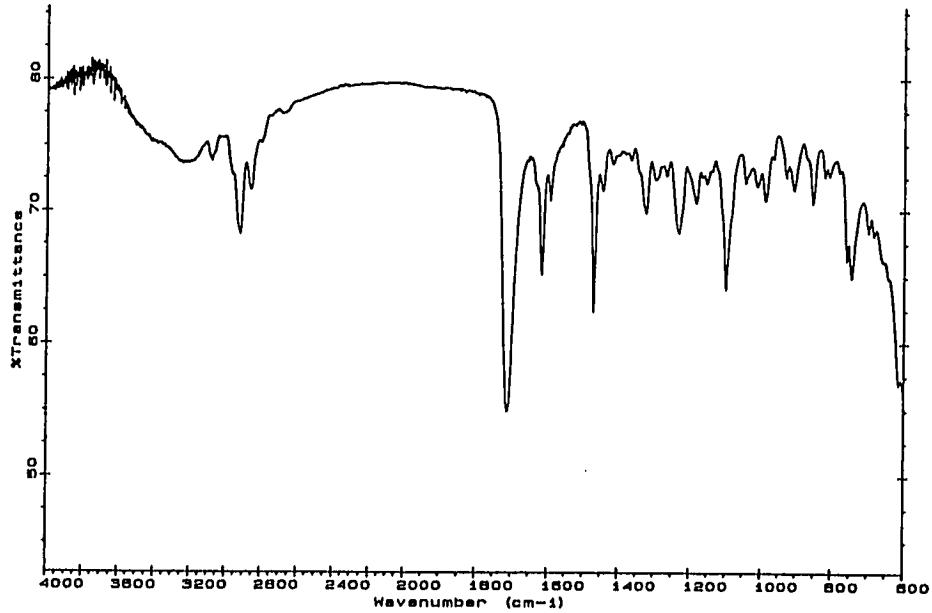
Exact Mass:		
	Calculated for $C_{20}H_{22}N_2O_2$	322.1681
	Found	322.1681

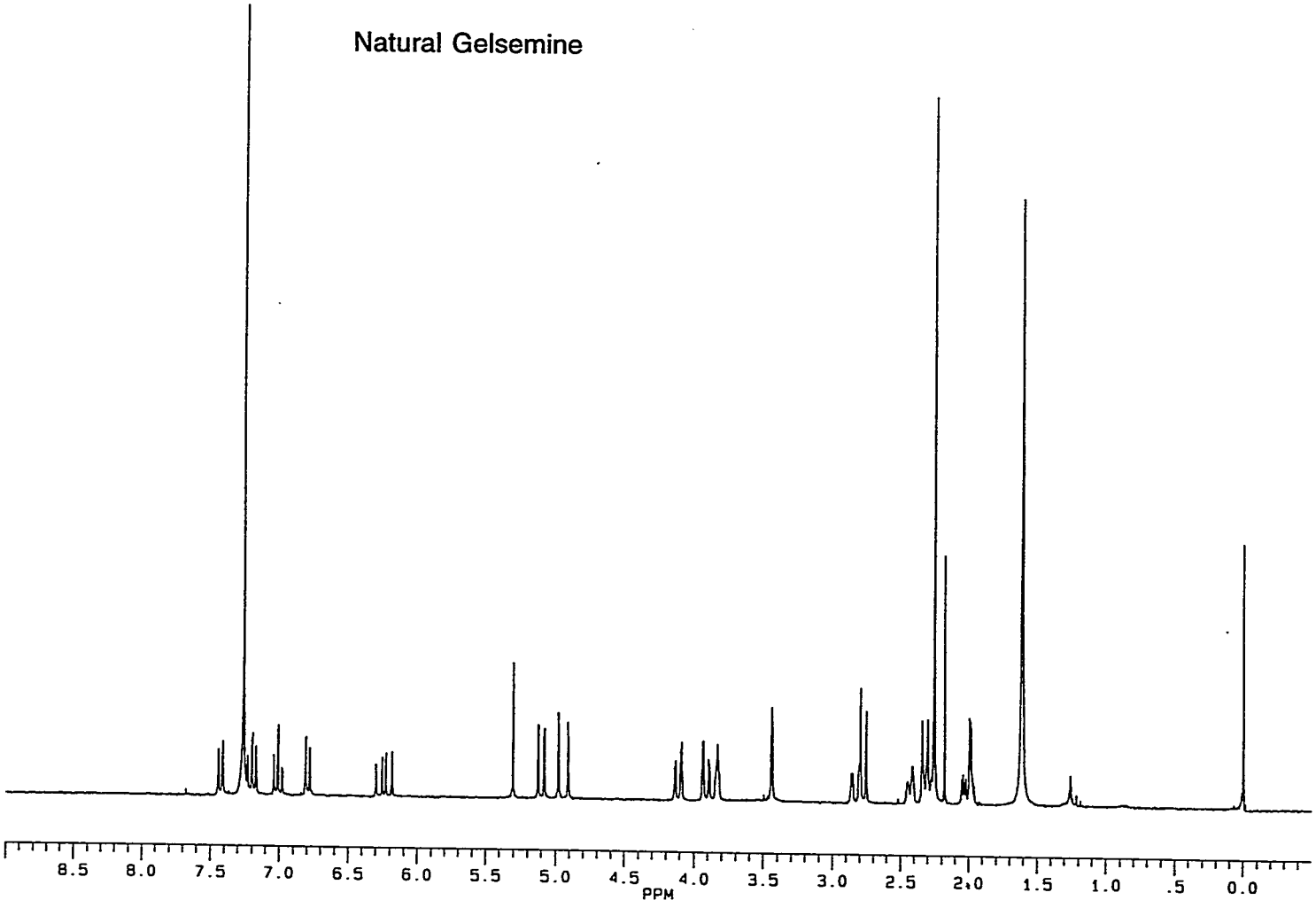

NH
O
O
N
Me
1
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

Compound 1 continued:








Natural Gelsemine
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

Appendix: X-ray Data for Compound **253**

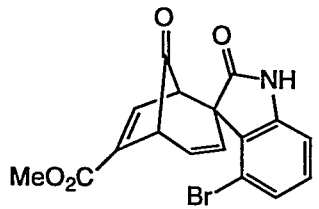
X-ray Experimental

A beige, irregular block (0.4 x 0.4 x 0.7 mm^3) of **253** cut from a larger crystal was chosen for data collection. The crystal was mounted on a glass fiber with epoxy cement. Data collection was carried out on an automated Rigaku AFC5S four-circle diffractometer using the TEXSAN data collection package (Rigaku MSC Automatic Data Collection Control software, v 5.0; Molecular Structure Corp., The Woodlands, TX, 1990). The unit cells was determined by the careful refinement of 22 random reflections ($8.35° \leq 2\theta \leq 15.34°$). The crystal was shown to be triclinic and the more common centrosymmetric setting, $P\bar{1}$, was chosen on the basis of intensity statistics. This choice was shown to be correct by successful refinement of the structure.

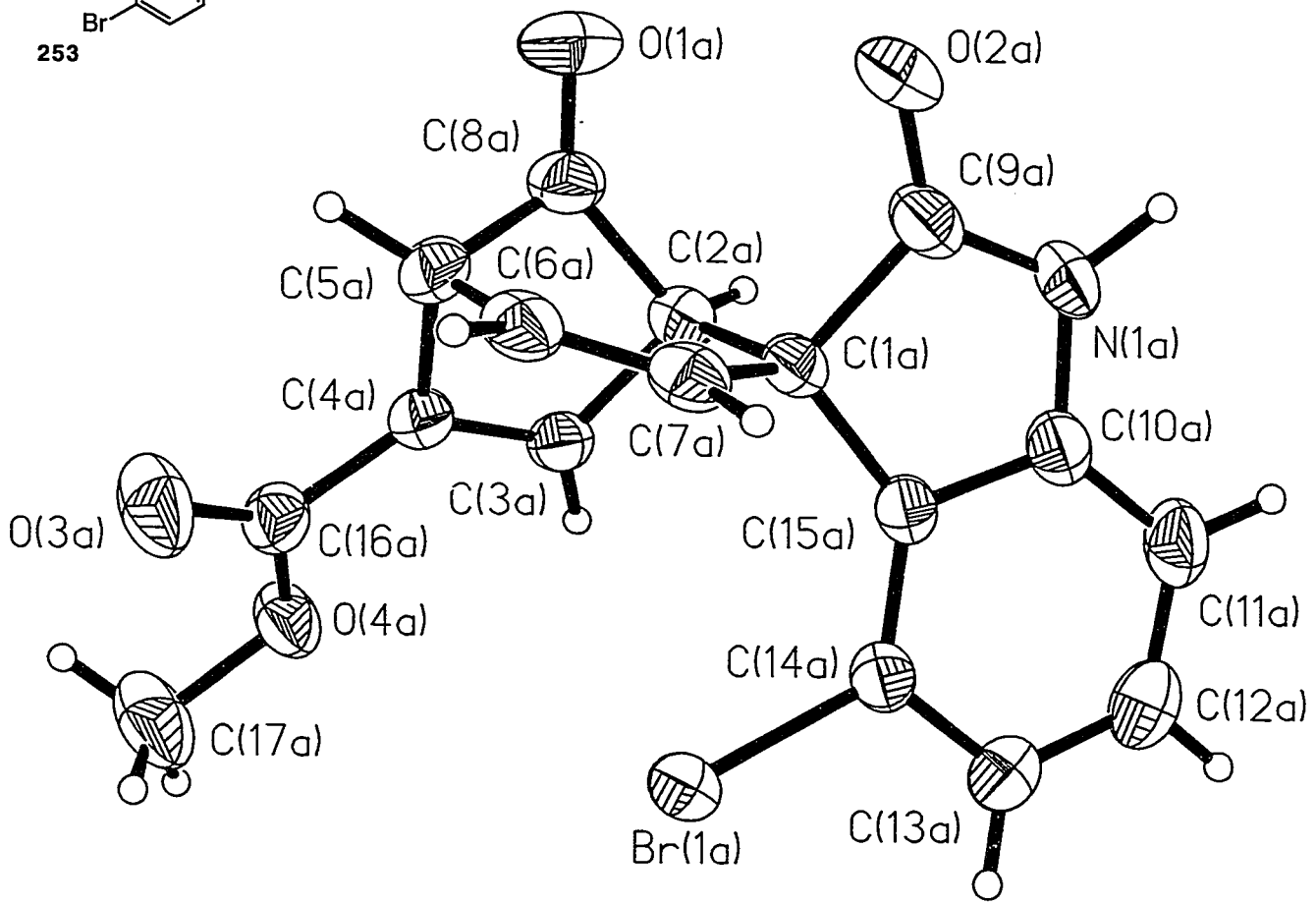
The structure was solved using the SHELXL-PC (v. 4.2, Siemens Crystallographic Research Systems, Madison, WI, 1990) package, which located all the non-hydrogen atoms. Structure refinement on F^2 was carried out with SHELXL-93 (G. M. Sheldrick, SHELXL-93, Univeristät Göttingen, Göttingen, Germany, 1993). All the non-hydrogen atoms are refined anisotropically, and the hydrogen atoms were included in calculated positions using a riding model. The refinement converged with $R_1(F) = 0.0285$ and ${}_wR_2 = 0.0666$ for 220 parameters and 2468 observed reflections ($I > 2\sigma(I)$). The data collection and refinement parameters are summarized in Table 3. Positional and displacement parameters are given in Table 4, and selected bond metricals are included in Table 5, 6 and 7.

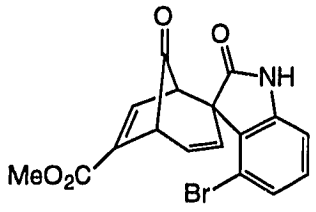
Table 3 *X-ray Experimental Details*

Empirical Formula	$C_{17}H_{12}BrNO_4$
Formula Weight	374.19
Temperature	293 K
Wavelength	0.71073 Å
Crystal System	triclinic
Space Group	$P\bar{1}$
Unit cell dimensions	a = 6.2720(10) Å
	b = 7.2140(10) Å
	c = 16.616(3) Å
	α = 84.49(3) °
	β = 87.96(3) °
	γ = 86.33(3) °
Volume	746.5(2)Å^3
Z value	2
Density (calculated)	1.665 Mg/m^3
Absorption coefficient	2.774 mm^{-1}
F_{000}	376
Crystal size	0.4x0.4x0.7 mm^3
θ range for data collection	2.46 to 27.49 deg
Index ranges	-7≤h≤4, -8≤k≤8, -19≤l≤20
Reflections collected	4936
Independent reflections	2481 [R(int) = 0.0168]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2836 / 4 /220
Goodness-of-Fit on F^2	1.058
Final R indices [I > 2sigma(I)]	R_1 = 0.0285, $_wR_2$ = 0.0666
R indices (all data)	R_1 = 0.0429, $_wR_2$ = 0.1039
largest diff. peak and hole	0.386 and -0.430 eÅ^{-3}


O
O
NH
MeO2C
Br

253


O(1a)
O(2a)
C(8a)
C(9a)
C(5a)
C(6a)
C(2a)
C(1a)
N(1a)
C(4a)
C(7a)
C(10a)
C(3a)
O(3a)
C(16a)
C(15a)
C(11a)
O(4a)
C(14a)
C(12a)
C(17a)
Br(1a)
C(13a)



253

Unit Cell Structure

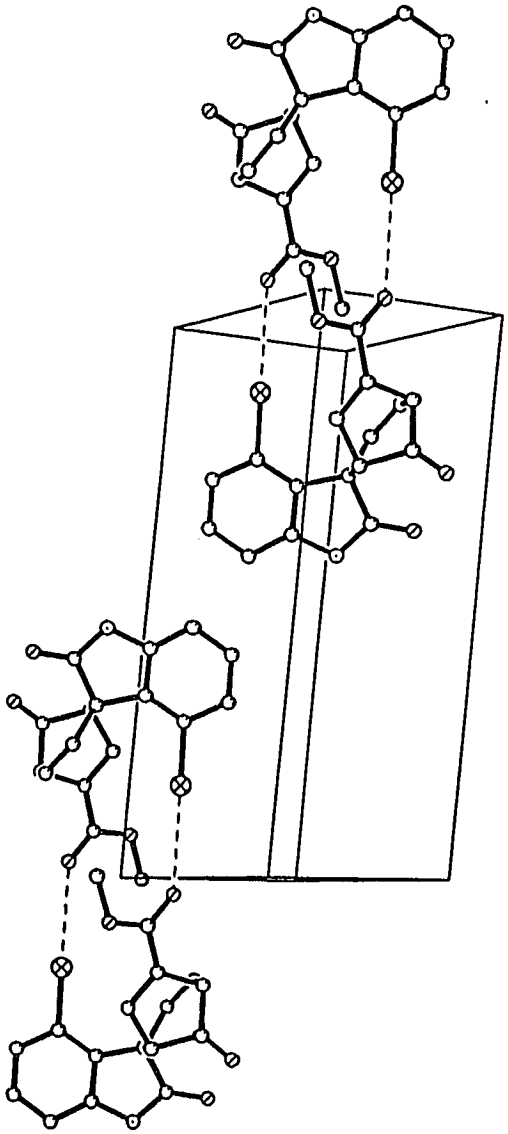


Table 4. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for compound **253**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)	Occupancy
Br(1)	0.08302(4)	0.25765(4)	0.16339(2)	0.03752(10)	1
O(4)	0.2247(3)	-0.2501(3)	0.07954(11)	0.0437(5)	1
N(1)	-0.2697(4)	0.0864(3)	0.44232(13)	0.0435(6)	1
C(3)	0.0329(4)	-0.1949(3)	0.2319(2)	0.0308(5)	1
O(3)	-0.0993(3)	-0.2614(4)	0.02868(12)	0.0588(6)	1
C(1)	-0.2349(4)	0.0141(3)	0.30738(14)	0.0312(5)	1
O(2)	-0.5326(3)	-0.0858(3)	0.39902(12)	0.0522(5)	1
O(1)	-0.3620(4)	-0.4391(3)	0.32176(14)	0.0587(6)	1
C(14)	0.0658(4)	0.2578(3)	0.2776(2)	0.0323(5)	1
C(13)	0.1997(5)	0.3720(4)	0.3130(2)	0.0397(6)	1
C(5)	-0.3059(4)	-0.2577(4)	0.1906(2)	0.0387(6)	1
C(4)	-0.0705(4)	-0.2383(3)	0.1681(2)	0.0319(5)	1
C(2)	-0.1164(4)	-0.1859(3)	0.3044(2)	0.0319(5)	1
C(15)	-0.0797(4)	0.1567(3)	0.32464(14)	0.0305(5)	1
C(16)	0.0133(4)	-0.2517(4)	0.0850(2)	0.0361(6)	1
C(7)	-0.3763(4)	0.0589(4)	0.2355(2)	0.0351(6)	1
C(17)	0.3193(5)	-0.2599(6)	0.0000(2)	0.0627(10)	1
C(6)	-0.4163(4)	-0.0644(4)	0.1847(2)	0.0369(6)	1
C(12)	0.1846(5)	0.3871(4)	0.3951(2)	0.0476(7)	1
C(10)	-0.0987(5)	0.1837(4)	0.4069(2)	0.0374(6)	1
C(11)	0.0323(5)	0.2950(4)	0.4433(2)	0.0465(7)	1
C(8)	-0.2817(4)	-0.3159(4)	0.2803(2)	0.0385(6)	1
C(9)	-0.3698(5)	-0.0018(4)	0.3877(2)	0.0398(6)	1

Table 5. Bond lengths [Å] and angles [°] for compound **253**.

Br(1)- C(14)	1.897(2)
O(4)- C(16)	1.327(3)
O(4)- C(17)	1.435(3)
N(1)- C(9)	1.352(4)
N(1)- C(10)	1.401(4)
C(3)- C(4)	1.335(4)
C(3)- C(2)	1.503(3)
O(3)- C(16)	1.202(3)
C(1)- C(7)	1.512(4)
C(1)- C(15)	1.514(3)
C(1)- C(9)	1.553(3)
C(1)- C(2)	1.584(3)
O(2)- C(9)	1.220(3)
O(1)- C(8)	1.197(3)
C(14)- C(15)	1.379(4)
C(14)- C(13)	1.395(4)
C(13)- C(12)	1.378(4)
C(5)- C(6)	1.513(4)
C(5)- C(8)	1.520(4)
C(5)- C(4)	1.522(4)
C(4)- C(16)	1.469(4)
C(2)- C(8)	1.530(4)
C(15)- C(10)	1.399(3)
C(7)- C(6)	1.324(4)
C(12)- C(11)	1.386(4)
C(10)- C(11)	1.379(4)

C(16)- O(4)- C(17)	116.0(2)
C(9)- N(1)- C(10)	111.8(2)
C(4)- C(3)- C(2)	110.7(2)
C(7)- C(1)- C(15)	117.9(2)
C(7)- C(1)- C(9)	111.1(2)
C(15)- C(1)- C(9)	101.2(2)
C(7)- C(1)- C(2)	110.4(2)
C(15)- C(1)- C(2)	110.9(2)
C(9)- C(1)- C(2)	104.2(2)
C(15)- C(14)- C(13)	120.3(2)
C(15)- C(14)- Br(1)	122.1(2)
C(13)- C(14)- Br(1)	117.6(2)
C(12)- C(13)- C(14)	120.1(3)
C(6)- C(5)- C(8)	106.1(2)
C(6)- C(5)- C(4)	108.0(2)
C(8)- C(5)- C(4)	97.9(2)
C(3)- C(4)- C(16)	128.1(2)
C(3)- C(4)- C(5)	109.9(2)
C(16)- C(4)- C(5)	121.8(2)

C(3)- C(2)- C(8)	98.5(2)
C(3)- C(2)- C(1)	112.0(2)
C(8)- C(2)- C(1)	106.9(2)
C(14)- C(15)- C(10)	117.8(2)
C(14)- C(15)- C(1)	133.8(2)
C(10)- C(15)- C(1)	108.4(2)
O(3)- C(16)- O(4)	124.4(2)
O(3)- C(16)- C(4)	123.1(2)
O(4)- C(16)- C(4)	112.5(2)
C(6)- C(7)- C(1)	123.4(3)
C(7)- C(6)- C(5)	121.6(2)
C(13)- C(12)- C(11)	121.0(3)
C(11)- C(10)- C(15)	122.8(3)
C(11)- C(10)- N(1)	127.7(2)
C(15)- C(10)- N(1)	109.4(2)
C(10)- C(11)- C(12)	117.7(2)
O(1)- C(8)- C(5)	129.2(3)
O(1)- C(8)- C(2)	127.9(3)
C(5)- C(8)- C(2)	102.8(2)
O(2)- C(9)- N(1)	127.0(2)
O(2)- C(9)- C(1)	125.2(2)
N(1)- C(9)- C(1)	107.8(2)

Table 6. Anisotropic displacement parameters ($Å^2$) for compound **242**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 \cdot a^{*2} \cdot U11 + ... + 2hka^*b^*U12]$

Atom	U11	U22	U33	U23	U13	U12
Br(1)	0.0422(2)	0.0405(2)	0.03011(14)	-0.00115(10)	0.00326(10)	-0.00961(11)
O(4)	0.0344(11)	0.0657(13)	0.0326(10)	-0.0116(9)	0.0046(8)	-0.0086(9)
N(1)	0.055(2)	0.0492(14)	0.0266(11)	-0.0075(10)	0.0100(10)	-0.0047(12)
C(3)	0.0293(14)	0.0288(13)	0.0344(13)	-0.0031(10)	0.0019(11)	-0.0038(10)
O(3)	0.0430(13)	0.099(2)	0.0374(11)	-0.0187(11)	-0.0067(9)	-0.0061(12)
C(1)	0.0292(14)	0.0372(13)	0.0275(12)	-0.0048(10)	0.0041(10)	-0.0052(11)
O(2)	0.0472(13)	0.0660(14)	0.0440(12)	-0.0090(10)	0.0200(10)	-0.0148(11)
O(1)	0.0537(14)	0.0519(12)	0.069(2)	0.0087(11)	0.0117(11)	-0.0208(11)
C(14)	0.033(2)	0.0341(13)	0.0301(12)	-0.0059(10)	0.0003(10)	-0.0014(11)
C(13)	0.039(2)	0.0351(14)	0.045(2)	-0.0069(12)	-0.0030(12)	-0.0043(12)
C(5)	0.031(2)	0.046(2)	0.042(2)	-0.0135(12)	0.0021(12)	-0.0140(12)
C(4)	0.0299(14)	0.0333(13)	0.0334(13)	-0.0062(10)	0.0021(10)	-0.0072(11)
C(2)	0.0309(14)	0.0343(13)	0.0303(13)	-0.0011(10)	-0.0001(10)	-0.0026(11)
C(15)	0.0333(14)	0.0311(13)	0.0273(12)	-0.0055(10)	0.0004(10)	-0.0004(10)
C(16)	0.031(2)	0.041(2)	0.0377(14)	-0.0088(11)	-0.0009(11)	-0.0054(11)
C(7)	0.0241(14)	0.045(2)	0.0355(13)	0.0002(12)	0.0026(10)	-0.0029(11)
C(17)	0.044(2)	0.104(3)	0.041(2)	-0.017(2)	0.0103(14)	-0.005(2)
C(6)	0.0232(14)	0.054(2)	0.0342(13)	-0.0033(12)	0.0010(10)	-0.0080(12)
C(12)	0.050(2)	0.046(2)	0.050(2)	-0.0151(14)	-0.0118(14)	-0.0053(14)
C(10)	0.045(2)	0.0361(14)	0.0306(13)	-0.0047(11)	0.0014(11)	0.0013(12)
C(11)	0.061(2)	0.049(2)	0.0310(14)	-0.0124(12)	-0.0056(13)	-0.002(2)
C(8)	0.032(2)	0.038(2)	0.045(2)	-0.0051(12)	0.0081(12)	-0.0073(12)
C(9)	0.042(2)	0.043(2)	0.0333(14)	-0.0038(12)	0.0099(12)	-0.0002(13)

Table 7. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for compound **253**

Atom	x	y	z	U(eq)	Occupancy
H(1A)	-0.324(6)	0.087(5)	0.4978(13)	0.080	1
H(3A)	0.183(3)	-0.176(5)	0.232(2)	0.080	1
H(13)	0.2995(5)	0.4380(4)	0.2811(2)	0.048	1
H(5)	-0.3750(4)	-0.3476(4)	0.1611(2)	0.046	1
H(2)	-0.0478(4)	-0.2313(3)	0.3552(2)	0.038	1
H(7A)	-0.440(6)	0.184(3)	0.232(2)	0.080	1
H(17A)	0.4717(5)	-0.2579(6)	0.0026(2)	0.094	1
H(17B)	0.2657(5)	-0.1551(6)	-0.0351(2)	0.094	1
H(17C)	0.2835(5)	-0.3734(6)	-0.0207(2)	0.094	1
H(6A)	-0.512(5)	-0.028(5)	0.142(2)	0.080	1
H(12)	0.2778(5)	0.4601(4)	0.4184(2)	0.057	1
H(11)	0.0190(5)	0.3079(4)	0.4985(2)	0.056	1

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