Recent Progress in the Synthesis of Indole Alkaloids

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RECENT PROGRESS IN THE SYNTHESIS OF INDOLE ALKALOIDS[1]

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ABSTRACT.—Reductive photocyclization of enamides has been proved as a useful reaction for the construction of the skeleton of indole alkaloids, thus providing a general and convenient synthesis of alkaloids. This synthetic methodology features first synthesizing the skeleton of alkaloids followed by the elaboration of a partial structure with the appropriate substituents, and has been successfully applied to the synthesis of various groups of indole alkaloids including ergot, yohimbine, and corynantheine groups. Further, successful extensions have also been achieved in the synthesis of geissoschizine and isositsirikines, which are structurally featured as having an olefinic side chain, thereby bringing about the development of a new synthetic methodology for the stereoselective isomerization of the olefinic double bond.

Our involvement in the synthesis of indole alkaloids has been triggered by the finding of a useful synthetic reaction of enamide photocyclization, particularly the cyclization in the presence of hydride reagent, that is, reductive photocyclization, which is described in part one of this review. Then in part two the application of this reaction to total synthesis of indole alkaloids is described. The indole alkaloids are divided into three groups: yohimbines, which contain a basic skeleton of this group of alkaloids; heteroyohimbines, which feature the presence of a heteroatom, mainly oxygen, in the terminal ring E; and corynanthe alkaloids, which have a ring-opened structure at the terminal ring and contain an ethylidene side chain, thereby involving the geometrical problem of an olefinic double bond (Figure 1). The double bond has drawn us further to the study on the stereochemical problem for the introduction of stereogenic and geometrical centers. In part three of this review, our study on the newly developed stereoselective addition reaction to the olefinic double bond is described.

PART ONE: THE REACTION THAT HAS DIRECTED OUR INTERESTS TO THE SYNTHESIS OF INDOLE ALKALOIDS.—As documented well by Ninomiya and Naito (1), enamide photocyclization has been established as one of the most useful reactions for the construction of the skeleton of alkaloids, particularly isoquinoline alkaloids. The rationale for this application is based on the fact that enamide A has a six-π-conjugated electron system, thereby undergoing smooth cyclization under a photochemical condition in a conrotatory manner to form a six-membered cyclic intermediate B, from which hydrogen migrates thermally and suprafacially in a 1,5- manner to afford the dehydrolactam C (Scheme 1). It is observed that this smooth photocyclization takes place nonoxidatively at room temperature. This reaction has been successfully applied to the synthesis of the skeleton of various alkaloids including isoquinoline alkaloids such as phenanthridines (i.e., benzo[*c*]phenanthridine), protoberberine groups, and indole alkaloids of ergoline group. However, sometimes we have encountered a problem with this reaction with the formation of didehydrolactams D even under nonoxidative conditions.

A breakthrough in the problem has been attained by the finding of the useful procedure of reductive photocyclization (2). The structure of a proposed cyclic intermediate B should contain an iminium double bond, which is readily reduced by hydride ion.

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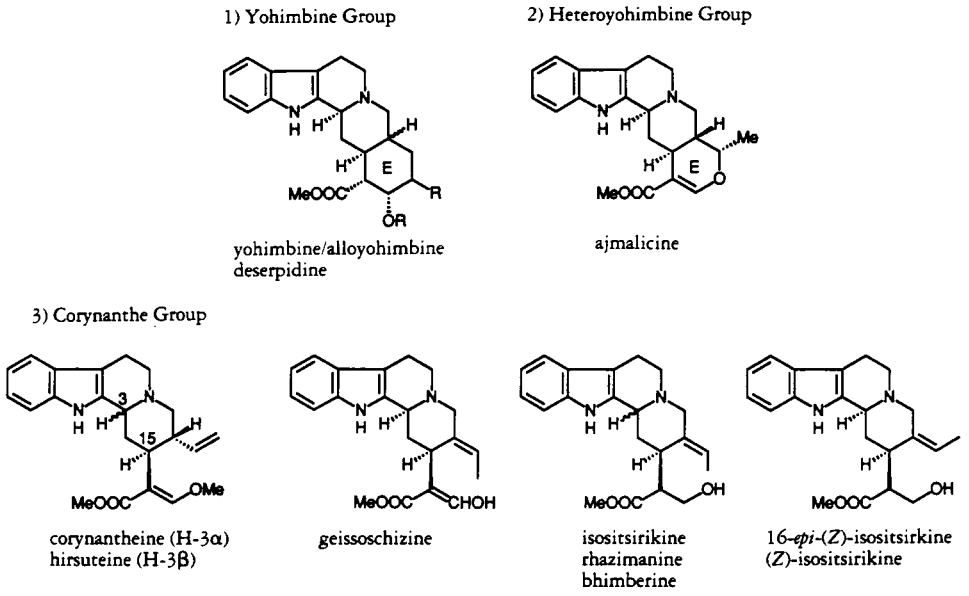
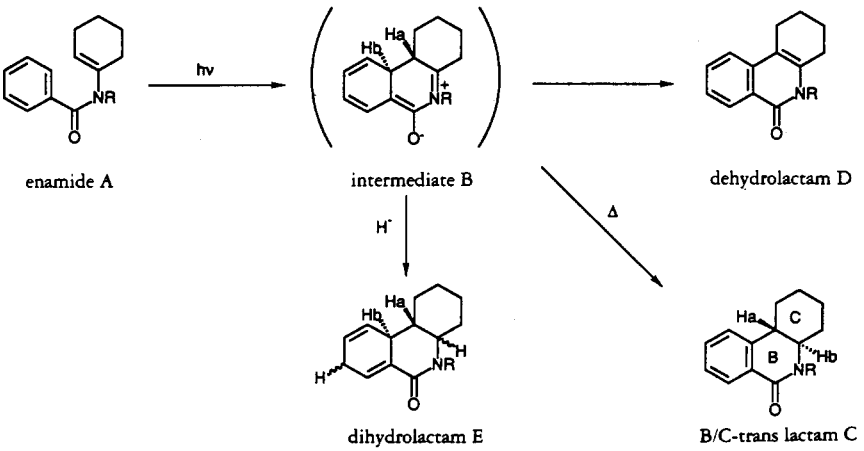
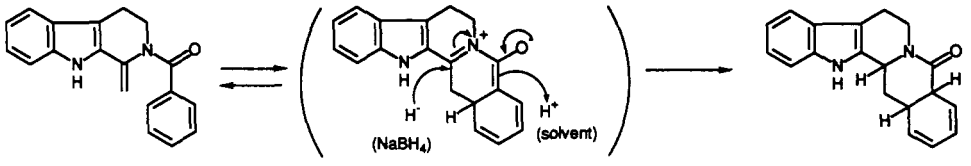


FIGURE 1. Indole alkaloids targeted for synthesis.

Therefore, $NaBH_4$ was added to the reaction mixture of enamide in a suitable solvent and irradiated. A new and very smooth photocyclization proceeded to form the saturated lactams E homogeneously as a result of attack of hydride ion to the proposed intermediate B (Scheme 2). Practically, the enamide **1** for the synthesis of the yohimbine group of alkaloids was prepared from harmalane by simple acylation with benzoyl chloride in good yield, dissolved in a suitable solvent, and $NaBH_4$was added. In order to make the reaction mixture homogeneous, 10% EtOH was added. Irradiation was carried out at a low temperature of about 0–10°, and the reaction was readily checked by tlc of the reaction mixture to see the rapid disappearance of the spot for the enamide with the appearance of a new spot for the product. The products were obtained as a mixture of two lactams **2** and **3** differing with respect to the position of protonation (Scheme 3). However, in order to establish this reaction as a potential synthetic method, the reaction procedure for the formation of homogeneous product **3** had to be established. This was



SCHEME 1



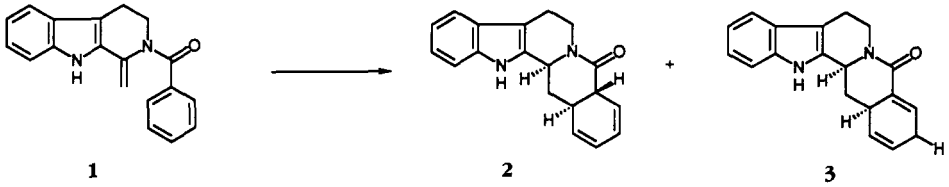
1 B hydrogenated lactam E

SCHEME 2

achieved by the choice of solvent. MeCN was the solvent of choice for this photocyclization, giving rise to a homogeneous lactam **3** in an excellent yield.

The results of reductive photocyclization have not only provided added potential for this reaction but also proved the reaction mechanism of the photocyclization. Of course, the feature of this methodology is the facile one-step construction of the alkaloid skeleton. Therefore, the remaining steps for total synthetic work are just to introduce substituents stereochemically into the skeleton with modification to the desired structures. This type of synthetic approach toward alkaloids has not normally been done.

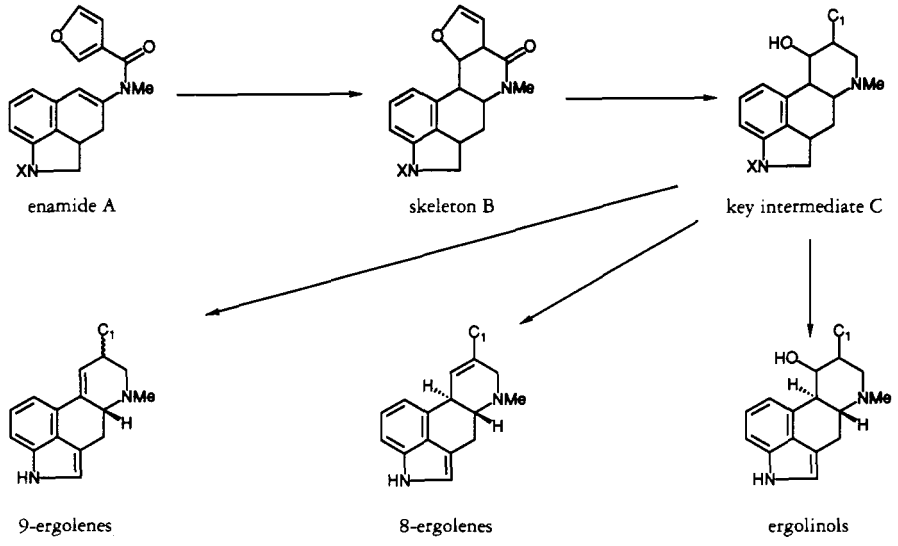
Previously, we have successfully applied this reductive photocylization for the synthesis of the ergoline and ergolene groups of alkaloids as also reviewed by Ninomiya



1 2 3

solvent	yield	Yield
C_6H_6/MeOH	7%	21%
Et_2O/MeOH	17%	32%
MeCN/MeOH	–	98%

SCHEME 3



enamide A skeleton B key intermediate C

9-ergolenes 8-ergolenes ergolinols

SCHEME 4

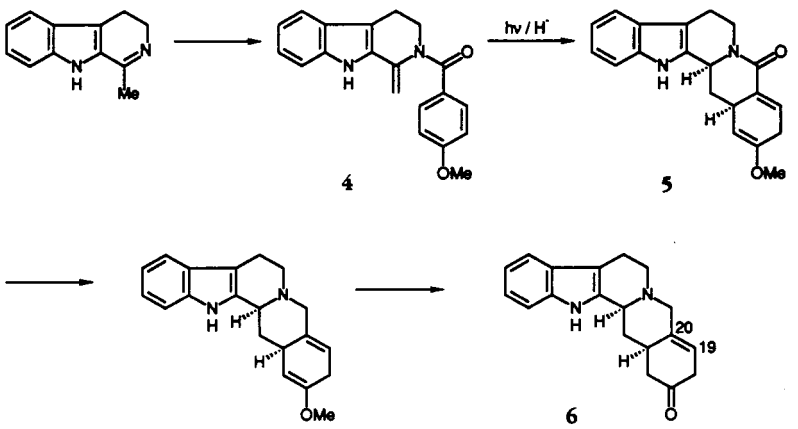
and Kiguchi (3). A typical example of this approach for the synthesis of a group of alkaloids having a common structural feature has been shown (Scheme 4). Ergot alkaloids including lysergic acid, lysergols, lysergine (9-ergolenes); elymoclavine, agroclavine (8-ergolenes); fumigaclavines (ergolinols); and many others, were synthesized from a common key intermediate C, prepared by reductive photocyclization of enamide A.

Our interests have now been directed toward the synthesis of other types of indole alkaloids as listed in Figure 1. As above, our strategy has followed the track of the syntheses of a large group of alkaloids having analogous structures.

PART TWO: APPLICATION OF REDUCTIVE PHOTOCYCLIZATION OF ENAMIDE TO THE SYNTHESIS OF INDOLE ALKALOIDS.—Our synthetic strategy may be described as catching all fish in a pond with one net. We picked the indole alkaloids summarized in Figure 1 as our targets. They are divided into three groups. The yohimbine group of alkaloids, consisting of yohimbine, alloyohimbine, 19,20-dehydroyohimbines, deserpidine, and reserpine, represents the alkaloids having a basic structure of the dodecahydroindolo[2,3-*a*]benzo[*g*]quinolizine skeleton. The second group of alkaloids consists of the alkaloids having an oxygen atom in the terminal ring, known trivially as heteroyohimbines and represented here by ajmalicine. The third group contains the alkaloids having a ring-opened structure at the terminal ring, called the corynanthe group, which would be formed as a result of oxidative cleavage of a ring, thereby having an olefinic side chain, as exemplified by corynantheine, geissoschizine, isositsirikines.

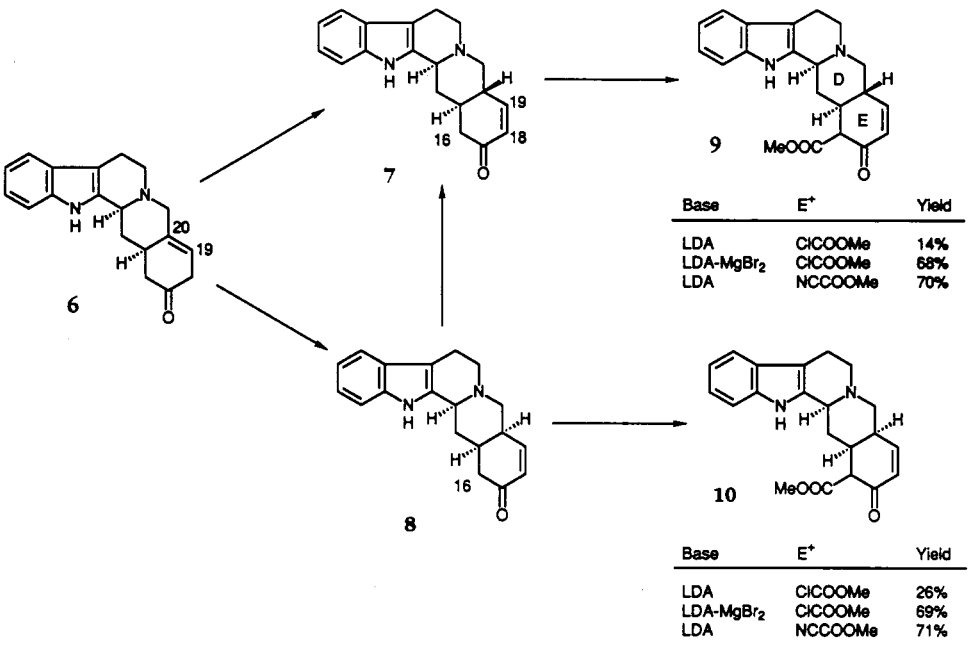
SYNTHESIS OF THE YOHIMBINE GROUP OF ALKALOIDS.—*Yohimbine, alloyohimbine, deserpidine, and 19,20-dehydroyohimbines (4).*—The enamide **4** having an additional methoxy group was prepared by simple acylation with *p*-methoxybenzoyl chloride and irradiated in the presence of $NaBH_4$. Reductive photocyclization proceeded as expected to afford a homogeneous product almost quantitatively which contains an enol-ether moiety in the terminal ring and therefore was expected to be readily convertible to the corresponding ketone **5** upon acid treatment. First the lactam carbonyl group was reduced and the resulting enol ether was treated with acid. The expected enone **6** was obtained in good yield. The double bond at the 19-position was not shifted from this unconjugated position because of its stable conformation of this enone with a double bond at the ring junction, making the molecule rather planar (Scheme 5).

It was expected that with the migration of a double bond from the ring junction to



SCHEME 5

a conjugated position with the carbonyl group, hydrogen would be introduced into the 20 position possibly from either side of the molecule, thereby giving rise to the stereoselective formation of the D/E-cis or -trans ring system. Upon investigation of various conditions we have established the stereoselective introduction of hydrogen into the ring junction by changing the reaction temperature. When the unconjugated enone **6** was treated with acid at an elevated temperature of 85°; the D/E-trans enone **7** was obtained stereoselectively in 75% yield, while on treatment with Si gel at room temperature, the D/E-cis enone **8** was obtained in 90% yield. Further the cis enone was readily converted into the trans enone when heated at 85°, thereby suggesting that the trans enone is a thermally stable isomer, as suggested from its molecular conformation. The trans enone has a rather planar conformation while the cis isomer has a folded conformation (Scheme 6).

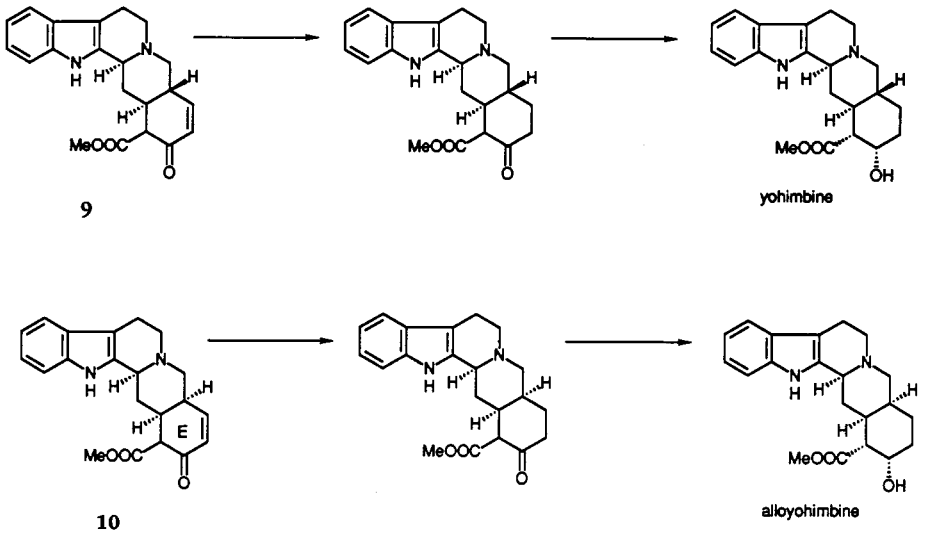


SCHEME 6

With quantities of these trans and cis enones in hand, the introduction of an ester group into the hindered 16 position was investigated. Previously several attempts had been made to introduce an ester group into this 16 position, but all failed. We started with the enone which has clearly different reactivities at the 16 and 18 positions and investigated direct acylation of the 16 position. In order to overcome the steric hindrance present in the 16 position for acylation, it was assumed that the reaction would proceed via a metallic enolate, which is known to have various forms according to the reaction conditions used, for example, *O*-metallated enolate, *C*-metallated enolate, or ion-paired enolate. For the *C*-acylation, it was suggested that the form of ion-paired enolate that would be preferentially formed by treatment with base in the presence of magnesium salt would provide an advantage over others with respect to their acylation. Based on these considerations, the enone was treated first with LDA followed by ethyl chloroformate in the presence of magnesium bromide. The result was good, giving the desired C-16 acylated products **9** and **10** in 68–69% yield, while in the absence of magnesium salt,

only 14–26% yield of *C*-acylation was observed. Further, following the work of Mander and Sethi (5), cyanoformate was applied in place of chloroformate and succeeded in 70% yield of *C*-acylation into the 16 position. These results are in good agreement with the discussion on the form of intermediary enolate for *C*-acylation in addition to the hard and soft acid-base principle. Thus we have succeeded in the first regioselective introduction of the ester group into the 16 position of both enones with D/E-cis and -trans configurations in good yields.

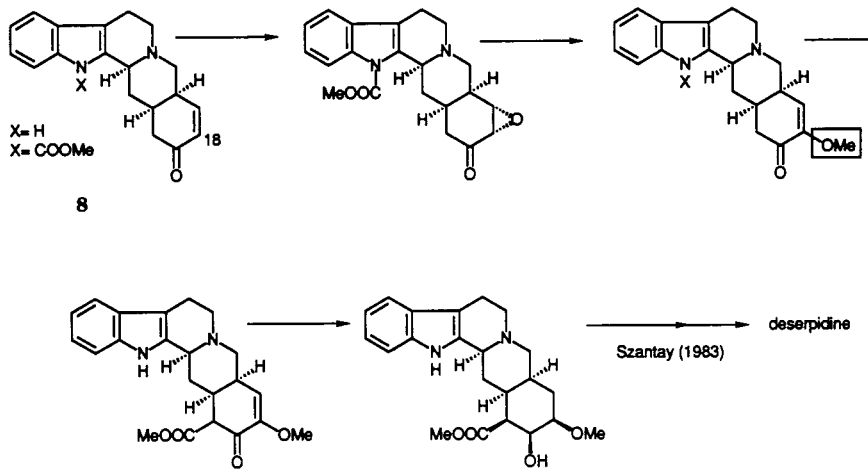
The remaining steps for total synthesis of yohimbine and alloyohimbine were carried out according to the reported route. This synthetic route for these popular alkaloids provides the simplest and the most convenient route with respect to the number of steps and overall yields (Scheme 7).



SCHEME 7

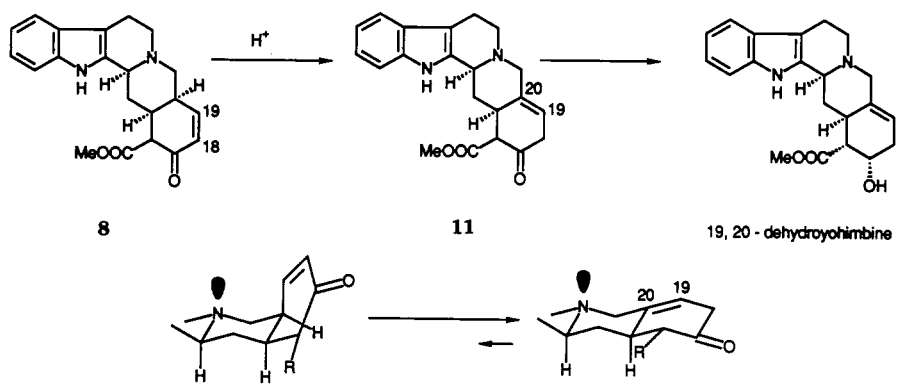
The generality of this synthetic methodology including enamide photocyclization was beautifully provided by another synthesis of deserpidine (6), which has an additional methoxy group in the 18 position. Total synthesis of deserpidine was quite similarly achieved just by adding steps for the introduction of an additional methoxy group at the 18 position to the synthetic intermediate A of yohimbine as shown in Scheme 8.

A group of alkaloids of the yohimbine-type with a double bond at the 18,19 position is known. As is clear from our synthetic methodology we have synthesized the 18,19-dehydroyohimbine type of compounds and investigated the migration of this double bond from the unconjugated position to the conjugated. Considering the molecular models of these compounds, it is clear that the compound with a double bond at the ring junction and the D/E-trans compound have rather stable planar conformation while the D/E-cis has unstable folded conformation. Therefore we have treated the D/E-cis conjugated enone with base expecting back migration of a double bond from the conjugated 20,21 position to the unconjugated 19,20 position (Scheme 9). The isomerization occurred very smoothly either by treatment with K_2CO_3 in MeOH at 0° or by treatment with concentrated H_2SO_4 under reflux. A yield of 70–73% was achieved for this back migration. Of course no isomerization was observed from the D/E-trans isomer which gave only the MeOH adduct. The difference in their migratory abilities can be explained as follows: the ^1H nmr shows that the D/E-cis-18,19-enone **8** exists in solution as an equilibration mixture of its keto and enol forms, thereby weakening the



SCHEME 8

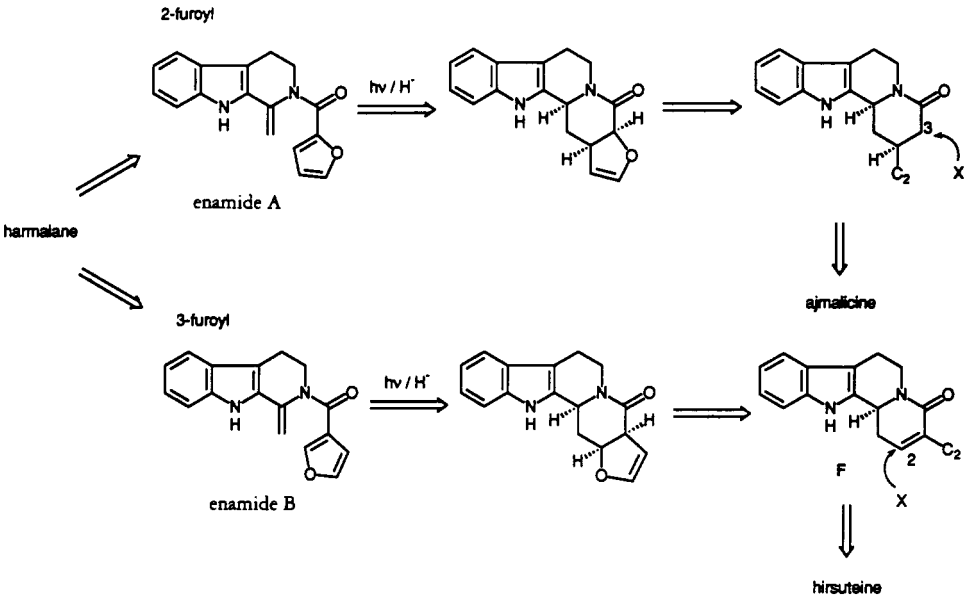
contribution of the conjugated enone. Its folded conformation, which makes the compound unstable, would provide facile isomerization to a stable and planar conformation **11**. On the other hand, the D/E-trans conjugated enone, which exists as a stable and planar conformation in solution, would be resistant to isomerization and instead form an MeOH-adduct. Finally, reduction of these enones with $NaBH_4$ furnished total synthesis of 19,20-dehydroyohimbines, which were separated by chromatography (Scheme 9).



SCHEME 9

SYNTHESIS OF HETEROYOHIMBINES.—*Ajmalicine, corynantheine, hirsuteine, geissoschizine, isositsirikines.*—As shown in Figure 1, we picked ajmalicine as the next target alkaloid, followed by the third group of alkaloids for the application of our synthetic methodology. Ajmalicine is pharmacologically the most important of this group.

Synthetic strategy for the heteroyohimbine alkaloids.—In order to synthesize all these modified yohimbines (7) by one methodology, we decided to introduce a furan ring into the enamides which upon irradiation in the presence of $NaBH_4$ were expected to give the photocyclized new ring systems of five rings containing a dihydrofuran moiety at the terminal position (Scheme 10). The following ring-opening of the dihydrofuran would give rise to the ring-opened compounds, which would play an important key role in the following processes toward total syntheses of the respective alkaloids. The idea of introducing a furan ring was supported by our previous introduction of a furan ring in the syntheses of ergoline-type alkaloids which were achieved via the route of the

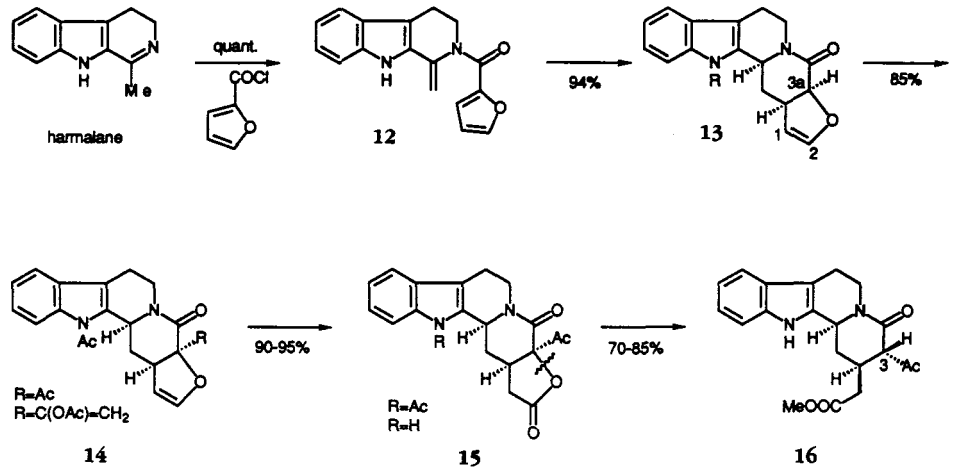


SCHEME 10

photocyclized product as the common key intermediate. The photocyclized lactam, five-ring system, from 2-furoylenamine, when the dihydrofuran ring is opened, would give a four-ring lactam, which would have reactivity enough for structural modification.

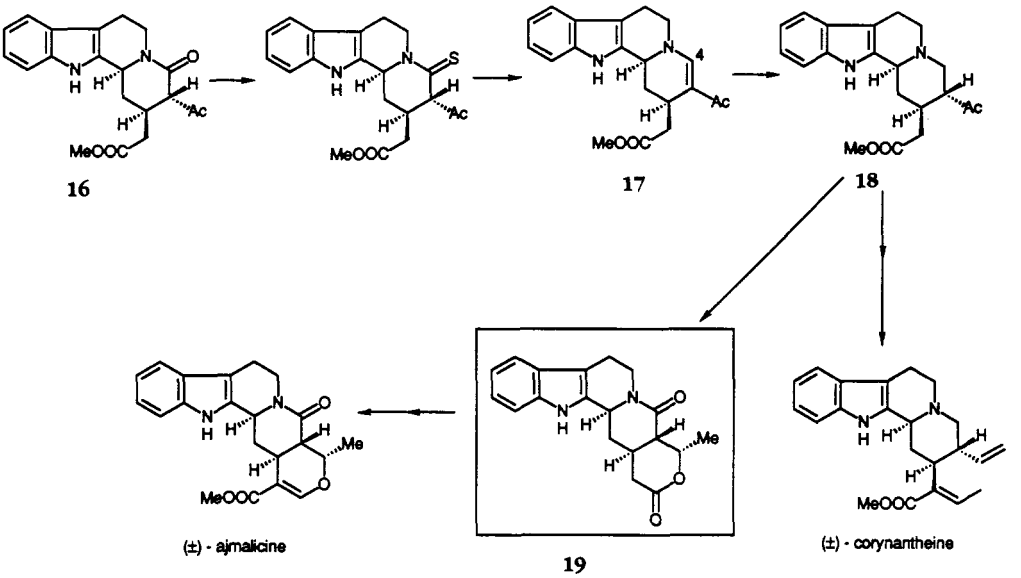
Synthesis of Ajmalicine by Use of 2-Furoylenamine as Enamide.—As depicted in Scheme 11, the enamide for the synthesis of ajmalicine was prepared by acylation of harmalane with 2-furoyl chloride (8). Reductive photocyclization proceeded smoothly to afford the homogeneous lactam **13** with a dihydrofuran ring in 94% yield. In order to introduce two-carbon substituent, direct introduction of an acetyl group into the ring junction of the photocyclized product was investigated, because this position adjacent to the lactam carbonyl is expected to be rather active. Upon various investigations we succeeded in introducing an acetyl group by treating the lactam **13** with LDA followed by Ac_2O (Scheme 11). The desired acetyl compound **14** was obtained in 85% yield, with the formation of the secondary product corresponding to further acetylation of the primary product. In order to convert the acetylated product to the key compound for total synthesis, the acetyl derivative was oxidatively hydrolyzed to give the γ-lactone **15** in 95% yield, which was then reduced with zinc in HOAc. Esterification of the resulting hydroxycarboxylic acid with CH_2N_2 yielded, in 70–85% yield, the tricarbonyl compound **16**, which had been synthesized and utilized as an important key intermediate in the total synthesis of ajmalacine by G. Massiot and found to be identical with the authentic sample upon direct comparison.

Though total synthesis of ajmalicine was formally achieved, we have carried out further steps to the alkaloid as shown in Scheme 12. The lactam carbonyl group in the tricarbonyl compound **16** was selectively reduced first by thiolation of a lactam carbonyl to thiocarbonyl, followed by desulfurization with Raney nickel to give the desulfurized enamine **17**. Saturation with sodium hydrogen borocyanide afforded the dicarbonyl compound **18**, which had been synthesized by several groups and further converted into corynantheine, thus completing formal total synthesis of corynantheine. For the conversion to ajmalicine, the ketonic carbonyl in the dicarbonyl compound was reduced with $NaBH_4$ to yield the δ-lactone **19**, which had been already converted to ajmalicine.



SCHEME 11

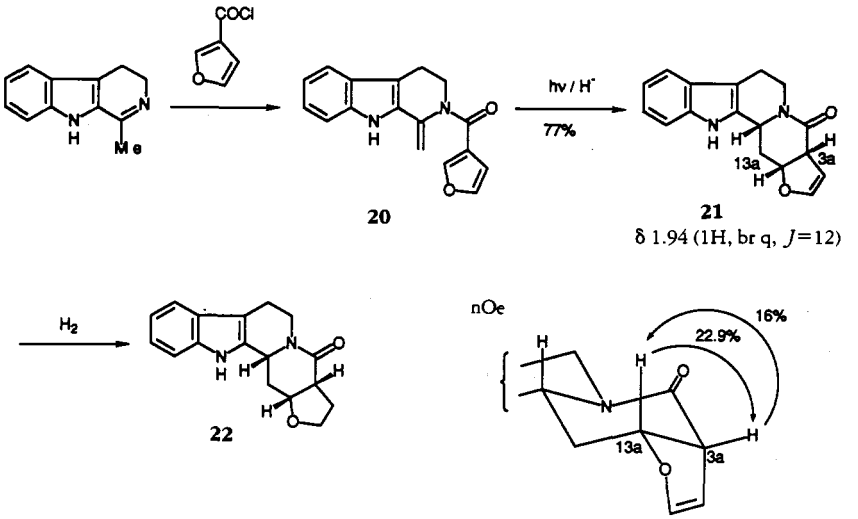
SYNTHESIS OF CORYNANTHE ALKALOIDS BY USE OF 3-FUROYLENAMINE-1.—The remaining targets for our methodology were the corynanthe alkaloids, including hirsuteine, geissoschizine, and isositsirikines (9) as shown in Figure 1. These alkaloids, particularly isositsirikines, contain an olefinic side chain, thereby providing an interesting geometrical problem for their stereoselective synthesis.



SCHEME 12

Synthesis of key intermediate.—Our synthetic strategy for these alkaloids is mentioned briefly in Scheme 10 and summarized as follows: the synthesis of these ring-opened alkaloids, which can be described as four-ring alkaloids having two two-carbon side chains at the 15 and 20 positions. The introduction of a furan ring provides one two-carbon chain. Therefore, the way to introduce the second two-carbon chain was the major problem to be investigated. From the synthetic standpoint, we picked the enamide **20** of 3-furoylenamine-type as the starting compound. The synthetic route is described as

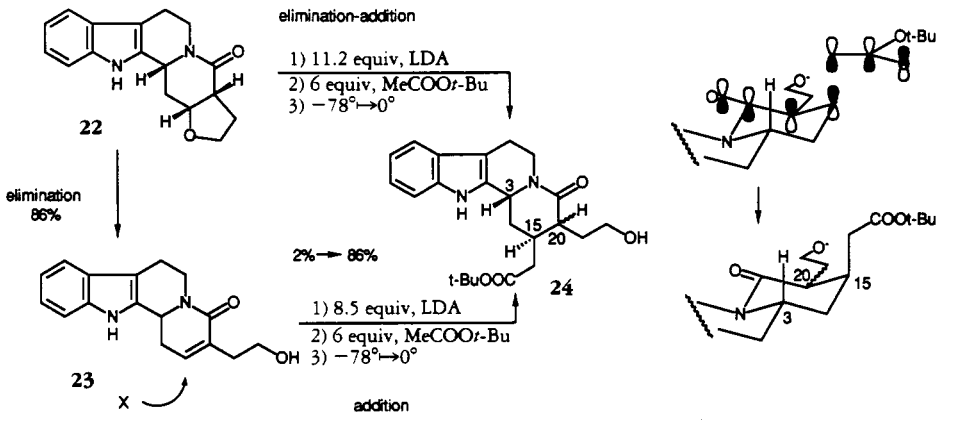
in Scheme 10; photocyclization would afford a basic skeleton D which would be then ring-opened to form the four-ring lactam F with an a,β-unsaturated enone grouping. Therefore, a Michael-type addition reaction would be expected at the β position to introduce the second carbon chain. According to this strategy we could expect the synthesis of all members of this type of alkaloids from one common key intermediate. We started the synthesis of corynanthe alkaloids by preparing the enamide **20** from harmalane by acylation with 3-furoyl chloride. Irradiation of this enamide in the presence of $NaBH_4$ also proceeded smoothly to give the homogeneous lactam **21** with a dihydrofuran in 77% yield (Scheme 13). The structure of this lactam as having a D/E-cis ring junction was established from its nmr spectrum, which showed a large coupling constant of 12 Hz for H-3a and H-13a, in addition to nOe value of 16.0–22.9% between these two hydrogens. The double bond was readily reduced to give the saturated lactam **22** quantitatively.



SCHEME 13

Ring opening of the tetrahydrofuran of compound **22** would give the lactam with a two carbon side chain at the position next to the lactam carbonyl (Scheme 14). The ring opening reaction of tetrahydrofuran **22** was successfully achieved by treatment with LDA at −78° to give the four-ring lactam **23** with a 2-hydroxyethyl group at the 20 position in a 86% yield. Therefore, in view of synthesizing the key compound **24**, we then investigated the introduction of the second two-carbon unit, acetate, into the β-position of this unsaturated lactam.

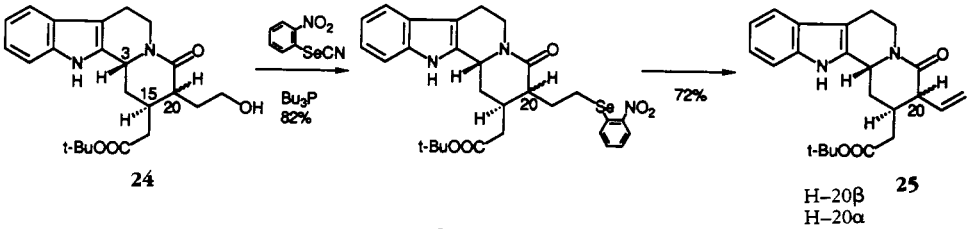
The well-studied Michael addition reaction was then applied to this compound. The unsaturated lactam **23** was treated with LDA at a low temperature followed by addition of tertiary butyl acetate, and the temperature was gradually raised to 0°. The addition reaction did occur to give the expected product **24** as a 1:1 mixture of cis- and trans-adducts, but only in 2% yield. Upon detailed investigation of the reaction condition, we have reached the optimum conditions shown with the yield of 86% by changing the amount of base and acetate. Further, noticing that these two steps, elimination and addition, were carried out under the same basic condition, we have checked a possibility of carrying out these two steps in one pot and found that under the conditions shown by altering the amount of base from 8.5 equiv to 11.2 equiv, one pot elimination-addition



SCHEME 14

was established with the overall yield of 67%. Though the yield was not so improved, the convenience of the reaction procedure provided a great advantage. This facile addition reaction could be explained in terms of orbital overlapping of the approaching acetate to the enolate as shown in Scheme 14. Now we have established the preparation of the four-ring lactam **24** with two two-carbon side chains at the 15 and 20 positions.

Synthesis of hirsuteine and hirsutine.—Among the target alkaloids, hirsuteine and hirsutine have a vinyl group as their side chain. We now have compound **24** with 2-hydroxyethyl group at the 20 position. Therefore, simple dehydration would give a compound with a vinyl group. The 2-hydroxyethyl group was readily converted into the desired vinyl group via the route including phenylselenation (Scheme 15). The 2-hydroxyethyl derivatives, which were obtained as a separable 1:1 mixture of cis and trans adducts, were treated with *o*-nitrophenylselenocyanide in the presence of tributylphosphine to form the intermediary phenylselenates in 82% yield. These were then oxidatively cleaved by the action of H_2O_2 to give the vinyl derivatives **25** in 72% yield.



SCHEME 15

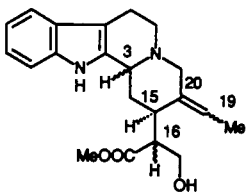
The lactam **25** with a vinyl group was reduced with aluminum hydride to give the corresponding quinolizine (Scheme 16). Formylation into the 16 position was readily achieved by treatment with ethyl formate in the presence of LDA, although in low yield (45%). Then *t*-Bu ester was converted into the methyl ester by treatment with HCl gas in absolute MeOH at −20°. Finally, methylation with CH_2N_2 gave the methyl enol ether, which was found to be identical with natural hirsuteine. Catalytic hydrogenation of a vinyl group in the side chain afforded hirsutine.

SYNTHESIS OF ISOSITSIRIKINES BY DEVELOPING THE REACTION OF MICHAEL-TYPE ADDITION OF THIOLS TO ELECTRON-DEFICIENT OLEFINS.—We have chosen the indole

SCHEME 16

alkaloids of the isositsirikine group as our next and last targets. The isositsirikine alkaloids represent a group of alkaloids having an ethylidene side chain in the terminal ring E, thereby posing an interesting geometrical problem with respect to their synthesis and stereochemistry (9).

Isositsirikines are the alkaloids having the structure of the corynanthe group (10) and contain three stereogenic centers in addition to one geometrical isomerism, therefore consisting of eight possible stereoisomers (Figure 2). However, only four isomers,



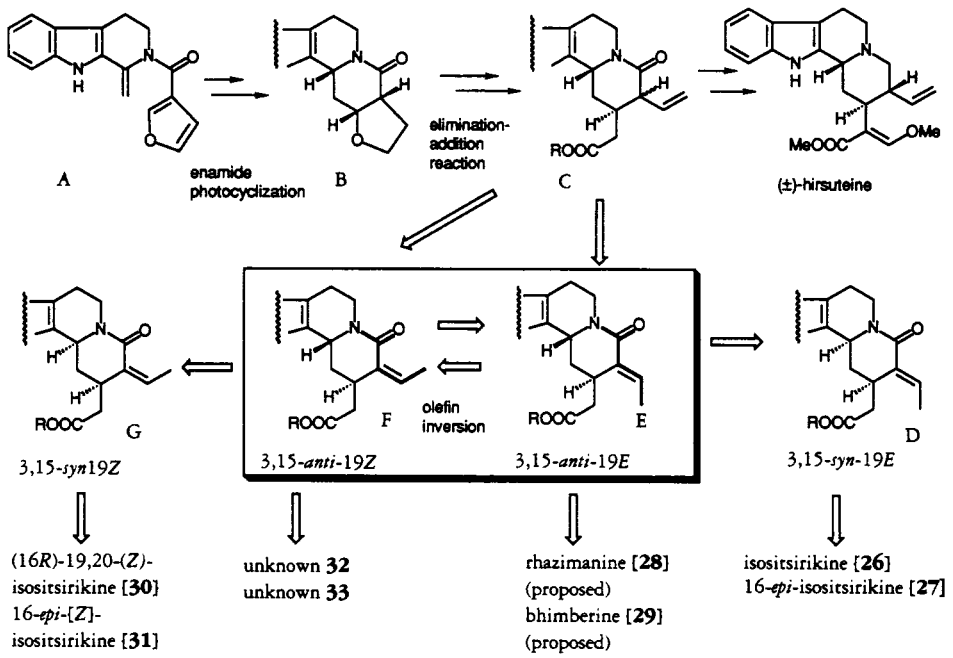
	19	H-3	H-16	
26	*E*	α	β	isositsirikine
27	*E*	α	α	16-epi-isositsirikine
28	*E*	β	β	rhazimanine (proposed)
29	*E*	β	α	bhimberine (proposed)
30	*Z*	α	β	(16*R*)-19,20-(*Z*)-isositsirikine
31	*Z*	α	α	16-*epi*-(*Z*)-isositsirikine
32	*Z*	β	β	unknown
33	*Z*	β	α	unknown

FIGURE 2. Isositsirikine alkaloids.

isositsirikine [**26**], 16-*epi*-isositsirikine [**27**], (16*R*)-19,20-(*Z*)-isositsirikine [**30**] and 16-*epi*-(*Z*)-isositsirikine [**31**] have been structurally established from their chemical and spectral data. Recently, one pair of isomers, rhazimanine [**28**] (11) and bhimberine [**29**] (12), were isolated, and their structures were proposed mainly from their spectral analysis. In order to resolve the structural problems of all these compounds, the best way seems to be the unequivocal synthesis of all eight possible isomers.

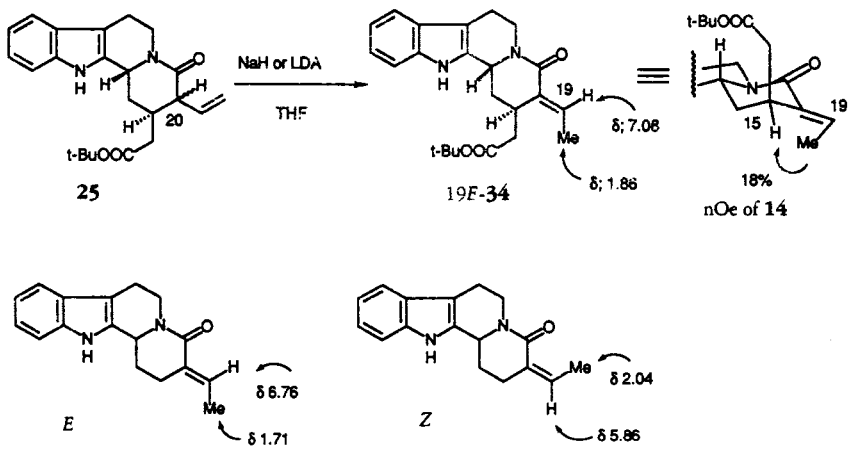
Synthetic strategy.—Our strategy for the synthesis of the isositsirikine group of alkaloids is shown in Scheme 17. Starting from the enamide A with a 3-furoyl group, photocyclization afforded the skeleton of the alkaloids. Ring opening and concomitant introduction of a two-carbon unit yielded the key intermediate C for the synthesis.

In order to achieve total synthesis, four stereoisomers as key intermediates (D–G) would become the most important compounds. First we tried the migration of a vinylic double bond into the ethylidene, hoping to obtain either the 19*E*- (E) or 19*Z*- (F) ethylidene derivative. Then if achieved, the remaining steps are the isomerization of a double bond from *E*- to *Z*- or from *E*- to *E*- and conversion of ring junction from 3β- to 3α-configuration. If we succeeded, total synthesis of all eight possible stereoisomers **26–33** would become possible from these four isomeric compounds D, E, F, and G.



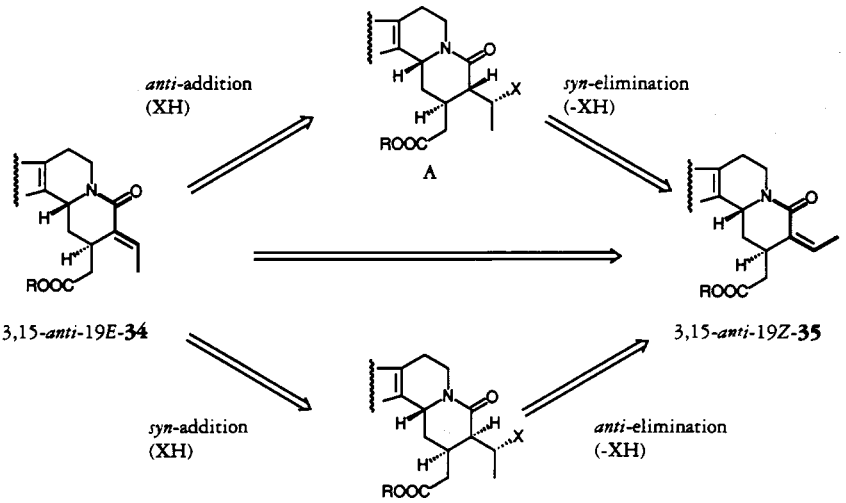
SCHEME 17

Isomerization of the vinyl group to the ethylidene group.—Because of the expected stability of the conjugated position of a double bond, the vinyl derivative **25** was treated with base (Scheme 18). Smooth isomerization was observed in good yield, giving a homogeneous ethylidene derivative **34**, which was proved to have 19*E* geometry from its nmr data. The homogeneity would be derived from a result of steric hindrance between lactam-carbonyl and ethylidene methyl groups as clearly shown on the model, which shows stable conformation of this isomer compared with the unstable conformation of the 19*Z*-isomer, as expected from stereochemical repulsion between lactam carbonyl and terminal methyl groups. The compound **34** thus obtained has the configuration of 3,15-*anti*-19*E* orientation and is one of four intermediates. Therefore, our strategy for the synthesis of the unstable isomer, that is, the conversion of *E*-isomer to *Z*-isomer, had a serious stereochemical hurdle to overcome.



SCHEME 18

Interconversion of geometrical isomers of the ethylidene group from Z-*ethylidene to* E-*isomer and* E-*isomer to* Z-*isomer*.—In hope of establishing a general methodology for the geometrical isomerization of olefins from *Z* to *E* or from *E* to *Z*, we planned the strategy as shown in Scheme 19 by applying the combination of reactions of *anti*-addition coupled with *syn*-elimination. We had the 19*E*-isomer **34**. Therefore, first, *anti*-addition of XH to the *anti*-adduct (A), which was then subjected to *syn*-elimination, would produce this conversion.



SCHEME 19

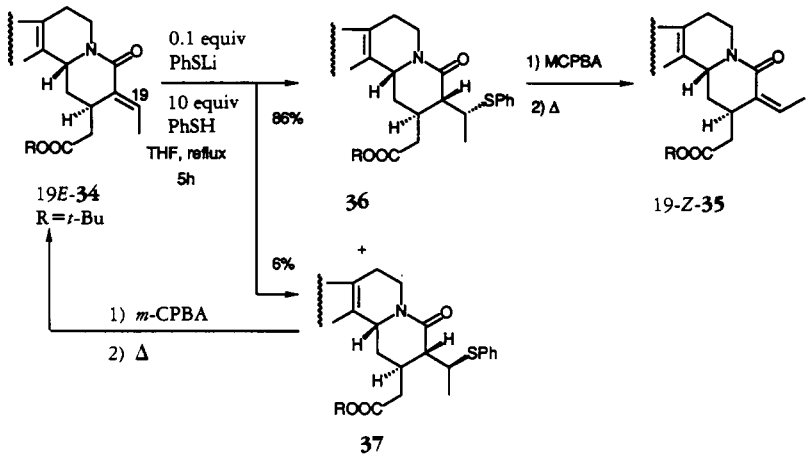
Actually, as Freund and Winterfeldt (13) described, only the conversion from the unstable 19Z-isomer **35** to the stable 19*E*-isomer **34** had been achieved, and all attempts for back conversion from the 19*E*- to the 19*Z*-isomer have not been successful.

*Conversion of 3,15-*anti-*19E-isomer to* anti-*19Z-isomer*.—Actual conversion was carried out as shown in Scheme 20 after some unsuccessful and not satisfactory studies. The 19*E*-ethylidene lactam **34** was treated with thiophenol in the presence of lithium thiophenoxide as base in THF under 5 h reflux. The adduct was obtained as a mixture of two products, *anti*-adduct **36** as a major and *syn*-adduct **37** as a minor product. The separated adducts were oxidized to the corresponding sulfoxides by the oxidizing mixture OXONE. The sulfoxides obtained as an epimeric mixture were then subjected to thermal elimination, giving the homogeneous olefin quantitatively, thus proving the stereochemistry of the intermediates and the structures of the products.

The mechanism of this stereoselective conversion of olefin is explained in terms of the formation of an intermediary complex which includes thiophenol and thiophenoxide ion as well.

Back conversion from anti-*19Z-isomer* **35** *to* anti-*19E-isomer* **34**.—The fact that Freund and Winterfeldt (13) had succeeded only in the conversion of the unstable 19*Z*-ethylidene derivative **35** to the stable *E*-isomer **34** under conventional conditions clearly suggested difficulty in their back conversion, the reason coming from the steric repulsion expected in the proximity of the methyl group of the ethylidene and the lactam-carbonyl group. However, this was overcome by applying the newly established Michael-type addition of thiophenol to the electron-deficient double bond (14).

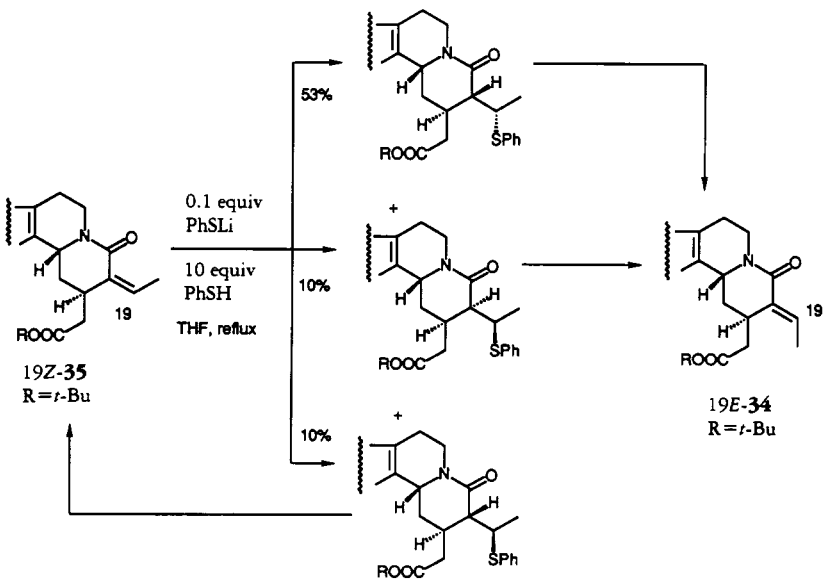
Sterically resisted back conversion was also achieved as shown in Scheme 21. The 19*Z*-olefin **35** was treated with thiophenol in the presence of lithium thiophenoxide in



SCHEME 20

THF under refluxing temperature. The major adduct, which has a trans stereochemistry, was obtained and then subjected to elimination via its sulfoxide. Again the sulfoxide was treated under thermal *syn*-elimination conditions to furnish the 19*E*-isomer **34**.

Practical conversion of the geometry of the ethylidene group in the key intermediate.—We picked the key intermediate **34** which carries the 19-ethylidene group and has a 3β and 15α configuration. This 19*E*-isomer **34** was treated with 10 M equiv of thiophenol in the presence of 1 equiv of lithium thiophenoxide in THF under refluxing temperature for 5 h. The expected Michael adduct was obtained in good yield as a mixture of *anti*-adduct **35** (86%) and *syn*-adduct **37** (6%), thus showing the addition reaction to be of a highly stereoselective nature. The *anti*-adduct **36** was oxidized with *m*-CPBA to give the corresponding sulfoxide. Thermal treatment of this sulfoxide in refluxing toluene yielded the eliminated olefin **35** as a single product quantitatively, which was proved to



SCHEME 21

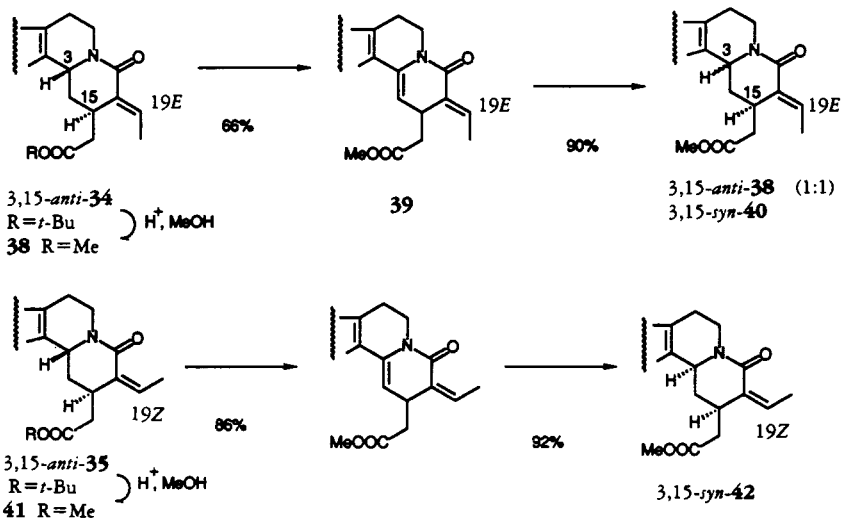
be the 19*Z*-isomer **35** upon comparison with the authentic sample along with spectral assignment.

Similarly, the minor *syn*-adduct **37** was converted into the starting 19*E*-isomer **34** upon similar treatment, thereby establishing the stereochemistry of these two adducts **36** and **37**. The stereoselective addition of thiophenol to ethylidene group in **34** and *syn*-elimination to **35** would be explained in terms of stereoselective attack of thiophenoxide ion to the ethylidene group from the opposite side of the molecule with an axial ester group, thus forming the enolate.

Protonation from thiophenol would occur from the opposite side of the intermediate to form the trans adduct with high stereoselectivity. Elimination of the corresponding sulfoxide proceeds in a manner of forming a cyclic intermediate as shown.

According to the same idea, the back conversion of the unstable 19*Z*-ethylidene group in the key intermediate **35** was also successfully carried out to furnish the stable 19*E*-isomer, thus assuring the result reported by Freund and Winterfeldt (13). Similarly, the isomerization of the ethylidene group in four key intermediates was carried out, thus furnishing four pairs of stereoisomers having *E*- and *Z*-configurations.

*Conversion of 3,15-*anti *configuration into 3,15-*syn *configuration.*—As shown in Scheme 22, the next problem was the epimeric inversion of the configuration at the 3 position, that is, inversion from the 3β-hydrogen to 3α-orientation.

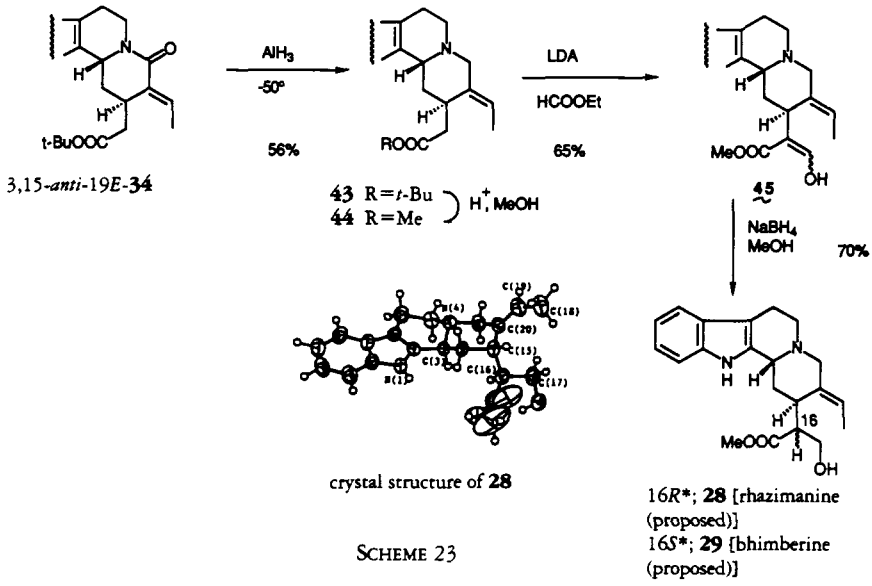


SCHEME 22

For this purpose, we have applied the procedure established by Bohlmann *et al.* (15) in the synthesis of these alkaloids. The key intermediate **34** having H-3β was treated with oxygen in trifluoroacetic acid in the presence of cupric diacetate for the dehydrogenation to introduce a double bond into the 3,14 position. Thus the enamine **39** was obtained and then hydrogenated by $NaBH_4$ in HOAc. The introduction of a double bond occurred smoothly in good yield to give a 1:1 mixture of saturated lactams **38** and **40** which were readily separated.

Similarly, the other key intermediate **35** having 3β-hydrogen was also smoothly converted into the 3α-isomer **42**, thereby completing the synthesis of eight possible intermediary stereoisomers **34**, **35**, **40**, and **42** for total synthesis of alkaloids.

Completion of total synthesis of eight possible stereoisomers of isositsirikines.—The lactam **34**, which has the 19*E*-ethylidene group and H-3β, was reduced with AlH_3 at a low temperature to give the amine **43** in 56% yield (Scheme 23). The *t*-Bu ester was converted into the corresponding methyl ester **44** and then formylated with HCOOEt in the presence of LDA to introduce a formyl group into the 16 position in 65% yield. The formyl derivative **45** was reduced with $NaBH_4$ in MeOH to give 1:1 mixture of saturated compounds **28** and **29**, which were then separated.



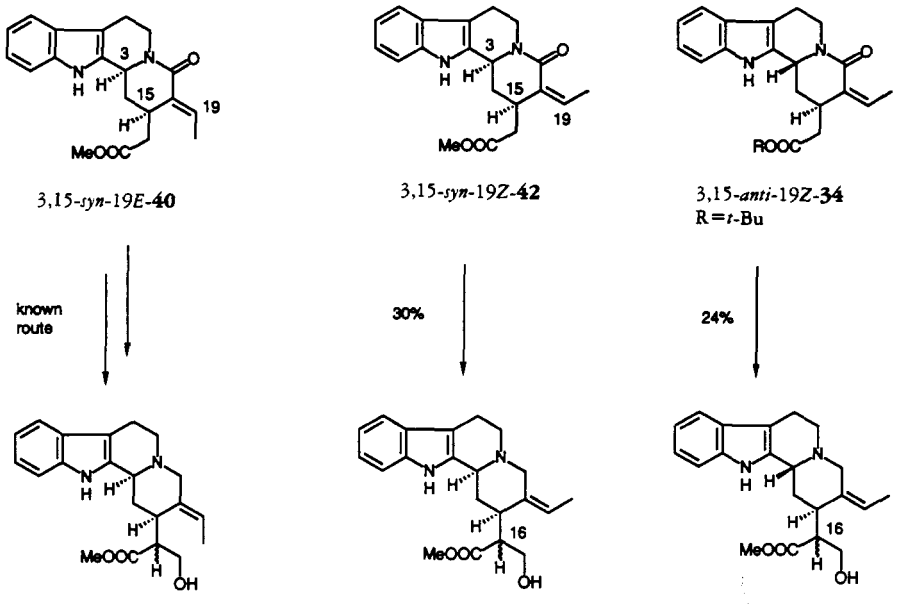
SCHEME 23

Both products have the same structure (including stereochemistry) as those proposed for natural rhazimanine and bhimberine. The structures of the synthetic compounds were unambiguously proved from their spectral data and also by X-ray crystallography (16). However direct comparisons have clearly shown that they are not identical with the natural products; therefore, the structures proposed by Atta-ur-Rahman require reinvestigation. Later, Prof. Winterfeldt has also synthesized the same compounds and reached the same conclusion. Also with the synthetic intermediates **34**, **40**, and **42**, similar synthetic treatment furnished the remaining six stereoisomers **26**, **27**, **30**, **31**, **32**, and **33**, thus completing the synthesis of all eight possible stereoisomers including the alkaloids and unnatural stereoisomers (Scheme 24).

In conclusion, our approach toward the synthesis of the isositsirikine group of alkaloids has proved to be very efficient by producing all members of the stereoisomers of this group of alkaloids from common synthetic intermediates by analogous routes.

PART THREE: DEVELOPMENT OF NEW SYNTHETIC METHODOLOGY: STEREOSELECTIVE ADDITION REACTON OF THIOLS TO OLEFINS.—During the course of our investigation on the synthesis of indole alkaloids having geometrical isomerism in their substituents, we have succeeded in the development of a new stereoselective addition of thiophenol to a double bond. By taking advantage of this finding, we have intensively tackled this problem in order to develop this stereoselective addition reaction as a useful synthetic methodology for natural products.

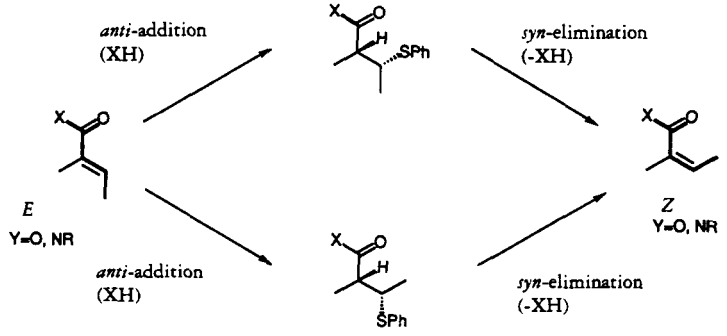
STEREOSELECTIVE ISOMERIZATION OF ELECTRON-DEFICIENT OLEFINS.—As shown in the previous section, we have discovered a new stereoselective addition reaction of thiophenol to a double bond present in the structures of a group of indole alkaloids. The



SCHEME 24

nature of this double bond can be designated as an electron-deficient olefin. Therefore, the results can be depicted in abstracted form (Scheme 25).

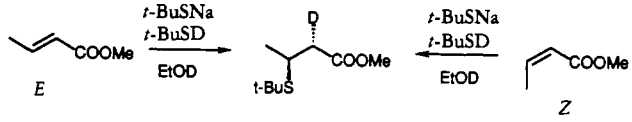
According to the literature, nucleophilic addition of thiophenol to α,β-unsaturated esters has attracted the interests of chemists for many years (17–19). However, stereochemical information is rarely available in the reactions of not only cyclic but also acyclic compounds (20–23).



SCHEME 25

Recently, the stereochemical aspect of the reactions in acyclic systems has drawn the attention of organic chemists, not only from the reaction mechanism standpoint but also from the synthetic point of view. However, only a few cases have been reported. Morig *et al.* (24) reported the stereoselective addition of *t*-Bu mercaptan to crotonates in the presence of base but obtained the same adduct from both *Z*- and *E*-esters, thus showing no stereospecificity (Scheme 26).

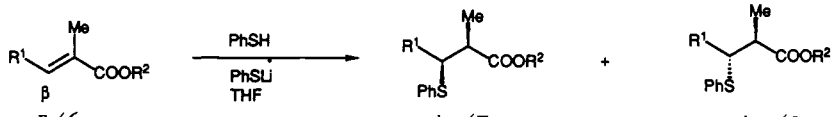
One of the goals to achieve in this respect would be the establishment of a



SCHEME 26

stereospecific reaction, which has recently been discovered in the addition reaction of thiols to electron-deficient olefins (25).

STEREOSELECTIVE ADDITION OF THIOPHENOL TO α,β-UNSATURATED ESTERS AND NITRILES.—The search for the optimal reaction condition for stereoselective addition of thiophenol to electron-deficient olefins was carried out first by using a pair of α,β-unsaturated esters with *E* and *Z* geometry. The results of the addition reaction of thiophenol to the β-position of crotonates with *E* geometry are shown in Scheme 27.



E-**46** *erythro*-**47** *threo*-**48**

a; $R^1=R^2=Me$ **b**; $R^1=Et$, $R^2=Me$ **c**; $R^1=n$-Pr, R^2Me **d**; $R^1=Ph$, $R^2=Me$ **e**; $R^1=t$-Bu, $R^2=Et$	Entry	Substrate	PhSLi (equiv)	PhSH (equiv)	Temp. (°C)	Yield (%)	Ratio **47**:**48**
	1	**46a**	3	3	20	90	91: 9
	2	**46a**	0.1	10	20	99	96: 4
	3	**46a**	0.1	1.2	20	95	94: 6
	4	**46a**	0.1	10	0	59	96: 4
	5	**46a**	—	10	20	—	—
	6	**46a**	Et_3N(3)	3	20	53	93: 7
	7	**46a**	1.2	MeOH	20	—	—
	8	**46a**	1.2	—	20	—	—
	9	**46a**	PhSNa(0.1)	10	20	87	93: 7
	10	**46b**	0.1	10	20	85	87:13
	11	**46c**	0.1	10	20	95	85:15
	12	**46d**	0.1	10	20	99	81:19
	13	**46e**	0.1	10	20	25	57:43[b]

[a]Determined by 200 and 500 MHz ^{1}H nmr.
[b]Stereochemical assignments of **47e** and **48e** have not been established.

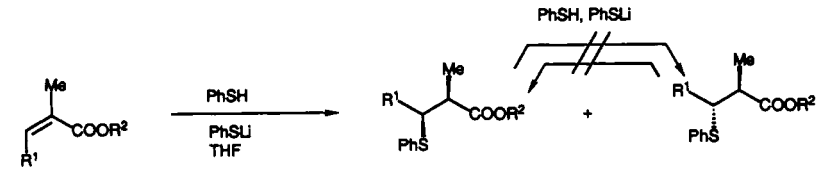
SCHEME 27

The best result was obtained as in the entry 2. The *E*-ester **46** was treated with a 10 equiv amount of thiophenol in the presence of a catalytic amount of lithium thiophenoxide (0.1 equiv) at room temperature. The adduct was obtained in quantitative yield with high stereoselectivity as in the *erythro*-**47**/*threo*-**48** ratio of 94:6, showing preferential formation of the erythro-adduct. In entries 10–13, we investigated the effect of substituents. Except in the case of a bulky group like the *t*-Bu group, good results of stereoselective addition were consistently observed.

The *Z*-ester **49** was used for an addition reaction, shown in Scheme 28, which also proceeded smoothly to give *threo*-**48** as the major product. Since interconversion between these two stereoisomeric products, erythro and threo, was not observed, the results show these adducts as the products were kinetically controlled.

In addition, coupled with previous evidence on the stereoselective formation of the erythro adduct from the *E*-esters, these results show the addition reaction was of a

Addition Reaction of Thiophenol to *Z*-Esters



Z-**49** *erythro*-**47** *threo*-**48**

a; $R^1=R^2=Me$
b; $R^1=Et$, $R^2=Me$
c; $R^1=n$-Pr, $R^2=Me$
d; $R^1=Ph$, $R^2=Me$

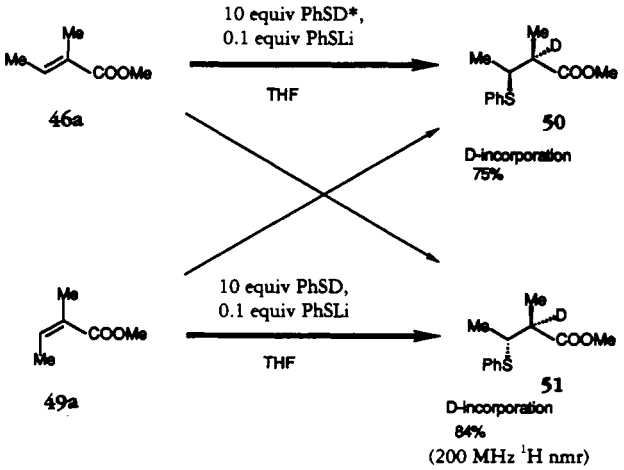
Entry	Substrate	PhSLi (equiv)	PhSH (equiv)	Temp. (°C)	Yield (%)	Ratio[a] **47:48**
1	**49a**	0.1	10	20	85	14:86
2	**49a**	1.2	—	20	—	—[b]
3	**49a**	PhSNa(0.1)	10	20	83	22:78
4	**49b**	0.1	10	20	61	17:83
5	**49c**	0.1	10	20	86	18:82
6	**49d**	0.1	10	20	82	66.34

[a]Determined by 200 MHz ^{1}H nmr.
[b]Isomerization of **49a** to *E*-ester **46a** was observed.

SCHEME 28

stereospecific nature. This has provided the first example demonstrating both stereoselectivity and stereospecificity in the Michael-type addition reaction.

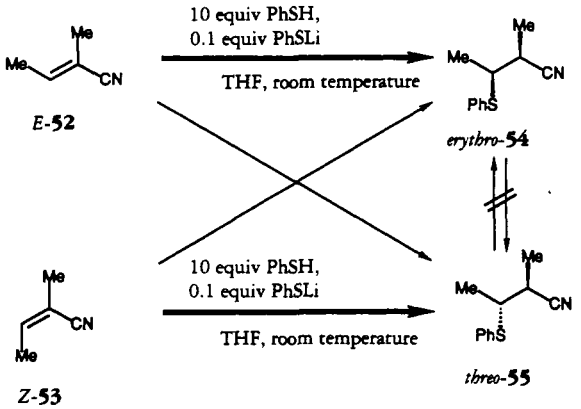
In order to establish the role of thiophenol as a proton source, a pair of isomeric esters **46a** and **49a** were treated with deuterium thiophenoxide in the presence of a catalytic amount of lithium thiophenoxide in THF. With high incorporation of deuterium in both cases, homogeneous adducts **50** and **51** were obtained, thereby establishing the role of thiophenol as a proton source (Scheme 29).



SCHEME 29

Similar stereochemical results were observed on the addition of thiophenol to α,β-unsaturated nitriles **52** and **53** (Scheme 30). *Erythro*-**54** was obtained stereoselectively from the addition reaction to *E*-olefin (**52**) with cyano group, while *threo*-**55** was obtained predominantly from *Z*-olefin (**53**).

ADDITION OF THIOPHENOL TO *E*- AND *Z*-AMIDES.—The stereospecific *anti*-addition shown in Scheme 30 was applied to the corresponding amides to see the scope of the

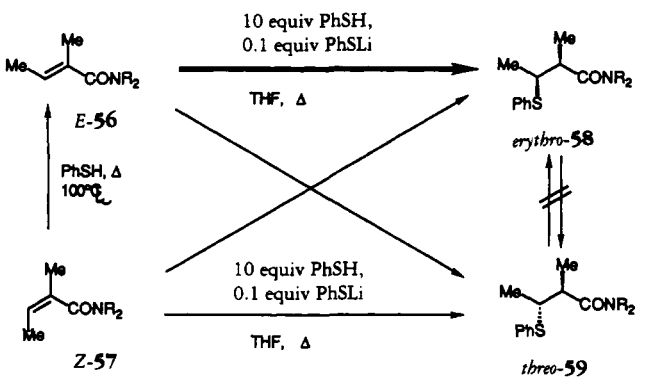


Substrate	Yield (%)	Ratio 54:55
E-52	92	96: 4
Z-53	95	13:87

SCHEME 30

reaction. The addition occurred only at high temperature and the results were different. The *E*-amides **56a–c** underwent smooth stereoselective *anti*-addition under the same condition to afford *erythro*-**58** with the ratio as shown in Scheme 31. The result was a 93% yield of addition product with the excellent ratio of 95:5 as shown in entry 2. On the other hand, when the *Z*-ester **57** was heated at refluxing temperature of THF, the isomerization to *E*-ester occurred preferentially, and then the addition gave the identical *erythro*-**58**. Therefore, the addition reaction in these amides is shown to be stereoselective but not stereospecific.

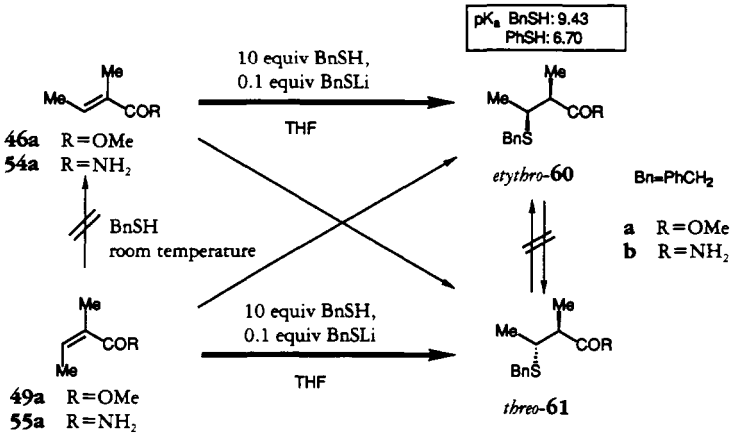
ADDITION OF BENZYL MERCAPTAN.—From the results obtained above, this addition reaction can be carried out at a lower temperature with ease when a thiol such as benzyl mercaptan is used. The high nucleophilicity of benzyl mercaptan allows for the result.



a; R=H
b; R=Et
c; R+R=$(CH_2)_4$

Entry	Substrate	Yield (%)	Ratio 58:59
1	**56a**	93	95: 5
2	**56b**	82	99: 1
3	**56c**	49	96: 4
4	**57a**	92	25:75
5	**57b**	—	—
6	**57c**	trace	50:50

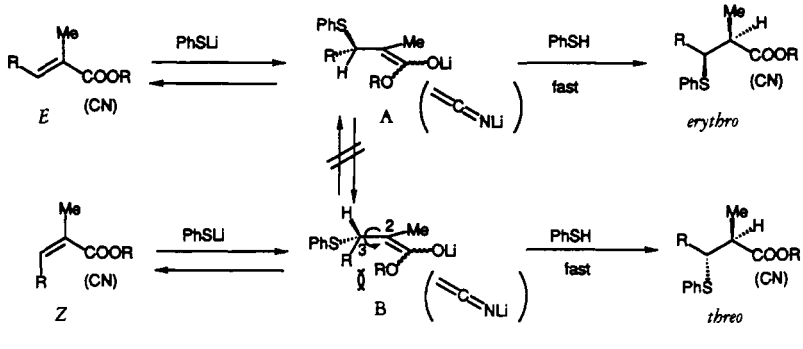
SCHEME 31



Entry	Substrate	Temp. (°C)	Yield (%)	Ratio **60**:**61**
1	**46a**	0	98	98: 2
2	**56a**	0	94	99: 1
3	**49a**	0	98	10:90
4	**57a**	0	88	16:84

SCHEME 32

With these two pairs of esters and amides, benzyl mercaptan was used in place of thiophenol. The addition reaction also proceeded smoothly and as expected to form the corresponding erythro and threo adducts, thus showing the stereospecific nature of the addition (Scheme 32). In entries 1 and 2, both *E*-ester **46a** and amide **54a** afforded the corresponding erythro adducts with very high stereoselectivity, while in the entries 3 and 4, both *Z*-ester **49a** and amide **55a** afforded threo adducts preferentially, thus adding another example of stereospecificity.

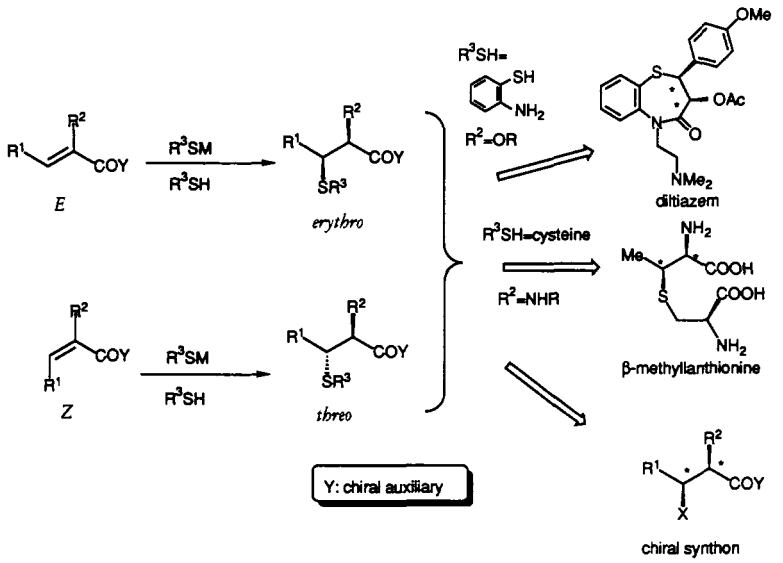


SCHEME 33

MECHANISM FOR STEREOSELECTIVE AND STEREOSPECIFIC *anti*-ADDITION.—We have proposed a stepwise mechanism involving enolate in the presence of lithium thiophenoxide as base (Scheme 33). The *E*- or *Z*-esters would form the corresponding enolates A and B. Apparently from the steric congestion, enolate B would be more unstable than A (26). However, very fast protonation from thiophenol which is present in excess in the reaction solution would occur instantly, and in addition, the presence of a stereoelectronic effect by the phenylthio group present in the enolate determines the direction of protonation

to afford the corresponding products prior to isomerization. The supporting evidence was reported by Chiang *et al.* (26), who reported that protonation to the enolate occurs much faster than to the enol.

SUMMARY OF STEREOSPECIFIC NUCLEOPHILIC *anti*-ADDITION.—It is now established that the stereochemical control of the formation of erythro or threo adduct can be done by the choice of the olefin structure under conditions of the Michael addition, that is, treatment of thiol in the presence of lithium thiophenoxide. From the electron-deficient *E*-olefin in the case of esters, the erythro adduct can be prepared stereoselectively, while the threo adduct can be prepared with high stereoselectivity from the *Z*-olefin. Further, this highly stereoselective addition reaction can be applied to asymmetric introduction of two contiguous stereogenic centers by applying a chiral auxiliary method (Scheme 34) (27).



SCHEME 34

ACKNOWLEDGMENTS

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