THE SYNTHESIS OF 4-SUBSTITUTED INDOLES

AND THEIR ELABORATION TO THE ERGOT ALKALOIDS

by

Paul Hsiao-tseng Liang

B.A., Columbia University
(1977)

Submitted in partial fulfillment
of the requirements for the
degree of

Doctor of Philosophy

at the

Massachusetts Institute of Technology

September, 1981

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Signature redacted

Signature of Author.....
Department of Chemistry
July 31, 1981

Signature redacted

Certified by.....
George H. Büchi
Thesis Supervisor

Signature redacted

Accepted by.....
Glenn A. Berchtold
Chairman, Departmental Graduate Committee

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This thesis has been examined by a Committee of the Department of Chemistry as follows:

Professor William H. Rastetter: Signature redacted
Chairman

Professor George H. Büchi: Signature redacted
Thesis Supervisor

Professor Glenn A. Berchtold: Signature redacted

TO MY MOTHER

AND IN MEMORY OF MY FATHER

Acknowledgements

I would like to express my sincere gratitude to Professor Büchi, not only for his financial support in the form of a research assistantship (1978-1981), but also for his patience and understanding, and especially for sharing a small portion of his creative insights into organic synthesis. His high standards of scientific research will always be remembered.

Another important aspect of the past several years has been the opportunity to meet and exchange ideas, both chemistry and otherwise, with a wide variety of people in our group from different corners of the world. Their often too brief stays in our laboratories have provided an invaluable experience which, along with their unique personalities, will never be forgotten. Their names are too many, but special mention must be made of Hans Wüest and Bernard Muller, both of whom helped me get off on the right track, and of Dr. Daniel Coughlin, with whom I not only shared the latter parts of this project (from 1980, beginning with the longer chained sulfides), but also many nights out on the town.

Financial support in the form of a teaching assistship (1977-1978) from the Department of Chemistry is gratefully acknowledged.

I would also like to thank Manny Francisco for running most of my 250 MHz ^{1}H-NMR's, Mark DuPriest for running my UV's, and Patrick Tong for running my mass spectra. Special thanks to Judy Francisco for typing this manuscript.

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ABSTRACT

A synthesis of 4-substituted indoles is accomplished via a [2,3] sigmatropic rearrangement of a sulfur ylid from the 3-position of an oxindole. Tryptophan is converted to its corresponding 4-methylthiomethyl and 4-carboxaldehyde derivatives. Further elaborations to the ergot alkaloids lysergic acid and clavicipitic acid are investigated.

Thesis Supervisor: George H. Büchi

Title: Camille Dreyfus Professor of Chemistry

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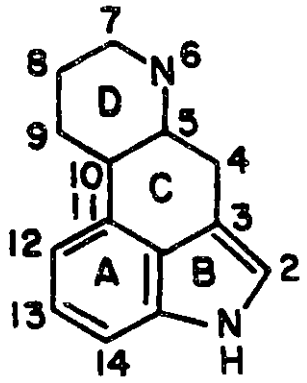
Introduction

The ergot alkaloids[1] are the metabolic products of various species of the parasitic fungus Claviceps. The fact that the most prominent source of these alkaloids is a fungus rather than a higher plant is just one of the many intriging features that have caused them to be the object of much interest. Throughout history, the ergot alkaloids have caused mass poisonings in both man and animals. "Ergotism" or "St. Anthony's fire" was originally a disease which affected Central Europe during the Middle Ages and claimed the lives of thousands of people who ingested bread prepared from rye flour contaminated with the ergot fungus.

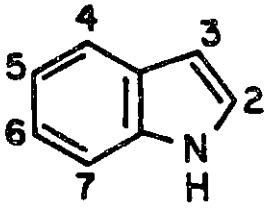
In later years, the more useful pharmacological properties[2] of ergot were recognized. The field of psychopharmacology was initiated by studies of the hallucinogen lysergic acid diethylamide (LSD) which provided the first structural prototype for the development of a whole class of similarly active drugs. The ergots have had a rich and varied history as therapeutic agents and are currently used in the treatment of postpartum hemorrhage, hypertension, and of poor peripheral and cerebral blood circulation, migraine attacks, and prolactin-dependent disorders.

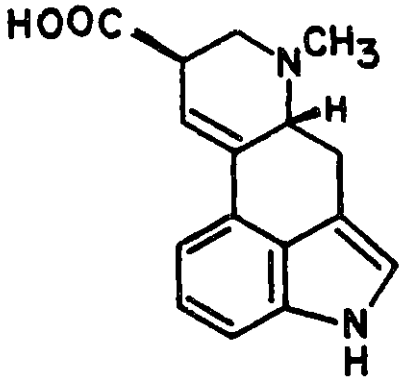
The ergot alkaloids consist of a series of 3,4-disubstituted derivatives of indole, the majority of which possess the tetracyclic ring structure designated as ergoline (Figure 1). Their members can be subdivided into two main groups: the lysergic acid derivatives and the

Figure 1.

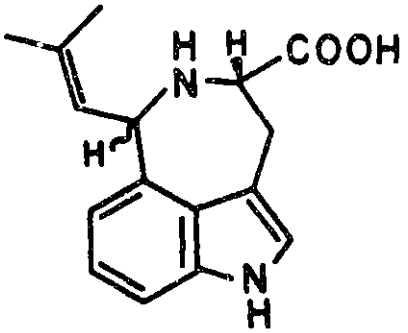


Ergoline





Lysergic Acid



Clavicipitic Acid

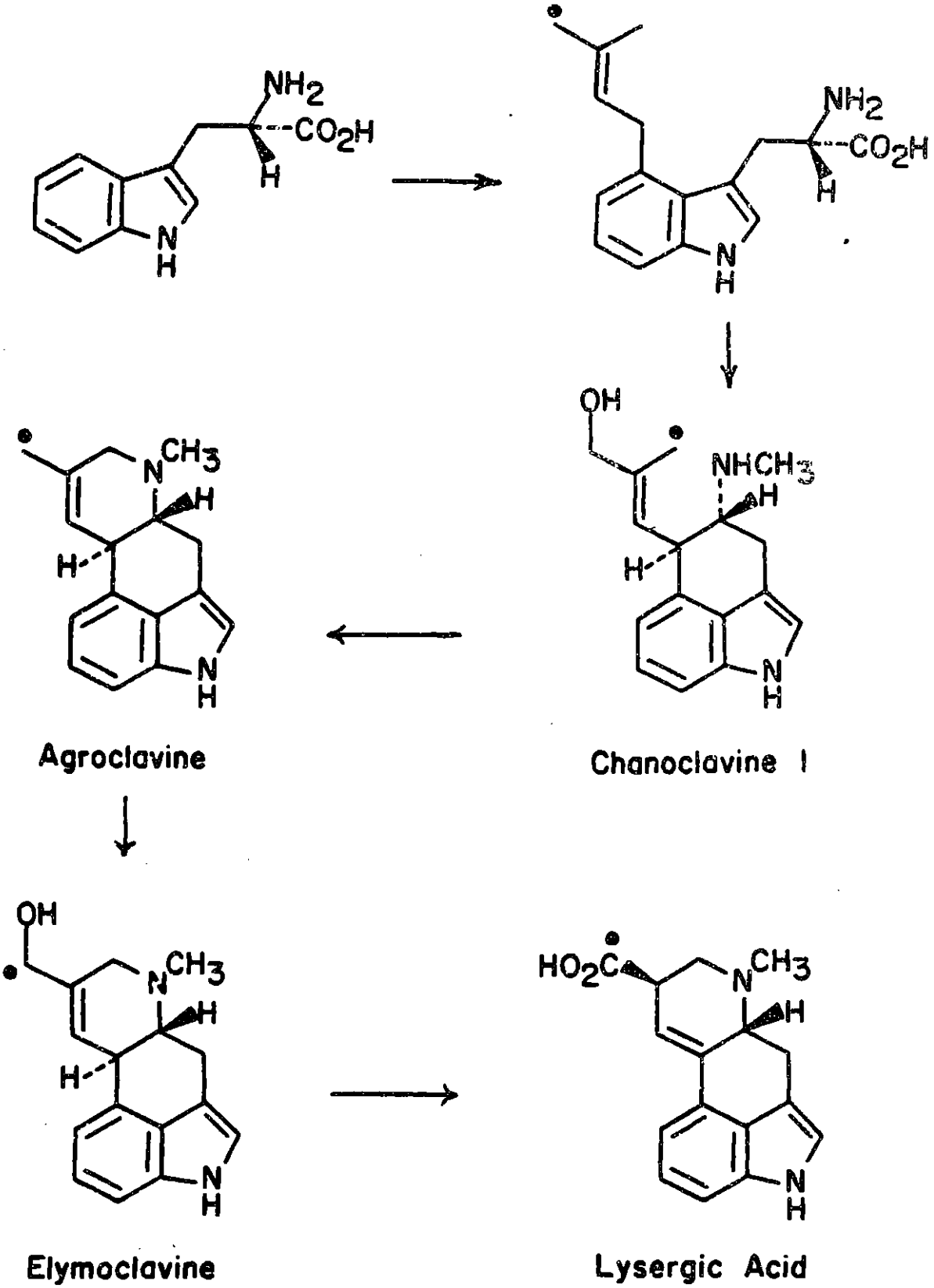
simpler clavine series.

Consideration of synthetic routes to the ergots presents a considerable challenge in the construction of the carbon-carbon bond at the 4-position of indole (or the C_{10}-C_{11} bond of the ergoline skeleton) since most electrophillic attacks prefer the 5 or 7-position.[3] This problem has been overcome in a wide variety of ingenious methods which have been recently thoroughly reviewed.[4]

Our approach to the synthesis of 4-substituted indoles and their further elaboration to the ergot alkaloids, in particular lysergic acid and clavicipitic acid, is based on proposed hypotheses of the mechanistic mode of formation of the known intermediates in the biosynthesis of the ergots. By mimicking the way nature forms these substances, we not only hope to learn more about their biogenesis, but also hope to arrive at a more efficient and elegant synthesis.

In studies of the biosynthesis of lysergic acid (Figure 2)[5] early feeding and incorporation experiments had shown that L-tryptophon is indeed the intermediate alkaloid precursor, which is then isoprenylated at the 4-position. This was proven by the isolation of dimethylally tryptophan and the enzyme catalyzing its formation from ergot cultures in which alkaloid synthesis had been inhibited by the exclusion of oxygen or by the addition of ethionine. Conversion to chanoclavine I involves methyl hydroxylation, decarboxylation and N-methylation, and closure of ring C. The formation of the D ring of agroclavine probably involves chanoclavine I-aldehyde as an intermediate. Interestingly,

Figure 2.

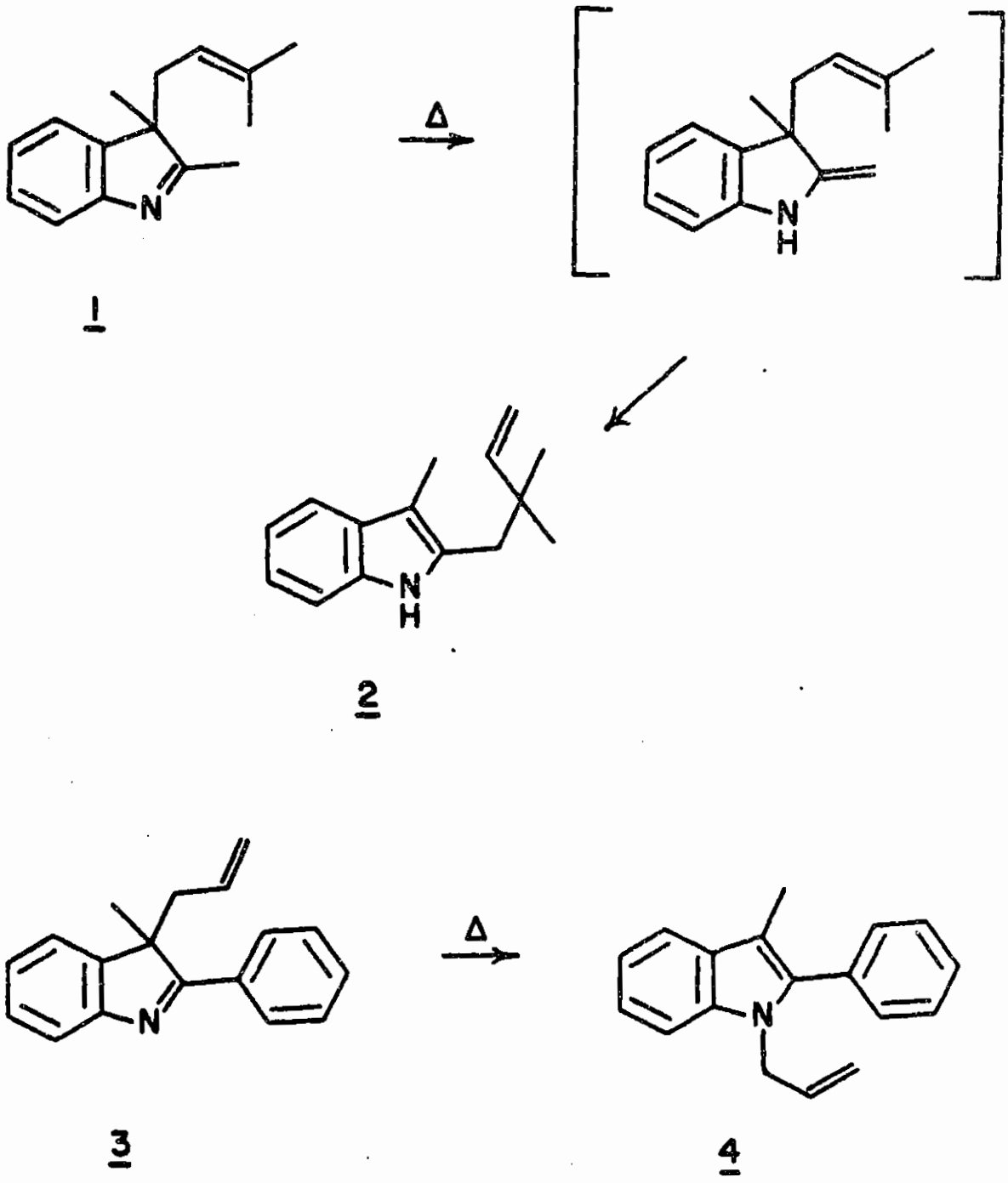

NH2
CO2H
H
N
H
NH2
CO2H
H
N
H
OH
NHCH3
H
H
N
H
N
CH3
H
H
N
H
Agroclavine
Chanoclavine I
OH
N
CH3
H
H
N
H
HO2C
N
CH3
H
N
H
Elymoclavine
Lysergic Acid

this would mean a second cis/trans isomerization of the prenyl olefin to facilitate the ring closure. Other labeling studies have shown that a first isomerization occurs in the formation of chanoclavine I. Agroclavine is then again hydroxylated to elymoclavine which is finally oxidized and isomerized to lysergic acid.

Thus the intermediacy of dimethylallyl tryptophan poses problems since attack of the electrophillic dimethylallyl pyrophosphate should not occur at the electron defficient 4-position. Such considerations led Grigg (Figure 3)[6] to study the alkylation of indoles at the more nucleophillic 3-position and to test the site specificity and ease of sigmatropic rearrangements of these 3-allyl indoles. Heating the indolenine 1 for 15 h at 181° or 4 h at 205° led to an 88% yield of the indole 2. Thus, following the imine-enamine tautomerization, the [3,3] sigmatropic rearrangement occurred to the 2-position. When the 2-position was blocked to prevent enamine formation as in 3, rearrangement occurred onto nitrogen to produce 4. The corresponding indolines were also heated but produced complex mixtures. In any case, no 4-substituted indoles could be detected.

In similar studies, Baldwin's attempted rearrangement of the non-isolated indolenine 6 (Figure 4),[7] produced from the Fischer indole cyclization of the hydrozone 5, only resulted in the N-alkylated product 7. Wenkert's pyrolysis of indoline 8 simply produced various fragmentation products based on the intermediacy of a benzyl-allyl radical pair

Figure 3.



1

2

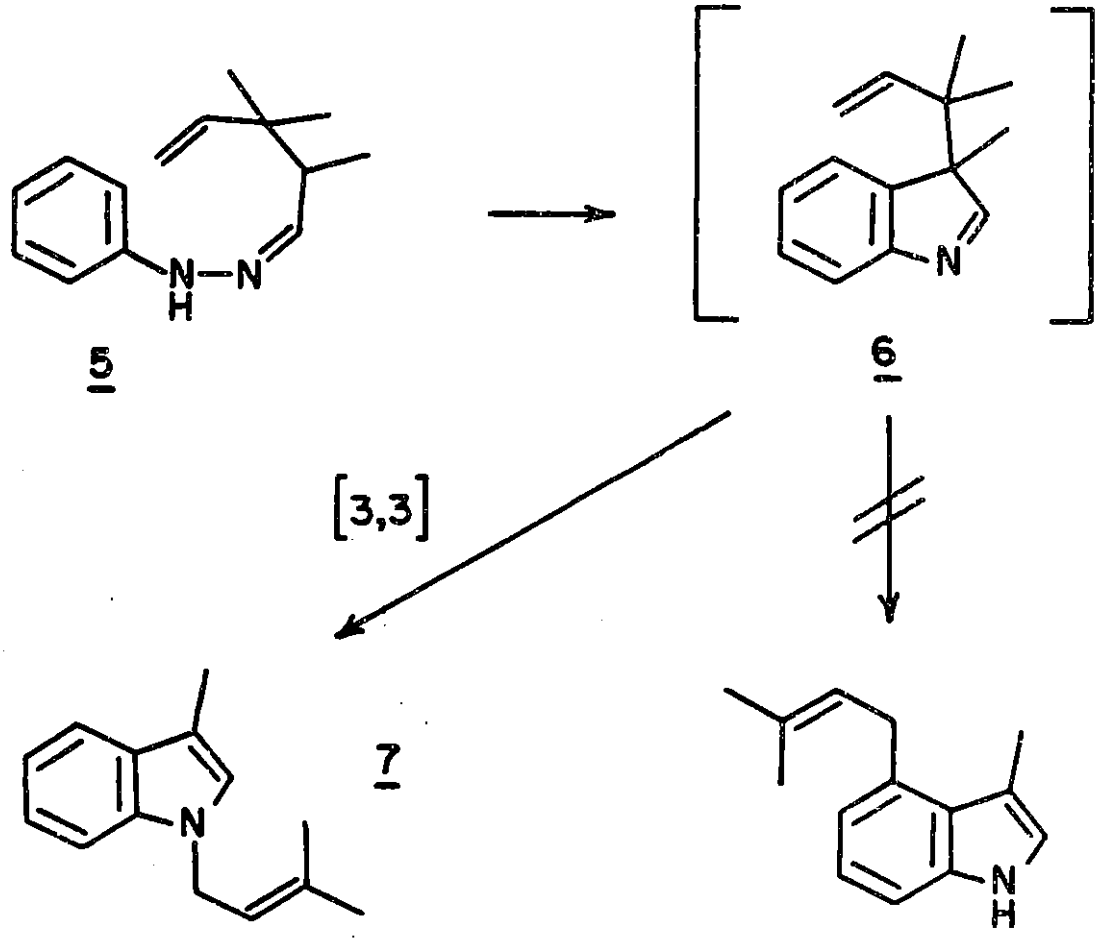
3

4

Order for [3,3] process:

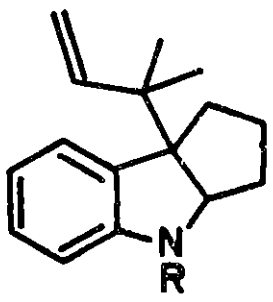
C_2 alkyl > N >>> C_4

Figure 4.



5 6 7

9% yield



8

whose recombination leads to sterically less encumbered products.[8] Thus the feasability of a Cope rearrangement into the benzene ring has been thus far shown to be unlikely.

Another possible source of the 4-substituted indoles is the [2,3] sigmatropic rearrangement of a sulfur ylid[9,10] from the 3-position. Due to the investigations of Revesz (Figure 5),[11] it was concluded that the deprotonation of the sulfonium salt 11, prepared by mixing the tryptophan derivative 9 with a preformed sulfonium complex 10 to give the ylid 13, is much less favorable than the elimination of the sulfide to the indole 12. We therefore began studies on the oxindole derivatives of skatole and tryptophan in the hope that the additional amide functionality would decrease the elimination problem.

After successful functionalization of the 4-position, our two main ergot alkaloid targets were lysergic acid and clavicipitic acid. Lysergic acid[12] has been synthesized by Kornfold/Woodward,[13] Julia,[14] Ramage,[15] and Oppolzer.[16] Our approach (Figure 6) involved elaboration to the imino-diene 14 followed by an intramolecular Diels Alder[17] to form the ring system of lysergic acid.

Clavicipitic acid was isolated and its structure determined by Floss,[18] who called it a "derailment" along the ergoline biosynthetic pathway (after the isoprenylation of tryptophan). Clavicipitic acid is not converted to the tetracyclic ergolines and is a mixture of eprimers at C_{10}, the major isomer having a trans configuration at C_5-C_{10} with

Figure 5.

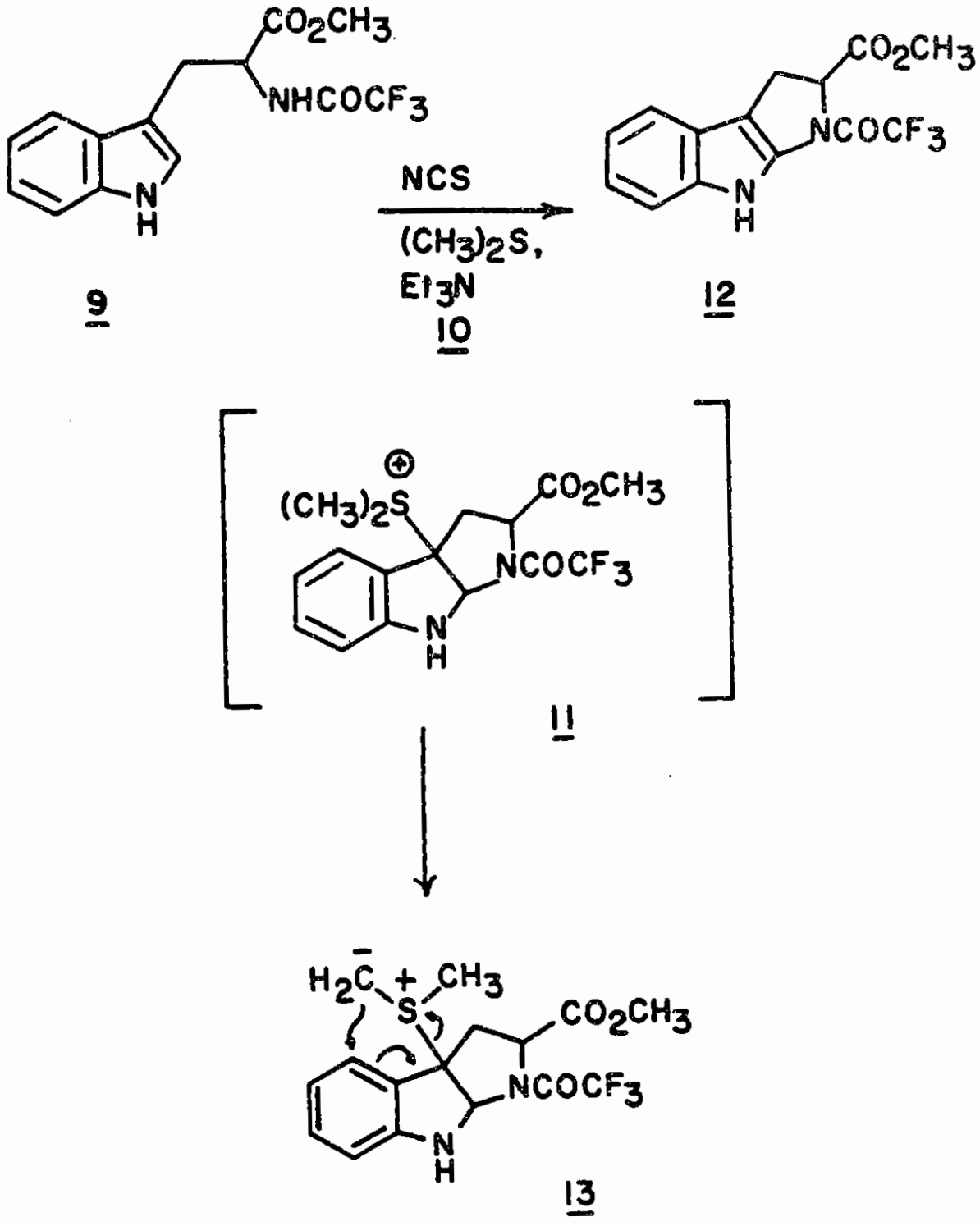
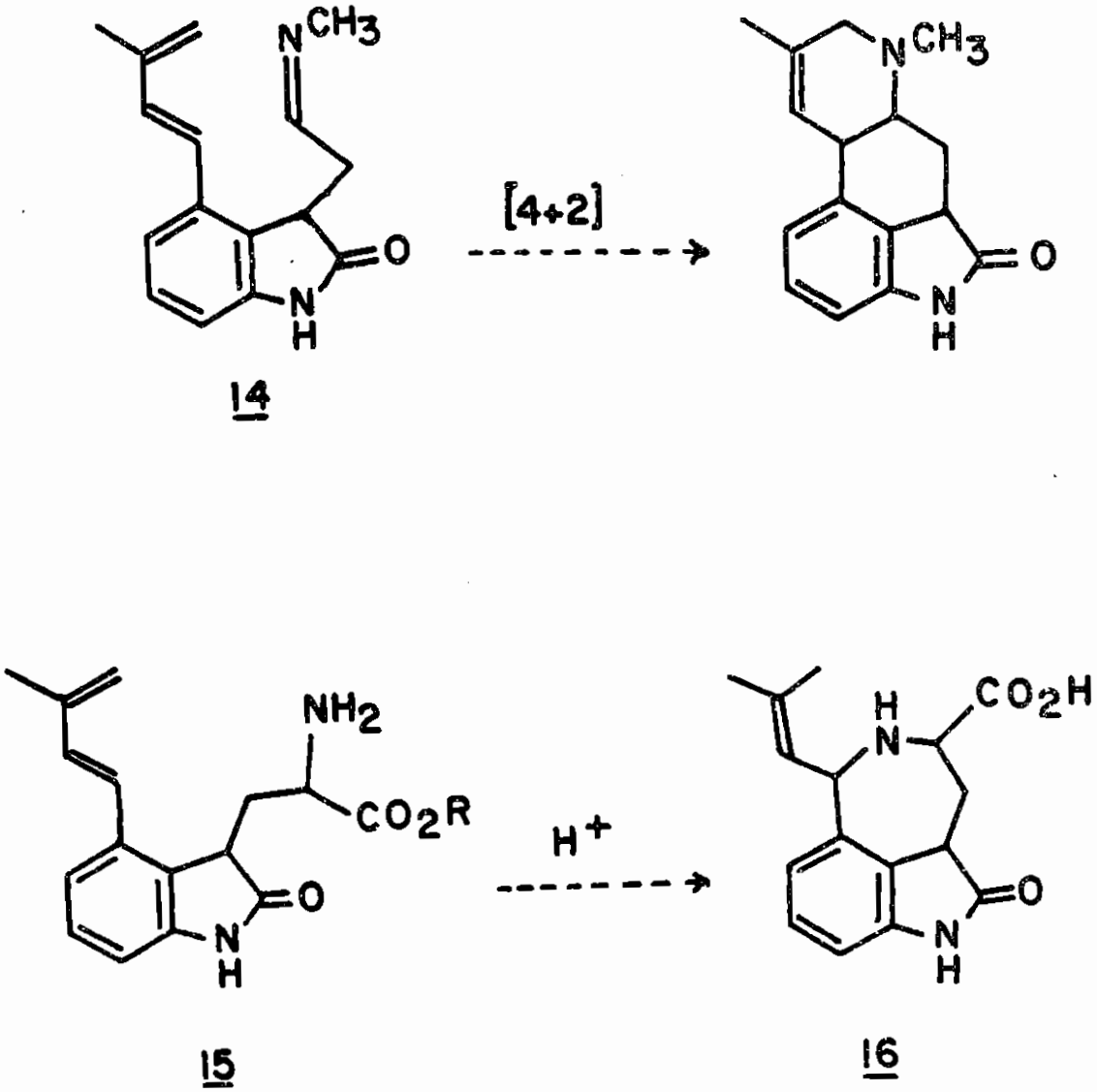

CO2CH3
NHCOCF3
N
H
9
NCS
(CH3)2S,
Et3N
10
CO2CH3
NCOCF3
N
H
12
(CH3)2S
CO2CH3
NCOCF3
N
H
11
H2C
CH3
S
CO2CH3
NCOCF3
N
H
13

Figure 6.



respect to the seven-membered ring. Our initial approach (Figure 6) involved acid cyclized cyclization of amino-diene 15 to form the C-ring 16.

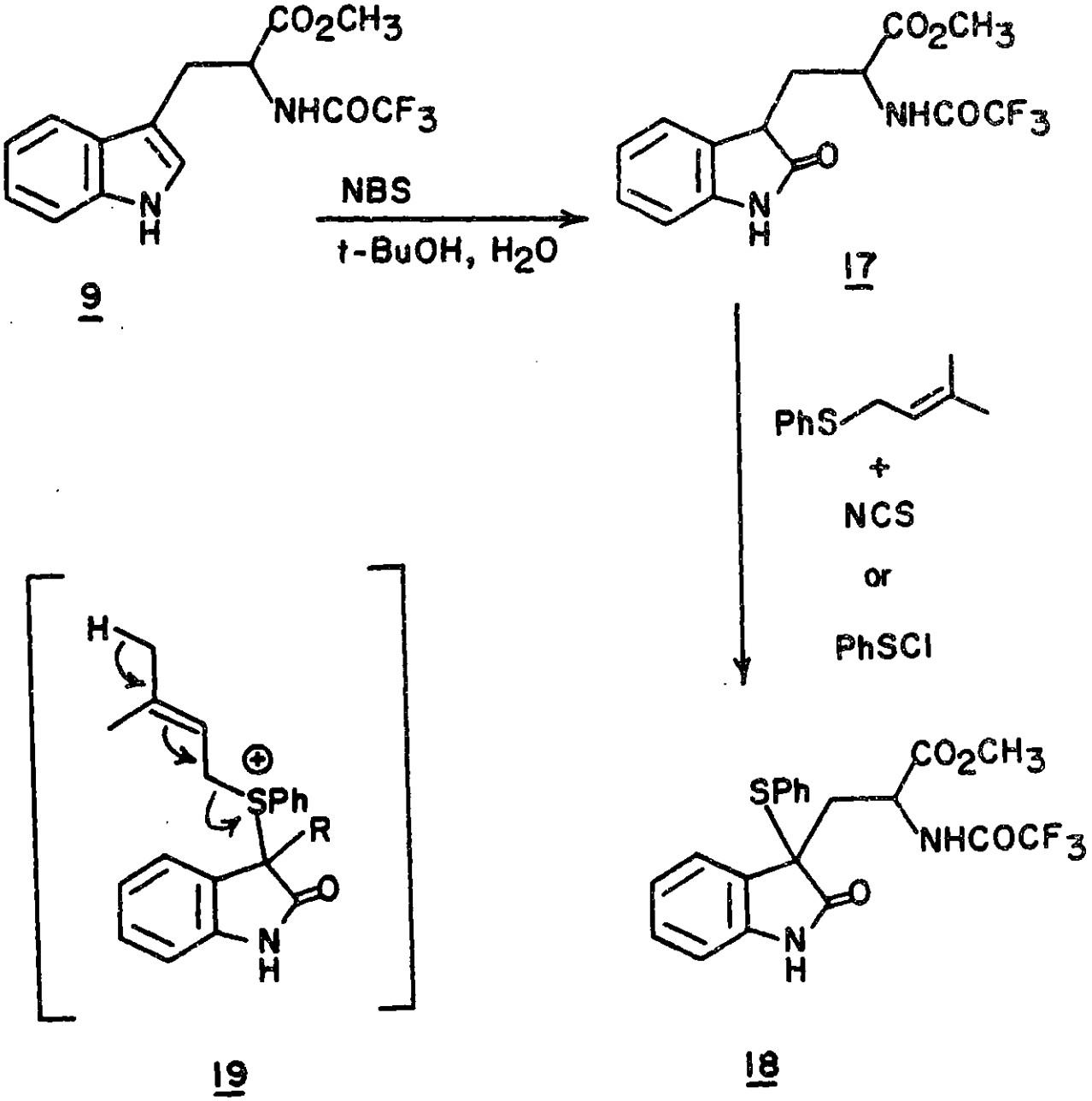
Discussion

A. Rearrangement to a 6-Substituted Oxindole

Our initial approach to the desired [2,3] sigmatropic rearrangement involved alkylation of the 3-phenylthio tryptophan derivative 18 with prenyl halides to form our desired sulfonium salts (Figure 7). A method of preparing 18 involved initial oxidation of the di-protected tryptophan derivative 9 with one equivalent of N-bromosuccinimide in aqueous t-butanol.[19] Careful separation by flash chromatography produced oxindole 17 in 47% yield as a fine white powder, which was treated with phenyl sulfenyl chloride, generated in situ from thiophenol and N-chlorosuccinimide,[20] to form the two diastereomers of the desired sulfide 18 in 45% yield.

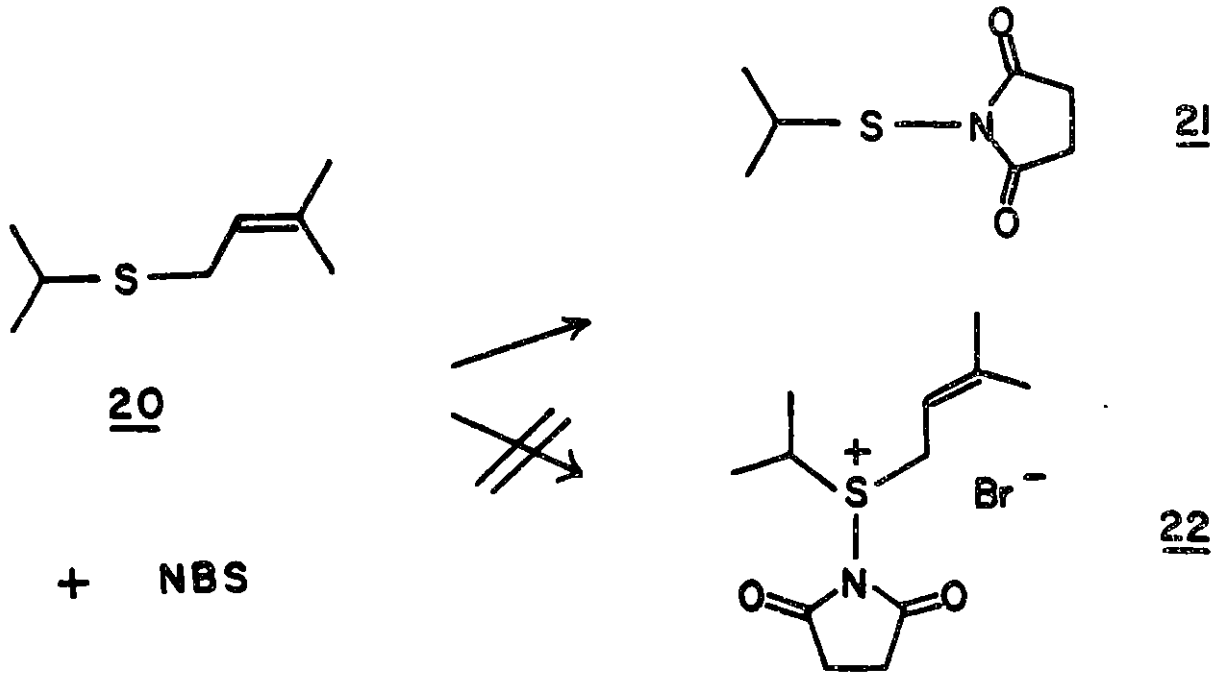
Unfortunately the use of a phenyl sulfide such as 18, rather than an alkyl sulfide (to prevent any possible competitive formation of undesired ylid rather than the prenyl ylid) resulted in lower nucleophilicity and increased steric hindrance of the sulfide. A variety of reaction conditions, including in situ generation of prenyl iodide from the bromide and tetrabutylammonium iodide, and the addition of silver tetrafluoroborale, failed to alkylate the phenyl sulfide 18. The corresponding more nucleophillic para-methoxyphenyl sulfide was also prepared in an analogous manner but again none of the desired sulfonium salt could be formed.

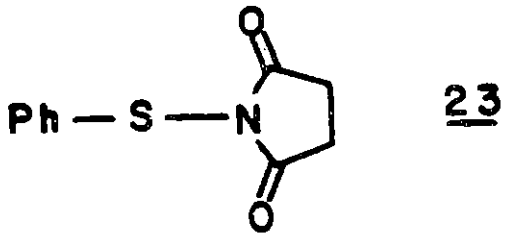
Figure 7.



The direct formation of the sulfonium salt from the unsubstituted oxidole 17 was also investigated. Following standard procedures for generating sulfonium complexes, the phenyl prenyl sulfide was mixed with NCS at 0°,[21] and to this resulting complex was added the oxindole 17. None of the desired salt could be isolated, although upon the addition of sodium methoxide in an attempt to form the ylid, the phenyl sulfide 18

Figure 8.

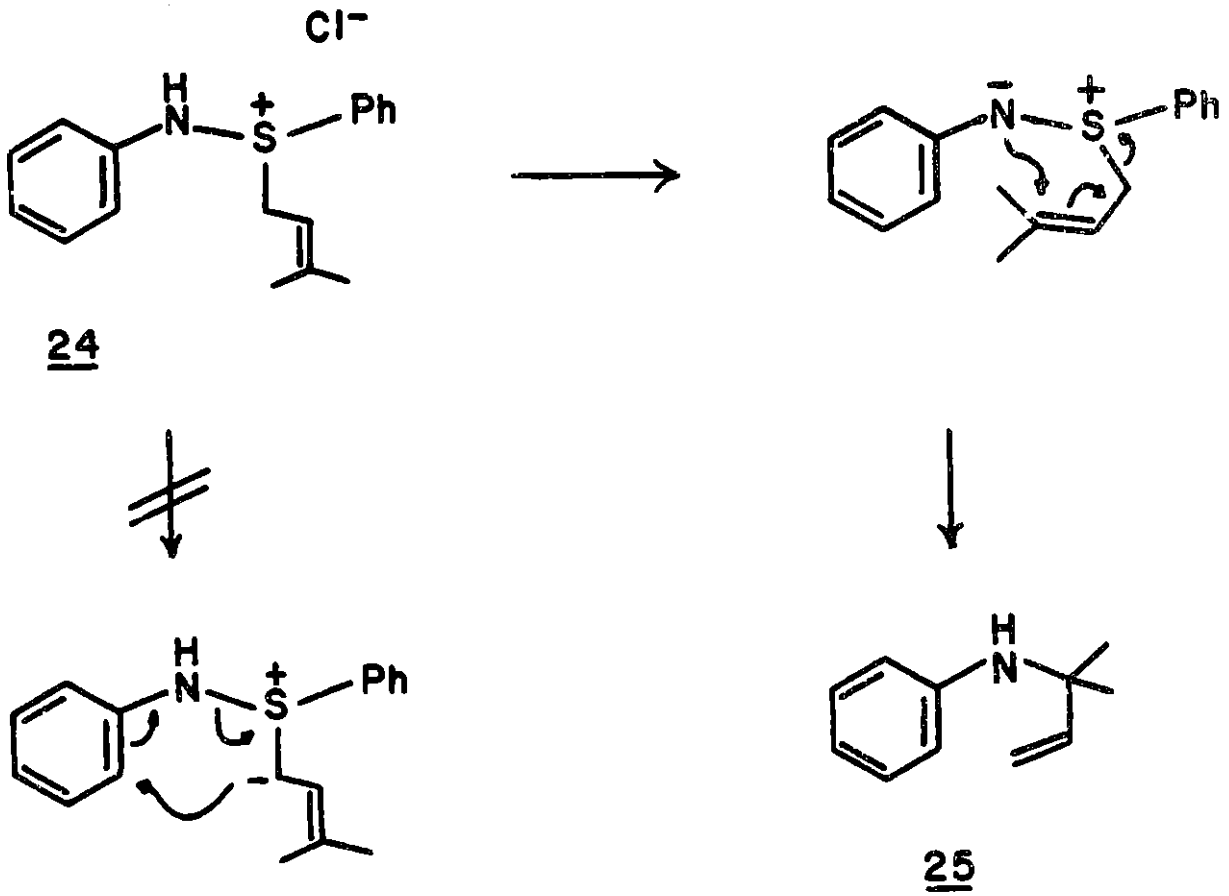




was isolated. If it is assumed that the sulfonium salt 19 had formed, then the methoxide casued the elimination of isoprene. In similar studies, when Baumberger[22] tried to isolate salt 22 (Figure 8), the only product he isolated was the sulfenimide 21. Indeed, the phenyl sulfenimide 23 could be the actual alkylating agent in the formation of sulfide 18.

Thus far the prenyl side chain seemed to be the source of most of

Figure 9.



our problems. In order to test the feasibility of using a phenyl prenyl sulfide in forming a sulfonium salt and rearranging the ylid, the phenyl prenyl sulfide was subjected to the same conditions as in Gassman's synthetic procedure for the ortho functionalization of aromatic amines via intramolecular rearrangements of ylids derived from azasulfonium salts.[23]

When aniline (Figure 9) was combined with phenyl prenyl sulfide, prepared from thiophenol and prenyl bromide, followed by addition of t-butyl hypochlorite, the azasulfonium salt 24 was formed as a deep violet solution in acetonitrile/methylene chloride (3:1) at - 40°. After treatment with sodium methoxide, workup and purification, it was found that the reaction cleanly produced the N-alkylated aniline derivative 25 in 61% yield.

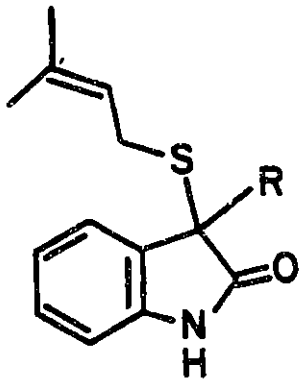
To avoid the undesired rearrangement, N-methyl aniline was used under the same conditions, but not surprisingly, decomposition occurred and no identifiable products were found due to the labile protons of the N-methyl group.

Returning to the original approach of forming a sulfonium salt from a sulfide, it was thought that the reversal of the order of formation of the desired salt might lead to more encouraging results, i.e. first formation of sulfide 26 (Figure 10) with the prenyl group already attached, and then conversion to the salt.

Sulfide 26 could not be formed in the same manner as the corresponding aryl sulfides. Stirring the oxindole with prenyl mercaptan and NCS

resulted in no reaction.

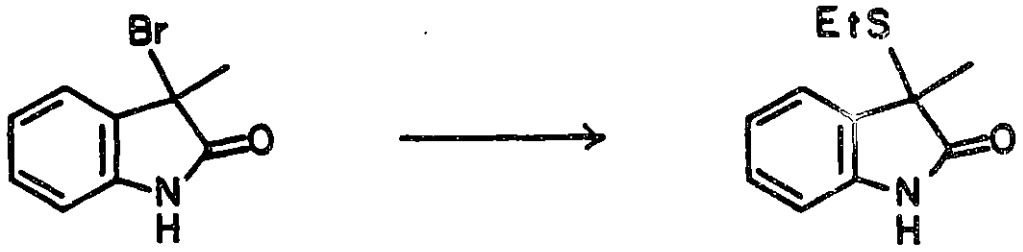
Figure 10.



26

Another approach involved displacement of the very reactive bromine in 3-bromooxindoles. Substitution is known to take place by nucleophiles of the oxygen, sulfur and nitrogen series.[24] It has been reported that the bromooxindole 33, when refluxed with sodium ethyl mercaptide in THF, forms the sulfide 27 in 80% yield (Figure 11).[20]

Figure 11.

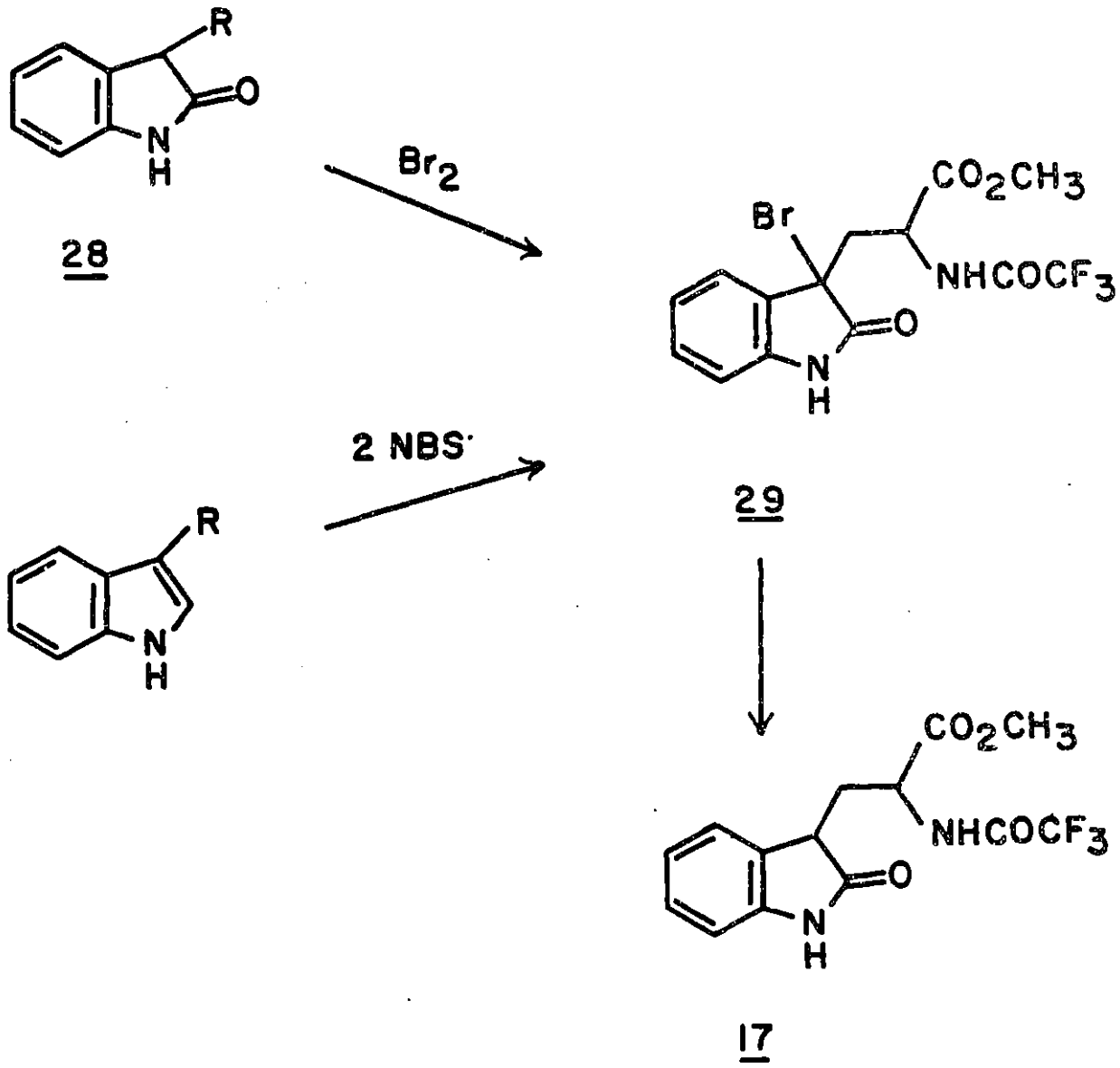


33 27

The desired bromide 29 (Figure 12) can be obtained either by bromination of the oxindole 28 in almost quantitative yield,[20] or more conveniently by direct treatment of the indole with two equivalents of NBS in anhydrous t-butanol.[19]

The sodium prenyl mercaptide was generated by the addition of prenyl mercaptan, prepared by the procedures of Moore and Trego,[25] to a solution of sodium hydride in either anhydrous THF or DMF. If the reaction was

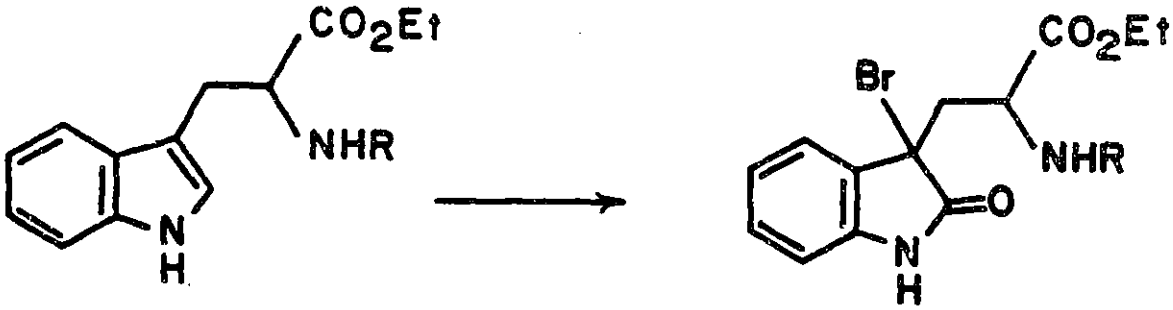
Figure 12.


R
O
N
H
28
Br2
2 NBS·
Br
CO2CH3
NHCOCF3
O
N
H
29
R
N
H
CO2CH3
NHCOCF3
O
N
H
17

carried out in an inverse order, i.e. the sodium prenyl mercaptide added to the bromooxindole, or of only one equivalent of the mercaptide was used, the major product was the unsubstituted oxindole 17.

The maximum yields of the desired sulfide was less than 10%. In order to increase the yield, changes in the protective groups were studied. Since methyl esters are known to demethylate under similar conditions, the ethyl ester 32a was prepared in three steps from tryptophan (Figure 13). The yield did not increase for the displacement reaction and so the nitrogen protective group was next changed to the very stable para-toluenesulfonyl group[26] (compound 32b). Unfortunately, there was almost no detection of the desired sulfide after many attempts at displacement, perhaps due to the bulkiness of the protective groups hindering the 3-position.

Figure 13.



31 A R = $COCF_3$ 32 A

B R = Ts B

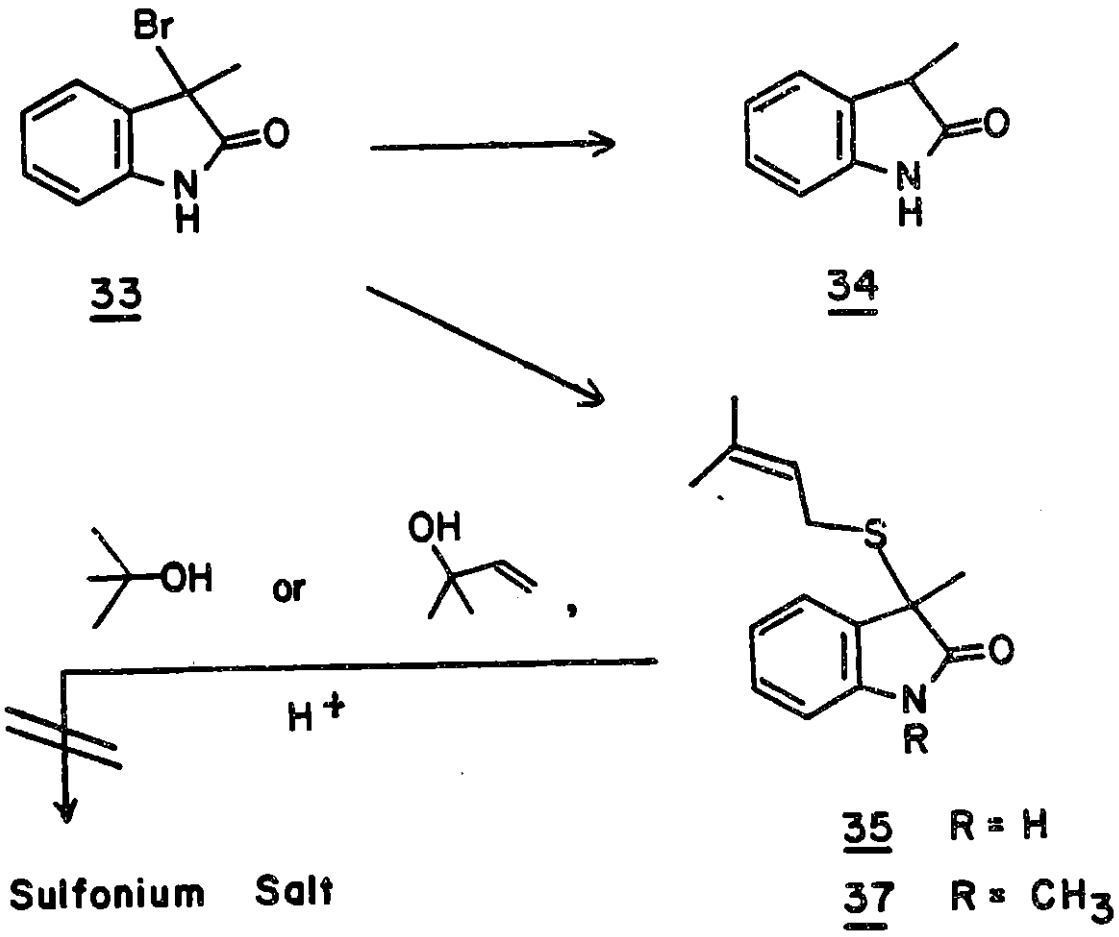
In order to avoid any more difficulties with protective groups, the 3-methyl-3-bromooxindole 33 was prepared from skatole[19] (Figure 14). Attempted displacement with sodium prenyl mercaptide again either failed or produced very low yields of desired product. Attempted duplication of the displacement with sodium ethyl mercaptide resulted in almost exclusive formation of oxindole 34 leading to speculation about the mechanism of the reaction which will be discussed later.

When the bromooxindole 33 was added to a stirred solution of the sodium prenyl mercaptide (prepared by refluxing prenyl mercaptan and sodium in ether followed by collection of the salt) in t-butanol, the desired sulfide 35 was isolated in 15% yield after chromatography and recrystallization into long white needles. Inversing the order of addition increased the yield to 25%.

With the prenyl sulfide side chain in the 3-position, what remained was conversion to a sulfonium salt, again preferrably without any further α-protons. Treatment of 35 with t-butanol or isopropanol and perchloric acid in methylene chloride, a known method for conversion of sulfides to sulfonium salts,[27] was not successful. The harsh reaction conditions resulted simply in decomposition of the starting material. Treatment with dimethylvinylcarbinol and trifluoroacetic acid also resulted in decomposition due to the long reaction times necessary.

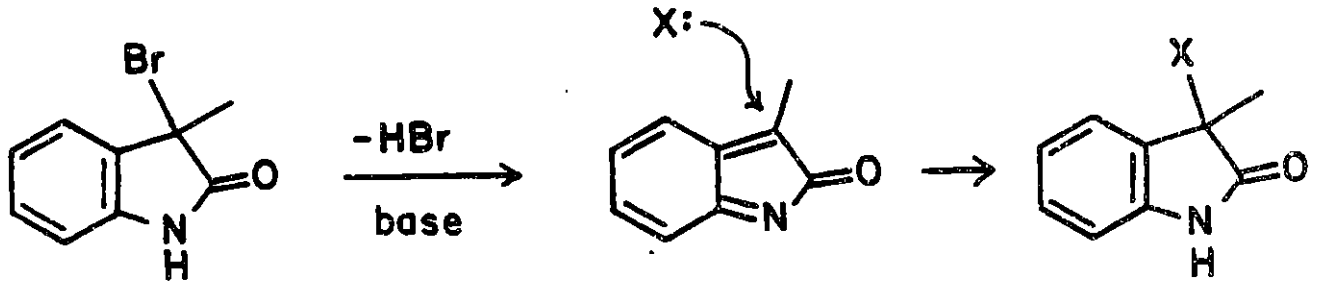
Protection of the amide proton of the prenyl sulfide 35 with sodium hydride/methyl iodide in DMF resulted in the N-methyloxindole 37

Figure 14.

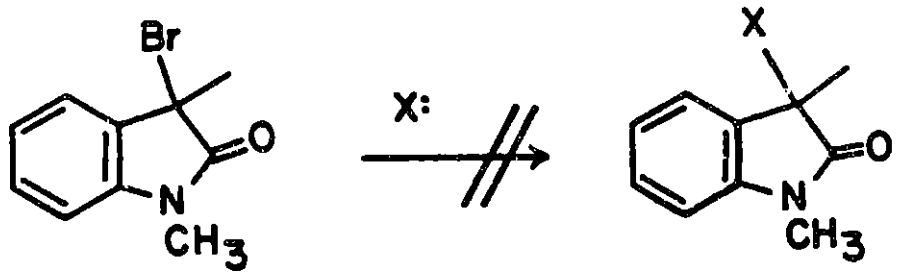


in 98% yield (Figure 14). The amide could not be protected earlier since treatment of the bromooxindole 33 with sodium hydride resulted in decomposition and presumably loss of hydrogen bromide. Also, it was later discovered (see Figures 15 and 23) that displacements do NOT occur at the 3-position of bromooxindoles when the amide proton is replaced by, for example, a methyl group.

Figure 15.



33



36

This again raises serious doubts about the assertion that this mechanism is simply an S_N2 displacement. Perhaps an elimination/addition mechanism would be more feasible.

Further attempted alkylation of sulfide 37 with benzyne, generated either from 2-bromochlorobenzene and butyl lithium[28] or from 2-bromofluorobenzene and magnesium,[29] which would have resulted in simultaneous formation of the desired ylid, did not result in any rearranged products. Alkylation was difficult at the hindered sulfide and more vigorous conditions resulted in decomposition of starting material.

Due to a number of examples of activated α-anions of sulfides rearranging,[30] the prenyl sulfide 37 was treated directly with strong bases under a variety of conditions, often followed by the quenching of the hopefully rearranged mercaptide with methyl iodide. No rearranged products could be detected. Nucleophillic bases such as butyl lithium simply attacked the amide.

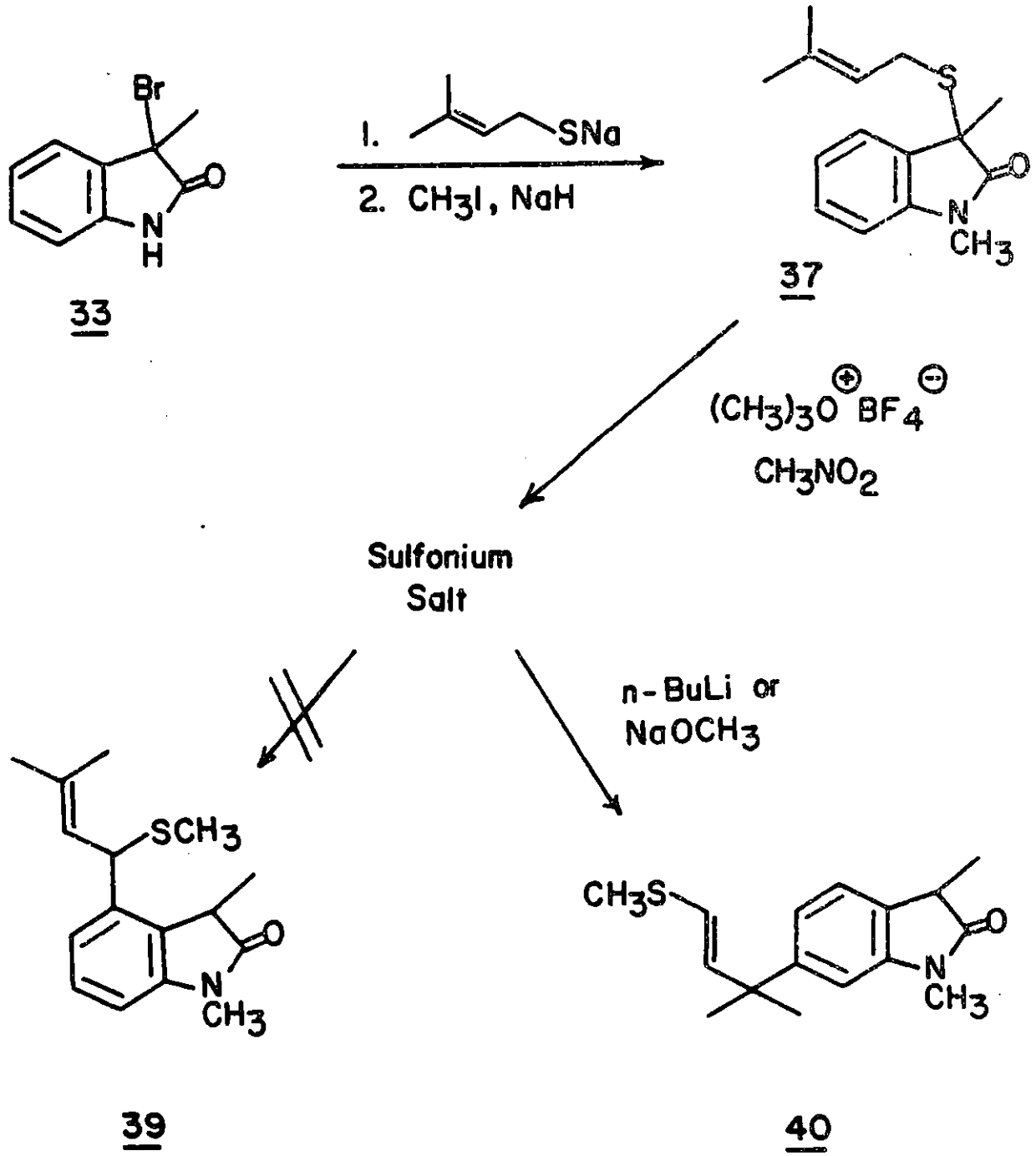
Since the most activated alkyl halides did not alkylate the prenyl sulfide 37, at least under mild enough conditions which could be tolerated, the more reactive trimethyloxoniumfluoroborate[31] was tried. Alkylation was successful but slower compared with the alkylation of other less hindered sulfides. More stringent conditions were needed: excess Meerwein's salt (∿ 2 equivalents), the polar solvent nitromethane, and longer reaction times. TLC monitoring of the reaction never indicated the total disappearance of starting material, and the sulfonium salt could not be

isolated due to its instability caused by the steric crowding of the 3-position. Transfer of solvent to THF and the addition of butyl lithium at -78° followed by slow warming to room temperature over a few hours resulted in a rather clean rearrangement product (Figure 16).

The success of the first rearrangement into the aromatic system of the oxindole was indicated in the NMR by the appearance of a methyl doublet at δ 1.48 coupled to a methine quartet at δ 3.44, the integration of only three aromatic protons, and the methyl sulfide singlet at δ 2.29. The only doubt about the exact structure was raised by the very large coupling constant (J = 15 Hz) between the two protons on the prenyl side chain, which could not easily be explained in the desired product 39. Unfortunately, 270 MHz NMR analysis of the aromatic region indicated the presence of a 6-substituted rather than a 4-substituted oxindole: the two ortho protons at C-4 and C-5 are clearly coupled to each other (J = 6.2 Hz) along with a small meta-coupling between the protons at C-5 and C-7 (J = 1.3 Hz). All the spectral data agrees with the vinyl sulfide 40[32] as the final rearrangement product. TLC monitoring of the hydrolysis of a trace amount of the vinyl sulfide with mercuric chloride in aqueous acetonitrile produced a new spot which gave a positive DNP test for aldehydes.

Proof that rearrangement had occurred after the addition of base was shown when the Meerwein alkylation reaction was concentrated before the addition of base and the NMR of the intermediate did not indicate

Figure 16.


Br
N
H
33
1.
SNa
2. CH3I, NaH
S
N
CH3
37
(CH3)3O⊕ BF4⊖
CH3NO2
Sulfonium
Salt
n-BuLi or
NaOCH3
SCH3
N
CH3
39
CH3S
N
CH3
40

the presence of any rearranged products. Varying the reaction conditions did not produce any 4-substituted products (Table 1).

Table 1.

Condition	Result
1) Standard conditions: 2 equiv. $Me_3O^+BF_4^-$; 1.5 equiv. BuLi at -78°, warm to room temperature.	6-substituted N-methyl oxindole 40
2) Maintaining temp. at -78° (not allowing to warm to room temperature).	"
3) Use of equilibrating bases such as sodium methoxide (excess).	"
4) Use of 1 equiv. $Me_3O^+BF_4^-$.	Mixture of starting material, N-methyl s.m., and 6-substituted oxindole 40.

Analyzing the formation of the 6-substituted product 40 from the prenyl sulfide 37, two mechanisms can be postulated (Figure 17):

a) The desired [2,3] rearrangement occurs but the intermediate 42, rather than aromatizing, immediately undergoes a [3,3] rearrangement followed by aromatization to the final product 40. The [3,3] is facilitated both by the steric crowding of intermediate 42 and by the formation of a vinyl sulfide. Doubts about this mechanism are raised by the facts that the [3,3] occurs at -78°, which is very unusual for a Cope rearrangement which normally require higher temperatures, and that excess base does not affect the reaction by aromatizing intermediate 42 (see Table 1). At least some 4-substituted product would be expected to be isolated, which is not the case.

b) The ylid 41 fragments as shown to the oxindole anion 43 and the sulfonium ion 44 which recombine to form 40. The electrophilic species 44 prefers to react at the tertiary carbon and therefore the oxindole anion must react at the least hindered site, i.e. the 6-position rather than the more crowded 3 or 4-positions.

It was initially hoped that mechanism (a), i.e. consecutive rearrangements, was taking place since it at least involved the intermediacy of our desired 4-substituted oxindole. To test this hypothesis, sulfide 45 (Figure 18) was needed in the hope that the conjugated olefin would less likely rearrange again in the intermediate 46. Also, the carboalkoxy group would be suitably placed in a synthesis of lysergic

Figure 17.

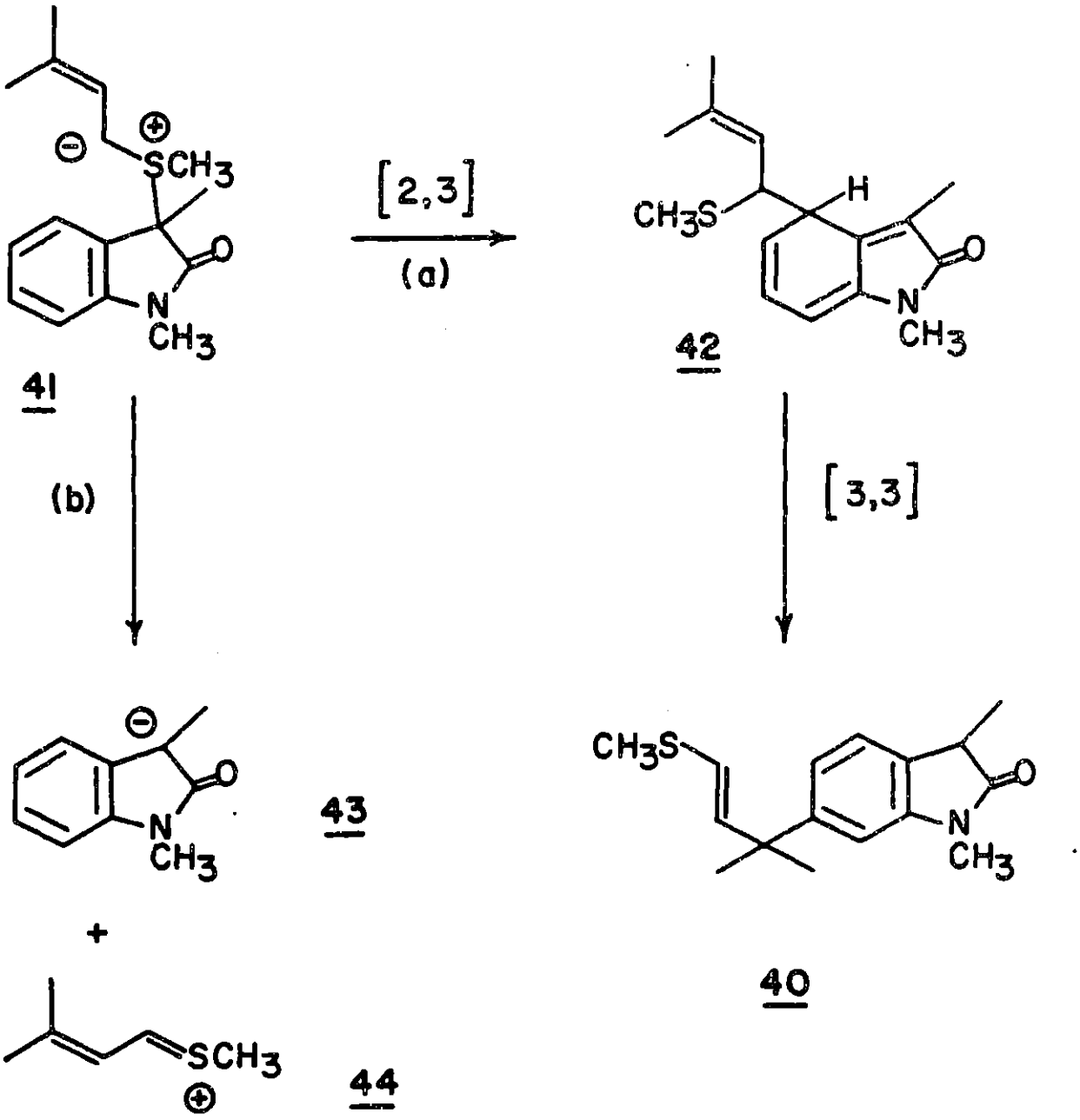
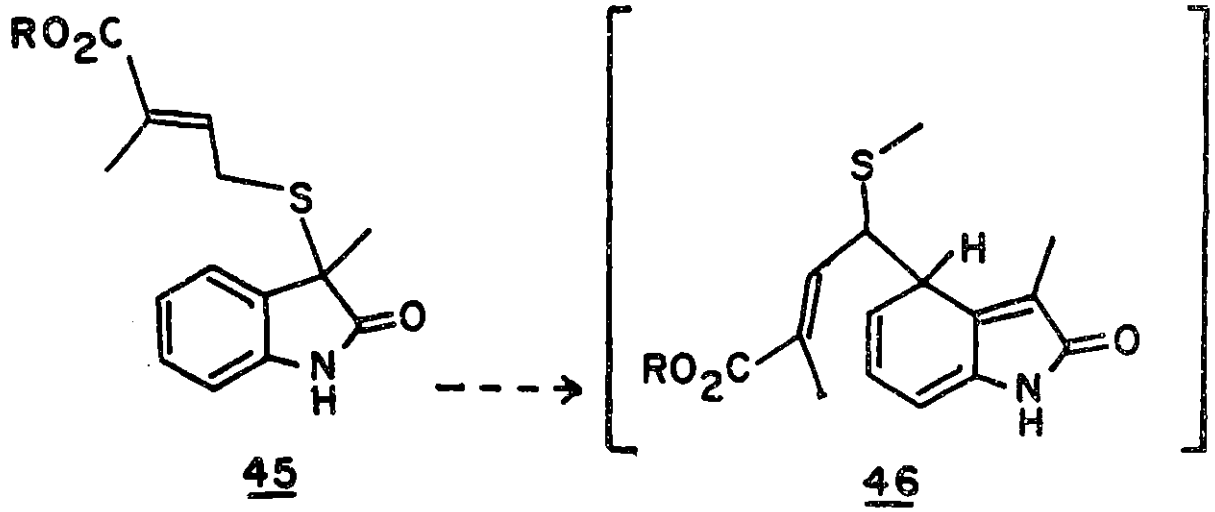


Figure 18.


RO2C
S
O
N
H
45
RO2C
S
H
O
N
H
46

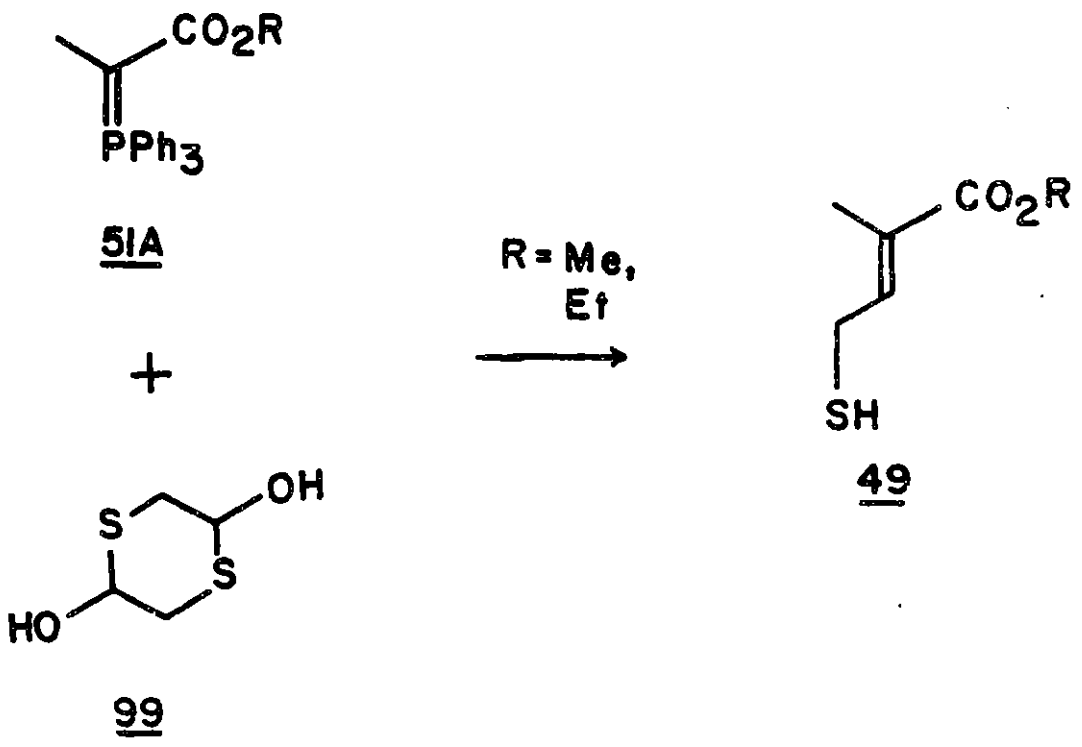
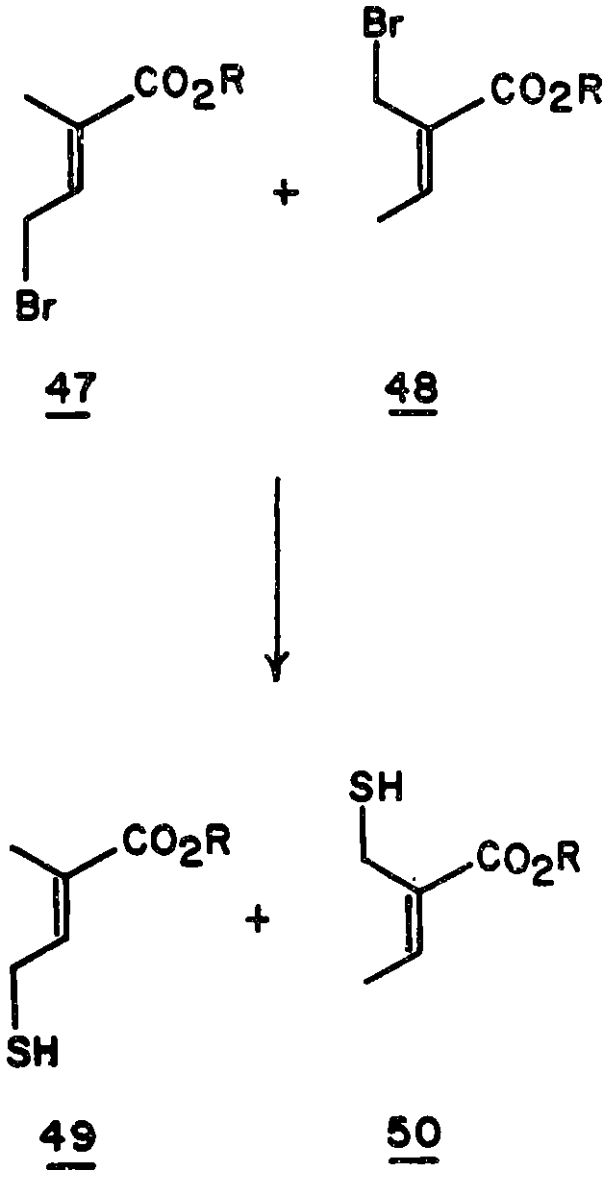

CO2R
PPh3
51A
+
R = Me, Et
CO2R
SH
49
OH
S
S
HO
99

Figure 18 (continued).

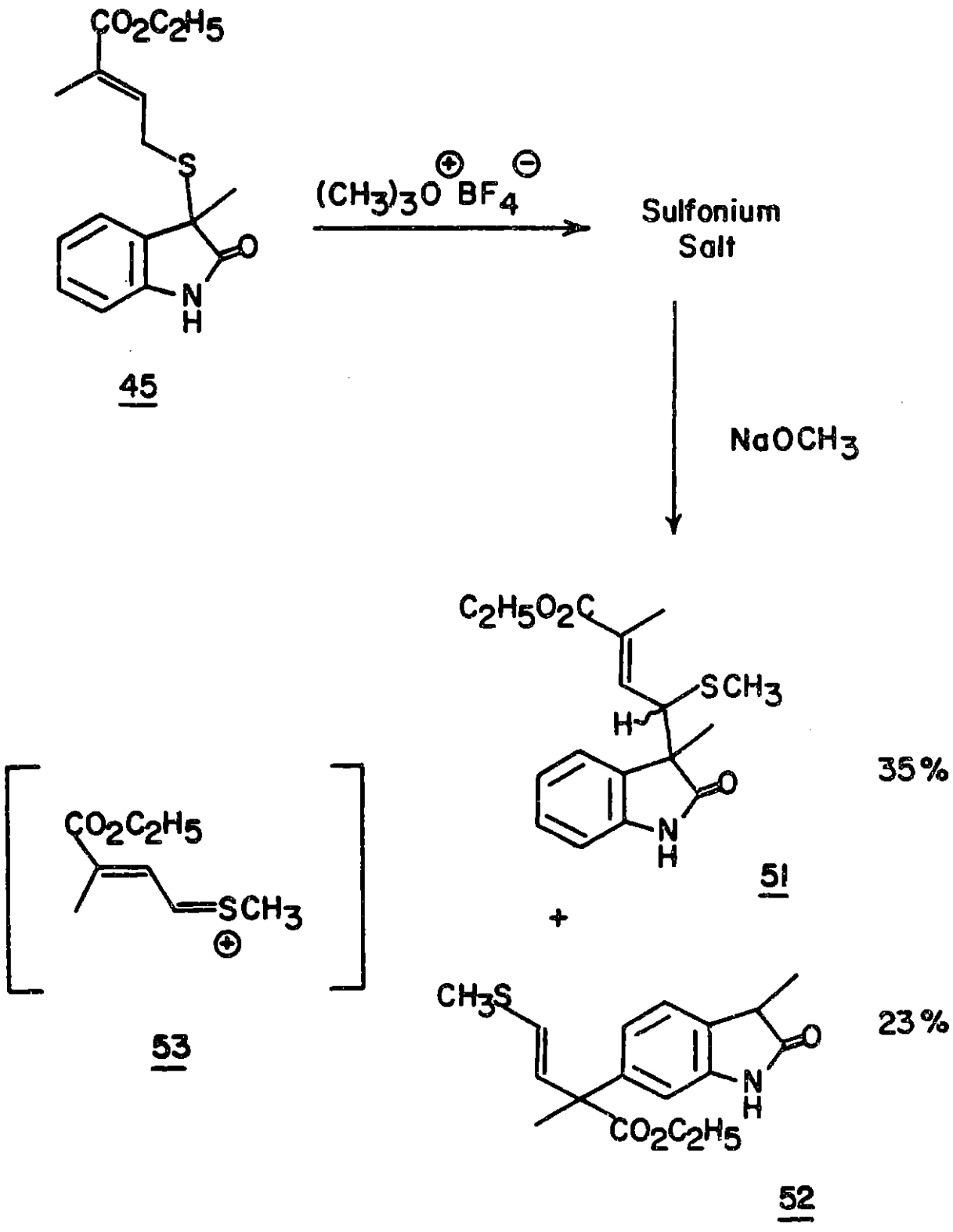


acid.

A 2:1 mixture of bromides 47 and 48[33] was converted to their mercaptans by treatment with thiourea followed by basic hydrolysis and esterification in the hope that the intramolecular hydrogen bonding of 50 would help separate it from 49. The mercaptans proved to be too difficult to separate by conventional means and so a new convenient method of preparing 49 was desired. It was found that stirring the ylid 51a[34] with p-dithiane-2,5-diol 99 in methylene chloride yielded the desired mercaptans in 65-70% after distillation.

Conversion to the sodium salt with sodium hydride in ether (95%) and reaction with the bromooxindole 33 produced the desired sulfide 45 in 31% yield. Treatment with trimethyloxonium fluoroborate followed by ylid formation with sodium ethoxide yielded two main products, both derived from the fragmentation and recombination mechanism proposed earlier (Figure 19). The 6-substituted product 52 could be rationalized as before, but now, because of the added ester functionality of the electrophile 53, recombination can now occur at the less hindered secondary carbon with the more hindered tertiary 3-position of the oxindole to produce 51.

Figure 19.


CO2C2H5
S
O
N
H
45
(CH3)3O BF4
Sulfonium
Salt
NaOCH3
C2H5O2C
SCH3
H
O
N
H
51
35%
+
CO2C2H5
SCH3
53
CH3S
O
N
H
CO2C2H5
23%
52

B. Claisen/Cope Approach

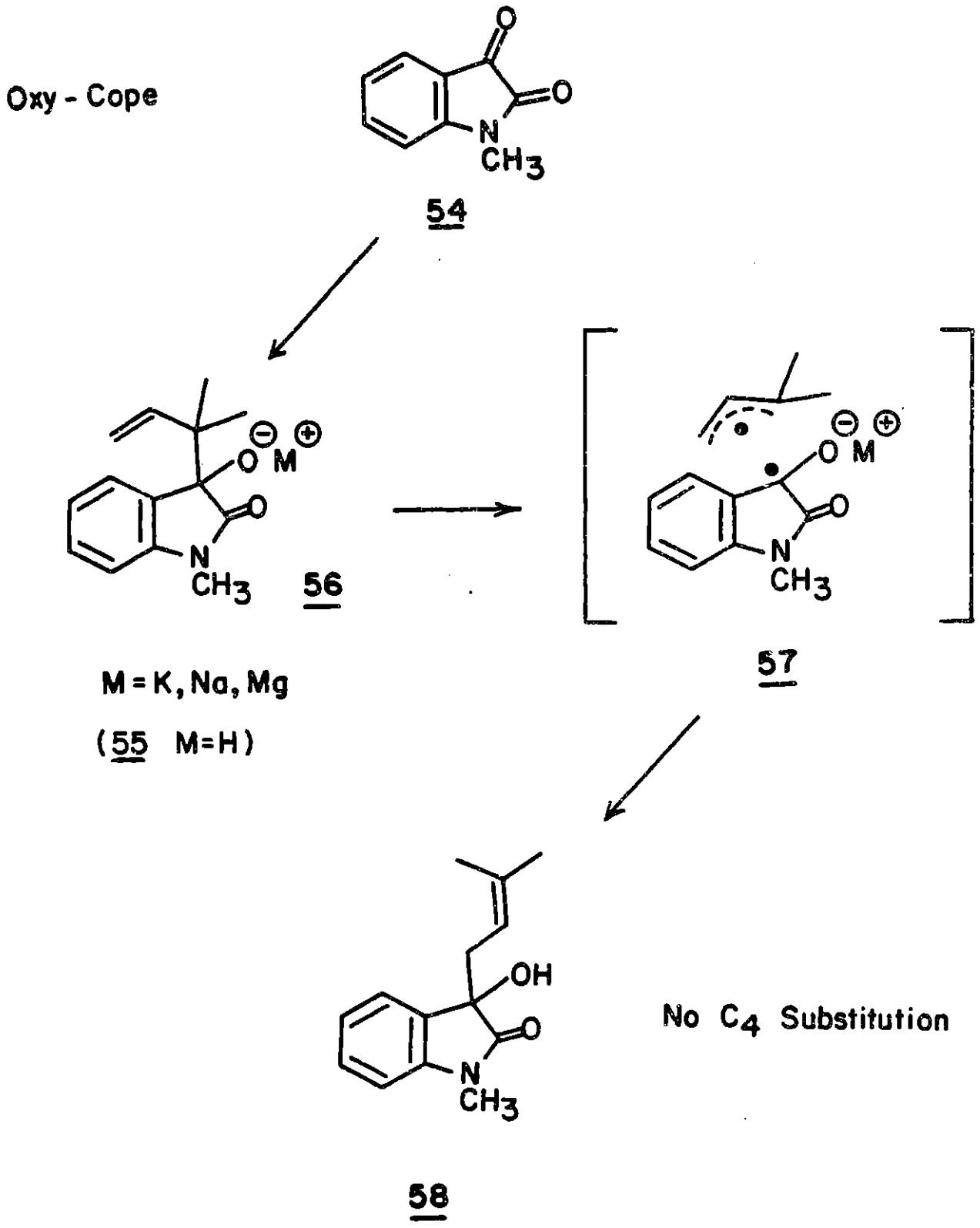
Due to the inability of forming 4-substituted indoles from the sulfur ylid approach thus far, our focus temporarily switched to studying the [3,3] sigmatropic rearrangement[35] as a possible route to the desired indoles.

Although the harshness of the reaction conditions of the Cope rearrangement would not be suitable to the oxindole system, it was hoped that the base accelerated Oxy-Cope[36] would be more compatible and also overcome the unreactivity of the aromatic system. Thus, the desired "dienol" which would produce the 4-prenyl oxindole if rearrangement was successful, was prepared in one step by the treatment of isatin with prenyl magnesium chloride[37] in THF resulting in attack at the more reactive carbonyl in 25% isolated yield. The low yield could be overcome by first protection of the amide with sodium hydride/methyl iodide in DMF to yield an orange solid 54 in 70%, followed by the Grignard to yield the alcohol 55 in 65% as a light yellow orange crystal (Figure 20).

The hydroxy oxindole 55, when treated with potassium hydride in DME at room temperature, immediately fragmented and recombined to the 3-prenyl derivative 58 in quantitative yield.

The desired bond to be broken in the rearrangement is obviously too weak due to the severe steric crowding to withstand conditions for rearrangement. TLC monitoring of the reaction seconds after the addition of base indicated the total disappearance of starting material and

Figure 20.

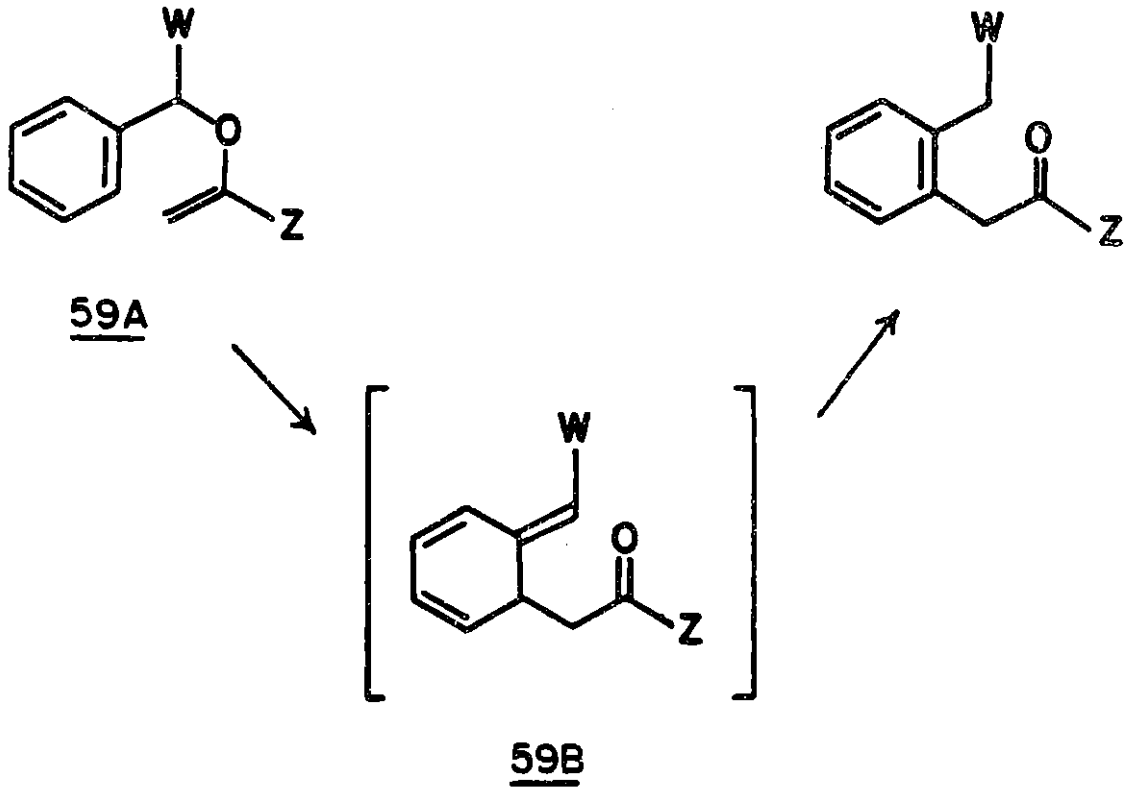


appearance of product in a very clean reaction. To help suppress the cleavage reaction, the ionic character of the metal alkoxide bond was decreased by employing the more electronegative alkali metal Na^+ rather than K^+, and by trying solvents of weaker solvating capacity (THF and then ether), but the final results did not change as the very facile cleavage and recombination to the less hindered end of the pernyl group predominated. Even heating of the magnesium alkoxide resulted in 58, and relfuxing the alcohol 55 in xylene slowly resulted in the emergence of 58 after 5 hours.

Although the Claisen rearrangement[38] of allyl phenyl ethers[39] is well exemplified, the [3,3] sigmatropic rearrangement of benzyl vinyl ethers 59a (W = H) is generally not possible. However, a suitably positioned substituent W greatly facilitates the rearrangement by stabilizing the intermediate 59b[40] (Figure 21). An example is the reaction of ethyl mandelate derivatives 59c in the Claisen ortho ester rearrangement providing regiospecific syntheses of substituted arenes 66. The nature of X, whether electron donating or electron withdrawing, does not affect the reaction, which is also compatible with a wide array of functionality.

This reaction is ideally suited for our oxindole system due to the position of the amide to stabilize the rearranged intermediate. The desired starting alcohol 62 has been prepared by Himman and Bauman[24] by the reaction of bromo oximole 33 with sodium bicarbonate in aqueous

Figure 21.



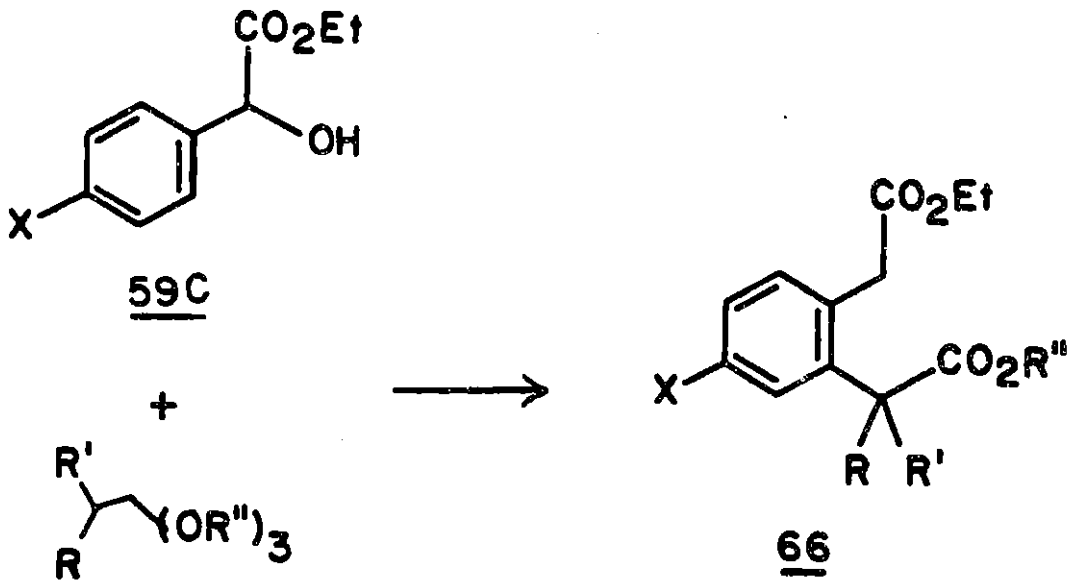
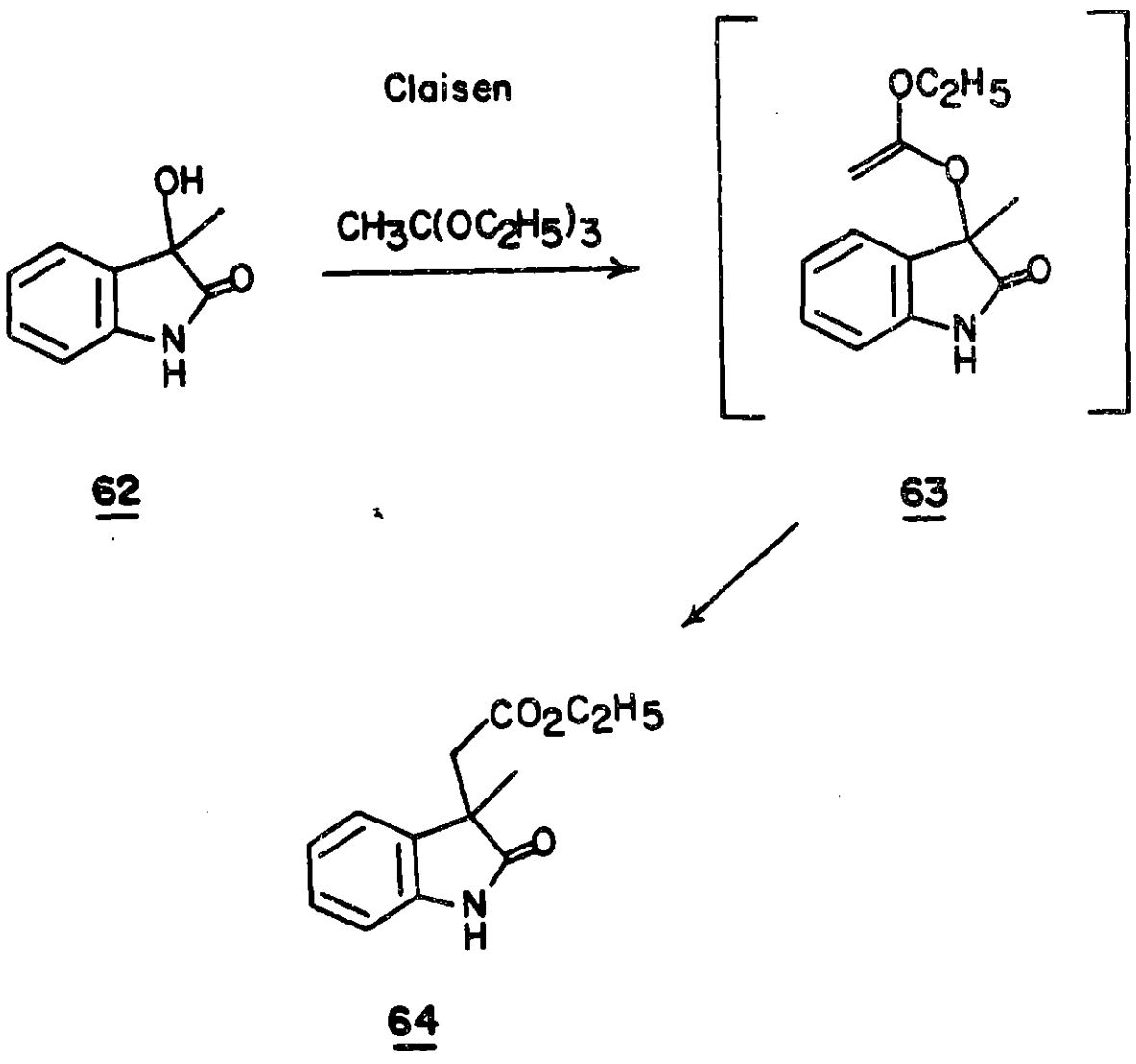


Figure 22.



62 63 64

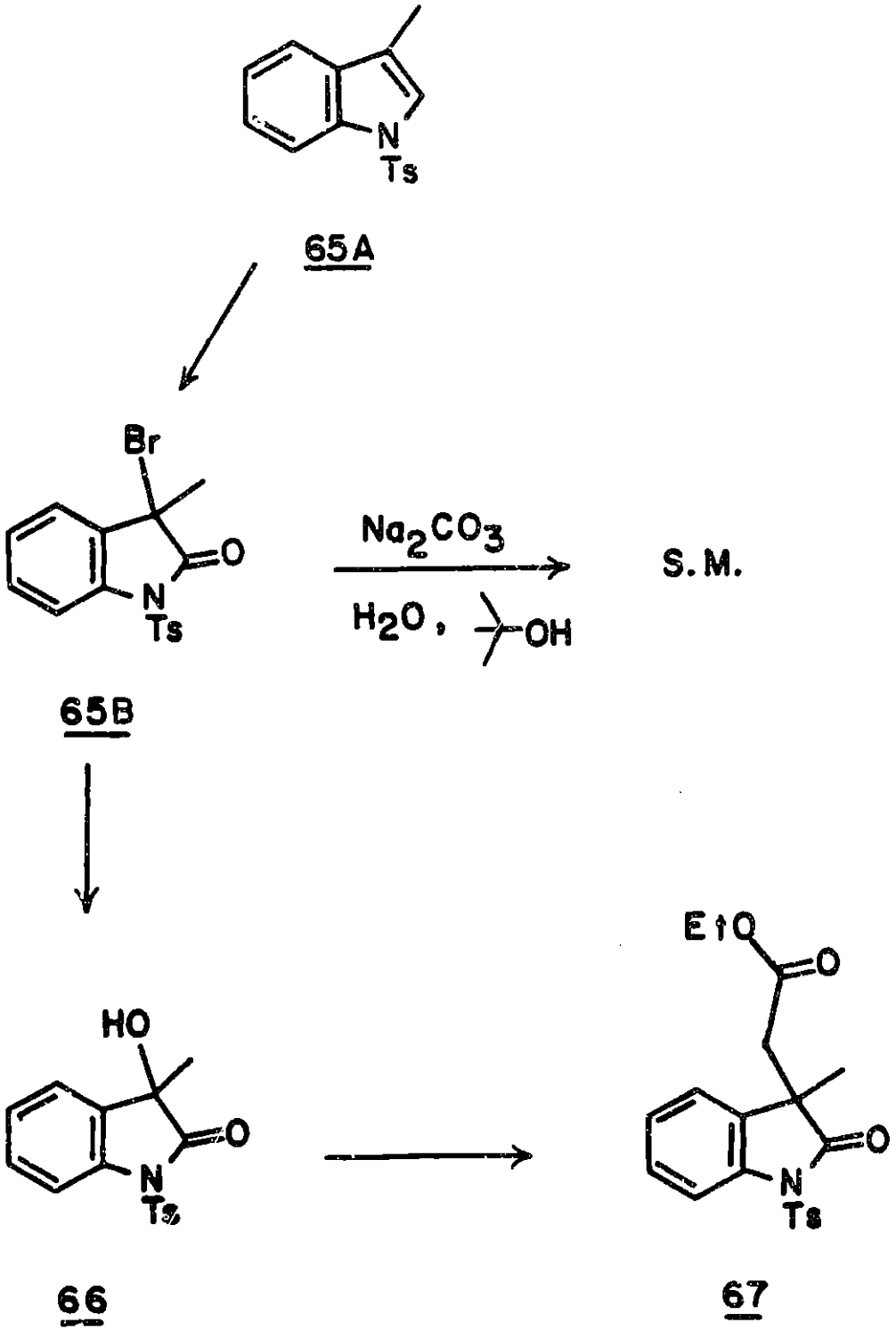
No C_4 Substitution

t-butanol in 84% yield (Figure 22). Heating the hydroxy oxindole 62, triethylorthopropionate and catalytic hexanoic acid up to 220° yielded again the fragmentation product 64 in 32%. Similar results were obtained with triethylorthoacetate.

In order to test the effects of an electron withdrawing group on the fragmentation process, N-tosyl skatole 65a was prepared in 83% yield from the treatment of skatole with sodium hydride/tosyl chloride. Oxidation with two equivalents of N-bromosuccinimide in t-butanol gave the bromo oxindole 65b in 27%. Stirring 65b with sodium bicarbonate in aqueous t-butanol as before die NOT produce the desired alcohol 66, but resulted simply in isolation of starting material (Figure 23). This again lends doubt to the proposed mechanism of this reaction as simply being an S_N2 displacement at the tertiary center since its success depends on the free N-H of the oxindole being available. However, this problem was overcome by the addition of silver acetate to a solution of the bromo oxindole 65b in aqueous THF to yield 66 in 60%. Heating 66 with triethylorthoacetate still produced the fragmentation product 67, although in poorer yield (13%) due to greater decomposition. No 4-substituted product could be detected.

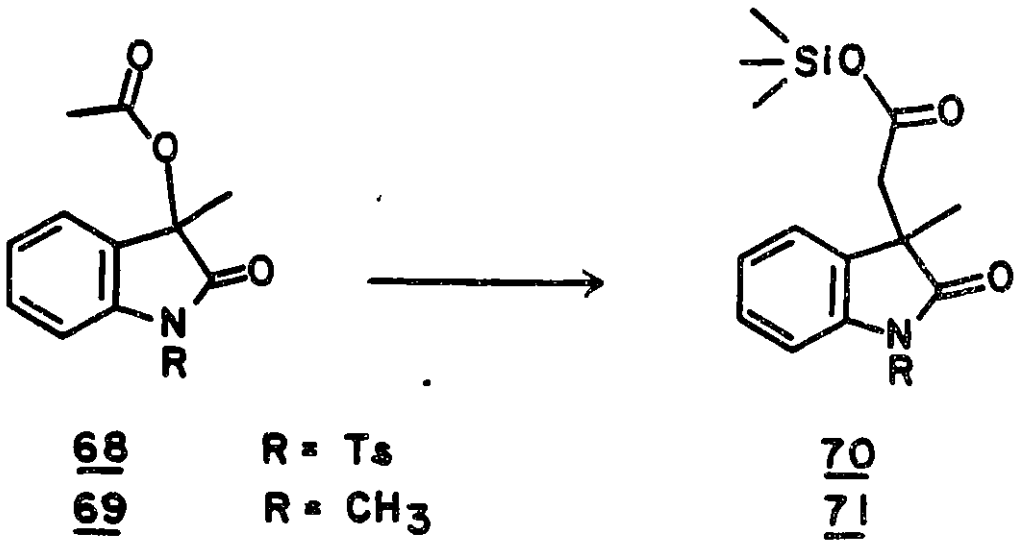
The ester enolate Claisen rearrangement[41] of benzylic esters as the enolate anions or the corresponding silyketene acetals,[42] to produce 4-substituted oxindoles, was studied next (Figure 24). The two desired esters 68 and 69 were prepared from their corresponding bromo oxindoles 65 and 70 in 44% and 63% yields, respectively, by stirring with silver

Figure 23.



acetate in dry THF. Unfortunately, treatment of either 68 or 69 with LDA followed by quenching with trimethylsilylchloride or t-butyldimethylsilyl-chloride yielded primarily fragmentation products 70 and 71 in the 10%-30% range.

Figure 24.



68 R = Ts
69 R = CH_3

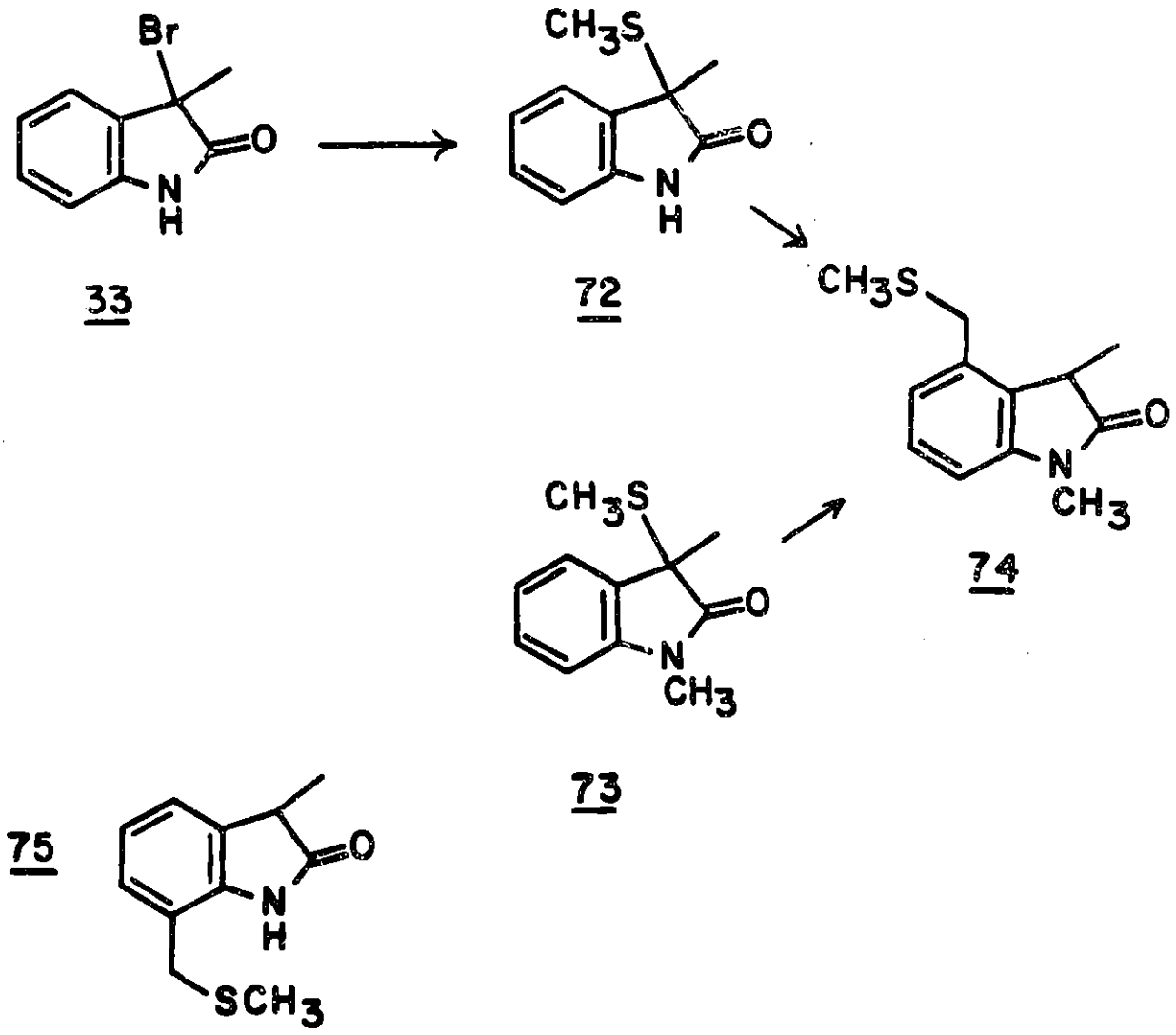
70
71

C. [2,3] Sigmatropic Rearrangement to a 4-Substituted Oxindole.

Our investigations next returned to the [2,3] sigmatropic rearrangement since this was the only approach that resulted in any aromatic substitution of the oxindole system, albeit in the wrong position.

To simplify matters, the methyl sulfide 72 (Figure 25) was prepared from the bromo oxindole 33 by displacement with sodium methyl mercaptide to yield the white crystalline compound 72 in 22% yield followed by the

Figure 25.



usual methylation of the oxindole to yield 73 in 86%. Treatment of sulfide 72 or 73 with trimethyloxonium fluoroborate followed by ylid formation with butyl lithium, as before, yielded (40%) another rearrangement product. This time 250 MHz NMR analysis indicated the product to be the 4-substituted oxindole 74. The aromatic pattern clearly showed the two doublets at δ 6.98 (J = 7.8 Hz) and δ 6.74 (J = 7.8 Hz) for the aromatic protons at C-5 and C-7, respectively, both ortho coupled to the proton at C-6. The fact that the oxindole is 4-substituted (and not 7-substituted) is further reinforced by the observance that the benzylic methylene protons are an AB quartet (J = 13.6 Hz). Their non equivalency is due to their close proximity to the chiral center at C-3. In contrast, Revesz[43] had prepared and identified the 7-substituted oxindole 47b. Because of their further distance from the chiral center, the benzylic protons are a singlet at δ 3.72 (60 MHz). Also, the aromatic protons are much closer together (δ 6.90 - 7.26) as compared to the 4-substituted oxindole.

Alkylation and rearrangement of the free N-H oxindole 72 yielded the same N-methyl 4-substituted oxindole 73. Apparently the conditions of this reaction cause N-methylation rather than the usual O-methylation of amides with Meerwein's salt.[44] Use of at least two equivalents of Meerwein's salt was necessary since one equivalent did not preferentially alkylate the sulfide over the amide. Use of one equivalent usually resulted in a mixture of starting material, N-methyl starting material

and N-methyl rearranged products (see Table 1).

An easier and more efficient method of carrying out the [2,3] sigmatropic rearrangement to the 4-methylthiomethyl oxindole 76 was found by stirring the bromo oxindole 33 and silver tetrafluoroborate in neat methyl sulfide at 0° for several hours followed by the addition of THF and sodium methoxide solution at -78° (Figure 26). Rearrangement to 76 occurred readily at -78° although the reaction was allowed to warm to ensure completion. The advantages of this method are several:

1.) the avoidance of preparing the 3-thiooxindoles in low yields (20-30%);

2.) the versatility of preparing a wide variety of sulfides which can be used in the alkylation and which can easily be recovered in most cases by column chromatography due to the relatively low polarity of the longer chained sulfides;

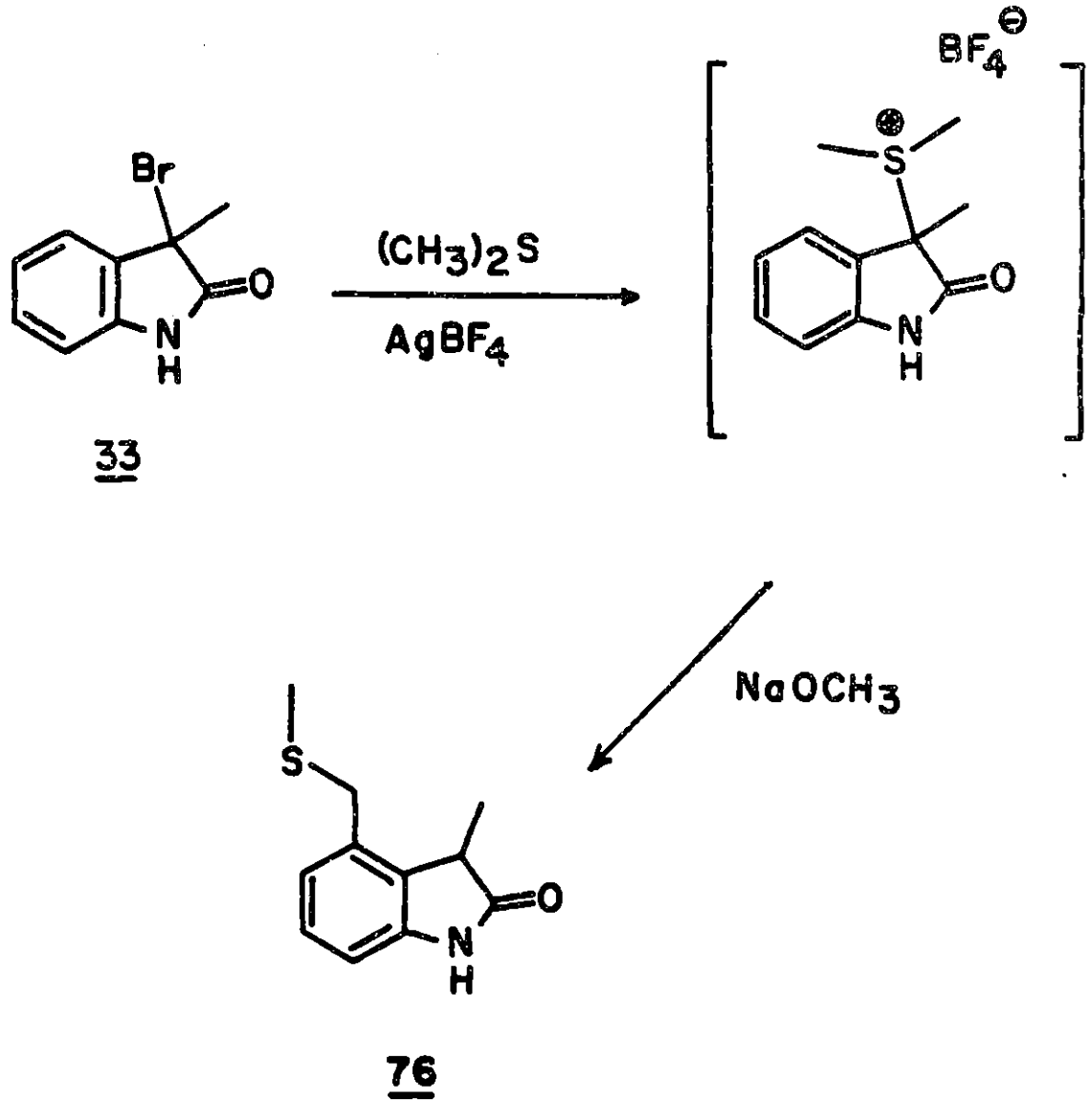
3.) the oxindole amide proton can be left unprotected and is unaffected during the course of the reaction as compared with the Meerwein's salt method which methylated the amide;

4.) the better yields for alkylation and rearrangement (70-95% compared to 40-50%).

Also, this efficient method of rearrangement made it easier to try a variety of longer chained sulfides in order to migrate the entire five carbon unit to the 4-position as a further proof of the possibility of the [2,3] sigmatropic rearrangement as the source of dimethyallyl tryptophan in the biosynthesis of the ergot alkaloids.

Figure 26.

[2,3] Process for Substitution at C_4



Attempted alkylation and rearrangement of longer chained sulfides usually resulted in either failure of alkylation, or the predominance of unwanted side reactions of the desired ylid (Table 2).

Selective ylid formation was foreseen to be a problem with isopentenylmethyl sulfide 83 but it was hoped that the homoallylic position would slightly favor the secondary ylid (Figure 27). The addition of sodium ethoxide to the salt 90 produced exclusively the wrong ylid and the undesired and useless rearranged product 88 in 40% yield.

Alkylation with diisopentenyl sulfide 77 (Figure 28), prepared in 75% yield from the reaction of sodium sulfide and excess isopentenyl tosylate 93, was sluggish and ylid formation 94 resulted in an intramolecular β hydride abstraction and elimination[46] to the isopentenyl sulfide 85 in 24% yield.

Substituting a phenyl group for one of the neopentyl groups by the reaction of sodium phenyl mercaptide and isopentenyl tosylate 93 produced phenyl isopentenyl sulfide 78 in 80% yield. Unfortunately the phenyl group lowered the nucleophilicity of the sulfide so that no alkylation occurred. The addition of two methoxy groups to the phenyl ring, i.e. sulfide 79, prepared in the same manner as 78 in 77% yield, resulted in better alkylation but ylid formation resulted in several unidentifiable products and no 4-substituted oxindole.

Both the thiophene derivatives 81 and 82 alkylated very easily but addition of base resulted in 3-methyloxindole 87 with tetrahydrothiophene

Table 2.

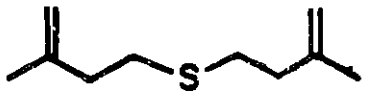
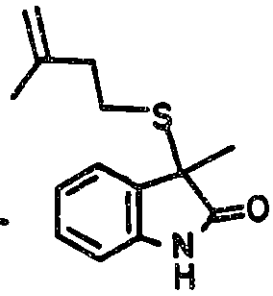
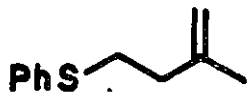
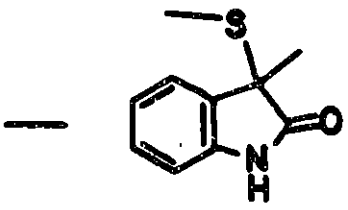
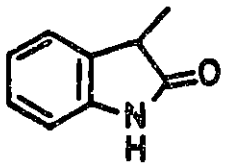
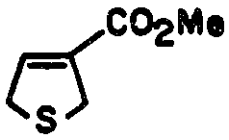
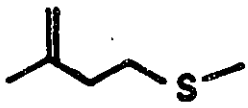
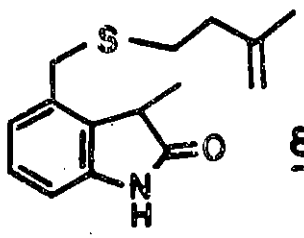
Sulfide		Result
77		 85 (24%)
78		— No Alkylation
79		— Alkylation, no [2,3]
80		 86 (95%)

Table 2 (continued).

81  —  **87** (55%)

82[45]  — Alkylation, no [2,3]

83  —  **88** (40%)

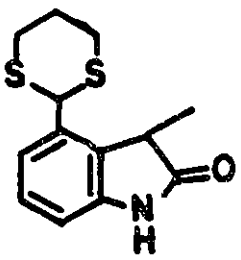
84  —  **89** (12%)

Figure 27.

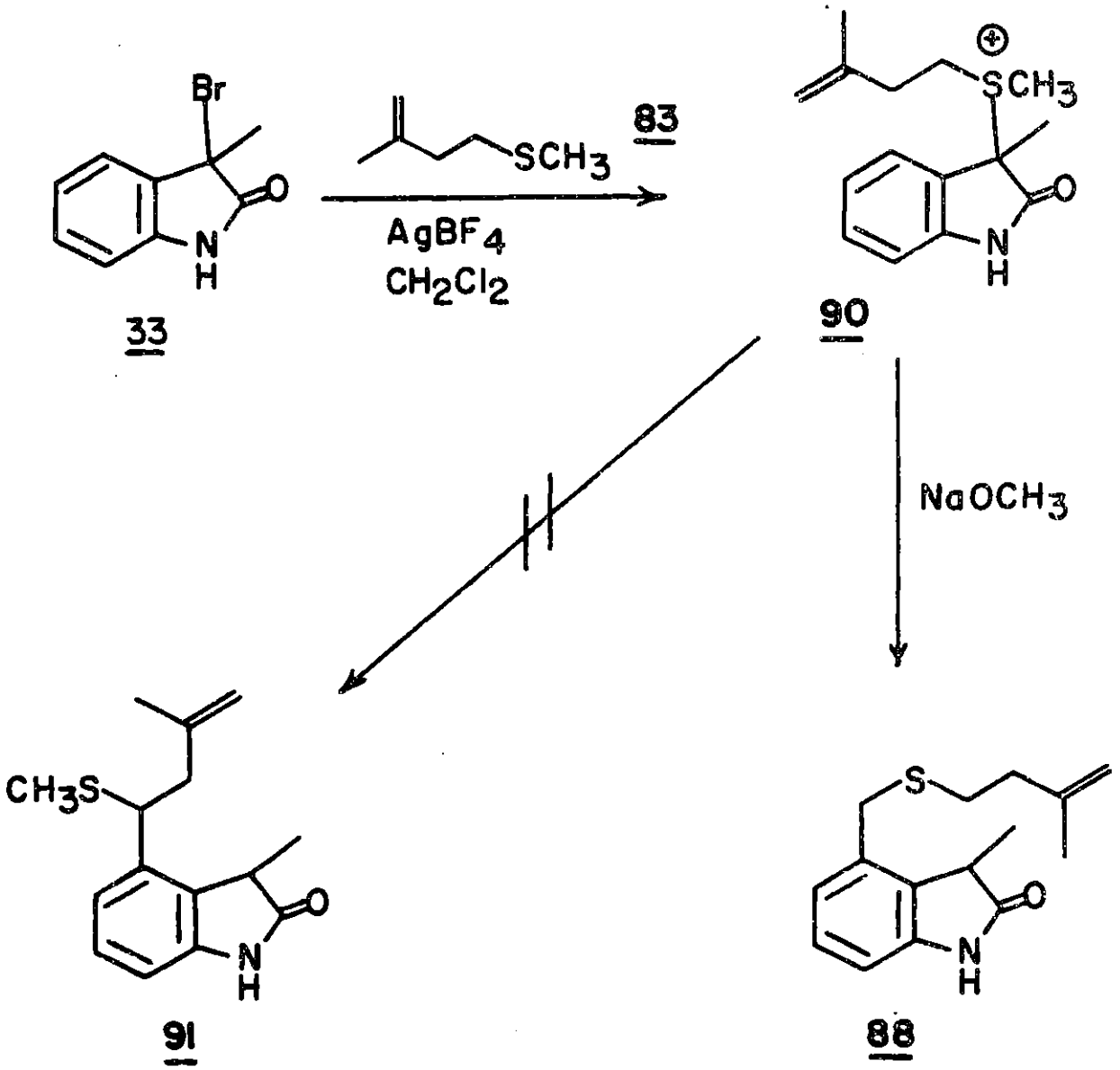
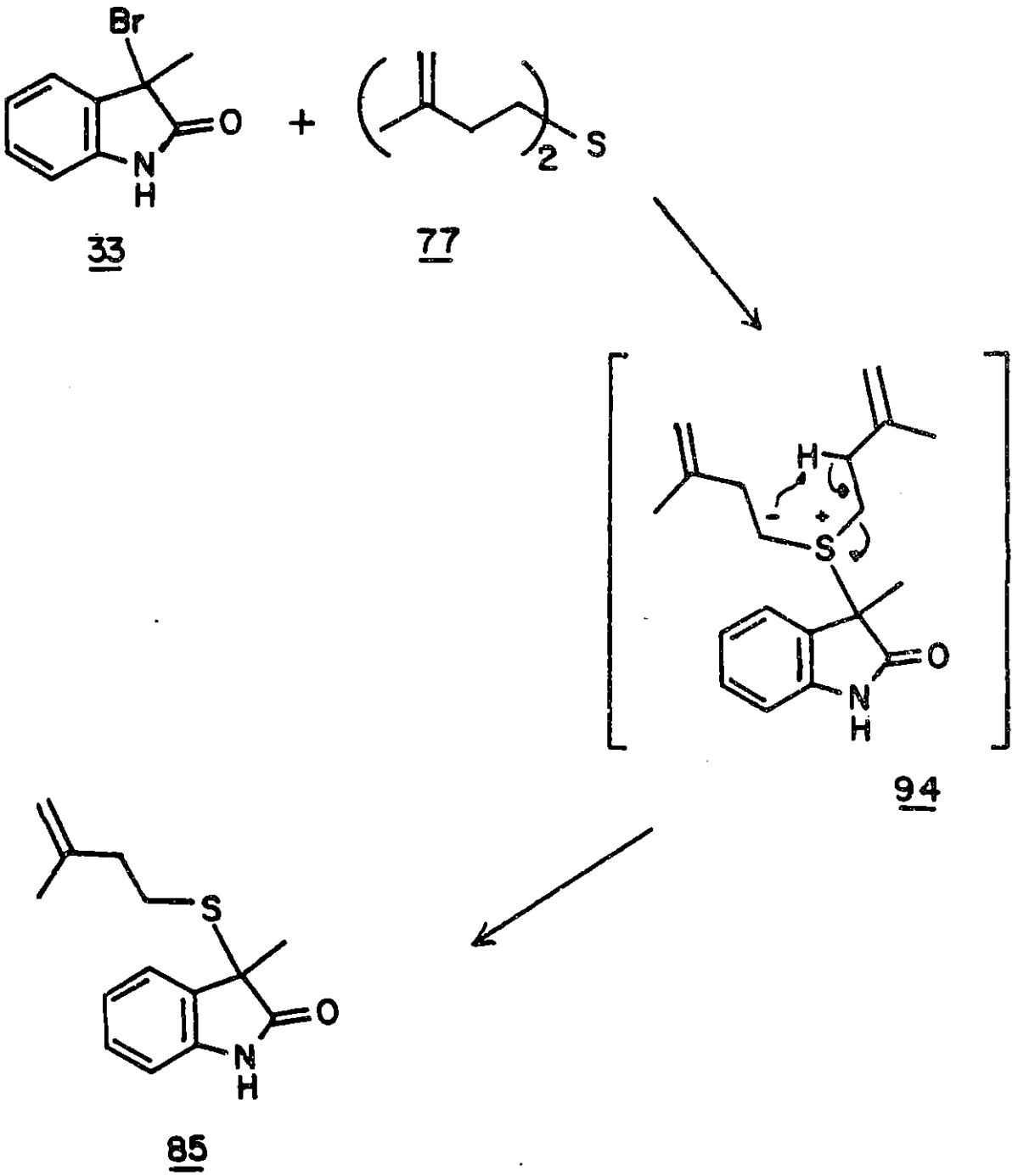

Br
O
N
H
33
SCH3
83
AgBF4
CH2Cl2
⊕
SCH3
O
N
H
90
NaOCH3
CH3S
O
N
H
91
S
O
N
H
88

Figure 28.



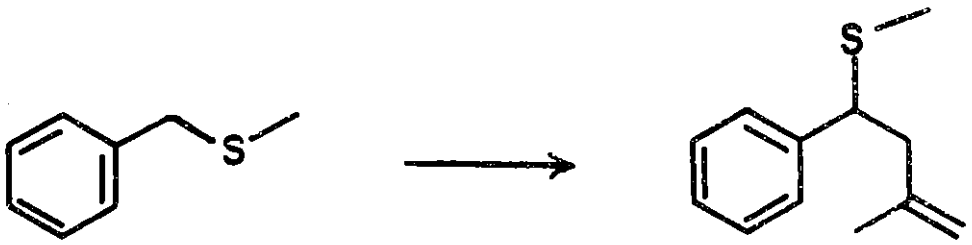
81 and unidentifiable ring opened products with 82.

Rearrangement with the dithiane 84 was successful although in poor yields (12%).

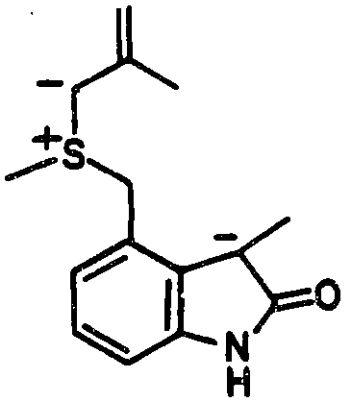
Due to the problems encountered with the longer chained sulfonium ylids, attention was returned to the further elaboration of the 4-position of the thiooxindole 76. Alkylation of the sulfide with methallyl halide followed by another [2,3] rearrangement would produce the desired carbon framework.

The appropriate reaction conditions were first worked out with benzyl methyl sulfide 95 (Figure 29). Alkylation with methallyl chloride was not successful under a variety of conditions including heating and the addition of tetrabutylammoniumiodide. The chloride was converted[47] to the iodide which again was sluggish to alkylate 95. But the addition of silver tetrafluoroborate to a solution of the sulfide 95. But the addition of silver tetrafluoroborate to a solution of the sulfide 95 and methallyl iodide followed by the addition of sodium methoxide solution yielded the desired rearrangement product 96 in 37%. When these conditions were applied to the thiooxindole 76 no rearrangement could be detected. The sulfide seemed to alkylate (by TLC) but the addition of base only produced eventual decomposition. The formation of the oxindole anion first would lower the stability of the desired ylid causing preferential formation of the undesired ylid 97 which cannot rearrange and therefore simply decomposes.

Figure 29.



95 96

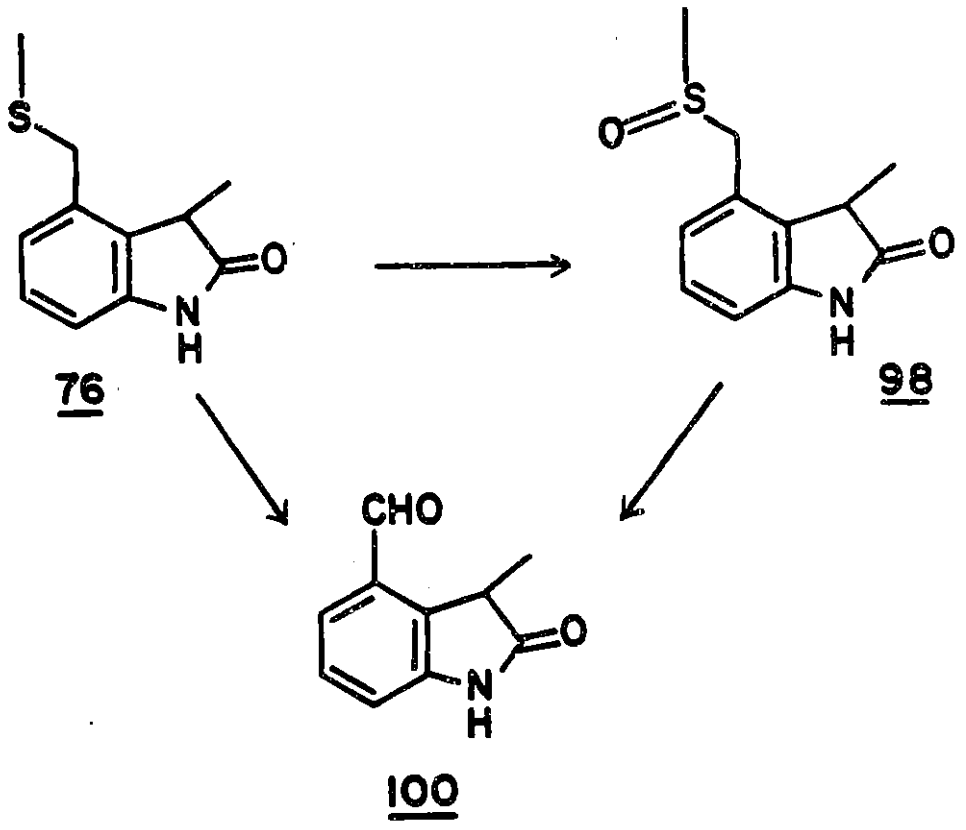


97

The sulfide 76 was next oxidized to the sulphoxide 98 in quantitative yield with sodium meta periodate[48] in the hope that the addition of two equivalents of strong base would form the dianion[49] which, when treated with one equivalent of alkylating agent, would react at the less stable

site, i.e. alpha to the sulphoxide. Treatment of 98 with excess LDA followed by methallyl iodide produced an unidentifiable product which the infrared spectrum did not indicate to be a sulphoxide. To test the stability of the intermediate anion or dianion, the reaction was quenched with water after addition of LDA. The same product as before appeared and no starting material could be detected. Apparently the initial oxindole anion is unstable and results in elimination of the sulphoxide.

Figure 30.

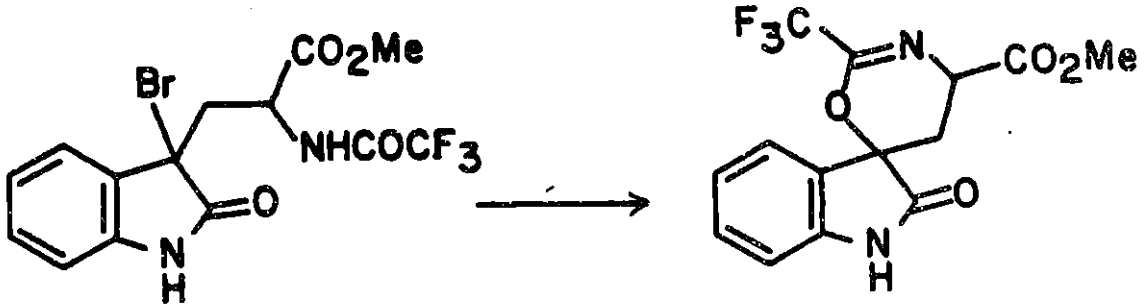


Finally, Gassman's procedure[50] for converting benzyl sulphides to aldehydes succeeded with sulphide 76 to form the potentially very versatile 4-carboxaldehyde 100 (Figure 30). Chlorination of the sulphide with N-chlorosuccinimide resulted in a Pummerer rearrangement[51] followed by hydrolysis with red mercuric oxide and boron trifluoride etherate to 100 in 22% yield. Later, a more efficient method of carrying out this conversion was discovered in our labs by Dr. Dan Coughlin by conversion to the sulphoxide with sodium meta periodate[48] followed by Pummerer rearrangement with chlorotrimethyl silane and hydrolysis with aqueous trifluoroacetic acid. Yields from sulphide to aldehyde range from 40-50%.

D. Attempted Elaboration to Lysergic Acid

The sequence of reactions leading to the 4-carboxaldehyde 100 was then applied to the tryptophan series. The [2,3] rearrangement of the ylid derived from the tryptophan bromo oxindole 29 (Figure 31) was hindered by displacement of the sulphonium salt by the amide anion to form

Figure 31.



29 102

102. Inverse addition of the salt to base in the hope that ylid formation would be faster than amide anion formation, did not change the result. The problem was finally overcome by simply starting out with the N-methyl tryptophan methyl ester 103 prepared by Eschenmoser.[52] The N-methyl product would eventually be desired in a synthesis of lysergic acid (Figure 32). Bromo oxindole 105 was arrived at in the usual manner followed by alkylation and rearrangement to 106 in 85% yield. Conversion to the key 4-carboxaldehyde 107 was accomplished in 20-40% yield. Conversion to the desired diene was carried out by reaction with three equivalents of the ylid 108 to produce 109 in only 25% yield.[53] The low yield was due to the lability of the protective groups. The diene's two protective groups were then simultaneously removed with lithium hydroxide to the amino acid which, without further purification, was subjected to several conditions for formation of imine and Diels Alder cycloaddition[17] (Table 3).

In no instances were any tetracyclic products obtained and the severe conditions usually resulted in decomposition of the starting material. Whether the problem lies in the sensitivity of the aromatic diene, or in imine formation, or in the cycloaddition, is not clear due to the lack of isolatable products. Most recently, Oppolzer has utilized an imino Diels Alder in his synthesis of lysergic acid which does not start with tryptophan.[16]

Figure 32.

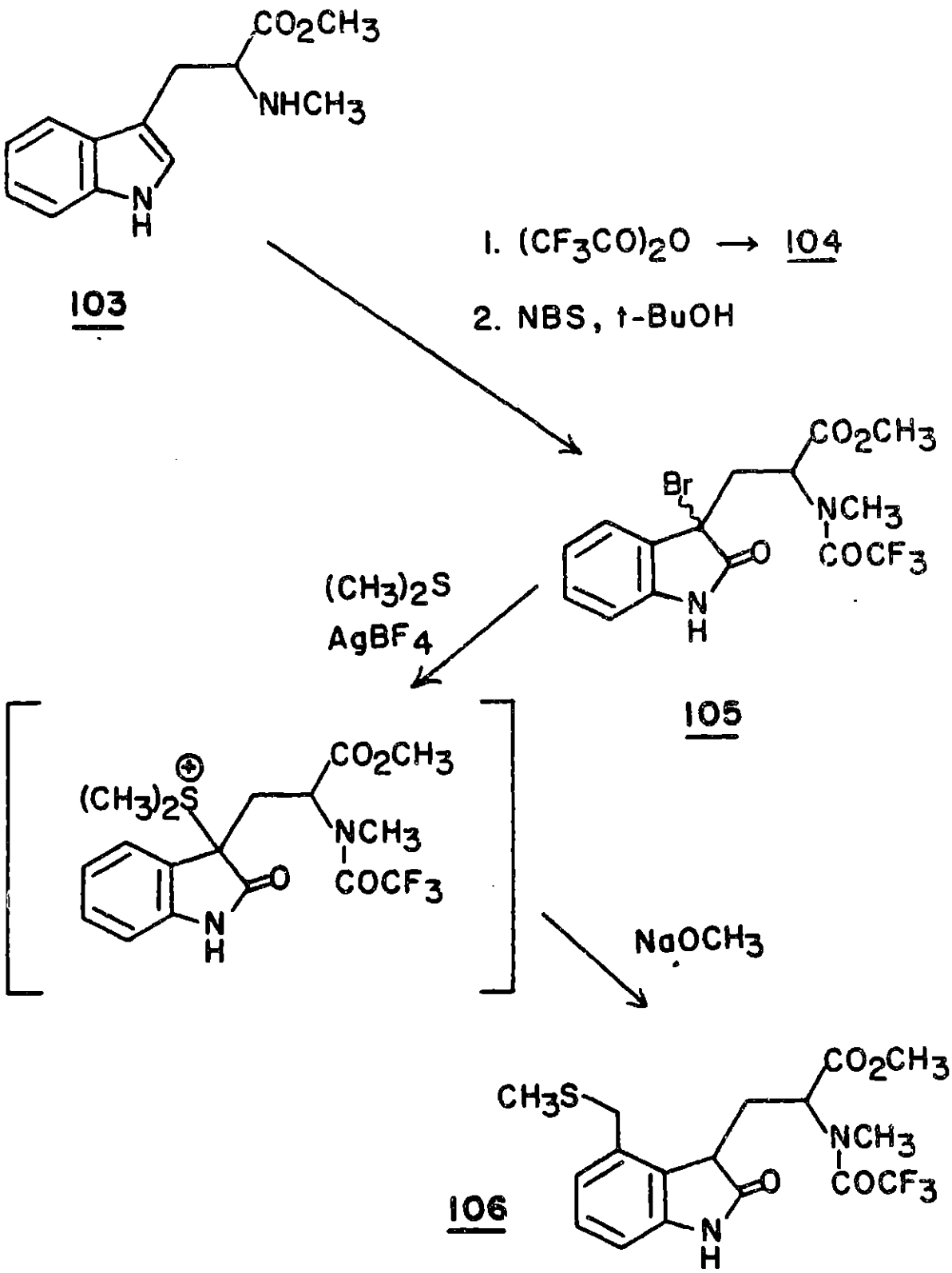

CO2CH3
NHCH3
N
H
103
1. (CF3CO)2O → 104
2. NBS, t-BuOH
Br
NCH3
COCF3
O
N
H
105
(CH3)2S
AgBF4
(CH3)2S
CO2CH3
NCH3
COCF3
O
N
H
NaOCH3
CH3S
CO2CH3
NCH3
COCF3
O
N
H
106

Figure 32 (continued).

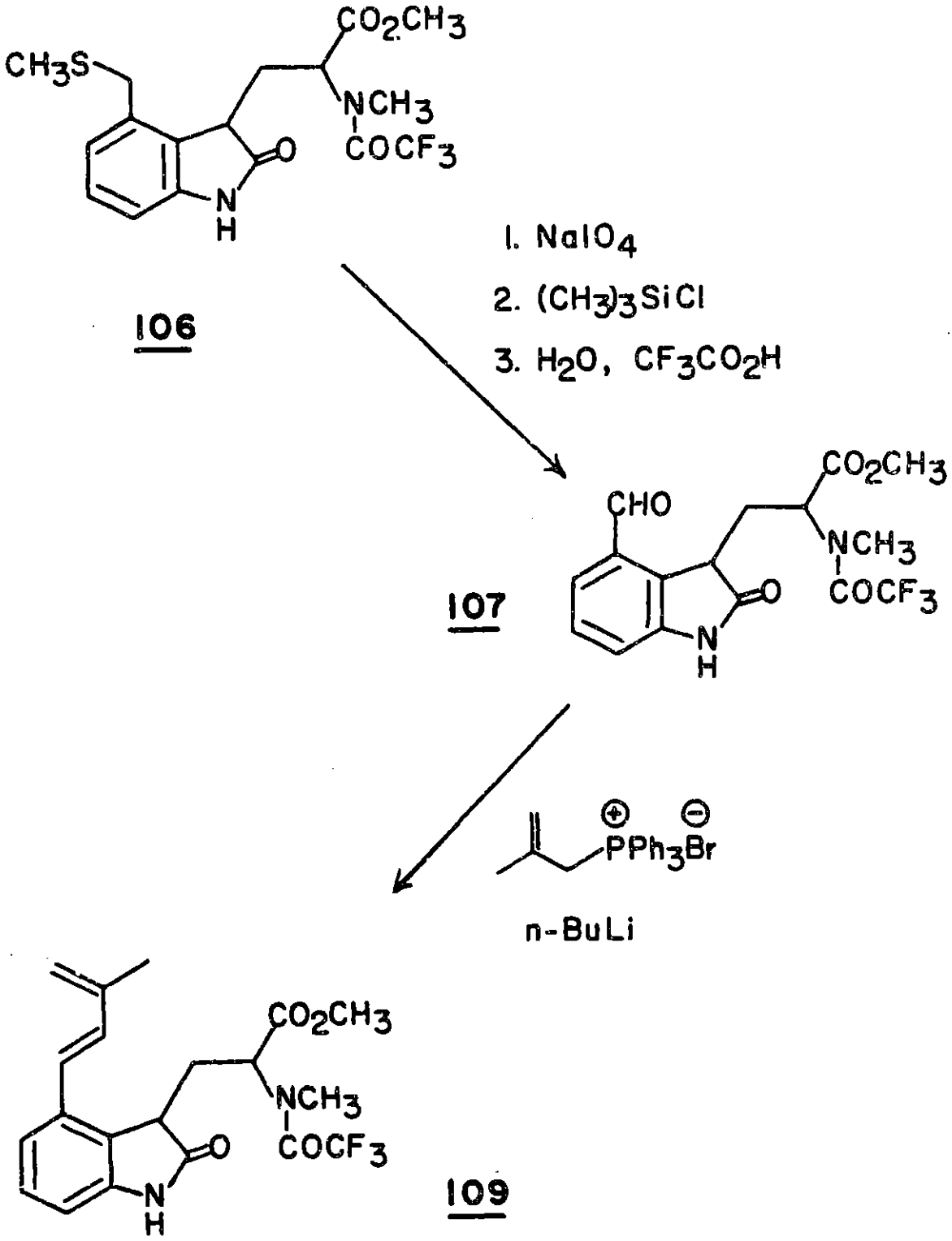


Table 3.

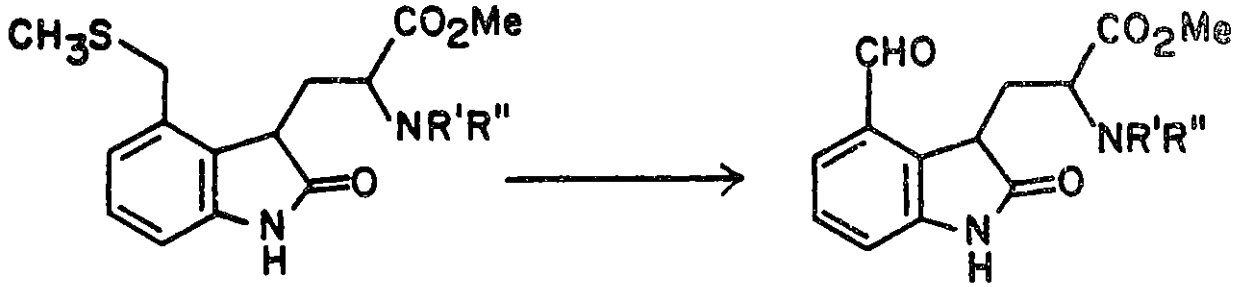
Condition	Reference	Result
$POCl_3$, sealed tube, 200°		Decomposition
$POCl_3$, sealed tube, 100°		"
$SOCl_2$, sealed tube, 200°		"
DCC, p-TSOH, dioxane 80°	54	Mostly starting material
DMSO, CCl_3SO_2Cl		"
$Pb(OAc)_4$, THF/HMPT, 5°	55	"

E. Elaboration to Clavicipitic Acid.

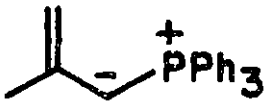
Our approach to clavicipitic acid initially involved a similar route to the diene required for lysergic acid with the exception of the amine protective groups. The need for a protective group which would not interfere with the sigmatropic rearrangement (as the secondary amide of the trifluoroacetyl group did) and which could be selectively removed in the presence of an ester led us to select the phthaloyl group.[56] N-phthaloyl tryptophan methyl ester 116 was prepared, oxidized to the bromooxindole 117, rearranged to the 4-substituted oxindole 110 (in greater than 90% yields) and converted to the 4-carboxaldehyde 113 (Figure 33). Unfortunately, the phthaloyl protected aldehyde 113 would not undergo the Wittig condensation with the previously prepared ylid 108. Grignard reactions were also unsuccessful with 113 due to the lability of the phthaloyl group to nucleophillic attack.

Therefore the phthaloyl group was removed from the sulfide 110 with hydrazine and acetic acid[57] and could be replaced with other protective groups such as the trifluoroacetyl and the trichloro-t-butyloxycarbonyl (TCBOC)[62] groups to form sulfides 111 and 112 respectively. They were then converted as before to their corresponding aldehydes 114 and 115. Figure 33 summarizes the reactions of the three differently protected aldehydes with the two phosphorous ylids 108 and 122.[58] The results with the less nucleophilic stabilized ylid 122 were much more compatible with the range of protective groups. Only a slight excess of ylid 122 was necessary in

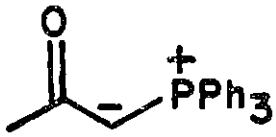
Figure 33.



110	R' R" = PTH	113
111	R' = H, R" = $COCF_3$	114
112	R' = H, R" = TCBOC	115



108



122

113	No	Yes
114	Yes	Yes
115	No	Yes

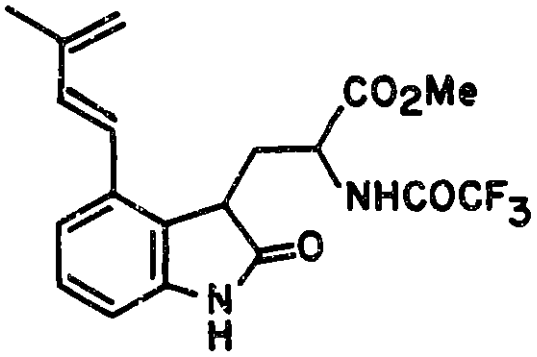
the reactions[59] (as compared with over three equivalents of 108). The reactions were easier to carry out (strong bases and anhydrous conditions were not necessary) and produced yields of 30-40% higher than with 108.

Meanwhile, attempted acid catalyzed cyclization of the amide 123 was not successful with, for example, trifluoroacetic acid, and usually resulted in recovery of starting material. Attempted selective deprotection of the trifluoroacetyl group under a large variety of conditions[60] usually resulted in no reaction or removal of both protective groups due to the increased susceptibility to hydrolysis of the intermediate α-amino ester. The amino acid thus formed also could not be re-esterified back to the amino-ester due to the sensitivity of the diene.

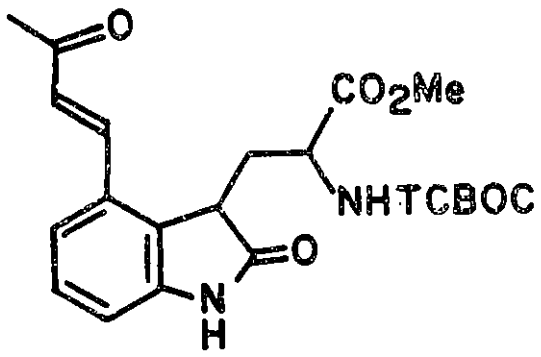
Due to the problems of the acid catalyzed cyclization we next investigated the Michael reaction as a source of the C-ring of clavicipitic acid. Treatment of the enone 125 with bases (triethylamine and sodium methoxide) did not result in any 1,4 addition of the amide[61] to form the tricyclic product. The trifluoroacetyl group presumably again could not be selectively removed. The TCBOC group of enone 124 also could not be reductively removed (Zn/HOAc) without reducing the enone.

In returning to the phthaloyl series (Figure 35) the enone 118 is protected as the dioxalane 119 by refluxing in benzene/ethylene glycol with catalytic p-toluenesulfonic acid (in 41% yield over two steps from the aldehyde 113). The amine is then freed as before with hydrazine and acetic acid to 120 which is then immediately treated, due to its questionable stability, with acetone and 1.2 equivalents of p-TsOH which not only

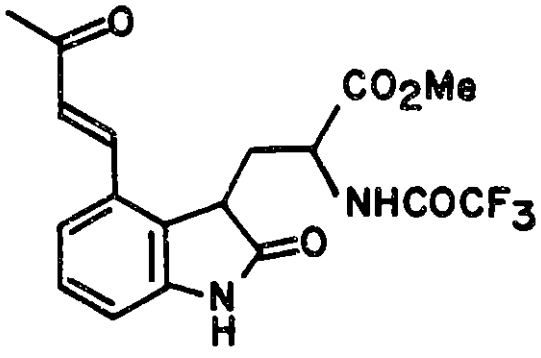
Figure 34.



123



124



125

Figure 35.

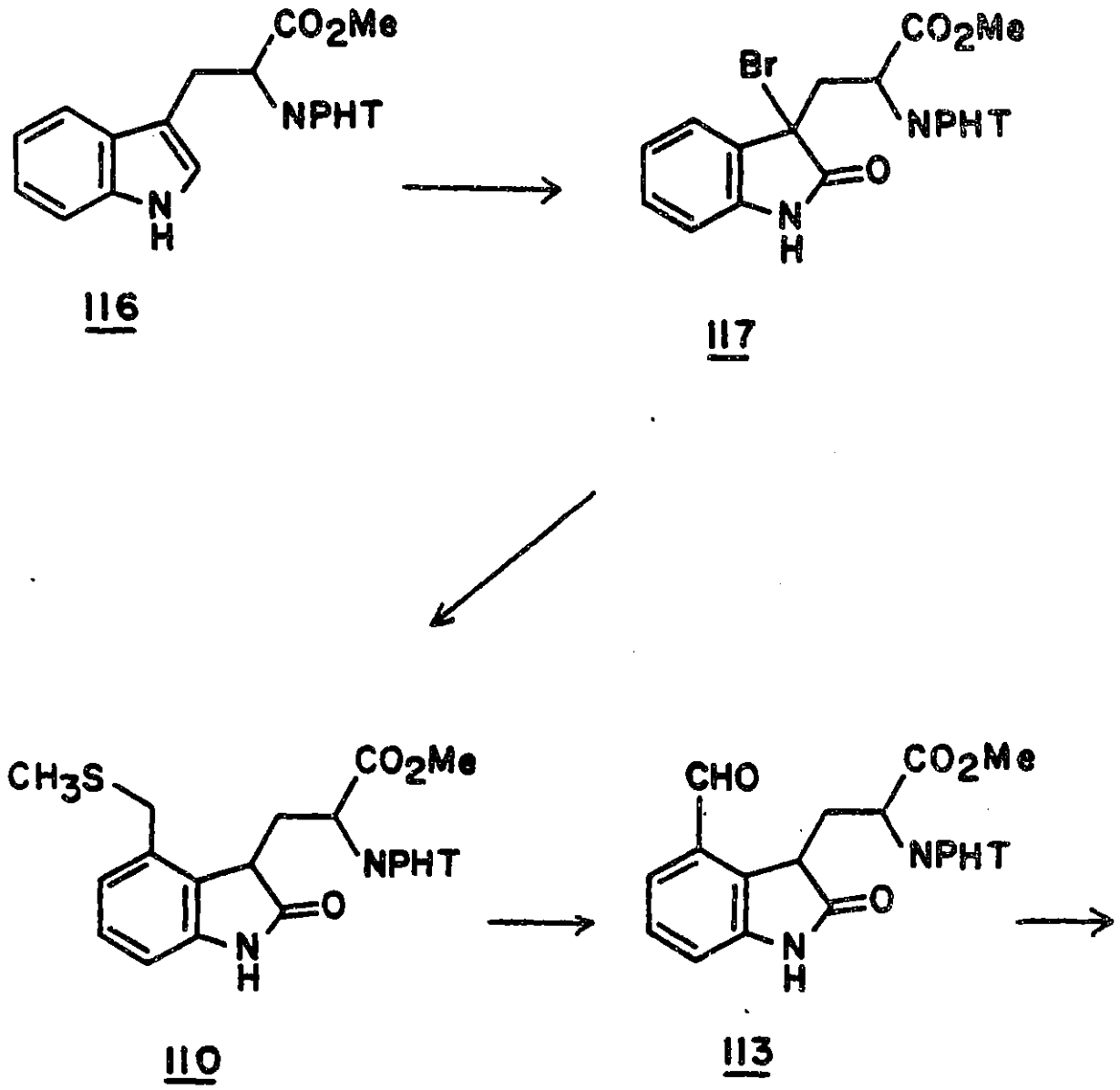
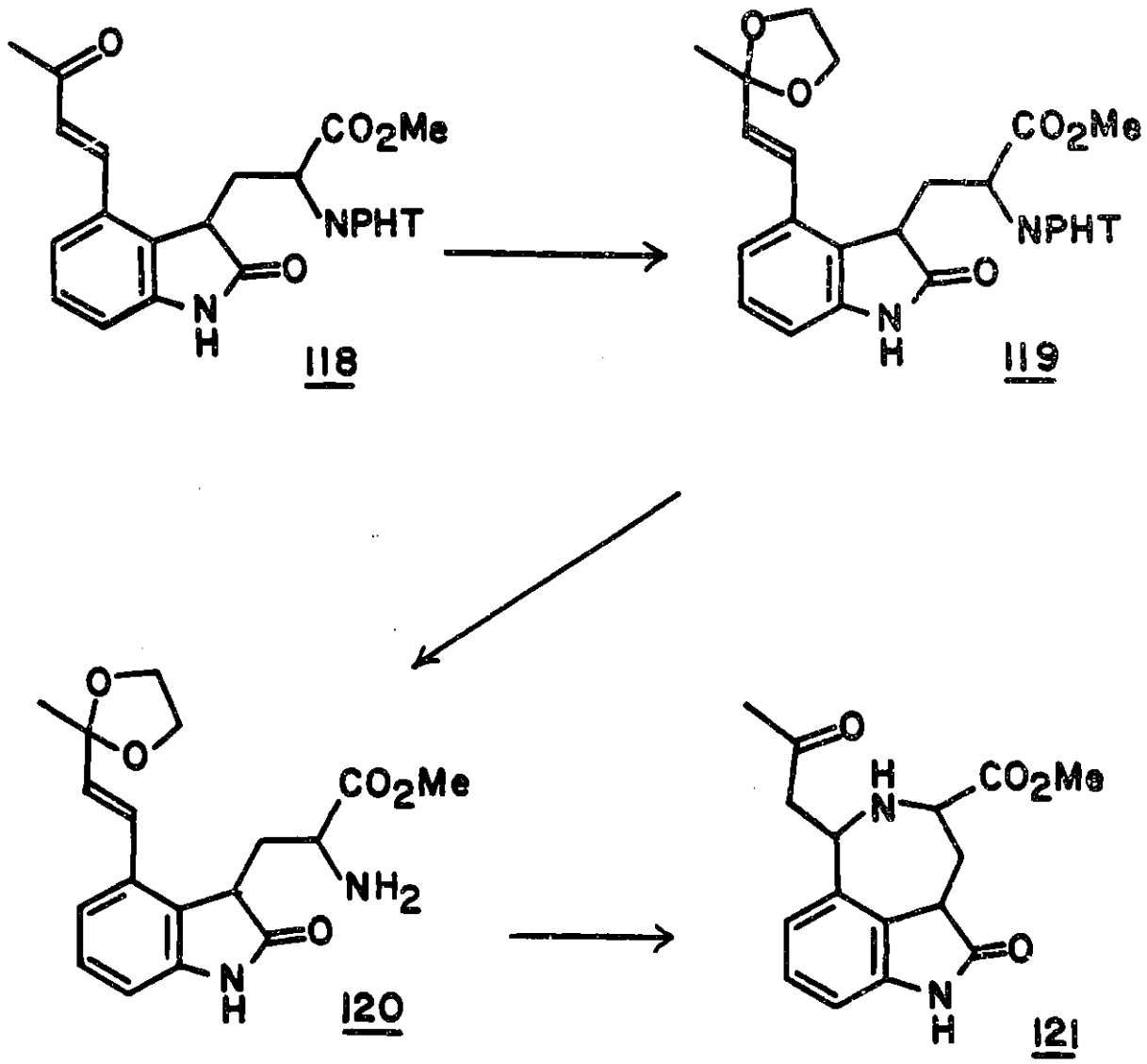


Figure 35 (continued).



removed the ketal but also resulted in the 1,4 addition to the tricyclic product 121 in 45% yield from the dioxalane 119 (3 steps). The greater than usual amount of p-TsOH necessary for the trans ketalization is due to the presence of the free amine. (If catalytic amount is used, only the starting amino ketal is isolated).

The three rings of clavicipitic acid are now present in 121 and what remains is conversion of the methyl ketone to a dimethyl olefin (for example, by treatment with methyl grignard or lithium followed by dehydration) and reduction of the oxindole to the indole with the methyl ester intact since only the NMR spectra of acetylclavicipitic acid methyl ester has been published[62] and provided to us by E. S. Waight.

Experimental

Proton magnetic resonance (NMR) spectra were determined on a Varian T-60 (60 MHz) or a Perkin-Elmer R-24B spectrometer (60 MHz), unless denoted 270 MHz which were determined on a Bruker Hx-270 instrument, or 250 MHz which were determined on a Bruker wm 250. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard. Ultraviolet (UV) and visible spectra were recorded on a Perkin-Elmer 202 spectrometer and are reported in nanometers (nm). Infrared (IR) spectra were determined on either a Perkin-Elmer 237B or 397 grating spectrometer. Low resolution mass spectra were obtained on a Varian MAT-44 spectrometer. Melting points were determined on a Reichert hot stage microscope and are uncorrected.

Analytical thin layer chromatography (TLC) was conducted on precoated 0.25 mm silica gel 60 F-254 plated (EM Reagents) purchased from Scientific Products, Inc. Prepative layer chromatography was performed on either 0.5, 1.0 or 2.0 mm silica gel plates purchased from Analtech, Inc. Flash chromatography was conducted with Woelm silica gel (0.032-0.063 mm), and standard column chromatography with Woelm silica gel (0.063-0.200 mm) purchased from ICN Nutritional Biochemicals.

"Dry" solvents were distilled shortly before use from an appropriate drying agent. Ether, tetrahydrofuran (THF), and dimethoxyethane (DME) were distilled under dry argon from sodium metal using benzophenone ketyl as an indicator. Methanol was distilled from magnesium methoxide.

Nitromethane was distilled from calcium chloride and stored away from light. Methyl sulfide was distilled form sodium; diisopropyl amine from potassium hydroxide; chlorotrimethylsilane and methylene chloride from calcium hydride; and dimethylformamide was dried by storage over 4A molecular sieves for 24 hours.

All other solvents were "Reagent Grade". Distilled in glass ethyl acetate was purchased from Rainin Instrument Co. and was not purified further for flash chromatography.

Methyl-2-trifluoroacetylamino-3-(oxindol-3-yl)-propanoate (17): N-Bromosuccinimide (4.8 g, .0270 mol) was slowly added to a solution of N-trifluoroacetyl-dl-tryptophan methyl ester (8.1 g, .0258 mol) dissolved in 250 mL t-butanol/water (95:5) at 20-25°. The mixture was stirred for 3.0 h, concentrated (bath T≤35°) and diluted with 200 mL ethyl acetate, which was washed with brine and water. The aqueous layers were further extracted with ethyl acetate, and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was chromatographed (250 g silica gel, 3:1 hexane/ethyl acetate) to obtain 7.0 g yellow foam which crystallized from ether to yield 4.0 g (47%) white crystals: mp 109-113°; IR ($CHCl_3$) 3410, 3200, 3050, 2950, 1760 (sh), 1735 (br), 1710 (sh), 1690 (sh), 1625, 1560, 1485, 1475, 1440, 1170 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.6 (m, 2), 3.6 (m, 1), 3.7 and 3.8 (2s, 3), 5.0 (m, 1), 7.3 (m, 4), 8.7 (m, NH), 9.6 (m, NH); mass spectrum (70eV) m/e (rel intensity) 331 (1), 330 (5.4, M^+), 209 (2), 173 (5),

156 (2), 147 (11), 146 (100), 145 (17), 144 (3), 132 (12), 128 (17), 70 (8).

Ethyl-2-trifluoroacetylamino-3-(oxindol-3-yl)-propanoate (17, Ethyl Ester): N-Bromosuccinimide (4.98 g, .028 mol) was slowly added to a solution of N-trifluoroacetyl-l-tryptophan ethyl ester 31a (8.9 g, .027 mol) dissolved in 300 mL t-butanol/water (95:5) at 15-20°. After stirring 3.0 h, the mixture was concentrated (bath T$\leq$35°), filtered through a celite pad with ether to remove some of the succinimide, concentrated again, diluted with ethyl acetate, and washed with water and brine. The aqueous layers were further extracted with ethyl acetate and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (50 mm column, 5:2 pet ether/ethyl acetate) to yield 5.5 g solid which was recrystallized (ethyl acetate/hexane) to yield 4.2 g (45%) white fluffy crystals: mp 140-143°; IR ($CHCl_3$) 3410, 3200, 2990, 1760 (sh), 1730 (br), 1710 (sh), 1690 (sh), 1620, 1565, 1445, 1435, 1165 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.25 and 1.35 (2t, 3, J=7Hz), 4.8 (m, 1), 6.8-7.4 (m, 4), 8.6 (d, NH, J=6Hz), 9.5 (d, NH, J=13 Hz); mass spectrum (70 eV) m/e (rel intensity) 344 (3.2, M^+), 270 (2), 173 (9), 147 (13), 146 (100), 145 (15), 133 (9), 132 (26), 130 (14), 128 (14), 118 (5), 104 (11), 103 (7), 77 (15), 69 (7), 51 (7), 43 (6).

Methyl-2-trifluoroacetylamino-3-(3-phenylthiooxindol-3-yl)-propanoate (18): Freshly distilled benzene thiol (.235 mL, 2.3 mM) was slowly added to a stirred suspension of N-Chlorosuccinimide (.307 g, 2.3 mM) in 1.0 mL anhydrous THF under an argon atmosphere at 0°. After stirring for 15 min, the oxindole 17, dissolved in 1.0 mL THF, was added, warmed to room temperature, and stirred 20 h. The solution was concentrated at room temperature, chromatographed (35 g aluminum oxide, activity grade II, 2:1 hexane/ethyl acetate). The two diastereomers (a: .289 g, 29%), b: .158 g, 16%) were separated: a: IR ($CHCl_3$) 3410, 3200, 3050, 2950, 1760 (sh), 1735 (br), 1710 (sh), 1690 (sh), 1625, 1550, 1475, 1440, 1175 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.8 (m, 2), 3.7 (s, 3), 4.4 (m, 1), 6.7-7.3 (m, 10), 7.9 (s, NH); mass spectrum (70 eV) m/e (rel intensity) 439 (2.5, M^+), 331 (10), 330 (55), 329 (15), 298 (15), 270 (41), 217 (39); b: IR ($CHCl_3$) 3410, 3200, 3050, 2950, 1760 (sh), 1735 (br), 1710 (sh), 1690 (sh), 1625, 1550, 1475, 1440, 1175 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.8 (d, 2, J=6 Hz), 3.55 (s,3), 4.7 (m,1), 6.7-7.8 (m, 10), 8.6 (s, NH); mass spectrum (70 eV) m/e (rel intensity) 439 (2.2, M^+), 331 (17), 330 (100), 329 (20), 298 (22), 297 (11), 270 (68).

N-(1,1-Dimethyl-2-propenyl)-aniline (25): Aniline (.250 g, 2.68 mM) and phenyl prenyl sulfide (.960 g, 5.4 mM) were dissolved in 40 mL anhydrous acetonitrile/methylene chloride (3:1) at -50° under an argon atmosphere in diffused light. To this solution was added slowly t-butylhypochlorite (.380 g, 3.5 mM) dissolved in 2.0 mL methylene

chloride which had been previously cooled to -78°. The solution gradually turned dark violet and was stirred for 3.0 h at -50°, and warmed to -20° for 1.0 h. The reaction was then cooled to -60° and the 2N sodium methoxide solution (5.2 mL, 10.4 mM) was added and stirred at -60° for 1.5 h, slowly allowed to warm to room temperature, and stirred 20 h. The solution was evaporated, diluted with water, and extracted with methylene chloride, washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed (70 g alumina, activity I, 98% hexane/ethyl acetate) to yield .265 g (61%) light orange oil: IR ($CHCl_3$) 3410, 3090, 3050, 2980, 2920, 2860, 1600, 1500, 1410, 1315, 1250, 1180, 990 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.35 (s, 6), 3.5 (s, NH), 4.9-5.3 (m, 2), 6.0 (dd, 1, J=18, 12 Hz), 6.5-7.4 (m, 5); mass spectrum (70 eV) m/e (rel intensity) 161 (13.8, M^+), 146 (28), 93 (93), 92 (22), 77 (19), 69 (27), 66 (16), 65 (24), 58 (21), 51 (19), 43 (100), 42 (39), 41 (84), 39 (43).

Methyl-2-trifluoroacetylamino-3-(3-bromooxindol-3-yl)-propanoate (29): The oxindole 17 (1.0 g, 3.0 mM) was suspended in 7.0 mL carbon tetrachloride and warmed to 50°. Bromine (.485 g, 3.0 mM), dissolved in 4.0 mL CCl_4, was slowly added, and the reaction was heated to 80-85° for 15 min. The orange solution was allowed to cool to room temperature and concentrated. The solid residue was recrystallized ($CHCl_3$/Hexane) to yield 1.18 g (95%) white crystals: mp 139-143°; IR ($CHCl_3$) 3410, 3200, 2950, 1760 (sh), 1735 (br), 1710 (sh), 1620, 1435, 1170 cm^{-1}; ^{1}H-NMR

($CDCl_3$) δ 3.15 (m, 2), 3.7 and 3.8 (2s, 3, 6 Hz), 4.6 (m, 1), 6.9-7.7 (m, 5), 8.7 (d, NH, J=14 Hz); mass spectrum (70 eV) m/e (rel intensity) 410 (2.3, M^+), 408 (2.3, M^+), 329 (38), 297 (10), 269 (38), 268 (11), 216 (33), 188 (20).

N-Trifluoroacetyl-l-tryptophan ethyl ester (31a): HCl gas was slowly bubbled into a suspension of l-(+)-tryptophan (25.0 g, .123 mol) in 500 mL absolute ethanol. After 5 min, the tryptophan dissolved, and the HCl gas was passed through for another 30 min. The solution was stirred 20 h at room temperature, during which time a white precipitate appeared. The reaction was diluted with ether and filtered. The white hydrochloride salt was dried under high vacuum and then partitioned between 600 mL ether and 300 mL aqueous K_2CO_3 solution cooled in an ice bath. The aqueous layer was further extracted with ether and the combined organic layers were dried (Na_2SO_4) and concentrated to 22.0 g light yellow oil, which was dissolved in 200 mL ether and 120 mL trifluoroacetic acid at 0°. Trifluoroacetic anhydride (13.4 mL, .095 mol) was slowly added and stirred for 20 min at 0° and then concentrated (bath T≤35°) to a white solid which was recrystallized (ether/hexane) three times to yield 14.9 g (36% overall) of off white crystals: mp 120-121°; IR ($CHCl_3$) 3480, 3400, 2990, 1760 (sh), 1730 (br), 1710 (sh), 1530, 1460, 1295 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.2 (t, 3, J=8 Hz), 3.4 (d, 2, J=6 Hz), 4.15 (q, J=8 Hz), 4.9 (m, 1), 6.8-7.6 (m, 5), 8.2 (s, NH); mass spectrum (70 eV) m/e (rel intensity) 328 (0.9, M^+), 131 (12), 130 (100), 129 (10), 103 (6),

102 (4), 77 (9), 69 (6), 51 (4), 45 (4).

N-(p-Toluenesulfonyl)-l-tryptophan ethyl ester (31b): The l-tryptophan ethyl ester hydrochloride salt (15.0 g, 56.0 mM) was dissolved in 200 mL THF/H_2O (1:1). Triethylamine was added to this solution followed by the slow addition of p-toluenesulfonyl chloride (12.3 g, 64.0 mM). After stirring for 1.5 h, the reaction was concentrated and extracted with ether, washed with water and brine, dried ($MgSO_4$), and concentrated to a white sticky foam which was crystallized (ether/hexane) to yield 18.9 g (88%) white crystals mp 90-91°; IR ($CHCl_3$) 3475, 3350, 2950, 1735, 600, 1340, 1160, 1095 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.95 (t, 3, J=7 Hz), 2.25 (s, 3), 3.15 (d, 2, J=6 Hz), 3.85 (q, 2, J=7 Hz), 4.2 (t, 1, J=6Hz), 5.4 (s, NH), 6.8-7.6 (m, 9), 8.4 (s, NH); mass spectrum (70 eV) m/e (rel intensity) 386 (2.9, M^+), 157 (3), 131 (15), 130 (100), 129 (41), 103 (9), 91 (24), 77 (12), 65 (10), 39 (7).

Purification of t-butanol[19]: 500 mL t-butanol was dried (Na_2SO_4) and filtered. The filtrate was treated with 7.0 g Darco G-60 activated carbon at 50° for 10 min and filtered.

Ethyl-2-(p-toluenesulfonylamino)-3-(3-bromooxindol-3-yl)-propanoate (32b) (This procedure can also be used for 32a): The N-(p-toluenesulfonyl)-sulfonyl)-l-tryptophan ethyl ester 31b (1.0 g, 2.56 mM) was dissolved in 50 mL purified t-butanol (see above) and cooled with a cold water bath to

22-23° (below which temperature the t-butanol freezes). N-Bromosuccinimide (.926 g, 5.2 mM) was slowly added over one hour and then stirred another 2.0 h. The light green solution was concentrated (bath T≤35°) and purified by flash chromatography (40 mm column, 3:2 pet ether/ethyl acetate) to give a yellow foam which was crystallized (ether) to yield .430 g (35%) light yellow fluffy crystals: mp 137-139°; IR ($CHCl_3$) 3300, 3950, 1735 (br), 1710 (sh), 1620, 1470, 1340, 1160, 1095 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (t, 3, J=7 Hz), 2.35 (s, 3), 3.0 (d, 2, J=8 Hz), 3.75 (m, 3), 6.7-7.9 (m, 9), 8.9 (s, NH); mass spectrum (70 eV) m/e (rel intensity) 482 (0.2, M^+), 480 (0.2, M^+), 332 (7), 330 (7), 300 (3), 288 (8), 286 (4), 247 (12), 246 (17), 173 (11), 172 (13), 155 (12), 123 (35), 102 (19), 91 (90), 65 (35), 45 (64), 44 (100), 39 (48).

3-Bromo-3-methyloxindole (33): (A modified procedure of Hinman and Bauman[19]) To a solution of skatole (5.2 g, 39.6 mM) in 260 mL of purified t-butanol, was added over a period of one hour in small portions N-bromosuccinimide (14.2 g, 79.8 mM) with stirring at 22-23° (cold water bath). After 2.0 h, the mixture was concentrated (bath T≤35°). After addition of 50 mL of anhydrous ether to the syrupy residue, the crystals of succinimide were filtered and washed with 50 mL of ether. The filtrate was concentrated and further purified by flash chromatography (40 mm column, 3:2 pet ether/ethyl acetate) and

recrystallization (ether) to yield 4.9 g (55%) slightly yellow crystals: mp 220-222°; IR ($CHCl_3$) 3420, 3200, 3000, 1740 (sh), 1720 (br), 1620, 1470, 1440, 1380, 1320, 1190, 1125, 1040 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.05 (s, 3), 6.9-7.5 (m, 5), 9.3 (s, NH); mass spectrum (70 eV) m/e (rel intensity) 227 (3.8, M^+), 225 (4.2, M^+), 147 (14), 146 (100), 145 (10), 128 (50), 127 (39), 117 (35), 116 (28), 91 (27), 90 (41), 89 (42), 63 (31), 62 (30), 58 (34), 51 (34), 50 (35), 39 (42), 38 (32).

Sodium Prenyl Mercaptide: Prenyl mercaptan (5.0 g, .049 mol), dissolved in 10.0 mL anhydrous ether, was slowly added to a stirred suspension of sodium (1.13 g, .049 mol) in 50 mL ether. The suspension was refluxed for 3.0 h and stirred for 20 h at room temperature. The white salt was filtered under an inert atmosphere, washed with petroleum ether to remove any disulfide, and dried (some small pieces of sodium may need to be removed by hand).

3-)3-Methyl-2-butenylthio)-3-methyloxindole (35): The bromooxindole 33 (2.4 g, 10.6 mM) was slowly added to a suspension of the sodium prenyl mercaptide (see above) (2.0 g, 16.1 mM) in 125 mL of purified t-butanol. The reaction became cloudy, and after stirring for 30 min, was concentrated (bath T≤35°). The residue was purified by flash chromatography (50 mm column, 3:2 pet ether/ethyl acetate) to yield .810 white solid which was recrystallized (ethyl acetate/hexane) to yield .635 g (25%) long white needles: mp 114-115°; IR ($CHCl_3$) 3420, 3200, 3000, 2920,

1720 (sh), 1710 (br), 1620, 1465, 1375, 1320, 1120 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.45 (s, 3), 1.60 (s, 3), 1.65 (s, 3), 2.90 (m, 2), 5.0 (m, 1), 6.9-7.4 (m, 4), 9.8 (s, NH); mass spectrum (70 eV) m/e (rel intensity) 247 (1.1, M^+), 179 (3), 150 (6), 149 (8), 148 (12), 147 (74), 146 (100), 145 (51), 128 (20), 127 (20), 117 (20), 116 (18), 101 (32), 100 (26), 90 (23), 67 (25), 41 (81).

3-Isopropylthio-3-methyloxindole: The bromooxindole 33 (2.0 g, 8.8 mM) was slowly added to a suspension of sodium isopropyl mercaptide (1.29 g, 1.32 mM; prepared in the same manner as the sodium prenyl mercaptide) in 100 mL of purified t-butanol. After stirring for 30 min, the reaction was concentrated (bath $T \leq 35°$) and the residue was purified by flash chromatography (50 mm column, 3:2 pet ether/ethyl acetate) and recrystallization (ethyl acetate/hexane) to yield .426 g (22%) white crystals: mp 105-108°; IR ($CHCl_3$) 3420, 3200, 3000, 2950, 2925, 1720 (sh), 1710 (br), 1620, 1465, 1380, 1370, 1320, 1185, 1120, 1045 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (d, 3, J=8 Hz), 1.2 (d, 3, J=8 Hz), 1.15 (s, 3), 2.5-3.0 (m, 1), 7.0-7.4 (m, 4), 9.6 (s, NH); mass spectrum (70 eV) m/e (rel intensity) 221 (1.7, M^+), 178 (2), 150 (6), 148 (8), 147 (62), 146 (100), 145 (11), 128 (43), 118 (11), 117 (21), 116 (11), 103 (5), 91 (19), 90 (17), 89 (16), 77 (15), 65 (13), 43 (22), 41 (31), 39 (25).

3-Bromo-1,3-dimethyloxindole (36): To a stirred solution of N-methyl skatole (5.3 g, 37.3 mM) in 250 mL purified t-butanol at 22-23° (cold water bath) was slowly added N-bromosuccinimide (14.2 g, 80.0 mM) over 1 h. After stirring another 2 h at 22°, the solvent was removed under reduced pressure (water bath T$\leq$35°) to an orange oil which was diluted with ether and filtered. The filtrate was concentrated and purified through a 70 mm flash chromatography column (2:1, pet ether/ethyl acetate) to yield 8.6 g yellow solid which was washed with ether/hexane to yield 6.2 g (70%) bromooxindole: mp 102-103°; IR ($CHCl_3$) 3000, 2950, 1720 (sh), 1710, 1610, 1490, 1470, 1440, 1370, 1340, 1300, 1240, 1200 (br), 1160, 1100, 1060, 1040, 1020 cm^{-1}; ^{1}H-NMR ($CDCl_3$)δ 2.0 (s, 3), 3.2 (s, 3), 6.6-7.5 (m, 4).

1,3-Dimethyl-3-(3-methyl-2-butenylthio)-oxindole (37): To a stirred suspension of sodium hydride (0.220 g of a 50% oil dispersion washed three times with hexane, 4.6 mM) in 60 mL of dry DMF at 0° under argon was added the thiooxindole 35 (1.0 g, 4.1 mM) in 30 mL DMF. After 30 min at 0°, the methyl iodide (0.44 mL, 7.0 mM) in 10 mL DMF was added and stirred for 1 h at 0°. The reaction was diluted with ether and washed twice with water and twice with brine to remove the DMF, and then dried (Na_2SO_4). Removal of solvents under reduced pressure afforded 1.1 g of crude oxindole which was distilled in a Kugelrohr oven to yield 0.99 g (94%) clear liquid (oven temp. 200°, 0.03 mm):

UV (95% EtOH) max 212 (28600), 257 (6800), 289 (sh, 1100); IR ($CHCl_3$) 3000, 2920, 1720 (sh), 1710 (br), 1610, 1490, 1465, 1445, 1370, 1340, 1100, 1020 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.45 (s, 3), 1.60 (s, 3), 1.65 (s, 3), 3.05 (k, 2, J=8 Hz), 3.2 (s, 3), 5.0 (t, 3, J=8 Hz), 6.7-7.4 (m, 4); mass spectrum (70 eV) m/e (rel intensity) 261 (0.5, M^+), 162 (11), 161 (100), 160 (51), 159 (38), 146 (16), 132 (14), 131 (15), 130 (44), 118 (27), 117 (14), 103 (10), 91 (12), 89 (11), 77 (16), 69 (23), 68 (27), 67 (34), 65 (16), 63 (12), 53 (30), 51 (20), 41 (62), 39 (43).

1,3-Dimethyl-6-(1,1-dimethyl-3-methylthio-2-propenyl)-oxindole (40): To a stirred solution of the trimethyloxonium fluoroborate (0.089 g, 0.60 mM) in 0.6 mL dry nitromethane at -30° (MeOH-H_2O-Dry Ice bath) under argon in semi-darkness was added the thiooxindole 37 (0.075 g, 0.287 mM) in 0.1 mL nitromethane and stirred for 2 h between -20° and -30°. The light brown solution was cooled to -78° and 2.0 mL dry ether was added. The white precipitate which appears is allowed to settle and the clear solvent is syringed away. This procedure for removing the nitromethane is repeated three times. Dry THF (0.8 mL) is added followed by the slow addition of butyl lithium (0.10 mL, 2.2 N, 0.42 mM) at -78°. After stirring for 1 h at -78°, the solution is allowed to warm to room temperature over 2 h during which time the solution becomes cloudy yellow green. The reaction is diluted with water, extracted with ether, washed with brine, and dried (Na_2SO_4). Removal of solvents under

reduced pressure afforded 0.125 g crude oxindol which was purified on a 1000 μ silica plate (2:1, pet ether:ethyl acetate) to yield 0.045 g (57%) yellow oil: UV (95% EtOH) max 211 (33,700), 252 (13,600), 284 (sh, 2100); IR ($CHCl_3$) 3000, 2950, 2925, 1720 (sh), 1710 (br), 1620, 1465, 1380, 1300, 1260, 1100 (br) cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.47 (s, 6), 1.48 (d, 3, J=7.7 Hz), 2.29 (s, 3), 3.25 (s, 3), 3.44 (q, 1, J=7.7 Hz), 5.65 (d, 1, J=15 Hz), 6.05 (d, 1, J=15 Hz), 6.82 (d, 1, J=1.3Hz), 7.07 (dd, 1, J=6.2, 1.3 Hz), 7.21 (d, 1, J=6.2 Hz); mass spectrum (70 eV) m/e (rel intensity) 277 (2), 276 (6), 275 (27, M^+), 229 (18), 118 (100), 227 (10), 213 (28), 212 (47), 161 (29), 160 (50), 130 (10), 117 (12), 115 (40), 91 (10), 77 (14), 69 (10), 67 (12), 57 (12), 43 (18), 42 (10), 41 (25).

3-Methyl-3-(3-carboethoxy-2-butenylthio)-oxindole (45, R = Et): To a stirred suspension of the sodium mercaptide of 49 (0.68 g, 37.4 mM) in 40 mL dry t-butanol was slowly added the bromooxindole 33 (0.588 g, 2.6 mM) over 5 min. After another 10 min at room temperature, the reaction was concentrated by 50% (water bath temp $\leq 35°$), diluted with water, and extracted with ether, washed with brine, and dried ($MgSO_4$). Removal of solvent under reduced pressure and purification through a 30 mm flash chromatography column yielded 0.250 g (31%) sulfide: mp 114-117°; IR ($CHCl_3$) 3450, 3200, 1720 (sh), 1710 (br), 1620, 1470, 1370, 1320, 1280, 1180, 1110 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.2 (t, 3, J=8 Hz), 1.7 (s, 3), 3.2 (m, 2), 4.1 (q, 2, J=8 Hz), 6.6 (m, 1), 7.0-7.5 (m, 4), 10.0 (br,

NH); mass spectrum (70 eV) m/e (rel intensity) 305 (0.1, M^+), 178 (2), 159 (11), 150 (6), 148 (11), 147 (84), 146 (100), 145 (12), 128 (34), 118 (10), 117 (18), 99 (8), 91 (18), 90 (13), 89 (11), 85 (10), 77 (15), 71 (10), 63 (6), 59 (7), 53 (20), 45 (14), 43 (18), 41 (12), 39 (21).

3-Carbomethoxy-2-butenyl-1-thiol (49, R = Me): A suspension of the phosphorane 51a (10.0 g, 28.6 mM) and the dithiane 99 (4.6 g, 30.0 mM) in 300 mL methylene chloride was stirred at room temperature for 15 h. The mixture was filtered and the filtrate was concentrated. The residue was diluted with 200 mL pet ether and the triphenylphosphine oxide was filtered and the filtrate concentrated. Distillation yielded 2.7 g (65%) of the mercaptan as a clear liquied (bp 42-43°, 0.15 mm): IR (NaCl) 3000, 2950, 2550, 1710 (br), 1640, 1440, 1350, 1270, 1200, 1120, 1080 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.5 (t, SH, J=8 Hz), 1.9 (br s, 3), 3.3 (m, 2), 3.8 (s, 3), 6.9 (m, 1).

3-Carboethoxy-2-butenyl-1-thiol (49, R = Et): Prepared in the same manner as R = Me: The phosphorane 51a (13.5 g, 37.1 mM) and the dithiane 99 (5.4 g, 37.1 mM) in 500 mL methylene chloride for 3 h yielded 4.1 g (70%) clear mercaptan (bp 46-47°, 0.01 mM): IR (NaCl) 3000, 2950, 1710 (br), 1640, 1440, 1360, 1270, 1180, 1110, 1080 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.3 (t, 3, J=8 Hz), 1.5 (t, SH, J=8 Hz), 1.9 (s, 3), 3.3 (m, 2), 4.2 (q, 2, J=8 Hz), 6.8 (m, 1).

Sodium Mercaptide of 49: To a stirred suspension of sodium hydride (1.13 g of a 50% oil dispersion washed three times with hexane, 23.5 mM) in 20 mL dry ether at 0° under argon was slowly added the mercaptan 49 (R = Et) (4.0 g, 25.0 mM) in 10 mL ether over 10 min. After 1 h at 0°, the yellow suspension was diluted with pet ether, filtered and the white mercaptide washed with pet ether. Drying under high vacuum yielded 4.1 g (95%) white solid stored under argon.

(α-Carboethoxy-ethylidene)-triphenylphosphorane (51a, R = Et): (a modified procedure of Isler, et al[34]): To a stireed solution of triphenylphosphine (10.0 g, 38.0 mM) in 40 mL dry benzene under argon was slowly added the α-bromopropionate (6.3 g, 35.0 mM) over 30 min. The cloudy solution is heated at 70° for 15 h during which time a thick precipitate appeared. The solvent was removed under reduced pressure and the residue was diluted with ether, filtered and washed with pet ether. The cream colored salt was dried under high vacuum and then dissolved in 100 mL water and filtered to remove insoluble impurities. The filtrate was placed in a 250 mL round bottom flask along with a pinch of phenolphthalein. 3 N sodium hydroxide solution was added until the pink color remained. The yellow gum which precipitated was washed three times with water (by stirring and decanting the water away), and after drying under high vacuum, the oil was crystallized with pet ether/ethyl acetate to yield 4.2 g (33%) light yellow solid: mp 156-157°.

Fragmentation Products (51) and (52): To a solution of the sulfide 45 (0.107 g, 0.35 mM) in 2.0 mL dry CH_2Cl_2:CH_3NO_2 (1:1) at -5° under argon in semi-darkness was added the trimethyloxonium fluoroborate (0.185 g, 1.25 mM) and stirred 3 h at 0°. The reaction was cooled to -78° and sodium ethoxide solution (3.1 mL, 0.43 M, 1.35 mM) was slowly added. After 1 h at -78° and warming to room temperature over 2 h, the solution was quenched with water, extracted with methylene chloride, washed with brine, and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 0.101 g crude oil which was purified through a 10 mm flash chromatography column (2:1, pet ether:ethyl acetate) to yield 0.039 g (35%) 51 and 0.026 g (26%) 52. 51: IR ($CHCl_3$) 3450, 3200, 2950, 2925, 2875, 1720 (sh), 1700 (br), 1620, 1470, 1440, 1380, 1370, 1320, 1270, 1240, 1220 (br), 1110 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.2 (t, 3, J=8Hz), 1.6 (s, 3), 1.9 (2 s, 3), 2.0 (s, 3), 4.0 (d, 1, J=10 Hz), 4.1 (q, 2, J=8 Hz), 6.3 (d, 1, J=10 Hz), 6.8-7.5 (m, 4), 8.5 (br, NH); mass spectrum (70 eV) m/e (rel intensity) 319 (0.3, M^+), 226 (3), 192 (7), 183 (3), 174 (11), 173 (89), 161 (55), 160 (47), 147 (12), 146 (27), 145 (24), 130 (16), 128 (48), 127 (100),117 (38), 99 (82), 97 (59), 91 (18), 90 (18), 85 (20), 77 (26), 69 (20), 65 (24), 53 (36), 45 (29), 43 (37), 41 (40), 39 (26). 52: IR ($CHCl_3$) 3450, 3250, 3000, 2950, 1720 (br), 1630, 1560, 1540, 1210, 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.2 (t, 3, J=8 Hz), 1.5 (d, 3, J=8 Hz), 1.6 (s, 3), 2.3 (s, 3), 3.4 (q, 1, J=8 Hz), 4.2 (q, 2, J=8 Hz), 5.85 (d, 1, J=16 Hz), 6.2 (d, 1, J=16 Hz), 6.8-7.3 (m, 3), 8.5 (br, NH); mass spectrum (70 eV) m/e (rel intensity) 320

(0.7), 319 (1.6, M^+), 246 (11), 199 (18), 198 (100), 197 (11), 184 (5), 170 (36), 160 (2), 128 (12), 115 (10), 91 (6), 45 (13), 43 (12).

3-Methyl-3-butene-1-thiol: To a stirred solution of thiourea (18 g, 0.24 mol) in absolute ethanol (200 mL) was added 3-methyl 3-butenyl toluenesulfonate[64] (57 g, 0.24 mol), and the mixture refluxed for 2 h. Rotary evaporation of the ethanol gave the crude isothiouronium salt which was hydrolized with sodium hydroxide (18 g, 0.45 mol) in water (200 mL) under reflux for 2 h. After cooling to 0°, the hydrolysis mixture was acidified with dilute H_2SO_4 and extracted twice with ether. The ether layers were combined and washed with water than brine, and dried (Na_2SO_4). The ether was removed by distillation through a Vigreux column under argon. After removal of the ether, the residual oil was diluted to give the pure thiol 6.8 g, (25%): bp 35°, 15 mm; ^{1}H-NMR ($CDCl_3$) δ 1.41 (t, 1, J=7 Hz), 1.72 (br s, 3), 2.13-2.87 (m, 4), 4.67-4.87 (m, 2).

N-Methylisatin (54): To a stirred suspension of sodium hydride (0.36 g, of a 50% oil dispersion washed three times with hexane, 7.5 mM) in 60 mL dry DMF under argon at 0° was added isatin (1.0 g, 6.8 mM) in 30 mL DMF. The dark violet solution is stirred 30 min at 0°. Methyl iodide (0.62 mL, 10.0 mM) in 10 mL DMF was added and stirred 1 h at 0°. The orange solution is diluted with water and extracted with ether, washed twice with water and twice with brine, and dried ($MgSO_4$). Removal of solvent

under reduced pressure afforded 0.71 g (65%) pure red orange solid: mp 128-131°; IR ($CHCl_3$) 3050, 3000, 2950, 1740 (br), 1610 (sh), 1605, 1460, 1360, 1320, 1240, 1160, 1110, 1090, 1040 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.15 (s, 3), 6.7-7.6 (m, 4).

3-(1,1-Dimethyl-2-propenyl)-3-hydroxy-1-methyloxindole (55): To a stirred solution of N-methylisatin 54 (0.700 g, 4.35 mM) in 10 mL dry THF under argon was added the prenyl magnesium cloride (20 mL, 0.4 M solution, 8.0 mM) at room temperature and stirred 1.5 h. The dark solution is poured into saturated ammonium chloride ice solution and extracted with ether, washed with brine, and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 1.2 g crude red oil which was purified through a 40 mm flash chromatography column (2:1, pet ether: ethyl acetate) to yield 0.633 g (65%) light yellow orange crystals: mp 88-90°; IR ($CHCl_3$) 3550, 2950, 2925, 1720 (sh), 1710 (br), 1610, 1490, 1470, 1380, 1350, 1100, 1080 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.1 (2s, 6), 3.1 (s, 3 and OH), 5.0 (dd, 1, J=18, 2 Hz), 5.1 (dd, 1, J=11, 2 Hz), 6.05 (dd, 2, J=18, 11 Hz), 6.6-7.4 (m, 4); mass spectrum (70 eV) m/e (rel intensity) 231 (0.9, M^+), 164 (11), 163 (100), 162 (85), 161 (6), 133 (5), 117 (7), 116 (8), 106 (6), 105 (12), 104 (14), 92 (7), 91 (7), 78 (12), 77 (28), 69 (34), 53 (11), 51 (15), 41 (72), 39 (25).

3-Hydroxy-1-methyl-3-(3,3-dimethyl-2-butenyl)-oxindole (58): To a stirred suspension of potassium hydride (0.0452 g of a 25% oil dispersion washed with hexane, 0.28 mM) in 1 mL dry DME under argon was added the alcohol 55 (0.050 g, 0.22 mM) in 1 mL DME at room temperature. After 2 h, the reaction was cooled with an ice bath, quenched with water, extracted with ether, washed with brine, and dried ($MgSO_4$). Removal of solvent under reduced pressure yielded 0.050 g (100%) pure solid: IR ($CHCl_3$) 3300 (br), 2900, 1720 (sh), 1710 (br), 1620, 1470, 1380, 1340, 1080 (br) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.5 (s, 3), 1.6 (s, 3), 2.6 (d, 2, J=8 Hz), 3.1 (s, 3), 3.5 (br, OH), 5.0 (t, 1, J=8 Hz), 6.7-7.4 (m, 4); mass spectrum (70 eV) m/e (rel intensity) 231 (0.9, M^+), 163 (70), 162 (53), 134 (4), 133 (6), 119 (5), 117 (9), 116 (11), 105 (18), 104 (21), 92 (11), 91 (14), 83 (11), 79 (14), 78 (17), 77 (42), 71 (10), 69 (52), 65 (14), 57 (15), 55 (15), 53 (12), 51 (16), 43 (28), 41 (100), 39 (33).

3-Methyl-1-p-toluenesulfonylindole (65a): To a stirred suspension of sodium hydride (2.0 g, 50% oil dispersion washed three times with hexane, 42.0 mM) in 160 mL dry DMF at 0° under argon was slowly added to skatole (5.0 g, 38.2 mM) in 40 mL DMF. After 1 h at 0°, the tosyl chloride (11.5 g, 60.0 mM) was added and stirred 2 h at 0°. A distillation head was attached and the DMF removed under reduced pressure (bp 50°, 15 mm). The residue was diluted with 250 mL ether and 5 mL methanol and 5 mL pyridine was added and stirred 20 min at room temperature. The ether was

then washed with water and twice with brine, and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 12.0 g crude tosylate which was purified through a 50 mm flash chromatography column (4:1, pet ether: ethyl acetate) to yield 9.0 g (83%) crystalline tosylate: mp 114-115°; IR ($CHCl_3$) 3100 (sh), 3050 (br), 2900, 2850, 1600, 1490, 1440, 1360, 1300, 1270, 1160, 1120, 1080, 1020, 1000 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.2 (s, 3), 2.25 (s, 3), 7.0-8.0 (m, 9).

3-Bromo-3-methyl-1-p-toluenesulfonyloxindole (65b): Prepared in the same manner as 36: The tosylate 65a (2.0 g, 7.0 mM) and NBS (3.56 g, 20.0 mM) in 75 mL purified t-butanol yielded after purification through a 40 mm flash chromatography column (7:1, pet ether:ethyl acetate) 0.710 g (27%) bromooxindole: mp 155° (dec.); IR ($CHCl_3$) 1760 (br), 1600, 1460, 1380, 1320, 1300, 1160, 1080 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.0 (s, 3), 2.4 (s, 3), 7.2-8.1 (m, 8).

3-Hydroxy-3-methyl-1-p-toluenesulfonyloxindole (66): To a stirred solution of the bromooxindole 65 (0.79 g, 2.07 mM) in 8 mL THF:H_2O (3:1) was added the silver acetate (0.410 g, 2.46 mM) at room temperature and stirred 4 h. The grey solts were filtered and the filtrate extracted with ether, washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded after purification through a 40 mm flash chromatography column (3:1, pet ether:ethyl acetate) 0.390 g (60%) alcohol: mp 105-107° ; IR ($CHCl_3$) 3550, 3350 (br), 3050, 1770 (sh),

1750 (br), 1600, 1380, 1360, 1220, 1180, 1120, 1080 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.5 (s, 3), 2.4 (s, 3), 2.9 (br, OH), 7.2-8.0 (m, 8); mass spectrum (70 eV) m/e (rel intensity) 317 (1, M^+), 163 (16), 162 (100), 101 (11), 146 (27), 145 (12), 144 (66), 135 (10), 134 (15), 120 (26), 117 (14), 116 (60), 92 (30), 91 (93), 90 (39), 89 (22), 77 (17), 65 (50), 51 (16), 43 (94), 39 (30).

3-Acetoxy-3-methyl-1-p-toluenesulfonyloxindole (68): To a stirred solution of the bromooxindole 65b (0.600 g, 1.57 mM) in 5 mL dry THF under argon at room temperature was added the silver acetate (0.534 g, 3.2 mM) and stirred 15 h. The reaction was filtered and the filtrate was washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded after purification through a 30 mm flash chromatography column (3:1, pet ether:ethyl acetate) 0.250 g (44%) acetate: mp 132-135°; IR ($CHCl_3$) 3050, 2950, 1760, 1740, 1600, 1460, 1370, 1240, 1220, 1200, 1170, 1090 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.6 (s, 3), 1.9 (s,3), 2.35 (s, 3), 7.0-8.0 (m, 8); mass spectrum (70 eV) m/e (rel intensity) 359 (0.2, M^+), 162 (32), 146 (16), 145 (26), 117 (12), 91 (36), 65 (16), 43 (100), 40 (23).

1-Acetoxy-1,3-dimethyloxindole (69): Prepared in the same manner as 68: The bromooxindole 36 (3.0 g, 12.5 mM) and the silver acetate (4.2 g, 25.0 mM) in 30 mL dry THF yielded after purification through a 50 mm flash chromatography column (3:1, pet ether:ethyl acetate) 1.71 g (63%)

acetate: mp 64-65°; IR ($CHCl_3$) 3000, 2950, 1730 (br), 1720 (br), 1620, 1490, 1470, 1440, 1370, 1350, 1300, 1240, 1220 (br), 1120, 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.6 (s, 3), 2.0 (s, 3), 3.2 (s, 3), 6.6-7.5 (m, 4); mass spectrum (70 eV) m/e (rel intensity) 219 (15, M^+), 176 (16), 162 (14), 161 (21), 160 (86), 146 (10), 134 (36), 132 (26), 130 (24), 118 (21), 117 (22), 103 (11), 91 (21), 90 (15), 89 (15), 78 (13), 77 (38), 65 (22), 63 (16), 51 (22), 43 (100), 39 (13).

Trimethylsilyl-2-(3-methyl-1-p-toluenesulfonyloxindol-3-yl)-ethanoate (70): To a stirred solution of LDA (0.167 mM prepared from 0.018 g diisopropylamine, 0.18 mM, and 0.167 mM butyl lithium in 0.5 mL dry THF) at -78° was added the oxindole 68 (0.050 g, 0.139 mM) in 0.8 mL THF over several minutes. After 2-3 min the white precipitate was quenched with TMS-chloride (0.021 mL, 0.167 mM). The clear solution was allowed to warm to room temperature and stirred overnight. The reaction was diluted with water, extracted with ether, washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure and purification of the crude oil on a 1000 μ silica plate (3:1, pet ether: ethyl acetate) yielded 0.015 g (25%) silyl ester: IR ($CHCl_3$) 3050, 2950, 1780, 1600, 1480, 1460, 1350, 1300, 1250, 1170, 1100, 1060, 1020 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.2 (s, 9), 1.7 (s, 3), 2.4 (s, 3), 3.1 (d, 1, J=18 Hz), 4.2 (d, 1, J=18 Hz), 7.1-7.8 (m, 8); mass spectrum (70 eV) m/e (rel intensity) 277 (1), 276 (4), 236 (2), 235 (6), 234 (30), 232 (7), 218 (7), 216 (8), 186 (4), 155 (5), 149 (9), 139 (5), 116 (5), 115 (5), 92 (5),

91 (39), 75 (14), 79 (12), 73 (100), 72 (11), 65 (22), 45 (23), 43 (23).

3-Methyl-3-methylthiooxindole (72): To a suspension of sodium methyl mercaptide (0.892 g, 16.0 mM) in 125 mL dry t-butanol was slowly added the bromooxindole 33 (2.4 g, 10.6 mM). After 2 h at room temperature, the t-butanol is removed under reduced pressure (water bath temp $\leq 35°$) and the residue is diluted with water and extracted with ether, washed with brine, and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 1.8 g yellow oil which was purified through a 50 mm flash chromatography column (2:1, pet ether:ethyl acetate) to yield 0.497 g (22%) white solid: mp 145-148° ; IR ($CHCl_3$) 3450, 3200, 3000, 1720 (sh), 1710 (br), 1620, 1460, 1320, 1200, 1120 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) δ 1.7 (s, 3), 1.9 (s, 3), 6.9-7.5 (m, 4), 9.7 (br, NH); mass spectrum (70 eV) m/e (rel intensity) 194 (3), 193 (6, M^+), 150 (3), 147 (54), 146 (100), 145 (11), 129 (7), 128 (61), 118 (18), 117 (29), 116 (12), 103 (7), 91 (30), 90 (28), 89 (29), 77 (25), 65 (23), 64 (12), 63 (25), 52 (12), 51 (24), 50 (14), 47 (24), 46 (13), 45 (35), 39 (37), 38 (11).

1,3-Dimethyl-3-methylthiooxindole (73): Prepared in the same manner as 37: The thiooxindole 72 (0.25 g, 1.3 mM), sodium hydride (0.077 g, 1.6 mM) and methyl iodide (0.16 mL, 2.3 mM) afforded a brown oil which was purified through a 20 mm flash chromatography column (2:1, pet ether: ethyl acetate) to yield 0.230 g (86%) yellow green oil: IR ($CHCl_3$) 3000, 2920, 1720 (sh), 1710 (br), 1610, 1480, 1460, 1370, 1340, 1200

(br), 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.7 (s, 3), 1.95 (s, 3), 3.3 (s, 3), 6.9-7.7 (m, 4); mass spectrum (70 eV) m/e (rel intensity) 207 (3, M^+), 198 (2), 161 (24), 160 (45), 132 (14), 130 (11), 124 (16), 117 (13), 110 (22), 97 (12), 95 (11), 85 (15), 83 (14), 81 (11), 77 (15), 74 (10), 73 (100), 71 (18), 69 (20), 67 (10), 59 (24), 57 (32), 56 (12), 55 (29), 45 (20), 44 (19), 43 (43), 41 (30).

1,3-Dimethyl-4-methylthiomethyloxindole (74): Prepared either from 1.) N-Methyl thiooxindole 73, or 2.) unprotected thiooxindole 72:

1.) To a stirred solution of trimethyloxonium fluoroborate (0.163 (0.163 g, 1.1 mM) in 0.8 mL dry nitromethane at -30° (MeOH-H_2O-Dry Ice bath) under argon in semi-darkness was added the thiooxindole 73 in 0.2 mL nitromethane and stirred 2 h at -20°. The solution was cooled to -78° and 2.0 mL dry ether was added. The white precipitate is allowed to settle and the clear solvent is syringed away. This procedure for removing nitromethane is repeated three times. Dry THF (0.8 mL) was added followed by the slow addition of butyl lithium (0.25 mL, 2.2 N, 0.55 mM) at -78°. After stirring 1 h at -78°, the solution was allowed to warm to room temperature over 2 h. The reaction was diluted with water, extracted with ether, washed with brine, and dried (Na_2SO_4). Removal of solvent under reduced pressure afforded 0.82 g oil which was purified on a 1000 μ silica plate (3:1, pet ether:ethyl acetate) to yield 0.048 g (45%) solid;

2.) To a stirred suspension of the thiooxindole 72 (0.050 g, 0.259 mM) in 0.5 mL dry nitromethane at -20° under argon in semi-darkness was added the trimethyloxonium fluoroborate (0.077 g, 0.52 mM) and stirred 2 h at -20°. The reaction was cooled to -78° and sodium ethoxide solution (2.0 mL, 0.43 M, 0.86 mM) was slowly added and stirred 1 h at -78° followed by warming to room temperature over 2 h. The reaction was diluted with water, extracted with ether, washed with brine, and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 0.060 g crude oil which was purified through a 10 mm flash chromatography column (2:1, pet ether:ethyl acetate) to yield 0.0246 (43%) sulfide: IR ($CHCl_3$) 3000, 2920, 1720 (sh), 1700 (br), 1605, 1460, 1380, 1340, 1300, 1120, 1000 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.54 (d, 3, J=7.7 Hz), 2.03 (s, 3), 3.21 (s, 3), 3.64 (q, 1, J=7.7 Hz), 3.65 (d, 1, J=13.6 Hz), 3.82 (d, 1, J=13.6 Hz), 6.74 (d, 1, J=7.8 Hz), 6.98 (d, 1, J=7.8 Hz), 7.24 (t, 1, J= 7.8 Hz); mass spectrum (70 eV) m/e (rel intensity) 221 (13, M^+), 174 (24), 173 (100), 160 (17), 159 (19), 146 (21), 145 (22), 144 (34), 132 (11), 131 (23), 130 (24), 115 (17), 103 (17), 91 (19), 89 (15), 77 (18), 71 (10), 65 (15), 63 (12), 57 (14), 55 (13), 51 (16), 43 (23).

3-Methyl-4-methylthiomethyloxindole (76): To a stirred solution of silver tetrafluoroborate (1.3 g, 6.6 mM) in 10 mL dry methyl sulfide at 0° under argon in semi-darkness was slowly added the bromooxindole 33 (1.0 g, 4.4 mM). After stirring 2.5 h at 0°, the suspension was cooled to -78° and the sodium methoxide solution (5.0 mL, 1 N, 5.0 mM) was

slowly added, stirred 1 h at -78° and allowed to warm to 0° over another hour. The mixture was quenched with saturated NH_4Cl solution and filtered through a medium pored scintered glass funnel containing a pad of silica. The salts were washed with ether and the filtrate further extracted with ether. The ethereal layers were washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 0.800 g crude oxindole which was purified through a 30 mm flash chromatography column (3:2, pet ether:ethyl acetate) to yield 0.650 g (70%) solid: mp 118-120°; IR ($CHCl_3$) 3450, 3200 (br), 3000, 2920, 1720 (sh), 1700 (br), 1620, 1600, 1450, 1320, 1240, 1210, 1020 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.57 (d, 3, J=7.7 Hz), 2.03 (s, 3), 3.63 (d, 1, J=13.6 Hz), 3.66 (q, 1, J=7.7 Hz), 3.81 (d, 1, J=13.6 Hz), 6.86 (d, 1, J=7.7 Hz), 6.94 (d, 1, J=7.7 Hz), 7.17 (t, 1, J=7.7 Hz), 9.5 (br, NH).

Bis-(3-methyl-3-butenyl)sulfide (77): To a stirred suspension of sodium sulfide monohydrate (10.0 g, 42 mmol) in absolute ethanol (250 mL) was added 3-methyl-3-butenyl toluenesulfonate (93)[64] (20.0 g, 83.2 mmol) and the solution refluxed for 4 h. The ethanol was distilled from the solution through a Vigerux column until the pot residue was about 75-100 mL, at which time the pot was cooled to room temperature and water (300 mL) was added. The solution was extracted twice with 200 mL portions of pentane and the pentane layers combined, washed successively with water and brine, then dried (Na_2SO_4). Rotary evaporation of the pentane gave a yellow oil which was distilled from a small piece of sodium to give

the sulfide (5.2 g, 75%): bp 100-105°, 10 mm; IR (thin film) 3070, 2910, 1640, 1440, 1370, 890 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.21 (br s, 6), 2.1-2.8 (m, 8), 4.68 (br s, 4).

3-Methyl-3-butenyl phenyl sulfide (78): To a stirred suspension of sodium hydride (4.32 g of a 50% mineral oil dispersion, washed three times with hexane, 90 mmol) in dry ether (100 mL) cooled to 0°, was added benzenethiol (9.18 g, 83 mmol) in ether (20 mL) dropwise over 20 min, care being taken to avoid vigorous gas evolution. After complete addition of the thiol the mixture was stirred at room temperature for 2 h. The suspension was then cooled to 0° and a solution of 3-methyl-3-butenyl p-toluenesulfonate (93)[64] (20.0 g, 83 mmol) in dry ether (20 mL) was added dropwise over 20 min, then stirred for 10 h. The suspension was poured into ice water (300 mL) and extracted twice with pentane (150 mL). The combined pentane extracts were washed with water, brine, then dried (Na_2SO_4). After removal of the solvent by rotary evaporation, the residual yellow oil was distilled to yield the sulfide (12.0 g, (81%): bp 137-142°, 10 mm; IR (thin film) 3070, 2960, 2930, 1645, 1580, 1480, 1440, 1375, 1085, 1021, 885, 740, 690 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.73 (br s, 3), 2.12-2.52 (m, 2), 2.84-3.12 (m, 2), 4.70-4.88 (br s, 2), 7.10-7.48 (m, 5).

2,4-Dimethoxyphenyl 3-methyl-3-butenyl sulfide (79): To a stirred suspension of sodium hydride (2.2 g of a 50% oil dispersion washed three times with dry hexane, 46 mmol) in dry THF (100 mL) was added 2,4-dimethoxy benzene thiol[65] (7.0 g, 41 mmol) in THF (20 mL), dropwise over 30 min. The suspension was then refluxed for 2 h, cooled to room temperature, and 3-methyl-3-butenyl p-toluenesulfonate (9.88 g, 41 mmol) in THF (20 mL) added dropwise over 15 min, and the resulting suspension refluxed for 3 h. Work up involved pouring into water (500 mL) and extracting twice with ether (200 mL). The combined ether extracts were washed with water, brine, dried (Na_2SO_4) and rotary evaporated to give an oil which was distilled to give the sulfide 7.6 g (77%): bp 140-145°, 0.007 mm; IR (thin film) 2960, 2945, 1600, 1575, 1485, 1460, 1440, 1360, 1300, 1280, 1235, 1205, 1180, 1160, 1080, 1030, 965, 895 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.66 (br s, 3), 2.1-2.5 (m, 4), 3.7 (s, 3), 3.78 (s, 3), 4.8 (br s, 2), 6.3 (m, 2), 7.1 (m, 1).

Methyl 3-methyl-2-butenyl sulfide (80): To a stirred suspension of sodium methyl mercaptide (14.2 g, 0.2 mol) in dry ether (100 mL) cooled to 0°, was added 1-bromo-3-methyl-2-butene (29.06 g, .195 mol) dropwise over 20 min. The suspension was then refluxed for 8 h, cooled to 0° and ethanol (10 mL) added continuously. The slurry was poured into ice water (200 mL) and extracted twice with pentane (200 mL). The pentane extracts were combined, washed with water, then brine and dried (Na_2SO_4). Removal of the pentane by rotary evaporation left a yellow oil which was

distilled to afford the sulfide 12.0 g (53%): bp 80-90°, 60 mm; IR (thin film) 2960, 2930, 1662, 1435, 1372, 1235, 1100, 980, 840, 765, 680 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.72 (br d, 6, J=6 Hz), 2.02 (s, 3), 3.07-3.20 (br d, 2, J=8 Hz), 5.08-5.48 (m, 1).

2-Methyl-4-methylthio-4-phenyl-1-butene (96): To a stirred solution of benzyl methyl sulfide 95 (0.100 g, 0.725 mM) and methallyl iodide (0.201 g, 1.1 mM) in 0.4 mL dry methylene chloride was added the silver tetrafluoroborate (0.165 g, 0.85 mM) at 0° under argon in semi-darkness. After stirring 3.5 h at 0°, the reddish mixture was cooled to -78° and sodium methoxide solution (1.5 mL, 1 N, 1.5 mM) was slowly added. The yellow suspension was stirred at -78° for 1 h, warmed to room temperature, diluted with ether and filtered through a medium pored scintered galss funnel containing a pad of silica. The filtrate was washed with water and brine, and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 0.100 g red oil which was purified through a 10 mm flash chromatography column (3% ethyl acetate in pet ether) to yield 0.051 g (37%) sulfide: IR ($CHCl_3$) 2950, 2900, 1600, 1440, 1370, 1240, 1220, 1070, 1020 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.65 (s, 3), 1.8 (s, 3), 2.55 (d, 2, J=8 Hz), 3.75 (m, 1), 4.6 (br s, 2), 7.2 (br s, 5); mass spectrum (70 eV) m/e (rel intensity) 192 (6, M^+), 145 (12), 138 (10), 137 (100), 129 (13), 128 (12), 121 (12), 105 (10), 103 (13), 91 (27), 77 (17), 43 (12), 41 (22), 39 (15).

3-Methyl-4-methylsulfinylmethyloxindole (98): To a stirred solution of sodium meta periodate (1.02 mL, 0.5 N in H_2O, 0.51 mM) at 0° was added the thiooxindole 76 (0.100 g, 0.483 mM) in 1 mL methanol. After 5 h at 0°, the mixture was filtered, the filtrate was concentrated and the residual aqueous phase was extracted with methylene chloride three times, washed with brine, and dried ($MgSO_4$). Removal of solvent under reduced pressure yielded .108 g (100%) pure yellow foam: IR ($CHCl_3$) 3450, 3200 (br), 3000, 1720 (sh), 1710 (br), 1620, 1460, 1310, 1040 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.55 (d, 3, J=8 Hz), 2.6 (2 s, 3), 3.6 (q, 1, J=8 Hz), 4.1 (m, 2), 6.7-7.5 (m, 3), 9.7 (br, NH).

3-Methyloxindole-4-carboxaldehyde (100): To a stirred solution of the thiooxindole 76 (0.100 g, 0.483 mM) in 2 mL dry carton tetrachloride under argon at room temperature was slowly added the N-chlorosuccinimide (0.071 g, 0.530 mM) and stirred 1 h by which time the suspension became cloudy. The reaction was then refluxed 1 h and the resulting red mixture was filtered and the filtrate concentrated to 0.070 g yellow oil which was dissolved in 0.5 mL THF and added to a suspension of red mercuric oxide (0.105 g, 0.483 mM) and $BF_3 \cdot Et_2O$ (0.06 mL, 0.483 mM) in 2.5 mL 20% THF in water, and stirred 2 h at room temperature by which time the orange color disappears. The mixture was diluted with ether, filtered and the filtrate further extracted with ether. The ethereal layers were washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 0.066 g crude product which was purified

on a 1000 μ silica plate (1:1, pet ether:ethyl acetate) to yield 0.18 g (22%) aldehyde: IR ($CHCl_3$) 3450, 3200 (br), 1720 (br), 1700 (sh), 1610, 1600 (sh), 1460, 1310, 1160 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.5 (d, 3, J=8 Hz), 3.7 (q, 1, J=8 Hz), 6.9-7.4 (m, 3), 8.9 (br, NH), 10.1 (s, 1).

N-Methyl-N-trifluoroacetyl-l-tryptophan methyl ester (104): To a stirred solution of the N-methyltryptophan methyl ester 103 (12.0 g, 51.7 mM) in 150 mL ether at 0° was added 80 mL trifluoroacetic acid followed by trifluoroacetic anhydride (9.9 mL, 70.0 mM) and stirred 20 min at 0°. Removal of solvent under reduced pressure (water bath T≤35°) and purification of the residue through a 70 mm flash chromatography column (7:3, pet ether:ethyl acetate) yielded 15.4 g (90%) acetamide: IR ($CHCl_3$) 3450, 3400, 3050, 3000, 2950, 1730 (br), 1700, 1450, 1430, 1410, 1340, 1240 (br), 1150, 1090, 1010 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.8 (br s, 3), 3.35 (m, 2), 3.65 (s, 3), 5.0 (m, 1), 6.8-7.6 (m, 5), 8.3 (br, NH); mass spectrum (70 eV) m/e (rel intensity) 329 (2), 328 (9.5, M^+), 201 (11), 131 (12), 130 (100), 128 (8), 103 (9), 77 (13), 69 (12), 42 (21).

Methyl-2-methyltrifluoroacetylamino-3-(3-bromooxindol-3-yl)-propanoate (105): To a stirred solution of tryptophan derivative (11.2 g, 34.1 mM) in 600 mL purified t-butanol at 22-23° (cold water bath) was slowly added the NBS (12.8 g, 72.0 mM) over 1 h. After stirring another 2 h at 22°, the solvent was removed under reduced pressure (water bath T≤35°)

and the residue was diluted with ether and filtered to remove the succinimide. The filtrate was concentrated affording a dark green foam which was first passed through a 50 mm flash chromatography column (2:1, pet ether:ethyl acetate) to remove any remaining succinimide. The resulting light green foam was divided in two and each half was purified through a 50 mm flash column (2:1) finally yielding 6.5 g (45%) slightly orange foam: IR ($CHCl_3$) 3420, 3200 (br), 3000, 2950, 1730 (br), 1690, 1620, 1470, 1240, 1200 (br), 1150, 1090 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.8 (br s, 3), 3.25 (m, 2), 4.85 (m, 1), 6.7-7.4 (m, 4), 9.2 (br, NH); mass spectrum (70 eV) m/e (rel intensity) 424 (8), 423 (4, M^+), 422 (10), 265 (13), 226 (50), 224 (55), 210 (16), 167 (12), 146 (16), 145 (16), 110 (18), 103 (16), 102 (17), 59 (24), 44 (32), 42 (100).

Methyl-2-methyltrifluoroacetylamino-3-(4-methylthiomethyloxindol-3-yl)-propanoate (106): To a stirred suspension of silver tetrafluoroborate (0.69 g, 3.6 mM) in 10 mL dry methyl sulfide at 0° under argon in semi-darkness was added the bromooxindole 105 (1.0 g, 2.36 mM) and stirred 3.5 h at 0-10°. Dry THF (10 mL) was added and cooled to -78° followed by the slow addition of sodium methoxide solution (5.5 mL, 1 N, 5.5 mM) and stirred 2 h at -78° by which time the color changed from light brown to light yellow. The mixture was quenched with saturated NH_4Cl solution and filtered through a medium pored scintered glass funnel containing a pad of silica. The filtrate was washed with water and brine, and dried ($MgSO_4$). Removal of solvent under reduced pressure and purification

through a 50 mm flash chromatography column (7:3, pet ether:ethyl acetate) yielded .807 g (85%) yellow foam: IR ($CHCl_3$) 3425, 3200 (br), 3000, 2950, 2900, 1720 (br), 1700 (br), 1620, 1600, 1450, 1430, 1240 (br), 1150, 1080 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.95 and 2.05 (2 s, 3), 2.7-3.0 (m, 2), 3.15 (br s, 3), 3.65 (s, 3), 3.7 (m, 3), 4.8 (m, 1), 6.5-7.4 (m, 3), 9.0 (br, NH); mass spectrum (70 eV) m/e (rel intensity) 404 (8, M^+), 309 (10), 307 (10), 229 (23), 198 (16), 170 (42), 169 (26), 158 (15), 146 (25), 145 (14), 130 (24), 117 (18), 116 (17), 115 (20), 110 (23), 103 (10), 102 (11), 91 (11), 90 (18), 89 (23), 77 (16), 69 (70), 63 (15), 59 (25), 55 (30), [illegible] (100).

Methyl-2-methyltrifluoroacetylamino-3-(4-formyloxindol-3-yl)-propanoate (107): To a stirred solution of sulfide 106 (0.350 g, 0.868 mM) in 5 mL dry carbon tetrachloride under argon at room temperature was slowly added the N-chlorosuccinimide (0.128 g, 0.960 mM) over 5 min. After 1 h at room temperature and 1 h at reflux, the reaction was filtered and the filtrate concentrated to 0.084 g orange foam which was dissolved in 2 mL THF and added to a suspension of red mercuric oxide (0.188 g, 0.868 mM) and $BF_3 \cdot Et_2O$ (0.11 mL, 0.868 mM) in 6 mL 20% THF/H_2O to afford 0.346 g crude yellow foam which was purified through a 30 mm flash chromatography column (1:1, pet ether:ethyl acetate) to yield 0.088 g (27%) white foam: IR ($CHCl_3$) 3420, 3200 (br), 3000, 2950, 1730 (sh), 1710 (br), 1690, 1610, 1450, 1240, 1200, 1140, 1080 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.8 (m, 2), 2.7 and 3.1 (2 br s, 3), 3.6 (s, 3), 3.65 (m, 1), 4.9 (m, 1),

6.7-7.4 (m, 3), 9.1 (br, NH), 9.9 and 10.3 (2 s, 1).

Methyl-2-methyltrifluoroacetylamino-3-[4-(3-methylbutadienyl)oxindol-3-yl]-propanoate (109): To a stirred suspension of the phosphonium salt of 108 (0.930 g, 2.34 mM) in 5.0 mL dry THF at room temperature under an argon atmosphere was slowly added butyl lithium (2.4 M, 0.81 mL, 1.94 mM) over 5 min. After 30 min the aldehyde 107 (0.225 g, 0.606 mM), dissolved in 3 mL THF, was added to the red solution and stirred another 20 min. The reaction was quenched with saturated NH_4Cl and extracted with chloroform. The organic layers were washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 1.2 g red gum which was purified by flash chromatography (30 mm column, 3:2, pet ether:ethyl acetate, crude material applied to the column in a minimum amount of chloroform) to yield 0.0734 g diene (30%): UV (95% EtOH) max 253 (14700), 285 (sh, 6600), 297 (sh, 5000); IR ($CHCl_3$) 3420, 3200 (br), 3000, 2950, 1730 (sh), 1710 (br), 1690 (sh), 1610, 1590, 1440, 1310, 1240, 1140, 1080 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.99 and 2.03 (2 s, 3), 2.58 (m, 1), 2.96 and 3.24 (2 d, J=1.5 Hz, 3), 3.10 (m, 1), 3.55 and 3.95 (2 m, 1), 3.70 and 3.77 (2 s, 3), 4.80 and 5.05 (2 m, 1), 5.15 (m, 2), 6.40 (d, J=15 Hz, 1), 6.75 (m, 1), 6.90 (d, J=15 Hz, 1), 7.20 (m, 2), 6.90 and 7.15 (2 br, NH).

Methyl-2-phthalimido-3-(4-methylthiomethyloxindol-3-yl)-propanoate (110): To a stirred suspension of silver tetrafluoroborate (0.528 g, 2.72 mM) in 8 mL dry methyl sulfide at 0° under argon was added the bromide 117 (0.800 g, 1.8 mM) and stirred 3 h at 0°. The suspension was cooled to -78° followed by the addition of 8 mL dry THF and methanolic sodium methoxide solution (4.0 mL, 1 N, 4.0 mM). The reaction was protected from direct light, stirred 1 h at -78° and then allowed to warm to 0° over another hour. Saturated ammonium chloride solution was added and filtered through celite. The aqueous layer was further extracted with chloroform and the organic layers were washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 0.950 g yellow foam which was purified by flash chromatography (1:1, pet ether:ethyl acetate) and recrystallized (ethyl acetate:hexane) to yield 0.71 g (91%) sulfide: mp 212-214°; UV (95% EtOH) max 219 (53300), 239 (sh, 13500), 249 (sh, 8100), 264 (sh, 5600), 291 (3300); IR ($CHCl_3$) 3660, 3600, 3430, 3020 (sh), 3000, 2900 (sh), 2430 (sh), 2395, 1785, 1720, 1615, 1595, 1380, 1230, 1210 (sh), 1030 (br), 920 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 1.95 and 2.05 (2 s, 3), 2.8-2.9 (m, 1), 3.25-3.4 (m, 1), 3.60 (d, 1, J=15 Hz), 3.72 and 3.73 (2 s, 3), 3.87 (d, 1, J= 15 Hz), 5.2 (m, 1), 6.75-7.25 (m, 3), 7.65-7.90 (m, 4), 8.72 (m, NH).

Methyl-2-phthalimido-3-(4-methylsulfinylmethyloxindol-3-yl)-propanoate (sulfoxide of 110): To a stirred suspension of sulfide 110 (0.500 g, 1.2 mM) in 12 mL methanol at 0° was added the aqueous sodium meta-periodate solution (2.8 mL, 0.5 M, 1.4 mM) and stirred for 6 h at 0°. The reaction was concentrated, diluted with water and extracted with chloroform. The organic layers were washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded a foam which was purified by flash chromatography (4% methanol in chloroform) to yield 0.49 g (92%) light yellow foam [NOTE: Because of the solubility problems of the sulfoxide, purification was usually not carried out until after the next step, aldehyde 113]: IR ($CHCl_3$) 3440 (sh), 3000 (br) 2400 (br), 1780 (sh), 1720 (br), 1620, 1600, 1440, 1390, 1220 (br), 1110, 1040 (br, s=0), 750 (br) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.55, 2.62, 2.64 and 2.70 (4 s, 3), 2.73-3.48 (m, 2), 3.71 (4 s, 3), 3.70-4.47 (m, 2), 4.91-5.36 (m, 1), 6.33-7.26 (m, 3), 7.57-7.82 (m, 4), 9.41-9.71 (m, NH); mass spectrum (70 eV) m/e (rel intensity) 377 (1, M^+-$SOCH_3$), 317 (1), 231 (2), 219 (3), 218 (1), 214 (1), 132 (3), 203 (2), 202 (1), 200 (1), 198 (1), 191 (2), 190 (4), 189 (2), 188 (4), 187 (6), 172 (9), 170 (23), 160 (9), 148 (6), 130 (16), 119 (10), 115 (10), 104 (21), 85 (10), 76 (21), 71 (12), 70 (11), 69 (14), 57 (25), 44 (100).

Methyl-2-trifluoroacetylamino-3-(4-methylthiomethyloxindol-3-yl)-propanoate (111): To a stirred suspension of the phthaloyl sulfide 110 (2.0 g, 4.7 mM) in 40 mL methanol was added acetic acid (1.1 mL,

18.8 mM) and anhydrous hydrazine (0.6 mL, 18.8 mM) and refluxed 5 h under argon. The reaction was concentrated, diluted with 10% aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layers were washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 0.850 g white solid (2.9 mM) which was suspended in 7 mL dry ether at 0°. 4 mL trifluoroacetic acid was added followed by trifluoroacetic anhydride (0.35 mL, 3.7 mM). After stirring at 0° for 30 min, the solvents were removed under reduced pressure and the residue purified by flash chromatography (3:2, pet ether:ethyl acetate) to yield 0.70 g white foam: IR ($CHCl_3$) 3425, 3200 (br), 3040, 2950, 2910, 1720 (br), 1620, 1595, 1560 (br), 1450, 1430, 1320, 1220 (br), 1160 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.02 and 2.10 (2 s, 3), 2.1-2.4 (m, 1), 2.75-3.05 (m, 1), 3.55-3.95 (m, 3), 3.75 and 3.85 (2 s, 3), 4.80 (m, 1), 6.80-7.35 (m, 3), 8.55-9.55 (m, 2 NH).

Methyl-2-(trichloro-t-butyloxycarbonylamino)-3-(4-methylthiomethyloxindol-3-yl)-propanoate (112): To a stirred suspension of the phthaloyl sulfide 110 (2.0 g, 4.7 mM) in 40 mL methanol was added acetic acid (1.1 mL, 18.8 mM) and anhydrous hydrazine (0.60 mL, 18.8 mM) and refluxed 3 h. The reaction was filtered and the filtrate was concentrated, diluted with saturated $NaHCO_3$ and extracted with ethyl acetate. The organic layers were washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 1.04 g (72%, 3.4 mM) crude amine as a

yellow foam which was suspended between 7.0 mL ether and 7.0 mL water at 0°. To this stirred red suspension was added 6.0 mL 1 N sodium hydroxide solution followed by the chloroformate (1.44 g, 6.0 mM) in 6.0 mL dioxane. The yellow suspension was stirred 2.5 h at 0°. The aqueous phase was extracted with ether, and the organic layers were washed with water and brine, and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 2.2 g yellow oil which was purified by flash chromatography (50 mm column, 2:3, pet ether:ethyl acetate) to yield 0.71 g (31%) white foam: IR ($CHCl_3$) 3420, 3200 (br), 3000, 2950, 2900, 1730 (sh), 1710 (br), 1690 (sh), 1620, 1600, 1500, 1450, 1430, 1380, 1360, 1160, 1040 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.84 and 1.85 (m, 6), 2.01 and 2.07 (2 s, 3), 3.4-3.8 (m, 2), 3.6-3.9 (m, 5), 3.72 and 3.76 (2 s, 3), 4.45 (m, 1), 6.2 (m, NH), 6.80-6.95 (m, 2), 7.15 (m, 1), 8.55 and 9.25 (2 br s, NH).

Methyl-2-phthalimido-3-(4-formyloxindol-3-yl)-propanoate (113): To a suspension of the sulfoxide of 110 (0.100 g, 0.23 mM) in 0.5 mL dry THF at 0° was added chlorotrimethyl silane (0.086 mL, 0.69 mM) and stirred at room temperature for 3 h. Water (0.5 mL) was added followed by trifluoroacetic acid (0.1 mL) and stirred another 2 h. The reaction was diluted with water and extracted with ethyl acetate. The organic layers were washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded a yellow oil which was purified by flash chromatography (1:1, pet ether:acetone) to yield 0.640 g (71%) of aldehyde:

mp 187-191°; UV (95% EtOH) max 219 (41400, 239 (sh, 18100), 250 (sh, 13400), 297 (2400), 332 (1500); IR ($CHCl_3$) 3650, 3600, 3420, 3000 (br), 2390, 2320 (sh), 1770 (sh), 1730 (sh), 1710, 1690 (sh), 1605, 1590 (sh), 1380, 1260 (sh), 1310 (br), 1020, 915 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.95-3.3 (m, 2), 3.69 and 3.72 (2 s, 3), 3.9-4.15 (m, 1), 5.0 (m, 1), 6.65-7.1 (m, 3), 7.66 (m, 2), 7.81 (m, 2), 8.65 and 8.70 (2 m, NH), 9.94 and 10.02 (2 s, 1).

Methyl-2-trifluoroacetylamino-3-(4-formyloxindol-3-yl)-propanoate (114): Prepared in the same manner as 113: Sulfide 111 (0.70 g, 1.8 mM) and sodium metaperiodate solution (5.4 mL, 0.5 M, 2.7 mM) in 20 mL methanol yielded 0.8 g crude sulfoxide which was treated with chlorotrimethylsilane (0.75 mL, 5.9 mM) in 5 mL dry THF, followed by 5 mL water and 0.75 mL trifluoroacetic and to yield after flash chromatography (3:2, pet ether:ethyl acetate) 0.341 g (49%) foam: IR ($CHCl_3$) 3410, 3200 (br), 3030, 1720, 1700 (sh), 1610, 1590, 1575 (br), 1455, 1435, 1390, 1320, 1210 (br), 1165, 910, 700, 645 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.21-2.43 (m, 1), 2.54-2.77 (m, 1), 3.70 and 3.90 (2 s, 3), 2.95-3.15 (m, 1), 3.75-4.00 (m, 1), 7.22-7.28 (m, 1), 7.5-7.62 (m, 2), 8.81 and 9.26 (2 br s, NH), 9.71 and 9.79 (2 br s, NH), 10.01 and 10.06 (2 s, 1).

Methyl-2-(trichloro-t-butyloxycarbonylamino)-3-(4-formyloxindol-3-yl)-propanoate (115): To a stirred solution of the sulfide 112 (0.435 g, 0.873 mM) in 9.0 mL methanol at 0° was added aqueous sodium metaperiodate solution (0.5 M, 2.6 mL, 1.3 mM) and stirred 4.5 h at 0°. The reaction was concentrated, diluted with water and extracted with ethyl acetate. The organic layers were washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 0.475 g yellow foam which was dissolved in 2.6 mL dry THF at 0° under an argon atmosphere. To this stirred solution was added chlorotrimethylsilane (0.33 mL, 2.6 mM) and after 3.0 h at room temperature, 5.0 mL water was added followed by 0.25 mL trifluoroacetic acid and stirred 1.0 h at room temperature. The reaction was further diluted with water and extracted with ethyl acetate. The organic layers were washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 0.475 g yellow foam which was purified by flash chromatography (30 mm column, 1:1, pet ether:ethyl acetate) to yield 0.192 g (47%) aldehyde: IR ($CHCl_3$) 3420, 3200 (br), 3000, 2950, 2825, 2750, 1730 (sh), 1710 (br), 1690 (sh), 1610, 1590, 1500, 1450, 1430, 1380, 1360, 1310, 1160, 1040 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 1.84 and 1.86 (2 s, 6), 2.4-2.75 (m, 2), 3.74 and 3.77 (2 s, 3), 4.01 (m, 1), 3.4 and 3.6 (2 m, 1), 6.20 and 6.40 (2 m, NH), 7.25 (m, 1), 7.49 (m, 2), 9.75 (m, NH), 10.03 and 10.05 (2 s, 1).

N-Phthaloyl-l-tryptophan methyl ester (116): A stirred solution of o-methoxycarbonyl benzoic acid (18.0 g, 100 mM) in 50 mL thionyl chloride was refluxed for 1 h. The excess thionyl chloride was distilled away under reduced pressure (20 mm) and three portions of benzene (50 mL each) were successively added and distilled to remove the last traces of $SOCl_2$. The remaining acid chloride was dissolved in 50 mL dry THF and added dropwise over 30 min to a stirred solution of tryptophan methyl ester hydrochloride (22.8 g, 85 mM) in 200 mL dry THF containing 29 mL triethylamine at 0°. After stirring another 2 h at 0°, the reaction was poured into a liter of water and left for 20 h. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 27.5 g (93%) pure gum: IR ($CHCl_3$) 3470, 3050, 2950, 1775, 1740, 1710, 1465, 1455, 1390, 1240 (br), 1100, 1085, 1015, 880, 710 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 3.74 (d, 2, J=9 Hz), 3.79 (s, 3), 5.41 (t, 1, J=9 Hz), 7.00-7.29 (m, 4), 7.58-7.79 (m, 5), 7.96 (br s, NH); mass spectrum (70 eV) m/e (rel intensity) 348 (4, M^+), 289 (2), 202 (4), 201 (25), 170 (4), 145 (2), 144 (3), 143 (2), 142 (2), 141 (2), 131 (12), 130 (100), 129 (10), 128 (4), 115 (5), 104 (8), 103 (9), 102 (4), 78 (3), 77 (15), 76 (10), 51 (4), 43 (6).

Methyl-2-phthalimido-3-(3-bromooxindol-3-yl)-propanoate (117): To a stirred solution of the phthaloyl tryptophan methyl ester 116 (27.5 g, 79.0 mM) in 1500 mL purified t-butanol at 20-23° C was slowly added N-bromosuccinimide over 1 h and then stirred another 2 h. The solvent was removed under reduced pressure and the residue diluted with 500 mL ether. The succinimide was filtered and the filtrates concentrated to a gum which was purified by flash chromatography (80 mm column, 3:2 followed by 1:1, pet ether:ethyl acetate) to afford a pure foam which was crystallized with ethyl acetate:pet ether to yield 26.0 g (74%) white fluffy solid: mp 184-185° (dec.); IR ($CHCl_3$) 2250, 1720 (sh), 1705, 1380, 1360, 900, 705, 650 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 3.44-3.67 (m, 2), 3.73 (br s, 3), 4.61 (m, 1), 6.73-6.89 (m, 1), 7.12-7.50 (m, 3), 7.61 (m, 2), 7.85 (m, 2), 8.9 (m, NH); mass spectrum (70 eV) m/e (rel intensity) 363 (1), 330 (4), 304 (3), 202 (5), 275 (1), 219 (2), 187 (6), 160 (3), 157 (2), 156 (8), 146 (5), 145 (6), 144 (2), 133 (3), 132 (11), 131 (4), 130 (8), 129 (5), 128 (6), 117 (6), 116 (5), 115 (3), 105 (5), 104 (21), 103 (9), 102 (5), 96 (7), 95 (6), 94 (8), 93 (6), 90 (6), 89 (6), 82 (70), 81 (77), 80 (93), 79 (100), 78 (78), 77 (15), 76 (26), 75 (11), 59 (11), 50 (10).

Methyl-2-phthalimido-3-[4-(1-butene-3-onyl)oxindol-3-yl]-propanoate (118): A stirred suspension of the aldehyde 113 (1.0 g, 2.55 mM), the ylid 122 (1.26 g, 3.83 mM) and benzoic acid (0.061 g, 0.50 mM) was refluxed in 70 mL benzene for 4 h. The light orange solution was

concentrated to an oil which was diluted with saturated $NaHCO_3$ and extracted with ethyl acetate. The organic layers were washed with brine and dried. Removal of solvent under reduced pressure afforded 2.5 g oil which was purified by flash chromatography (3:2 pet ether:acetone) to yield 1.5 g yellow foam which still contained the difficult to be separated triphenyl phosphine oxide. This mixture was used in the next step. A small amount was crystallized (acetone:pet ether) to pure white crystals of enone: mp 214-215°C; UV (95% EtOH) max 214 (46900), 239 (sh, 18100), 263 (16500), 291 (17200); IR ($CHCl_3$) 3420, 3200 (br), 3000, 2950, 1775 (sh), 1730 (sh), 1710 (br), 1665, 1610, 1580, 1450, 1430, 1380, 1350 (sh), 1250, 1200, 1100, 970 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.48 and 2.51 (2 s, 3), 2.90 (m, 1), 3.30 (m, 1), 3.68 and 3.74 (2 s, 3), 4.00 (m, 1), 5.11 (m, 1), 6.36 (d, J=16 Hz, 1), 6.80 (m, 3), 7.55 (d, J=16 Hz, 1), 7.65 (m, 4), 8.52 (br, NH).

Ethylene Ketal of 118 (119): A suspension of the anone 118 (1.1 g containing some triphenylphosphine oxide, 2.55 mM) and anhydrous p-toluenesulfonic acid (0.088 g, 0.50 mM) was refluxed in 25 mL benzene and 10 mL ethylene glycol with a Dean Stark trap for 3 h. The reaction was concentrated, diluted with 10% aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layers were washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure and purification by flash chromatography (50 mm column, 3:2, pet ether:acetone) yielded a yellow

foam which was crystallized in methanol affording 0.491 g (41% from aldehyde 113) white solid: UV (95% EtOH) max 218 (44600), 239 (sh, 19700), 255 (15000), 291 (8600); IR ($CHCl_3$) 3420, 3200 (br), 3000, 2950, 1775 (sh), 1730 (sh), 1720 (br), 1690 (sh), 1610, 1590, 1450, 1430, 1380, 1210 (br), 1100, 1030, 870 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.58 and 1.59 (2 s, 3), 2.90 (m, 1), 2.20 (m, 1), 3.65 and 3.72 (2 s, 3), 3.90 (m, 1), 4.08 (m, 4), 4.75 and 5.05 (2 m, 1), 5.92 and 6.25 (2 d, J=17 Hz, 1), 6.60-6.95 (m, 4), 7.4-7.8 (m, 4), 8.51 and 8.65 (2 br s, NH); mass spectrum (30 eV) m/e (rel intensity) 477 (2), 476 (5, M^+), 461 (2), 432 (1), 431 (1), 415 (1), 414 (4), 396 (4), 383 (5), 382 (17), 354 (2), 267 (3), 258 (15), 243 (5), 242 (6), 232 (6), 230 (3), 227 (3), 219 (30), 197 (17), 196 (100), 187 (50), 183 (12), 182 (16), 160 (25), 132 (12), 111 (19), 87 (90), 73 (15), 67 (17), 45 (10), 44 (17), 43 (25), 40 (10), 32 (82).

Tricyclic oxindole (121): To a stirred solution of the phthalimido ketal 119 (0.200 g, 0.42 mM) in 3.0 mL methanol was added the acetic acid (0.076 mL, 1.26 mM) and refluxed under an argon atmosphere for 4 h. The reaction was concentrated, diluted with 10% aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layers were washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 0.140 g (0.405 mM) oil (120) which was dissolved in 4 mL acetone followed by the addition of anhydrous p-toluenesulfonic acid (0.083 g, 0.486 mM), and stirred 20 h at room temperature. The

reaction was diluted with 10% aqueous sodium bicarbonate until basic and extracted with ethyl acetate. The organic layers were washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 0.190 g crude orange oil which was purified by flash chromatography (20 mm column, 1:1, pet ether:acetone) to yield 0.054 g (44% from 119: 3 steps) solid. Recrystallization from ethyl acetate afforded fine needles: mp 198-199°; UV (95% EtOH) max 215 (32800), 240 (sh, 12400), 263 (11800), 290 (12600); IR ($CHCl_3$) 3420, 3200(br), 3000, 2950, 1775 (sh), 1730 (sh), 1710 (br), 1665, 1580, 1445, 1430, 1380, 1360 (sh), 1250, 1200, 1100, 970 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.2-1.7 (m, NH), 2.18 and 1.29 (2 s, 3), 2.7-2.9 (m, 2), 3.0-3.1 (m, 2), 3.73 (m, 1), 3.72 and 3.74 (2 s, 3), 4.0 (m, 1), 4.35 and 4.65 (2 m, 1), 6.65-6.75 (m, 2), 7.15 (m, 1), 8.45 (m, NH); mass spectrum (25 eV) m/e (rel intensity) 304 (0.9), 303 (4), 302 (14, M^+) 259 (3), 247 (1), 246 (7), 245 (43), 244 (10), 243 (47), 229 (3), 217 (15), 216 (100), 202 (2), 201 (15), 200 (3), 199 (8), 187 (2), 186 (13), 185 (98), 184 (23), 183 (7), 182 (2), 175 (4), 174 (30), 173 (4), 172 (8), 171 (4), 167 (3), 159 (8), 158 (28), 157 (12), 156 (8), 133 (4), 130 (14), 115 (6), 89 (4), 44 (4), 43 (33), 32 (4).

Methyl-2-trifluoroacetylamino-3-[4-(3-methylbutadienyl)oxindol-3-yl]-propanoate (123): To a stirred suspension of the phosphonium salt of 108 (7.3 g, 18.4 mM) in 37 mL dry THF under an argon atmosphere was slowly added butyl lithium (6.3 mL, 2.4 M, 15.2 mM) over 5 min at room

temperature. After 30 min, the aldehyde (1.87 g, 5.08 mM), dissolved in 25 mL THF was added over 10 min and stirred another 20 min. The reaction was diluted with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layers were washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 3.5 g red foam which was purified by flash chromatography (50 mm column, 1:1, pet ether:ethyl acetate) to yield 0.725 g (36%) of white solid: IR ($CHCl_3$) 3420, 3200 (br), 3050, 3000, 2954, 1740 (sh), 1720 (br), 1690 (sh), 1605, 1580, 1560, 1445, 1430, 1320, 1230, 1160, 1015, 960, 890 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.03 and 2.05 (2 s, 3), 2.1-2.25 (m, 1), 2.75-3.0 (m, 1), 3.74 (m, 1), 3.73 and 3.83 (2 s, 3), 4.65 and 4.85 (2 m, 1), 5.19 (m, 2), 6.45 and 6.58 (2 d, 1, J=16 Hz), 6.80 (m, 1), 6.90 (d, 1, J=16 Hz), 7.75 (m, 2), 9.25 (m, NH), 8.95 and 9.4 (2 m, NH).

Methyl-2-trifluoroacetylamino-3-[4-(1-butene-3-onyl)oxindol-3-yl]-propanoate (125): A stirred suspension of the aldehyde 114 (0.218 g, 0.61 mM), ylid 122 (0.232 g, 0.73 mM) and benzoic acid (0.008 g, 0.06 mM) in 10 mL benzene was refluxed 3 h. Removal of solvent under reduced pressure afforded a white residue which was diluted with 10% aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layers were washed with brine and dried. Removal of solvent under reduced pressure and flash chromatography (3:2, pet ether:ethyl acetate) yielded 0.121 g enone (49%): IR ($CHCl_3$) 3420, 3200, 3010, 1750 (br), 1720, 1700 (sh), 1695 (sh), 1685, 1610, 1585, 1450, 1430, 1220 (br sh),

1180 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.20-2.48 (m, 1), 2.45 and 2.47 (2 s, 3), 2.83-2.93 (m, 1), 3.80-3.89 (m, 1), 3.74 and 3.90 (2 s, 3), 4.78-4.95 (m, 1), 6.73 and 6.76 (2 d, 1, J=16 Hz), 6.93-7.00 (m, 1), 7.18-7.28 (m, 2), 7.56 and 7.65 (2 d, 1, J=16 Hz), 8.89 and 9.02 (2 br s, NH), 9.43 (m, NH); mass spectrum (70 eV) m/e (rel intensity) 398 (3, M^+), 296 (1), 226 (2), 214 (32), 210 (1), 200 (2), 198 (3), 197 (4), 196 (18), 185 (2), 184 (5), 183 (7), 182 (9), 172 (10), 171 (9), 170 (16), 158 (4), 154 (6), 144 (8), 130 (6), 129 (6), 128 (5), 127 (6), 115 (8), 102 (7), 69 (11), 59 (6), 43 (100).

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Biographical Note

The author, son of Paul Y. and Julia S. Liang, was born on January 5, 1956 in Taipei, Taiwan. Two years later, he and his parents moved to the United States where they became citizens in 1965. He attended primary and secondary schools in New York City and graduated from Regis High School in 1973. He then studied at Columbia University where he initiated his interest in organic chemistry research in the laboratories of Professor Gilbert Stork and graduated with a Bachelor of Arts Degree in May, 1977. The author then entered the Massachusetts Institute of Technology where he completed the requirements for the Ph.D. degree under the supervision of Professor George Büchi in July 1981.

The author has accepted a research position in the Biochemicals Department of E. I. du Pont de Nemours and Co., Wilmington, Delaware, starting in September 1981.